100 Years of the Wolff Rearrangement

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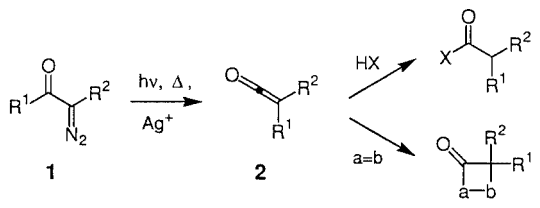
The conversion of α-diazo ketones into ketenes, and products derived therefrom, was discovered by Wolff in 1902. Major applications of the Wolff rearrangement, such as the Arndt–Eistert reaction (homologation of carboxylic acids) and the ring contraction of cyclic ketones, have been with us for some while. Nevertheless, substantial progress has been made recently. The reaction mechanism has been explored by means of matrix isolation, time-resolved spectroscopy, and computation. Full retention of configuration of the migrating group has been established by using enantioselective chromatography. The Arndt–Eistert reaction has witnessed a renaissance in the field of natural products, in particular β-amino acids and β-peptides. Ring-contracting Wolff rearrangements and ketene cycloadditions have been applied in syntheses of increasingly complex, biologically active target molecules. These accomplishments, as well as unsolved problems, are addressed in the present review.

1. Introduction

The Wolff rearrangement[1] is initiated by the loss of nitrogen from α-diazocarbonyl compounds **1**. A 1,2-shift of



Scheme 1. The Wolff rearrangement

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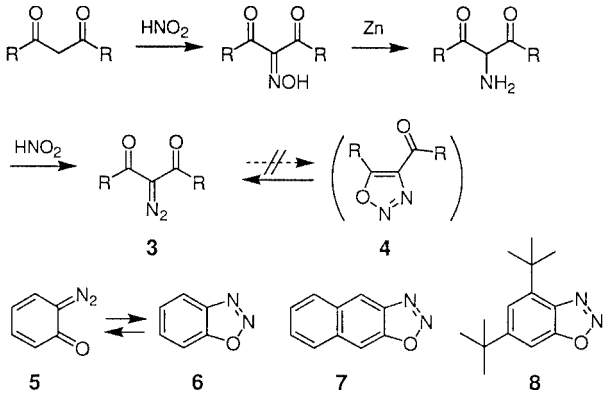
R^1 leads to ketenes **2** which can react with nucleophiles (HX) to give (derivatives of) carboxylic acids, or undergo [2+2] addition with unsaturated systems (a=b) (Scheme 1).

The Wolff rearrangement has been widely used in organic synthesis for the homologation of carboxylic acids (Arndt−Eistert reaction, $R-CO_2H \rightarrow R-COCHN_2 \rightarrow R-CH_2CO_2H$) and for ring contractions leading to strained cyclic systems. Applications of biochemical interest include the design of β-peptides, DNA cleavage, and photoaffinity labeling. The Wolff rearrangement has achieved commercial importance in the photolithography industry. The mechanism of the Wolff rearrangement has also received much attention. Loss of nitrogen and 1,2-shift can occur in concert or sequentially, by way of carbonyl carbenes and/or oxirenes. Recent advances in time-resolved spectroscopy, matrix isolation, and computation have contributed substantially to the elucidation of the complex reaction profile.

The first report on the Wolff rearrangement appeared in 1902.[2] On the occasion of the 100th anniversary, the present status will be reviewed, with emphasis on results from the past decade.

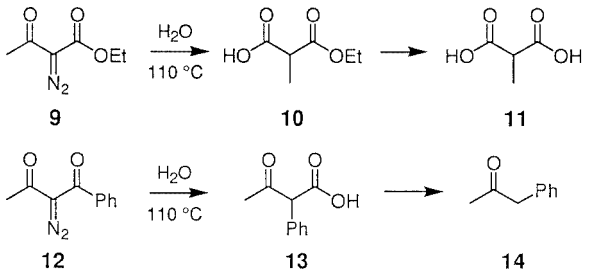
2. Historical

Ludwig Wolff (1857−1919) started his academic career at the University of Strasbourg, as a student of Rudolph Fittig (Ph.D. 1882). From 1891 to his death, Wolff was Professor of Analytical Chemistry at the University of Jena. At the turn of the century, Wolff obtained 2-diazo-1,3-diketones **3** by the route shown in Scheme 2.[2,3] He regarded these compounds as 1,2,3-oxadiazoles **4** (“diazoanhydrides”) as they differed in color and reactivity from simple α-diazo ketones. However, the electron-withdrawing effect of the additional carbonyl groups is sufficient to explain the data. The acyclic structure **3** was soon adopted[4] and later confirmed by IR[5] and X-ray analyses.[6] On benzoanellation, the 1,2,3-oxadiazole structure becomes more significant. The equilibrium **5** ⇄ **6** ranges from > 90% **5** in methanol to 84% **6** in hexane and in the gas phase.[7] The 1,2,3-oxadiazoles **7**[8] and **8**[9] prevail in solution and in the solid state.



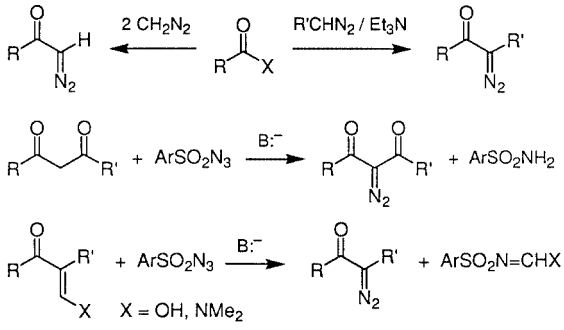
Scheme 2. The 1,2,3-oxadiazole problem

On heating ethyl 2-diazo-3-oxo-butyrate (**9**) with water, Wolff obtained ethane-1,1-dicarboxylic acid (**11**, “isosuccinic acid”) by way of the ethyl ester **10** (Scheme 3). Under similar conditions, 2-diazo-1-phenylbutane-1,3-dione (**12**) afforded 1-phenylpropan-2-one (**14**).[2] The first examples of the Wolff rearrangement indicated that a 1,2-shift occurred and that the migratory aptitudes were Ph > Me > OEt. However, it was not obvious how water was incorporated en route to the carboxylic acids **10** and **13**, respectively. A few years later, Staudinger developed the chemistry of ketenes,[10] and Schröter obtained diphenylketene (**2**, $R^1 = R^2$ = Ph) on heating 2-diazo-1,2-diphenylethanone (“azibenzil”, **1**, $R^1 = R^2$ = Ph).[11] These results suggested that the formation of carboxylic acids in “aqueous” Wolff rearrangements proceeds by way of ketenes. Wolff adopted this mechanism in a comprehensive paper which also described silver-ion catalyzed rearrangements of α-diazo ketones, such as diazoacetophenone (**1**, R^1 = Ph, R^2 = H).[12]



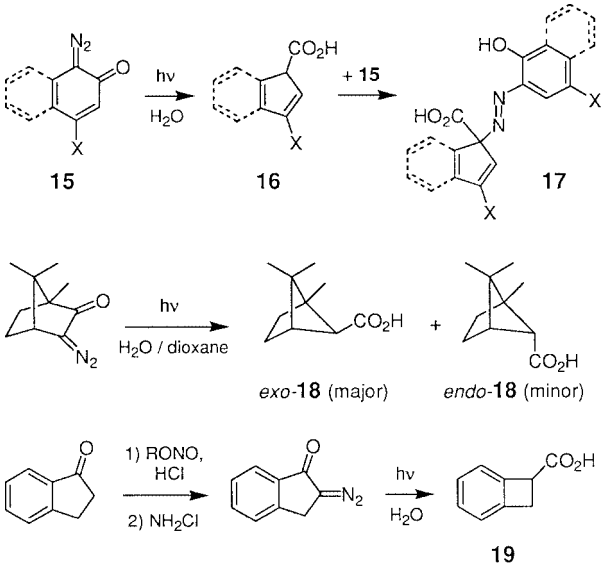
Scheme 3. First examples of the Wolff rearrangement

For over twenty years, the Wolff rearrangement was considered as an oddity with little potential for synthesis. This attitude changed dramatically when efficient methods for the preparation of α-diazo ketones were developed, among which the acylation of diazoalkanes and the diazo transfer reaction proved to be most versatile (Scheme 4).[13] The seminal paper by Arndt and Eistert on the homologation of carboxylic acids, published in 1935,[14] triggered an avalanche of applications. Silver ion catalysis was the method of choice. The first review on the Arndt−Eistert reaction appeared as early as 1942,[15] with 72 references and 76 recorded examples!



Scheme 4. Important methods for the preparation of α-diazoketones

Ring contraction by light-induced Wolff rearrangement was first observed with 2-diazocyclohexa-3,5-dienones ("*o*-quinone diazides", **15**). Although "quinone diazides" **15** had been used for many years in the Diazotype process, the reaction remained obscure until the products were identified as cyclopentadienecarboxylic acids **16**.[16] Without special precautions, coupling of **16** with excess **15** leads to the azo compounds **17** (Scheme 5). Photolysis proved to be an efficient procedure for the Wolff rearrangement of acyclic and alicyclic diazo ketones.[17] This experience prompted syntheses of strained molecules, among which **18**[18] and **19**[19] were the first examples. The utilization of ketenes, generated by Wolff rearrangement, for [2+2] cycloaddition reactions also began in the fifties. The photolysis of α-diazo ketones in the presence of imines was found to give β-lactams (Scheme 1, a=b = RN=CR′R′′).[20] By 1960, the stage was set for a thorough scrutiny of the mechanism and for extensive synthetic applications of the Wolff rearrangement.



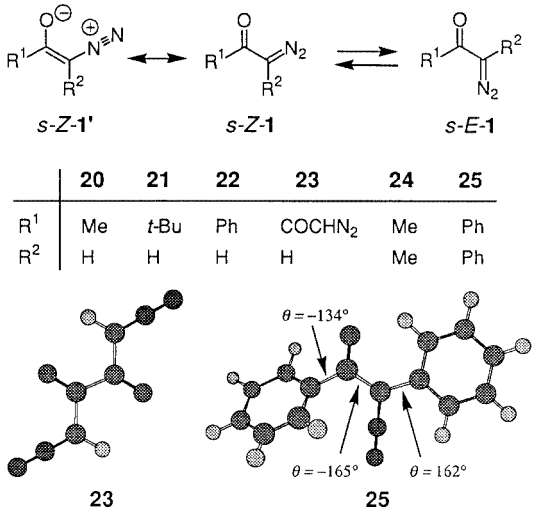
Scheme 5. Early ring contractions by means of the Wolff rearrangement

3. Mechanism

An important mechanistic question in the Wolff rearrangement is whether nitrogen extrusion and 1,2-shift occur in a concerted manner or stepwise by way of a carbene intermediate (Section 3.2.). Conformational control of the Wolff rearrangement has often been cited in support of concertedness. Therefore, the steric preferences of α-diazocarbonyl compounds will be reviewed before the mechanism of their rearrangement is discussed in some detail.

3.1. Stereochemistry of α-Diazocarbonyl Compounds

α-Diazo ketones assume a planar configuration of the O=C−C=N_2 group, unless bulky substituents interfere. The C−C bond possesses partial double bond character, as illustrated by the resonance structure **1′** (Scheme 6). Sizeable rotational barriers (55−65 kJ/mol), separating *s*-*Z* and *s*-*E* conformers of **1**, were suggested on the basis of IR and UV spectroscopic data,[21] and conclusively demonstrated by NMR studies.[22] As a rule, diazomethylketones (R^2 = H) show two sets of NMR signals at −40 °C which were assigned to *s*-*Z* (major) and *s*-*E* (minor) conformers by means of coupling constants (R^1 = H) and (lanthanide induced) chemical shifts.[22,23] For example, the equilibrium constants, K = [*s*-*E*]/[*s*-*Z*], observed for diazoacetone (**20**) at −40 °C were 0.180 ($CDCl_3$, NMR),[22] 0.168 (CCl_4, IR),[24a] and 0.325 (benzene, dipole moment).[24b] Rather small differences in enthalpy, $\Delta\Delta H_f$ = ΔH_f(*s*-*E*-CH_3COCHN_2) − ΔH_f(*s*-*Z*-CH_3COCHN_2), of 3.7 kJ/mol (CCl_4, IR)[24] and 3.8 kJ/mol (benzene, dipole moment)[24b] were derived from the temperature dependence of K. Unlike diazoacetone, 3,3-dimethyl-1-diazo-2-butanone (**21**) and diazoacetophenone (**22**) prefer the *s*-*Z* conformation strongly (> 98%). The dipole moments of **22** and some 4-X derivatives are in excellent agreement with those calculated for the *s*-*Z* conformers.[24c] The X-ray crystal structures of 1,4-bisdiazo-2,3-butanedione (**23**),[25] of the homologue $N_2CH-CO-CH_2-CH_2-CO-CHN_2$,[26a] and of diazoacetophenone (**22**)[26b] confirm the *s*-*Z* conformation for the $CO-CHN_2$ groups. In the crystalline state of **22**, the angle between the plane of the $COCHN_2$ group and the plane of the benzene ring is less than 2°.[26b] Semiempirical (AM1) and ab initio [HF/6-31G(d)] computations indicate 1.6−2.9° distortion for gaseous **22** and some 4-X derivatives.[27]

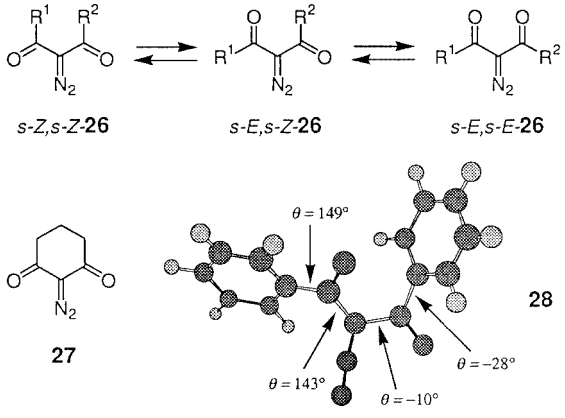


Scheme 6. Conformers of α-diazoketones

Attractive interaction between the negatively charged oxygen and positively charged nitrogen (see **1′**) is thought to stabilize the *s*-*Z* conformation of diazo ketones. If R^2 = H, the preference for *s*-*Z* is accentuated by bulky substituents since R^1 interferes more strongly with the diazo group in the *s*-*E* conformer than with hydrogen in the *s*-*Z* conformer. For $R^2 \neq$ H, the electronic effect favoring *s*-*Z* is opposed by the steric repulsion of R^1 and R^2. 3-Diazobutan-2-one (**24**) was found to be a mixture of conformers

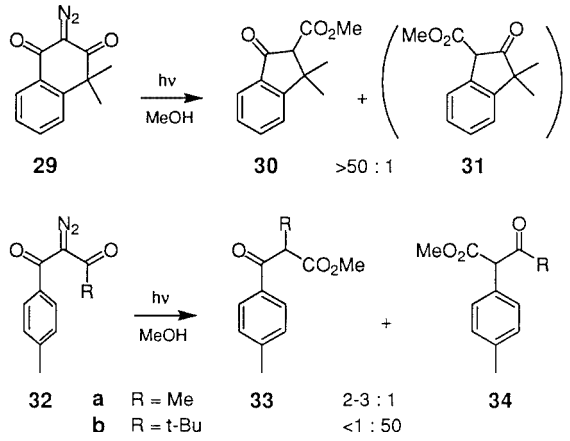
in which the *s*-*E* form predominates: $\Delta\Delta H_f = -6.1$ kJ/mol ($CDCl_3$, NMR)[28] and -6.4 kJ/mol (benzene, dipole moment).[24b] With bulkier substituents, the $CO-CN_2$ group will be distorted from planarity. The effect is demonstrated by the X-ray structure of 2-diazo-1,2-diphenylethanone (**25**) which shows an O−C−C−N dihedral angle of 165° (rather than 180° for *s*-*E*).[29] The benzene rings are also twisted out of the planes of the carbonyl and diazo groups, respectively. Computations suggest that the deviations from planarity could be more severe in the gas phase (and, presumably, in solution) than in the crystal.[30] Such distortions destabilize the ground state, lower the rotational barrier, and complicate the assignment of conformers. For example, the observed dipole moments, intermediate between those calculated for the *s*-*Z* and *s*-*E* conformers, cannot distinguish between rapidly equilibrating conformers and a single distorted structure.[31]

2-Diazo-1,3-diketones (**26**) can assume three ($R^1 = R^2$) or four ($R^1 \neq R^2$) planar conformations (Scheme 7). Dipole moments,[32] IR[33] and NMR spectroscopic data[34] indicate that the *s*-*Z*,*s*-*Z* conformer prevails with R^1, R^2 = alkyl and with R^1 = 4-X−C_6H_4, R^2 = alkyl. Comparison with cyclic, *s*-*Z*,*s*-*Z*-constrained compounds, such as **27**, supports the assignment. Equilibration of *s*-*Z*,*s*-*Z* and *s*-*E*,*s*-*Z* conformers was observed with R^1 = mesityl, R^2 = alkyl. Diaroyldiazomethanes (R^1, R^2 = aryl) exist as mixtures of *s*-*E*,*s*-*Z* and *s*-*Z*,*s*-*E* rotamers which interconvert by way of the *s*-*E*,*s*-*E* form.[34] X-ray analysis of 2-diazo-1,3-diphenylpropane-1,3-dione (**28**) confirmed the *s*-*E*,*s*-*Z* conformation and revealed substantial deviations from planarity.[6] Distortion by bulky substituents leads to decreasing thermal stability of diazo ketones, due to inhibition of resonance.[35]



Scheme 7. Conformers of 2-diazo-1,3-diketones

2-Diazo-1,3-dicarbonyl compounds are well suited to demonstrate stereocontrol of the Wolff rearrangement as two groups (R^1, R^2 in **26**) can migrate competitively. Compound **29**, whose cyclic structure enforces a planar conformation, was found to react with virtually exclusive migration of the alkyl group (**30/31** > 50, Scheme 8).[36] The acyclic analogues **32** also prefer the *s*-*Z*,*s*-*Z* conformation but deviate from planarity (**a** < **b**).[34] The molecular distortion of **32** promotes aryl migration, which is competitive with **32a** (→ **33/34** = 2−3) and predominates with **32b** (→ **33/34** < 0.02).[36]



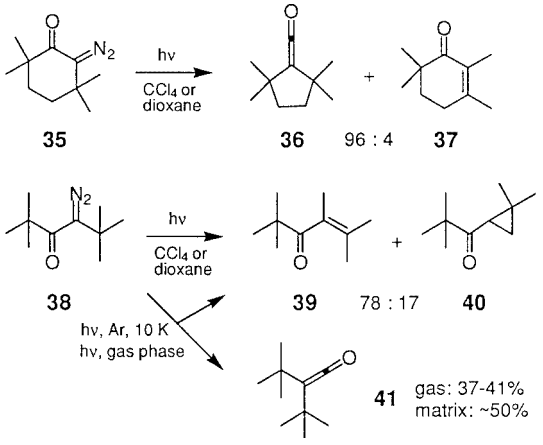
Scheme 8. Torsional effects in the Wolff rearrangement

3.2. Concerted and Stepwise Reaction Paths

The concerted Wolff rearrangement can be viewed as displacement of nitrogen by the migrating group. Neighboring group participation (anchimeric assistance) is widespread in heterolytic processes,[37] but is rarely encountered in homolyses.[38] Therefore, concerted Wolff rearrangements should proceed from the ground and singlet excited states of α-diazo ketones, rather than from triplet excited states. Neighboring group participation is normally detected from stereochemical and kinetic studies. Application of these probes to diazo ketones will be reviewed in the following paragraphs, before more specific methods are discussed.

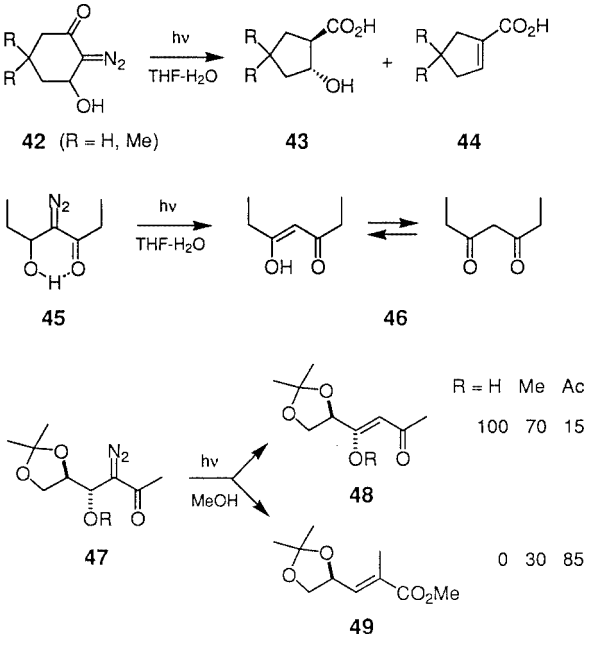
In the *s*-*Z* conformation of α-diazo ketones [(*s*-*Z*)-**1**] the leaving and migrating groups (N_2, R_1) are deployed in an ideal antiperiplanar geometry for concerted extrusion/rearrangement. In 1966, Kaplan postulated that ketenes arise solely from the *s*-*Z* form.[22b] This idea was later corroborated in a study of 3,3,6,6-tetramethyl-2-diazocyclohexanone (**35**) and 2,2,5,5-tetramethyl-4-diazo-3-hexanone (**38**).[39] Photolysis of the *s*-*Z* locked diazo ketone **35** in aprotic solvents afforded 96% of the ring-contracted ketene **36**, along with very minor amounts of the unsaturated ketone **37** (Scheme 9). In contrast, photolysis of **38** in solution gave only traces of the ketene **41**. Instead, the ketones **39** (major) and **40** (minor) were obtained which arise by 1,2 shift of a

methyl group and intramolecular C−H insertion, respectively. The lack of Wolff rearrangement was attributed to the presumed *s-E* conformation of **38**,[39] although a strongly twisted geometry is more likely.[31b] In fact, the ketene **41** is formed from **38** in the gas phase[40] and in a cryogenic matrix.[41]



Scheme 9. Conformational control of the Wolff rearrangement

Related evidence came from studies on α-diazo-β-hydroxy ketones. The cyclic compounds **42** gave high yields of ring-contracted acids **43** and **44** (Scheme 10).[42] 4-Diazo-5-hydroxy-3-heptanone (**45**), on the other hand, reacted exclusively by way of 1,2-H shift to give heptane-3,5-dione (**46**).[42a] The behavior of **45** could be due to the preferred *s-E* conformation, which is stabilized by a hydrogen bond. Alkylation or acylation of the hydroxy group will eliminate the hydrogen bond. This obvious test was not applied to **45** but was performed on the diazo ketones **47**. While the hydroxy compound (R = H) reacted exclusively by 1,2-H shift (→ **48**), Wolff rearrangement (→ **49**) took place, at least in part, with the methoxy (R = Me) and acetoxy (R = Ac) derivatives.[43] α-Diazo-β-hydroxy ketones and the analogous carbenes were also studied computationally.[44]



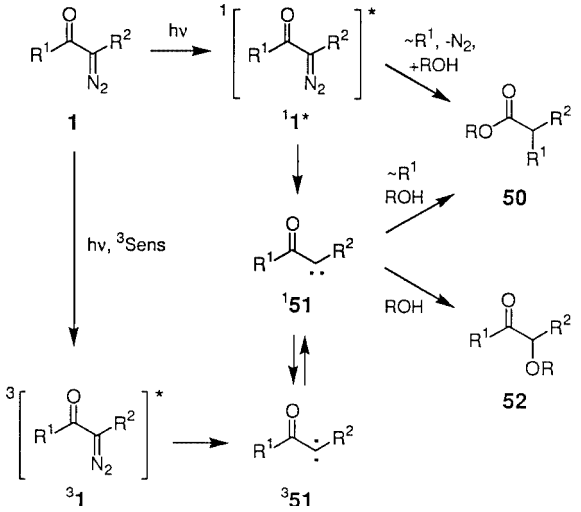
Scheme 10. Rearrangements of α-diazo-β-hydroxyketones

In summary, cyclic, *s-Z* locked diazo ketones undergo the Wolff rearrangement readily,[45] in accordance with a concerted mechanism. Exceptions are found only if ring contraction creates excessive strain (see Section 4.3.). The record of acyclic diazo ketones is varied. Examples of presumed *s-E* conformers which are reluctant to rearrange (**38**, **45**, **47**) were mentioned above. On the other hand, some established *s-E* diazo ketones, such as 2-diazo-1,2-diphenylethanone (**25**), produce ketenes with ease. Hence the stereochemical argument for concertedness is suggestive rather than conclusive.

Kinetic evidence for anchimeric assistance can, in principle, be obtained from the rates of the *thermal* decomposition of α-diazo ketones. Care must be taken to eliminate the accelerating effect of protic nucleophiles which are added as ketene traps.[46] Thorough studies on 4-X−C_6H_4−CO−CN_2−Ph (4-X-**25**) afforded a linear Hammett plot (log$k$ = 0.75σ − 2.89).[47] These data exclude the *onset* of anchimeric assistance as X is varied (nonlinear Hammett plots are characteristic of such systems).[37] In retrospect, the choice of substrate was unfortunate since the *s-E* conformation of **25** disfavors neighboring group participation. Diazoacetophenone (**22**) strongly prefers the *s-Z* conformation; hence 4-X-**22** would be better suited than 4-X-**25** for Hammett analysis. However, the only kinetic studies with 4-X-**22** were performed in the presence of Ag^+, where rate-determining complexation to the catalyst is likely.[48] The rate constants of various diazo ketones argue against concerted nitrogen extrusion and rearrangement *in the ground state*.[49] Thus Ph−CO−CHN_2 (**22**, k_{373} = $6.8\cdot10^{-6}$ s^{-1}) and Ph_3C−CO−CHN_2 (k_{373} = $1.0\cdot10^{-5}$ s^{-1}) decompose at similar rates while Ph−CO−CN_2−Ph (**25**, k_{373} = $2.8\cdot10^{-2}$ s^{-1}) reacts much faster. The rates are strongly influenced by the stablity of the intervening carbonyl carbene whereas the nature of the migrating group plays a minor role.

The reactivity of the *excited singlet state* of α-diazo ketones was elucidated by comparison of direct and sensitized photolyses (Scheme 11). Energy transfer from a triplet sensitizer, such as Ar_2CO, generates triplet carbonyl carbenes (**1** → ^{3}**1** → ^{3}**51**) which add to alkenes[50] or abstract hydrogen from solvent molecules.[51] In the absence of good scavengers, intersystem crossing leads to singlet carbonyl carbenes (^{1}**51**), many of which undergo O−H insertion (→ **52**) competitively with Wolff rearrangement. The product distributions thus obtained are compared to those of direct photolyses (**1** → ^{1}**1*** → ^{1}**51**). An excess of Wolff product from direct photolysis points to concerted rearrangement of ^{1}**1***. Tomioka applied this method to a variety of α-diazo ketones (Table 1).[52] The product ratios **50**/**52** obtained from direct irradiation were regularly higher than those from sensitized photolyses. Evidence of the concerted reaction ^{1}**1*** → **50** was thus furnished for a good selection of

substrates. It is less clear *how much* of the Wolff product **50** stems from the concerted rearrangement of ^{1}**1***. All sensitized runs recorded in Table 1 were performed with a fivefold excess of Ar_2CO, and it is unlikely that complete sensitization was achieved in each case.



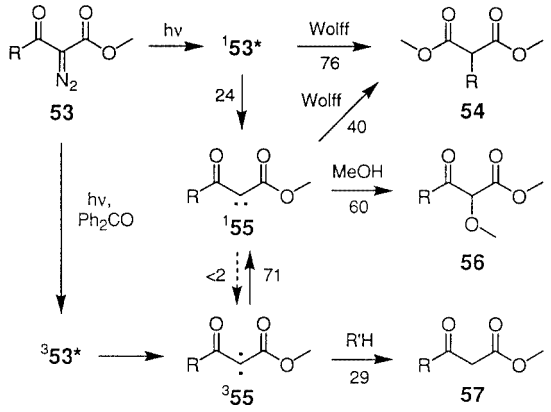
Scheme 11. Direct vs. triplet sensitized photolysis of diazoketones

Table 1. Direct versus sensitized photolyses of diazo ketones **1**

R^1	R^2	**50/52**		Ref.
		hν	*hν*, Ph_2CO[a]	
CH_3	Ph	1.43	0.39	[52a]
Ph	CH_3	1.35	0.49	[52a]
Ph	CH_2CH_3	3.85	1.87	[52a]
Ph	$CH(CH_3)_2$	16.8	4.25	[52a]
$PhCH_2$	H	> 100	8.71	[52b]
$(CH_3)_3C$	H	> 100	2.70	[52b]
$-(CH_2)_4-$		> 100	22.5	[52b]
$-(CH_2)_5-$		> 100	> 50	[52b]
Ph	$COCH_3$	1.33	0.42[b]	[52c]
Ph	$CO_2CH_2CH_3$	1.55	0.27[b]	[52c]

[a] Solvent: methanol; $[Ar_2CO]/[1] = 5$. [b] Sensitizer: 4-methylbenzophenone.

More recently, the reaction paths of 2-diazo-3-keto esters (**53**) were dissected quantitatively (Scheme 12).[53] Photolysis of **53** in methanol afforded **54** (Wolff rearrangement) and **56** (O−H insertion). In the presence of benzophenone, **57** (H abstraction) was found in addition to **54** and **56**. With increasing concentration of Ph_2CO, both **56** (a product of the singlet carbene ^{1}**55**) *and* **57** (a product of the triplet carbene ^{3}**55**) increased at the expense of **54**, as illustrated in Figure 1 for R = *n*Bu. Obviously, a large fraction of **54** does not arise from **55**. The partitioning of the various intermediates (Scheme 12) was estimated from the product distributions of direct and *completely* sensitized photolyses (obtained by extrapolating the computed lines in Figure 1, $[Ph_2CO] \rightarrow \infty$). According to this analysis, concerted and nonconcerted extrusion of nitrogen from the excited singlet state of the diazo compound (^{1}**53***) occur in the ratio of about 3:1. Wolff rearrangement and O−H insertion (1:1.5) of the singlet carbene (^{1}**55**) are much faster than spin inversion. The triplet carbene (^{3}**55**) prefers intersystem crossing to H abstraction from methanol (2.5:1). These numbers depend but slightly on R unless a double bond is introduced [R = R′CH=CH$(CH_2)_n$, $n = 2-3$]. In that case, intramolecular addition of ^{3}**55** minimizes intersystem crossing to the singlet.



Scheme 12. Photolysis of 2-diazo-3-ketoesters. Numbers are for R = *n*Bu

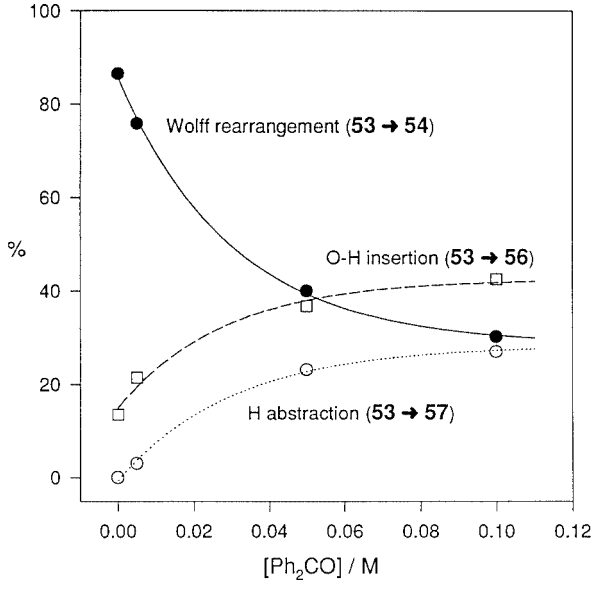


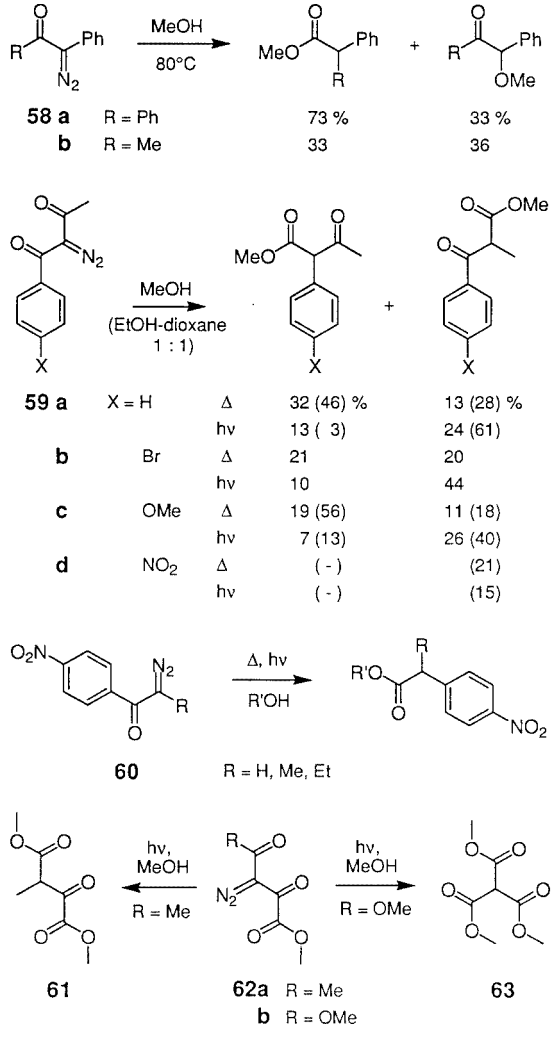
Figure 1. Photolyses of methyl 2-diazo-3-oxoheptanoate (**53**, R = *n*Bu) in methanol with benzophenone as sensitizer; product distributions (%) are shown as functions of the concentration of benzophenone

3.3. The Migrating Group

3.3.1. Migratory Aptitudes

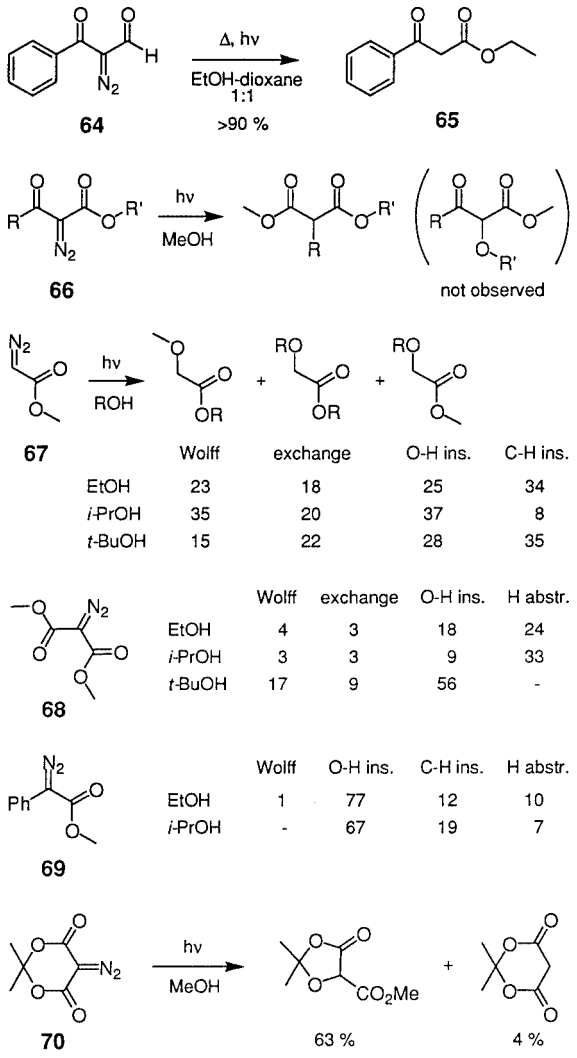
Migratory aptitudes in the Wolff rearrangement are influenced not only by the nature of the migrating group but also by the conformation of the reactant (Section 3.1.) and by the dichotomy of concerted and nonconcerted reaction paths (Section 3.2.). The ranking of alkyl and aryl groups is, therefore, uncertain. The ratios of Wolff rearrangement

to intermolecular capture observed with **58a**,**b** indicate that phenyl migrates more readily than methyl (Scheme 13).[54] The order Ph > Me also holds for the *thermolysis* of 2-diazo-1-phenylbutane-1,3-dione (**59a**) where both groups compete in the Wolff rearrangement.[52c,55] On *photolysis* of **59a**, however, methyl migrates in preference to phenyl. Different degrees of concertedness,[52c] as well as the effect of temperature,[56] could account for this discrepancy. Substituents on the phenyl ring affect the migratory aptitude but moderately, with the exception of 4-NO_2: **59d** was found to rearrange with exclusive methyl shift.[55] In the absence of a competitor, however, the 4-nitrophenyl group does migrate, as illustrated by **60**.[57] Similarly, methoxycarbonyl cannot compete with methyl in the rearrangement of **62a** to give **61**, but migrates in **62b** which is converted into **63**.[58] Perfluoroalkyl groups also appear to migrate reluctantly, as indicated by the efficient intermolecular capture of perfluoroalkanoylcarbenes.[59]



Scheme 13. Migratory aptitudes of carbon-centered groups

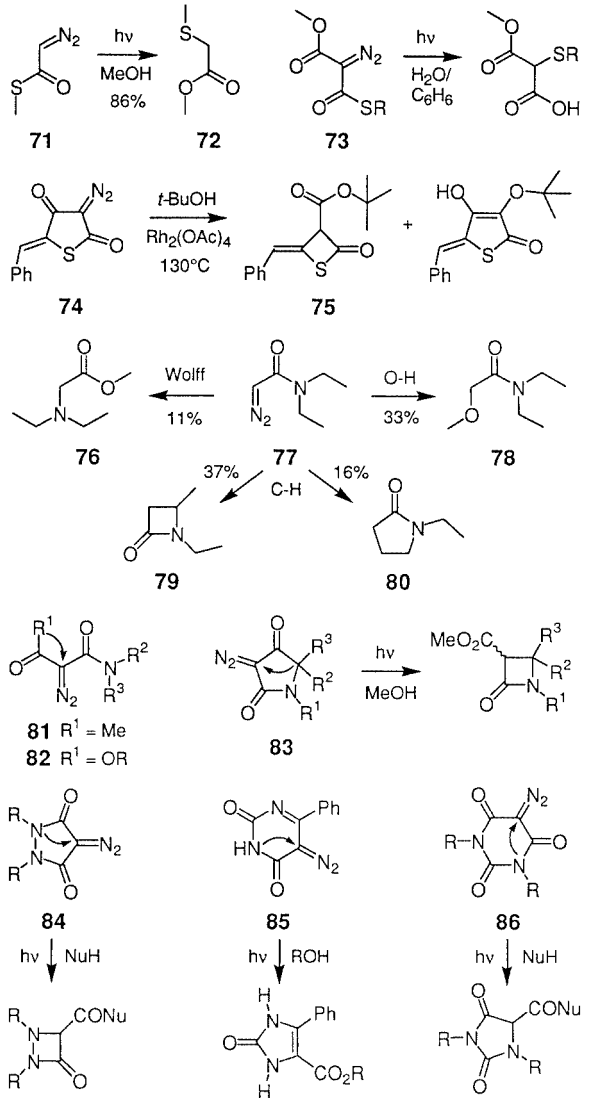
The migratory aptitude of hydrogen exceeds that of phenyl: the rearrangement of **64** was reported to give **65** (Scheme 14).[55] Alkoxy groups, on the other hand, are inferior to alkyl or aryl in their migratory aptitude. Alkyl 2-diazo-3-ketocarboxylates (**66**) were found to rearrange with exclusive migration of R,[17b,52c,53,60] even for R = Cl_2C=CCl,[61] CO_2Me (**62b**),[58] and CF_3.[41] Alkoxy shifts occurring on photolysis (not thermolysis) of alkyl diazoactetates (**67**) were discovered independently by Westheimer[62] and Strausz,[63] some 80 years after **67** was prepared by Curtius. The Wolff rearrangement of **67** competes with intermolecular O−H and C−H insertion reactions of the carbonyl carbene. Partial exchange with alkoxy groups from the solvent points to a dissociative mechanism which has not been fully clarified.[63] Photolyses of dialkyl diazomalonates (**68**) give rise to a similar product pattern, except that H abstraction takes place instead of C−H insertion.[64] Methyl α-diazo-α-phenyl acetate (**69**) shows only traces of Wolff rearrangement.[65] It appears that increasing stabilization of the intervening carbene (**67** < **68** < **69**) minimizes the 1,2-alkoxy shift. However, conformational effects are also important, as attested by the efficient ring contraction of **70**.[66]



Scheme 14. Migratory aptitudes of hydrogen and of alkoxy groups

Thioalkyl groups migrate more readily than alkoxy groups. Photolysis of **71** in methanol afforded **72** as the only product (Scheme 15).[67] The behavior of **71** contrasts mark-

edly with that of the oxygen analogue **67** (Scheme 14). In the malonyl monothioester systems **73**, SR (R = Me, *t*Bu, Ph, etc.) rather than OMe was found to migrate.[68] An analogous comparison of thioalkyl with alkyl has not been made. In the Rh^{II}-catalyzed ring contraction **74** → **75**, the vinyl group migrates in preference to sulfur.[69]



Scheme 15. Migratory aptitudes of alkylthio and (di)alkylamino groups

Wolff rearrangement is only a minor process in the photolysis of *N,N*-diethyldiazoacetamide (**77** → **76**). Aside from O−H insertion with methanol (→ **78**), intramolecular C−H insertion leading to lactams (→ **79** + **80**) prevails (Scheme 15).[70,71] As **76** was not obtained in triplet sensitized photolyses, the 1,2-shift of NR_2 is likely to proceed from the excited singlet state of **77**.[71] Not surprisingly, 2-diazo-3-oxobutanamides (**81**)[71b] and 3-diazo-2,4-pyrrolidinediones (**83**)[72] rearrange by way of alkyl shifts. Intramolecular formation of β-lactams[73] and intermolecular insertion,[74] rather than migration of alkoxy and/or amino groups, were observed on photolysis of **82**. By contrast, the α-diazolactams **84**,[75] **85**,[76] and **86**[77] were found to undergo 1,2-amino shifts efficiently.

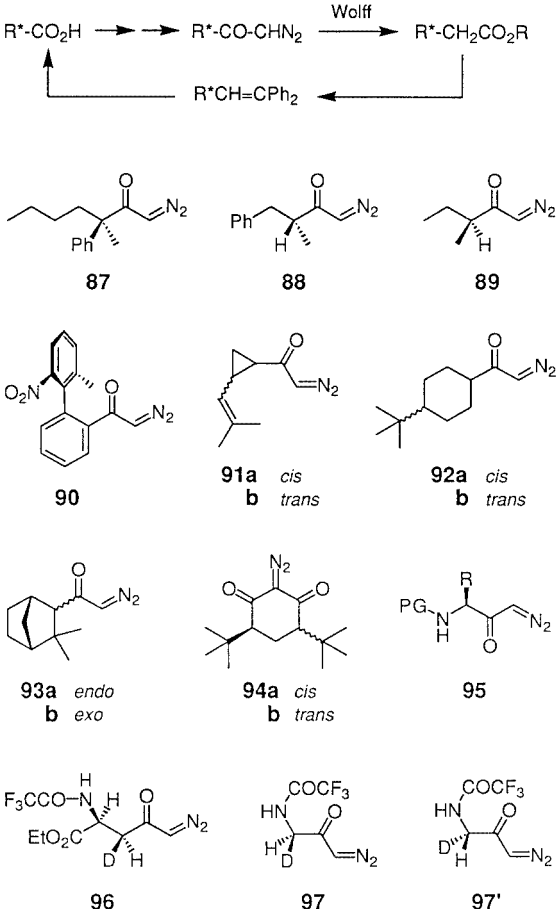
In summary, the qualitative ranking of migratory ability in *photochemical* Wolff rearrangements is H > alkyl ≥ aryl > SR > OR ≥ NR_2. For *thermal* reactions, the ranking is H > aryl ≥ alkyl, while heteroatoms do not migrate. Increasing conjugation of migrating group *p* orbitals with the π* orbital of the carbonyl group seems to lower the migratory ability. However, the ranking for the Wolff rearrangement is similar to that for 1,2-shifts of substituted alkylcarbenes, $R^1R^2R^3C-CH: \rightarrow R^2R^3C=CHR^1 + ...$, in which "bystander assistance" of nonmigrating groups is a complicating factor.[78] Even the "upgrading" of alkyl groups in photochemical, relative to thermal, reactions recurs in alkylcarbene rearrangements.[79] The ranking of migratory aptitudes is still not fully understood. The 1,2-H shift of formylcarbene ($O=CH-CH: \rightarrow O=C=CH_2$) is the only Wolff rearrangement for which the energy barrier (21−23 kJ/mol) was computed by high-level ab initio methods.[80] For comparison, at the CCSD(T)/DZP level of theory, barriers of 22, 37, and 76 kJ/mol were derived for 1,2-migrations of *sec*. H, *prim*. H, and Me, respectively, in ethylmethylcarbene.[81] Semiempirical (AM1) methods were employed to compare **24** with **38**,[82] and to analyze substituent effects on the rearrangement of **25**.[83] A comprehensive theoretical investigation of migratory aptitudes has yet to appear.

3.3.2. Stereochemistry

The pioneering studies with nonracemic α-diazo ketones date back to the Forties when absolute measures of enantiomeric purity were not available. Therefore, Arndt−Eistert homologation of R^*CO_2H was followed by Barbier−Wieland degradation of $R^*CH_2CO_2H$ to regenerate R^*CO_2H and compare optical rotations (Scheme 16). The tertiary alkyl group of **87**[84] and the axially chiral biaryl group of **90**[85] were thus found to migrate with virtually complete retention of configuration whereas the secondary alkyl group of **88** was partially racemized.[86] Wiberg and Hutton compared Arndt−Eistert products with those from the sequence $R^*CO_2H \rightarrow R^*CH_2OH \rightarrow R^*CH_2Cl \rightarrow R^*CH_2CN \rightarrow R^*CH_2CO_2H$, thus avoiding degradation of $R^*CH_2CO_2H$.[87] The rearrangement of **88** was induced by photolysis in methanol (81% retention of configuration), $PhCO_2Ag/Et_3N$/MeOH (90% retention), Ag_2O/MeOH (78% retention), and $Ag_2O/Na_2S_2O_3/H_2O$/dioxane (72% retention). In contrast, application of these methods to **89** gave the expected products with 97±3% retention of configuration. More recently, thermal Arndt−Eistert reactions of 2-methylbutanoic acid (by way of **89**) and of 2-methylhexanoic acid were found to give the homologous acids with ≥ 99.5% *ee*, as shown by means of enantioselective GC.[88]

Migration of secondary alkyl groups with complete retention of configuration was confirmed with *pairs* of diastereomers, which gave rise to distinct products (*cis* → *cis*, *trans* → *trans*, etc.).[89] The examples shown in Scheme 16 were scrutinized by sensitive analytical methods (GC,

NMR). The homologation reactions involving **91**,[89b] **92**,[89d] and **93**[89f] are supplemented by the ring contraction of **94**.[90] Work with optically active compounds was resumed recently, starting from *N*-protected α-amino acids.[91] The Wolff rearrangement of all tested diazo ketones **95** proceeded with full retention of configuration. However, carbamate-protected phenylglycine was partially (ca. 20%) racemized on conversion into **95**, R = Ph. Analogous results were obtained in the ultrasound-promoted Wolff rearrangement of **95** (PG = Fmoc).[92] Retention of configuration was also established for the migration of primary, deuterium-labeled alkyl groups, as in **96**[93] and **97**.[94]



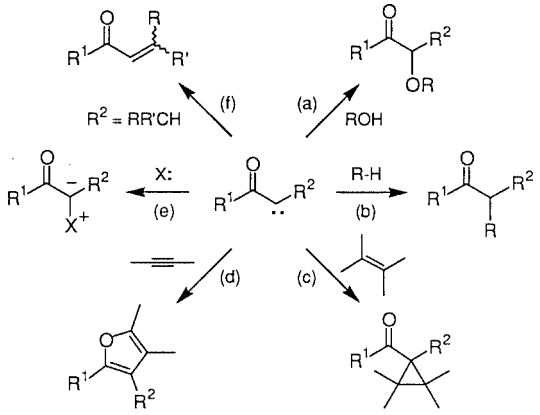
Scheme 16. Selected diazoketones which were shown to rearrange with retention of configuration

In summary, retention of configuration attests to the strictly intramolecular mechanism of Wolff rearrangements involving 1,2-C shifts. In contrast, 1,2-O shifts proceed with partial exchange of OR groups, which points to a dissociative mechanism (Section 3.3.1. and Scheme 14).

3.4. Carbonyl Carbenes

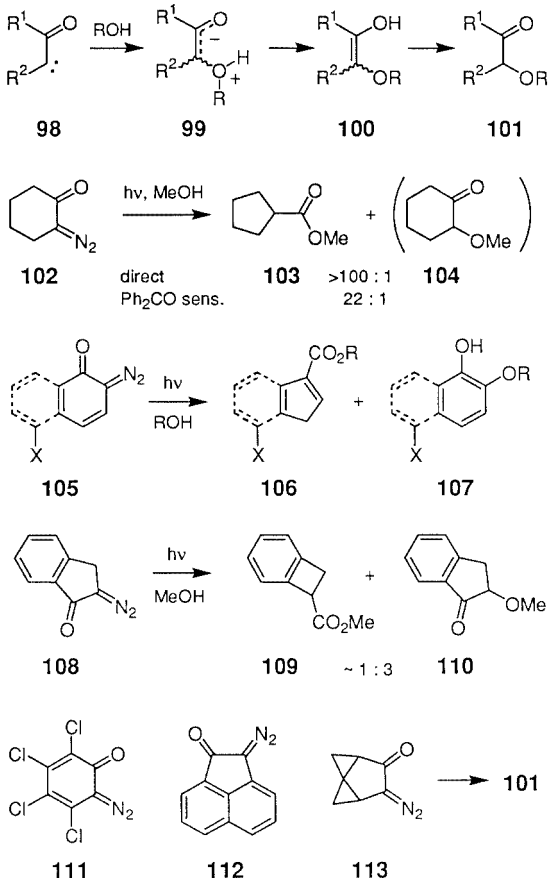
3.4.1. Competing Reactions

The carbonyl carbenes intervening in stepwise Wolff rearrangements can be scavenged competitively with ketene formation (Scheme 17).



Scheme 17. Reactions of carbonylcarbenes that can compete with the Wolff rearrangement

a) The reaction of carbenes with alcohols to give ethers,[95] a very fast process,[96] was used extensively to distinguish stepwise and concerted Wolff rearrangements (Section 3.2.). The O−H insertion of carbonyl carbenes is thought to involve electrophilic attack at the oxygen atom of ROH (**98** → **99**),[95,97] followed by or associated with proton transfer to the carbonyl oxygen (**99** → **100**, Scheme 18). For a series of carbenes with R^2 = aryl, the enols **100** were identified by time-resolved spectroscopy.[98] As a rule, photolyses of acyclic diazo ketones generate car-



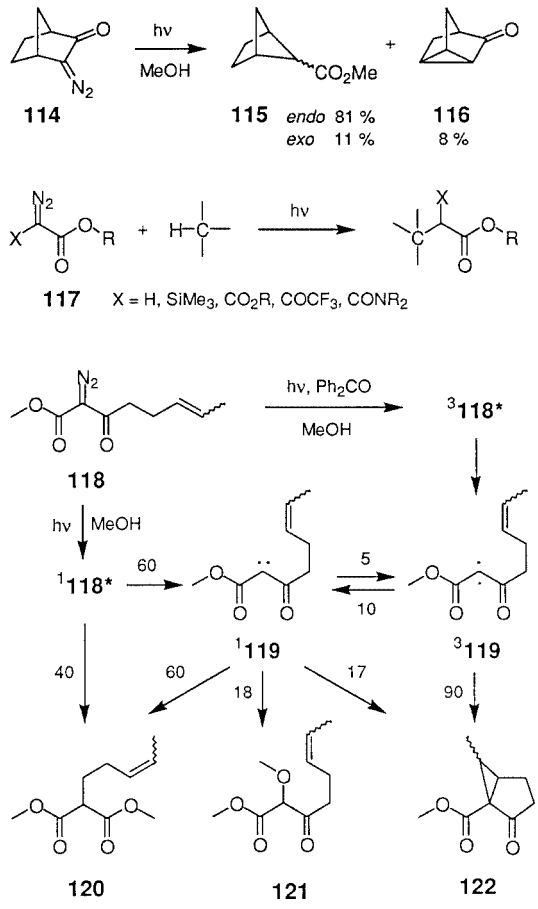
Scheme 18. O−H insertion reactions of carbonylcarbenes

bonyl carbenes that can be scavenged by alcohols (Table 1). Cyclic diazo ketones give results that depend on the individual structure. 2-Diazocyclohexanone (**102**) produces high ratios of methyl cyclopentanecarboxylate (**103**) to 2-methoxycyclohexanone (**104**) in both direct and sensitized photolyses.[52b] The excited singlet state ^{1}**102***, which can undergo concerted Wolff rearrangement, should be bypassed in the sensitized photolysis. The poor yield of **104** even in the presence of benzophenone points to fast ring contraction of the intervening carbonyl carbene. In contrast, 2-diazocyclohexa-3,5-dienones (**105**), the unsaturated analogues of **102**, give substantial amounts of the ethers **107** in addition to the ring-contracted esters (**106**). The yields of **107** range from 9−16% for 2-diazonaphthalen-1-ones[99] to 50% for the parent compound.[100] The photolysis of 2-diazo-1-indanone (**108**) in MeOH was found to afford both 2-methoxy-1-indanone (**110**, 50%) and methyl benzocyclobutene-1-carboxylate (**109**, 15%).[101] Photolysis of the diazo ketones **111**,[102] **112**,[103] and **113**,[104] leads to O−H insertion but does not induce ring contraction. Electronic effects (**111**), as well as ring strain of the predicted products (**112**, **113**), are thought to impede the Wolff rearrangement.

b) C−H insertion reactions of carbonyl carbenes do not compete with 1,2-shifts of alkyl and aryl groups. Exceptions to this rule occur if C−H insertion is strongly favored or Wolff rearrangement is strongly disfavored. Thus photolysis of 3-diazobicyclo[2.2.1]heptan-2-one (**114**) afforded 8% of tricyclo[2.2.1.0^{2,6}]heptan-3-one (**116**) together with 92% of the Wolff product **115** (Scheme 19).[105] A C5−H bond of **114** is ideally disposed for interaction with the carbenic site. Diazoacenaphthenone (**112**, Scheme 18)[103] and related species[106] insert readily into C−H bonds of the solvent, rather than forming highly strained Wolff products. Owing to the low migratory aptitude of OR, C−H insertion is often the only reaction of diazoesters **117**, with X = H,[107] $SiMe_3$,[108] CO_2R,[64,107,109] $COCF_3$,[110] and $CONR_2$.[74] Formation of β-lactams, by intramolecular C−H insertion, is characteristic of diazoamides (see **77**, Scheme 15).[70,71,111]

c) Stereoselective reaction of *singlet* carbonyl carbenes with C=C double bonds was observed only with precursors such as **111**, **112**, and **117**. Rapidly rearranging carbonyl carbenes (R^1 = alkyl or aryl) can add to alkenes from their *triplet* states,[50] as illustrated by the intramolecular reactivity of **119** (Scheme 19).[53] On benzophenone sensitization, formation of the adduct **122** increases at the expense of Wolff rearrangement (→ **120**) and O−H insertion (→ **121**) (Figure 2). Concomitantly, the stereoselectivity of the addition process decreases. Dissection of the competing reaction paths reveals that Wolff rearrangement is the major reaction of ^{1}**119** while C=C addition of ^{3}**119** is fast relative to intersystem crossing.

Diazo ketones that undergo Wolff rearrangement thermally or photochemically can be diverted to (enantioselective) C=C addition and C−H insertion reactions by means of (chiral) transition metal catalysts. These reactions are thought to involve metal carbenes (carbenoids) and are extremely useful for organic synthesis.[112] Few examples of



Scheme 19. Reactions of carbonylcarbenes with C−H and C=C bonds

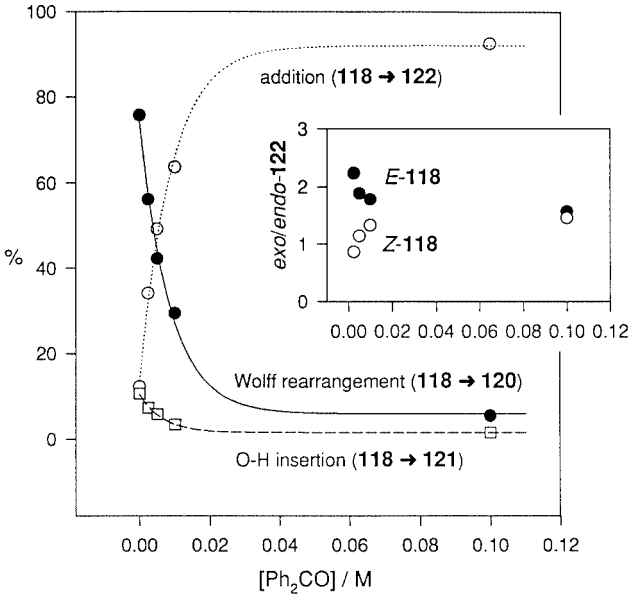
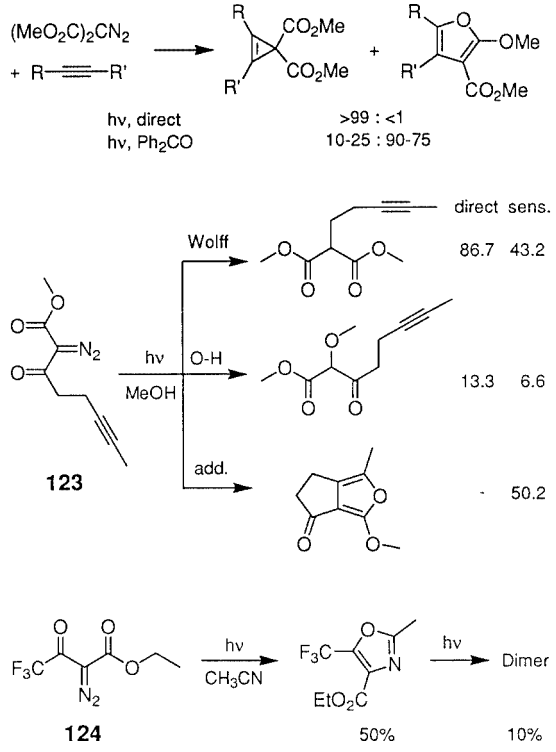


Figure 2. Photolyses of methyl 2-diazo-3-oxo-6-octenoate (**118**) in methanol with benzophenone as sensitizer; average product distributions (%) obtained from *E*-**118** and *Z*-**118** are shown as functions of the concentration of benzophenone; the inset shows the *exo*:*endo* ratios of **122** as functions of the concentration of benzophenone, starting with *E*-**118** and *Z*-**118**, respectively

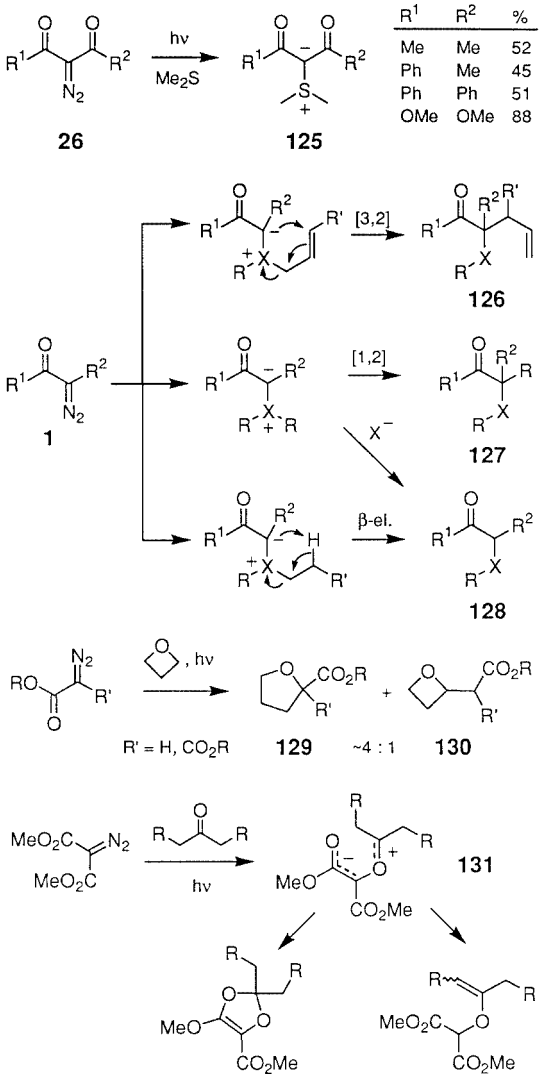
transition metal-catalyzed Wolff rearrangements are known which will be mentioned in due course (see Schemes 15, 38, 44, 45, 79, and 90).

d) The reactions of carbonyl carbenes with alkynes parallel those with alkenes, except that furans are often formed instead of or in addition to cyclopropenes. Photolyses of alkyl diazoacetates in the presence of alkynes afforded cyclopropenes with moderate yields.[113] The results of direct and sensitized photolyses of diazomalonates suggest that cyclopropenes arise from the singlet state and furans from the triplet state of the intervening carbene (Scheme 20).[114] This notion is supported by the intramolecular reactivity of **123**.[115] Comparison of **123** with **118** (Scheme 19) indicates that triplet carbonyl carbenes add more efficiently to alkenes than to alkynes. Some carbonyl carbenes are trapped by nitriles with formation of 1,3-oxazoles,[116] as exemplified by **124**.[116a] Not surprisingly, **111**[102a] and **112**[103] (Scheme 18) also react with alkynes to give furans, and with nitriles to give 1,3-oxazoles.



Scheme 20. Reactions of carbonylcarbenes with triple bonds

e) Carbonyl carbenes accept the nonbonding electron pair(s) of heteroatoms with formation of ylides.[117] Stable sulfonium ylides **125** were obtained on photolysis of 2-diazo-1,3-dicarbonyl compounds **26** in the presence of dimethyl sulfide (Scheme 21).[118] Even readily rearranging precursors (R^1, R^2 = alkyl, aryl) gave respectable yields of **125**, attesting to efficient interception of carbonyl carbenes by Me_2S. However, cyclic substrates such as **27** (Scheme 7) did not afford ylides, with the exception of **70**, which gave 21% of **125**.[118d] These results parallel the data reported above for ROH scavenging. While 1,2-shifts (→ **127**, X = S) of **125** require elevated temperatures,[118c] analogous ylides derived from allyl sulfides undergo 2,3-shifts (→ **126**, X = S) spontaneously.[119]

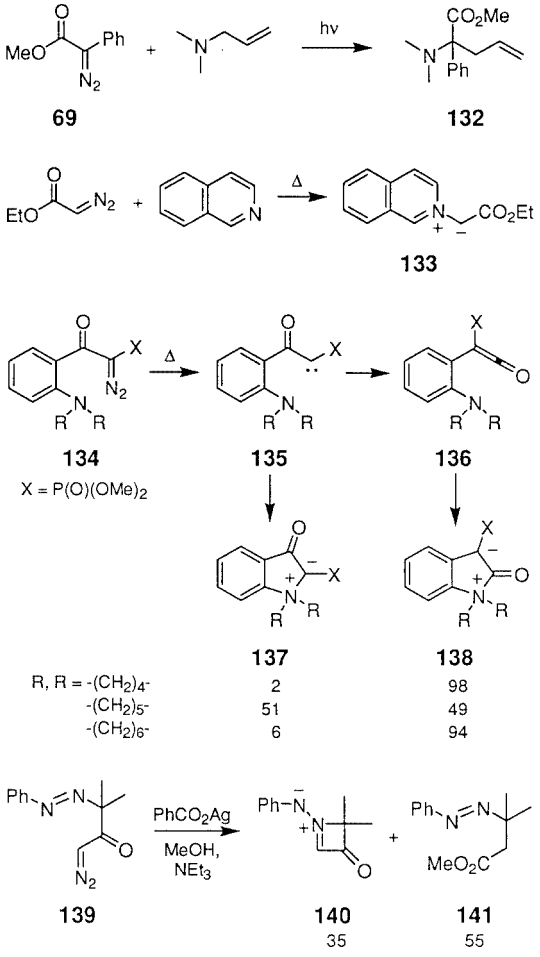


Scheme 21. Formation of ylides from sulfides, ethers, and ketones

In contrast to dialkyl sulfides, ethers do not scavenge readily rearranging carbonyl carbenes (R^1 = alkyl, aryl). However, formation of ylides competes with C−H insertion if diazoesters are photolyzed in the presence of ethers. Most often, products of the general structure **128** (X = O) arise by dealkylation of the elusive oxonium ylides.[107c,120] Allylic ethers accept carbonyl carbenes at the double bond, with cyclopropanation, and at the oxygen atom, with subsequent [3,2] sigmatropic shifts (→ **126**, X = O).[119,121] Ring strain promotes [1,2] alkyl shifts of the oxonium ylides (→ **127**, X = O), as illustrated by the ring expansion of oxetane leading to **129**.[97,122] Ketones undergo C−H insertion as well as formation of carbonyl ylides **131**, the latter giving rise to enol ethers and acetals (Scheme 21).[123]

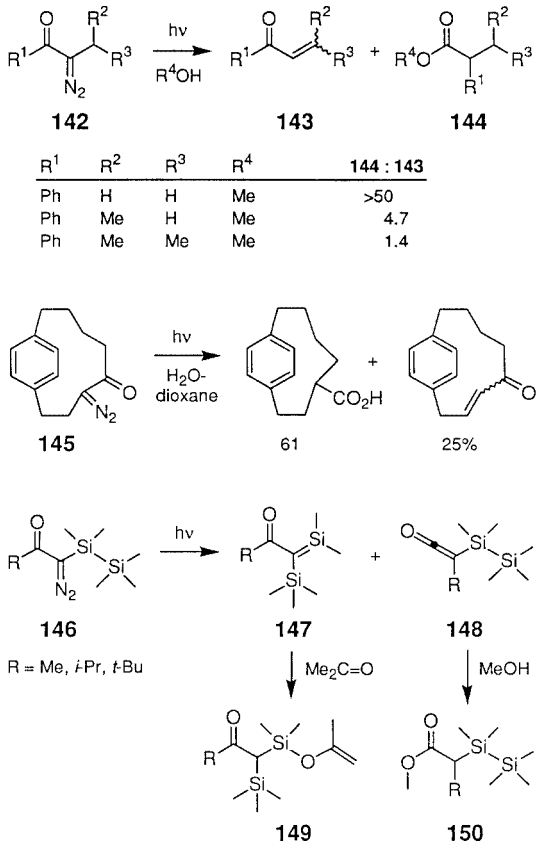
With aliphatic tertiary amines, C−H insertion prevails over ylide formation.[124] However, C−N insertion to give **132** was observed on photolysis of **69** in the presence of allyldimethylamine,[124b] and the stable ylide **133** was obtained by heating ethyl diazoacetate with isoquinoline

(Scheme 22).[125] The carbenes **135**, generated from **134**, were trapped by the *o*-diakylamino group (→ **137**) competitively with Wolff rearrangement (→ **136**).[126] The structures of both the ammonium ylide **137** and the mesoionic compound **138** were confirmed by X-ray analysis. The silver-ion assisted decomposition of **139** afforded the azomethine imine **140** together with the homologous ester **141**.[127] These examples of intramolecular scavenging are remarkable in that readily rearranging carbonyl carbenes are involved (R^1 = aryl in **135**, R^1 = alkyl in **139**).



Scheme 22. Formation of ylides from amines and azo compounds

f) The 1,2-shift of a hydrogen atom to the divalent carbon is one of the most common reactions of alkylcarbenes.[128] With diazo ketones **142**, where a C−H bond is adjacent to the diazo function, 1,2-H shifts to give α,β-unsaturated ketones **143** were observed early on (Scheme 23).[45,129] 1,2-H shift (→ **143**) and Wolff rearrangement (→ **144**) proceeded competitively in photolyses of **142** whereas silver ion-catalysis afforded **143** exclusively. The formation of **143** is promoted by alkyl groups in the β-position of **142**.[52a] The effect of β-OH groups is even stronger,[130] as illustrated by **45**[42a] and **47**[43] (Scheme 10). 2-Diazocyclohexanone (**102**, Scheme 18) and 2-diazocycloheptanone gave only traces of cycloalkenones,[52b] but more 1,2-H shift was observed with larger rings,[45] such as the [8]paracyclophane **145**.[131] α-Diazo esters with β-C−H bonds (**142**, R^1 = OR) afford acrylic esters as the only products; Wolff rearrangement (OR shift) is not competitive.[132]



Scheme 23. 1,2 Shifts from the β position of α-diazoketones

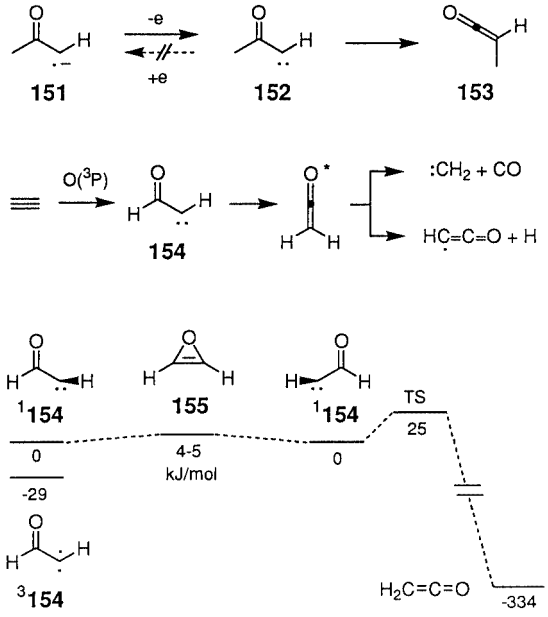
1,2-H shifts, **142** → **143**, were formerly thought to be diagnostic of carbonyl carbenes as intermediates. However, evidence has been accumulated that 1,2-H shifts can proceed from photochemically excited diazo precursors, in concert with the loss of nitrogen.[133] Therefore, the formation of α,β-unsaturated ketones cannot serve as a criterion that distinguishes stepwise and concerted mechanisms of the Wolff rearrangement. (1,2-H shifts are useful, however, to detect carbene−carbene rearrangements, see Section 3.5.).

Alkyl shifts from the β-position are limited to α-diazo ketones that lack β-C−H bonds and undergo the Wolff rearrangement with difficulty; 4-diazo-2,2,5,5-tetramethylhexan-3-one (**38**, Scheme 9) meets these conditions.[39−41] Photolysis of **146** was found to induce 1,2-silyl shifts (→ **147**) which compete with Wolff rearrangement (→ **148**).[134] The silene **147** and the ketene **148** were trapped with acetone (→ **149**) and methanol (→ **150**), respectively.

3.4.2. Gas-Phase Experiments and Computations

Few gas-phase photolyses of diazo ketones have been reported,[40,59b,66a,297] and none of these aimed at the detection of carbonyl carbenes by spectroscopic methods. However, fluorinated carbonyl carbenes have been trapped with alkynes in the gas phase.[59b] The neutralization-reionization approach[135] to acetylcarbene (**152**) was pursued by Schwarz (Scheme 24).[136] The radical anion **151** is readily

generated by electron capture in negative ion chemical ionization of diazoacetone with N_2O as a reagent gas. The neutralization-reionization ($^{-}NR^{+}$) spectrum of **151** (in which two electrons are detached consecutively) was found to differ completely from the charge reversal ($^{-}CR^{+}$) spectrum (in which the charge is inverted by two-electron transfer in a single collision). Although neutralization of the radical anion **151** must produce the carbene, **152** is no longer present when reionization occurs. This conclusion was confirmed by the $^{-}NR^{-}$ spectrum of **151** in which the recovery signal hardly exceeded the signal-to-noise ratio. Clearly, **152** is unstable on the microsecond time scale of the experiment, due to Wolff rearrangement. Reactions of oxygen atoms [O(^{3}P)] with acetylene,[137a−137c] higher alkynes,[137d] and hexafluorobutyne[137e] were studied using the crossed molecular beams technique and product energy distributions. The data strongly support the initial formation of formylcarbene (**154**) from acetylene, although the lifetime of **154** and the region where intersystem crossing occurs are still uncertain.



Scheme 24. Gas-phase studies on carbonylcarbenes

Much computational effort has been devoted to formylcarbene (oxoethylidene, **154**) as the prototypical carbonyl carbene. At various levels of theory, the *s*-*Z* conformer of the planar triplet, ^{3}**154**, is assigned as the ground state.[138,139] The lowest singlet state ^{1}**154** is found to be nonplanar, with the carbene−H bond nearly perpendicular to the plane of the formyl group.[80,139] The potential energy surface (PES) of **154** (Scheme 24) is sensitive to the level of theory employed. Ab initio methods with high levels of electron correlation and extended basis sets [CCSD(T)//6-311G(df,p)] predict a barrier of 21 kJ/mol for the 1,2-H shift that converts **154** into ketene.[80] A barrier of only 4−5 kJ/mol is estimated for the 1,2-oxygen shift (carbene−carbene rearrangement) that involves oxirene (**155**) as an intermediate or transition state (see Section 3.5.). DFT creates a similar PES,[140] with a barrier of 25 kJ/mol for ketene formation and a singlet-triplet energy difference of 10−15 kJ/mol [G3(MP2)//B3LYP and W1′].[141] The B3LYP//6-311++G(d,p) level of theory places the nonplanar singlet state of acetylcarbene (^{1}**152**) below methyloxirene ($\Delta\Delta H_f$ = 12 kJ/mol), and predicts a barrier of 17−19 kJ/mol for the conversion of **152** into methylketene (**153**).[136] The barrier to Wolff rearrangement for methoxycarbonyl carbene was computed [G3(MP2)//B3LYP] to be 26 kJ/mol,[141] similar to that of **154**. This result does not conform with the observed migratory aptitudes in solution, H >> OR (Section 3.3.1.).

3.4.3. Matrix Isolation

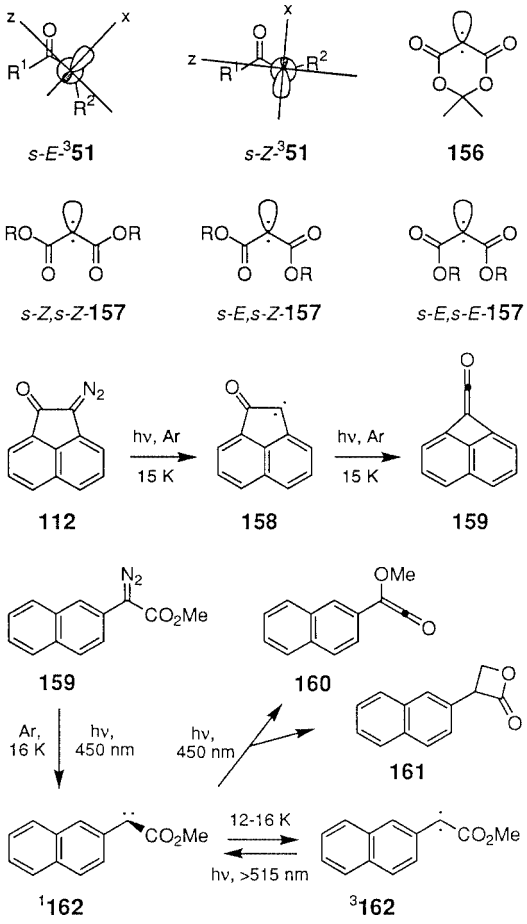
The low temperature and the lack of diffusion in a rigid, frozen matrix enhance the kinetic stability of reactive molecules. Using matrix isolation, many carbenes were identified spectroscopically, probed for photochemical or thermal rearrangements, and trapped with reactive components of "doped" matrices.[142] The spectroscopic methods commonly used for carbonyl carbenes are infrared (IR) and electron spin resonance (ESR) spectroscopy. IR spectra provide a wealth of structural information, particularly if the bands are assigned by means of isotopic shifts and/or computed vibrational frequencies. Despite recent gains in sensitivity (FTIR), fairly high carbene concentrations and transparent (inert gas) matrices are required. The advantage of ESR spectroscopy is the high selectivity and sensitivity for triplet carbenes, which can be detected in very low concentration. Moreover, ESR is applicable to organic glasses and crystalline powders as well as to inert gas matrices. ESR spectra are evaluated in terms of the zero-field splitting (ZFS) parameters *D* and *E* (interaction energies in cm^{-1}). *D* measures the average distance between (≈ delocalization of) the unpaired electrons in π-conjugated carbenes. *E* measures the deviation from cylindrical symmetry. For a linear triplet carbene *E* = 0 is expected while smaller bond angles lead to larger values for *E*.

ESR spectra of various carbonyl carbenes have been reported (Table 2). For many acyclic carbonyl carbenes, two signals were observed, which were assigned to conformers of the nearly planar triplet state (note that *s*-*E* diazo ketones correspond to *s*-*Z* carbenes, and vice versa). The conformers of matrix-isolated carbonyl carbenes differ in stability (rate of decay) but do not interconvert.[145,146] Assignments were based on a point spin model which predicts $D_{s\text{-}E} \leq D_{s\text{-}Z}$.[149] Better alignment of the z-axis with the *r* vector of the carbonyl group, as in *s*-*E*-^{3}**51**, enhances the spin density on the carbonyl oxygen and lowers *D* (Scheme 25). Interaction of R^1 and R^2 leads to more distortion from planarity for *s*-*E*-^{3}**51** than for *s*-*Z*-^{3}**51**, hence $E_{s\text{-}E} \geq E_{s\text{-}Z}$. Three conformers are possible for the triplet ground state of bis(methoxycarbonyl)carbene (**157**), and three ESR spectra were in fact observed (Table 2). However, the *D* value of the cyclic *s*-*E*,*s*-*E*-constrained analogue **156** is smaller than any of the *D* values obtained for **157**.[149] Therefore, it was concluded that only two conformers of **157** in different matrix sites were present.

Table 2. ESR spectra of triplet carbonyl carbenes, $R^1CO-C-R^2$

R^1	R^2		Matrix	T [K]		D [cm^{-1}]	E [cm^{-1}]	Ref.
$C(CH_3)_3$	$C(CH_3)_3$		glass[a]	22		0.497	0.077	[143]
			cryst.[b]	22		0.500	0.074	
CF_3	CF_3		cryst.[b]	11	*s-E*	0.572	0.079	[144]
					s-Z	0.605	0.034	
CF_3	C_2F_5		cryst.[b]	10	*s-E*	0.553	0.091	[145]
					s-Z	0.558	0.029	
C_2F_5	CF_3		cryst.[b]	10	*s-E*	0.563	0.080	[145]
					s-Z	0.564	0.039	
Ph	Ph		glass[a] cryst.[b]	77	–	0.385	0.052	[146]
				77	*s-E*	0.312	0.052	
					s-Z	0.392	0.052	
OMe	H		glass[c]	10	*s-E*	0.617	0.053	[147]
					s-Z	0.663	0.030	
OEt	H		glass[c]	10	*s-E*	0.616	0.053	[147]
					s-Z	0.661	0.031	
OMe	4-$O_2N-C_6H_4$		glass[d]	15	*s-E*	0.453	0.038	[148]
					s-Z	0.452	0.027	
$O-C(CH_3)_2O-CO$		**156**	glass[e]			0.578	0.035	[149]
OMe	CO_2Me	**157**	glass[e]			0.604	0.031	[149]
						0.606	0.051	
						0.615	0.034	
1,8-$C_{10}H_6$		**158**	Ar	15		0.406	0.026	[150]
OMe	2-naphthyl	**162**	Ar	16	*s-E*	0.415	0.040	[151]
					s-Z	0.437	0.036	

[a] Methylcyclohexane/isopentane = 4:1. [b] Polycrystalline powder of the appropriate diazo ketone. [c] Methylcyclohexane. [d] Ethanol. [e] 2-Methyltetrahydrofuran.

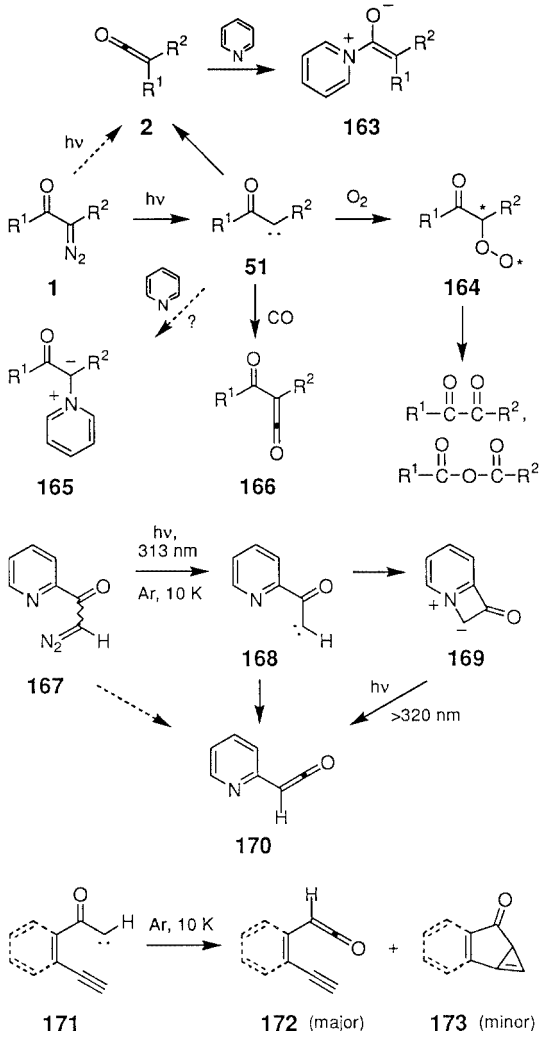


Scheme 25. Carbonylcarbenes in low-temperature matrices

Most of the triplet carbonyl carbenes listed in Table 2 have not been detected by IR spectroscopy, which is a much less sensitive spectral probe than is ESR. As a rule, photolysis of matrix-isolated diazo ketones generated only the IR spectra of ketenes.[41] An exception is diazoacenaphthenone (**112**) whose photolysis in an Ar matrix produced IR bands of carbene **158** ($\nu_{C=O}$ = 1665 cm^{-1}) along with those of ketene **159** ($\nu_{C=O}$ = 2127 cm^{-1}).[150] The assignment was confirmed by correlating the decay of the IR and ESR signals of **158** on continued irradiation. Analogous observations were made when the naphthalene ring of **112** was replaced with azulene or acenaphthene.[150] The reversible interconversion between singlet and triplet 2-naphthyl(methoxycarbonyl)carbene (**162**) has recently been monitored.[151] Photolysis (450 nm) of matrix-isolated diazo ester **159** produced ^{3}**162** which was identified by its UV/Visible, IR, and ESR spectra. Irradiation of ^{3}**162** (> 515 nm) generated a new species whose optical and IR spectra were in agreement with DFT calculations for ^{1}**162**. The spectra of ^{3}**162** were recovered in the dark at 12–16 K. Upon irradiation of ^{1}**162** at 450 nm, the recovery of ^{3}**162** was accompanied by the formation of ketene **160** and β-lactone **161**. The DFT results indicate that conformational changes create a barrier for the interconversion of ^{1}**162** with ^{3}**162**.

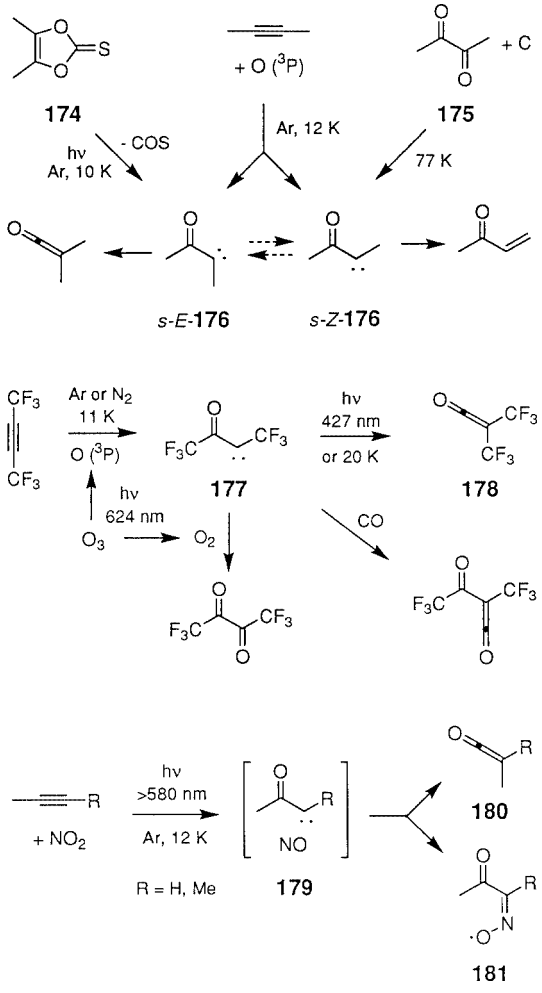
Carbon monoxide and oxygen have been used to trap matrix-isolated carbonyl carbenes, including **157**, **158**, and **162**. The reaction of CO with carbonyl carbenes **51** leads to α-oxoketenes **166**[152] which are readily distinguished from ketenes **2** by the shift of $\nu_{C=C=O}$ to higher wavenumbers (Scheme 26). In CO-doped argon matrices, the Wolff rearrangement of **157** was suppressed to an extent depending

on the concentration of CO, and **166** (R^1 = OMe, R^2 = CO_2Me) was formed.[153,154] The Wolff rearrangement of **157** was also suppressed by oxygen, but less efficiently than by CO.[153] The trapping of carbonyl carbenes by O_2 produces carbonyl oxides **164** whose secondary reactions are variable. A ketone was eventually obtained from **157**[153] whereas an acid anhydride resulted from **158**.[150] The generation of carbonyl carbenes in pyridine-doped matrices gave rise to ketene-derived zwitterions **163** rather than to carbene-derived ylides **165**.[154,155] In contrast, matrix photolysis of 2-diazoacetylpyridine (**167**) yielded ylide **169** in addition to ketene **170**.[156] Continued irradiation of **169** led to ring opening with formation of **170**. When the carbonyl carbenes **171** were generated in an argon matrix, intramolecular addition to triple bonds (→ **173**) was found to compete with Wolff rearrangement (→ **172**).[157]



Scheme 26. Trapping of matrix-isolated carbonylcarbenes

Alternative routes to carbonyl carbenes were also studied under matrix conditions. The photolytic elimination of COS from the thioxocarbonate **174** afforded dimethylketene (Scheme 27).[158] When butane-2,3-dione (**175**) was deoxygenated by cocondensation with carbon vapor at 77 K, 3-buten-2-one was the predominant product.[159] Both dimethylketene and 3-buten-2-one were formed in the photolysis of 3-diazobutan-2-one[158] and in the reaction of 2-butyne with O(^{3}P) atoms (triggered by photolysis of Ar/ozone/2-butyne matrices).[160a] The products point to the intervention of 3-oxo-2-butylidene (**176**), but how to explain the divergent product ratios? Photolysis of **174** is supposed to generate *s*-*E*-**176** while the deoxidation of **175** should lead to *s*-*Z*-**176** (the conformation of **175** is exclusively *s*-*E*). The selectivity of product formation parallels the preference of *s*-*Z* diazo ketones for rearrangement (Section 3.2.) but is inconsistent with a twisted, nearly perpendicular conformation of singlet **176** (cf. computations for **152** and **154**, Section 3.4.2.).



Scheme 27. Alternative routes to matrix-isolated carbonylcarbenes

In contrast to **176**, hexafluoro-3-oxo-2-butylidene (**177**) has been directly observed in the light-induced (624 nm) reaction between ozone and hexafluorobutyne.[160b] The key to success was a nitrogen matrix which appeared to stabilize **177** and allowed the assignment of $\nu_{C=O}$ = 1591 cm^{-1} to **177**. Product growth curves demonstrated that carbene **177** was a primary product whereas ketene **178** and hexafluorobutane-2,3-dione were secondary products. Irradiation (427 nm) of **177**, as well as raising the matrix temperature to 20 K, resulted in the formation of ketene **178**. In CO-doped matrices, **177** was trapped as an α-oxoketene, with a

concomitant decrease of **178**. Oxygen transfer from photoexcited NO_2 to propyne or 2-butyne was shown to generate **179**, that is carbonyl carbene caged with NO.[161] Recombination of **179**, leading to the iminoxy radical **181**, competed with Wolff rearrangement to give ketene **180**.

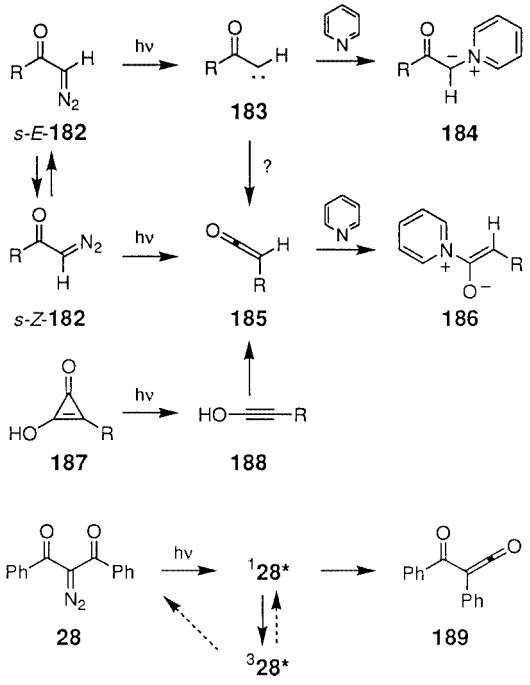
3.4.4. Laser Flash Photolysis (LFP)

Time-resolved spectroscopy allows the direct observation of short-lived intermediates that can be generated photochemically by means of pulsed lasers.[162] In order to study a species of interest by UV/Vis spectroscopy, it must possess a useful chromophore ($\varepsilon > 10^2$ м$^{-1}$cm^{-1}, $\lambda_{max} > 250$ nm). Thus carbonyl carbenes, $R^1CO-C-R^2$, can be detected by UV/Vis spectroscopy if R^2 = Ar but not if R^2 = H, alkyl, or COR. Lifetimes of methoxycarbonyl(phenyl)carbene[163] (generated by LFP of **69**) and methoxycarbonyl(2-naphthyl)-carbene (**162**)[164] were measured, but contributions of the Wolff rearrangement, if any, to the rates of carbene decay could not be assessed.

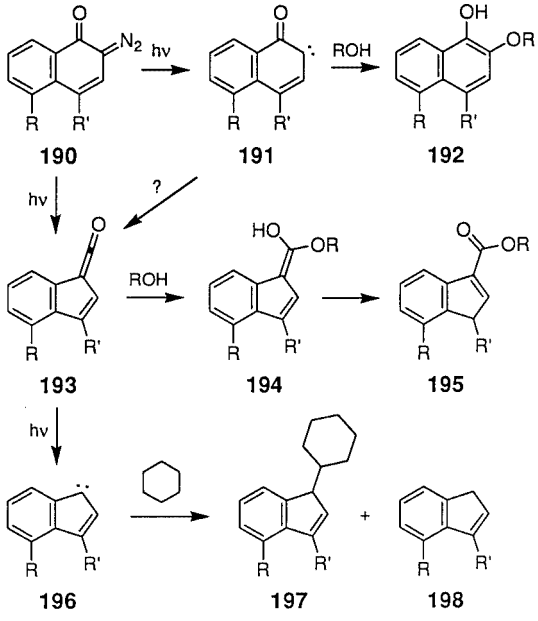
Reaction rates of "invisible" carbenes can be derived by monitoring the growth of strongly absorbing products, e.g. ylides. The "ylide probe technique", introduced by Platz and Jackson,[165] was applied to ethoxycarbonyl carbene,[166] bis(methoxycarbonyl)carbene (**157**),[167] and thio analogues,[68c] focusing on carbene lifetimes and intermolecular reactions. LFP of diazo ketones **182** (R = H, Me, *i*Pr, *t*Bu) in the presence of pyridine or acetone showed that the yields of the presumed ylides decrease with increasing bulk of R.[168] Toscano suggested that scavengeable carbonyl carbenes **183** arise from *s*-*E*-**182** whereas excited *s*-*Z*-**182** produces ketene **185** by a concerted route (Scheme 28). A point of concern is that the products absorbing at ≈ 450 nm might be ketene-derived zwitterions **186** rather than carbene-derived ylides **184**. The ketenes **185** can also be produced photochemically from hydroxycyclopropenones **187**, by way of alkynols **188**.[169] When **182** and **187** (R = Ph, 1-naphthyl) were flash-photolyzed in the presence of pyridine, the rates of absorbance growth at 450 nm were exactly the same.[170] These data support the reaction path **182** → **185** → **186**, at least for R = Ar. On the other hand, the lifetimes of formylcarbene (**183**, R = H) measured by the ylide technique (0.2−0.7 ns, in CH_2Cl_2) and by transient grating spectroscopy (0.9 ns, in CH_2Cl_2) were in reasonable agreement.[171] The transient grating waveform indicated a rapid, unresolvable heat release (74%) and a slower, resolvable heat release (26%, τ = 0.9 ns). The former process has been associated with the concerted Wolff rearrangement, **182** → **185**, and the latter with carbene decay.

LFP of 2-diazo-1,3-diphenyl-1,3-propanedione (**28**) gave rise to two transients with overlapping absorptions and lifetimes of 15 μs and > 500 μs, respectively.[172] The 15 μs transient reacted rapidly with triplet quenchers, including oxygen, and was assigned as the triplet state of **28**. In addition to intersystem crossing, ^{1}**28*** forms ketene **189** which was trapped by primary and secondary amines (but not by pyridine) with formation of zwitterions.

Considerable effort has been devoted to the diazonaphthalenones **190**, owing to their importance in photolithography. On nanosecond LFP of **190** in protic solvents, the absorbance at 335 nm rises abruptly in a time within the laser pulse and then increases more slowly over a period of ca. 100 ns. Two successively formed intermediates were assigned as ketene **193** and enol **194** by means of their pH-rate profiles (Scheme 29).[173] The conversion of **193** into **194**[174] and of **194** into **195**[175] was explored in some detail. Although the carbenes **191** were trapped by protic solvents with formation of **192** (9−15%, see Section 3.4.1.), spectral evidence for the intervention of **191** was obtained only by



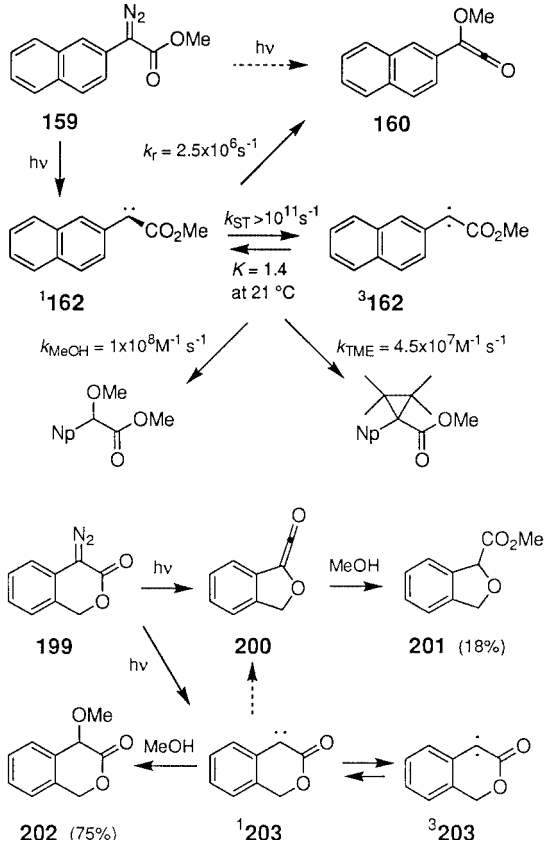
Scheme 28. LFP studies of α-diazoketones with UV-VIS detection



Scheme 29. LFP-UV-VIS studies of 2-diazo-1-naphthoquinones

picosecond LFP of **190**, $R^1 = R^2 = H$, in methanol.[99b] While photolysis (bleaching of the ground state absorption of **190**) was complete within 8 ps, a short-lived transient was observed, with a decay rate of $5 \cdot 10^{10}$ s^{-1} and λ_{max} = 323 nm. A third intermediate, in addition to **193** and **194**, was also detected when **190**, $R^1 = SO_2OPh$, $R^2 = H$, was flash-photolyzed in cyclohexane.[176] In a two-laser experiment, 248 nm pulses (KrF laser) generated **193** which was subsequently photolyzed by 337 nm pulses (N_2 laser) to give indenylidene (**196**). Reaction of **196** with cyclohexane eventually produced **197** (by C−H insertion) and **198** (by abstraction of hydrogen). Indenylidene-derived products were obtained only at a μs time delay between the two laser pulses whereas ns and ms time delays were ineffective. The "slow" formation of ketene **193** points to a precursor whose nature has not been clarified (possibly ^{3}**191** which slowly reaccesses the singlet surface and then rearranges?).

As indicated above, LFP studies with UV/Vis detection provide a wealth of kinetic data but suffer from problems in assigning the transients. Recently, time-resolved IR spectroscopy (TRIR) has been developed as an alternative to UV/Vis detection.[177] TRIR supplies structural information not available from UV/Vis experiments. Thus ketenes are readily detected due to their absorption at ca. 2100 cm^{-1}. In the case of methoxycarbonyl(2-napthyl)carbene (**162**), ^{1}**162** (1650 cm^{-1}), ^{3}**162** (1620 and 1584 cm^{-1}), and ketene **160** (2096 cm^{-1}) could be monitored (Scheme 30).[178] The quenching rate constants for ^{1}**162** and ^{3}**162** were the same, consistent with fast spin equilibration. At ambient temperature, ^{3}**162** is but slightly favored over ^{1}**162** (K = 1.4, ΔG = 0.8 kJ/mol). From femtosecond pump-probe spectroscopy, a lower limit for the rate of ^{1}**162** → ^{3}**162** crossing of 10^{11} sec^{-1} was obtained.[179] In the absence of quenchers, the rate of ketene growth equals the rate of carbene decay. The ketene **160** arises almost exclusively from the carbene **162**. The lack of a concerted route, **159*** → **160**, is probably due to the highly preferred *E* conformation of **159**.[151] Wolff rearrangement, **162** → **160**, proceeds more slowly than intermolecular quenching of **162**.



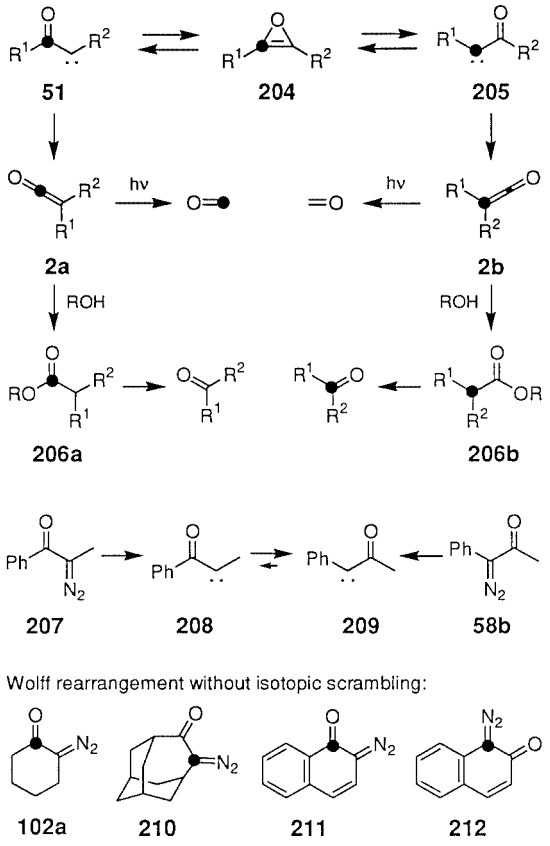
Scheme 30. LFP-TRIR studies of α-diazocarbonyl compounds

Contrasting results were obtained by LFP of 4-diazo-3-isochromanone (**199**).[180] The ketene **200** (2116 cm^{-1}) and the triplet carbene ^{3}**203** (1686 cm^{-1}) were monitored. In argon-saturated Freon 113, ^{3}**203** decayed with a lifetime of 530 ns, which was reduced to less than 50 ns in oxygen-saturated Freon 113. The ketene IR band, however, was fully developed within 50 ns and did not increase thereafter. It appears that the excited singlet state of **199** partitions to give ketene **200** and carbene **203**. Judging from the ratio of the eventual products **201** and **202**, carbene **203** predominates. The failure of **203** to rearrange could be due to rapid quenching (formation of azine, $k_{199} = 5 \cdot 10^8$ $M^{-1}s^{-1}$, or ether, $k_{MeOH} = 4 \cdot 10^7$ $M^{-1}s^{-1}$). Wolff rearrangement from a diazo excited state was also observed with 5-diazo-2,2-dimethyl-1,3-dioxane-4,6-dione (**70**, Scheme 14).[181] According to picosecond IR spectroscopy in polymeric matrices, **70** produces the ring-contracted ketene within 20 ps.[182]

3.5. Oxirenes

3.5.1. Carbene−Carbene Rearrangements

Oxirenes have attracted attention as the smallest, potentially antiaromatic heterocycles.[183] The intervention of oxirenes in the Wolff rearrangement was considered as early as 1935.[184] Oxirenes **204** can mediate the interconversion of isomeric carbonyl carbenes, **51** and **205** (Scheme 31). Such carbene−carbene rearrangements have been detected by means of isotopic labeling or by scavenging of isomeric carbonyl carbenes. If **204** and **205** intervene, a carbon isotope which is originally in the carbonyl position will be distributed between both the carbonyl and α-carbon of the ketene **2** and the carboxylic acid/ester **206**. In the case of a concerted Wolff rearrangement, or a carbonyl carbene **51** that does not equilibrate, the label will be recovered exclusively in the carbonyl position of **2** and **206**. Labeling of the diazo carbon gives inverse results. Early studies, which failed to detect isotopic scrambling,[185] were later revised.[186−188] Wolff rearrangements in the gas phase and in hydrocarbon solvents were analyzed by measuring the isotopic ratio of CO from the photolysis of ketene **2**. This method is likely to overestimate the contribution of **204**/**205** since photolyses of ketenes are known to proceed with isotopic scrambling.[188,189] Carboxylic acids and esters **206**, obtained from Wolff rearrangements in nucleophilic solvents, were analyzed for their isotopic distributions by means of ^{13}C NMR, mass spectrometry, or oxidative degradation.



Scheme 31. Interconversion of carbonylcarbenes, as detected by means of isotopic labels

Table 3. Photolyses of carbon-labeled diazo ketones $R^1-CO-CN_2-R^2$

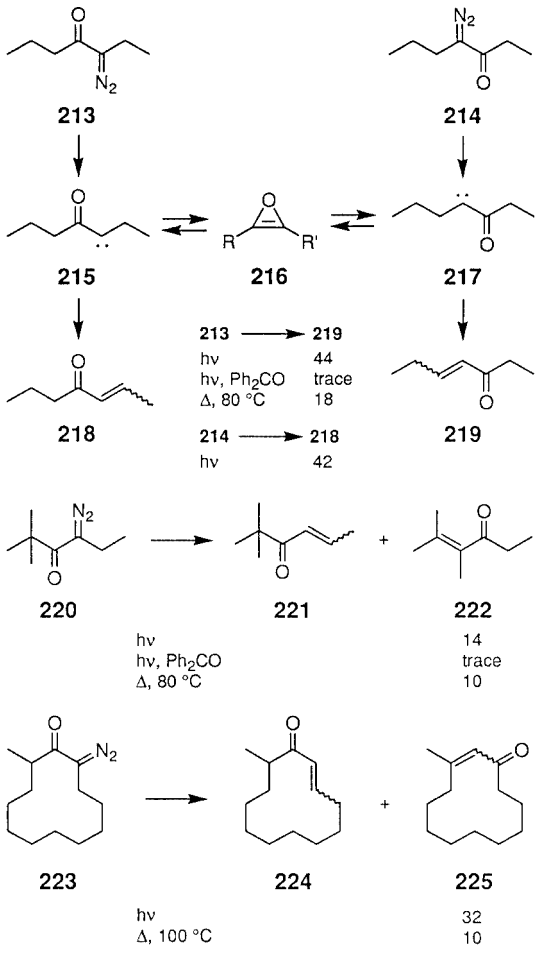
R^1	R^2		Phase	% $R^1-C-CO-R^2$	Ref.
H	H		$Et_2O/PhCH_2OH$ (95:5)	7	[190,191]
Me	H	**20**	gas	21	[192,193]
			$Et_2O/PhCH_2OH$ (95:5)	4	[194]
			MeOH	7	[193]
H	Me		gas	19	[192]
			MeOH	5	[193]
Me	Me	**24**	gas	50	[192]
			cyclopentane	35	[188,192]
			dioxane/H_2O (1:1)	31	[188]
Ph	H	**22**	cyclopentane	31	[188,193]
			dioxane/H_2O (13:2)	12	[191]
			dioxane/H_2O (1:1)	18	[191]
			MeOH	8	[188]
Ph	Me	**207**	cyclopentane	83	[193]
			dioxane/H_2O (13:2)	61	[191,195]
			dioxane/H_2O (1:1)	46	[193]
			MeOH	35	[193]
Me	Ph	**58b**	cyclopentane	12	[193]
			dioxane/H_2O (13:2)	3	[191,195]
Ph	Ph	**25**	cyclohexane	33	[188]
			dioxane/H_2O (13:2)	15	[187]
			dioxane/H_2O (1:1)	11	[187]
EtO	H		gas	32	[196]
MeO	H	**67**	gas	32	[196]

The isotopic scrambling in **206** tends to decrease with increasing nucleophilicity of the solvent (that is, decreasing lifetime of ketene **2**), but structural effects clearly prevail (Table 3).

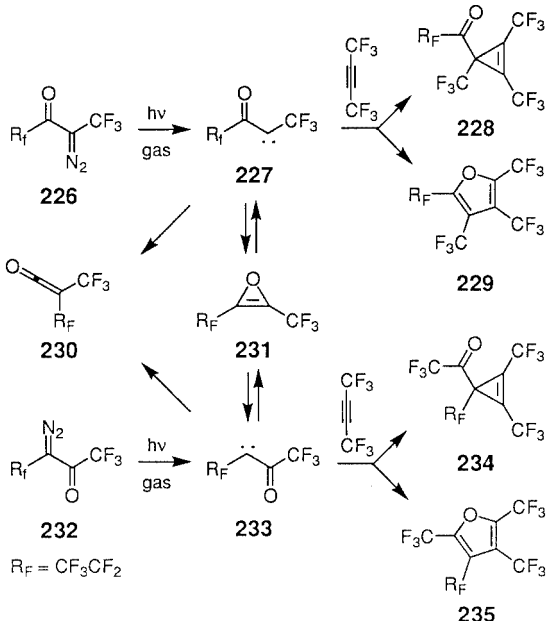
The interconversion of carbonyl carbenes is affected by carbene stabilities, conformational effects, and/or migratory aptitudes. The Wolff rearrangements of both **207** and **58b** proceed mainly by way of **209**,[191,193,195] since phenyl conjugation stabilizes **209** relative to **208**. The partial conversion of (alkoxycarbonyl)carbenes, ROCO−CH, into (alkoxy)(formyl)carbenes, RO−C−CHO,[196] is probably driven by the developing n-p interaction. Degenerate rearrangements ($R^1 = R^2$) increase in the order H < Ph ≤ Me (Table 3). An even (50%) distribution of the label is not attained, except in the gas phase photolysis of 2-diazobutanone ($R^1 = R^2$ = Me). The observed order of substituents is in line with migratory aptitudes. With decreasing migratory aptitude of R, carbonyl carbene interconversion should increase at the expense of ketene formation. Moreover, the concerted Wolff rearrangement will decrease as the *s-Z* conformation of the diazo ketone is disfavored. In contrast to **24**, the *s-Z* constrained cyclic diazo ketones **102a**,[197] **210**,[198] **211**,[199,200] **212**,[199] and **7** (Scheme 2)[201] were found to undergo Wolff rearrangement without scrambling of the isotopic label.

Evidence of oxirene intervention was also obtained from 1,2 shifts that convert carbonyl carbenes into α,β-unsaturated ketones (Scheme 32). Photolysis of 3-diazo-4-heptanone (**213**) afforded a 56:44 mixture of enones **218** and **219**.[202,203] An inverse ratio of **218** and **219** (42:58) was observed on photolysis of 4-diazo-3-heptanone (**214**).[204] These data indicate nearly complete equilibration of the carbonyl carbenes **215** and **217** by way of oxirene **216**. In contrast, photolyses of 1-diazoalkan-2-ones, $R-CH_2-CO-CHN_2$, produced only 3−5% of alkenals, R−CH=CH−CHO.[202] Carbene−carbene rearrangement, followed by a 1,2-methyl shift, converts **220** into **222**, although the direct 1,2-H shift leading to **221** prevails.[202] The formation of both **224** and **225** from **223** attests to carbonyl carbene interconversion in a 12-membered ring (as opposed to 6- and 7-membered rings, see above).[205] Ratios of isomeric enones are not affected by ketene automerization, which is a possible source of error in studies based on isotopic distribution. However, the "enone method" can be applied only to diazo ketones with dissimilar alkyl substituents.

Intermolecular scavenging of carbonyl carbenes has also been used to detect oxirene-mediated interconversions. Gas-phase photolyses of **226** and **232** in the presence of hexafluoro-2-butyne produced mixtures of cyclopropenes (**228**, **234**) and furans (**229**, **235**) in addition to ketene **230** (Scheme 33).[59b] The product ratios **228**:**234** = **229**:**235** = 0.75 were the same regardless of which diazo ketone, **226** or **232**, was the starting material. Complete equilibration of the carbenes **227** and **233** by way of oxirene **231** is in line with the low migratory aptitude of perfluoroalkyl groups (see Section 3.3.1). The O−H insertion reaction of arylcarbenes (**241** → **242**) was combined with 1,2-H shifts (**237**



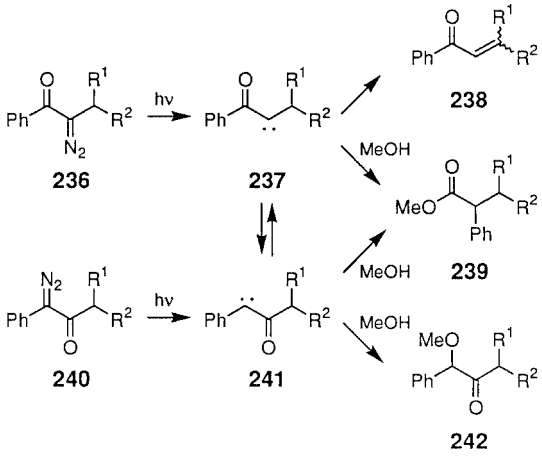
Scheme 32. Interconversion of carbonylcarbenes, as detected by the formation of isomeric enones (numbers are % of all enones)



Scheme 33. Interconversion of perfluorocarbonylcarbenes, as detected by scavenging with hexafluorobutyne

→ **238**) to study the interconversion of **237** with **241** (Scheme 34).[206] Photolyses of **236** and **240** in methanol gave similar product distributions, pointing to equilibration of **237** and **241**. As the number of methyl substituents is increased (**a** < **b** < **c**), enone formation by way of **237** increases at the expense of the O−H insertion reaction, **241** → **242**.

In summary, consistent results were obtained if various probes of carbonyl carbene interconversion were applied to *direct photolyses* of diazo ketones. For example, the Wolff products derived from ^{13}C-**24** (Table 3) as well as the enone mixtures obtained from **213** and **214** (Scheme 32) attest to a facile interconversion of 2-oxoalkylidenes. The rearrangement of **208** to give **209** (= **237a** → **241a**) was detected by both isotopic scrambling (Table 3) and trapping of **209** with methanol (Scheme 34). Unfortunately, the data on *sensitized photolyses* and *thermolyses* of diazo ketones are scanty and equivocal. Only traces of isomeric enones were obtained from sensitized photolyses of **213** and **220** (Scheme 32) whereas sensitization had no adverse effect on the interconversion of **237** and **241** (Scheme 34). The thermolysis of labeled 2-diazo-1,2-diphenylethanone (**25**) was reported to proceed without isotopic scrambling.[197,198] However, thermolyses of **213**, **220**, and **223** produce isomeric enones (**219**, **222**, and **225**, respectively), albeit less efficiently than photolyses do (Scheme 32). Therefore, the potential role of singlet excited states in carbonyl carbene interconversions cannot be assessed.



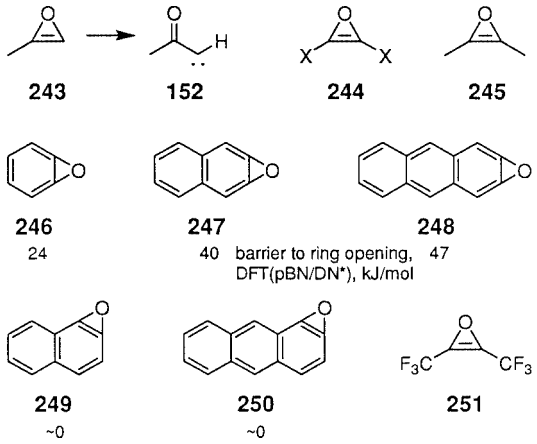
	R^1	R^2	yield (%)	238	239	242
236a	H	H	hv	trace	52.9	39.1
= **207**			hv, Ph_2CO	trace	17.6	53.6
240a			hv	trace	50.0	35.0
= **58b**			hv, Ph_2CO	trace	18.7	47.5
236b	Me	H	hv	9.9	46.6	12.1
			hv, Ph_2CO	17.6	28.3	15.1
240b			hv	5.1	51.3	12.5
236c	Me	Me	hv	28.2	38.7	2.3
			hv, Ph_2CO	32.5	25.1	5.9
240c			hv	26.6	36.1	1.4

Scheme 34. Interconversion of carbonylcarbenes, as detected by 1,2-H shifts and scavenging by methanol

3.5.2. Computation and Matrix Isolation

1,2-Oxygen shifts in carbonyl carbenes point to the intervention of oxirenes but do not distinguish intermediates from transition structures. This problem has been addressed, with mixed success, by means of computation and matrix isolation. Comprehensive studies of the C_2H_2O potential energy surface were published by Radom, Schaefer et al. who also reviewed earlier work.[80,207] The main conclusion was that the PES linking formylcarbene (**154**) and oxirene (**155**, Scheme 24) is extremely flat. At the CCSD(T)/6-311G(df,p) and CCSD(T)/cc-pVTZ(f,g) levels of theory, a PE minimum is found for oxirene, with a barrier to ring opening of 1−2 kJ/mol. CCSD(T)/6-311G(d,p) methods, MP4 perturbation theory, and DFT methods all show oxirene to be a transition structure.

At the B3LYP/6-311++G(d,p) level of theory, methyloxirene (**243**) corresponds to a PE minimum energetically close to acetylcarbene (**152**).[136] However, the transition structure linking **243** with **152** could not be located (Scheme 35). Of all oxirenes with the formula **244**, where X = BH_2, CH_3, NH_2, OH, F, only dimethyloxirene (**245**) was shown to be a true minimum on the PES.[208] Similar results were obtained for monosubstituted oxirenes.[209] Push-pull substitution apparently does not have a stabilizing effect on oxirene.[210] DFT as well as ab initio methods predict that benzooxirene (**246**) is kinetically stabilized, with a barrier to ring opening of 22−24 kJ/mol.[211] The barrier increases on "linear" benzoanellation (**247**, **248**) but vanishes in the "angular" series (**249**, **250**).[212] 2-Oxo-3,5-cyclohexadienylidenes are not stationary points on the PES, or are significantly lower in energy than the oxirenes. This would explain why benzooxirenes are not accessible from diazo precursors such as **7** (Scheme 2),[201] **211**, and **212** (Scheme 31).[199,200]



Scheme 35. Oxirenes studied by computation and/or matrix isolation

The radical cation of oxirene, **155**$^{\cdot+}$, was produced in the gas phase by dissociative ionization of oxazole, isoxazole, and [1,3]dioxol-2-one (vinylene carbonate).[213] Neutralization-reionization mass spectrometry did not regenerate **155**$^{\cdot+}$, oxirene being unstable on the μs time scale of NRMS. The gas phase loss of N_2 from ionized diazoacetone was shown to generate the methyloxirene cation radical, **243**$^{\cdot+}$. Again, NRMS indicated that **243** is unstable, rearranging mainly to methylketene and propenal.[214]

Attempts at isolating oxirenes in cryogenic matrices were not successful,[41] with two possible exceptions. Dimethyloxirene (**245**) was detected as a minor product when 3-diazobutan-3-one (**24**, Scheme 6) was photolyzed in a xenon matrix at 20 K.[215] Irradiation at > 230 nm converted **245** into dimethylketene. The assignment of an IR band at 2137 cm^{-1} to the C=C bond of **245** is in accordance with high-level calculations.[208] Matrix isolation of the perfluoroalkyloxirenes **231** (Scheme 33) and **251** was also claimed[216] and disputed.[59b,59c] The addition of oxygen atoms to hexafluorobutyne in cryogenic matrices was recently shown to produce the carbene **177** (Scheme 27, Section 3.4.3.) rather than the oxirene **251**.[160b] Many of the IR bands assigned to **177** match the bands previously attributed to **251**. The carbonyl stretch of **177** was unambiguously identified in N_2 matrices but was barely detected in Ar matrices where the earlier work was performed. A reinvestigation of the diazo route to **177**/**251** would seem in order.

4. Applications

4.1. Utilization of Ketenes from the Wolff Rearrangement

4.1.1. Reactions with Nucleophiles

The conversion of ketenes into carboxylic acids, esters, or amides is an important step in synthetic applications of the Wolff rearrangement, such as Arndt−Eistert homologation (Section 4.2.) and ring contraction (Section 4.3.). The generation of short-lived ketenes by flash photolysis of diazo ketones has served to elucidate the kinetics and mechanism of nucleophilic addition reactions to ketenes.[217] The hydration of ketenes to form carboxylic acids shows uncatalyzed, hydroxide-ion catalyzed, and hydronium-ion catalyzed components, $k_{obs} = k_{H_2O} + k_{HO^-}[HO^-] + k_{H^+}[H^+]$ (Table 4). A good linear correlation was found between $\log k_{H_2O}$ and $\log k_{HO^-}$, which implies that both uncatalyzed and hydroxide-ion catalyzed hydration proceed by nucleophilic attack on the carbonyl carbon atom of the ketene.[223] This mechanism is also consistent with large rate-retarding

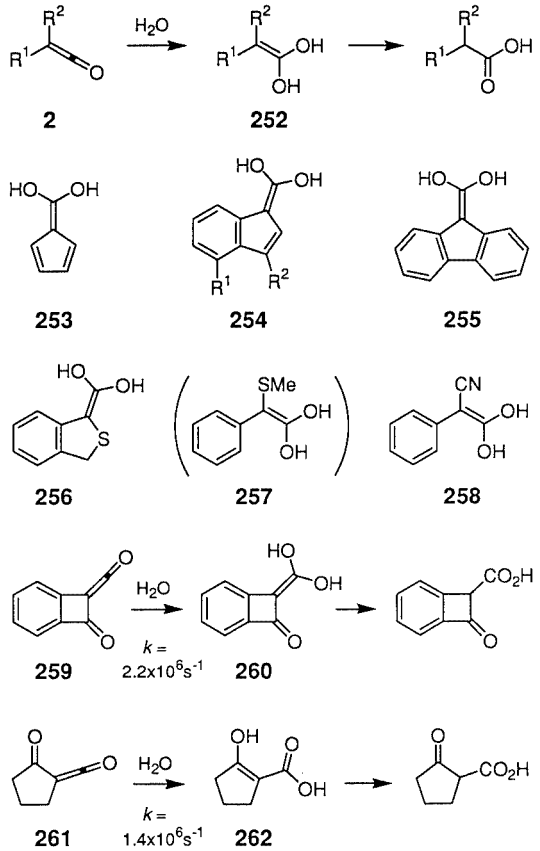
Table 4. Rate constants for the hydration of ketenes $R^1R^2C{=}C{=}O$[a]

R^1 [a]	R^2	k_{H_2O} [s^{-1}]	k_{HO^-} [$M^{-1}s^{-1}$]	k_{H^+} [$M^{-1}s^{-1}$]	Ref.
H	H	$3.65\cdot10^1$	$5.26\cdot10^4$	$1.01\cdot10^4$	[218]
*n*Bu	H	$9.90\cdot10^1$	$3.29\cdot10^4$	$3.98\cdot10^3$	[219]
Ph	H	$4.77\cdot10^3$	$1.22\cdot10^6$	–	[219]
Mesityl	H	$1.35\cdot10^2$	$1.01\cdot10^5$	$4.67\cdot10^0$	[220]
Ph	Et	$1.03\cdot10^1$	$6.05\cdot10^3$	–	[221]
Ph	Ph	$2.75\cdot10^2$	$6.11\cdot10^4$	–	[222]

[a] Data obtained by LFP of diazo ketones in aqueous solutions at 25 °C. For a comprehensive list, including data from other sources, see ref.[223]

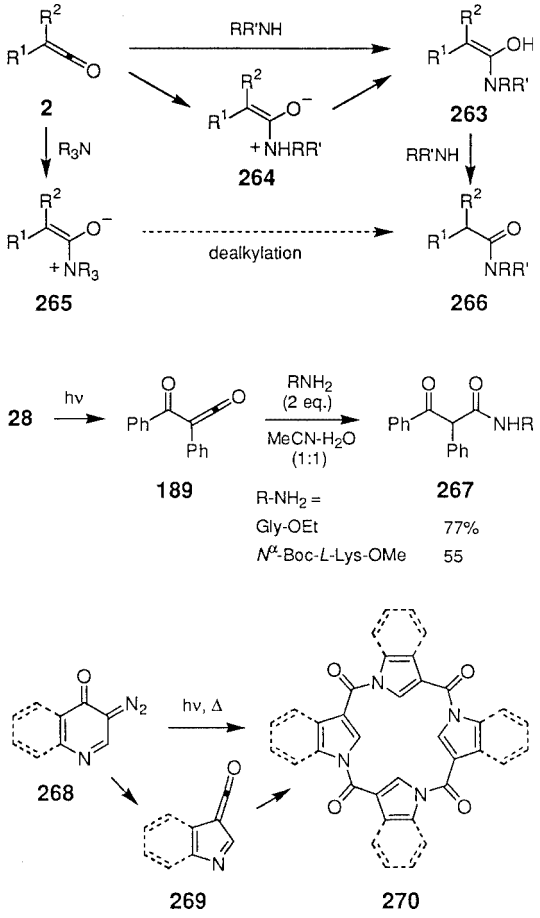
effects of bulky groups (Table 4), small solvent isotope effects,[221,222] and molecular orbital theory.[224]

Enols of carboxylic acids **252** were found to intervene on the reaction path from ketenes **2** to carboxylic acids (Scheme 36). The cyclopentadiene moiety stabilizes enols strongly. Therefore, **253** was the first carboxylic acid enol to be characterized in aqueous solution,[225] followed by the benzo analogues **254**[173] and **255**[226] which were generated from diazoquinones. While **256** was rapidly formed (k_{H_2O} = $2.2\cdot10^5$ s^{-1}) and readily monitored,[227] the acyclic analogue **257** (k_{H_2O} = $1.3\cdot10^2$ s^{-1}) could not be detected.[228] The difference in reactivity of the ketene precursors is attributed to steric effects. While many acyclic carboxylic acid enols, such as **257**, ketonize more rapidly than they are formed, **258** stands out as an observable species.[229] Acylketenes (α-oxoketenes) are remarkably reactive species;[230] their hydration rates compare with those of cyclopentadienylideneketenes. Different types of enols have been detected, depending on ring size, as illustrated by **259** → **260**[231] and **261** → **262**.[232]



Scheme 36. Rates and mechanism of ketene hydration

Flash photolysis of diazo ketones has also been used to study the reactions of ketenes with amines. An intermediate identified as either zwitterion **264** or amide enol **263** (Scheme 37) was observed by TRIR.[233] The decay of **263**/**264** is dependent on amine concentration and leads to the formation of amide **266**. The kinetic data for primary and secondary amines (Table 5) can be rationalized in terms of the steric effects exerted by both amine and ketene substituents. The influence of *para* substituents on phenylketene reactivity points to negative charge development in the transition state. Tertiary amines (Et_3N, pyridine) react more slowly than secondary amines by ca. 3 orders of magnitude. A persistent zwitterion **265** [$R^1 = R^2 = COC(CH_3)_3$] was obtained from 4-dimethylaminopyridine and dipivaloylketene.[233c] Benzoyl(phenyl)ketene (**189**) was efficiently trapped with amines even in aqueous solution.[234] Under these conditions, the yields of amides **267** were better with



Scheme 37. Reactions of ketenes with amines

Table 5. Bimolecular rate constants ($M^{-1}s^{-1}$) for the reactions of ketenes $R^1R^2C{=}C{=}O$ with amines in acetonitrile solution at 23 °C[233b]

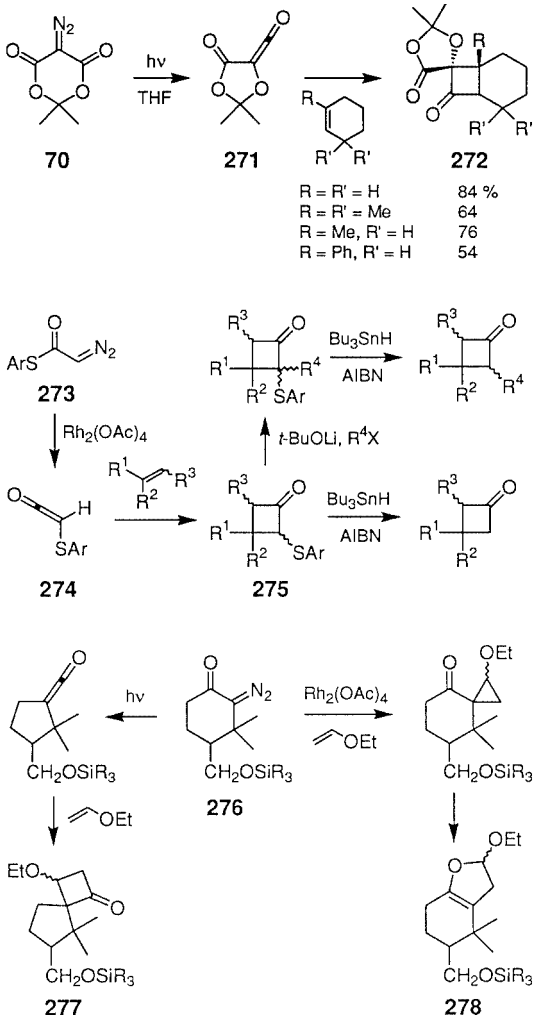
R^1	R^2	nBuNH$_2$	iPrNH$_2$	Et$_2$NH	Piperidine
tBu	H	$1.6\cdot10^6$	$7.7\cdot10^5$	$4.6\cdot10^5$	$6.7\cdot10^6$
Ph	H	$3.3\cdot10^8$	$1.2\cdot10^8$	$4.8\cdot10^8$	$5.0\cdot10^8$
4-MeOC$_6$H$_4$	H	$2.2\cdot10^8$	$9.5\cdot10^7$	$3.3\cdot10^8$	$5.1\cdot10^8$
4-CNC$_6$H$_4$	H	$8.7\cdot10^8$	$5.8\cdot10^8$	$9.5\cdot10^8$	$1.4\cdot10^9$
4-NO$_2$C$_6$H$_4$	H	$1.1\cdot10^9$	$8.1\cdot10^8$	$9.5\cdot10^8$	$1.6\cdot10^9$
PhCH=CH	H	$5.1\cdot10^8$	$1.6\cdot10^8$	$4.9\cdot10^8$	$8.0\cdot10^8$
Ph	Ph	$1.1\cdot10^7$	$4.4\cdot10^6$	$1.2\cdot10^7$	$1.5\cdot10^7$
Ph	PhCO	$2.3\cdot10^7$	$9.4\cdot10^6$	$2.1\cdot10^7$	$3.8\cdot10^7$

amino acid derivatives than with more basic amines. A unique aminoketene self-reaction was induced by loss of nitrogen from **268**, tetramerization of **269** affording **270**.[235]

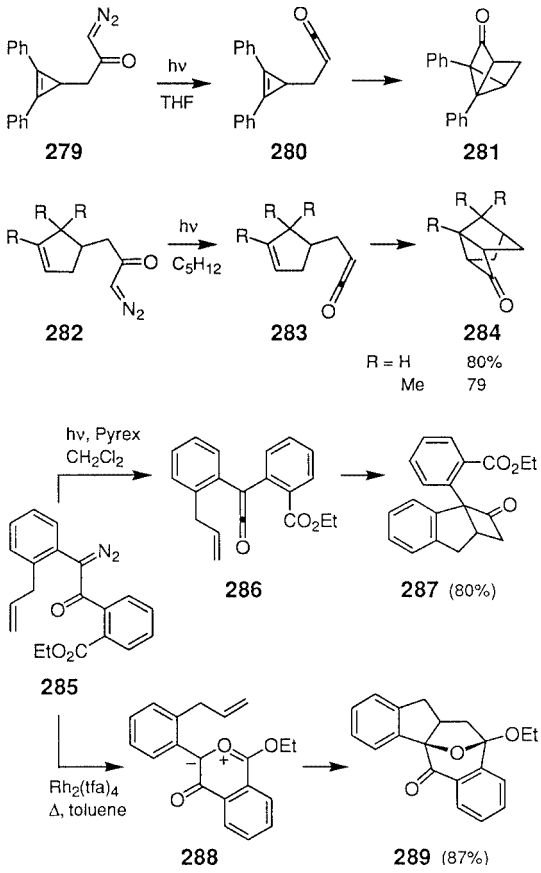
4.1.2. Cycloaddition Reactions

The [2 + 2] cycloaddition of ketenes with alkenes constitutes a popular method for the synthesis of cyclobutanones.[236] The Wolff rearrangement has been used to generate ketenes that are difficult to make otherwise, such as **271** (Scheme 38).[237] The products formed by photolysis of **70** in the presence of alkenes were first regarded as cyclopropanes.[237a] The correct structures **272** were established later by X-ray analysis.[237b] The Wolff rearrangement of α-diazo thiolacetates **273** was recently found to be catalyzed by $Rh_2(OAc)_4$.[238] The thio-substituted ketenes **274** thus generated add to a variety of alkenes to afford cyclobutanones **275** which were desulfurized either directly or after α-alkylation. Useful oxidative transformations of **275** were also reported. The behavior of **273** is unusual. As a rule, the action of $Rh_2(OAc)_4$ on diazo ketones induces carbenoid addition to alkenes rather than Wolff rearrangement. For example, the photochemical reaction of **276** with ethoxyethene afforded cyclobutanone **277** (88%) while catalysis with $Rh_2(OAc)_4$ led eventually to dihydrofuran **278** (70%).[239] Analogous results were obtained with a series of related diazo ketones.

The first intramolecular cycloaddition of a "Wolff ketene" was reported by Masamune who photolyzed diazo ketone **279** to obtain 2,6-diphenyltricyclo[2.2.0.0^{2,6}]hexan-3-one (**281**) by way of **280** (Scheme 39).[240] While **281** was not isolated, tricyclo[3.2.1.0^{3,6}]octan-4-one (**284**, R = H)[241] and its 6,7,7-trimethyl derivative (**284**, R = Me)[242] were prepared in 80% yield from the diazo precursors **282**. Photolysis is the method of choice for such transformations. Thus **285** produced the intramolecular cycloadduct **287** of ketene **286** on irradiation.[243] On the other hand, rhodium(II) catalysis led to carbenoid attack at the ester group with formation of carbonyl ylide **288** which was then trapped by the double bond to give **289**. When **290** was heated in decane, intramolecular C=C addition (→ **291**) and C−H insertion (→ **292**) of the carbonyl carbene competed with the Wolff rearrangement leading to cyclobutanones **293** and **294** (Scheme 40).[244] Key steps in a synthesis of the diterpene (±)-aphidicolin (**298**) were (i) irradiation of **295** to achieve intramolecular cycloaddition of the

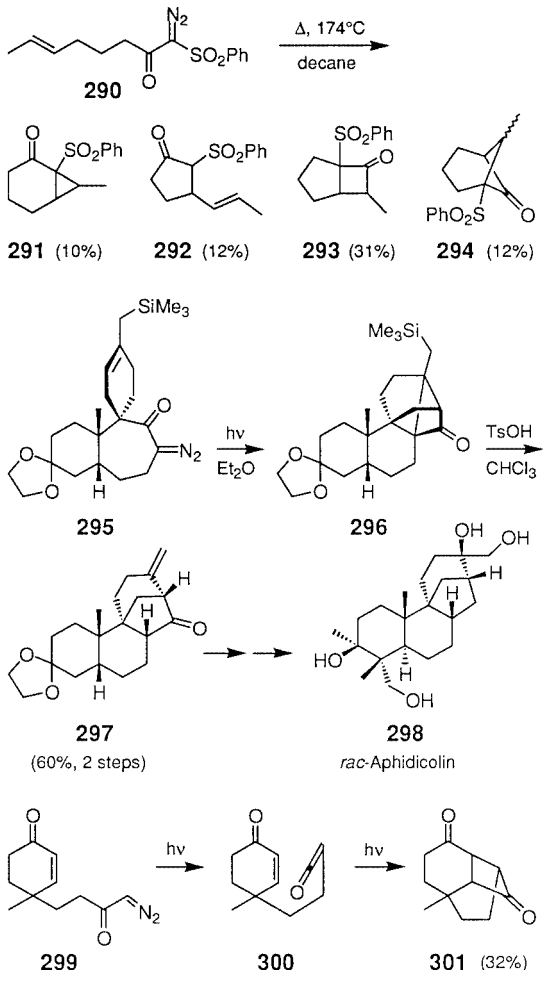


Scheme 38. Intermolecular [2+2] cycloaddition of ketenes with alkenes



Scheme 39. Intramolecular [2+2] cycloaddition of ketenes with alkenes

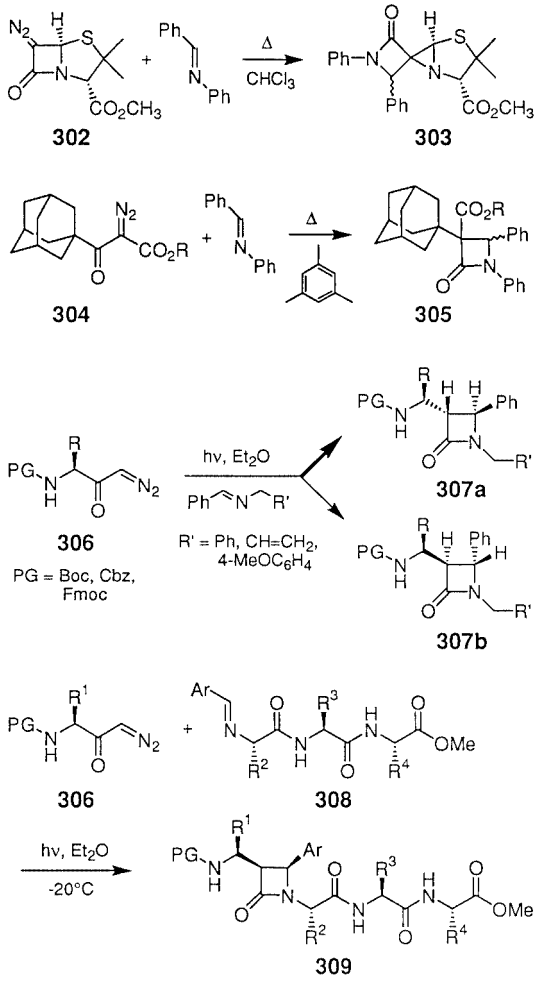
ring-contracted ketene (→ **296**), and (ii) protolysis of the cyclobutanone ring in **296** to give **297**.[245]



Scheme 40. Intramolecular [2+2] cycloaddition of ketenes with alkenes

The intramolecular cycloaddition of "Wolff ketenes" to enones, e.g. **299** → **300** → **301**, differs in mechanism from the examples cited above.[246] Ketene **300**, generated by non-photolytic methods, did not add to the electron-deficient C=C bond of the enone. The reaction of **300** to give **301** is a cycloaddition of photoexcited enone to a double bond which happens to be part of a ketene. This reaction will occur only if the two reactive sites are connected with a three-atom tether, and the products will be 1,4-diketones. Numerous examples have been studied, with yields of 30−40%.[246]

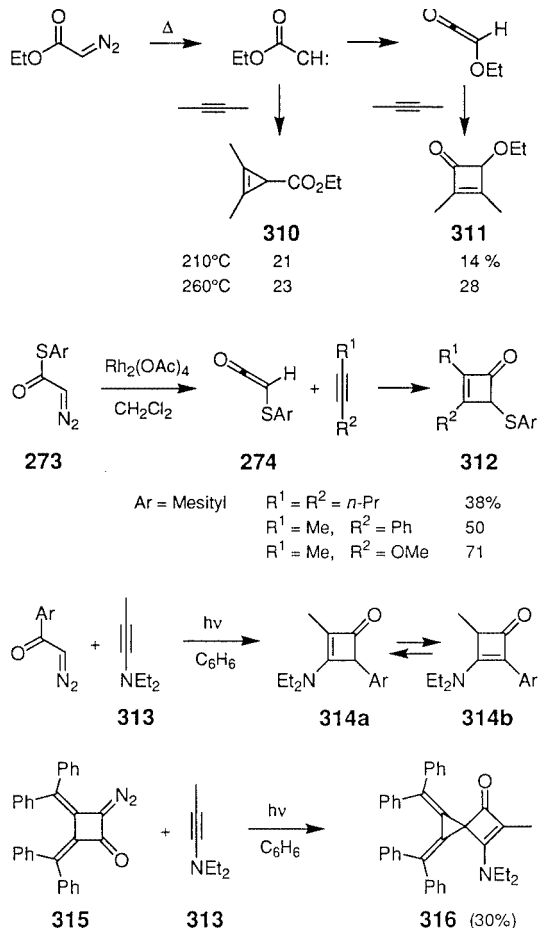
Cycloaddition reactions of ketenes leading to β-lactams were early observed when diazo ketones were decomposed photochemically[20a] or by means of silver oxide in the presence of C=N bonds.[20b] Diphenylketene, generated thermally from 2-diazo-1,2-diphenylethanone (**25**), was added to a large variety of imines.[247] Recent examples, **302** → **303**[248] and **304** → **305**[249] (Scheme 41), illustrate the scope of diazo ketones that have been used. New efforts in this field were triggered by the current interest in peptidomimetics. The incorporation of β-lactams in oligopeptide strands should stabilize β-turns. Photolysis or microwave pyrolysis of amino acid-derived diazo ketones **306** in the presence of imines provided the stereoisomeric β-lactams **307**, both with *trans* configuration at the lactam ring.[250] The **307a/307b** ratio ranged from 60:40 to 93:7, depending on the size of R. Additional control of the stereoselectivity can be exerted by the use of chiral imines. This effect is also operative in the reaction of **306** with peptide-derived imines **308**.[251] In some cases, only a single stereoisomer of the β-lactam **309** was obtained.



Scheme 41. [2+2] Cycloaddition reactions of ketenes with imines

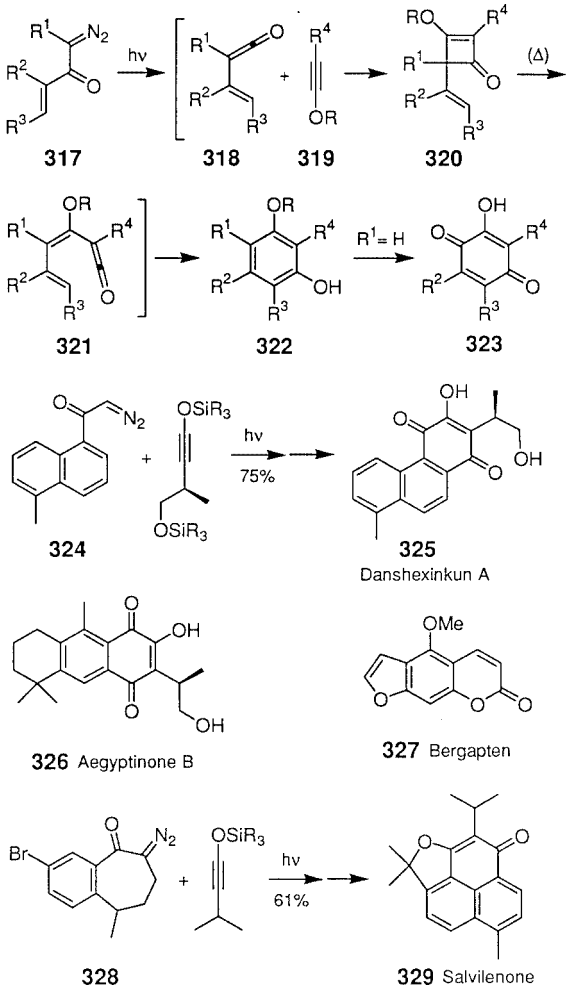
The Wolff rearrangement has also been used to generate ketenes for cycloaddition reactions with alkynes. Flow pyrolysis of ethyl diazoacetate in the presence of 2-butyne gave two major products, **310** and **311**, resulting from addition of ethoxycarbonyl carbene and ethoxyketene, respectively, to the triple bond (Scheme 42).[252] Arylthioketenes **274**, made by rhodium(II)-catalyzed rearrangement of **273**, were added to a variety of alkynes to give cyclobutenones **312**.[238] Cycloaddition of **274** with methoxypropyne proceeded more efficiently than with less-activated alkynes. The alkynylamine **313** was found to accept arylketenes which were generated by photolysis of aroyldiazomethanes.[253] The cyclobutenones **314** thus obtained were mixtures of tautomers among which **314a** predominated. Even the

cyclopropylideneketene arising from ring contraction of **315** was added to **313** with formation of **316**.[254]



Scheme 42. [2+2] Cycloaddition reactions of ketenes with alkynes

When vinylketenes **318** were generated from diazo ketones **317** in the presence of alkynes **319**, a sequence of [2+2] cycloaddition (→ **320**), cycloreversion (**320** → **321**), and electrocyclic ring closure (**321** → **322**) led to highly substituted arenes (Scheme 43, Table 6).[255] The solvent of choice was 1,2-dichloroethane, and in some cases the conversion of **320** into **322** was completed by heating at reflux. With R^1 = H and R = SiR'_3, the products **322** were readily oxidized and deprotected to give 2-hydroxyquinones **323**. The first natural product synthesized along these lines was maesanin [**323**, R^1 = R^2 = H, R^3 = OMe, R^4 = $-(CH_2)_9-CH=CH$-*n*Bu], the active constituent of an East African tribal medicine.[256] Efficient total syntheses of several diterpenoid quinones isolated from the traditional Chinese medicine *Dan Shen* have been reported, e.g., **324** →→ **325**.[257] Aegyptinones, antifungal and antibacterial quinones (e.g., **326**) from *Salvia aegyptiaca*, were obtained by similar routes.[258] A convergent total synthesis of the furocoumarin bergapten (**327**), starting from 2-furoyldiazomethane, was also developed.[259] A somewhat different strategy, utilizing the ring contraction of **328**, was applied in the total synthesis of the phenalenone diterpene salvilenone (**329**).[260]



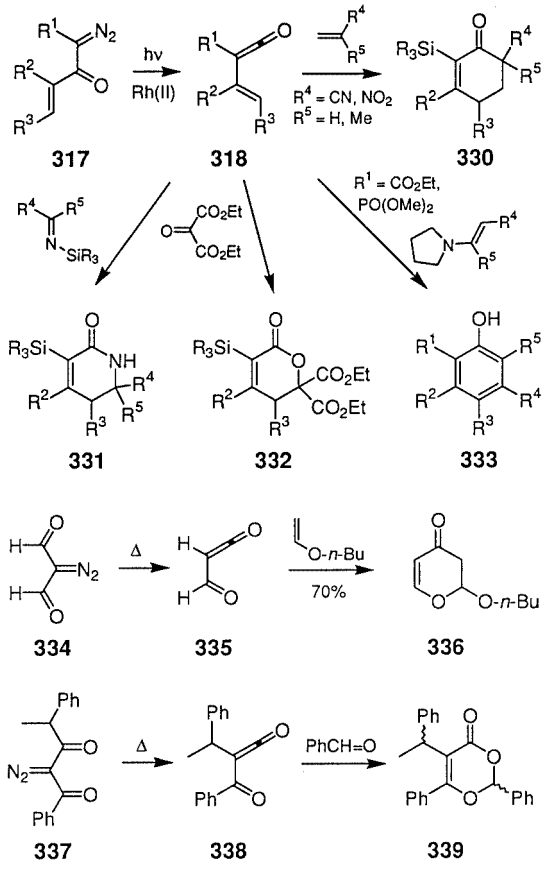
Scheme 43. Annulation strategy based on ketene + alkyne cycloaddition

Table 6. Synthesis of highly substituted arenes from diazo ketones and 1-methoxybutyne (**317** → **322**)[255]

R^1	R^2	R^3	R^4	R	Yield (%)
H	Me	Me	Et	Me	46
H	Me	MeO	Et	Me	31
H		$-(CH_2)_2-$	Et	Me	56
H		$-(CH_2)_4-$	Et	Me	50
H		$-CH=CH-CH=CH-$	Et	Me	49
Me		$-CH=CH-CH=CH-$	Et	Me	51
H		$-O-CH=CH-$	Et	Me	44

[4 + 2] Cycloaddition reactions of vinylketenes **318** are also known, particularly if R^1 = SiR_3,[261] CO_2R, and $PO(OR)_2$.[262] It should be noted that α-silyl-α-diazo ketones, $R'CO-CN_2SiR_3$, undergo Wolff rearrangement on photolysis[263] and rhodium(II) catalysis[264] whereas thermolysis proceeds by way of a silyl shift from carbon to oxygen.[265] Photolysis of **317**, R^1 = SiR_3, in the presence of electron-poor alkenes,[261a] imines, and keto esters[261b] afforded cyclohexenones **330**, unsaturated lactams **331**, and lactones **332**, respectively (Scheme 44). Cycloaddition of

318, $R^1 = CO_2R$ or $PO(OR)_2$, with enamines involved elimination of the amino group to give phenols **333**.[262]

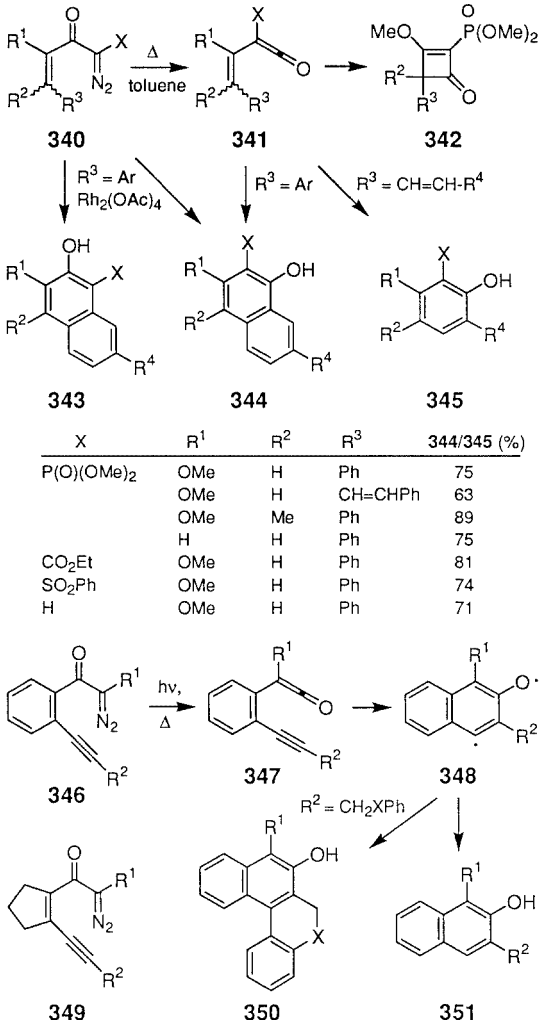


Scheme 44. [4+2] Cycloaddition reactions of π-conjugated ketenes

Although ketoketenes (α-oxoketenes) are very reactive in [4 + 2] cycloadditions,[152] the Wolff rearrangement of 2-diazo-1,3-diketones has rarely been used in that context. Formylketene (**335**), generated by decomposition of diazomalondialdyde (**334**) in refluxing *n*-butyl vinyl ether, produced dihydro-γ-pyrone **336**, which furnished γ-pyrone on treatment with acid.[266] (Acyl)(phenyl)ketenes from thermolyses of $PhCO-CN_2-COR$ were reacted with alkynyl ethers to give γ-pyrones and azulenones competitively, albeit in poor yield.[267] Dimerization of a ketoketene by way of [4 + 2] cycloaddition has been reported,[268] although polymerization appears to be more common.[269] (Benzoyl)(penyl)ketene (**189**, Scheme 37) and related ketoketenes have been added to the C=N bond of isothiocyanates.[270] Thermal decomposition of **337** furnished **338** as the major (90%) ketoketene which was trapped by benzaldehyde to give **339** with almost no diastereoselectivity (≈ 1.5:1).[271]

4.1.3. Pericyclic Reactions

Cyclization of alkenylketenes produces cyclobutenones, although the reverse reaction is more widely used. Cyclobutenones **342** were obtained on thermolysis of β,γ-unsaturated diazo ketones **341**, X = P(O)(OMe)$_2$, R^1 = OMe, R^2, R^3 = alkyl (Scheme 45).[272] With R^3 = aryl or alkenyl, 6π-cyclization of **341**, leading to phenols **344** and **345**, respectively, took place (see also **321** in Scheme 43). This reaction was first observed with X = CO_2Me, R^1 = H, R^2, R^3 = aryl.[273] Many examples were provided with X = P(O)(OMe)$_2$, and a few with X = SO_2Ph and X = H.[272] *E*/*Z* isomers gave similar results, apparently due to equilibration at the ketene stage. The double bond(s) of **340**/**341** can be part of heterocycles.[274] On catalysis with rhodium(II) acetate, formal C−H insertion (**340** → **343**) was found to compete with Wolff rearrangement (**340** → **341** → **344**).[275] Electron-donating substituents R^2 and R^4 favor the formation of **344** whereas the carbenoid route prevailed in the case of electron acceptors.



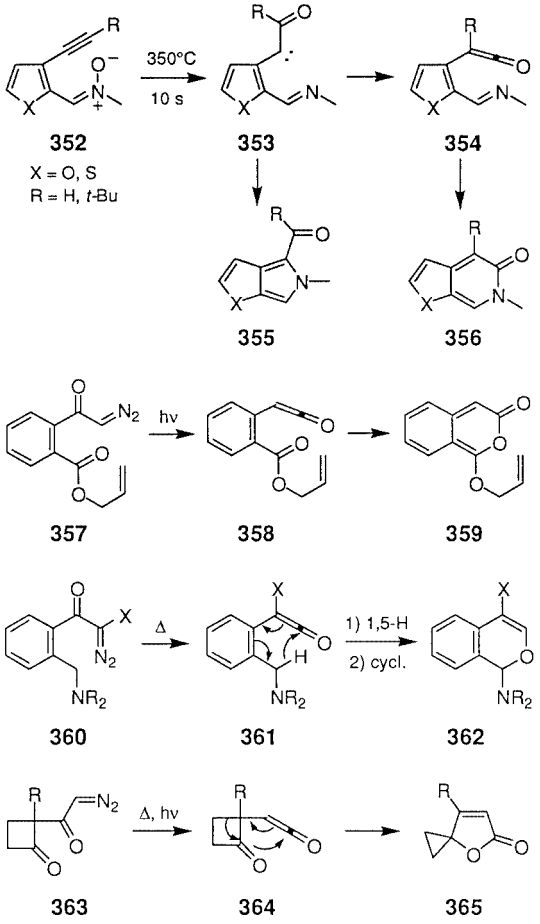
X	R^1	R^2	R^3	344/345 (%)
P(O)(OMe)$_2$	OMe	H	Ph	75
	OMe	H	CH=CHPh	63
	OMe	Me	Ph	89
	H	H	Ph	75
CO_2Et	OMe	H	Ph	81
SO_2Ph	OMe	H	Ph	74
H	OMe	H	Ph	71

Scheme 45. Cyclization reactions of alkenyl- and dienylketenes

A novel cyclization mechanism applies when the terminal double bond of dienylketenes is replaced with a triple bond. Surprisingly, photolysis or thermolysis of **346** produced the same type of phenols that was obtained from **340**, compare **351** with **345**.[276] Rearrangement of **346** generates ketenes **347**, which then ring close to biradical intermediates **348**. Hydrogen abstraction from the solvent eventually affords **351**. If π bonds are tethered to the alkyne (R^2 = $CH_2CH_2CH=CH_2$, CH_2CH_2Ph, or CH_2OPh), intramolecular addition at the biradical stage, followed by hydrogen transfer, leads to **350**.[276] The diazo ketones **349** were de-

signed as mimics of the neocarcinostatin radical-generating system.[277] Although the chemistry of **349** closely paralleled that of **346**, the observed DNA cleavage was found not to involve a biradical such as **348**. Studies with diaroyldiazomethanes indicated that benzoylketenes are responsible for G-selective cleavage of DNA, whereas nonselective cleavage is due to hydrogen abstraction by triplet carbonyl carbenes.[234,278]

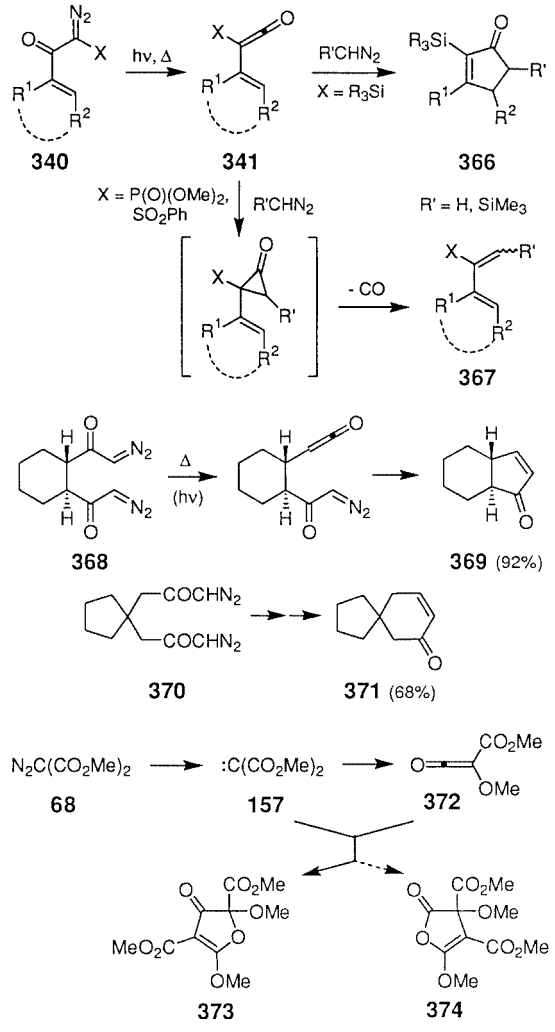
Flash pyrolysis of the nitrones **352** afforded **355** and **356** as major products, which is reasonably explained by oxygen transfer with formation of carbonyl carbene **353** (Scheme 46).[279] Cyclization of carbene **353** competes with Wolff rearrangement to generate **354**, a dienylketene bearing nitrogen in the terminal position, which gives rise to **356**. Ketene cyclization involving a carbonyl group, **358** → **359**, was induced by photolysis of **357**.[280] A 1,5-H shift to the C=O group of ketene **361**, followed by cyclization, accounts for the formation of **362** from **360**, X = $P(O)(OMe)_2$ or CO_2-*t*Bu.[281] Two alkoxy groups cannot replace the dialkylamino group in activating the benzylic hydrogen for 1,5-H shift. 2-Oxocyclobutylideneketenes **364** could be generated photochemically from **363** at −50 °C (IR detection). On warming, an intriguing sigmatropic rearrangement of **363** occurred, with formation of 5-spirocyclopropylbutenolides **365**.[282]



Scheme 46. Pericyclic reactions of ketenes involving hetero atoms

4.1.4. Reactions with Diazo Compounds and Carbenes

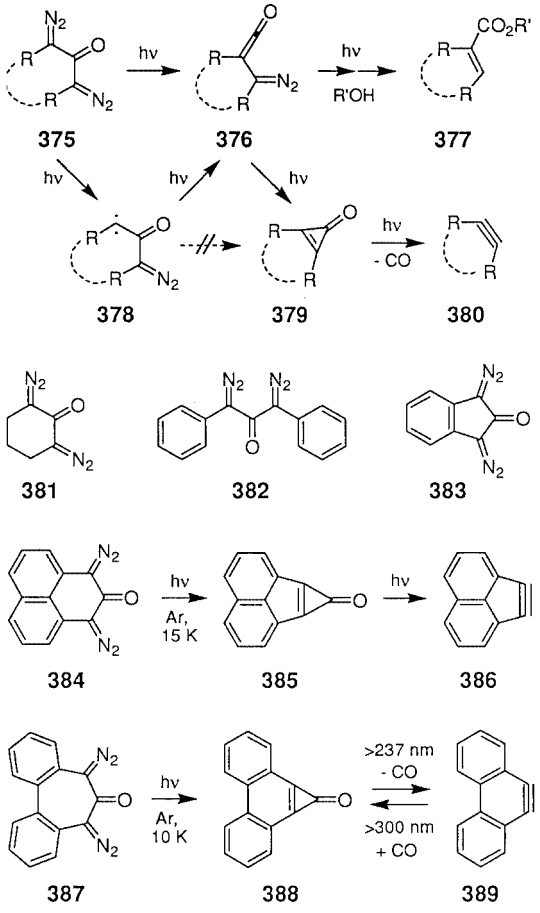
Ketenes react with diazomethanes by [2 + 1] cycloaddition to give cyclopropanones.[283] Most often, these reactions were performed with ketenes from non-nitrogeneous sources. Stereochemical studies and a theoretical analysis have been published.[284] (Alkenyl)(silyl)ketenes **341**, X = SiR_3, generated by Wolff rearrangement of **340**, were found to accept diazomethanes in a novel [4 + 1] annulation, with formation of cyclopentenones **366** (Scheme 47).[285] Electron-withdrawing groups [X = $P(O)(OMe)_2$, SO_2Ph], on the other hand, lead to the formation of alkenes **367**, presumably by way of cyclopropanones.[286] An analogous intramolecular reaction of bis(diazo)diketones produced cyclic enones, as exemplified by the conversion of **368** into **369**, and of **370** into **371**, preferably by thermolysis.[287] Reaction of intermediate ketenes with the remaining diazo ketone group, by way of cyclopropanones, is most likely. In the case of dimethyl diazomalonate (**68**), however, some evidence for ketene-carbene interaction was adduced. Photolysis of **68**



Scheme 47. Reactions of ketenes with diazo compounds or carbenes

afforded **373** as the only "dimeric" product whereas thermolysis of **68** gave small amounts of **374** in addition to **373**.[288] Ketene **372**, generated by an independent route, was not scavenged by **68**. Therefore, **373** and **374** are thought to arise from reactions of carbene **157** with ketene **372**.

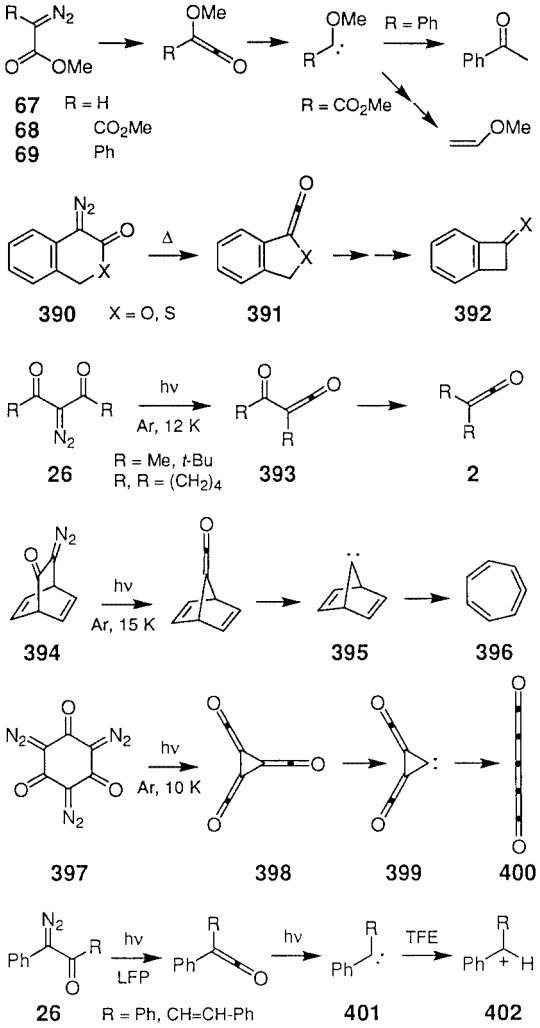
α,α′-Bis(diazo)ketones **375** (for example, **381**) were early found to give α, β-unsaturated acids or esters **377** on photolysis in protic media (Scheme 48).[289] Minor amounts of β, γ-unsaturated esters and of β-alkoxy esters were also detected.[290] Irradiation of 1,3-diazo-1,3-diphenylpropan-2-one (**382**), using monochromatic light at 436 nm, resulted in the isolation of diphenylcyclopropenone (**379**, R = Ph) whereas at shorter wavelengths diphenylacetylene (**380**, R = Ph) was obtained.[290] Matrix isolation proved to be helpful in elucidating the reaction mechanism. Irradiation (> 274 nm) of **381** in argon at 8 K gave first diazoketene **376** and then cyclopropenone **379** (both with R---R = $(CH_2)_4$, IR detection).[291] Similar results were obtained with **383**.[292] Triplet diazocarbonyl carbenes **378** were also detected (IR, ESR) in matrix photolyses of **381**[293] and **383**.[292,294] Most remarkably, further irradiation converted **378** into **376** (rather than **379**). These findings exclude a route to **379** which would be analogous to the familiar reaction $CH_2N_2 + :CH_2 \rightarrow H_2C{=}CH_2$, and would bypass the Wolff rearrangement **375** → **376**. However, matrix photolyses of **384**[291] and **387**[295] gave the cyclopropenones **385** and **388**, respectively, as the first detectable intermediates. Decarbonylation of the cyclopropenones led to matrix isolation of highly strained alkynes. In contrast to acenaphthyne (**386**), phenanthryne (**389**) was found to react with CO to regenerate **388** upon photoexcitation.[295] High-level computational studies have been performed on the interconversion of ketenylcarbenes, cyclopropenones, and alkynes.[296]



Scheme 48. Photochemistry of α,α′-bis(diazo)ketones

4.1.5. Decarbonylation

Wolff rearrangement, followed by decarbonylation of the resulting ketenes, produces carbenes. Gas phase decomposition of diazo esters **67**,[196] **68**,[297] and **69**[298] gave products that were most likely derived from alkoxycarbenes (Scheme 49). On vacuum pyrolysis of 4-diazoisochroman-3-one (**390**, X = O), benzocyclobutenone (**392**, X = O) was eventually formed.[299] Ketene **391**, X = O, decarbonylates to the oxacarbene which rearranges to give **392**. When 4-diazoisothiochroman-3-one (**390**, X = S) was thermolyzed, both **391** and **392**, X = S, were detected by PE spectroscopy.[300]

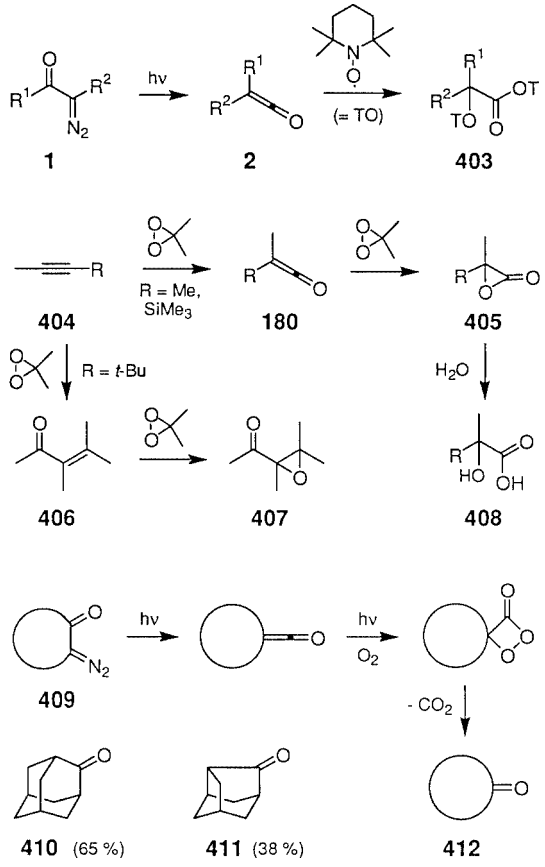


Scheme 49. Wolff rearrangement followed by ketene decarbonylation

Broad-band irradiation of 2-diazo-1,3-diketones **26** in Ar matrices at 12 K produced ketoketenes **393** in less than 10 min. On increasing the photolysis time to > 3 h, decarbonylation **393** led to a second Wolff rearrangement, with formation of ketenes **2**.[301] The photodecarbonylation method was used to generate matrix-isolated 1,2,4,6-cycloheptatetraene (**396**) from diazo ketone **394**, by way of 7-norbornadienylidene (**395**).[302] The formation of 1,2,3,4-pentatetraen-1,5-dione (C_5O_2, **400**) by photolysis of diazo ketone **397**[303] in an argon matrix can be viewed as threefold Wolff rearrangement (**397** → **398**), followed by decarbonylation (**398** → **399**) and cyclopropylidene−allene rearrangement (**399** → **400**). Flash pyrolysis of **397** also furnished **400,** along with C_3O_2.[303] LFP of diazo ketones **26** was used to generate arylcarbenes **401** in weakly acidic solvents, such as trifuoroethanol (TFE). Proton transfer with formation of carbocations **402** was thus demonstrated.[304] Diaryldiazomethanes, the usual precursors of **401**, are rapidly decomposed by TFE whereas diazo ketones **26** persist.

4.1.6. Oxidation

Ionization potentials (IP) of arylketenes were obtained by vacuum pyrolysis of diazoacetophenone (**22**) and of 4-X derivatives in a PE spectrometer.[27a] 2,2,6,6-Tetramethylpiperidinyloxy (TEMPO, TO) was found to react with ketenes **2** to give 1,2 adducts **403** (Scheme 50).[305] 1,4-Adducts



Scheme 50. Oxidation and degradation of "Wolff ketenes"

were produced with α,β-unsaturated ketenes. Various ketenes were generated by Wolff rearrangement for kinetic studies which showed that the reactivities with TEMPO and with H_2O are correlated with unit slope.[305] The rates of TEMPO addition to pentafulvenones served as a test for cyclopentadienyl radical destabilization.[305d]

The adducts **403** are derivatives of α-hydroxycarboxylic acids **408**. Oxidation of alkynes **404** with dimethyldioxirane was established as an alternate route to **408**.[306] Oxygen transfer to alkynes gives rise to carbonyl carbenes (see Section 3.4.3. and Scheme 27). Wolff rearrangement, further oxidation of **180**, and hydrolysis of **405** account for the formation of **408** (R = Me, 40%; R = $SiMe_3$, 93%). With R = *t*Bu, however, 1,2-methyl shift (→ **406**) prevailed over Wolff rearrangement, leading to **407** as the major product (40%). Oxidative degradation of ketenes, with formation of ketones and CO_2, was achieved when diazo ketones were irradiated at −78 °C while passing oxygen through the reaction mixture.[307] The one-pot preparation of cycloalkanones, **409** → **412**, is exemplified by 2-adamantanone (**410**, 65%) and 2-noradamantanone (**411**, 38%).

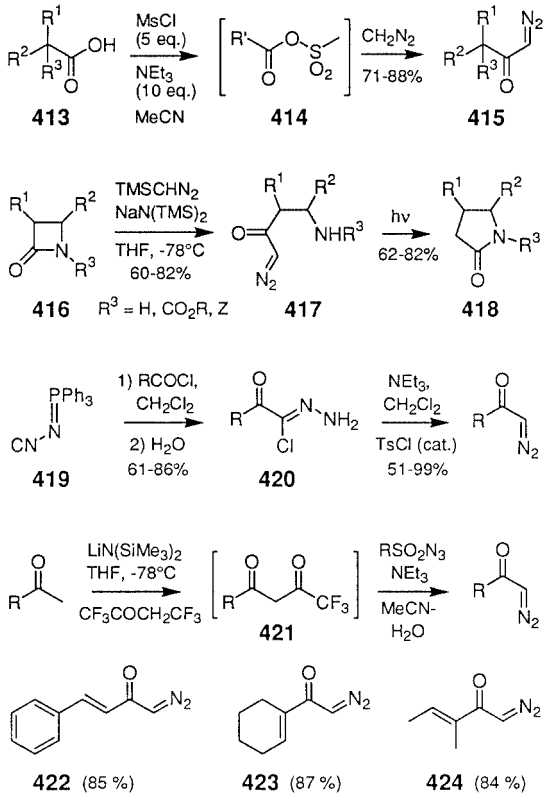
4.2. Homologation of Carboxylic Acids (Arndt−Eistert Reaction)

4.2.1. Advances in Methodology

The acylation of diazomethane using acid chlorides or anhydrides is a familiar procedure for the preparation of diazomethyl ketones R−CO−CHN_2 (Scheme 4).[13] With non-enolizable acids (R = Ar, *tert*-alkyl), the use of excessive amounts of diazomethane can be avoided by adding one equivalent of triethylamine. Mixed carboxylic-carbonic anhydrides R−CO−O−CO−OR′, generated in situ from the carboxylic acid and alkyl chloroformates, are attacked by diazomethane at the more reactive carbonyl group to give R−CO−CHN_2. Dicyclohexylcarbodiimide[308] or cyanuric chloride[309] were also used as "coupling reagents". With few exceptions, these reagents offer no significant advantage over conventional procedures.

The synthesis of sterically hindered α-diazo ketones **415** is often inefficient or even impossible to achieve using standard methods. In order to activate sterically encumbered carboxylic acids **413** for attack by diazomethane, reactive acyl mesylates **414** were generated in situ (Scheme 51).[310] The one-pot protocol reliably afforded diazo ketones **415** with quaternary α-carbon atoms (72−93% yield). The procedure failed with simple, unblocked carboxylic acids which were converted into symmetrical anhydrides.

Trimethylsilyldiazomethane ($TMSCHN_2$) has been recommended as a non-explosive and non-mutagenic alternative to hazardous diazomethane in acylation reactions.[311] An additional bonus of $TMSCHN_2$ is facile deprotonation to give a strongly nucleophilic carbanion. Thus ring opening of β-lactams **416** with the anion of $TMSCHN_2$ and photolytic rearrangement of the resulting diazo ketones **417**



Scheme 51. Novel or improved syntheses of diazomethylketones

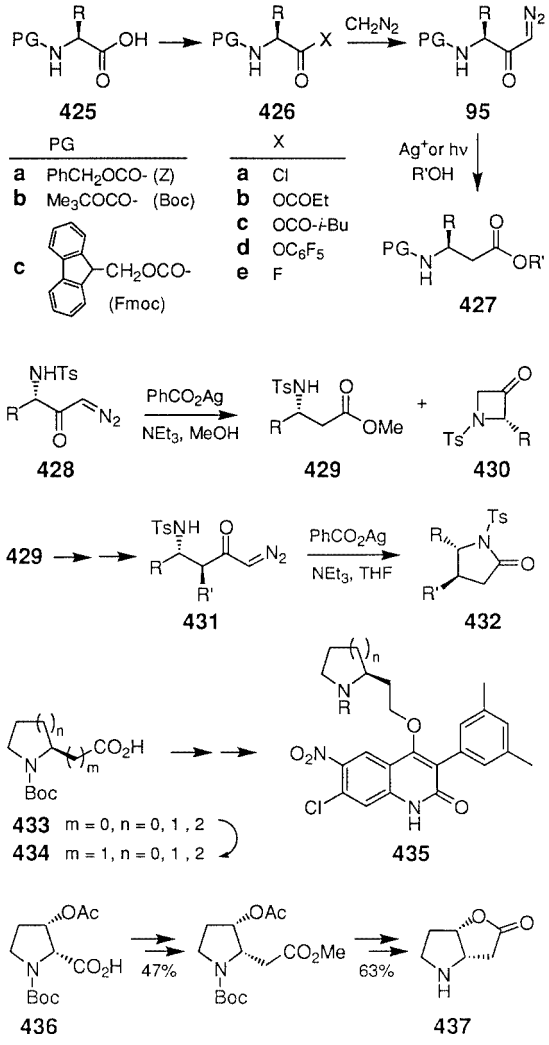
provided γ-lactams **418**.[312] *N*-Isocyanotriphenyliminophosphorane (**419**) was also proposed as a substitute for diazomethane.[313] Acylation of **419** with acid chlorides takes place on the isocyano group to give after hydrolysis α-ketohydrazidoyl chlorides **420**. Dehydrochlorination of **420**, with formation of diazo ketones, is mediated by tosylation of the terminal nitrogen atom.

Direct diazo transfer to methyl ketones is usually not a feasible process. The methyl group is best activated by trifluoroacetylation of the kinetically generated lithium enolate with 2,2,2-trifluoroethyl trifluoroacetate.[314] Deacylative diazo transfer from RSO_2N_3 (R = Me, 4-MeC_6H_4 or 4-$C_{12}H_{25}C_6H_4$) to **421** completes the formation of diazomethyl ketones. This procedure proved particularly valuable in the preparation of α,β-unsaturated diazo ketones, such as **422**−**424**, which cannot be obtained by acylation of diazomethane. Octan-2-one afforded mixtures of 1-diazooctan-2-one and 3-diazooctan-2-one, but significant regiocontrol (9:1) was achieved when lithium 2,2,6,6-tetramethylpiperidide was employed to generate the kinetic enolate.

Silver ion catalysis is the first choice for effecting Wolff rearrangement of diazo ketones. Because heterogeneous conditions using a suspension of silver oxide can prove erratic, homogeneous systems involving complexed silver ions are often preferred. Silver benzoate−triethylamine, developed more than fifty years ago,[57b] serves as the most popular catalyst to date. Product purification is facilitated by the use of silver trifluoroacetate−triethylamine (in contrast to benzoic acid, trifluoroacetic acid is volatile and readily soluble in water).[315] A further improvement involves the use of ultrasound, which strongly enhances the rate of reaction.[316] More importantly, *base-free*, Ag^+-catalyzed Wolff rearrangements were found to proceed smoothly at room temperature on sonication − a promising protocol for base-sensitive substrates.[92,317] Silver ion catalysis tends to fail with sterically hindered diazo ketones. In such cases, photolysis is the method of choice. The presence of sulfur appears to poison silver catalysts. Fortunately, α-diazothiolacetates can be rearranged by means of rhodium(II) acetate (**273** → **274,** Schemes 38 and 42).[238] There are other exceptions to the rule that Rh^{II} does not promote rearrangement, see Scheme 15,[69] Scheme 44,[262,264] and Scheme 45.[273,275] Wolff rearrangement was found to be a major pathway in the Rh^{II}-catalyzed decomposition of diazoacetylcycloalkanes.[318]

4.2.2. Homologation of α-Amino Acids

β-Amino acids are components of many biologically active products, including the anticancer agent paclitaxel (Taxol®), HIV protease inhibitors, and β-lactam antibiotics.[319] The incorporation of β-amino acids into peptides



Scheme 52. Homologation of α-amino acids

strongly affects the secondary structure and the rate of enzymatic degradation. Natural α-amino acids are the ideal starting material for the preparation of β-amino acids.[320] Early studies established that α-phthaloylamino acids were suitable for Arndt−Eistert homologation.[321] The synthesis of Z- or Boc-protected aminoacyldiazomethanes **95** by standard methods faces some drawbacks.[308,321,322] The requisite acid chlorides **426aa** and **426ba** (Scheme 52) tend to racemize and decompose spontaneously to the corresponding Leuchs anhydrides. This has favored the use of mixed anhydrides obtained from **425a**,**b** with ethyl chloroformate/NEt_3[91] or isobutyl chloroformate/*N*-methylmorpholine.[323] Although racemization is thus avoided, inadvertent hydrolysis of the mixed anhydrides limits the yields of **95a**,**b**. Unlike **426aa** and **426ba**, Fmoc-amino acid chlorides **426ca** were recently found to be stable coupling agents which give the corresponding diazo ketones in 92−97% yield.[324] Mixed anhydrides, **426cb**[325] and **426cc**,[326] were slightly inferior to **426ca** in the preparation of **95c**. The pentafluorophenyl esters **426ad−cd**[327] (made from **425a−c** with C_6F_5OH and dicyclohexylcarbodiimide) and the N-protected amino acid fluorides **426ae−ce**[328] (made from **425a−c** with DAST) also afforded diazo ketones **95** in excellent yield. A selection of β-amino acids and esters produced by these methods is given in Table 7.

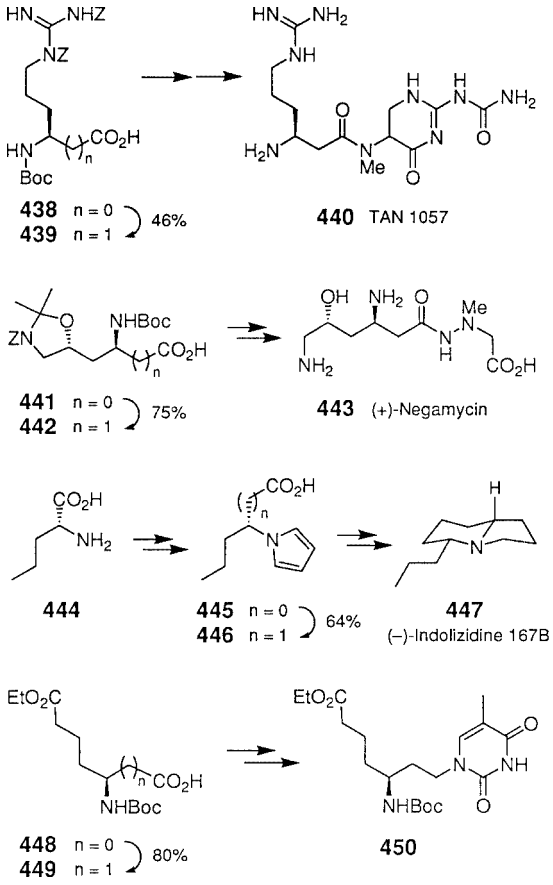
Table 7. Arndt−Eistert homologation of selected α-amino acids

425	X	**95** (%)	Catalyst	R′	**427** (%)	Ref.
Z-Ala	OCOEt	80	$PhCO_2Ag/NEt_3$	Me	95	[91]
	OC_6F_5	96	$PhCO_2Ag/Na_2CO_3$	H	86	[327]
Boc-Ala	OC_6F_5	96	$PhCO_2Ag/Na_2CO_3$	H	92	[327]
	F	93	$PhCO_2Ag$	H	92	[328]
Fmoc-Ala	Cl	93	$PhCO_2Ag$	H	90	[324]
	OCO-*i*Bu	68	CF_3CO_2Ag/NEt_3	H	72	[326]
	OC_6F_5	93	$PhCO_2Ag$	H	84	[327]
Boc-Val	OCOEt	88	CF_3CO_2Ag/NEt_3	H	93	[315]
	OC_6F_5	94	$PhCO_2Ag/Na_2CO_3$	H	90	[327]
	F	94	$PhCO_2Ag$	H	90	[328]
Fmoc-Val	Cl	97	$PhCO_2Ag$	H	80	[324]
	OCO-*i*Bu	75	CF_3CO_2Ag/NEt_3	H	75	[326]
	OC_6F_5	97	$PhCO_2Ag$	H	80	[327]
Boc-Leu	OCOEt	98	$PhCO_2Ag/NEt_3$	Me	87	[315]
Fmoc-Leu	Cl	96	$PhCO_2Ag$	H	82	[324]
	OCO-*i*Bu	87	CF_3CO_2Ag/NEt_3	H	66	[326]
	OC_6F_5	96	$PhCO_2Ag$	H	79	[327]
Z-Phe	OCOEt	88	$PhCO_2Ag/NEt_3$	Me	73	[91]
	OC_6F_5	91	$PhCO_2Ag/Na_2CO_3$	H	86	[327]
Boc-Phe	OCOEt	76	$PhCO_2Ag/NEt_3$	Me	89	[91]
	OCO-*i*Bu		$PhCO_2Ag/NEt_3$	Me	75[a]	[323]
	OC_6F_5	91	$PhCO_2Ag/Na_2CO_3$	H	91	[327]
Fmoc-Phe	Cl	92	$PhCO_2Ag$	H	50	[324]
	OCOEt		$PhCO_2Ag$/son.[b]	H	82[a]	[92]
	OC_6F_5	92	$PhCO_2Ag$	H	80	[327]
Z-Phg	OC_6F_5	93	$PhCO_2Ag/Na_2CO_3$	H	84	[327]
Fmoc-Phg	F	90	$PhCO_2Ag$	H	85	[328]
	OCOEt		$PhCO_2Ag$/son.[b]	H	70[a]	[92]

[a] Overall yield. [b] Sonication in ultrasound cleaning bath.

While the N−H bonds of **95a−c** do not interfere with rearrangement, diazo ketones **428**, derived from *N*-tosyl-protected α-amino acids, gave both homologous esters **429** and N−H insertion products **430**.[329] Diazo ketones **431**, bearing tosylamino groups in the β-position, decomposed with complete Wolff rearrangement. In THF, γ-lactams **432** (R′ = H) were the only products. α-Alkylation of **429** with LDA as the base proceeded with high *anti* selectivity (95:5) to give **431** (R = alkyl), which was transformed to enantiomerically pure pyrrolidinones **432**.[330]

The homologation of Z- or Boc-protected proline[311,331] was extended to 4- and 6-membered ring analogues **433**.[332] The products **434** were used to develop gonadotropin-releasing hormone (GnRH) receptor antagonists **435**. The Arndt−Eistert sequence was applied to (2*R*,3*S*)-3-acetoxyproline (**436**) in a synthesis of the Geissman−Waiss lactone **437**,[333] a precursor of many pyrrolizidine alkaloids. A convergent synthesis of the cyclodepsipeptide (+)-jasplakinolide was based on homologation of Boc-tyrosine-OTBDMS.[334] The conversion of orthogonally protected arginine **438** into the homologue **439**[335] was used to prepare TAN 1057 (**440**), an antibiotic with strong activity against methicillin-resistant strains of *Staphylococcus aureus* (Scheme 53).[336] An approach to the peptide antibiotic (+)-negamycin (**443**) has been reported which starts from **441** and proceeds by way of **442**.[337a] Blastidic acid, a component amino acid of the antibiotic blasticidin S, was synthesized from N^{α}-Boc-N^{γ}-Z-L-α,γ-diaminobutyric acid by

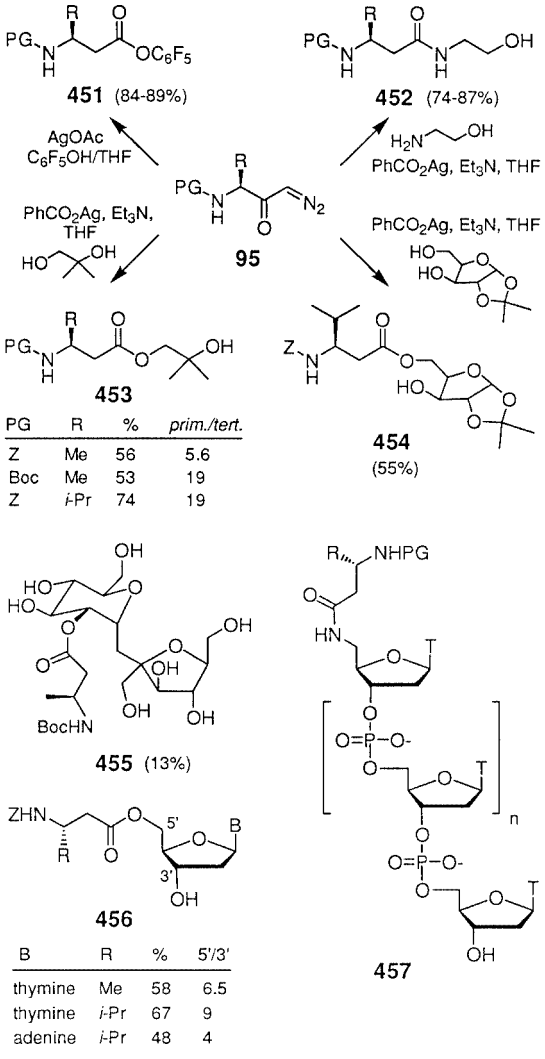


Scheme 53. Syntheses of complex molecules by way of β-amino acids

means of an Arndt–Eistert reaction.[337b] The conversion of **444** into **445** was followed by homologation, **445** → **446**, in a synthesis of (−)-indolizidine 167B (**447**), a frog skin constituent.[338] By a similar route, the indolizidine alkaloid (−)-monomorine was obtained from L-alanine.[338] (Additional examples of alkaloid synthesis will be reviewed in Section 4.2.4.). The homologue **449** of Boc-α-aminoadipic acid benzyl ester (**448**) has been considered as a building block for the preparation of nucleic acid analogues **450** with a flexible polyamide backbone.[339]

Although the Wolff rearrangement of **95** is most often performed in the presence of water or methanol, other nucleophiles can be used to scavenge the intervening ketenes. Silver ion-catalyzed decomposition of **95** in the presence of pentafluorophenol gave pentafluorophenyl esters of β-amino acids (**451**) in good yield and purity (Scheme 54).[340] (For applications of **451** in peptide synthesis, see below). The chemoselectivity of the acylation reaction was examined with 2-aminoethanol, which reacted exclusively at the amino group with formation of **452**.[341] The primary hydroxy group of 3-methylbutane-1,3-diol was acylated preferentially (→ **453**), the selectivity being affected by the bulk of R and PG. Isopropylidene-D-xylofuranose provided an example of discrimination between primary and secondary OH groups: **454** was obtained in 55% yield with a selectivity of 19:1.[341] Hexoses with only one unprotected OH group were efficiently acylated, e.g. α-D-galactose bis-acetonide with Z-Ala-CHN_2 (76%).[91] Fructose produced a complex product mixture from which 13% of **455** was isolated.[341] 2′-Deoxynucleosides were acylated at 5′-OH in preference to 3′-OH, with formation of **456** as the major product. Adenosine was acylated rather indiscriminately whereas isopropylidene-protected adenosine gave 48% of the 5-homoalanyl derivative.[341] Amino-modified oligonucleotides were acylated both in DMF solution and by solid-phase techniques to obtain conjugates **457** (75% with $n = 6$, R = Me, and PG = Z).[342]

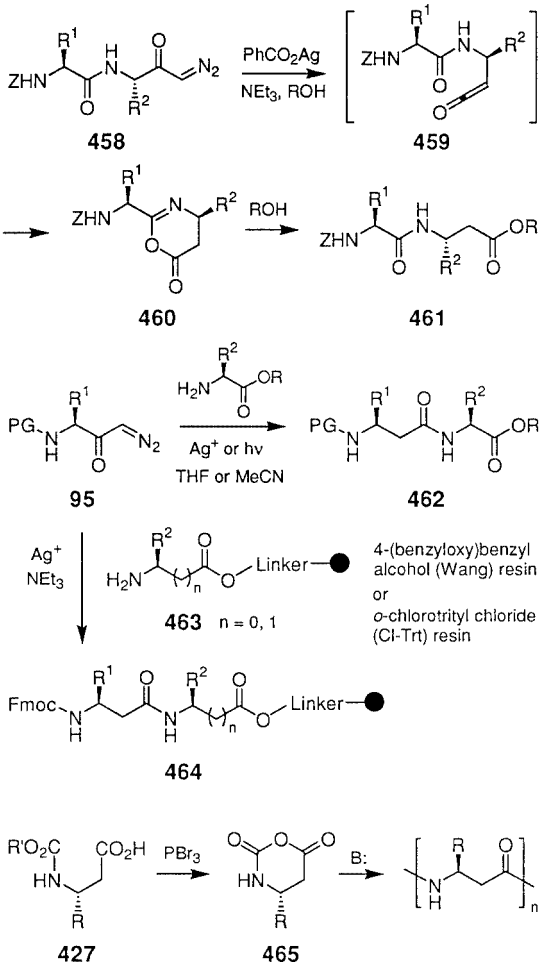
The incorporation of β-amino acids into peptides has been achieved by the following methods: a) Homologation of the C-terminus parallels the homologation of α-amino acids (Scheme 52) and has been performed analogously. Ketenes **459** generated by Wolff rearrangement of **458** were found to give **461** by way of 4,5-dihydro-2,3-oxazin-6-ones **460** which react rather slowly (Scheme 55).[343] b) Wolff rearrangement with concomitant acylation of the peptide *N*-terminus, **95** → **462**, has been used more frequently. Various β-homoarginine dipeptides were prepared by photolysis of



PG	R	%	prim./tert.
Z	Me	56	5.6
Boc	Me	53	19
Z	*i*-Pr	74	19

B	R	%	5′/3′
thymine	Me	58	6.5
thymine	*i*-Pr	67	9
adenine	*i*-Pr	48	4

Scheme 54. Acylation reactions with *N*-protected α-aminoketenes

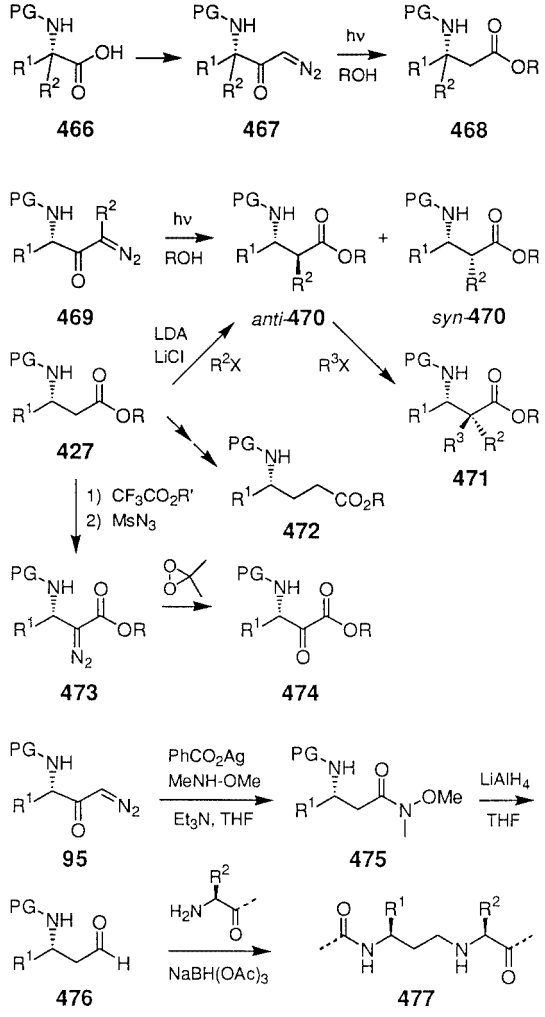


Scheme 55. Incorporation of β-amino acids into peptides

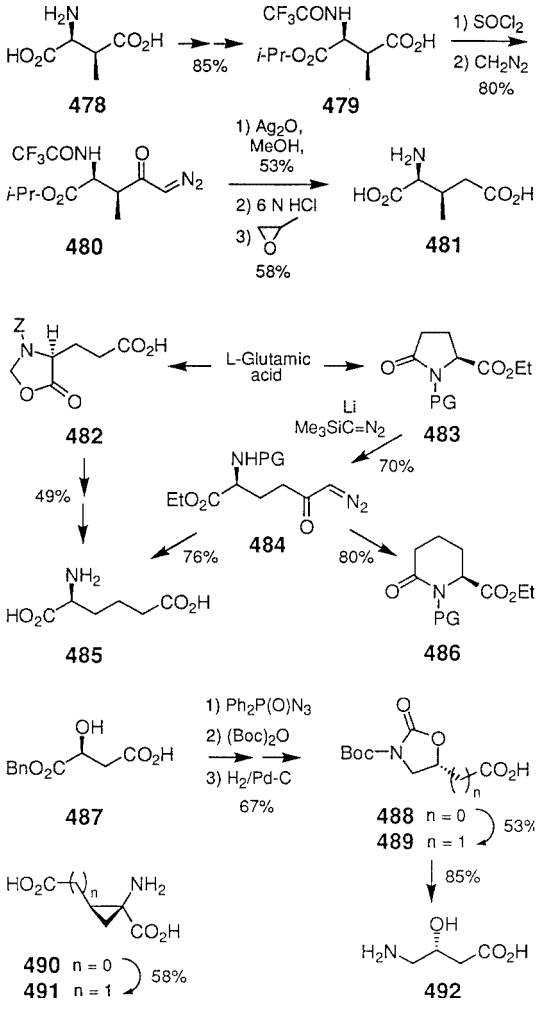
N^{α}-Boc-N^{γ}-Z,Z-Arg-CHN_2 in the presence of α-amino esters (55−76%).[335] Repeated application of the Ag^+-induced Wolff rearrangement afforded peptides containing a sequence of up to six β-amino acids.[315] Highly efficient solid phase syntheses based on Fmoc-**95** have been developed, **463** → **464**.[326,344] c) Carbamoyl-protected β-amino acids **427** have been converted into *N*-carboxyanhydrides **465** which give oligo(β-peptides) on base-induced polymerization.[345] d) Conventional fragment coupling using pentafluorophenyl or trichloroethyl esters has been widely applied in the synthesis of linear and cyclic β-peptides.[346] Short-chain β-peptides are remarkable for their high tendency to form helices. The question "how to stabilize or break β-peptidic helices" has been addressed extensively.[315,347]

The Arndt−Eistert homologation of α,α-disubstituted α-amino acids, **466** → **468**, suffers from severe problems with both the preparation of diazo ketones **467** and their subsequent photolytic rearrangement (Scheme 56).[348] Diazo ketones **469**, obtained by alkylation (KHDMS, HMPA, R^2X) of **95**, rearranged to give α-substituted β-amino acids **470** with moderate diastereoselectivity (*anti*/*syn* ≈ 6).[349] A more selective approach to *anti*-**470** involves alkylation of β-amino esters **427** while repeated alkylation afforded **471**.[91] Since homologation of N-protected β-amino acids, **427** → **472**, by way of diazo ketones turned out to be more difficult than expected (18−27% overall), other routes to **472** were preferred.[350] The synthesis of N-protected β-amino-α-keto esters **474** was achieved by diazo transfer to **427**, followed by oxidation of **473** with dimethyldioxirane.[351] *N*-Protected β-amino aldehydes **476** were prepared by Wolff rearrangement in the presence of *O*,*N*-dimethylhydroxylamine and subsequent reduction of **475** with $LiAlH_4$.[352] Reductive alkylation between the amino group of a resin-bound peptide and **476** served to introduce the amide bond surrogate, Ψ[CH_2CH_2NH]. Arndt−Eistert homologation with subsequent reduction of β-amino esters **427** to primary alcohols was involved in syntheses of (3*S*,4*S*)-4-amino-3-hydroxy-5-phenylpentanoic acid, a renin inhibitor,[323] and of several alkaloids (Section 4.2.4.). The electrophilic sulfenylation of β-amino ester enolates has also been studied.[353]

The Arndt−Eistert reaction can be applied to each carboxy group of an α-aminodicarboxylic acid. Examples for proximal carboxy groups have been given



Scheme 56. Useful transformations of β-amino acids

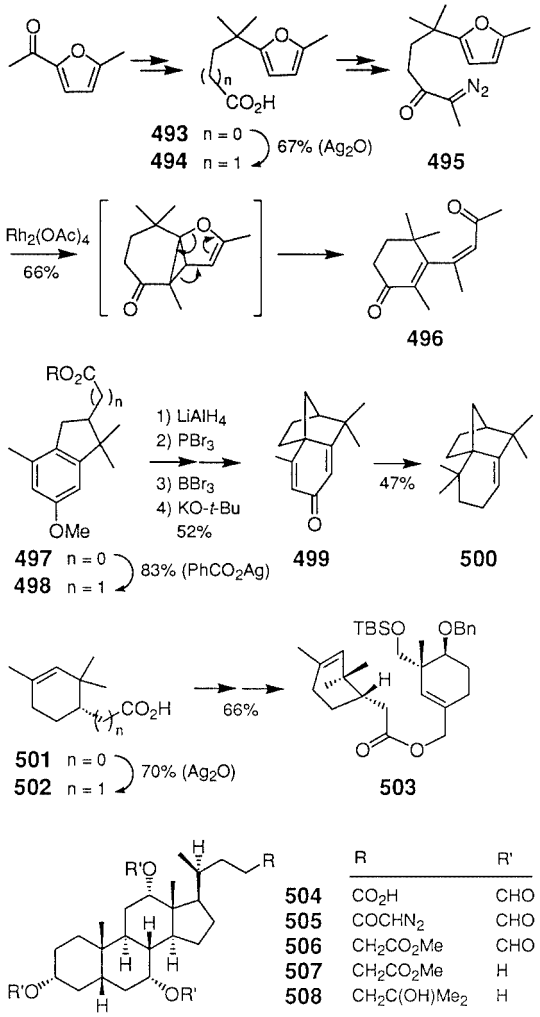


Scheme 57. Homologation of α-aminodicarboxylic acids

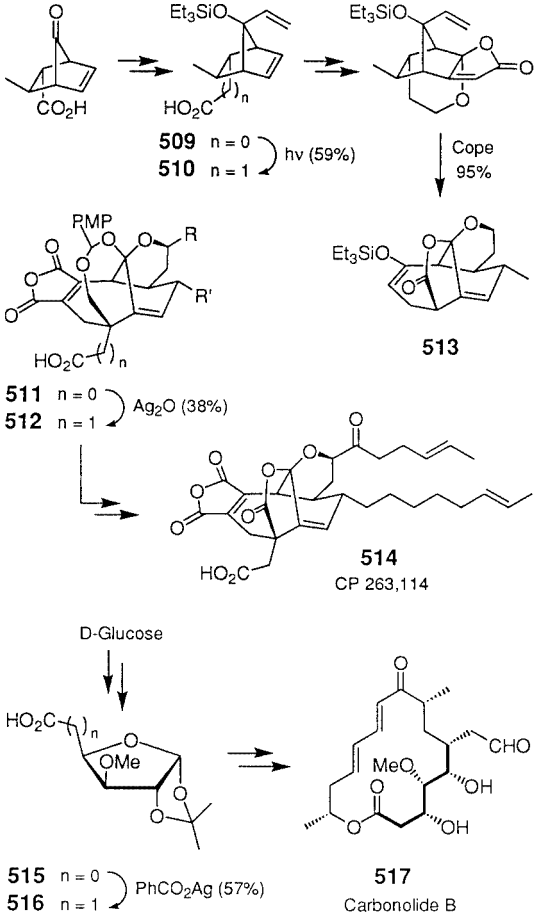
above.[328,339,346b,353] The homologation of distal carboxy groups is now addressed. (2*S*,3*S*)-3-Methylaspartic acid was protected (**478** → **479**) and converted into diazo ketone **480** (Scheme 57). Rearrangement of **480** and hydrolysis afforded (2*S*,3*R*)-3-methylglutamic acid (**481**) which served to probe the mechanism of glutamate-utilizing enzymes (Scheme 57).[354] L-α-aminoadipic acid (**485**) was synthesized from L-glutamic acid by applying the Arndt−Eistert protocol to **482**.[355] A similar route led to α-(methylamino)adipic acid.[317] Alternatively, *N*-alkoxycarbonylpyroglutamates **483** were treated with $Me_3SiC(Li)N_2$ to obtain **484**. Ultrasound- and Ag^+-assisted rearrangement of **484** in water−THF gave (protected) **485** whereas 6-oxopipecolates **486** were formed in anhydrous conditions (yields refer to PG = Boc).[356] (*S*)-Malic acid-1-monobenzyl ester (**487**) was converted into **488** for homologation, **488** → **489**. Hydrolysis of **489** afforded 4-amino-3-hydroxybutanoic acid (**492**, GABOB), a compound of pharmacological importance due to its function as a neuromodulator.[357] Arndt−Eistert reaction of (protected) **490** provided (−)-(*Z*)-2,3-methano-L-glutamic acid (**491**), a metabotropic glutamate receptor (mGluR) agonist.[358]

4.2.3. Homologations in the Field of Terpenes, Steroids, and Macrolides

Diverse modes of diazo ketone decomposition were employed to synthesize (*Z*)-4-oxo-β-ionone (**496**) (Scheme 58).[359] Arndt−Eistert reaction, **493** → **494**, was followed by a $Rh_2(OAc)_4$-catalyzed intramolecular addition of diazo ketone **495**, which led to cleavage of the furan ring.[360] In a synthesis of isolongifolene (**500**), homologation of **497** (R = H) to give **498** (R = Me), set the stage for Ar_1-5 cyclization with formation of **499**, the precursor of **500**.[361] The preparation of **503**, a building block for the antitumor diterpene taxol®, proceeded from **501** by way of the homologous acid **502**.[362] 3α,7α,12α-Triformyl-5β-cholanic acid-(24) (**504**) was converted into 5β-cholestan-3α,7α,12α,25-tetrol (**508**) by way of the intermediates **505**−**507**.[363] Homologations of *all-trans*-retinoic acid ($PhCO_2Ag$, 45%)[364] and of abietic acid (Ag_2O, 16%)[365] have also been reported. The low yield of homoabietic acid illustrates the drawbacks of conventional Arndt−Eistert protocols, if applied to carboxylic acids with quaternary α-carbons. Novel methodology, involving acyl mesylates, has been designed to solve such problems.[310]



Scheme 58. Arndt−Eistert reactions aiming at terpenes and steroids



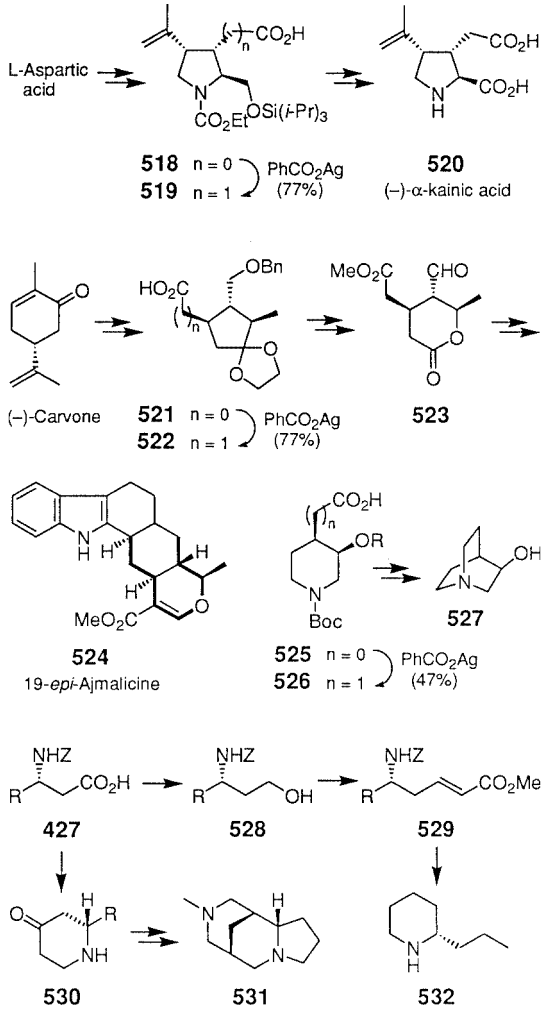
Scheme 59. Homologations leading to CP 263,114 and Carbonoide B

The fungus product CP 263,114 (**514**) is an inhibitor of farnesyl transferase which could be used to control the level of serum cholesterol. The Arndt−Eistert reaction of **509**, leading to **510**, was an essential step in a synthesis of the core fragment **513** (Scheme 59).[366] The homologation **511** → **512**, using newly developed methods,[310] was performed at an advanced stage of Nicolaou's total synthesis of **514**.[367] The C1−C6 segment of carbonolide B (**517**) was prepared from D-glucose by way of furanuronic acid homologation, **515** → **516**.[368] (Additional examples of macrolide synthesis will be given in Section 4.2.5).

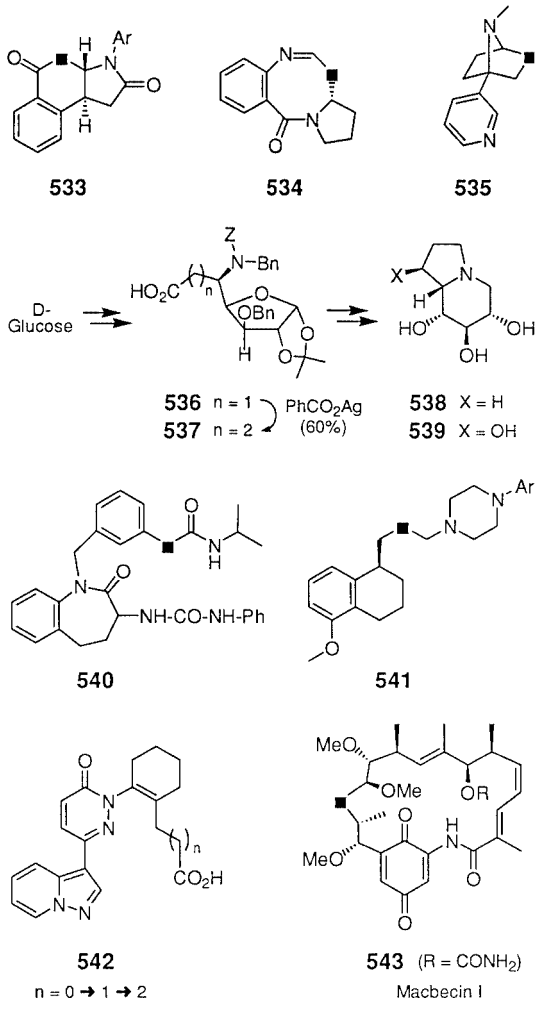
4.2.4. Homologations Directed to Alkaloids and Heterocycles

The Arndt−Eistert reaction **518** → **519** was an important step on the route from aspartic acid to α-kainic acid (**520**), which displays powerful neuroexcitatory and anthelmintic properties (Scheme 60).[369] Compound **523**, a building block for heteroyohimbine alkaloids such as 19-*epi*-ajmalicine (**524**), was made from (−)-carvone by way of **521** and **522**.[370] Hydroxyacid **525** (R = H), obtained stereoselectively by yeast reduction of the corresponding ketone, was protected and converted into **526** (R = MOM), a precursor to (*R*)-quinuclidin-3-ol (**527**).[371] β-Amino acids **427**, readily obtained by homologation of α-amino acids (Section 4.2.2.), were employed in many syntheses of alkaloids, e.g. **447** (Scheme 53). (*S*,*S*)-Homaline, an alkaloid isolated from the leaves of *Homalium* species, was obtained from β-HPhg by way of the β-lactam.[372] Addition of **427** to methyl acrylate, followed by Claisen condensation, afforded **530** which was used in the preparation of sparteine-like diamines, such as **531** (from proline).[373] γ-Amino alcohols **528** are conveniently made from β-amino acids **427** by $NaBH_4$ reduction of mixed anhydrides. Condensation of **528** with aldehydes provided tetrahydro-2*H*-1,3-oxazines,[374] and **528**, R = $CH_2CH_2CO_2CH_2Ph$, was used in an approach to the frog alkaloid gephyrotoxin.[375] MnO_2-oxidation of **528**, followed by Wittig reaction, provided **529** which was used in syntheses of (*S*)-(+)-coniine (**532**) and (*S*)-(−)-coniceine.[376]

Arndt−Eistert reactions of proline derivatives were instrumental to syntheses of azasteroid mimics **533**,[377] novel benzodiazocines such as **534**,[378] and conformationally constrained nicotine analogues, e.g., **535**.[379] (Scheme 61; the carbon atoms introduced in the course of homologation are marked by solid squares). D-Glucose was the starting mat-



Scheme 60. Arndt−Eistert reactions en route to alkaloids

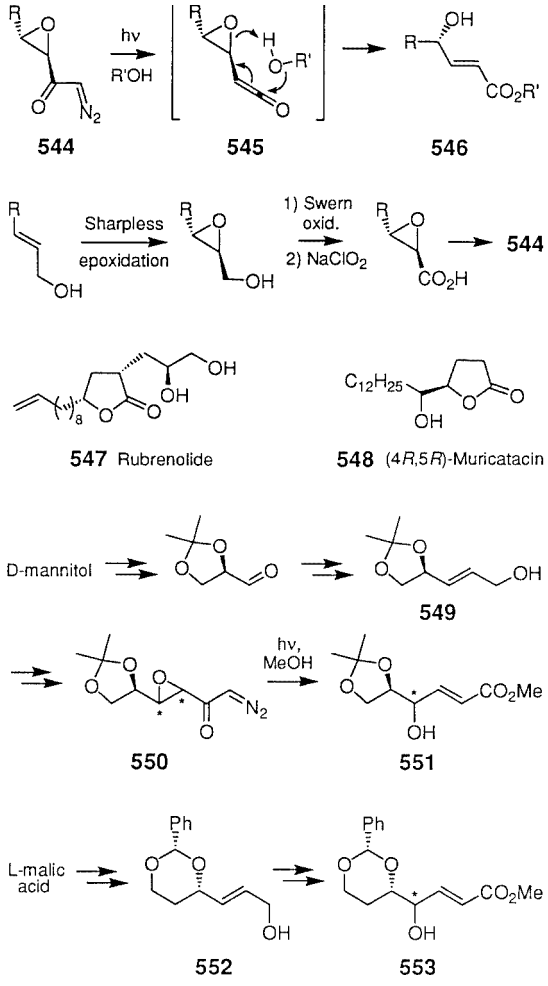


Scheme 61. Homologations directed to alkaloids and heterocycles

erial in a synthesis of 1-deoxycastanospermine (**538**) which involved the homologation of **536** to give **537**.[380] Castanospermine (**539**) shows promising glycosidase inhibitory activity. Arndt−Eistert reactions were used in syntheses of **540** (a neuropeptide Y receptor antagonist),[381] **541** (optimized for 5-HT1A receptor affinity),[382] and **542** (evaluated for adenosine A(1) and A(2a) receptor binding activities).[383] The precursor for the quinoid nucleus of ansamycin antitumor antibiotics, such as **543** (Macbecin I), was obtained by homologation of 2,5,1′-trimethoxy-2′-methyl-3-nitrobenzenepropanoic acid.[384]

4.2.5. Rearrangement of α,β-Epoxy Diazomethyl Ketones

Oxiranecarboxylic acids (glycidic acids) can be converted into α,β-epoxy diazomethyl ketones (**544**) by way of mixed anhydrides.[385] Photolysis of **544** in the presence of alcohols was found to give γ-hydroxy-α,β-unsaturated esters **546**.[386] Nucleophilic attack of alcohol R′OH on ketene **545** is thought to open the epoxide (Scheme 62). The *E* alkene esters **546** are the predominant products but small amounts (≤ 10%) of *Z* esters are also formed.[387] Nonracemic substrates are readily prepared from allylic alcohols using the Sharpless epoxidation, followed by conversion of the oxiranecarbinols to carboxylic acids. The photo-rearrangement



Scheme 62. Rearrangement of α,β-epoxy diazomethyl ketones

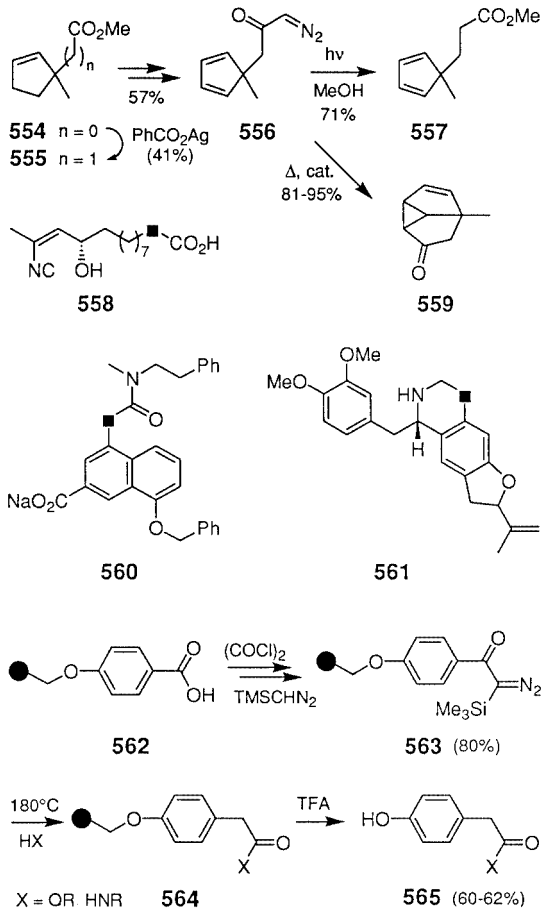
544 → **546** proceeds with retention of configuration at C-4.[387,388] Hydrogenation of **546** and subsequent lactonization afforded chiral 4-alkyl-γ-lactones [R = $(CH_2)_nCH_3$, n = 2−12],[388] as well as rubrenolide (**547**), a constituent of the Amazonian tree *Nectandra rubra*.[389] The macrolides synthesized by this approach include the C14−C23 subunit of cytochalasin B,[390] patulolide C (isolated from *Penicillium urticae*),[391] colletallol (isolated from *Colletrichum capsici*),[392] and pyrenophorol.[393]

Two adjacent hydroxyl groups of defined configuration, as in the naturally occurring γ-lactone muricatacin (**548**),[394] were introduced by sequential photorearrangements of **544** [R = $C_{12}H_{25}$ in the first step, R = $C_{12}H_{25}CH(OH)$ in the second step]. Alternatively, D-mannitol-derived **550** has been employed for the synthesis of 4,5,6-trihydroxy-2-alkene esters, such as the macrolide (−)-aspicilin (isolated from *Aspicilia gibbosa*).[395] 4,5,7-Trihydroxy-2-alkene esters **553** were constructed from the L-malic acid-derived intermediate **552**.[396] The configuration of the products depends on the tartrate auxiliary used in the Sharpless epoxidation of **549** and **552**, rather than the chiral center at C-5 (≥ 90% *de*). Therefore, the configuration at C-4 of **551** and **553** can be chosen at will.[396]

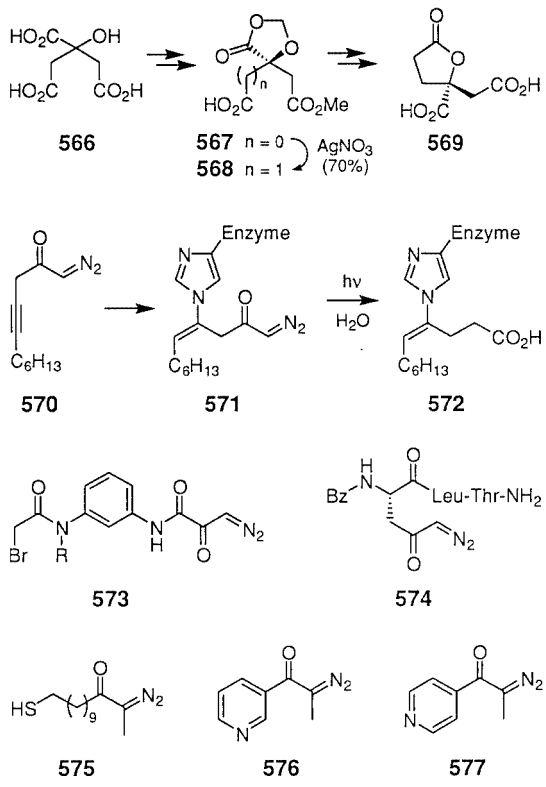
4.2.6. Miscellaneous Homologations

Ring strain of the migrating group is compatible with the Wolff rearrangement, as attested by the homologation of cubanecarboxylic acid.[397] Recent reports of efficient Arndt−Eistert reactions with cyclopropanecarboxylic acids include 2-alkenyl,[89b,398a] 2-aryl,[398b] 2-acylamino,[358] and spirocyclic derivatives.[398c] The presence of double bonds in the migrating group is also tolerated, in accordance with earlier results.[399] Thus, photochemical Wolff rearrangement of **556** afforded the homologous ester **557**, whereas thermal and catalytic decomposition led to the tricyclic ketone **559** (Scheme 63).[400] In the course of the synthesis of **556**, the Arndt−Eistert reaction **554** → **555** was effected by silver benzoate.[400] Undec-10-enoic acid was homologated en route to **558**, the desepoxy parent of the antibiotic aerocyanidin.[401] *all-cis*-Heneicosa-6,9,12,15,18-pentaenoic acid was also prepared by way of Arndt−Eistert reaction ($PhCO_2Ag$, 70%), in order to compare its biological properties with those of homologous acids present in fish oil.[402]

Arenecarboxylic acids with a variety of substitution patterns were homologated in an effort to optimize the GnRH antagonist **435** (Scheme 52).[403] The Arndt−Eistert reaction was successfully applied to 2′-methoxy-1,1′-binaphthyl-2-carboxylic acid (Ag_2O, EtOH, 60−70 °C, 82%).[404] Wolff rearrangement of the appropriate diazo ketone in the presence of *N*-methyl-*N*-(2-phenylethyl)amine (*hν*, 87%) was used in a synthesis of RG-14893 (**560**), a leukotriene receptor antagonist.[405] A "Wolff ketene" was scavenged with aqueous ammonia ($AgNO_3$, 100 °C, 70%) on a route to the tetrahydropapaverine-rotenone hybrid **561**, a potential inhibitor of electron transport.[406] A solid-phase procedure, **562** → **565**, which involves attachment to the Wang resin followed by thermal Wolff rearrangement, was de-



Scheme 63. Homologation of olefinic and aromatic carboxylic acids



Scheme 64. Rearrangements of aliphatic and immobilized diazoketones

veloped for the homologation of 4-hydroxybenzoic acid.[407]

In the aliphatic series, twofold homologation of 2-methylbutanoic acid by way of **89** (Scheme 16) was used to assign the configurations of sesterterpenoids from the diatom *Haslea ostrearia*.[408] A synthesis of (−)homocitric acid γ-lactone (**569**) from citric acid (**566**) has been reported in which resolution was achieved at the stage of **567**, prior to the Arndt−Eistert reaction, **567** → **568** (Scheme 64).[409] 1-Diazo-4-undecyn-2-one (**570**) was shown to inactivate the key enzyme in the biosynthesis of unsaturated fatty acids in *Escherichia coli*, β-hydroxydecanoyl thiol ester dehydrase, through *N*-alkylation of histidine-70 (→ **571**). Photoinduced Wolff rearrangement, **571** → **572**, involves attack of the ketene by one of two bound water molecules, as indicated by X-ray analysis.[410] Thiol specific photoactivatable cross-linking agents, such as **573**, were developed by combining the bromoacetyl function and the diazopyruvamide group.[411] Although Wolff rearrangements have been performed with simple derivatives of **573** and **574**,[412] the reactivity of the peptide-bound agents is not obvious.

A gold electrode modified with the diazo ketone **575** was prepared, and its photochemistry was investigated in the presence of methanol.[413] Grazing angle IR spectroscopy showed gradual loss of the diazo absorption, concomitant with changes in the carbonyl region indicating the formation of a methyl ester. Diazo ketones **576** and **577** were photolyzed as stable monolayers on single crystal Pt(110) surfaces.[414] The ketene absorption thus generated was stable to continued irradiation at 300−400 nm but disappeared when exposed to methanol. The data suggest that diazo ketones could be useful as photoreactive templates for surface modification.

4.3. Ring Contraction

4.3.1. Scope and Limitations

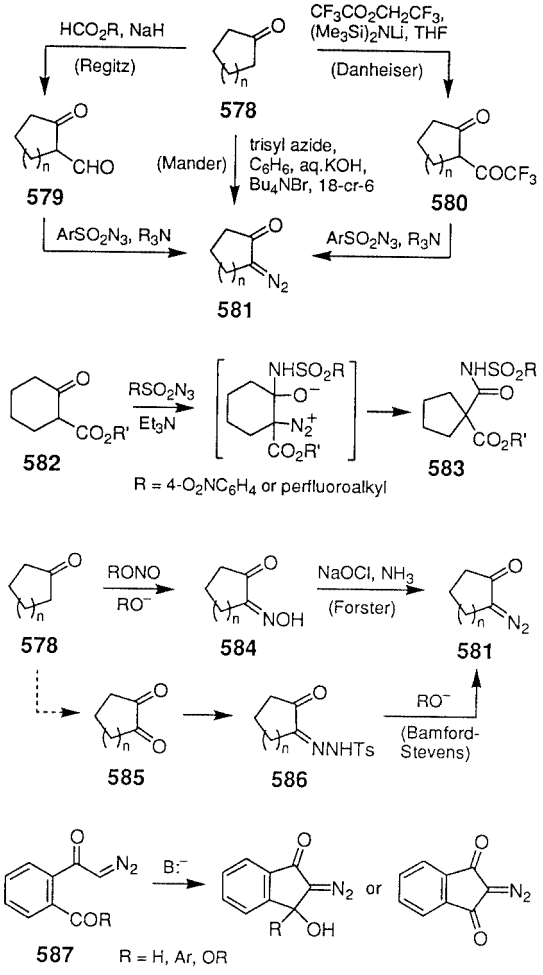
Diazo transfer from sulfonyl azides to enolates is the standard route to cyclic α-diazo ketones.[13] β-Diketones are efficiently converted into 2-diazo-1,3-diketones on exposure to tosyl azide in the presence of a weak base. Although triethylamine in acetonitrile is routinely used, K_2CO_3/MeCN,[415] Cs_2CO_3/THF,[416] Al_2O_3/KF/THF,[417] and $KF{\cdot}2H_2O/CH_2Cl_2$[418] were recommended as alternatives. Several sulfonyl azides were found to offer advantages in safety and facility of product separation over tosyl azide, the most popular diazo transfer reagent.[419] Polymer-bound arenesulfonyl azides appear to be suitable for column operation.[420]

Diazo transfer to the α-position of cycloalkanones requires the presence of a strong base which, in most cases, leads to undesired products. However, when 2,4,6-triisopropylbenzenesulfonyl azide (trisyl azide) is employed,

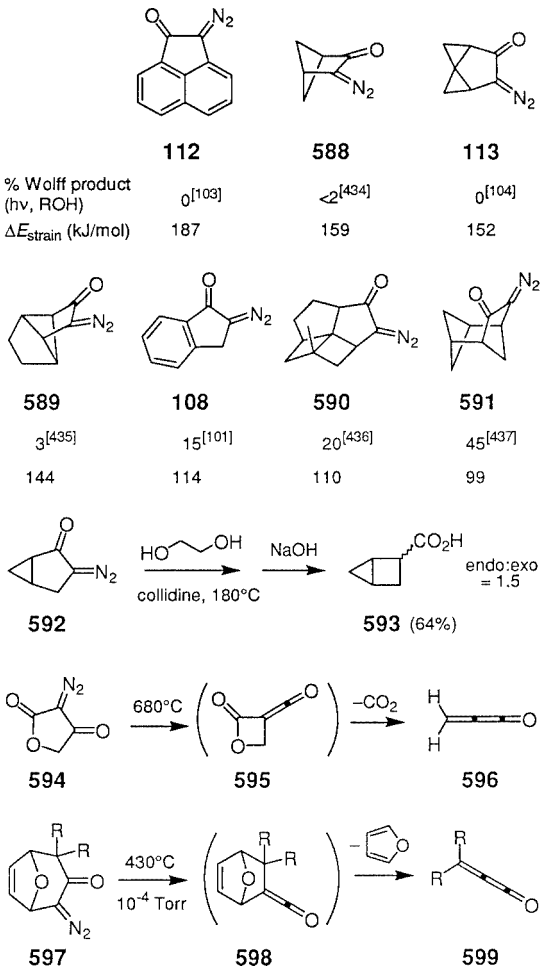
hindered cyclic ketones can be converted into α-diazo derivatives under phase-transfer conditions (Scheme 65).[421] The "Mander procedure" is very useful, except for substrates sensitive to aqueous basic hydrolysis (e.g., esters). Direct diazo transfer has also been accomplished by the addition of an equimolar mixture of a ketone and trisyl azide to a solution of potassium *tert*-butoxide in THF at −78 °C.[422] The best diazo transfer results are usually obtained by "activation" of ketones **578** in the form of α-formyl derivatives **579** ("Regitz procedure")[13c,13d] or trifluoroacetyl derivatives **580** ("Danheiser procedure").[314] Arenesulfonyl azides and triethylamine are the standard reagents used for "deacylating diazo transfer" to **579** and **580**. Excellent yields of **581** were obtained with the more reactive (but more hazardous) methanesulfonyl azide.[314a,423,424] 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) was recommended for sterically hindered α-formyl ketones **579**.[425] The acyl groups of **579**, **580**, and α-benzoyl ketones,[426] are transferred to the sulfonamide leaving group. β-Keto esters behave differently toward sulfonyl azides, as shown for **582**.[427] Diazo ketones were not obtained, although ring contraction did occur (→ **583**).

Other routes to cyclic diazo ketones are complementary to diazo transfer. The Forster reaction involves oxime formation at the α-position of a cyclic ketone, **578** → **584**, followed by treatment with chloramine, **584** → **581**. This method has been used extensively in the preparation of α-diazo ketones from indanones[428,429] and steroidal ketones.[430,431] The Bamford−Stevens reaction converts α-diketones **585** into α-diazo ketones **581** by cleavage of the derived tosylhydrazones **586** with base. This route is particularly useful if the diketones can be obtained by oxidation of hydrocarbons such as acenaphthene and phenanthrene.[103] Diazo transfer to beyeran-16-one failed whereas SeO_2-oxidation followed by Bamford−Stevens reaction afforded the desired diazo ketone.[432] As a rule, ring closure is not a practical approach to cyclic α-diazo ketones. However, diazoacetophenones **587** can undergo aldol- and Claisen-type reactions with *ortho* carbonyl groups.[433]

Photolysis is the method of choice for ring-contracting Wolff rearrangements. The *difference* in strain energy of the substrate and product, ΔE_{strain}, appears to be a limiting factor (Scheme 66; strain energies for the parent hydrocarbons were used, as computed with the MM2 force field). The yields of ring-contracted products are poor to negligible for $\Delta E_{strain} > 120$ kJ/mol, moderate for $\Delta E_{strain} = 100-120$ kJ/mol, and satisfactory for $\Delta E_{strain} < 100$ kJ/mol. The yields do not correlate with the strain energy of the products.



Scheme 65. Preparation of cyclic α-diazoketones



Scheme 66. Conditions for ring-contracting Wolff rearrangements

Whereas **112** and **113** fail to undergo Wolff rearrangement in solution, ring-contracted ketenes were observed after photolysis in an Ar matrix at 10−15 K (Section 3.4.3).[104,150] These findings indicate that nucleophilic capture of the intervening carbonyl carbenes (Section 3.4.1.) is faster than Wolff rearrangement. The computed barriers to the Wolff rearrangement of various carbonyl carbenes were found to correlate generally (but not always) with the exothermicity of ketene formation.[141]

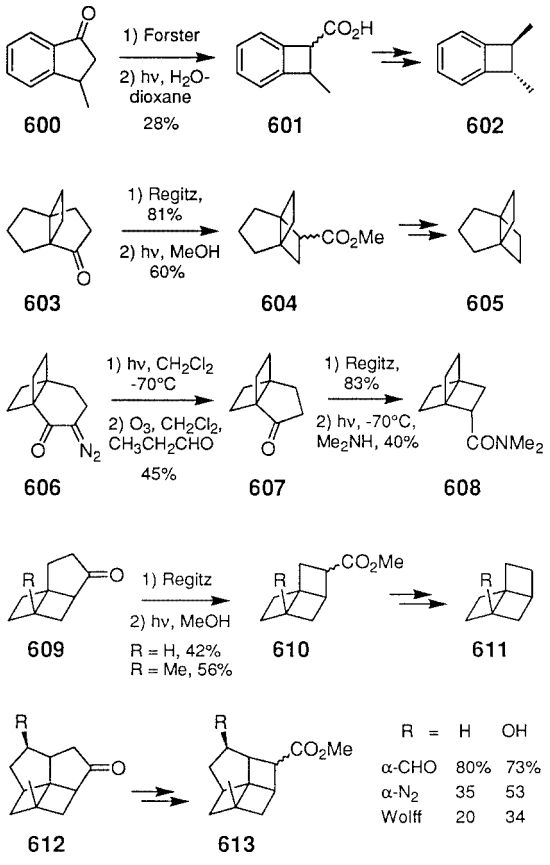
Few thermal reactions of cyclic diazo ketones have been reported. Photolysis of **592** in methanol/ ether gave only 20% of ring-contracted product while thermolysis in glycol-collidine, followed by alkaline hydrolysis, afforded 64% of **593**.[438] When vapor phase pyrolysates of **594** and **597** were codeposited with Ar onto a 14−22 K window, propadienone (**596**)[439] and some derivatives **599**[440] were obtained by cycloreversion of the ring-contracted ketenes **595** and **598**, respectively.

4.3.2. Strained Carbon Frameworks

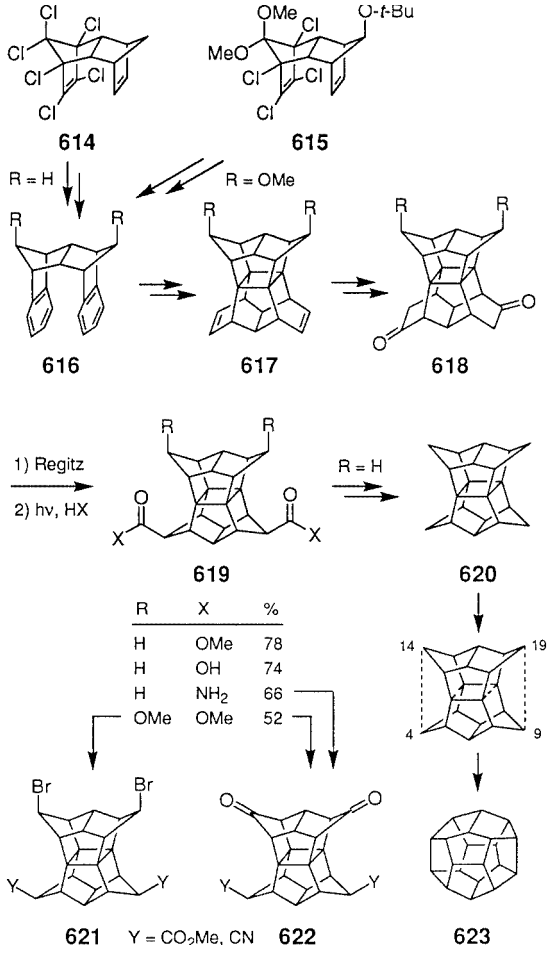
Benzocyclobutene-2-carboxylic acid (**19**, Scheme 5) was among the first strained compounds to be prepared by Wolff rearrangement,[19] and many derivatives were to follow.[19,101,441] The thermal cycloreversion of benzocyclobutenes generates *ortho*-quinodimethanes which can be trapped with dienophiles. Derivatives of **19** were thus converted into podophyllotoxin analogues.[428] The kinetics and mechanism of ring opening were probed with nonracemic *trans*-5,6-dimethylbenzocyclobutene (**602**).[429] Compound **602** was prepared from 3-methylindan-1-one (**600**), resolution being achieved at the stage of **601** (Scheme 67).

Both propellanes and fenestranes serve to explore the limits of distortion of the tetrahedral carbon atom. Ring-contracting Wolff rearrangements were key to syntheses of [3.2.2]propellane (**603** → **604** → **605**)[442] and the derivative **608** of [2.2.2]propellane (whose half-life was 28 min at 25 °C).[443] Low-temperature photolysis of **606**, followed by oxidation of the ketene intermediate to give the ring-contracted ketone **607**, is an essential of the route to **608**. Approaches to "flattened" quaternary carbon began with syntheses of tricyclo[4.2.0.0^{1,4}]octane[444] and its 6-methyl derivative[445] (**609** → **610** → **611**), went on to [4.4.5.5]fenestrane,[446] and culminated in derivatives of [4.4.4.5]fenestrane **613**, R = H[436] and OH.[447] The overall yields for the conversion of **612** into **613** (6% for R = H and 13% for R = OH) were much smaller than those for the less strained analogues, **609** → **610**.

In pagodane (**620**), the central cyclobutane ring forms part of several propellanes, and each of the quaternary carbon atoms is the center of a [5.5.5.5]fenestrane (Scheme 68). Prinzbach's synthesis of pagodane began with isodrine (**614**, formerly used as insecticide) and proceeded by way of **616**



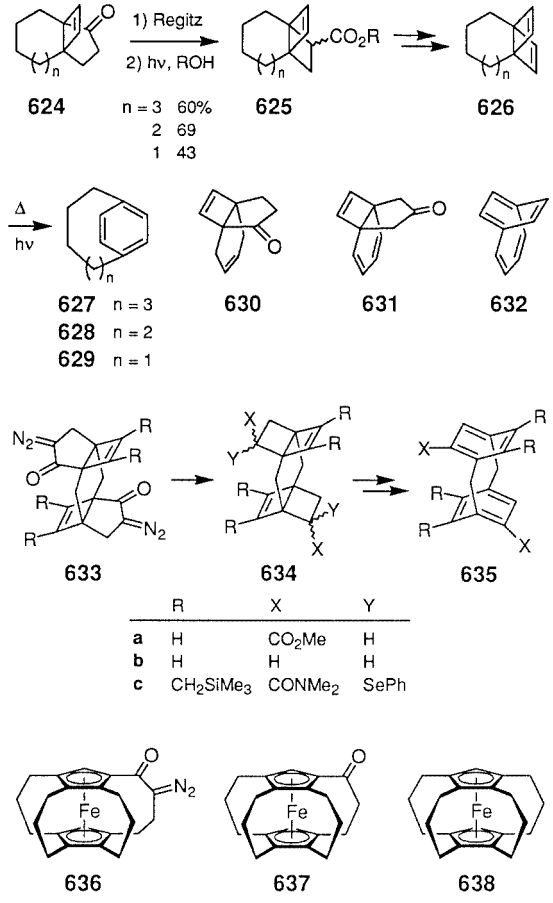
Scheme 67. Syntheses of benzocyclobutenes, propellanes, and fenestranes



Scheme 68. Synthesis of pagodane and dodecahedrane

and **617** to the diketone **618**.[448] Double ring contraction by means of Wolff rearrangement afforded **619** from which **620** was obtained. A similar route led to isopagodane, in which one "half" of **620** is rotated by 90°.[449] Pagodane displays fascinating chemistry,[450] and is isomeric with dodecahedrane (**623**). Two bonds at the periphery must be formed, and two bonds of the cyclobutane ring broken, in order to convert **620** into **623**. This reorganization has been achieved catalytically, albeit in low yield (2−8%). For a rational and efficient approach, functional groups at C-14 and C-19 were either carried through from **615**,[451] or introduced at the stage of **619**. Thus **619**, R = H, X = NH_2, was prepared by photochemical Wolff rearrangement in liquid ammonia and treated with $Pb(OAc)_2/I_2/h\nu$ to give immediately **622**, Y = CN.[452] After cleavage of the cyclobutane ring in **621** and **622**, bond formation of the S_N2- and aldol-type, respectively, proceeded smoothly.[453] A recent highlight from this field is (indirect) dehydrogenation of **623** with formation of C_{20}, the smallest fullerene.[454]

Cyclophanes are ideally suited to study benzene ring deformations.[455] Applications of the Wolff rearrangement in this field began with Allinger's syntheses of slightly strained [8]paracyclophane[456] and [7]paracyclophane.[457] The Dewar benzene route, **624** → **625** → **626**, was employed for highly strained paracyclophanes (Scheme 69). [6]Paracyclophane (**627**),[458] (*Z*)-[6]paracycloph-3-ene,[459] [6]-1,4-naphthalenophane and -anthracenophane[460] were obtained



Scheme 69. Syntheses of cyclophanes

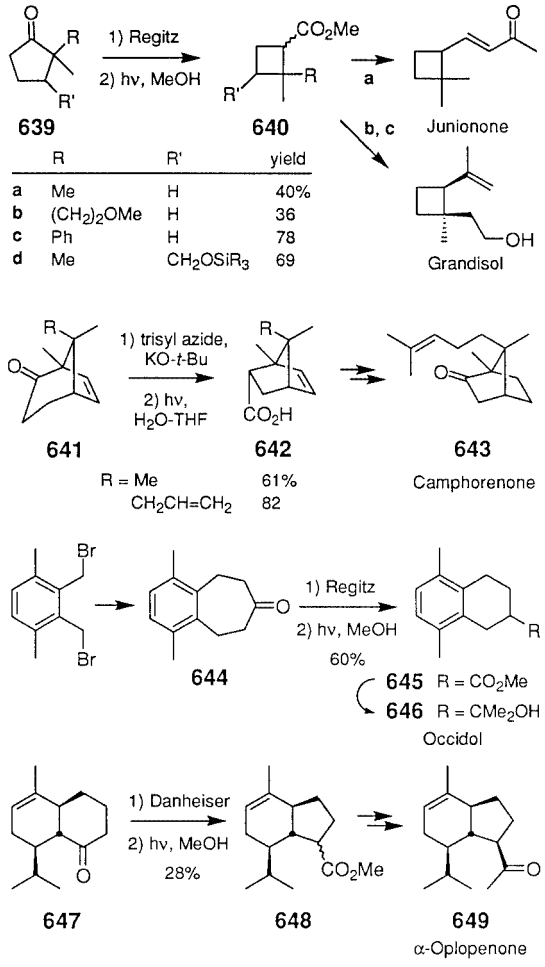
from Dewar benzene precursors at 60 °C. Even with n = 2[461] and n = 1,[462] the ring contraction approach to **626** was successful. The paracyclophanes **628** and **629** were generated photochemically from **626**. While [5]paracyclophanes have half-lives up to hours at room temperature, [4]paracyclophane was isolated in a matrix at 77 K for spectroscopic identification. The ring contractions of **630** and **631** differ strongly in yield (72 and 15%, respectively).[463] Therefore, the second double bond was introduced after ring contraction en route to the [4]paracyclophane diene **632**. Again, irradiation of the Dewar benzene precursor in an EPA glass at 77 K produced **632** as a detectable and scavengeable intermediate.[463]

The ultimate challenge in the synthesis of binuclear cyclophanes is [1.1]paracyclophane. Double ring contraction of **633a** afforded **634a**, from which **635a**[464] ($h\nu$, THF, −70 °C) and **635b**[465] ($h\nu$, EPA glass, 77 K) were prepared. Kinetic stabilization of **635** was achieved by the introduction of CH_2SiMe_3 groups. Remarkably, photolysis of **633c** in the presence of $PhSeNMe_2$ provided **634c** immediately, thus setting the stage for double bond formation.[466] The [1.1]paracyclophane **635c** was found to persist in solution up to 50 °C, and its structure was confirmed by X-ray analysis. The multi-bridged [3_4]ferrocenophane (**638**) was also prepared by means of a Wolff rearrangement.[467] The diazo ketone **636** failed to give a ring-contracted ester but afforded the ring-contracted ketone **637** (8%) when photolyzed in the presence of oxygen.

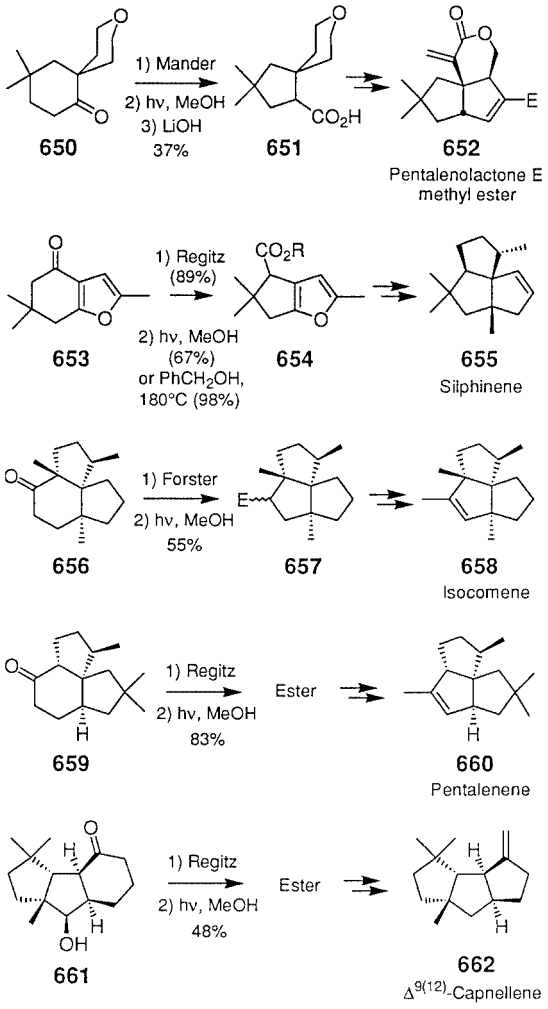
4.3.3. Natural Products and Related Targets

The Wolff rearrangement of 2-diazocyclopentanones was applied to the synthesis of monocyclic cyclobutane terpenoids.[468] Junionone, a vegetable monoterpenoid, was prepared from **639a** by way of **640a**, and planococcyl acetate, the pheromone of citrus mealy bug, from **639d** by way of **640d** (Scheme 70). Both **639b** and **639c** served as precursors for grandisol, a pheromone of boll weevil. The yield of **640b** (36% overall) was inferior to that of **640c** (78%), whereas the conversion of **640c** into grandisol was more intricate than that of **640b**. A stereoselective synthesis of camphorenone (**643**) was based on the ring contraction of bicyclo[3.2.1]oct-6-en-2-ones, **641** → **642**.[422] Wolff rearrangement was involved in the synthesis of occidol (**646**), a constituent of *Thuja occidentalis*, from **644** by way of **645**.[424] Other methods failed to convert **644** into **645**. The ring contraction **647** → **648**, targeted at the sesquiterpene ketone α-oplopenone (**649**), proceeded in moderate yield, due to inefficient diazotization.[423]

Various routes to tricyclic sesquiterpenes are based on the Wolff rearrangement. Ring contraction can occur early at a bicyclic stage, as exemplified by **650** → **651**[469] and **653** → **654**[425] (Scheme 71). Compound **651** was elaborated into pentalenolactone E methyl ether (**652**), a *Streptomyces* antibiotic, while **654** was intermediate in a synthesis of silphinene (**655**). Ring contraction of diazo ketones, followed by intramolecular 1,3-dipolar cycloaddition of nitrile oxides, was advanced as a general route to angular triquinanes such



Scheme 70. Syntheses of monocyclic and bicyclic terpenes



Scheme 71. Syntheses of tricyclic sesquiterpenes (E = CO_2Me)

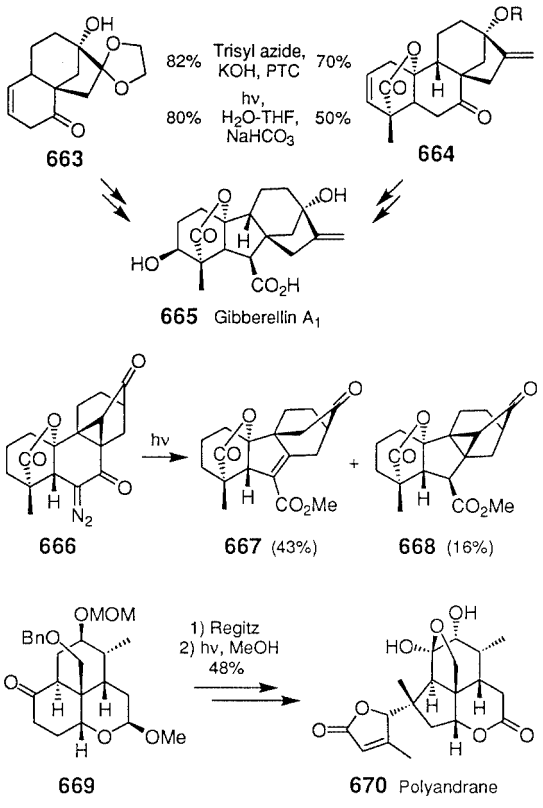
as **655**, **658**, and **660**.[470] Wolff rearrangement was involved at a late, tricyclic stage in syntheses of isocomene, **656** → **657** → **658**,[471] 3-oxosilphinene,[472] and pentalenene, **659** → **660**.[473a] The linear triquinane capnellene (**662**), isolated from the soft coral *Capnella imbricata*, was synthesized by ring contraction of **661**.[473b] Remarkably, the presence of a hydroxyl group in **661** did not seriously interfere with diazo transfer and Wolff rearrangement.

Gibberellins have received much interest as phytohormones, **665** being one of numerous variants. Again, Wolff rearrangements were performed "early" and "late" in the construction of the hexacyclic framework, as exemplified by **663**[474] and **664**,[475] respectively (Scheme 72). The lactone groups of **664** and **666** are tolerant to the Mander−Wolff reaction sequence. However, photolysis of **666** in methanol afforded **667** as the major product, with only a modest amount of the target ester **668**.[476] Fragmentation of the cyclopropane ring was avoided if the keto group of **666** was replaced with hydroxyl. In contrast to the examples given above, the lactone groups of polyandrane (**670**) were introduced after the ring contraction of **669** was completed.[477]

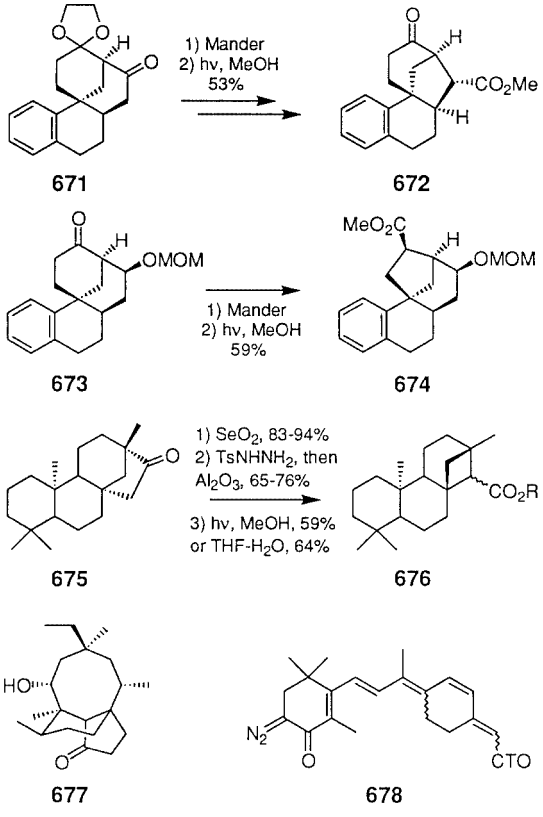
Some ring contractions in the terpene field were not carried on to specific natural products. An efficient Regitz−Wolff sequence provided access to the cedrane skeleton.[478] Asymmetric additions to chiral naphthyloxazolines served to synthesize nonracemic **671** and **673** from a common precursor (Scheme 73).[479] The ring contractions **671** → **672** and **673** → **674** open an entry to the tetracyclic ring systems of aphidicolin and scopadulcic acid, respectively.

The Wolff rearrangement has also been used to modify, rather than synthesize, natural products. Rings A[480] and D[430,431,481] of various steroids have been contracted. Most of this work is more than 30 years old, with few recent additions. It appears that biologically active products have not been obtained. The ring contraction of beyeran-16-one, **675** → **676**, served to check the proposed mechanism of the biosynthesis of bridged perhydroanthracene-type diterpenes.[432] The derivative **677** of the antibiotic pleuromutilin was ring-contracted in an attempt to reduce the rate of metabolism.[482] The photoreactive analogue **678** of *cis*-retinal was used in photoaffinity studies to determine the orientation of the chromophore in bovine rhodopsin.[483]

Some natural products containing nitrogen atoms have also been prepared by means of the Wolff rearrangement. Oxetanocin (**680**), an oxetanosyl-*N*-glycoside inhibiting the in vitro replication of HIV, was obtained from **679a** by way

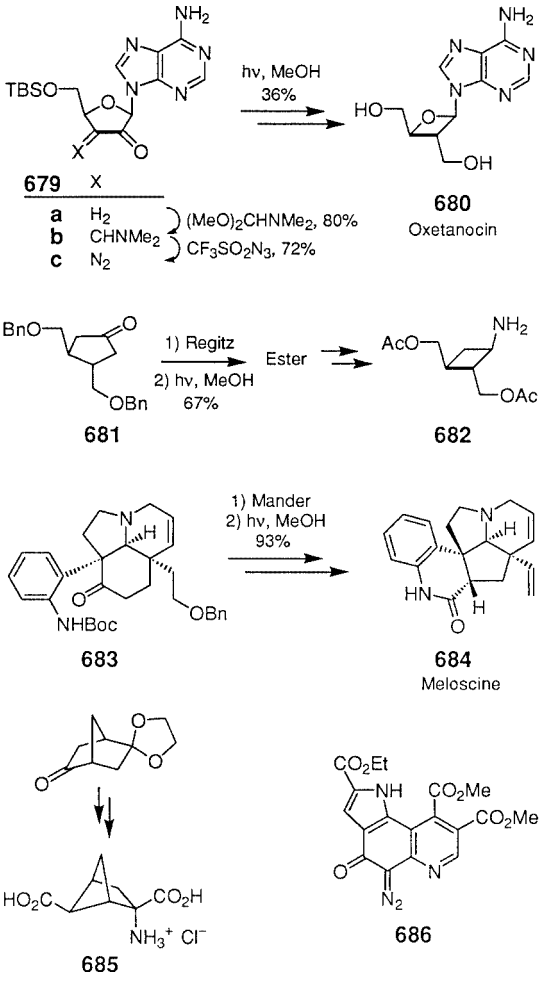


Scheme 72. Syntheses of gibberellins and polyandranes



Scheme 73. Diverse precursors and targets related to terpenes

of the enamine **679b** and diazo ketone **679c** (Scheme 74).[484] Ring contraction of **681** afforded **682**, a key intermediate for the synthesis carbocyclic oxetanocin analogues.[485] A total synthesis of the *Melodinus* alkaloid meloscine (**684**) has been achieved in which the ring contraction of **683** provided the carboxyl function for the lactam ring of **684**.[486] The ring contraction of norbornan-2,5-dione, first described by Meinwald,[487] was elaborated into a synthesis of 2-aminobicyclo[2.1.1]hexane-2,5-dicarboxylic acid (**685**), a metabotropic glutamate receptor (mGluR) agonist.[488] The diazoquinone **686** was designed for the photoaffinity labeling of dehydrogenases.[489] Wolff rearrangement of **686** in methanol gave the expected ester (76%) while photolysis in water was associated with decarboxylation (80%).

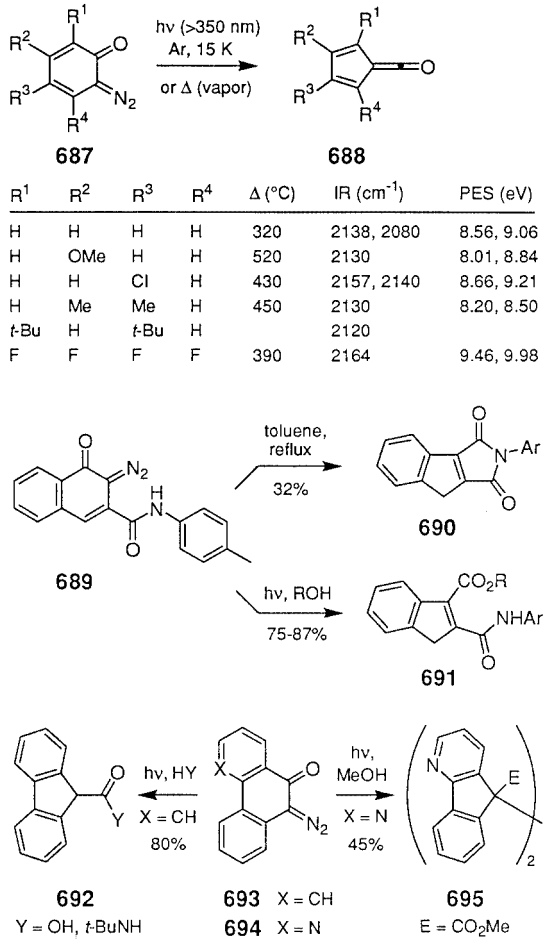


Scheme 74. Biomolecules containing nitrogen atoms

4.3.4. Diazoquinones (Quinonediazides). Photoresists

Smooth Wolff rearrangements of 6-diazocyclohexa-2,4-dien-1-ones (**687**) were observed on photolysis in Ar matrices and on vapor phase pyrolysis.[9] The fulvenones **688** were identified by IR and photoelectron spectroscopy, re-

spectively (Scheme 75). In solution, O−H and C−H insertion reactions can occur competitively with Wolff rearrangement, or even exclusively (Section 3.4.1.). The preference for a 1,2,3-oxadiazole structure, as in **7**[8] and **8**[9] (Scheme 2), does not interfere with ring contraction. Thermolyses of **689** proceeded with participation of the carboxamide group to give the imide **690** while photolyses in alcohols afforded the expected esters **691**.[490] While photolyses of 10-diazophenanthren-9-one (**693**) produced (derivatives of) 9-fluorenecarboxylic acid (**692**) in good yield,[491] ring contraction of the nitrogen analogue **694** was associated with dehydrodimerization to give **695**.[492]



R^1	R^2	R^3	R^4	Δ (°C)	IR (cm^{-1})	PES (eV)
H	H	H	H	320	2138, 2080	8.56, 9.06
H	OMe	H	H	520	2130	8.01, 8.84
H	H	Cl	H	430	2157, 2140	8.66, 9.21
H	Me	Me	H	450	2130	8.20, 8.50
t-Bu	H	*t*-Bu	H		2120	
F	F	F	F	390	2164	9.46, 9.98

Scheme 75. Wolff rearrangements of 6-diazocyclohexa-2,4-dienones

Derivatives of 2-diazonaphthalen-1-one are commercially applied in photolithography.[493] The photoresist technique is used to produce printing plates, printed circuit boards, and integrated circuits. If the solubility of a photoresist increases during irradiation, it is termed a positive resist. If the solubility decreases, it is a negative resist (Figure 3). The objective of developing is to remove the more soluble portions of the photoresist. If desired, the surface is modified further by etching (ablation of unprotected areas), stripping (removal of the remaining resist), and doping (to modify the conductivity).

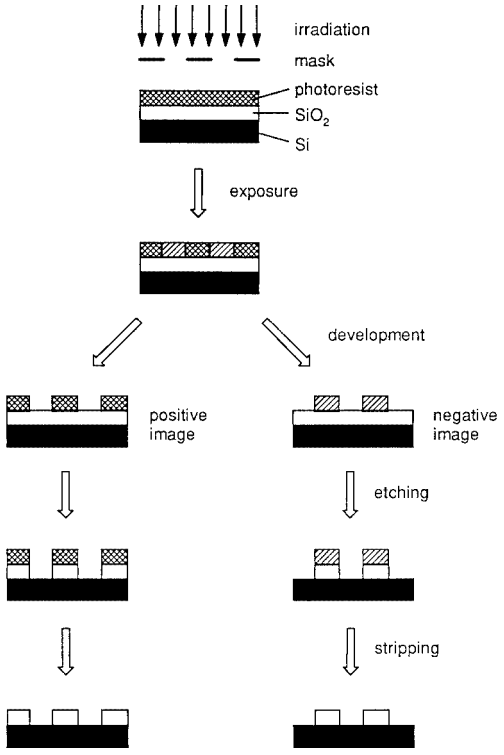
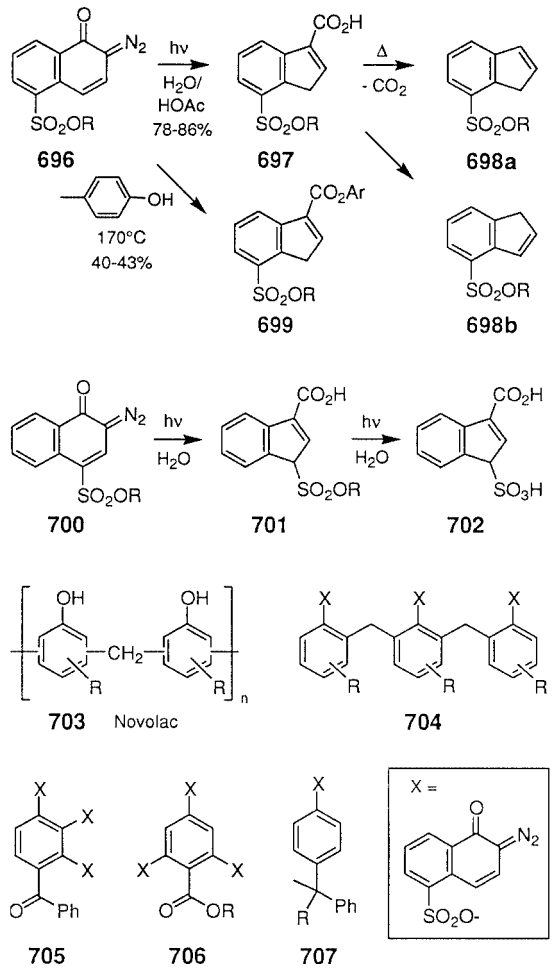


Figure 3. Schematic representation of the photolithographic process

In industrial resists, 2-diazonaphthalen-1-one-5-sulfonates (**696**) are used in combination with a novolac binder (a phenolic resin, **703**) (Scheme 76). The solubility of **703** is substantially reduced by interactions, presumably hydrogen bonds, with **696**. The photolysis of **696** proceeds according to the established mechanism (Section 3.4.4.). Good yields of indenecarboxylic acids **697** were obtained in aqueous acetic acid.[494] After irradiation of **696** in a novolac matrix at 77 K, both ketenes and ketene hydrates were detected by infrared spectroscopy.[495] Reaction of the intervening ketenes with hydroxyl groups of the novolac was modeled by decomposition of **696** in the presence of *p*-cresol to give **699**.[494] This undesired side-reaction is minimized by maintaining a sufficient concentration of water in the resist. Aqueous alkaline developers (pH 11.5−12.8) are used to dissolve the exposed areas of the resist where **696** was converted into **697** (positive photoresist). Decarboxylation of **697** at elevated temperatures, with formation of mixtures of isomeric indenes **698**,[496] strongly reduces the solubility of the exposed areas of the resist. This effect can be exploited for image reversal. In contrast to **696**, ring contraction of aryl 2-diazonaphthalen-1-one-4-sulfonates **700** is followed by light-induced hydrolysis of **701** to give sulfonic acids **702**.[494,495] In combination with an acid-dependent crosslinking agent, **700** provides negative photoresists.

The diazoquinones used in two-component resists include **705**−**707**. One-component systems, with the diazoquinone directly bound to the novolac or fragments thereof (**704**), are also known. Kinetic studies of the polyfunctional compounds **704**[497] and **705**[498] showed sequential, inde-



Scheme 76. 2-Diazonaphthalen-1-ones applied in photoresists

pendent reactions of the diazoquinone subunits. The relative quantum yields for **705** were found to be *o*-X/*m*-X/*p*-X = 0.3:0.9:1.0.[498] Light of λ = 350−450 nm is typically employed for the irradiation of diazoquinone-novolac materials. In the field of information storage resists sensitive to more energetic radiation are needed to produce ever smaller features.[499] Diazoquinones are not suited for short-wavelength UV irradiation, in contrast to 2-diazo-1,3-diketones.[182,500] However, both X-ray[501] and e-beam exposure[502] of diazoquinone-novolac resists gave promising results. Biosensors are among the most recent applications of photoresists.[503] The carboxyl groups of **697** were used to anchor peptides for specific cell-attachment or cell-detachment functions.

4.3.5. Diazodiketones

Wolff rearrangements of 3-diazo-1,2-diketones involve 1,2-shifts of acyl groups whereas alkyl or aryl groups migrate in the Wolff rearrangement of 2-diazo-1,3-diketones. Differences in migratory aptitude, which were observed in acyclic systems (Section 3.3.1., Scheme 13), apparently do not affect the ring contraction of cyclic diazodiketones. The same yield of anilide **709** was obtained when either **708** or **710** were heated in the presence of aniline (Scheme 77).[504]

The ring contraction of **714** is remarkable for both the β-lactam products **715** and the preparation of the 4-diazopyrrolidine-2,3-diones **714**, which starts from dichloromaleimides **711**.[505] The amines **713**, obtained from **712** by azide displacement and reduction, are diazotized to give **714** with concomitant hydrolysis of the vinyl chloride function. The synthesis of the bicyclic β-lactam **716** (ring contraction: 72% yield) illustrates the potential of this approach.[505] Photolysis of 3,6-bisdiazocyclohexane-1,2,4,5-tetraone (**717**) in an argon matrix led eventually to C_3O_2, by way of **718** and **719** as detectable intermediates.[506] Matrix-isolated C_4O_2 was obtained analogously from both **720** and **721**.[506a] Thia analogues of **717** and **720** were employed to generate C_5OS, C_4OS, and C_4S_2.[507]

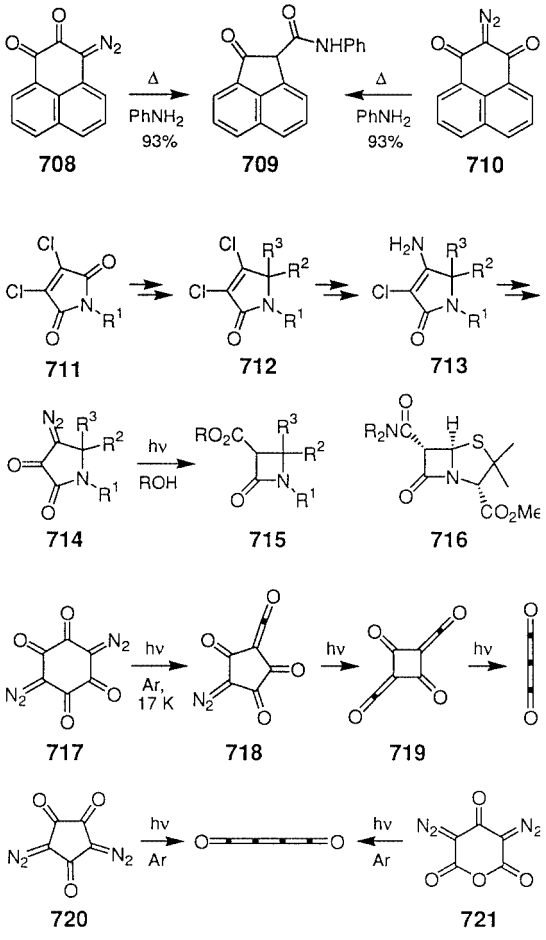
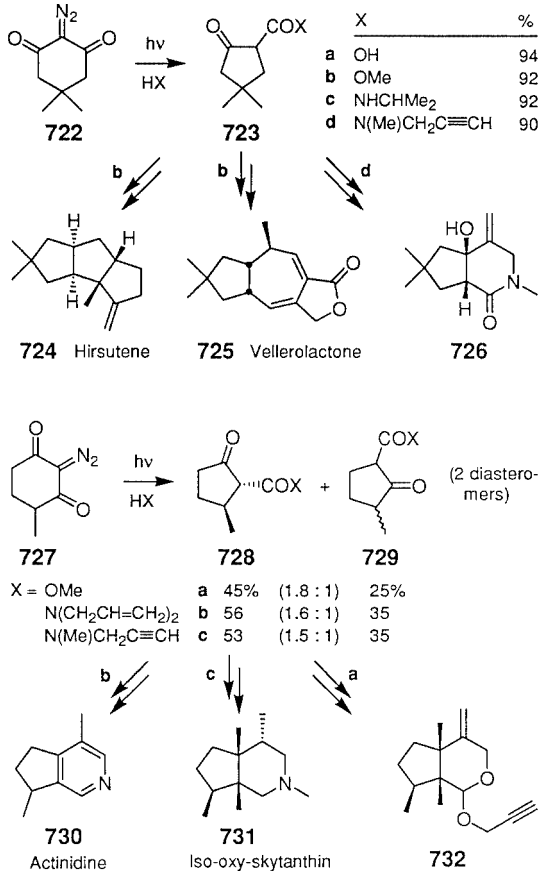


Figure 77. Wolff rearrangements of 3-diazo-1,2-diketones

Ring contractions of cyclic 2-diazo-1,3-diketones proceed smoothly with formation of β-keto acids,[90,508] esters,[36,66,90] and amides.[509] Yet relatively few applications in synthesis have been reported, probably due to the fact that β-keto esters are readily available by acylation of enolates (Claisen/Dieckmann condensation). The β-keto ester **723b**, obtained by ring contraction of 5,5-dimethyl-2-diazo-1,3-cyclohexanedione (diazodimedone, **722**), was used in syntheses of hirsutene (**724**)[510] and of the sesquiterpenoid fungal metabolites velleral and vellerolactone (**725**)[511]

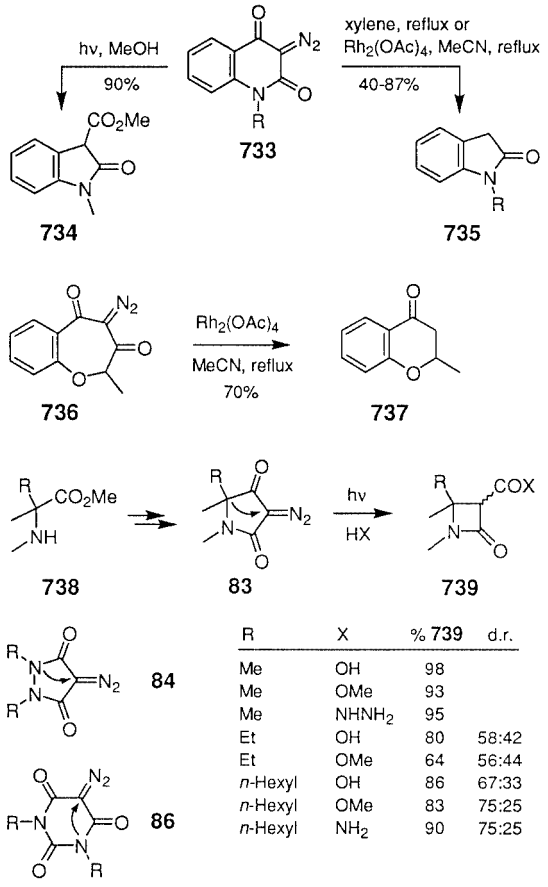
(Scheme 78). Photocyclization of **723d** and of related amides afforded δ-lactams such as **726**.[512] Moderate regioselectivity (1.5−1.8:1) was observed in ring contractions of 2-diazo-4-methylcyclohexane-1,3-dione (**727**).[513] Migration of C-4 produced *trans*-**728** while migration of C-6 gave **729** as a mixture of diastereomers. The amides **728b** and **728c** were used in syntheses of the monoterpene alkaloids actinidine (**730**)[513a,513d] and iso-oxy-skytanthine (**731**),[513b,513d] respectively, while the ester **728a** opened a short access to iridoid precursors such as **732**.[513c]



Scheme 78. Syntheses starting from 2-diazocyclohexane-1,3-diones

Photolysis of 3-diazo-1-methylquinoline-2,4-dione (**733**, R = Me) in methanol afforded the ring-contracted ester **734** (Scheme 79).[268] Thermal and rhodium(II)-catalyzed Wolff rearrangement of **733** (R = alkyl, allyl, benzyl) was accompanied by decarboxylation to give oxindoles **735**.[514] The Rh^{II}-catalyzed ring contraction, **736** → **737**, also proceeded with decarboxylation.[515] Numerous carboxy β-lactams (azetidin-2-one-3-carboxylic acids, **739**) have been synthesized from α-amino esters **738** by way of 3-diazopyrrolidine-2,4-diones **83**.[72] The ring contraction fails, however, if C-5 and/or N are not fully alkylated. Although **733** and **83** react with exclusive migration of carbon, ring contractions involving 1,2-shifts of nitrogen are also known, as in **84**[75] and **86**[77] (Section 3.3.1.).

Wavelength-dependent photoreactions of 2,4-bis(diazo)-1,2,3,4-tetrahydronaphthalene-1,3-dione (**740**) have been reported (Scheme 80).[516] In the presence of methanol, light

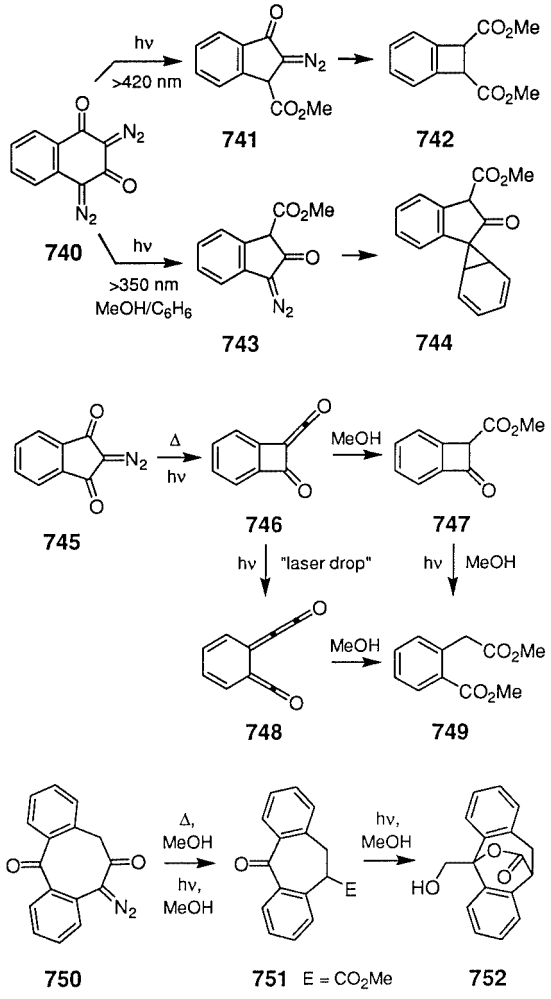


Scheme 79. Ring contraction of heterocyclic diazodicarbonyl compounds

of λ > 420 nm was found to decompose exclusively the Ar−CN_2−CO group, with formation of **741**. With light of > 350 nm, photolysis of the CO−CN_2−CO group dominated to give **743**. In an Ar matrix at 12 K, the ketene precursors of **741** (> 420 nm) and **743** (> 350 nm) were detected by IR spectroscopy. On continued irradiation, ring contraction of **741** afforded **742**. The ketocarbene derived from **743** did not undergo Wolff rearrangement but was trapped with benzene.

Gas phase pyrolysis of 2-diazoindane-1,3-dione (**745**) with methanol afforded 50% of methyl 2-oxobenzocyclobutenecarboxylate (**747**). In contrast, photolysis of **745** in methanol gave dimethyl homophthalate (**749**) as the major product.[101] Small amounts of **747** were detected after short irradiation times but were rapidly converted into **749** in a secondary photoreaction.[231] An alternate route to **749** appears to prevail under conditions of high photon flux, using the laser drop technique (small droplets of solution are excited by the focused beam of a pulsed laser).[517] The **749**:**747** ratio increased dramatically with increasing laser power, pointing to cleavage of the the initially produced ketene, **746** → **748**.

A different type of secondary photoreaction was observed with the vinylogous diazodiketone **750**.[518] When a solution of **750** in methanol was heated at reflux, 75% of the Wolff product **751** was obtained. However, **751** was not

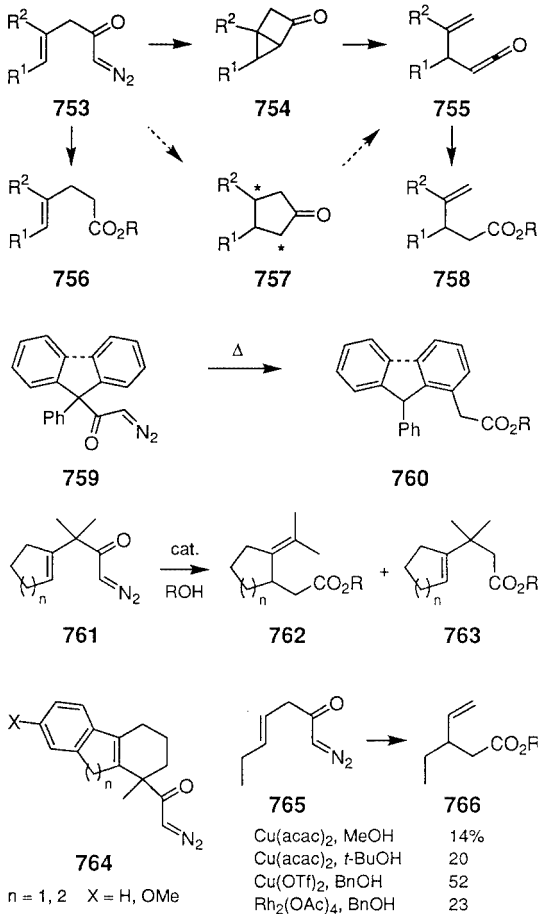


Scheme 80. Rearrangements of particular diazodicarbonyl compounds

detected after photolysis of **750**, rather the lactone **752** (35%) was formed. A rapid photoreaction of **751** with methanol (C=O → C(OH)CH_2OH), followed by lactonization, explains these findings.

5. Vinylogous Wolff Rearrangements

The decomposition of β,γ-unsaturated diazo ketones **753** can lead to products **758** that are distinguished from products **756** of the Wolff rearrangement by a formal 1,3-shift of the CH_2CO_2R group (Scheme 81). The conversion of **753** into **758** has, therefore, been termed "vinylogous Wolff rearrangement". Early evidence for an abnormal reaction path came from thermolyses of 1-diazo-3,3,3-triarylpropan-2-ones, **759** → **760**.[519] Studies with β,γ-unsaturated diazo ketones revealed that catalysis with Cu^{II} [520,521] and Rh^{II} [522] favors the vinylogous Wolff rearrangement. Thus, $CuSO_4$ and $Rh_2(OAc)_4$-catalyzed decomposition of **761** produced exclusively the vinylogous product **762**, silver oxide gave a mixture of **762** and **763**, and photolysis afforded predominantly the normal Wolff product **763** (Table 8). Similar results were obtained with **764**.[523] Insertion of the metal carbenoid into O−H bonds, −CO−CHN_2 → −CO−CH_2OR, is competitive in the catalyzed reactions.[523] "Inert" solvents, with 0.2−2% alcohol added, have been used to minimize the formation of α-alkoxyketones (Table 8). Acyclic precursors, such as **765**, gave only modest yields of vinylogous products.[520,522]



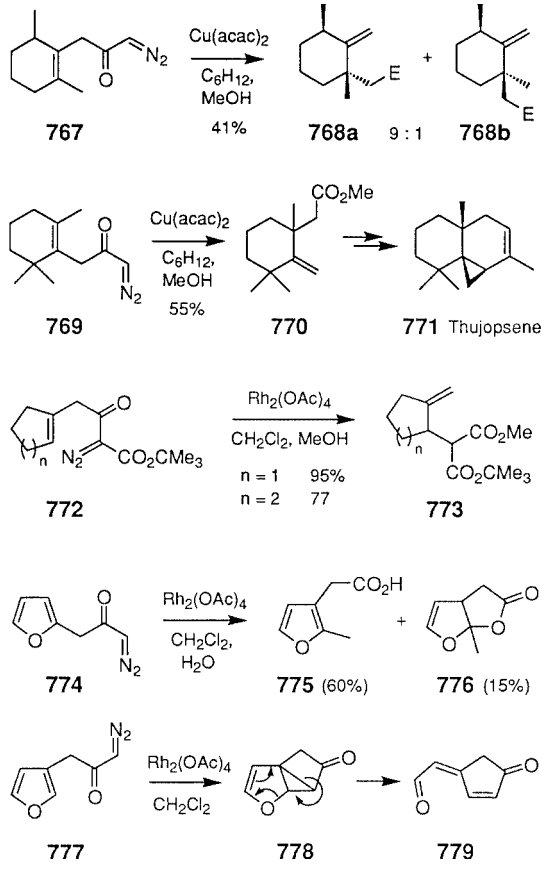
Scheme 81. Fundamentals of the vinylogous Wolff rearrangement

Table 8. Decomposition of β,γ-unsaturated diazo ketones **761**

n	Reaction conditions	**762** (%)	**763** (%)	Ref.
1	hν, MeOH	8	92	[520]
	Ag_2O, MeOH, Δ	42	58	[520]
	$CuSO_4$, cyclohexane, 2% MeOH, Δ	85	–	[520]
	$Rh_2(OAc)_4$, CH_2Cl_2, 0.5% MeOH	90	–	[522]
2	hν, MeOH	–	95	[520]
	Ag_2O, MeOH, Δ	5	50	[520]
	$CuSO_4$, cyclohexane, 2% MeOH, Δ	67	–	[520]
	$Rh_2(OAc)_4$, CH_2Cl_2, 0.5% MeOH	75	–	[522]
3	hν, MeOH	7	93	[520]
	Ag_2O, MeOH, Δ	28	61	[520]
	$CuSO_4$, cyclohexane, 2% MeOH, Δ	90	–	[520]

The vinylogous Wolff rearrangement is thought to proceed by way of intramolecular carbenoid addition to the double bond, **753** → **754**. In fact, bicyclo[2.1.0]pentan-2-ones generated by other routes were found to fragment with formation of β,γ-unsaturated ketenes.[524,525] In one case, the successive formation of **754** and **755** from **753** has been monitored by IR spectroscopy.[525] As an alternative to **754**, a dipolar/diradical species **757** has been considered. Conclusive evidence for this type of intermediate was not obtained.[525]

In vinylogous Wolff rearrangements leading to chiral products (e.g., **762** and **766**), asymmetric induction (7−31% *ee*) was achieved with nonracemic Rh^{II} complexes.[522] If diastereomers were formed, the *dr* was low, except for the conversion of **767** into **768** (Scheme 82).[526] A synthesis of thujopsene (**771**) and related terpenes used diazo ketones in three consecutive steps. The vinylogous Wolff rearrangement, **769** → **770**, was followed by homologation and intramolecular addition to obtain the skeleton of **771**.[527] 2-Diazo-3-keto esters **772** were found to rearrange with participation of the β,γ double bond, yielding **773**.[528] If the β,γ double bond is part of a heterocycle, the outcome depends critically on the position and nature of the heteroatom.[529] 1-Diazo-3-(2-furanyl)propan-2-one (**774**) underwent a vinylogous Wolff rearrangement, followed by rearomatization to give **775** and lactonization to give **776**. In contrast, 1-diazo-3-(3-furanyl)propan-2-one (**777**) produced the aldehyde **779**, due to a unique fragmentation pattern of the intervening bicyclo[2.1.0]pentanone **778**. The benzo derivatives of both **774** and **777** reacted by vinylogous Wolff rearrangement whereas the analogous benzothiophenes preferred other routes.[529]

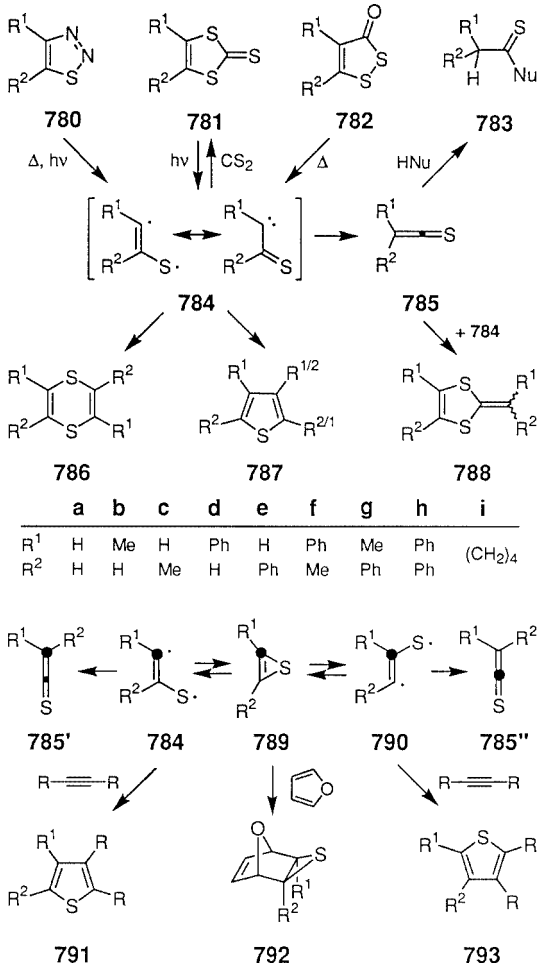


Scheme 82. Extensions of the vinylogous Wolff rearrangement

6. Hetero Wolff Rearrangements

6.1. 1,2,3-Thiadiazoles and Related Substrates

The thia analogues of α-diazo ketones prefer the cyclic structure **780** (Scheme 83), due to the lower energy of the C=S bond (≈ 570 kJ/mol) relative to C=O (≈ 800 kJ/mol). 1,2,3-Thiadiazoles **780** are generally prepared by thionyl chloride induced cyclization of sulfonyl- and acylhydrazones.[530] Thermal or photochemical extrusion of nitrogen from **780** generates intermediates **784** which have been viewed more as 1,3-diradicals than as thiocarbonyl carbenes. Reports on the direct observation of **784** are sparse. The ESR spectra produced by matrix photolysis of some 1,2,3-thiadiazoles at 100 K were similar to those of sulfur radicals.[531] On the other hand, irradiation of crystalline **780h** at 77 K gave rise to the ESR spectrum of triplet **784h**.[532] In this case, the "sulfur pattern" resulted from secondary photolytic decomposition. Upon warming, all



Scheme 83. Wolff rearrangement of 1,2,3-thiadiazoles

ESR signals disappeared with concomitant formation of the thioketene **785h**. Intermediates **784** have also been approached from 1,3-dithiole-2-thiones **781**[533] and from 1,2-dithiol-3-ones **782**.[534] Conversely, heating (200−220 °C) of **780** in the presence of carbon disulfide afforded **781**.[535]

Clean Wolff rearrangement of 1,2,3-thiadiazoles **780** was achieved by flash vacuum pyrolysis (Table 9).[536,537] Cocondensation of the pyrolysate with a solvent provided solutions of thioketenes **785** which were used for cycloadditions and reactions with nucleophiles (→ **783**).[538] Alternatively, heating of **780** in diglycol led directly to thioesters **783**, Nu = $O(CH_2)_2O(CH_2)_2OH$.[539] Photolyses of **780** give more complex product distributions, including 1,4-dithiines **786** and thiophenes **787** derived from **784** (Table 10). Thioketenes formed by Wolff rearrangement are eventually incorporated into 1,3-dithioles **788**, presumably by reaction of **785** with **784**.[540,541] Photolysis of **780d** in methanol afforded **783d** (Nu = OMe) and **788d** (≈ 1:1).[542]

Table 9. Thermolyses of 1,2,3-thiadiazoles **780**

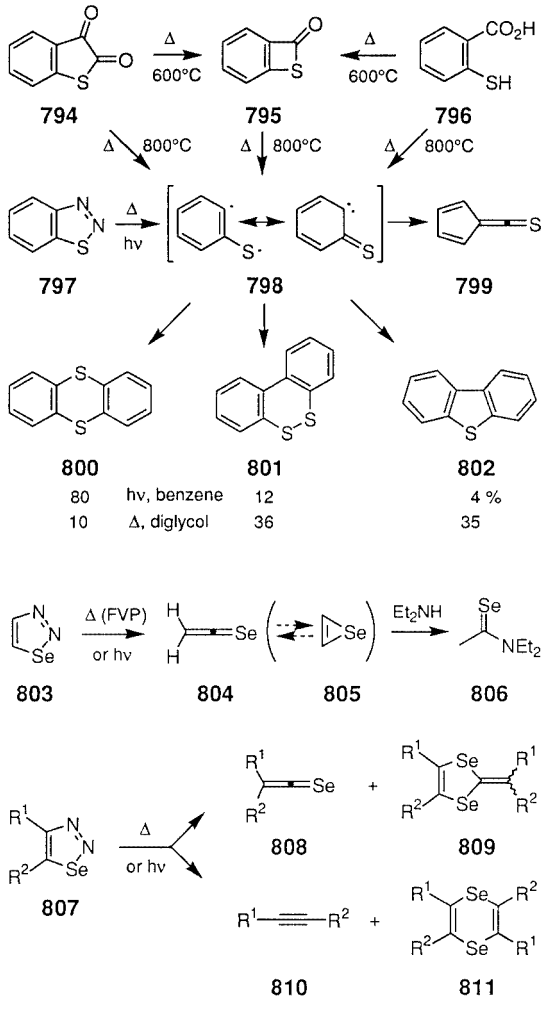
R^1	R^2	Conditions	Product	Yield (%)	Ref.
*t*Bu	H	580 °C, 10^{-4} Torr	thioketene	65−75	[536]
*t*Bu	Me	530 °C, 10^{-4} Torr	thioketene	70−80	[537]
Ph	H	580 °C, 10^{-4} Torr	thioketene	70	[536]
		230 °C, diglycol	thioester	36	[539]
Me	Ph	580 °C, 10^{-4} Torr	thioketene	71	[536]
Ph	Me	530 °C, 10^{-4} Torr	thioketene	60−70	[537]
Ph	*t*Bu	530 °C, 10^{-4} Torr	thioketene	60−80	[537]
Ph	Ph	580 °C, 10^{-4} Torr	thioketene	73	[536]
		230 °C, diglycol		–	[539]
Ph	CN	530 °C, 10^{-4} Torr	thioketene	29	[537]
$-(CH_2)_3-$		230 °C, diglycol	thioester	52	[539]
$-(CH_2)_4-$		230 °C, diglycol	thioester	95	[539]
$-(CH_2)_5-$		230 °C, diglycol	thioester	59	[539]
$-(CH_2)_6-$		230 °C, diglycol	thioester	71	[539]

Table 10. Photolyses of 1,2,3-thiatriazoles **780** in benzene

R^1	R^2	**786** (%)	**787** (%)	**788** (%)	Ref.
Ph	H	–	–	55	[540]
Ph	Ph	4	–	16	[540]
CO_2Et	H	–	4	45	[541b]
CO_2Et	Me	–	3	50	[541b]
CO_2Me	Ph	–	20	2	[540]
COMe	H	–	41	–	[541b]
COMe	Me	–	48	–	[541b]
COPh	Me	–	29	6	[541b]
$-(CH_2)_4-$		9	7	66	[541c]
$-(CH_2)_5-$		22	13	–	[541c]
$-(CH_2)_6-$		12	31	–	[541c]

Cyclization of **784** leads to thiirenes **789**. The parent thiirene (**789a**) has been prepared in an Ar matrix at 8 K by photolysis of **780a**[543,544] and **781a**.[533] Electron-withdrawing substituents (CF_3, CH_3CO, CO_2Me) appear to stabilize thiirenes.[543,545] The involvement of **789** under solution and gas-phase conditions has been probed with various techniques. Trapping with alkynes gave a single thiophene product, *either* **791** *or* **793**, from *pairs* of isomeric thiadiazoles, such as **780b**,**c**[546] and **780f**,**g**.[547] When **780**, R^1,R^2 = $-CMe_2OCMe_2-$, was photolyzed in the presence of furan, the thiirene was scavenged in a Diels−Alder reaction to give **792**.[548] The redistribution of ^{13}C labels is most informative. Irradiation of [4-^{13}C]-**780a** in EtOH/Et_2NH at 20 °C yielded the Wolff product **783a** (Nu = NEt_2) without randomization in the thioacetyl group.[549] However, scrambling of the label was observed on photolysis of **780a** in an EPA glass at 77 K[549] and on pyrolysis at 1100 K.[550] These findings suggest that thiirene can be regenerated from thioketene. The position of a ^{13}C label was completely retained in Wolff rearrangements of **780d**[542] and **780i**.[551] In contrast, **780e** reacted with partial (photolysis) to almost complete (thermolysis) 1,2-shift of sulfur.[542b] Conjugation of phenyl with the carbenic site stabilizes **784**, hence rearrangement proceeds from **790d** to **784d** (**790f** to **784f**) but not in the reverse direction.

The Wolff rearrangement of benzo-1,2,3-thiadiazole (**797**), with formation of fulvene-6-thione (**799**), was achieved by photolysis in an Ar matrix at 8 K[543b,552] and by flash pyrolysis (FVP) at 500−800 °C (Scheme 84).[536b,553] In the matrix studies, a transient was



Scheme 84. Wolff rearrangement of benzo-1,2,3-thiadiazoles and 1,2,3-selenadiazoles

assigned as benzothiirene. Fulvene-6-thione (**799**) was also obtained by FVP of benzo[*b*]furan-2,3-dione (**794**), benzothiet-2-one (**795**), and 2-mercaptobenzoic acid (**796**).[534,553,554] Benzoannelated **799** was prepared similarly.[554,555] On the other hand, photolysis and mild (230 °C) thermolysis of **797** gave thianthrene (**800**), dibenzo-1,2-dithiine (**801**), and dibenzothiophene (**802**) by dimerization of **798**.[556] The diradical/carbene **798** was also scavenged with alkenes, alkynes,[557] amines, azides, diazo compounds,[558] sulfur,[559] and carbon disulfide.[535] ^{13}C labeling excluded the intervention of benzothiirene in the liquid phase,[556] whereas 6-ROCO-**797**[556,560] and 6-MeO-**797**[561] gave conflicting results.

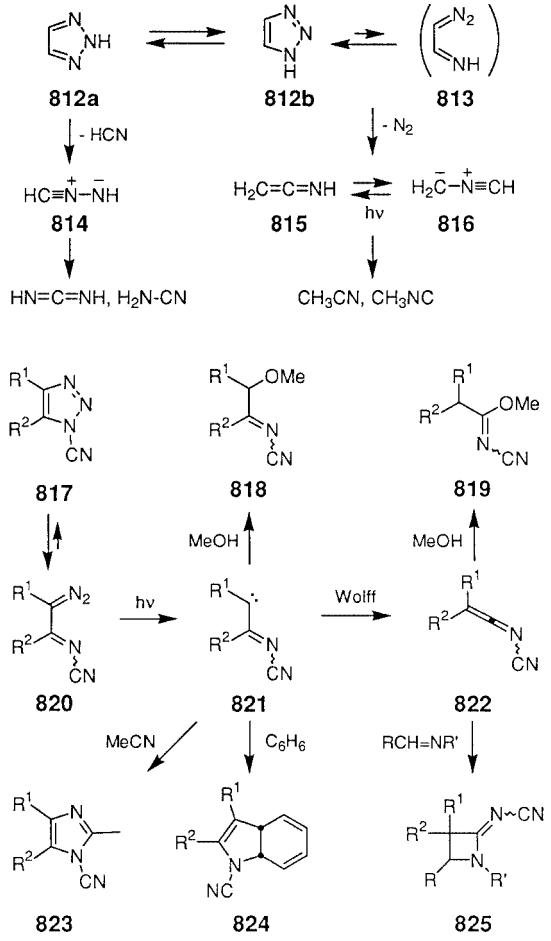
In summary, 1,2,3-thiadiazoles undergo Wolff rearrangement less efficiently than α-diazo ketones. Intermolecular reactions of the intervening thiocarbonyl carbenes often prevail. Thiirenes are more prone to matrix-isolation than thiocarbonyl carbenes. In accordance with the qualitative observations, computational studies place thiirene well below thioformylcarbene in energy.[562] The preparation of thioketenes from 1,2,3-thiadiazoles plays only a minor role in organic synthesis.[538] However, 1,2,3-thiadiazole-4-carboxylic acid was employed as a cross-linking agent for the photochemical conjugation of peptides to proteins.[563]

FVP of 1,2,3-selenadiazol (**803**) produced selenoketene (**804**) which was thoroughly identified by microwave,[564] IR,[565] and photoelectron spectroscopy.[566] Photolysis of matrix-isolated **803** (Ar, 8 K) gave **804**, acetylene, and selenirene (**805**)[544b,544c] whereas **805** was not detected in glassy matrices at 77 K.[567] Photolysis of **803** in cyclohexane/diethylamine at 20 °C afforded the selenoamide **806** in 95% yield.[567] Experiments with ^{13}C-**803** excluded the intervention of **805** at ambient temperature. However, scrambling of a ^{13}C label was observed upon FVP[568] and photolysis in rigid matrices.[567]

The extrusion of nitrogen from substituted 1,2,3-selenadiazoles **807** proceeds largely in parallel to that from 1,2,3-thiadiazoles **780** (Scheme 83). However, alkynes **810** are often the major products obtained from **807**, in contrast to 1,2,3-thiadiazoles **780**. Loss of Se from the selenium analogues of diradicals **784** is thought to be the reaction path to **810**. In fact, the use **807** (R^1 = Me, R^2 = H) has been suggested for the chemical vapor deposition of selenium-containing materials.[569] Thermolyses of **807** have been widely applied in the synthesis of (strained) cyclic and bicyclic alkynes.[570] FVP with trapping of the products in Ar at 12 K has, nevertheless, succeeded in preparing selenoketenes from 4-alkyl (**807**, R^1 = Me, *t*Bu)[565] and cycloalkeno-1,2,3-selenadiazoles [**807**, R^1,R^2 = $(CH_2)_3$, $(CH_2)_4$, and $(CH_2)_6$].[571] In solution, however, the yields of selenoketene-derived 1,3-diselenols **809** are moderate (R^1 = CO_2Et, R^2 = H, 18%; R^1 = CO_2Et, R^2 = Me, 12%)[572] to poor [R^1,R^2 = $(CH_2)_4$, 9%].[573] 1,4-Diselenines **811**, together with alkynes **810**, prevail.[574] Obviously, the tendency to undergo Wolff rearrangement decreases in the order α-diazo ketones > 1,2,3-thiadiazoles > 1,2,3-selenadiazoles.

6.2. 1,2,3-Triazoles and α-Diazoimines

The tautomers of 1,2,3-triazole (**812**) follow distinct reaction paths on photolysis in an argon matrix at 12 K.[575] 2*H*-1,2,3-Triazole (**812a**) was found to produce HCN and nitrilimine (**814**) which then isomerized to give carbodiimide and cyanamide (Scheme 85). Loss of nitrogen from the 1*H*-tautomer **812b** afforded ketenimine (**815**), the product of Wolff rearrangement, in photochemical equilibrium with nitrile ylide **816**. Acetonitrile and methyl isocyanide were formed by isomerization of **815** and **816**, respectively. Pyrolysis of **812** at 850 °C led to acetonitrile as the major product.[576] Photolyses of 4-phenyl-1,2,3-triazole and 4,5-diphenyl-1,2,3-triazole in solution produced modest amounts of (di)phenylacetonitrile.[577] α-Diazoimine **813** may be an intermediate in the reactions of **812b** but was not detected. Computationally, **813** was found to cyclize by way of a planar transition state (ca. 40 kJ/mol) to give **812b** which is more stable than **813** by ca. 65 kJ/mol.[578]



Scheme 85. Wolff rearrangement of 1,2,3-triazoles and α-diazoimines

1-R-1,2,3-triazoles generally exist as such unless the nitrogen carries an electron-withdrawing group.[579] Thus 1-cyano-1,2,3-triazoles **817** undergo ring opening to diazoimines **820** which were photolyzed in solution.[580] With R^1 = H, Wolff rearrangement generates ketenimines **822** which were detected by IR (Ar, 10 K or CH_2Cl_2, 77 K) or reacted

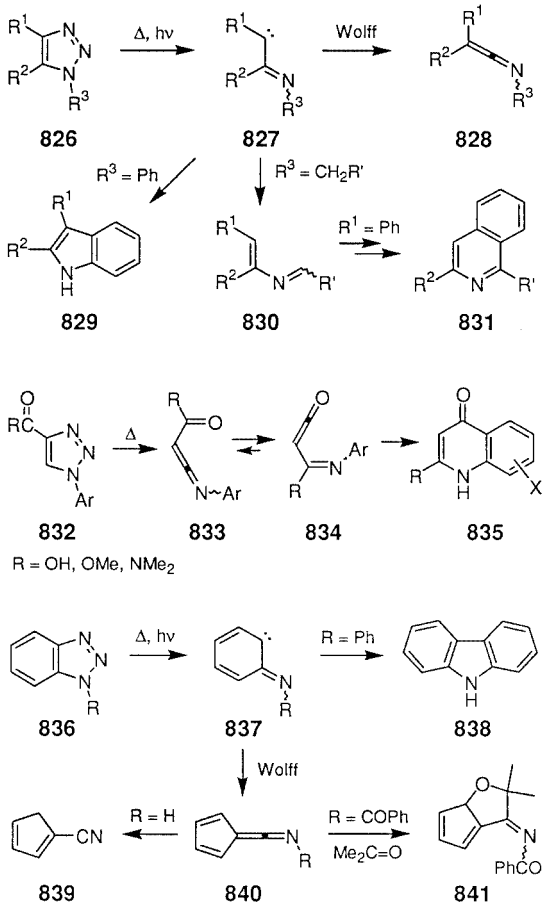
with methanol (→ **819**) and imines (→ **825**). Scavenging of the intervening carbenes **821** with methanol (→ **818**) was competitive, indicating a substantial barrier to rearrangement. With **820**, R^1 = Ph, R^2 = Me, the products were **823** (in MeCN) and **824** (in benzene). In this case, Wolff rearrangement was not observed, presumably due to stabilization of the carbene **821**.[580c,580d]

Nitrogen extrusion from 1-phenyl-1,2,3-triazoles (**826**, R^3 = Ph) generates carbenes **827** which undergo Wolff rearrangement (→ **828**) and cyclization (→ **829**) competitively (Scheme 86).[581] Ring contraction was achieved with R^1,R^2 = $(CH_2)_4$ and $(CH_2)_5$, and thermolysis was found to enhance the ratio of **828**/**829** relative to photolysis.[582] Carbene−carbene rearrangement, by way of 1*H*-azirines, can precede the formation of indoles, as indicated by the distribution of labels[583] and substituents.[584] In fact, azirines have been isolated from the thermolysis of **826**, R^3 = *N*-phthalimidyl.[585] The two major reaction paths of 1-alkyl-1,2,3-triazoles involve Wolff rearrangement (→ **828**) and cyclization to isoquinolines **831**.[586] H-Shift, **827** → **830**, followed by electrocyclization and dehydrogenation, is the likely route to **831**. Wolff rearrangement of 1-aryl-1,2,3-triazole-4-carboxylates and -amides, **832** → **833**, sets the stage for an oxoketenimine−imidoylketene rearrangement (1,3-shift of R, **833** → **834**) which leads eventually to 4-quinolones **835**.[587] Analogously, 1-(pyrazol-5-yl)-1,2,3-triazoles give rise to pyrazolo[1,5-*a*]pyrimidin-7-ones.[588]

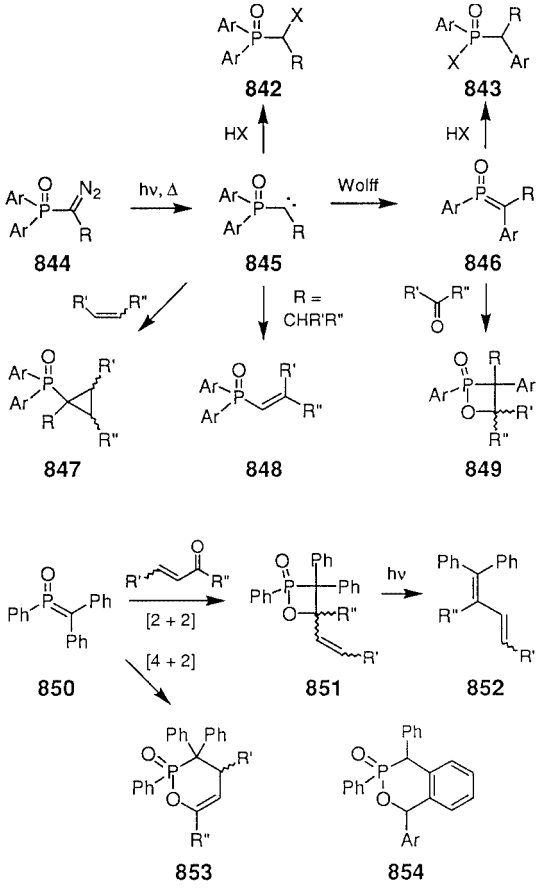
FVP of benzo-1,2,3-triazole (**836**, R = H) afforded > 90% of cyclopentadiene-1-carbonitrile (**839**), formed by Wolff rearrangement and subsequent isomerization of ketenimine **840**, R = H[589] Nitrile **839** was also obtained as the major product when **836** was photolyzed in the gas phase.[590] Ring opening, analogous to **812** → **813**, was observed on irradiation of **836**, R = H, in protic media (IR, UV/Vis).[590,591] In alcohols, Wolff rearrangement of the carbene **837** was barely competitive with H abstraction leading to aniline.[590] Numerous derivatives of **836** gave good yields of ring-contracted nitriles, provided that R = H.[589] In the case of R = Ar, cyclization of **837** to give (derivatives of) carbazole (**838**) prevails.[581,592] Wolff rearrangement is, at best, a side reaction.[593] Photolysis of 1-benzoyl-benzo-1,2,3-triazole (**836**, R = COPh) in acetone afforded **841**, formed by trapping of **840**, R = COPh, together with benzanilide.[592]

6.3. α-Diazophosphane Oxides, -Phosphinates, and Related Substrates

The extrusion of nitrogen from α-diazophosphane oxides **844** induces a P→C shift of aryl groups to give alkylidene(oxo)phosphoranes ("phosphenes") **846** (Scheme 87).[594] Spectroscopic evidence for the generation of phosphenes from **844** has not been reported, although



Scheme 86. Wolff rearrangements of (benzo)-1,2,3-triazoles



Scheme 87. Generation of phosphenes from α-diazophosphinoxides

some persistent species were prepared by different routes.[595] Reaction with water, alcohols and amines leads to phosphinic acids (**843**, X = OH), phoshinates (**843**, X = OR) and phosphinamides (**843**, X = NR_2), respectively.[596] The intervening carbenes **845** are also trapped by nucleophiles (→ **842**), alkenes (→ **847**),[597] and arenes,[598] sometimes to the exclusion of P→C shifts. The influence of R and Ar on the competing rearrangement and O−H insertion of **845** is illustrated in Table 11. 1,2-Shifts from the β-position, **845** → **848**, were also found to suppress the hetero Wolff rearrangement.[594,599]

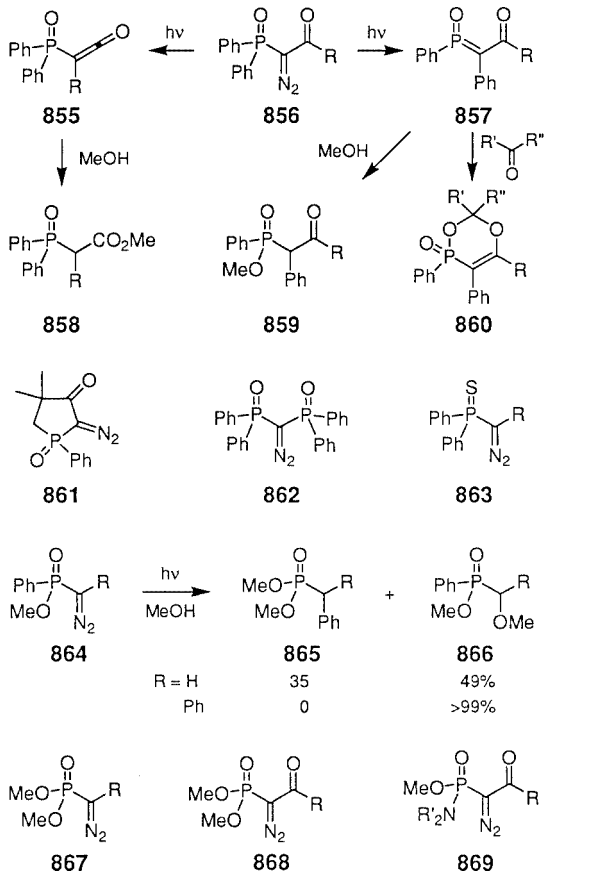
Table 11. Photolyses of α-diazophosphane oxides **844** in methanol[596]

Ar	R	**842** (%)	**843** (%)
Ph	Ph	100	–
4-MeO−C_6H_4	Ph	52	26
Ph	H	–	61
Ph	$CONH_2$	81	–
Ph	CO_2Et	22	61

Phosphenes **846** accept aldehydes and ketones with formation of oxaphosphetanes **849**.[600] α,β-Unsaturated carbonyl compounds undergo [2 + 2] addition, **850** → **851**, competitively with [4 + 2] cycloaddition, **850** → **853**.[598,600] Further irradiation of **851** leads to dienes **852** in a "photo-Wittig reaction". Acylketenes react with **850** in the [4 + 2] mode.[601] The six-membered cyclic structure **854** has been derived for adducts of aromatic aldehydes (ArCH=O, 2π) with **850** (4π).[602] Polyenes analogous to **852** were obtained, among other products, from reactions of **850** with (benzo)-tropone and pyrone.[603]

Some α-diazo-β-oxophosphane oxides **856** undergo Wolff-type P→C shifts (**856** → **857**) and C→C shifts (**856** → **855**) competitively (Scheme 88).[594,596] With R = Ph, the P→C shift dominates by a ratio of ≈ 4:1, as shown by the yields of esters **858** and **859** (Table 12). The effect of *p*-substituents conforms with expectation while bulky aryl groups tend to minimize the P→C shift. Aldehydes and ketones scavenge the acylphosphenes **857** by way of [4 + 2] cycloaddition.[604] The cyclic α-diazo-β-oxophosphinoxide **861** failed to undergo Wolff-type ring contraction, X−H insertion being the only reaction.[605] In contrast, photolysis of bis(diphenylphosphinyl)diazomethane (**862**) in the presence of water and methanol led to the formation of phosphinic acid (92%) and ester (46%), respectively.[606] α-Diazophosphanesulfides **863** (the thio analogues of **844**) were found to give moderate yields of Wolff products: R = Ph, 17% P→C;[607] R = COPh, 18% P→C and 9% C→C.[608]

The reactivity of methyl α-diazophosphinates **864** is similar to that of α-diazophosphane oxides **844**.[609] Substantial P→C phenyl shift was observed with **864**, R = H, whereas **864**, R = Ph, failed to rearrange. Dimethyl α-diazophosphonates **867** do not show P→C shifts of OMe.[594,610] However, α-diazo-β-oxophosphonates **868**[611] and α-diazo-β-oxophosphonamides **869**[612] undergo "normal" Wolff rearrangements (shift of R), even on catalysis with $Rh_2(OAc)_4$.[286]



Scheme 88. Reactivity of α-diazophosphane oxides, -phosphane sulfides, -phosphinates, and -phosphonates

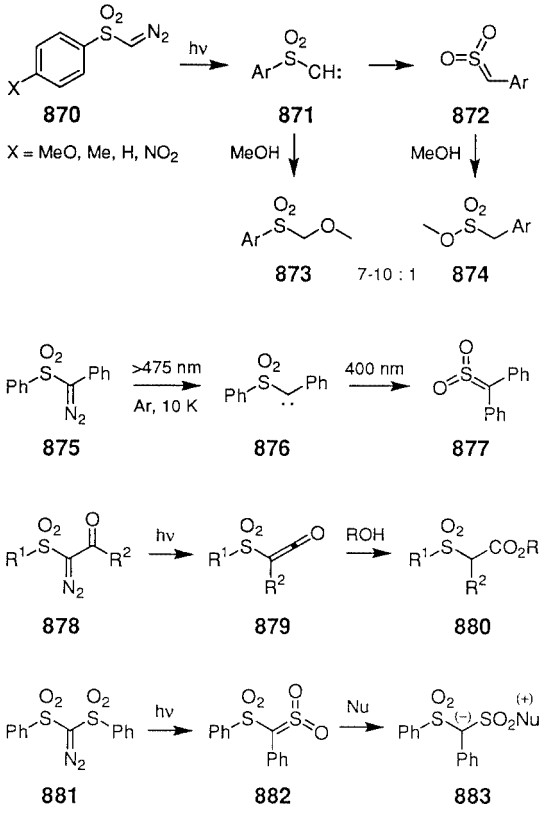
Table 12. Photolyses of α-diazo-β-oxophosphane oxides **856** in MeOH[594,596]

R	**859** (%)	**858** (%)	P→C/C→C
Me	15	–	–
Ph	44	12	3.7
4-MeO−C_6H_4	31	10	3.1
4-Me_2N−C_6H_4	14	23	0.6
4-O_2N−C_6H_4	28	10	2.8
1-naphthyl	33	37	0.9
9-anthryl	–	85	–
mesityl	–	40	–

6.4. α-Diazosulfones and -sulfoxides

α-Diazosulfones are stable compounds whose photolysis generates sulfonyl carbenes.[613] Studies with arylsulfonyldiazomethanes **870** gave the first evidence for the formation of sulfenes **872** by a hetero Wolff rearrangement of sulfonyl carbenes **871** (Scheme 89).[614] High product ratios **873**/**874** point to a low tendency of the aryl group to migrate, which is in obvious contrast to the behavior of analogous diazo ketones. The flash pyrolysis of phenylsulfonyl(*p*-tolyl)diazomethane was suggested to involve sulfene formation, with

subsequent extrusion of SO_2 to generate a diarylcarbene.[615] Irradiation of phenyl(phenylsulfonyl)diazomethane (**875**) in an argon matrix at 10 K with $\lambda > 475$ nm produced only a small amount of diphenylsulfene (**877**).[616] The main product was the carbene **876** which was readily trapped by oxygen. Irradiation with $\lambda = 400$ nm was required to induce the hetero Wolff rearrangement **876** → **877**. Again, the persistence of **876** stands in contrast to the reactivity of carbonyl carbenes which can rarely be matrix-isolated (Section 3.4.3.). In accordance with these observations, photolyses of α-diazo-β-oxosulfones **878** were found to produce ketenes **879**, rather than sulfenes.[617] In addition to being scavenged with alcohols (→ **880**), heterocumulenes,[618] and diazoalkanes,[286] the ketenes **879** were also employed in electrocyclization reactions.[272b]

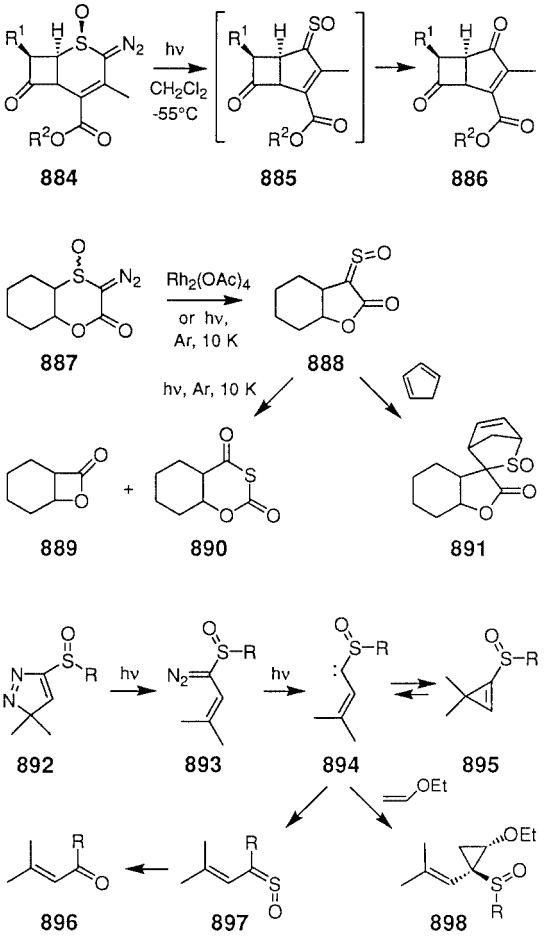


870 871 872 873 874 875 876 877 878 879 880 881 882 883

Scheme 89. Wolff rearrangements of α-diazosulfones

Irradiation of bis(phenylsulfonyl)diazomethane (**881**) in an argon matrix at 10 K generated the sulfonylsulfene **882**.[619] The intervening carbene could not be scavenged under matrix conditions although carbene-derived products were obtained in solution.[118b,619,620] Laser flash photolysis of **881** in acetonitrile led to detection of the sulfene **882** and the sulfene ylide **883** formed upon sulfene trapping by pyridine (Nu = pyridine; $k_f = 4 \cdot 10^6$ $M^{-1}s^{-1}$).[621] The kinetics of competitive sulfene quenching indicate that **882** reacts rapidly with anions ($k = 10^5 - 10^7$ $M^{-1}s^{-1}$) but rather slowly with alcohols and water ($k < 10^3$ $M^{-1}s^{-1}$). Nevertheless, **881** and related substrates have been utilized in photoresists for deep-UV lithography.[622] The sulfonic acids generated from **881** catalyze the crosslinking of acid-sensitive components in positive tone materials.

Both diazo transfer to sulfoxides[623] and treatment of sulfinyl chlorides with diazomethane[624] failed to give simple isolable α-diazosulfoxides, or products that were indicative of a hetero Wolff rearrangement. The first reported stable diazosulfoxides were the cephalosporin derivatives **884**.[625] Photolysis of **884** at −55 °C afforded the ring-contracted ketones **886** (40−60%) which are thought to arise by sulfur extrusion from the intervening sulfines **885** (Scheme 90).[626] Diazo transfer was also successful in preparing *cis* and *trans* isomers of the bicyclic diazosulfoxides **887**.[627] Decomposition of **887** by rhodium(II) catalysis proceeded by a Wolff-type rearrangement. The resulting sulfine **888** was trapped with dienes to give cycloadducts, e.g., **891**.[628] When **887** was irradiated in an Ar matrix at 10 K, sulfine **888** was identified by IR spectroscopy.[629] The configuration of the migrating carbon was retained, and the *s-Z* conformer of **888** was formed from both epimers of **887**. Further irradiation of **888** produced **889** and **890**, in some contrast to the **885** → **886** precedent.



884 885 886 887 888 889 890 891

892 893 894 895 896 897 898

Scheme 90. Hetero Wolff rearrangements of α-diazosulfoxides

Photolysis of 3-sulfinyl-3*H*-pyrazoles **892** was used to generate α,β-unsaturated sulfinylcarbenes **894**, presumably by way of diazo intermediates **893**.[630] Reversible cyclization (→ **895**, R = Et) and cycloaddition with alkenes (→ **898**) were found to compete with Wolff rearrangement (→ **897**). Photolysis of **892**, R = *p*-tolyl, in ethoxyethene af-

forded **896** and **898** in a 1:1 ratio. Depending on R, the sulfines **897** were isolated (R = $CH_2CH{=}CMe_2$), trapped with 2-diazopropane (R = Et), and converted into ketones **896**.

7. Conclusion and Outlook

The past decades have witnessed extraordinary progress in the exploration and utilization of the Wolff rearrangement. It is now clear that both stepwise and concerted mechanisms operate, often competitively. The stepwise mechanism is fairly well understood. Experiment and theory consistently describe carbonyl carbenes and their conversion into ketenes. However, activation barriers have not been obtained so far for Wolff rearrangements involving alkyl and aryl shifts. The *s-Z* conformation of α-diazo ketones appears to be a necessary but not a sufficient condition for the concerted Wolff rearrangement. Other influential factors, such as ring strain and carbene stability, have not received due attention. High-level theoretical studies of the concerted Wolff rearrangement are urgently needed.

Even less is known about the mechanism of catalytically induced Wolff rearrangements, although there is a wealth of preparatively useful protocols. Why do silver ions catalyze the decomposition of $R{-}CO{-}CHN_2$ but not that of $R{-}CO{-}CN_2R'$? Does the catalytic process involve deprotonation, or is the effect of R′ steric in origin? Scattered reports indicate that Rh^{II} complexes catalyze the Wolff rearrangement of some cyclic α-diazo ketones. However, systematic studies are lacking. A generally applicable catalyst for Wolff-type ring contractions would be extremely useful in organic synthesis.

Complete retention of configuration of the migrating group has now been definitively established by means of enantioselective chromatography. This invaluable feature of the Wolff rearrangement has been widely exploited in syntheses of biologically active molecules. In the case of diazo ketones $R{-}CO{-}CN_2R'$, a chiral center is created in the course of nucleophilic addition to the prochiral ketene RR′C=C=O. Chiral α-hydroxy esters and lactones were found to add with high diastereoselectivity to long-lived, isolable ketenes.[631] The enantioselective catalysis of the addition of achiral alcohols to prochiral ketenes was pioneered by Pracejus,[632] and highly efficient azaferrocene catalysts for this process have been designed.[633] However, procedures for asymmetric syntheses with short-lived ketenes generated by the Wolff rearrangement have yet to be developed.

This is not an exclusive list, but it does represent some of the remaining challenges. It will be exciting to see what imaginative new applications of the Wolff rearrangement come forth in the near future.

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