Organic Reaction Mechanisms - 1998: An Annual Survey Covering the Literature Dated December 1997 to November 1998. Edited by A. C. Knipe and W. E. Watts

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ORGANIC REACTION MECHANISMS · 1998

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Edited by

A. C. Knipe and W. E. Watts
University of Ulster
Northern Ireland

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Preface

The present volume, the thirty-fourth in the series, surveys research on organic reaction mechanisms described in the literature dated December 1997 to November 1998. In order to limit the size of the volume, we must necessarily exclude or restrict overlap with other publications which review specialist areas (e.g. photochemical reactions, biosynthesis, electrochemistry, organometallic chemistry, surface chemistry and heterogeneous catalysis). In order to minimize duplication, while ensuring a comprehensive coverage, the Editors conduct a survey of all relevant literature and allocate publications to appropriate chapters. While a particular reference may be allocated to more than one chapter, we do assume that readers will be aware of the alternative chapters to which a borderline topic of interest may have been preferentially assigned.

There has been only one change of author since last year. We welcome Dr C. Bedford as author of Reactions of Carboxylic, Phosphoric and Sulfonic Acids and their Derivatives. He replaces Dr W.J. Spillane, whose major contribution to the series, through provision of expert reviews since 1983, we wish to acknowledge.

We regret that publication has been delayed by late arrival of manuscripts, but once again wish to thank the production staff of John Wiley & Sons and our team of experienced contributors (now assisted by Drs J. Sherringham, P. Dimopoulos and D. P. G. Emmerson) for their efforts to ensure that the standards of this series are sustained.

A.C.K.
W.E.W.

CONTENTS

Organic Reaction Mechanisms - 1998: An Annual Survey Covering the Literature Dated December 1997 to November 1998. Edited by A. C. Knipe and W. E. Watts

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CHAPTER 1

Reactions of Aldehydes and Ketones and their Derivatives

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Formation and Reactions of Acetals and Related Species

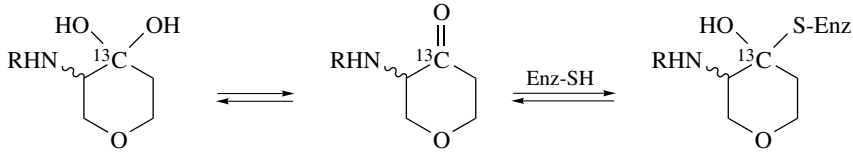
A comprehensive *ab initio* computational study of the anomeric effect in 1,3-dioxa systems has been designed to quantify anomeric effects in such compounds.[1] Energy changes associated with *O*-protonation (and deprotonation, where relevant) have been calculated for tetrahydropyran, its 2-hydroxy derivative, and for 1,3-dioxane, together with acyclic comparators such as methanol, dimethyl ether, and methoxymethanol. All major conformations have been treated and their geometric parameters quantified. The 3-oxaalkoxides exhibit a preference for axial (n_π) over equatorial (n_σ) protonation, by 2–3 kcal mol^{-1}. The COCOC acetals are stronger bases (at the acceptor oxygen)

than the simple ethers. Thus the anomeric effect plays an important role in the charged species.

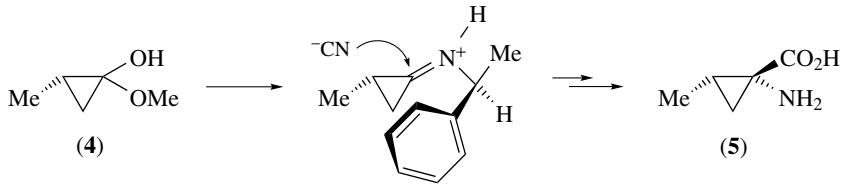
When trifluoroacetaldehyde ethyl hemiacetal [$F_3CCH(OH)OEt$] is treated with enamines in hexane at room temperature, it provides a source of the aldehyde under mild conditions.[2] Subsequent reaction with the enamine can be used to prepare β-hydroxy-β-trifluoromethyl ketones, $F_3CCH(OH)CH_2COR$. The enamine plays successive roles as base, ammonium counterion, and then carbon nucleophile as the sequence proceeds.

Two stereochemically defined isomeric benzaldehyde acetals, (*R*)- and (*S*)-$ArCH(OMe)(OPr^i)$, undergo methyl-for-methoxy nucleophilic substitution to give the corresponding isopropyl ethers, $ArCH(Me)(OPr^i)$, using $Me_2CuLi{-}BF_3.OEt_2$.[3] The degree of racemization observed indicated that the major route was S_N1, with free oxonium ion. The method relies on the acetal carbon being the only stereogenic centre.

The mechanism of inhibition of cysteine proteases by a tetrahydropyranone inhibitor has been probed using ^{13}C NMR labelling studies.[4] The carbonyl-labelled inhibitor (**1**; R = $CO^*CHBnNHCOCH_2CH_2CO_2Me$), is in equilibrium with its hydrate (**2**). Addition of the enzyme papain gives a new ^{13}C signal consistent with a 'hemithioketal' (**3**). The diastereomers of (**1**) have been separated, and although their absolute configurations have not been established, one of them inhibits the enzyme with a K_i of 11 μm (i.e. a binding constant of 9.1×10^4 mol^{-1}). The structure of the enzyme–inhibitor complex is proposed to mimic the tetrahedral intermediate formed during peptide hydrolysis.



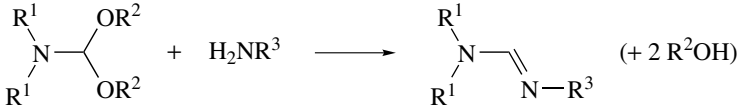
Methylcyclopropanone hemiacetal (**4**) undergoes an asymmetric Strecker reaction to give (*1R, 2S*)-(+)-*allo*-norcoronic acid (**5**) in good yield and high *de*.[5] The induction depends on the use of a chiral amine [e.g. (*S*)-α-methylbenzylamine] to control the face on which the intermediate iminium cation (**6**) is attacked.



meso-1,2-Diols have been desymmetrized to their monobenzyl ethers in >99% *ee* and up to 97% yield by converting them to their norbornene acetals and then carrying out an intramolecular halo-etherification under kinetic control.[6]

Cyclodextrins slow the rate of hydrolysis of benzaldehyde dimethyl acetal, $PhCH(OMe)_2$, in aqueous acid as the substrate binds in the cyclodextrin's cavity, producing a less reactive complex.[7] Added alternative guests compete for the binding site, displacing the acetal and boosting hydrolysis.

N,*N*-Dialkylformamide acetals (**7**) react with primary amines to give the corresponding amidines (**8**). Kinetics of the reaction of a range of such acetals with ring-substituted anilines—previously measured in neutral solvents such as methanol or benzene[8a]—have been extended to pyridine solution.[8b] In pyridine, the reactions are irreversible, with first-order kinetics in each reactant, and mechanistically different from those in non-basic solvents. Two mechanisms are proposed to explain Hammett plots for a range of anilines, in which the ρ value switches from negative to positive at a σ value of ca 0.5. The pyridine solvent substantially enhances the rate in the case of very weakly basic anilines.



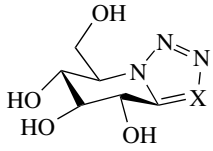
(**7**) (**8**)

A hypervalent iodine(III) reagent, Ph−I=O, together with TMS-azide, promotes direct α-azidation of cyclic sulfides: the reaction opens up a route to unstable *N*,*S*-acetals.[9]

Reactions of Glucosides and Nucleosides

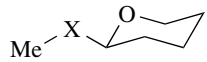
Two azolopyridines (**9a, 9b**; X = N, CH) have been employed as transition-state analogue inhibitors of retaining β-glycosidases, and of glycogen phosphorylase.[10] The roles of catalytic carboxylic acid and carboxylate groups in the β-glycosidases have been calculated; (**9a**) strongly inhibits such enzymes, while (**9b**) has a weaker effect. The difference is ascribed to (i) protonation of (**9a**) by enzymic catalytic acid [versus (**9b**), which has N replaced by CH] and (ii) a contribution from a charge-dipole interaction between the enzymic catalytic carboxylate nucleophile and the azole ring. The enzyme–inhibitor complexes were shown to be structure-invariant by X-ray crystallography. Calculations of the relative contributions of factors (i) and (ii) above to the difference in inhibition produced by the two compounds agree well with kinetic studies with both enzyme types.

Thioglycosides are not subject to acid-catalysed cleavage by glycosyl hydrolases: this effect, which allows them to act as inhibitors, is generally ascribed to their lower basicity.[11a] However, calculations on conformational changes in the model compounds



(**9**)

a; X = N
b; X = CH



(**10**)

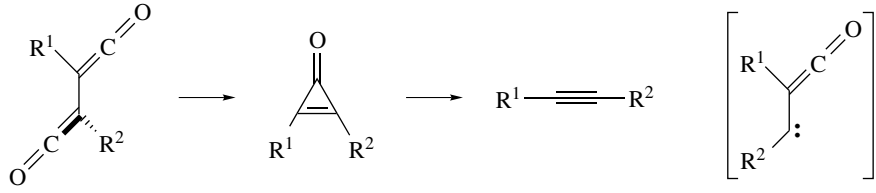
a; X = O
b; X = S

(**10a, 10b**; X = O, S) accompanying protonation indicate that, whereas protonation of the acetal leads to spontaneous collapse to the oxocarbenium ion, the corresponding protonation of the thioacetal yields a stable species.[11b]

Substituent effects on the endocyclic cleavage of glycosides by trimethylaluminium have been explained in terms of a cyclic C−H · · · O hydrogen-bonded intermediate.[12]

Reactions of Ketenes

1,2-Bisketenes (**11**) can decarboxylate and then ring close to give cyclopropenones (**12**); subsequent further decarboxylation yields alkynes (**13**).[13] A theoretical study shows that the first reaction is favoured by electronegative substituents, whereas electropositive substituents favour the second. The calculations do not indicate conclusively whether cyclopropenone formation is concerned, or proceeds via a *syn*-ketenylcarbene (**14**).



(**11**) (**12**) (**13**) (**14**)

Amination of ketene has been studied by *ab initio* methods.[14] Reactions of ammonia, its dimer, and its (mono)hydrate with ketene have been calculated and compared with earlier studies of ammonia (at lower levels of theory), of water, and of water dimer. In general, the results favour initial addition of ammonia to the C=O bond (giving the enol amide), as against addition to the C=C bond (which gives the amide directly). Amide formation is compared with the corresponding hydration reaction where enol acid and acid are the alternative immediate products. Most of the reactions, i.e. both additions and tautomerizations, are suggested to involve cyclic six-membered transition states.

Hydration of carbodiimide (HN=C=NH) is described under *Imines* below.

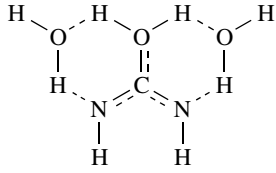
Formation and Reactions of Nitrogen Derivatives

Imines

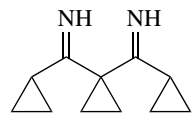
Two theoretical investigations of the condensation of formaldehyde and methylamine to form *N*-methylmethanimine ($H_2C{=}NMe$) have examined the reaction in the gas phase, and also considered the addition of discrete numbers of water molecules.[15,16] Various methods have been employed to quantify solvation-free energies for formation of the zwitterion $H_2C(O^-){-}\overset{+}{N}H_2Me$. In the gas phase, no minimum exists for C−N separations less than that found for the van der Waals complex, but a stable zwitterion is found when two water molecules are included.[15] Such specific inclusion of water has been extended to calculation of all of the barriers in this system.[16]

The factors involved in the attack of nitrogen nucleophiles on carbonyl compounds, e.g. the pK_a of the nitrogen, and the thermodynamics of the formation of neutral (T^0) versus zwitterionic ($T^{\pm}$) tetrahedral intermediates, have been discussed in terms of their influence on the form of the pH–rate profile.[17]

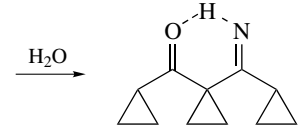
The catalysis of the addition of a water molecule to carbodiimide (HN=C=NH) has been investigated by computational methods, with the number of water molecules being varied.[18] The activation barrier is lowered by 11.6 kcal mol^{-1} with a second water molecule (similar to many such hydrations, e.g. those of CO_2, $H_2C{=}C{=}O$, etc.) as a strained four-membered ring is expanded to six atoms. However, a *third* water molecule lowers the barrier by a further 9.2 kcal mol^{-1}, and this occurs not by forming an eight-membered ring (which is worth little in energy terms), but through a second cyclic network [as in (**15**)].



(**15**)



(**16**)



(**17**)

Several cyclopropylimines have been synthesized and their reactions with a range of nucleophiles have been investigated.[19] Mild hydrolysis of diimine (**16**) produces, amongst other products, the β-ketoimine (**17**), stabilized by intramolecular hydrogen bonding.

The binding of pyridoxal 5′-phosphate (vitamin B_6) to enzymes has been modelled using homo- and co-polypeptides containing L-lysine as a source of reactive amino groups. This has now been extended to reaction of pyridoxal with polyallylamine, with the polymer acting as a control that cannot provide amido -CO- or -NH- functions to stabilize the Schiff base products,[20] as occurs in enzymes and polypeptides. Rate constants for the formation and hydrolysis of the imines have been measured and interpreted in terms of formation of the carbinolamine (in its neutral or zwitterionic form),

its conjugate acids, and subsequent dehydration. An acid-catalysed intramolecular process is ruled out, and carbinolamine formation is the rate-determining step, partly due to the effects of the hydrophobic macromolecular environment. Comparisons with enzymatic or polypeptide reactions with rate-limiting dehydration of carbinolamine are thus inappropriate.

Isoniazid, carbidopa, and hydralazine are hydrazine derivatives with therapeutic uses. They form Schiff bases with pyridoxal 5′-phosphate, and rate constants for their formation and hydrolysis have been measured in aqueous solution;[21] pH–rate profiles are reported and compared with that of hydrazine itself.

The kinetics of reactions between aroylpyruvic acids, $ArCOCH_2COCO_2H$, and arylamines in toluene show evidence of several mechanistic features: intramolecular carboxyl catalysis, and catalysis by a second molecule of nucleophile, either on its own, or in concert with an (external) carboxylic acid.[22] An extended solvent study shows an increase in the efficiency of the aforementioned intramolecular carboxyl catalysis with decreasing polarity of the solvent.[23] Hydrolysis of the related β-keto esters, methyl 4-aryl-2-arylamino-4-oxobut-2-enoates [$ArCOCH{=}C(NHAr)CO_2Me$] in aqueous dioxane is subject to general acid catalysis.[24]

The condensation of 5-chloro-2-amino-benzothiazoles and -benzoxazoles with α-bromoketones, PhCOCH(Br)R (R = H, Me, Et, 4-$C_6H_4SO_2Me$), produces a range of fused heterocycles;[25] the mechanisms involved have been investigated by isotopic labelling.

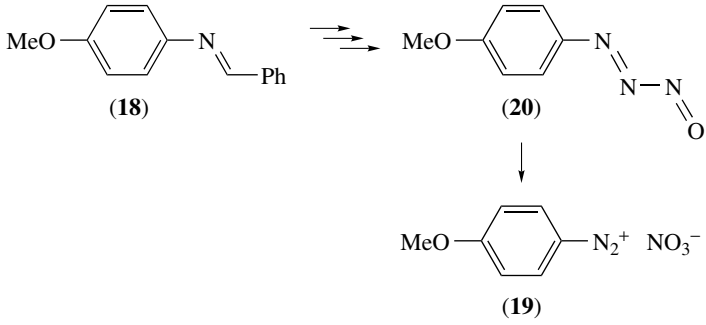
Alkaline hydrolysis of the hypnotic/anxiolytic drug diazepam yields 2-methylamino-5-chlorobenzophenone and its imine, via a dioxide intermediate.[26]

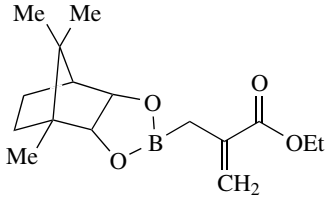
Several reports feature asymmetric synthesis using imines, particularly with organometallics. A chiral sulfoxide lithium salt, *p*-tolyl$-S^*(O)-CH_2Li$, has been added diastereoselectively to a series of *trans*-aldimines, $R^F-CH{=}N-C_6H_4-p$-OMe ($R^F = CF_3$, C_2F_5, CF_2CHF_2).[27a] The sulfoxide can be detached from the adduct to yield chiral amines, amino alcohols, or amino acids. Addition is under kinetic control, in contrast to similar imines which do not contain such fluoro substituents.[27b] Organolithiums have also been added enantioselectively to imines using C_2-symmetric bis(aziridine) ligands.[28]

Additions of organometallics to the C=N bond of imines, oximes, hydrazones, and nitrones have been reviewed,[29] with emphasis on the issues of reactivity and selectivity. Recent advances in enantioselective addition to imines *of ketones* are highlighted.

The use of enantio- and diastereo-selective reduction of endocyclic C=N bonds in the synthesis of biomolecules has been reviewed.[30]

Several reactions of imines of synthetic utility are reported. Nitric oxide reacts with *N*-benzylidene-4-methoxyaniline (**18**) in ether to give 4-methoxybenzenediazonium nitrate (**19**) and benzaldehyde.[31] Two mechanisms are proposed, both involving nitrosodiazene (**20**), and the preferred route is suggested to involve direct electrophilic reaction of NO to the imine double bond, favoured by the polarity of the latter.





(21)

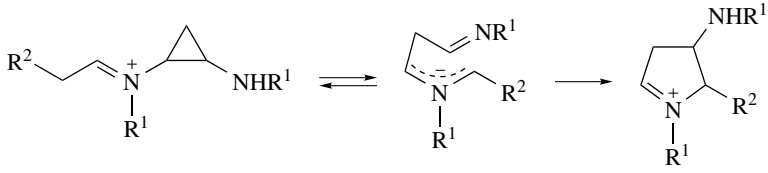
An allylboronate (**21**) reacts with imines in good yield to give homoallylic amines and α-methylene-γ-lactams with high *ee*.[32]

(*E*)-Benzylideneanilines have been added across 2,3-dihydrofurans to produce bicyclic azetidines regio- and stereoselectively;[33] a zwitterionic mechanism is proposed. An extensive range of reaction parameters have been calculated for the Mannich reaction of benzoxazole with formaldehyde/dimethylamine.[34] A molybdenum bis(imide) has been used to catalyse C=N bond formation in imine–imine metathesis reactions of synthetic interest;[35] the approach has been extended to alkylidene–imine, imide–imine, and imide–imide metatheses. 1-Substituted 1-phenyl-2,2,2-trifluoroethylamines have been synthesized asymmetrically via condensation of (*R*)-phenylglycinol [$PhCH(NH_2)CH_2OH$] and trifluoroacetophenone—to give a chiral oxazolidine—and subsequent ring opening.[36]

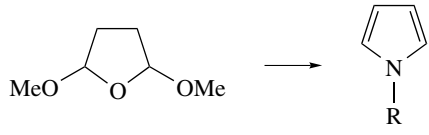
For a stereoselective dialkylzinc reaction with a phosphinoylimine, see *Addition to Organometallics* below; a resolution via a Schiff base is described under *Enolates*.

Iminium Ions and Related Species

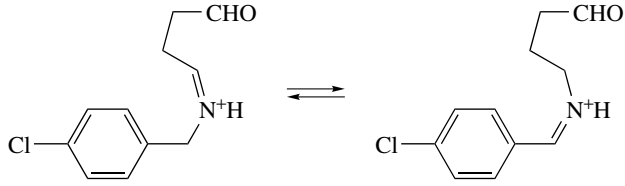
Cis- and *trans*-cyclopropane-1,2-diamines (both primary and secondary) react with a range of aldehydes, R^2CHO, to give pyrroles under very mild conditions.[37] ^1H NMR has been used to identify the intermediates. The key steps involve ring expansion of the monoiminium ion (**22**), via an azomethine ylid (**23**), to yield a dihydropyrrolium ion (**24**).



(**22**) (**23**) (**24**)



(**26**) (**25**)



(**27a**) (**27b**)

A new synthesis of arylmethylene- and arylmethine-pyrroles [**25**; R = $CH_2C_6H_4X$ and $CH(CO_2H)CH_2Y$] uses 2,5-dimethoxytetrahydrofuran (**26**).[38] The reaction is subject to acid–base catalysis, and is typically successful only in solvent mixtures of such character, e.g. acetic acid–pyridine. A mechanistic investigation has identified a number of iminium ion intermediates [e.g. tautomerism (**27a**) $\rightleftarrows$ (**27b**)] to explain by-products in particular cases.

Calculations of simple model Mannich reactions have focused on the role of iminium salt as potential Mannich reagent.[39]

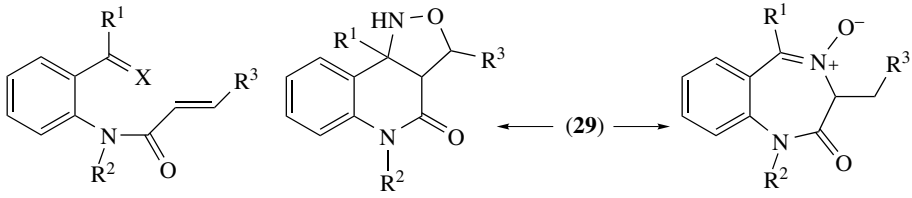
Oximes, Hydrazones, and Related Species

A range of benzaldehydes and acetophenones (**28**) with α, β-unsaturated amides in the *ortho*-position have been converted into their oximes (**29**).[40] Two major cyclization routes are then available:

(i) oxime–nitrone tautomerization followed by cycloaddition gives an isoxazoloquinolinone (**30**), i.e. a 5,6,6-tricycle with the (new) bridgehead carbons derived from the alkene; or

(ii) 1,3-azaprotio cyclotransfer to give a benzodiazepine *N*-oxide (**31**), i.e. a 6,7-bicyclic dipole.

The reaction of hydroxylamine with (**28**) has been investigated for a variety of substituent patterns, and the combinations which produce (**29**), (**30**), or (**31**) as major product have been characterized. Substituent R^3 has a significant electronic effect, while R^1 and R^2, together with 'buttressing' substituents placed *ortho* to both amide and carbonyl, have major steric influences on the outcome.



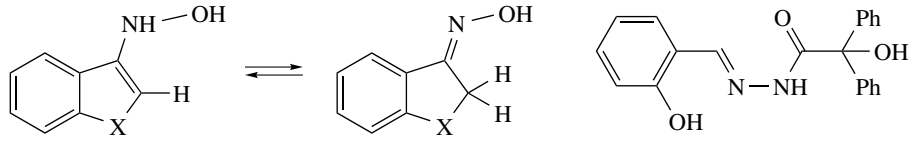
(**28**) X = O
(**29**) X = NOH

(**30**)

(**31**)

The pK_a values of a series of *para*- and *meta*-substituted benzaldoximes and phenyl methyl ketoximes, ArCR=NOH (R=H, Me), have been measured in DMSO.[41] The aldoximes exhibit $pK_a = 20.05 + 3.21\sigma_p$. The homolytic bond dissociation energy of the O–H bond has been estimated as 88.3 (aldoximes) and 89.2 kcal mol^{-1} (ketoximes) by relating the pK_a to the oxidation potential of the conjugate base (i.e. E_{ox} for $ArCR{=}NO^- \rightarrow ArCR{=}NO^{\cdot}$).

3-Hydroxyaminobenzo-furan and -thiophene (**32a**; X = O, S) are the unstable enamine tautomers of the corresponding oximes (**32b**). Kinetics of the tautomeric interconversions have been measured, yielding tautomeric constants:[42] the latter have been compared with the corresponding keto–enol constants. The enamines are ca 40 times less stable, relative to the oximes, than are the enols, relative to the ketones. The minor tautomers are ca 100 times more stable (relative to the major) for the benzothiophene system.



(**32a**)

X = O, S

(**32b**)

(**33**)

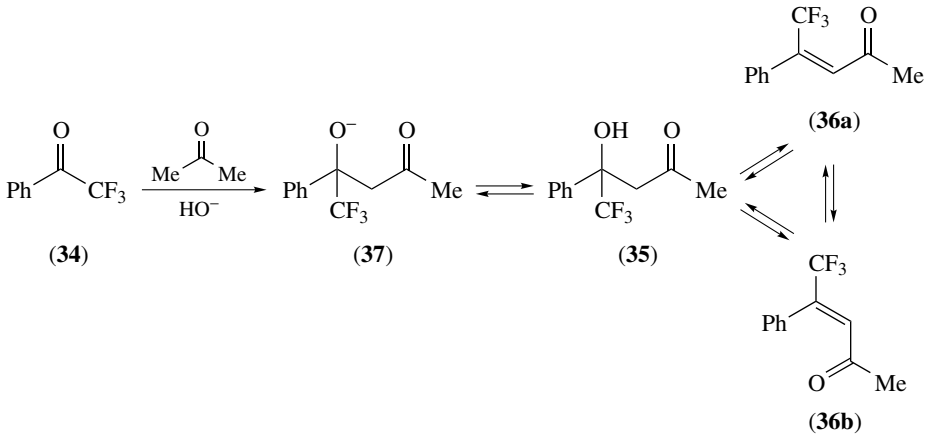
Aminolysis of *O*-aryloximes shows a third-order term for both pyrrolidine and piperidine bases; temperature effects on different routes are reported and explained.[43]

Hydrolysis of α-hydroxy-α-phenylbenzeneacetic acid salicylidenehydrazide (**33**) in aqueous ethanol proceeds via fast protonation, followed by rate-determining attack of water;[44] the results are compared with several related molecules.

Reactions of Schiff bases of pyridoxal 5′-phosphate and several therapeutic hydrazine derivatives are described earlier under *Imines*.

C–C Bond Formation and Fission: Aldol and Related Reactions

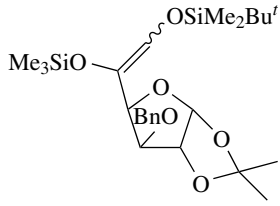
Rate and equilibrium constants have been determined for the aldol condensation of α,α,α-trifluoroacetophenone (**34**) and acetone, and the subsequent dehydration of the ketol (**35**) to the *cis*- and *trans*-isomeric enones (**36a**) and (**36b**).[45a] Hydration of the acetophenone, and the hydrate acting as an acid, were allowed for. Both steps of the aldol reaction had previously been subjected to Marcus analyses,[45b] and a prediction that the rate constant for the aldol addition step would be 10^4 times faster than that for acetophenone itself is borne out. The isomeric enones are found to equilibrate in base more rapidly than they hydrate back to the ketol, consistent with interconversion via the enolate of the ketol (**37**), which loses hydroxide faster than it can protonate at carbon.



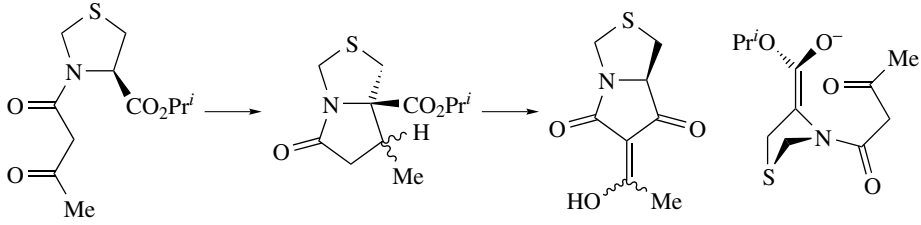
A Hammett correlation has been reported for the retroaldol reaction of a series of *para*-substituted benzylidenemalonitriles, $XC_6H_4CH{=}C(CN)_2$, catalysed by hydroxide in aqueous methanol.[46]

Regio-, Enantio-, and Diastereo-selective Aldol Reactions

A straightforward method for aldolizing unsymmetrical ketones on the more hindered side involves the use of catalytic titanium(IV) chloride in toluene at room temperature.[47] For examples using acyclic and cyclic ketones, and linear, branched, and aromatic aldehydes, the regioselectivity varied from 7:1 to >99:1, while the *syn*:*anti* ratios were moderate to good, and yields were in the range 62–91%. In contrast to other methods, base is not required, and the ketone can be used as is (i.e. the silyl enol ether is not required).



(**38**)



(**39**) (**40a,b**) (**41**) (**42**)

Silyl enol ether (**38**), derived from D-glucose, undergoes a useful one-carbon extension by way of an asymmetric aldol reaction;[48] the conditions of the indium(III) catalysis in water are very convenient.

A stereoselective intramolecular aldol reaction of thiazolidinecarboxylate (**39**) proceeds with retention of configuration to give fused heterocycles (**40a,b**; separable) and (**41**), the product of a retroaldol–acylation reaction.[49a] The selectivity is suggested to be directed by 'self-induced' axial chirality, in which the enolate generated in the reaction has a stereochemical 'memory,' being generated in an axially chiral form (**42**).[49b] The retroaldol step also exemplifies a stereoretentive protonation of an enolate.

The lithium enolate of di-*t*-butyl malonate undergoes a stereoselective aldol reaction with α-alkoxyaldehydes to give *anti*-1,2-diol derivatives;[50] in the case of the highly hindered 2-trityloxypropanal, the stereochemistry is reversed.

A series of *trans*-chelating chiral biferrocene diphosphine ligands enable a rhodium(I)-catalysed aldol reaction of 2-cyanopropionates to proceed in up to 93% *ee*.[51]

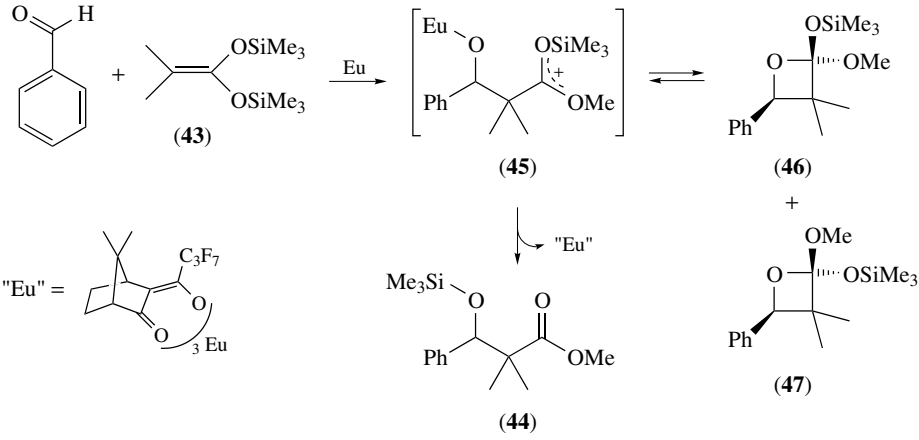
Asymmetric aldol additions of trichlorosilyl enolates of cyclic ketones to aldehydes have been studied, with a particular focus on the electronic effect of the aldehyde on the selectivity achieved.[52]

A review of enantioselective aldol additions of latent enolate equivalents covers a variety of Sn^{II}, boron, Ti^{IV}, Cu^{II}, lanthanide, and Lewis base catalysts.[53] Asymmetric aldol reactions using boron enolates have been reviewed (401 references).[54]

Mukaiyama and Other Aldol-type Reactions

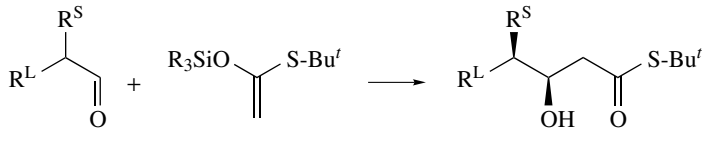
In the Mukaiyama cross-aldol reaction, an aldehyde and a ketene silyl acetal [e.g. (**43**)] react via Lewis acid catalysis to give a β-silyloxy ester (**44**). The reaction

is assumed to involve an intermediate cation (**45**), set up for intramolecular silicon transfer. However, in some cases the trimethylsilyl group can be captured by the carbonyl substrate, leading to catalysis by Me_3Si^+, i.e. an *achiral* route.[55a,b] It has now been shown that the 2+2-addition intermediates, (**46**) and (**47**), form reversibly in the presence of a chiral europium catalyst, equilibrating over 2 h at 20 °C in benzene.[55c] While considerably complicating the mechanistic scheme, their formation minimizes that of Me_3Si^+. The influence of the relative rates of the steps involved on the *ee* outcome is discussed with respect to the design of effective asymmetric catalysts.



A Mukaiyama-type aldol reaction of silyl ketene thioacetal (**48**) with an aldehyde with large and small α-substituents (e.g. Ph and Me), catalysed by boron trifluoride etherate, gives mainly the *syn*-isomer[56] (**49**), i.e. Cram selectivity. For the example given, changing R from $SiBu^tMe_2$ to $Si(Pr^i)_3$ raises the *syn* preference considerably, which the authors refer to as the 'triisopropylsilyl effect.' Even when the R^L and R^S groups are as similar as ethyl and methyl, a *syn*:*anti* ratio of 5.4 was achieved using the triisopropylsilyl ketene thioacetal.

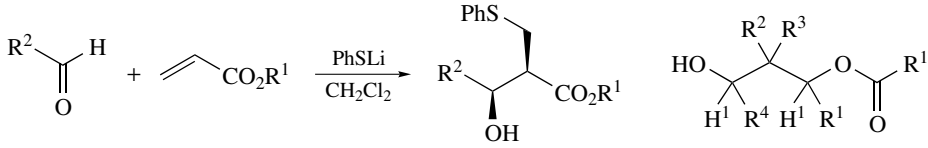
Samarium and other lanthanide iodides have been used to promote a range of Mukaiyama aldol and Michael reactions.[57] The syntheses show promise as enantioselective transformations, but the precise mechanistic role of the lanthanide has yet to be elucidated.



(**48**) (**49**)

A bulky methylaluminium diphenoxide has been used as a co-catalyst with trimethylsilyl triflate to effect diastereoselective Mukaiyama aldols, including cases with less reactive aldehydes, and with ketones.[58]

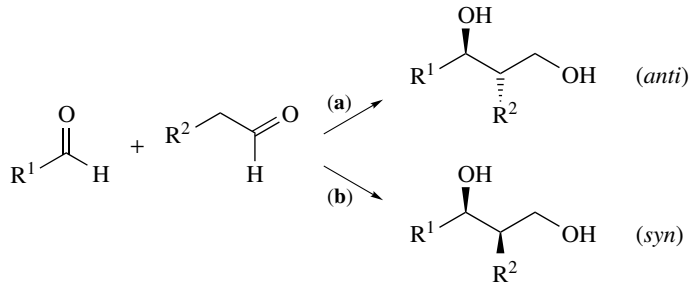
α-Phenylthiomethyl-β-hydroxy esters (**50**) can be prepared, predominantly as the *syn*-isomer, by a stereoselective one-pot Michael–aldol tandem reaction.[59] The seleno analogue can similarly be prepared (again, mainly *syn*), using PhSeLi in diethyl ether, but phenoxide ion is not sufficiently reactive for this sequence.



(**50**) (**51**)

In the aldol–Tishchenko reaction, a lithium enolate reacts with 2 mol of aldehyde, ultimately giving, via an intramolecular hydride transfer, a hydroxy ester (**51**) with up to three chiral centres (R^1, H^1 derived from R^1CH^1O). The kinetics of the reaction of the lithium enolate of *p*-(phenylsulfonyl)isobutyrophenone with benzaldehyde have been measured in THF.[60] A kinetic isotope effect of $k_H/k_D = 2.0$ was found, using benzaldehyde-*d*. The results and proposed mechanism, with hydride transfer rate limiting, are supported by *ab initio* MO calculations.

Complete control of the diastereoselectivity of the synthesis of 1,3-diols has been achieved by reagent selection in a one-pot tandem aldol–reduction sequence (see Scheme 1).[61] *Anti*-selective method (a) employs titanium(IV) chloride at 5 °C, followed by $Ti(OPr^i)_4$, whereas method (b), using the tetrachloride with a base at −78 °C followed by lithium aluminium hydride, reverses the selectivity. A non-polar solvent is required (e.g. toluene or dichloromethane, not diethyl ether or THF), and at the lower temperature the titanium alkoxide cannot bring about the reduction of the aldol. Tertiary alkoxides also fail, indicating a similarity with the mechanism of Meerwein–Ponndorf reduction.

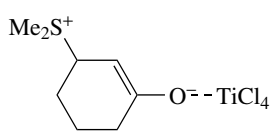


SCHEME 1

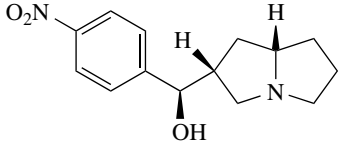
As part of a search for environmentally friendly solid acid–base catalysts, a modified Mg–Al hydrotalcite has been used as a base catalyst for aldol and Knoevenagel condensations.[62] Yields are often quantitative, reaction times are about 1h, the catalyst can be recovered by filtration, and only moderate temperatures are required (60 °C for the aldol, ambient for the Knoevenagel).

Chiral bicyclic 1,2,4-triazolium salts, in which a defined face of the heterocycle is hindered, catalyse the benzoin condensation with up to 80% *ee*, and with the opposite chirality to the corresponding thiazole catalysts.[63] Conformationally restricted chiral bicyclic thiazolium salts have been similarly investigated.[64]

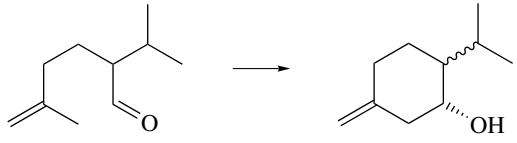
The Baylis–Hillman coupling of activated alkenes with aldehydes or ketones is a useful synthetic route, but can be very slow, even with catalysts from Group 15 (amines, phosphines), or, more recently, lanthanides. A chalcogen variant has now been reported,[65] in which 0.1 equiv. of catalyst gives high yields in 1 h at room temperature, using the condensation of *p*-nitrobenzaldehyde and cyclohex-2-enone as reference reaction. Most of the chalcogenides used were cyclic structures involving two heteroatoms (S/Se/N), but even dimethyl sulfide is effective in some cases. Several common Lewis acids were employed as co-catalysts, of which $TiCl_4$ at a level of 1 equiv. proved best. The mechanism is proposed to involve coordination of titanium at the enone oxygen, followed by, e.g., sulfide attack at the β-vinyl position to give a zwitterionic enolate (**52**), which then reacts with the aldehyde.



(**52**)



(**53**)



(**54**) (**55**)

A chiral pyrrolizidine (**53**) catalyses asymmetric Baylis–Hillman reactions.[66] Important structural features include an accessible nitrogen lone pair and a strategically placed hydroxy group; the latter may also interact with alkali metal cations, which catalyse the reaction.

Enal (**54**) undergoes intramolecular carbonyl–ene cyclization to give *cis*- and *trans*-alcohols (**55**).[67a] Lewis acids such as boron trichloride and tin tetrachloride (and also dimethylaluminium chloride[67b]) give predominantly the *cis* product, while the preference is reversed with the bulky $MeAlAr_2$(Ar = OC_6H_2-4-Br-2, 6-di-Bu^t). 'Open' and 'closed' chair-like transition states are considered and compared with previous

mechanistic models, but it is suggested that a boat-like state is required to explain the formation of *trans*-(**55**).

Activated enophiles such as aldehydes and keto diesters undergo ene reactions to give homoallylic alcohols:[68] a ruthenium(II) complex is employed as catalyst in an apparently stepwise process.

The Horner–Wadsworth–Emmons reaction has been explored by quantum-mechanical calculations on the formaldehyde–trimethylphosphonacetate [$O{=}P(OMe)_2{-}\bar{C}H{-}CO_2Me$] model system.[69] The reactants form an oxyanion, which can then ring close to an oxaphosphetane. The latter step was found to be rate determining in the gas phase, but solvation typically changes the course of the reaction significantly, making oxyanion formation rate limiting.

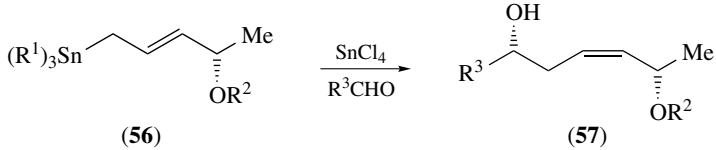
An asymmetric Horner–Wadsworth–Emmons reaction has been developed which uses an external chiral ligand to avoid the need to prepare chiral phosphonate derivatives.[70]

Allylations

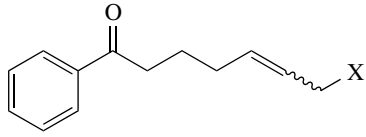
A theoretical study of allylboration of aldehydes shows that (i) an initial complex may form, but if so, it is weak, and predicted reactivity trends are unchanged whether it is taken into account or not, and (ii) electron delocalization from the aldehyde oxygen to the boron *p* atomic orbital governs the reaction.[71]

Tin(IV) halide-catalysed reactions of 4-, 5-, and 6-alkoxy(alk-2-enyl)stannanes exhibit 1,5-, 1,6-, and 1,7-asymmetric induction, respectively.[72a] For example, 4-substituted (pent-2-enyl)stannanes (**56**) give ε-hydroxy derivatives (**57**) with a *syn*:*anti* ratio of >30 for hydroxy and benzyloxy substrates (i.e. $R^2 = OH$, OCH_2Ph). A key allyltin trichloride intermediate has now been identified, and the transition states for its reaction with aldehyde have been calculated as being over 10 kcal mol^{-1} apart for the alternative product stereochemistries.[72b]

Intramolecular cyclization of tethered phenyl ketones (**58**; X = Br, $SiMe_3$) show contrasting stereochemical outcomes for indium catalysis of the alkyl bromides and fluoride ion-induced reaction of the allylsilanes.[73] The reactions thus allow complementarity in product diastereoselectivity, and the difference appears to be related to an



(**56**) (**57**)



(**58**)

intramolecular cyclic transition state in the former, versus an open-chain antiperiplanar one in the latter.

Chiral alkoxy- and aminomethyl-substituted α-allylsilyl carbanions have been reacted with aldehydes to give 1-silylhomoallylic alcohols with high γ-regioselection and *E*-stereoselection, and moderate to good *de*.[74]

(*E*)- or (*Z*)-γ-alkoxyallylstannanes, $Bu_3SnCH_2CH{=}CHOR$, undergo a light-promoted reaction with various classes of carbonyl compounds (aldehydes, ketones, α-diketones) to give homoallylic alcohols with retention of double-bond geometry.[75] A series of single electron transfers are proposed to account for the transformation.

A norpseudoephedrine auxiliary has been used to achieve >98% *ee* in the preparation of homoallylic alcohols from aliphatic alcohols and allylsilane.[76] On-line NMR spectroscopy has been used to shed light on the mechanism, including a diversion that occurs if the temperature is not kept low enough.

An allylzinc addition is described under *Addition of Organometallics* below.

Other Addition Reactions

General and Theoretical

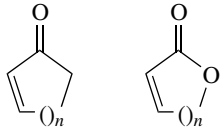
The intrinsic basicities of cyclopentenone and cyclohexenone (**59**), and their lactone analogues (**60**), have been accessed via measurement of their gas-phase proton affinities, and compared with the saturated carbonyl compounds in both cases.[77] The results indicate that:

(i) basicities are greater for the larger rings;
(ii) unsaturated lactones are more basic than their acyclic analogues; and
(iii) cyclic ketones are made more basic by α,β-unsaturation, whereas ketones are not.

Ab initio calculations identify the sources of these effects: for example, in unsaturated ketones the double bond participates fully in the change in charge distribution accompanying protonation, while in the unsaturated lactones, the ring oxygen impedes this shift of electron density.

The hydrogen-bond basicities of a very extensive range of aldehydes and ketones have been measured, and are reported in terms of Taft's pK_{HB} scale.[78]

Ab initio calculations on the interaction of HF with a wide variety of carbonyl types show correlations between the energy of hydrogen-bond formation and both the H−F



(**59**) (**60**)

$n = 1, 2$

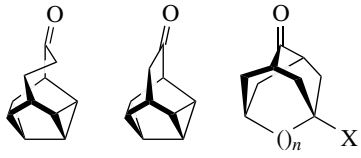
infrared stretching frequency and bond length.[79] However, a correlation of this energy with the atomic charge on the carbonyl oxygen in the isolated molecules failed, but the molecular electrostatic potential at the oxygen *does* show a linear relationship over the whole series studied.

Several theoretical and experimental approaches to understanding π-facial selectivities of nucleophilic additions have been described. The factors affecting selection in addition of nucleophiles to cyclohexanone and its thione analogue have been probed via *ab initio* calculations.[80] A wide range of nucleophile basicities have been included, while minimizing structural change, by using substituted acetylide and cyanide ions. As the nucleophile approaches, the carbonyl carbon becomes more electron deficient, with polarization in the π-bond not being compensated until very late in the addition. Examining the relative stabilities of the axial and equatorial transition states, the relationship to nucleophile basicity is found to be parabolic: *the axial preference is maximal for moderately basic anions*, and is diminished (or reversed) for the most and least basic. Hence the axial preference coincides with the maximum electron deficiency at the reaction site, and is reduced for reactions proceeding through very early or late transition states. Thus the axial approach appears to result from stabilization of the electron-deficient carbonyl carbon by σ_{C-H} hyperconjugation. This is further borne out by the greater axial preference in the case of the ketone versus the thione, consistent with the greater electron deficiency in the former.

When a nucleophilic reagent, Nu^-X^+ (or Nu−X), is reacted with a ketone, complexation of oxygen by X^+ may precede attack at carbon. Geometric changes associated with such complexation have been calculated for a series of 4-substituted cyclohexanones.[81] The results allow the facial selectivity of the subsequent nucleophilic attack to be predicted, and without the need to calculate the *transition-state* geometry.

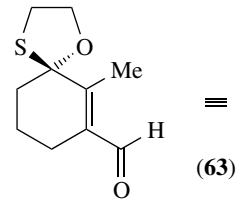
4-Substituted snoutan-9-ones **(61a)** undergo nucleophilic additions with the same facial selectivity as the corresponding norsnoutanones **(61b)**.[82a] However, the selectivity is markedly reduced, apparently owing to electrostatic effects in **(61a)**, and hyperconjugative interactions in **(61b)**.[82b]

The effect of remote halo substitution on the face selectivity of addition to 5-haloadamantan-2-ones **(62b)** has been extended to the corresponding nor- and homoadamantane systems, **(62a)** and **(62c)**, and to some of their aza and diaza analogues.[83] A *syn* approach of the nucleophile is favoured in all cases.



(**61a**) (**61b**) (**62a,b,c**)

a: $n = 0$
b: $n = 1$
c: $n = 2$



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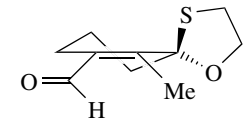
(**63**)



The diastereoselectivity of nucleophilic addition to 6-methyl-1-oxa-4-thia-spiro[4.5]dec-6-ene-7-carbaldehyde **(63)** has been explored for a variety of sp^3-, sp^2-, and *sp*-nucleophiles.[84a] In addition to having a strategically placed heteroatom, the position is also vinylogous. A range of selectivities was observed, from modest preference *anti* to sulfur, to a strong preference for *syn* in the case of phenylmagnesium bromide. The selectivities, which were sensitive to solvent polarity, were not explicable in terms of Wipf's dipole model.[84b,c] The *syn* selectivities observed for the sp^2/sp-nucleophiles investigated are speculated to arise from specific electrostatic attractions for S for such nucleophiles with their negative charges concentrated on carbon.

Hydration and Related Reactions

Calculations support a cooperative mechanism for the hydration of formaldehyde, acetaldehyde, acetone, and cyclohexanone in water.[85] The results are supported by determination of the rate constant for the neutral hydration of acetone, using labelled acetone and water. Conclusions include:

(i) four non-spectator water molecules are involved in neutral hydration;
(ii) acetaldehyde is hydrated *syn* to hydrogen; and
(iii) equatorial hydration of cyclohexanone is >100 times faster than axial hydration.

Gas-phase acid-catalysed additions of water and methanol to ethanol and its α-halo derivatives have been investigated by computation; both reactions are favoured by increasing the electronegativity of the halogen.[86]

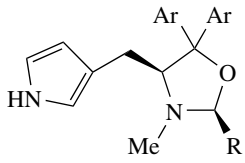
The energy barrier for the gas-phase addition of ammonia to formaldehyde has been calculated,[87] and a molecular dynamics study of its hydration in aqueous sulphuric acid is reported.[88]

For hydration of an α-aminotetrahydropyranone, and the hydrate and hydrate anion of α,α,α-trifluoroacetophenone, see under *Acetals* and *Aldols* above, respectively.

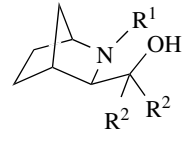
Addition of Organometallics

Several stereoselective dialkylzinc additions have been reported. The oxazolidine catalyst series **(64)** gives moderate *ee*s in the addition of diethylzinc to benzaldehyde.[89] Substituent effects on the mechanism of induction have been explored for a range of aliphatic and aromatic R groups, and two variants of Ar (*o*- and *p*-tolyl).

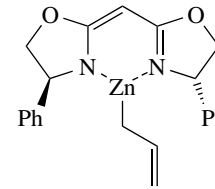
Chiral amines, $ArC^{*}H(R)NH_2$, can be prepared by addition of a dialkylzinc to *N*-(diphenylphosphinoyl)imines, $ArCH{=}N{-}P(=O)Ph_2$, using a suitable auxiliary, followed by acid hydrolysis to cleave the phosphorus moiety.[90] A series of 2-azanorbornylmethanols **(65)** give *ee*s up to 92%, and they also induce some enantioselectivity in additions to benzaldehyde. A highly organized transition state with two zincs is proposed: one coordinates the nitrogens of substrate and catalyst and the other coordinates the oxygens.



(**64**)



(**65**)

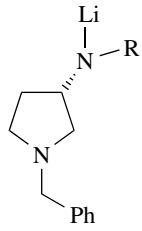


(**66**)

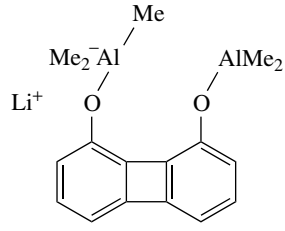
Other diethylzinc studies include enantioselective additions to benzaldehyde using aziridine alcohols as catalysts,[91] to ketones using a camphorsulfonamide–titanium alkoxide catalyst,[92] to aromatic aldehydes using (*S*)-valine-derived *N,S*-chelate ligands possessing a stereogenic nitrogen donor atom,[93] and using a chiral *o*-hydroxyphenyldiazaphospholidine oxide catalyst.[94]

A diastereomeric allylzinc **(66)** has been used to allylate alkyl ethynyl ketones with >90% *ee*.[95] The more substituted the alkyl group, the higher is the selectivity: adamantyl gives >99.9%. However, even $PhCH_2CH_2COC{\equiv}CH$ reacts with >90% *ee*, indicating that **(66)** can recognize small differences between the groups flanking the carbonyl.

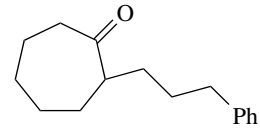
Among other enantioselective alkylations, a series of 3-aminopyrrolidine lithium amides (**67**; derived from 4-hydroxy-L-proline) have been used to induce high *ee*s in the addition of alkyllithiums to various aldehydes.[96] Structure–activity relationships are identified, and the role of a second chiral centre (in the R group) in determining the stereochemistry of the product is discussed.



(**67**)



(**68**)



(**69**)

A template (**68**) containing two aluminium centres, one nucleophilic and the other electrophilic, accelerates nucleophilic alkylation of aldehydes.[97]

Alkylation of the enolates of cycloalkane-1,3-diones has been carried out for ring sizes 7–10, using various reagents and solvents.[98] *O*-/*C*-Alkylation ratios are found to decrease generally with increasing ring size, an effect ascribed to greater steric strain in the conjugated enolate resonance contributor.

The concept of 'memory of chirality'[99a]—in which the chirality of the starting material is preserved in a reactive intermediate for a limited time—is discussed with particular reference to the *C*-alkylation of enolates of chiral ketones.[99b]

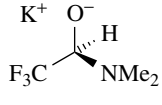
As part of a strategy of employing monosaccharides as a convenient source of chirality, organometallic additions to protected L-erythrulose derivatives have been carried out.[100] Employing silyl, benzyl, trityl, and acetonide protecting groups, the diastereoselectivities obtained are discussed in terms of chelation to the α-and/or the β-oxygen, and are compared with results for similar aldehydes.

Several approaches to stereoselective Grignard reactions are described. Placement of an L-fucose or D-arabinose unit β or γ to an aldehyde has been used to achieve highly diastereoselective addition of Grignard reagents (and of allyltributyltin with added magnesium bromide), exploiting coordination of the sugar ring oxygen to magnesium.[101]

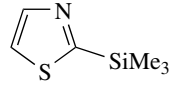
The mechanisms of addition of organomagnesium reagents to 2-hydroxypropanal (a model chiral α-alkoxycarbonyl compound) have been predicted for the gas phase by calculation.[102] Thermodynamics, barrier heights, stereochemistry, intra- versus inter-molecular routes, and stoichiometry ('assisted' intermolecular, using 2 equiv. of Grignard reagent) have all been investigated. A predictive model has been developed for the *anti*:*syn* product ratio in the addition of MeMgCl to such compounds, using quantum-mechanical calculations and a kinetic analysis.[103]

In an investigation of the stereoselectivity of nucleophilic addition to larger ring systems,[104] ethyl-, vinyl-, and ethynyl-lithium and -Grignard reagents have been added to 2-(3′-phenylpropyl)cycloheptanone (**69**). In all cases, the predominant product is the *cis*-alcohol, and calculations have been used to identify the steric and torsional effects in the transition state that favour this stereochemistry.

Fluoroform (CHF_3) efficiently trifluoromethylates aromatic aldehydes to the corresponding alcohols when deprotonated by potassium DMSylate in DMF.[105] This is surprising, as species such as KCF_3 have carbenoid character, and tend to be unstable. However, the reaction fails for solvents such as THF, and appears to depend on a highly specific role for DMF. It is proposed that 'CF_3^-' is trapped *in situ* by the solvent to form the *gem*-amino alcoholate (**70**), which acts as a stable, masked form of the anion, which then attacks the aldehyde, regenerating DMF.



(**70**)



(**71**)

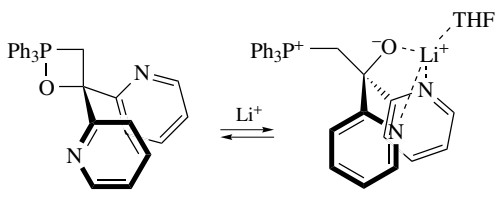
Dondoni pioneered the use of 2-(trimethylsilyl)thiazole (**71**) as a formyl anion equivalent for the homologation of aldehydes.[106a] Extension of this reaction to ketones would be very useful, but has thus far been restricted to trifluoromethyl cases.[106b] However, it has now been widened to include several α, α'-alkoxy ketones, as demonstrated in a new route to branched-chain monosaccharides.[106c] Aldehydes catalyse the reaction, although the scope is still limited: electrophilic aldehydes, such as 2-fluorobenzaldehyde, promote the addition of (**71**) to electrophilic ketones.

pH–rate profiles have been constructed for the reaction of barbiturate anions with 2- and 4-nitro- and 2,4-dinitro-benzaldehydes,[107] with the observed behaviour being explained in terms of tautomerism in the tetrahedral intermediate.

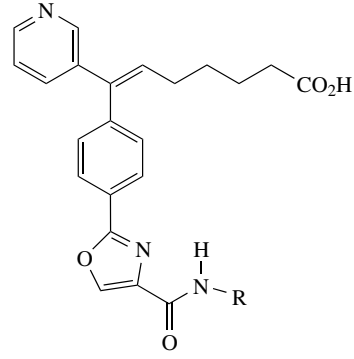
Several studies of the Wittig reaction, and newer variants, are reported.

Calculations on two Wittig reactants, alkylidenetriphenylphosphorane (a non-stabilized ylid) and its benzylidene analogue (a semi-stabilized one), have been used to identify the origin of the product selectivities for the two classes.[108] A planar transition state gives a *trans*-oxaphosphetane intermediate, while a puckered one leads to *cis*-. These two transition states were favoured by the semi- and un-stabilized reactants, respectively.

The stereochemical outcome of the Wittig reaction can depend on the presence or absence of lithium salts.[109a] This may be due to a betaine intermediate stabilized by lithium cation. A stable adduct of this type has now been observed during a Wittig reaction.[109b] When $Ph_3P{=}CH_2$ is treated with 2,2′-dipyridyl ketone, ^{31}P NMR shows the formation of an oxaphosphetane (**72**) and addition of lithium bromide gives the chelation-stabilized betaine lithium adduct (**73**).



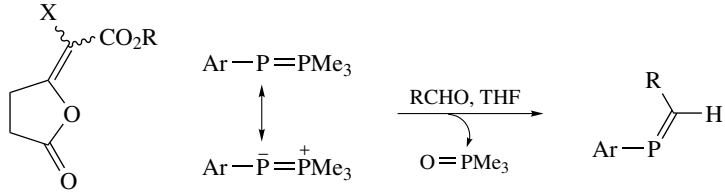
(**72**) (**73**)



(**74**)

The (E)-alkene (**74**) is formed from Wittig reaction of the corresponding phenyl 3-pyridyl ketone: the stereochemical preference is determined by an interaction (either hydrogen bonding or salt bridging) between the carboxylic acid chain being introduced and the amide 'tether' provided by the reactant.[110]

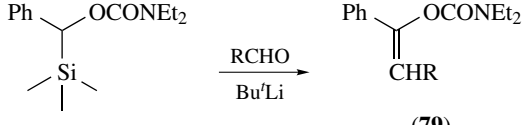
Halo-lactonization of ketophosphoranes has been achieved via reaction with cyclic anhydrides and subsequent halogenation.[111] The products, halo enol lactones (**75**), are synthetically useful compounds, and an alternative synthesis via incorporation of the halogen at the ylid stage is also described. Mechanistic investigation of the Wittig reactions involved reveals subtle variations in pathway, allowing optimum experimental conditions to be selected to allow for the variation in reactivity of different anhydrides and halides.



(**75**) (**76**) (**77**)

The thio-Wittig reaction, like the Wittig itself, may involve (thia)phosphetane or betaine-type structures as intermediates. A combined experimental and theoretical study over a wide range of conditions and of substrates (aliphatic vs aromatic, aldehyde- vs ketone-derived) suggests a mechanistic continuity, with solvent polarity and substrate electronic effects being the main influences on the transition from one mechanism to another.[112]

Two hindered phosphoranylidenephosphines, ArP=PMe$_3$ [**76**; Ar = 2,6-dimesitylphenyl and 2,4,6-tri(*t*-butyl)phenyl], have been prepared and are stable in the absence of air and water.[113] As the resonance suggests, they can enter into 'phospha-Wittig' reactions to produce phosphaalkenes (**77**). The reaction gave high yields of (*E*)-(**77**) in a few hours for a range of benzaldehydes (*p*-Cl/NO$_2$/OMe/NMe$_2$/H, F$_5$), and also for ferrocenecarboxaldehyde and pivaldehyde, but was unsuccessful for ketones.



(**78**) (**79**)
(*E* and *Z*)

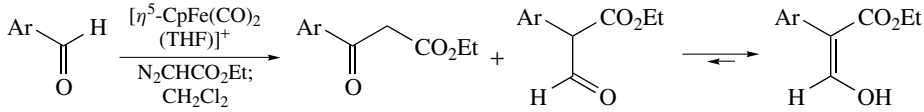
Peterson olefination, a silicon variant of the Wittig reaction, has been used to convert α-silyl benzyl carbamates (**78**) into trisubstituted vinyl carbamates (**79**) in moderate-to-good yields and with some *E*/*Z*-selectivity.[114]

Miscellaneous Additions

Building on a recently introduced reaction classification system that considers electronic effects,[115a,b] a descriptor for steric hindrance has been added.[115c] The expanded classification hierarchy has been applied to a range of representative reactions, including additions to carbonyl compounds, and enolate formation.

The use of pyridinium ylids in the synthesis of carbo- and hetero-cycles has been reviewed (157 references),[116] with a particular focus on nucleophilic addition–eliminations (Ad_N–$E_{1,n}$; $n = 2, 3, 6$).

Treatment of benzaldehydes with ethyl diazoacetate and a catalytic quantity of the iron Lewis acid $[\eta^5\text{-CpFe(CO)}_2\text{(THF)}]^+\text{BF}_4^-$ yields the expected homologated ketone (**80**). However, the major product in most cases is the aryl-shifted structure (**81a**), predominantly as its enol tautomer, 3-hydroxy-2-arylacrylic acid (**81b**).[117] This novel reaction occurs via a 1,2-aryl shift. Although the mechanism has not been fully characterized, there is evidence for loss of THF to give a vacancy for the aldehyde to bind to the iron, followed by diazoacetate attachment. The product balance is then determined by the ratio of 1,2-aryl to -hydride shift, with the former favoured by electron-donating substituents on the aryl ring. An alternative mechanism involving epoxide intermediates was ruled out by a control experiment.



(**80**) (**81a**) (**81b**)

Diazomethane has been used to transfer methylene with high diastereoselectivity to the carbonyl group of a series of β-ketosulfoxides, (R_S)-*p*-tolyl−S(O)−CHR−CO−$CH_xF_yCl_z$, giving the corresponding epoxides.[118]

A clean, Strecker-type synthesis of α-aminonitriles has been developed: amine, aldehyde, tributyltin cyanide, and scandium(III) triflate (as catalyst) are mixed together at room temperature.[119] Yields for a range of aliphatic and aromatic aldehydes are typically ca 90%, the solvent can be organic or aqueous, the 10% catalyst loading is recoverable and reusable, and the tin reagent is similarly recyclable.

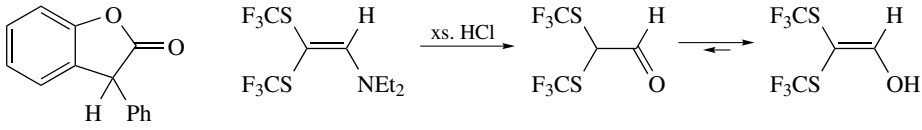
Enantioselective trimethylsilylcyanation of benzaldehydes has been achieved using a lanthanum alkoxide of a chiral binaphthol as catalyst.[120]

Thiols catalyse radical-chain addition of primary aliphatic aldehydes (R^1CH_2CHO) to terminal alkenes ($H_2C{=}CR^2R^3$) to give ketones, $R^1CH_2COCH_2CHR^2R^3$.[121] The thiol acts as an 'umpolung' catalyst to promote the transfer of the aldehydic hydrogen to the carbon-centred radical formed when an acyl radical adds to the alkene.

Cyclopropylaldehydes undergo addition reactions with tetramesityldisilene ($Mes_2Si{=}SiMes_2$) and with its germasilene analogue,[122] apparently involving biradical intermediates.

Enolization and Related Reactions

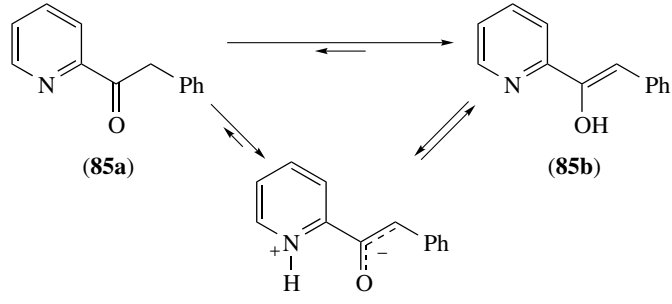
Rate and equilibrium constant measurements for the enolization of 3-phenylcoumaran-2-one (**82**) in aqueous dioxane indicate an enol content of ca 0.1%, a pK_a of 8.9 (6.0 for the enol tautomer), and a fairly symmetrical transition state for enolate anion formation: the Brønsted $\beta_B = 0.52$.[123] Below pH 5, enolization is independent of pH, occurring via *O*-protonation of the enolate.



(**82**) (**84**) (**83a**) (**83b**)

2,2-Bis [(trifluoromethyl)thio] acetaldehyde (**83a**) has been prepared from an enamine precursor (**84**), although refluxing in aqueous ethanolic HCl is required to effect this reaction.[124] The aldehyde is less stable than its enol tautomer (**83b**), and many reactions typical of aldehydes fail. For example, addition of aqueous silver nitrate immediately yields the silver salt of (**83b**), rather than giving precipitation of (elemental) silver. The (trifluoromethyl)thio substituent has pseudohalogenic character and, together with the hydroxy group, stabilizes the alkene tautomer in the manner of a 'push–pull' alkene. The enol–aldehyde equilibrium mixture in acetonitrile shows an apparent pK_a of 2.6 when titrated with aqueous hydroxide.

Enolization and ketonization kinetics and equilibrium constants have been reported for phenylacetylpyridines (**85a**), and their enol tautomers (**85b**), together with estimates of the stability of a third type of tautomer, the zwitterion (**85c**).[125] The latter provides a nitrogen protonation route for the keto–enol tautomerization. The two alternative acid-catalysed routes for enolization, i.e. *O*- versus *N*-protonation, are assessed in terms of pK_a differences, and of equilibrium proton-activating factors which measure the C–H acidifying effects of the binding of a proton catalyst at oxygen or at nitrogen.

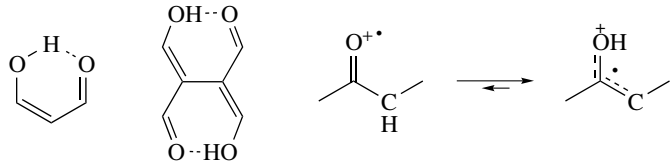


(**85a**) (**85b**) (**85c**)

Concerted acid–base catalysed enolizations of a range of simple aldehydes and ketones have been measured in water at 25 °C, using a range of substituted acetic acid–acetate buffers.[126] The buffer plots yield rate constants for acid (k_A) and base (k_B) catalytic terms in the normal way at low buffer concentrations. Extension up to higher concentrations (as far as [total buffer] = 2 M, typically) yields the third-order term (k_{AB}) via upward curvature of the plots. While k_{AB} does not have a simple correlation with either k_A or k_B, it *does* correlate with their product, i.e.

$\log k_{AB} \propto \log(k_A k_B)$. This simple yet powerful result indicates that concerted catalysis is significant only when both buffer acid and buffer base make comparable contributions. The correlation has a slope of about unity for the aldehydes studied, while for the ketones examined it falls in the range 0.5–0.6. A Brønsted β value and the kinetic solvent isotope effect for the concerted pathway are also reported, and a limited correlation between high enol content and a significant third-order term is also noted.

Malonaldehyde, $CH_2(CHO)_2$, exists as an intramolecularly hydrogen-bonded enol (**86**) in the vapour phase. Molecular dynamics calculations suggest that while a short O−O distance favours proton transfer to an (identical) tautomer, such proximity is neither a sufficient nor a necessary condition.[127]



(**86**) (**87**) (**88a**) (**88b**)

1,4-Dihydroxy-2,3-diformylbuta-1,3-diene (**87**) can undergo degenerate isomerization via the transfer of two hydrogens. It is claimed as the first example of a dyotropic molecule that undergoes concerted low-barrier (3.7 kcal mol^{-1}) double proton exchange.[128]

The greater stability of simple ketones relative to their enol tautomers is reversed on formation of the corresponding radical cations (**88a**) $\rightleftarrows$ (**88b**). In appropriate cases, ionization of the ketone to its cation is followed by spontaneous hydrogen transfer to give the enol radical cation. 1,5-Hydrogen transfer via a six-membered-ring transition state is a common route. Characterization of such mechanisms has been reviewed for a variety of such reactions in cryogenic matrices, where many of the processes that compete in solution are suppressed.[129]

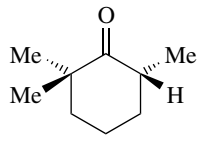
IR spectra of substituted acetophenones, *p*-XC_6H_4COMe, in chloroform suggest the presence of hydrogen-bonded dimers for X = H and NO_2, but not OMe;[130] such association may play a role in keto−enol tautomerization.

The mechanism of the thione-to-thiol rearrangement of *O*,*S*-dialkylxanthates, catalysed by pyridine-*N*-oxide, has been analysed by MO methods.[131]

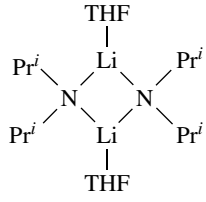
Kinetic and thermodynamic parameters have been measured for the chlorination of simple aliphatic and aryl alkyl ketones in strong acid media by chloramine-B (sodium *N*-chlorobenzenesulfonamide).[132] Catalysis of the monochlorination of acetaldehyde in anhydrous carbon tetrachloride by trichloroacetic acid, and by hydrogen chloride, are reported.[133] IR and UV spectroscopy have been used to probe the reaction of acetaldehyde with trichloroacetic acid in carbon tetrachloride.[134] Two cyclic 1:1 intermediates have been identified, and are found to be in equilibrium.

Enolates

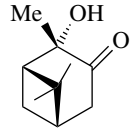
Rates of deprotonation of a simple ketone (**89**) by lithium diisopropylamide (LDA) in THF at −78 °C show a first-order dependence on ketone, and an order of 0.58 (±0.06) in base.[135] Alternative pathways involving the LDA monomer and its solvent-complexed dimer (**90**) are considered.



(**89**)



(**90**)



(**91**)

Racemic α-amino acid esters have been converted to single enantiomers by condensing them with 2-hydroxypinan-3-one (**91**), and then diastereoselectively protonating the resultant chiral Schiff base.[136]

Chiral α-sulfinyl alcohols have proved useful in enantioselective protonation of enolates.[137] Addition of lithium bromide enhances the *ee* in a number of cases, apparently via simultaneous coordination of lithium to the enolate and to the sulfinyl alcohol.

The reactivity of lithium enolates has been explored in a theoretical study of the isomers of C_2H_3OLi, such as the lithium enolate, the acyl lithium, and the α-lithio enol.[138] Imides containing a chiral 2-oxazolidine have been employed for enantioselective protonation of prochiral enolates.[139] A degree of kinetic control of the product E/Z-enolate ratio has been reported for the lithiation of 3,3-diphenylpropiomesitylene, using lithium amides/alkyls.[140]

Oxidation and Reduction of Carbonyl Compounds

Regio-, Enantio-, and Diastereo-selective Redox Reactions

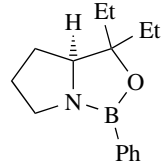
The enantioselective reduction of ketones has been reviewed (317 references).[141]

A detailed kinetic study of the enantioselective reduction of acetophenones, ArCOMe, to arylethanols, using a propan-2-ol–acetone couple and a chiral rhodium diamine catalyst, has been undertaken.[142] Non-linear effects on the % *ee* are observed, e.g. addition of achiral ketones can both slow the reaction *and* raise the *ee*. These effects can be rationalized in terms of the difference in reactivity of diastereomeric catalytic sites. The scope for exploiting such mechanistic insights so as to maximize the enantioselectivity is discussed.

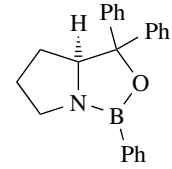
Enantioselective borane reduction of prochiral ketones catalysed by chiral oxaborolidines is of considerable synthetic utility, but the catalytic cycle has to compete with direct borane reduction of the ketone. Accordingly, precise kinetic data on the latter would help optimize conditions for the former. Such a study has been

undertaken for borane in tetrahydrofuran, where the 1:1 BH_3–THF complex is the reaction species, producing a mono- and then a di-alkoxyborane. Taking pinacolone (Bu^tCOMe) as model substrate, the reduction is found to be much slower with freshly prepared reagent, as against the commercial form, commonly stabilized by sodium borohydride.[143] Thus it is found that $NaBH_4$, and also borane decomposites, are catalysts. Changes in reaction order accompanying these catalyses are described, as well as autocatalytic effects. The significance of the results for the design of enantioselective borane reductions is discussed.

The authors then go on to measure the kinetics in the presence of two oxazaborole catalysts, (**92a**) and (**92b**).[144] The rate-determining step is the reaction of the ketone with an oxazaborole–borane complex, with the direct reduction competing with the catalytic cycle (as mentioned above). The oxazaborole reaction, like the direct reduction, is significantly accelerated by the presence of sodium borohydride.



(**92a**)



(**92b**)

Pinacol coupling of aldehydes to produce 1,2-diols is generally thought to proceed via intermediate ketyl radicals formed by single electron transfer. A titanocene catalyst is now reported to produce pinacols in high yield with high (*syn*) *de*: the key to the selectivity is suggested to be a dimeric titanium complex binding both ketyl radicals simultaneously.[145]

Pyridinium fluorochromate oxidizes cycloalkanones to the corresponding 1,2-diketones.[146] The kinetics have been studied in aqueous acetic–perchloric acid mixtures: relative reactivities are explained in terms of conformational and steric effects.

Other Redox Reactions

The reaction of chlorite (ClO_2^-) and formaldehyde produces formic acid and ClO_2, with further oxidation to carbon dioxide in the presence of excess oxidant. The oxidation is rapid, and appears to show oscillatory behaviour near completion.[147] Chloride is also produced, so simultaneous Cl (III) → (IV) and Cl (III) → (I) processes are occurring. Detailed mechanisms have been deduced to explain these phenomena. The apparent oscillations turn out to be mechanical in origin: rapid production of CO_2 bubbles distorts the absorbance readings used. HOCl has an autocatalytic role, reacting much more rapidly with ClO_2^- than with formic acid. As a result, ClO_2 is relatively inert under the conditions studied, to the extent that the chlorite–formaldehyde reaction is an effective, quantitative method of producing it.

The kinetics of the oxidation of a series of *para*- and *meta*-substituted benzaldehydes by quinolinium chlorochromate are first order in substrate, oxidant, and hydronium ion; the results were subjected to a Taft analysis.[148] Oxidation of 2-pyridinecarboxaldehyde to the acid by dichromate follows an unusual mixed fourth-order rate law: it is first order in hydronium ion and Cr(VI), and second order in aldehyde.[149]

Conversion of the thiocarbonyl group into carbonyl has been reviewed.[150] In general, hydrolytic methods catalysed by metal ions are recommended over oxidative methods, as the former are typically cleaner and more easily worked up.

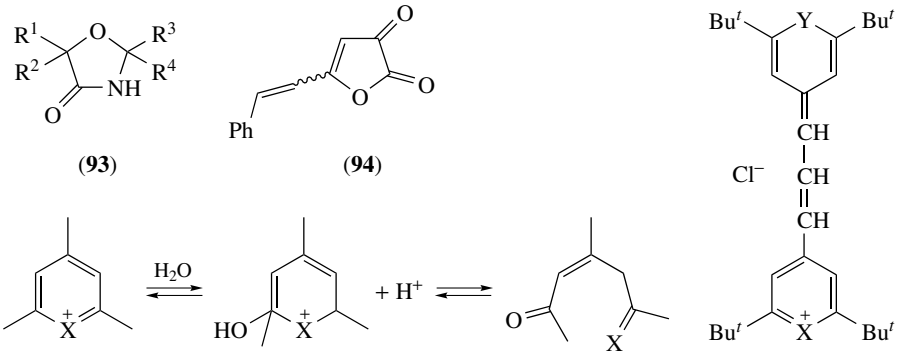
Other Reactions

A range of 1,3-oxazolidin-4-ones (**93**) have been prepared by cyclocondensation of cyanohydrins, $R^1R^2C(OH)CN$, with aldehydes or ketones, R^3COR^4, under anhydrous strong acid conditions.[151] The R groups used are mainly simple alkyl and aryl moieties, and the mechanism is discussed.

The structure of 5-(β-styryl)-2,3-dihydrofuran-2,3-dione (**94**) and its reactions with nucleophiles have been investigated, together with its synthesis via cyclization of cinnamoylpyruvic acid.[152]

Chalcogenopyrylium dyes such as (**95**; X, Y = O/S/Se/Te) have a wide variety of applications based on their near-IR absorbing properties; their hydrolytic stability is critical to their operation. Hydrolysis of simple analogues (**96**) exhibits pseudobase behaviour, with water attack at the 2-position releasing a proton, and setting up a ring-opening equilibrium to an enedione (**97**) $\rightleftarrows$ (**98**).[153a–c] Kinetics of hydrolysis have now been measured in aqueous solution over a wide range of pH for six X, Y combinations of (**95**).[153d] The pH–rate profiles show, as expected, an increase in rate with increasing pH, interrupted by a plateau region corresponding to the pK_a of the dye. The variations in the values of the second-order rate constant for hydroxide are explained in terms of competing effects on aromaticity and on cation stability as X is varied down Group 16.

Silyl propargyl alcohols, $XC{\equiv}CSiMe_2R^3$ [$X{=}R^1CH(OH)CHR^2CH(SPh)$], can undergo palladium(II)-catalysed cyclization to give 2,3-dihydrofurans, or alkyne



hydration to give γ-hydroxy ketones, XCOMe.[154] The mechanisms operating and the factors determining the product balance are discussed.

Absolute rate constants have been measured for the gas-phase reactions of hydroxyl radical with five methyl ketones, MeCOR: R=Me, Et, and $(CH_2)_nCHMe_2$(n = 0, 1, 2).[155]

The kinetics of the reaction of bromine atoms with simple aliphatic aldehydes have been measured by the fast-flow technique with resonance fluorescence detection, and by laser flash photolysis.[156]

A review of the thiocarbonyl group (758 references) covers the preparation, structure, and reactions of various classes of compounds containing this function.[157]

Semiempirical calculations have been used to study the mechanism of the ring opening of cyclopropanone and substituted analogues in a range of solvents of varying polarity.[158] Transition states and oxyallyl intermediates have been characterized, as have the effects of solvents on their stability. The results are also compared with kinetic data in the literature.

Semiempirical calculations on the Favorskii rearrangement of α-chlorocyclobutanone to cyclopropenecarboxylic acid suggest that it proceeds via a stepwise semibenzilic acid pathway, both in solution and *in vacuo*, rather than by a cyclopropanone rearrangement.[159]

The mechanism of the novel transformation of α-nitro- to α-hydroxy-ketones has been probed.[160] The reaction, which proceeds under basic aqueous conditions, requires that the α-nitro substrate be CH-acidic in the α'-position, and that it be readily deprotonated under the conditions employed. NO_2–OH exchange occurs with retention of configuration, with the hydroxyl oxygen being predominantly derived from the solvent. A mechanism involving neighbouring-group participation, via a Favorskii-like cyclopropanone intermediate, is proposed.

The reactions of the species H_3O^+, NO^+, and O_2^+ with a range of aldehydes and ketones have been studied by the selected ion flow tube (SIFT) method.[161] H_3O^+ protonates ketones and aldehydes, with the latter eliminating water under the conditions of measurement. Similarly, NO^+ associates with ketones, but this is followed by hydride transfer for the aldehydes. O_2^+ reactions typically produce several ionic products.

Formaldehyde, in aqueous acidic solution, undergoes cyclotrimerization to trioxane (1,3,5-trioxacyclohexane), and also disproportionation to methanol and formic acid, with some resultant formation of methyl formate.[162] The kinetic behaviour observed suggests a significant autocatalysis by formic acid.

N-(1-Adamantyl)hexafluorothioacetone *S*-imide, $(F_3C)_2C{=}S{=}NAd$, undergoes a range of dipolar cycloadditions with aromatic and aliphatic thiones.[163]

Kinetics of the acid hydrolysis of *N*-alkenyl derivatives of phenoxazine, phenothiazine, and carbazole in aqueous dioxane suggest an AS_E2 mechanism, based on the activation parameters and isotope effects.[164]

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CHAPTER 2

Reactions of Carboxylic, Phosphoric, and Sulfonic Acids and their Derivatives

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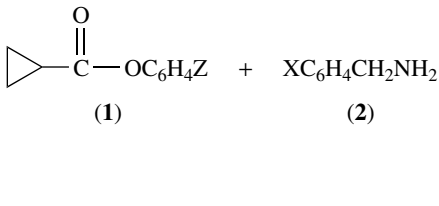
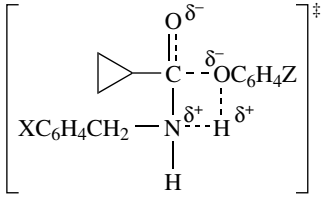
CARBOXYLIC ACIDS

Tetrahedral Intermediates

Kinetic studies of the reaction of Z-phenyl cyclopropanecarboxylates (**1**) with X-benzylamines (**2**) in acetonitrile at 55 °C have been carried out. The reaction proceeds by a stepwise mechanism in which the rate-determining step is the breakdown of the zwitterionic tetrahedral intermediate, $T^{\pm}$, with a hydrogen-bonded four-centre type transition state (**3**).[1] The results of studies of the aminolysis reactions of ethyl Z-phenyl carbonates (**4**) with benzylamines (**2**) in acetonitrile at 25 °C were consistent with a four- (**5**) and a six-centred transition state (**6**) for the uncatalysed and catalysed path, respectively.[2] The neutral hydrolysis of *p*-nitrophenyl trifluoroacetate in acetonitrile solvent has been studied by varying the molarities of water from 1.0 to 5.0 at 25 °C.[3] The reaction was found to be third order in water. The kinetic solvent isotope effect was $(k_{H_2O}/k_{D_2O}) = 2.90 \pm 0.12$. Proton inventories at each molarity of water studied were consistent with an eight-membered cyclic transition state (**7**) model.



(**1**) (**2**)



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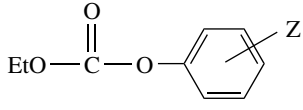

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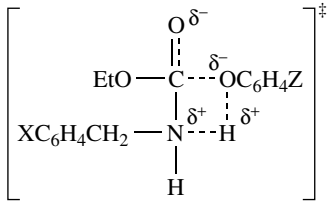
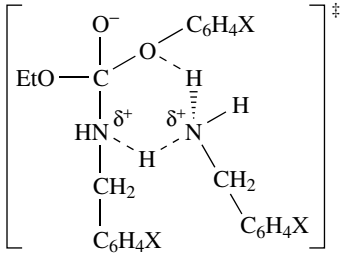
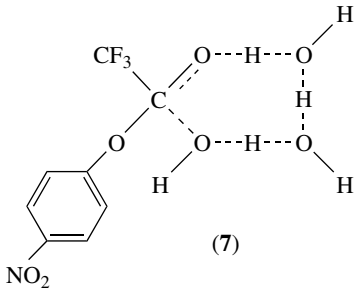


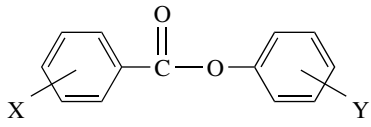
(**5**)



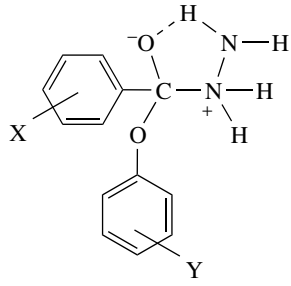
(**6**)



(**7**)



(**8**)



(**9**)

The kinetics of the aminolysis reactions of the α-effect nucleophiles hydrazine and hydroxylamine with Y-phenyl X-benzoates (**8**) have been reported.[4,5] The results demonstrated that the magnitude of the α-effect decreases with increasing electron-withdrawing ability of the acyl substituents. The authors propose that hydrazine stabilizes the transition state (**9**) by intramolecular H-bonding.[5]

Intermolecular Catalysis and Reactions

Reactions in Hydroxylic Solvents

(a) *Esters*

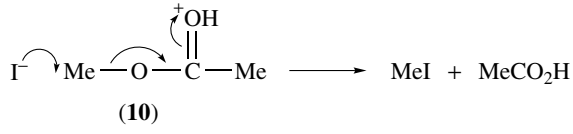
(i) *Formation*

In a kinetic study of the esterification of acetic acid with methanol in the presence of hydrogen iodide, iodimethane was identified as a by-product. The authors propose that this derives from iodide ion attack on protonated methanol.[6] However, attack by iodide ion on protonated methyl acetate (**10**) is more likely, since acetic acid is a better leaving group than ethanol.

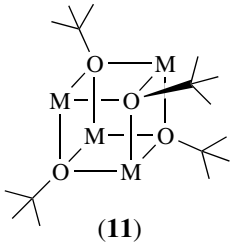
(ii) *Transesterification*

The mechanism and thermodynamics of transesterification of acetate–ester enolates in the gas phase have been investigated.[7] The catalytic effect of alkali-metal *t*-butoxide clusters on the rate of ester interchange for several pairs of esters has been determined in non-polar and weakly polar solvents. Reactivities increase in the order ($Li^+ < Na^+ < K^+ < Rb^+ < Cs^+$) with the fastest rates reaching 10^7 catalytic

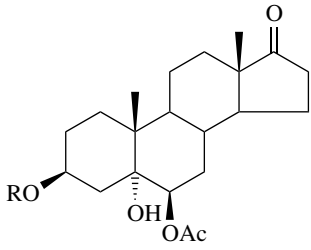
turnovers per hour. The heavier metals (K, Rb, Cs) exist in solution (and in the solid state) as tetrameric structures (**11**). The authors propose that the roles of the clusters in facilitating the rate of transesterification are to supply multiple cations within the cluster framework, these sites stabilizing developing negative charge in the transition state, and to provide scaffolding for first pre-coordinating the ester, potentially activating it, and then delivering the alkoxide nucleophile via a six-membered transition state along the stereoelectronically preferred Bürgi–Dunitz angle.[8]



(**10**)

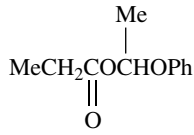


(**11**)



(**12**)

a; R = Ac
b; R = H



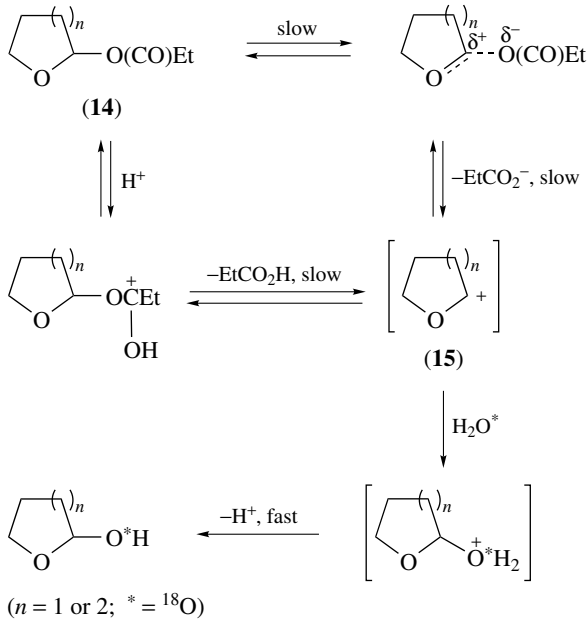
(**13**)

(iii) *Other reactions*

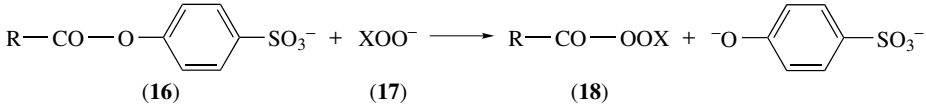
A comparison of the kinetics of alkaline hydrolysis of methyl, isopropyl and butyl acetates in propan-2-ol–water and *t*-butanol–water has revealed that the observed effects correlate with solvent structure.[9]

Tetracyanoethylene (TCNE) has been shown to be a mild catalyst, which possessed some stereoselectivity, for the hydrolysis of the esters of steroidal alcohols. For example, 3β, 6β-diacetoxy-5α-hydroxyandrostan-17-one (**12a**), when treated with TCNE in toluene–methanol (1:1) at 50 °C for 8 h, yielded the 3β-hydroxy compound (**12b**), the 6β-acetoxy group having survived unscathed.[10]

The acid-catalysed hydrolysis of the acylal, 1-phenoxyethyl propionate (**13**), has been studied using the PM3 method in the gas phase.[11] The kinetics and mechanism of the hydrolysis of tetrahydro-2-furyl and tetrahydropyran-2-yl alkanoates (**14**) in water and water–20% ethanol have been reported. In acidic and neutral media, kinetics, activation parameters, ^{18}O isotope-exchange studies, substituent effects, solvent effects and the lack of buffer catalysis pointed clearly to an A_{A1}-1 mechanism with formation of the tetrahydro-2-furyl or tetrahydropyran-2-yl carbocation as the rate-limiting step (Scheme 1). There is no evidence of a base-promoted $B_{AC}2$ mechanism up to pH 12.[12]

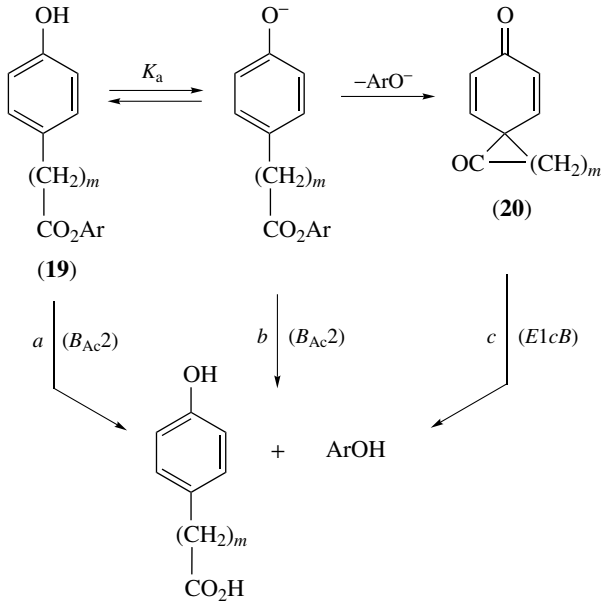


SCHEME 1



Structure–reactivity studies of the reactions between a range of anionic peroxide nucleophiles (**17**; R = H, MeCO, SO_3^-, PO_3^{2-}) and four 4-acyloxybenzenesulfonates [**16**; R = Me, Bu, $Me(CH_2)_7$, $Me_3CCH_2CH(Me)CH_2$] have been reported.[13] The rate data for 4-acetyloxybenzenesulfonate (**16**; R = Me) conformed to a Brønsted-type relationship with $\beta_{nuc} = 0.42 \pm 0.01$, similar to a value of 0.40 ± 0.01 for *p*-nitrophenyl acetate and the same range of peroxide nucleophiles determined earlier by the same group. A larger value of $\beta_{nuc} = 0.56 \pm 0.05$ was obtained for *n*-nonanoyloxybenzenesulfonate [**16**; R = $Me(CH_2)_7$], which was interpreted in terms of steric and polar interactions between the acyl substituents and the attacking peroxide nucleophile.[13] The effect of surfactants on this type of reaction[14] is discussed later on p. 41. These kinetic studies[13,14] were undertaken to provide a set of fundamental data that would provide a backdrop to the action of commercial 'peroxide bleach activators' (e.g. *n*-nonanoyloxybenzenesulfonate) which convert hydrogen peroxide to a better oxidant, an organic peracid (**18**; X = H).

Kinetic studies of the alkaline hydrolyses (pH 11–14) of a series of pentachlorophenyl esters of ω-(*p*-hydroxyphenyl)alkanoic acids (**19**; $m = 1$–4) have been reported.[15] The reasonably high nucleofugality of the pentachlorophenoxide (pK_a

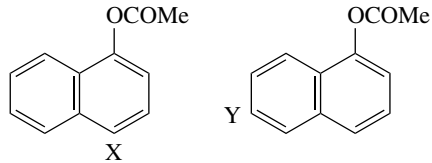


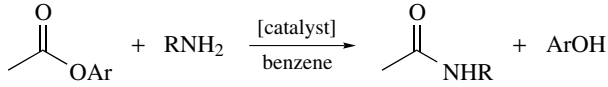
SCHEME 2

of C_6Cl_5OH is 4.79) was considered to be a driving force for the intervention of an *E*l*cB* pathway (path *c*) leading to spiro intermediates (**20**) (Scheme 2). In the event, there was no evidence for that pathway and the hydrolysis of all four esters (**19**; $m = 1–4$) occurred through the usual $B_{AC}2$ mechanism (path *a* or *b*).

Reactions of a wide range of substituted phenyl acetates with six α-effect nucleophiles have revealed little or no difference, compared with phenolate nucleophiles, in the values of the Leffler parameters. As a result, the case for a special electronic explanation of the α-effect is considered unproven.[16] Studies of the kinetics and mechanism of the aminolysis and alkaline hydrolysis of a series of 4-substituted (**21**)[17] and 6-substituted naphthyl acetates (**22**)[18] have revealed that, for electron-withdrawing substituents, aminolysis for both series proceeds through an unassisted nucleophilic substitution pathway.

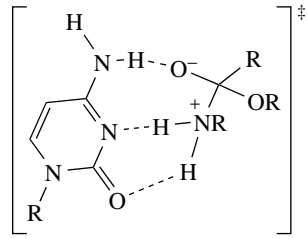
The catalysis by a protected nucleoside of the aminolysis by butylamine of *p*-nitrophenyl acetate in benzene (Scheme 3) has been reported. Interestingly, only 2′, 3′, 5′-*O*-tris(*t*-butyldimethylsilyl)cytidine showed any marked catalytic effect, the adenosine, guanosine and uridine analogues behaving merely as weak general base





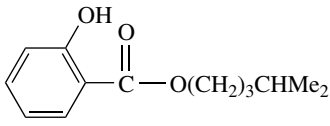
R = $(CH_2)_3Me$
Ar = *p*-$O_2NC_6H_4$

SCHEME 3

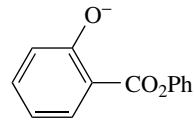


(**23**)

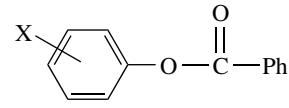
catalysts. The authors propose that a bifunctional mechanism operates, with the protected nucleoside stabilizing the aminolysis transition state (**23**) by simultaneous donation and acceptance of protons.[19]



(**24**)



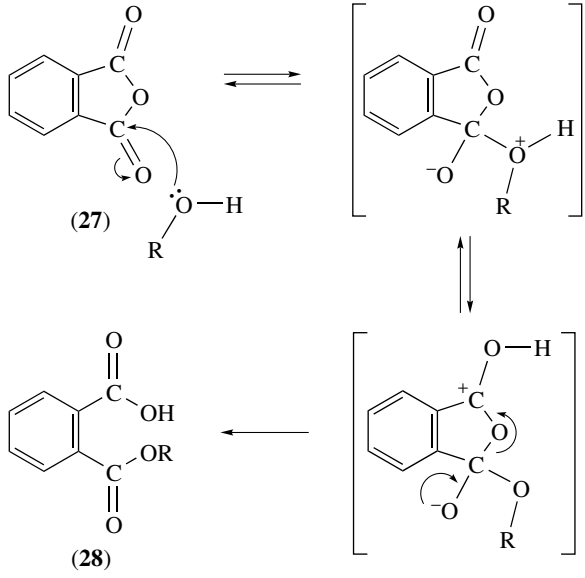
(**25**)



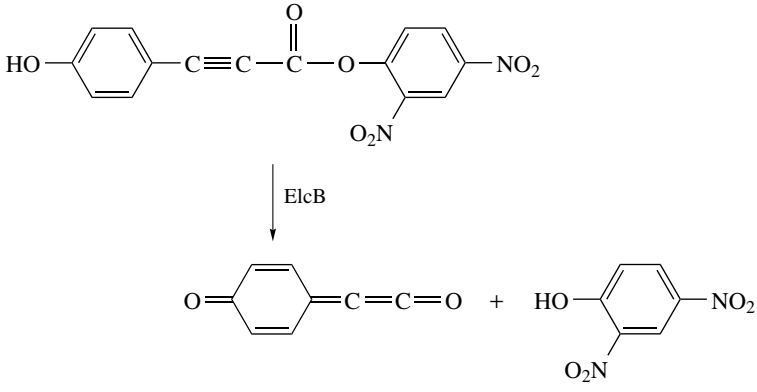
(**26**)

The kinetics of the alkaline hydrolysis of 2-methylpentyl salicylate (**24**) have been studied in various aqueous propanol and *t*-butanol mixtures and in mixtures of water and ethane-1,2-diol.[20] Further studies of the aminolysis of ionized phenyl salicylate (**25**) have been reported, in which it was observed that, in mixed acetonitrile–water solvents, glycine, 1,2-diaminoethane and 3-aminopropanol all reacted as did simple amines, via an intramolecular general-base-catalysed process.[21]

The influence of temperature on the *ortho* effect has been evaluated in the alkaline hydrolysis in aqueous DMSO solutions of *ortho*-, *meta*- and *para*-substituted phenyl benzoates (**26**).[22] The alcoholysis of phthalic anhydride (**27**) to monoalkyl phthalates (**28**) occurs through an *A*-2 mechanism via rate-determining attack of the alcohol on a carbonyl carbon of the anhydride (Scheme 4). Evidence adduced for this proposal included highly negative $\Delta S^{\ddagger}$ values and a ρ value of +2.1. In the same study, titanium tetra-*n*-butoxide and tri-*n*-butyltin ethanoxide were shown to act as effective catalysts of the half-ester formation from (**27**), the mechanism involving alkoxy ligand exchange at the metal as an initial step.[23]

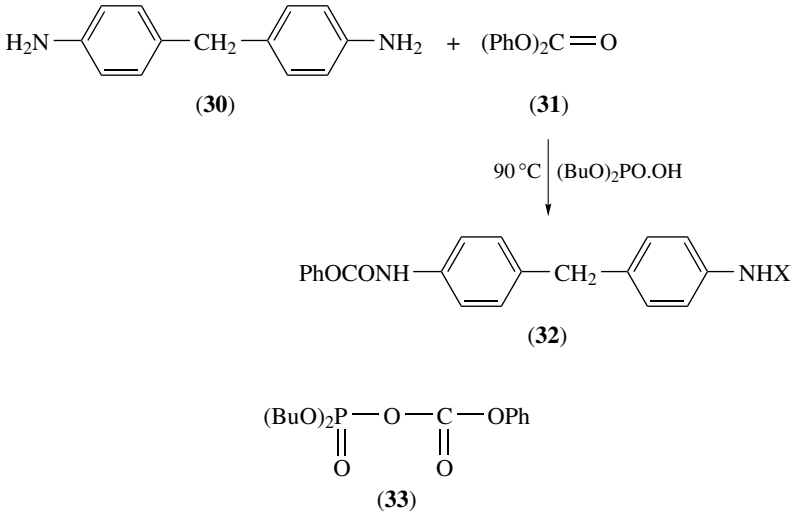


SCHEME 4



As an extension of studies of esters that hydrolyse by dissociative mechanisms, evidence for the operation of the *ElcB* pathway in the alkaline hydrolysis of 2,4-dinitrophenyl 4′-hydroxyphenylpropiolate (**29**) has been sought.[24] No firm conclusion was made, the data merely suggesting the occurrence of the *ElcB* pathway; the data were also consistent with the conventional $B_{AC}2$ pathway.[24]

In the presence of dibutyl phosphate as catalyst, 4,4′-methylenedianiline (**30**) reacts with diphenyl carbonate (**31**) in tetrahydrofuran at 90 °C to give the corresponding mono- (**32**; X = H) or di-carbamate (**32**; X = CO_2Ph), depending on



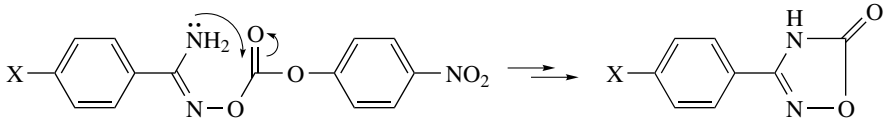
(**30**) (**31**)

(**32**)

(**33**)

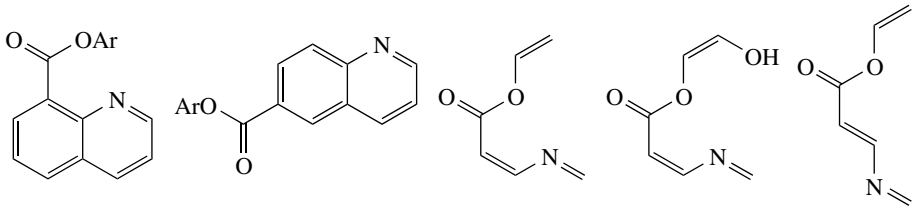
the reaction time.[25] Other organophosphorus acids, e.g. $Ph_2P(O)OH$, $(PhO)_2P(O)OH$ and $BuOP(O)(OH)_2$, are equally effective. The proposed mechanism involves the initial formation of a phosphocarbonate species (**33**), which is a more active carbonylating agent than the parent carbonate.[25]

The kinetics of the cyclization of 4-substituted benzamidoxime 4-nitrophenyl carbonates (**34**; X = H, Me, OMe, Cl, NO_2) in the pH range 8–11 to yield the corresponding heterocycles (**35**) have been studied.[26] At acidic pH, cyclization does not occur and the hydrolysis reaction predominates.



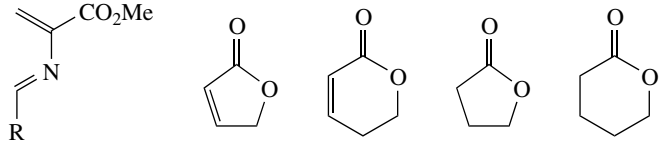
(**34**) (**35**)

The mechanisms of aminolysis of substituted phenyl quinoline-8- and -6-carboxylates, (**36**) and (**37**), have been evaluated using AM1 semiempirical and HF/6–31+G(d) *ab initio* quantum mechanical methods to study the ammonolyses of the model systems vinyl *cis*-3-(methyleneamino)acrylate (**38**), *cis*-2-hydroxyvinyl *cis*-3-(methyleneamino)acrylate (**39**) and vinyl *trans*-3-(methyleneamino)acrylate (**40**). Both experimental and computational results support the formation of a tetrahedral intermediate in the reaction. The results of this study are fully consistent with the experimental observations for the aminolyses of variously substituted phenyl quinoline-8- (**36**) and -6-carboxylates (**37**).[27]



(**36**) (**37**) (**38**) (**39**) (**40**)

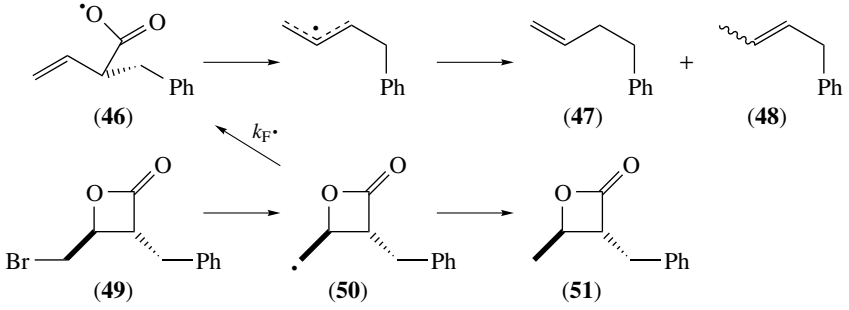
The azadiene bearing a carboxymethyl group (**41**; R = Ph) participates in the Diels–Alder reaction with both electron-rich and electron-deficient dienophiles. However, when groups of greater electron-withdrawing power replace the phenyl group (e.g. R = 4-$O_2NC_6H_4$, COPh, CO_2Et), reaction with only electron-rich dienophiles occurs. A rationale for these observations was made on the basis of a semiempirical molecular orbital study.[28]



(**41**) (**42**) (**43**) (**44**) (**45**)

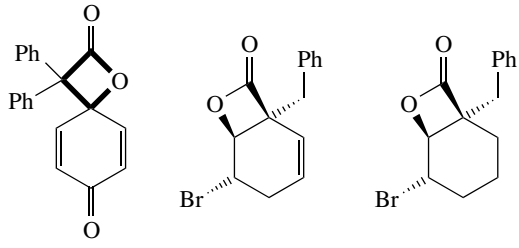
(b) *Lactones and derivatives*

Using Fourier transform ion cyclotron resonance techniques, the proton affinities of the prototypical α, β-unsaturated γ- (**42**) and δ-lactones (**43**) have been determined as 836 and 862 kJ mol^{-1}, respectively. This increase in basicity with the size of the ring also prevails for the saturated analogues (**44**) and (**45**).[29]



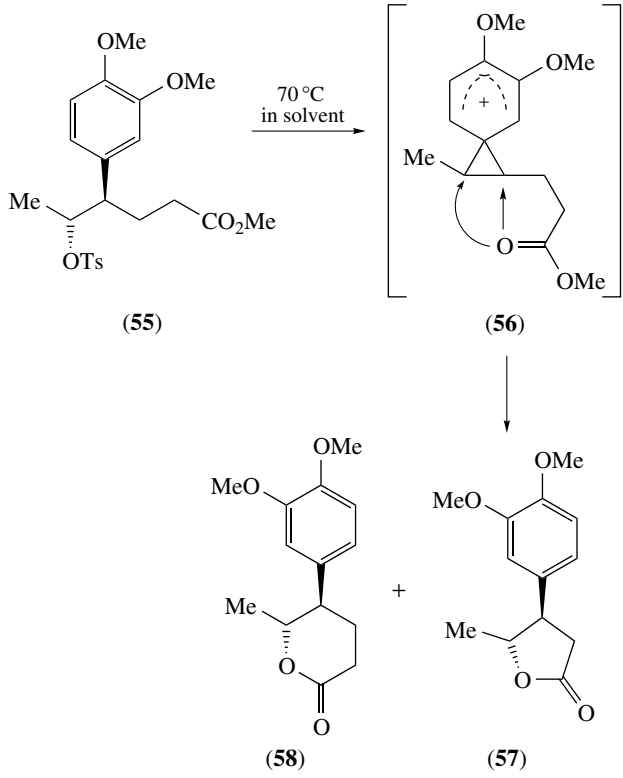
(**46**) (**47**) (**48**) (**49**) (**50**) (**51**)

In an investigation of the free-radical chemistry of β-lactones, a facile decarboxylative cleavage has been observed.[30] For example, the 4-bromo-β-lactone (**49**) reacted with $Bu_3SnH + 5\%(PhSe)_2$ to yield mainly (>95%) the isomeric alkenes (**47**) and



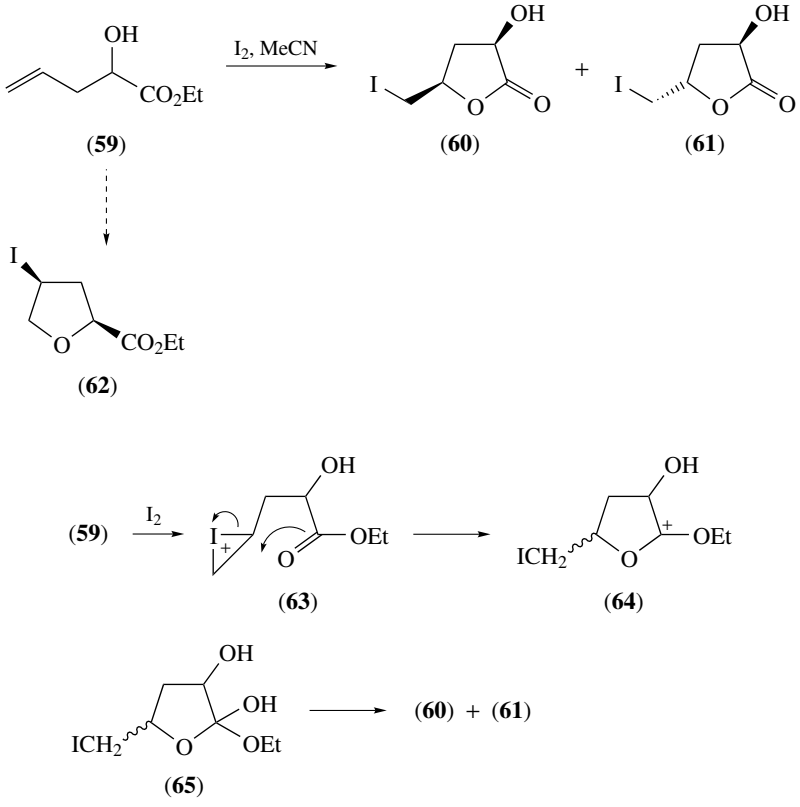
(**52**) (**53**) (**54**)

(**48**), the products of decarboxylation of the ring-opened radical (**46**). The precursor of (**46**) is the 2-oxetanon-4-ylcarbinyl radical (**50**), which is the first-formed intermediate from the 4-bromo-β-lactone (**49**). The ring system of the radical (**50**) remained intact when a molar equivalent of $(PhSe)_2$ was employed, and the saturated β-lactone (**51**) formed by hydrogen atom transfer from PhSeH [produced *in situ* from $(PhSe)_2$] was the major (80%) product. Three bicyclic β-lactones, (**52**), (**53**) and (**54**), were also studied and gave analogous products.[30]



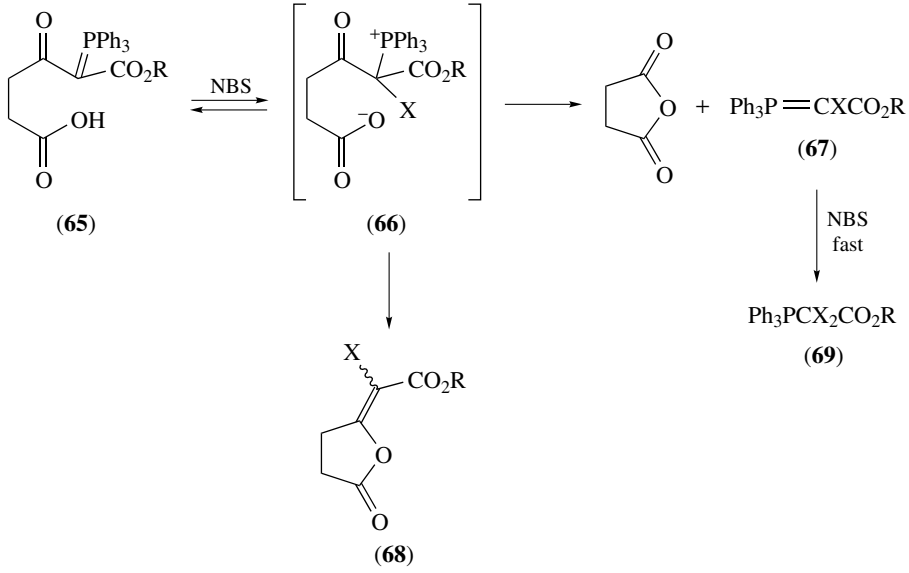
(**55**) (**56**) (**58**) (**57**)

Methyl 4-(3′, 4′-dimethoxyphenyl)-5-tosyloxyhexanoate (**55**) was transformed by heating in acetonitrile solvent at 70 °C into a mixture (2.6:1) of a γ- (**57**) and a δ-lactone (**58**). It is proposed that the products are formed via an intermediate phenonium ion (**56**).[31]

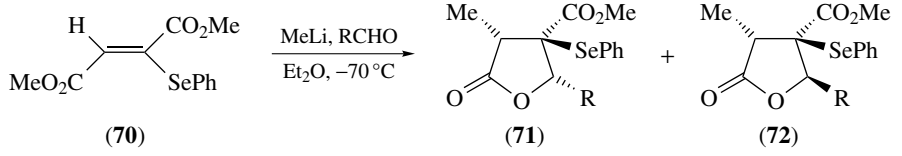


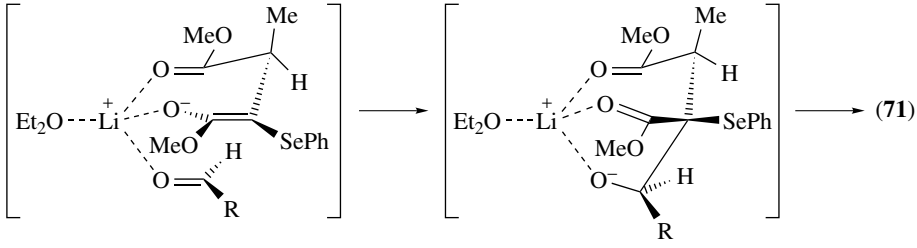
Attempted iodocyclization with iodine in moist acetonitrile of ethyl 2-hydroxypent-4-enoate (**59**) to give the iodotetrahydrofuran (**62**) gave instead a 2:1 mixture (80%) of *syn*- and *anti*-γ-lactones (**60**) and (**61**). Labelling studies with $H_2{}^{18}O$ indicated that the probable mechanism of the reaction involved initial attack of the ester group upon the iodonium ion (**63**) to yield a mixture of epimeric carbocations (**64**), which upon attack by water would yield the orthoesters (**65**), elimination of ethanol from which giving the epimeric γ-lactones (**60, 61**).[32]

The ketophosphorane (**65**; R = Me), the product of reaction between succinic anhydride and carbomethoxymethylenetriphenylphosphorane, undergoes reaction with *N*-bromosuccinimide (NBS) to yield the bromo enol lactone (**68**; X = Br, R = Me) as a 67:33 mixture of *E* and *Z* isomers. The *t*-butyl ester (**65**; R = Bu^t) gave 100% of the corresponding *E* isomer (**68**; X = Br, R = Bu^t).[33] The corresponding



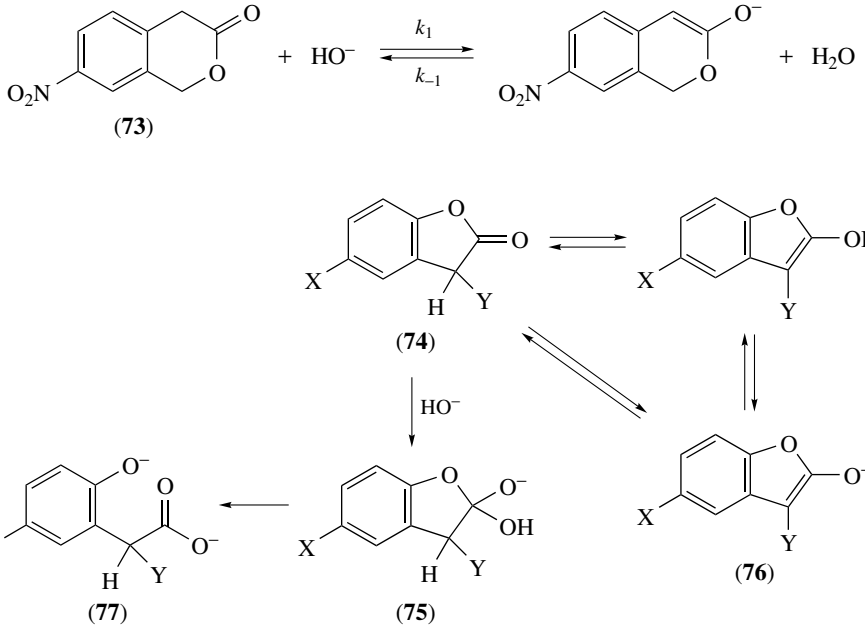
chloro and fluoro enol lactones were preparable using *N*-chlorosuccinimide or *N*-fluorodiphenylsulfonamide, respectively, in place of NBS. Other anhydrides such as glutaric, maleic, phthalic and phenylmaleic anhydrides were also used to prepare the analogous halo enol lactones.[33] The general mechanism of the reaction, illustrated by the ketophosphorane from succinic anhydride (**65**), involves attack by NBS to yield a tetrahedral bromo intermediate (**66**; X = Br) which can either break down to the anhydride and the bromo ylide [which is rapidly brominated by NBS to the dibromo ylide (**69**)], or progress to the bromo enol lactone (**68**; X = Br) via elimination of Ph_3PO.[33]





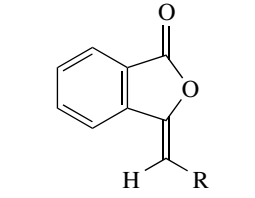
SCHEME 5

Aldehydes react with dimethyl 2-phenylselenofumarate (**70**) at −70 °C in diethyl ether in the presence of MeLi to give good yields of highly substituted 4-phenylselenobutano-γ-lactones (**71**) and (**72**). High diastereoselectivity [for benzaldehyde, (**71**):(**72**)−89:11] was rationalized by assuming the formation of a chelated intermediate between MeLi and (**70**), with approach of the aldehyde from the favoured *si*-face (Scheme 5).[34]

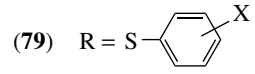


In solutions of sufficient basicity ([NaOH] $\gtrsim$ 0.1 mM) 7-nitroisochroman-3-one (**73**) undergoes reversible deprotonation to form the corresponding enolate. Although ester hydrolysis accompanies enolization, observable quantities of the enolate persist for several seconds. Rate constants for deprotonation by hydroxide ion [$k_1 = 1.31(\pm 0.06) \times 10^4\,\mathrm{l\,mol^{-1}s^{-1}}$], protonation of the enolate by water ($k_{-1} = 212 \pm 24\mathrm{s^{-1}}$), and lactone hydrolysis ($k_{OH} = 19.0 \pm 0.3\,\mathrm{l\,mol^{-1}\,s^{-1}}$) have been determined by monitoring the rates of formation and disappearance of the enolate. The kinetic data were used to calculate the acid dissociation constant for (**73**) (pK_a11.98).[35] Studies of the alkaline hydrolysis of the aromatic lactones coumaran-2-one (**74**; X,Y = H) and some 5-X-substituted 3-phenylcoumaran-2-ones (**74**; Y = Ph) have shown that at high pH the first step is the reversible formation of an enolate ion (**76**), but hydrolysis probably occurs via rate-limiting hydroxide addition to the carbonyl group of the parent compound (**74**) to yield a tetrahedral intermediate (**75**), which breaks down to the dianionic product (**77**).[36] Studies of the base-catalysed hydrolysis in 70% (v/v) aqueous dioxane at 30 °C of substituted 3-phenoxy- and 3-thiophenoxy-methylenephthalides (**78**) and (**79**) have been reported.[37] The rate-determining step in

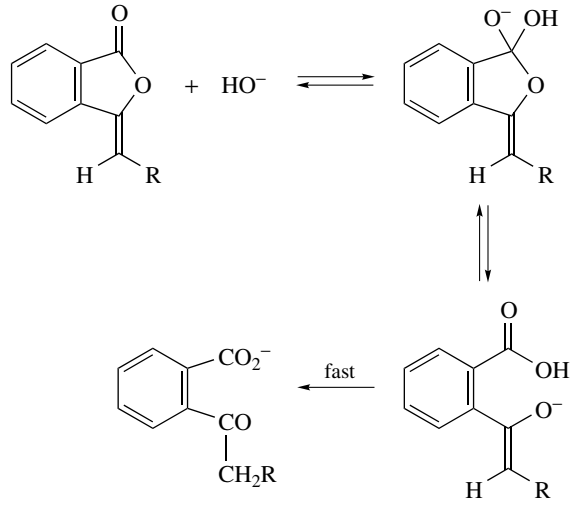
the reaction is considered to be the addition of hydroxide ion to the lactone carbonyl group, as shown in Scheme 6. An excellent correlation was found between the rates of alkaline hydrolysis, the carbonyl stretching frequencies measured in $CHCl_3$ or CCl_4 and Hammett σ constants.[37]



(**78**) R = O–C$_6$H$_4$–X



(**79**) R = S–C$_6$H$_4$–X

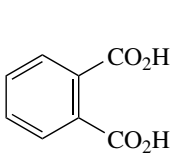


SCHEME 6

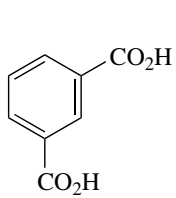
(c) *Acids and anhydrides*

Studies of the thermal degradation of several aromatic acids have been reported. Phthalic acid (**80**), but not isophthalic acid (**81**) or terephthalic acid (**82**), decomposes via dehydration to its anhydride at 140–160 °C. However, (**81**) and (**82**) and benzoic acid are thermally stable below 200 °C.[38] Dissociation constants of all 19 isomers of methyl-substituted benzoic acids (**83**) have been measured in methanol and DMSO. From the pK_a values, the substituent effects of the methyl groups were calculated and tentatively divided into polar and steric effects. Also, in the case

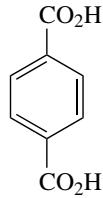
of polymethyl derivatives, the buttressing effect was calculated with reference to monomethyl derivatives. The steric effects may be classified as steric hindrance to resonance—observed only in derivatives with two *o*-methyl groups, and electrostatic induction in the deprotonated molecules—observed in all derivatives. Both effects make the acids stronger and both are attenuated in solution, in methanol more than in DMSO.[39]



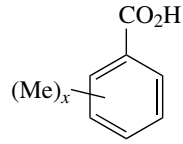
(**80**)



(**81**)

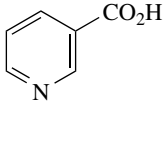


(**82**)

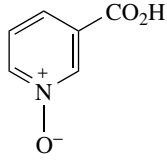


(**83**) $x = 1–5$

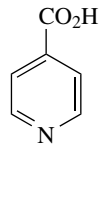
Kinetics of the reaction of diazodiphenylmethane (**92**) in a wide range of alcohols with pyridine and pyridine-*N*-oxide 3- and 4-carboxylic acids (**84**)–(**87**), 4-substituted benzoic acids (**88**),[40] *cis*-4-substituted cinnamic acids (**89**),[41] 2-(4-phenyl-substituted)cyclohex-1-enyl carboxylic acids (**90**), and 4′-substituted-biphenyl-2-carboxylic acids (**91**)[42] have been reported. Comparison of the new results for 4-substituted benzoic acids with the published results of data for 3-substituted benzoic acids was made,[40] and it was concluded that the most important solvent property influencing the rate of reaction appears to be the polarity of the alkyl group expressed as Taft's polar constant σ^*. Transmission coefficients in the cinnamic acids (**89**) were compared with those in the bicyclic acids (**90**) and (**91**).[41,42]



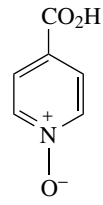
(**84**)



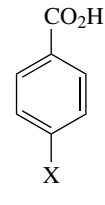
(**85**)



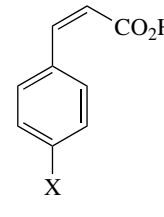
(**86**)



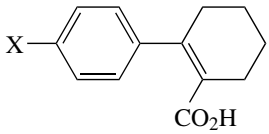
(**87**)



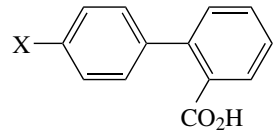
(**88**)



(**89**)



(**90**)

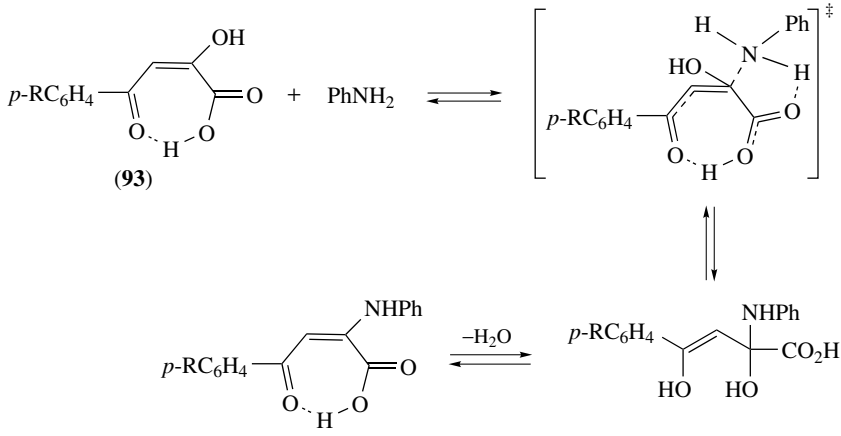


(**91**)

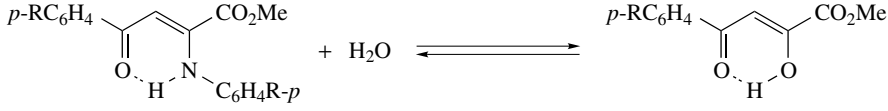
Ph_2CN_2

(**92**)

In the reactions of 4-substituted-benzoylpyruvic acids (**93**) with arylamines in toluene, intramolecular catalysis by the carboxyl group is observed (Scheme 7).[43] By extending these studies in a range of solvents using aniline only,[44] it was observed that the efficiency of intramolecular catalysis by the carboxyl group in these reactions increases with a decrease in the polarity of non-specific solvating solvents; for example, no catalysis is observed with dioxane as solvent.[44] A study of the reverse reaction by the same group[45] has shown that it proceeds via general acid catalysis (Scheme 8).

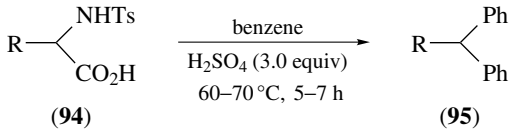


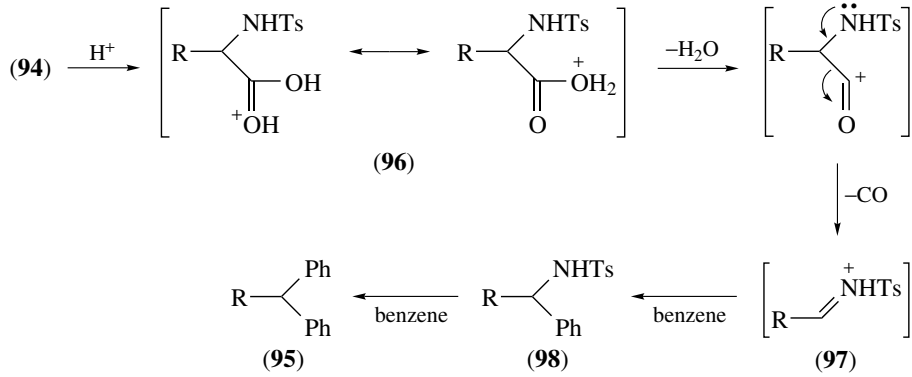
SCHEME 7



SCHEME 8

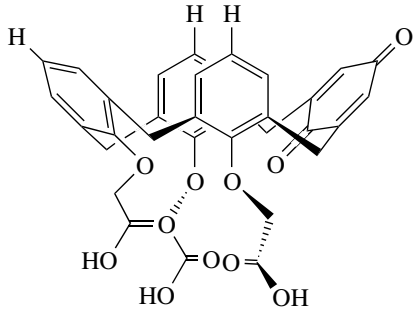
The reaction of various *N*-tosylated α-amino acids (**94**) with benzene in concentrated sulfuric acid yielded diphenyl derivatives (**95**).[46] The mechanism proposed for the reaction (Scheme 9) involves initial protonation of the carboxyl group to give (**96**), which suffers decarbonylation to the *N*-tosyliminium salt (**97**). This reactive electrophile (**97**) interacts with benzene to give a monophenyl compound (**98**) which, via a Friedel–Crafts reaction, interacts with another molecule of benzene to yield the diphenyl compound (**95**).[46] Toluene and *p*-xylene reacted analogously[46] to yield diarylated products.





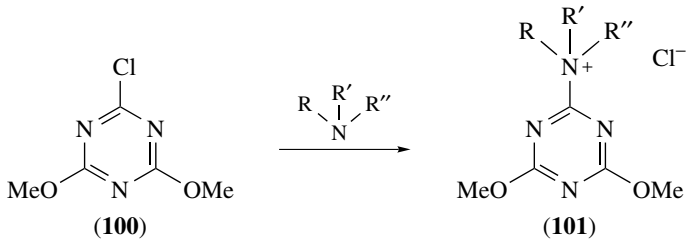
SCHEME 9

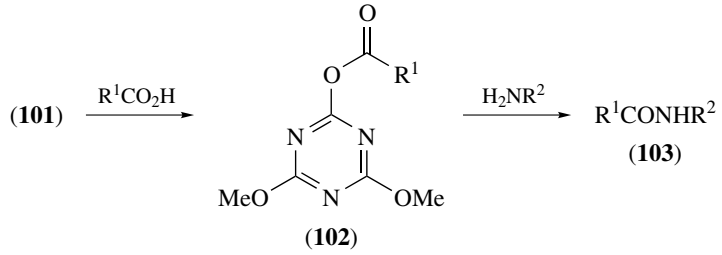
A new water-soluble calix[4]arene-triacid-monoquinone (**99**) has been synthesized and its ion-binding properties in aqueous solution were investigated by means of voltammetry and UV–visible spectrophotometry. The electrochemical behaviour of (**99**) is dependent on the concentration of Ca^{2+} ion rather than that of other alkaline earth metal ions or alkali metal cations. The selective response towards Ca^{2+} was achieved even in the presence of a large excess (>1000-fold) of interfering Na^{+} ion.[47]

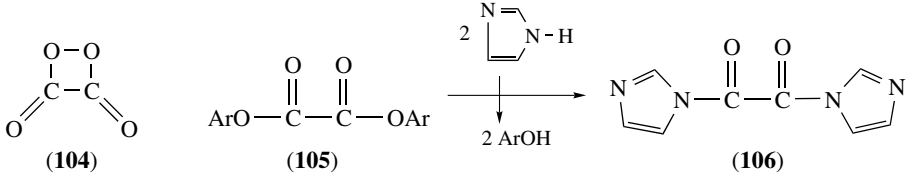


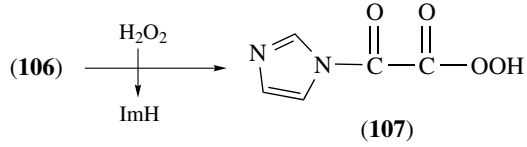
(**99**)

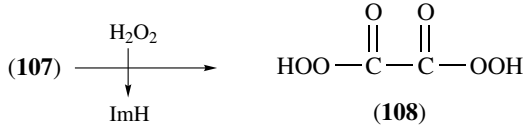
2-Chloro-4,6-dimethoxy-1,3,5-triazine (**100**) reacts with *N*-methylmorpholine at 20 °C to yield an isolable quaternary triazinylammonium salt (**101**; R = Me, R′, R″ = C_4H_8O). This salt can then be reacted with a carboxylic acid to yield a 2-acyloxy-4,6-dimethoxy-1,3,5-triazine (**102**), which, in turn, can be reacted with an amine to yield an amide (**103**).[48] This sequence of reactions provides an explanation for the 'activation' (formation of reactive ester) of the carboxylic acid function by 2-chloro-4,6-disubstituted-1,3,5-triazines (**100**) in the presence of hindered amines. Several other hindered amines may replace *N*-methylmorpholine in the process, but unhindered amines such as triethylamine and tributylamine were inactive.[48]

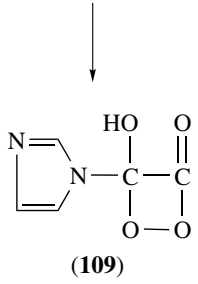

Cl
N
N
MeO
N
OMe
R
R′
R″
N
Cl⁻
N+
(100)
(101)


(101)
R¹CO₂H
O
O
R¹
N
N
MeO
N
OMe
H₂NR²
R¹CONHR²
(102)
(103)


O
O
C
C
O
O
(104)
ArO
O
C
C
O
OAr
(105)
2
N
N-H
2 ArOH
N
N
C
C
N
N
(106)


(106)
H₂O₂
ImH
N
N
O
O
C
C
OOH
(107)

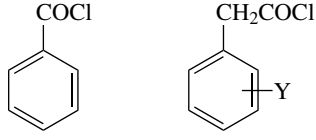

(107)
H₂O₂
ImH
HOO
O
O
C
C
OOH
(108)


N
N
HO
O
C
C
O
O
(109)

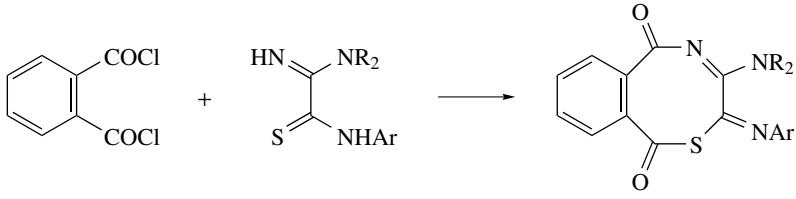
A stopped-flow kinetic investigation[49] of the imidazole-catalysed peroxyoxalate chemiluminescence reaction has led to the proposal that a dioxetanone (**109**) may be responsible for the chemiluminescence, rather than 1,2-dioxetanedione (**104**) which had been suggested previously. The reaction studied, that between bis (2,4,6-trichlorophenyl) oxalate (**105**) and hydrogen peroxide catalysed by imidazole, involves initial formation of 1,1′-oxalyldiimidazole (**106**); (**106**) then reacts with H_2O_2 to yield the monoperoxy acid (**107**), which can progress either to the diperoxy acid (**108**) or to imidazoylhydroxydioxetanone (**109**).[49]

(d) *Acid halides*

A kinetic study of the acylation of ethylenediamine with benzoyl chloride (**110**) in water–dioxane mixtures at pH 5–7 showed that the reaction involves mainly benzoylation of the monoprotonated form of ethylenediamine.[50] Stopped-flow FT-IR spectroscopy has been used to study the amine-catalysed reactions of benzoyl chloride (**110**) with either butanol or phenol in dichloromethane at 0 °C. A large isotope effect was observed for butanol versus butanol-*O*-*d*, which is consistent with a general-base-catalysed mechanism. An overall reaction order of three and a negligible isotope effect for phenol versus phenol-d_6 were observed and are consistent with either a base- or nucleophilic-catalysed mechanism.[51] Mechanistic studies of the aminolysis of substituted phenylacetyl chlorides (**111**) in acetonitrile at −15 °C have revealed that reactions with anilines point to an associative S_N2 pathway.[52]

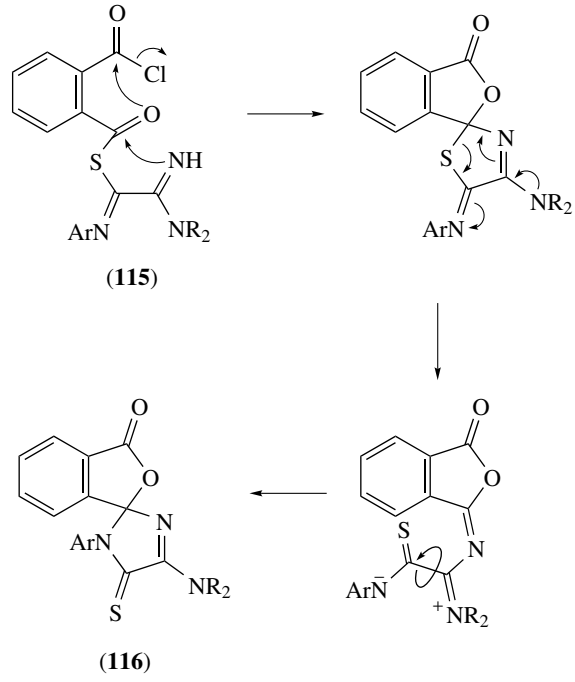


(**110**) (**111**)



(**112**) (**113**) (**114**)

The proposed formation of 2,5-benzothiazocine-1,6-diones (**114**; R = Pr) from the reaction of phthaloyl chloride (**112**) and amidino thioamides (**113**; R = Pr, Ar = 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$) in pyridine has been disproved. Instead, supported by an X-ray structure, the products have been shown to be spiro[4,4]lactones (**116**; R = Pr, Ar = 4-$O_2NC_6H_4$, 4-$MeOC_6H_4$). The proposed mechanism of formation of

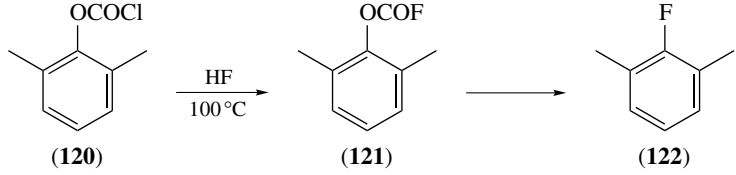


(**115**)

(**116**)

SCHEME 10

(**117**) (**118**) (**119**)

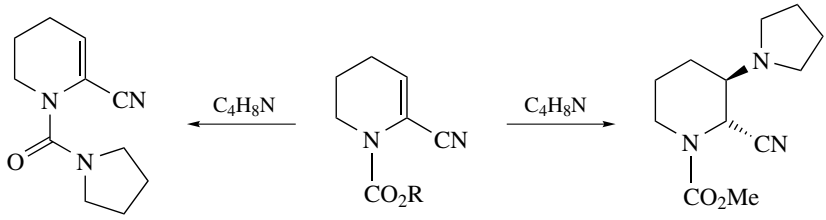


(**120**) (**121**) (**122**)

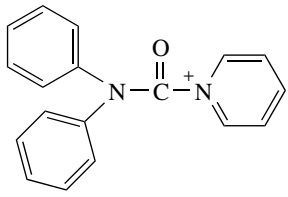
(**116**) involves initial intramolecular attack of the amidine group in a monosubstituted intermediate (**115**), as shown in Scheme 10.[53]

The extended (two-term) Grunwald–Winstein equation has been applied to the solvolyses of ethyl chloroformate (**117**) and ethyl chlorothioformate (**118**). For each substrate, there is evidence for two competing reaction channels.[54] Solvolysis

studies of substituted phenyl chloroformates (**119**) at various temperatures and pressures have revealed that reaction proceeds either via an addition–elimination reaction or via a synchronous S_N2-type process.[55] Kinetic studies of the solvolyses of 4-substituted phenyl chloroformates (**119**) in ethanol- and methanol–water mixtures have been reported.[56–58] The kinetic solvent isotope effects determined in D_2O, CH_3OD, and 50% D_2O–CH_3OD for the 4-MeO[57] and the 4-O_2N[58] compounds are consistent with a general-base-catalysed addition–elimination pathway. Treatment of 2,6-dimethylphenyl chloroformate (**120**) with anhydrous HF at 100 °C yields the corresponding fluoroformate (**121**), which upon heating at 200 °C decarboxylates to 2,6-dimethylfluorobenzene (**122**).[59]



(**123**) (**124**) (**125**)



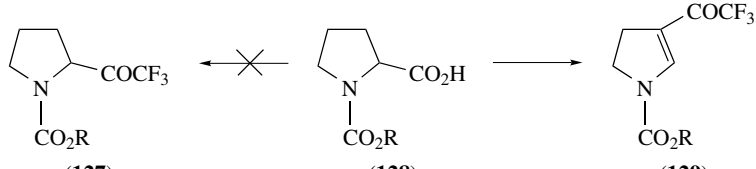
(**126**)

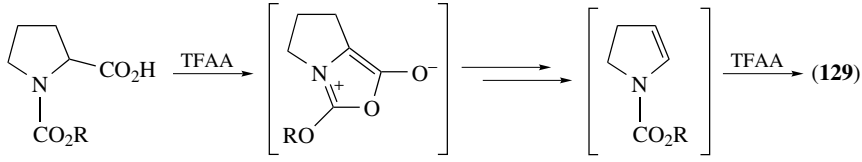
(e) *Ureas, carbamates, hydroxylamine, and derivatives*

A bicyclic urea (**123**) was an unexpected product of the reaction between pyrrolidine and the phenyl ester of 2-cyano-1,4,5,6-tetrahydro-1-pyridinecarboxylic acid (**124**; R = Ph); the corresponding methyl ester (**124**; R = Me) reacted, as expected, to give the product of Michael addition (**125**).[60] The better leaving ability of phenoxide vs methoxide presumably tilted the reaction towards the substitution rather than the addition product, although thiols (e.g. PhSH) underwent only the addition reaction.

Solvolyses of the *N,N*-diphenylcarbamoylpyridinium ion (**126**) were found to be subject to specific and/or general base catalysis, which could be eliminated by addition of perchloric acid or increased, especially in fluoroalcohol-containing solvents, by addition of pyridine. The uncatalysed solvolyses in aqueous methanol and aqueous ethanol involve a weakly nucleophilically assisted ($l = 0.22$) heterolysis and the solvolyses in the pure alcohols are anomalously slow.[61]

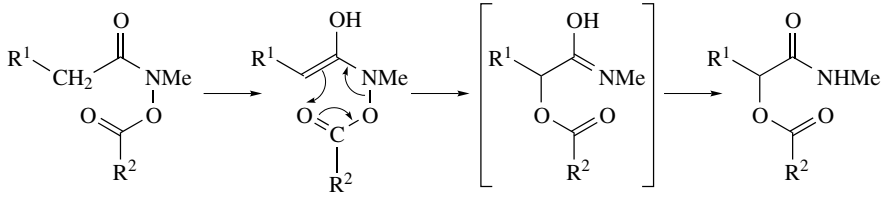
Under Dakin–West reaction conditions (trifluoroacetic anhydride–MeCN/80 °C/5 h), *N*-methoxycarbonylproline (**128**; R = Me) yielded *N*-methoxycarbonyl-4-trifluoroacetyl-2,3-dihydropyrrole (**129**; R = Me) and none of the expected Dakin–West product, the trifluoromethyl ketone (**127**).[62] A possible mechanism proposed by the authors[62] involves initial formation of a mesoionic 1,3-oxazolium-5-olate (**130**; R = Me), but the pathway to the *N*-methoxycarbonyl-2,3-dihydropyrrole (**131**; R = Me) and thence the final product (**129**; R = Me) was unexplained.[62]





An appraisal has been made of the available kinetic data on the acid hydrolyses of hydroxyamic acids. For *N*-substituted hydroxamic acids both *A*-2 and *A*-1 paths are recognized, but for primary hydroxamic acids there is evidence only for the *A*-2 pathway.[63]

The *O*-benzoyl derivative of *N*-methylphenylacetohydroxamic acid (**132**; R^1, R^2 = Ph) upon treatment with Et_3N in toluene at 110 °C for 1 h rearranged to *N*-methyl-2-benzoyloxyphenylacetamide (**134**; R^1, R^2 = Ph).[64] Most variations of R^1 (2-napththyl, PhCH=CH_2, PhCMe=CH_2, PhCBu=CH_2) or R^2 (Me, Bu^t, 4-$O_2NC_6H_4$) also gave the analogous products, the fastest reaction occurring with the 4-nitrobenzoyl compound (**132**; R^1 = PhCH=CH_2, R^2 = 4-$O_2NC_6H_4$). The mechanism proposed for the reaction was a novel [3,3]-sigmatropic rearrangement of the enol form of the *N*-methyl-*O*-acylhydroxamic acids (**133**) (Scheme 11).[64]

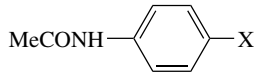


SCHEME 11

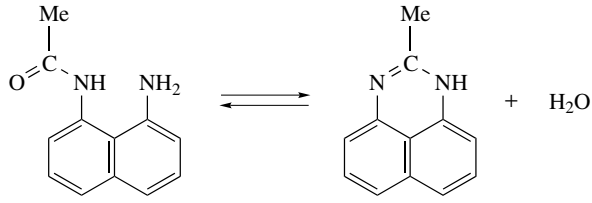
(f) *Amides and anilides*

The neutral and acid-catalysed mechanisms of hydrolysis of formamide, $HCONH_2$, have been revisited and a comparison made between *ab initio*, semiempirical and DFT results.[65] *Ab initio* MO calculations on the alkaline hydrolysis of *para*-substituted acetanilides (**135**) in the gas phase have shown that the activation energy depends on the nature of electron-withdrawing groups (e.g. $X = NO_2$, CN, Cl) but is invariant for electron-donating groups ($X = NH_2$, OMe).[66]

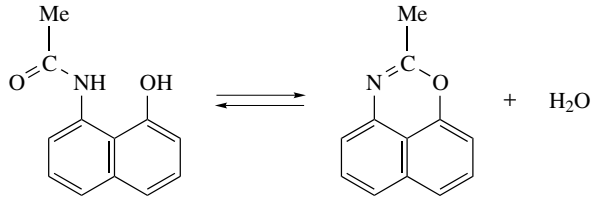
Theoretical calculations of minimum energy structures and thermodynamic terms using SCF theory with thermodynamic and solvation corrections have been made of the cyclization of 1-amino-8-(acetylamino)naphthalene (**136**) to give 2-methylperimidine



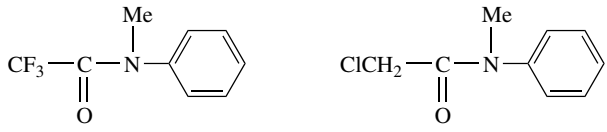
(**135**)



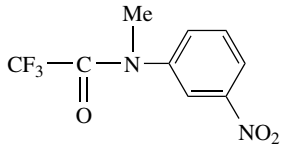
(**136**) (**137**)



(**138**) (**139**)



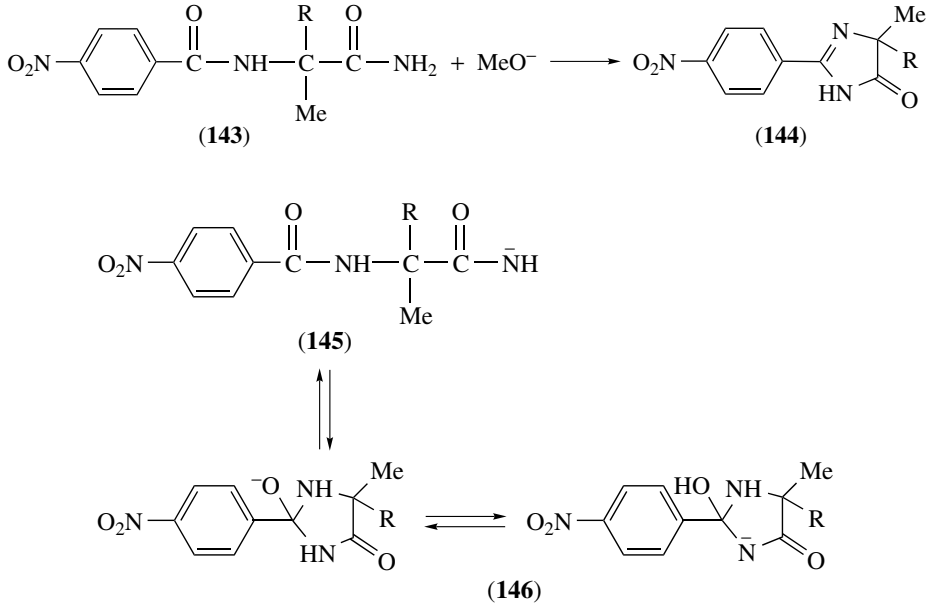
(**140**) (**141**)



(**142**)

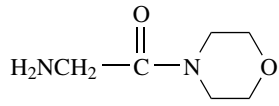
(**137**) with the liberation of water and of the related reaction of 1-hydroxy-8-(acetylamino)naphthalene (**138**) to 2-methylnaphtho[1,8-*b,e*][1,3]oxazine (**139**). The calculations predict that in the gas phase the former reaction is strongly thermodynamically favourable whereas the latter is much less favourable. The results are in qualitative agreement with experimental observations for the reaction in solution.[67]

Alkaline earth (Ba, Sr) metal ethoxides have been found to be more reactive than free ethoxide in the ethanolysis of simple activated amides such as *N*-methyl-2,2,2-trifluoroacetanilide (**140**), *N*-methyl-1-chloroacetanilide (**141**) and *m*-nitro-*N*-methyl-2,2,2-trifluoroacetanilide (**142**); enhanced catalysis was observed upon addition of equimolar amounts of 18-crown-6.[68]

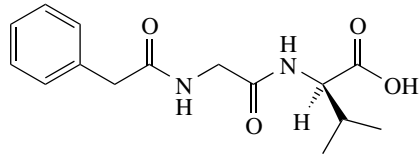


2-(4-Nitrobenzoylamino)-2,2-dimethylpropanamide (**143**; R = Me) reacts in methanol–DMSO solution with sodium methoxide to yield 5,5-dimethyl-2-(4-nitrophenyl)imidazol-4(5*H*)-one (**144**; R = Me).[69] The 4-methoxyphenyl derivative and the parent phenyl derivative react similarly, as do compounds in which variation of the 2-substitutent (R = Pr^i, Ph, 4-$O_2NC_6H_4$) was made. The mechanism of the cyclization probably involves initial formation of the anion of the alkanamide (**145**), which adds to the carbonyl group of the benzamido moiety to yield the tetrahedral oxyanion (**146**); proton transfer and dehydration then yield the heterocycle (**144**).[69]

The kinetics of hydrolysis in water at 70 °C and pH 2–11 of *N*-glycidylmorpholine (**147**) have been reported.[70]

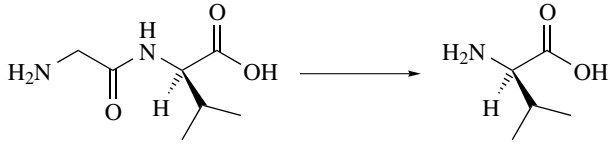


(**147**)



N-(phenylacetyl)glycyl-D-valine

(**148**)



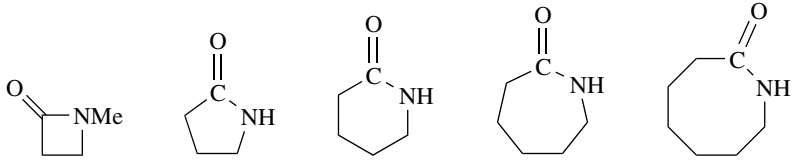
glycyl-D-valine D-valine

SCHEME 12

Except at extremes of pH and high temperature, peptide bond hydrolysis is a slow process that is difficult to quantify accurately. Using a new, highly fluorescent derivative of amines to quantify by HPLC the amine products of hydrolysis of *N*-(phenylacetyl)glycyl-D-valine (**148**), an acylic analogue of penicillin G, its pH–rate profile over the range pH 0–14 has been constructed.[71] Both hydrolysis products, glycyl-D-valine and D-valine (Scheme 12), are formed at all pHs, and it is shown that the rate constants (k_1, k_3) are very similar. At pH 7, where k_{H_2O} is dominant, the half-life of the glycyl-D-valine bond was found to be ca 265 years.[71]

(g) *Lactams*

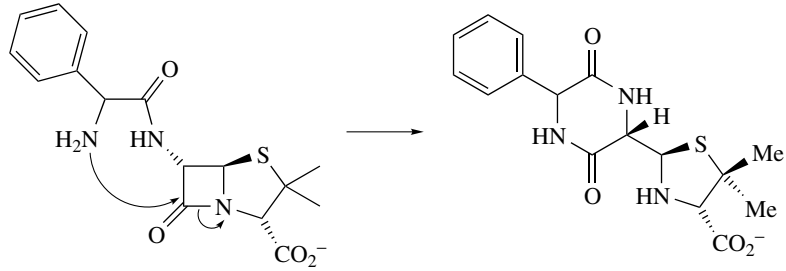
An *ab initio* study of the acid hydrolysis of β-lactams has yielded a value of 14.23 kcal mol^{-1} for the energy barrier for the opening of the ring.[72] Two theoretical studies of *N*-methyl-2-azetidinone (**149**) have been reported. In the first, semiempirical calculations



(**149**) (**150**) (**151**) (**152**) (**153**)

(PM3) were used to investigate solvent effects on the alkaline hydrolysis of (**149**)[73] and in the second, the effect of an ancillary water molecule on the neutral and alkaline hydrolysis mechanisms of *N*-methylazetidinone (**149**) was studied at the Hartree–Fock and MP2 levels using the 6–31G* and 6–31 + G* basis sets.[74]

Reaction rate constants obtained in moderately concentrated sulfuric acid for the hydrolysis of simple lactams of ring sizes five, six, seven and eight (**150**)–(**153**) as a function of acidity and temperature have been analysed using the excess acidity kinetic method.[75]



(**154**) (**155**)

$CH_3CH_2CH_2CN$

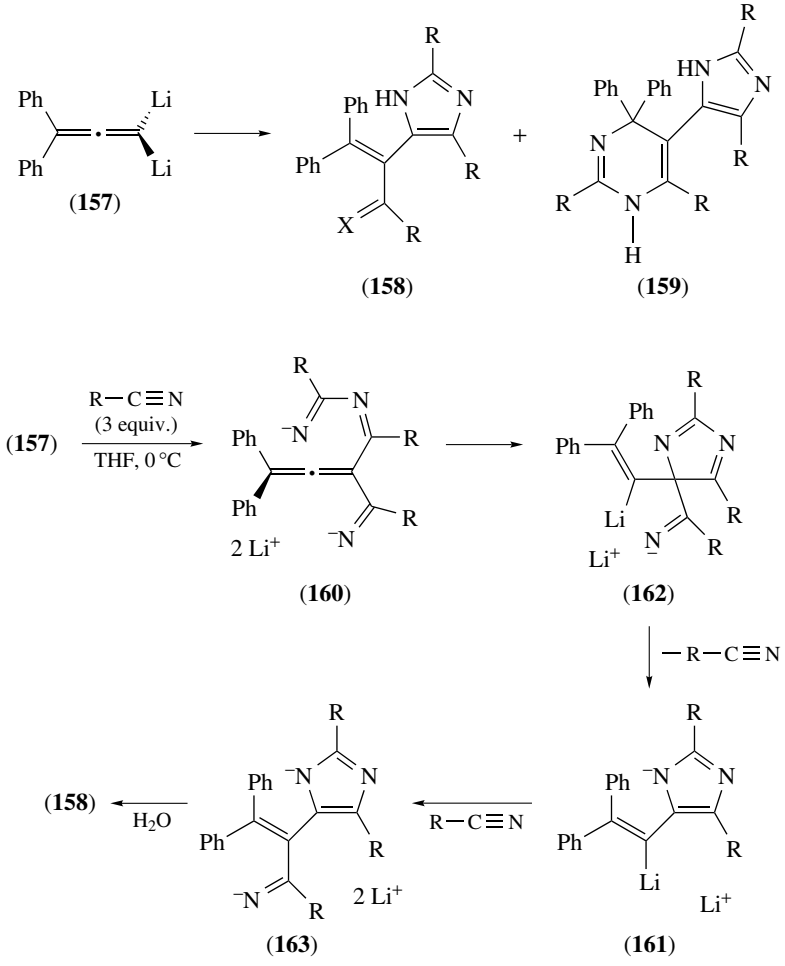
(**156**)

Kinetic studies of the 'unnatural' 6-α-epimer of ampicillin, 6-*epi*-ampicillin (**154**), have revealed an intramolecular process not undergone by ampicillin (or other 'natural' β-substituted penicillins).[76] At pH 6–9, intramolecular attack of the β-lactam carbonyl group by the side-chain amino group of (**154**) yields a stable piperazine-2,5-dione derivative (**155**). Theoretical calculations show that the intramolecular aminolysis of 6-*epi*-ampicillin nucleophilic attack occurs from the α-face of the β-lactam ring with an activation energy of 14.4 kcal mol^{-1}.[76] In other respects, the hydrolysis of the 6-α-epimer is unexceptional.

(h) *Non-heterocyclic nitrogen centres*

The effect of high pressure (128–2600 bar) and high temperature (330 °C) on the hydrolysis of butyronitrile (**156**) has been reported.[77]

A domino reaction of 1,1-diphenyl-3,3-dilithioallene (**157**) with benzonitrile yields both a yellow imidazole (**158**; R = Ph X = NH) (12%) and a colourless 5-imidazol-5-yl-1,4-dihydropyrimidine (**159**; R = Ph) (51%), the products, respectively, of the incorporation of three and four nitrile molecules.[78] The proposed mechanism (Scheme 13) involves initial formation of an intermediate (**160**) that is the product of the interaction of three molecules of benzonitrile with 1,1-diphenyl-3,3-dilithioallene (**157**), which cyclizes to (**162**; R = Ph) and then eliminates a molecule of benzonitrile to produce (**161**; R = Ph). Re-addition of benzonitrile at a different locus produces

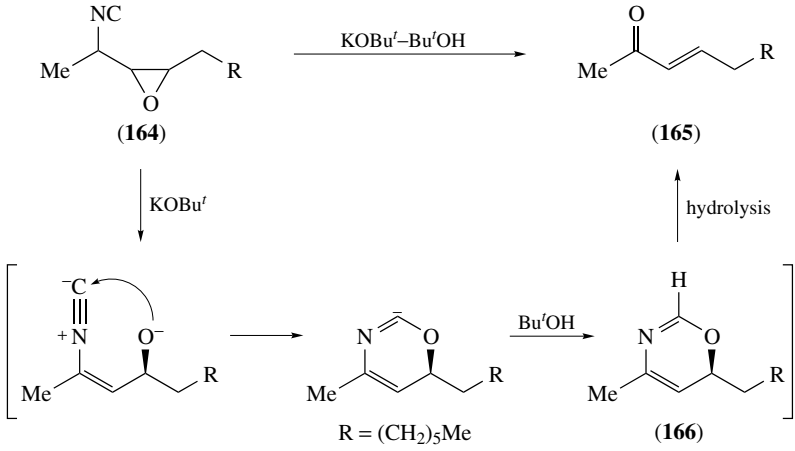


SCHEME 13

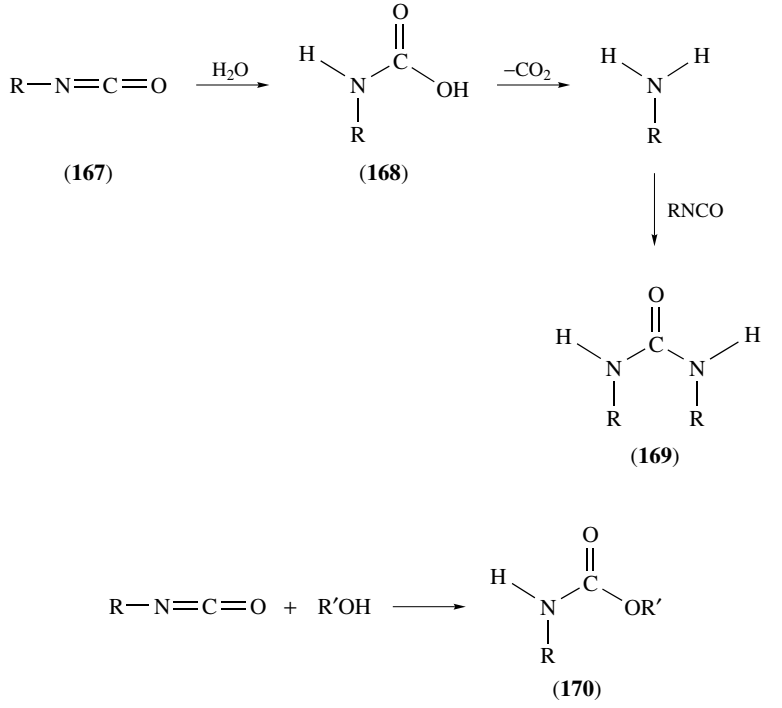
(**163**; R = Ph), which either can suffer protonation to give the imidazole (**158**; R = Ph) or can react with a further molecule of benzonitrile to yield, after several steps, the imidazoyl-1,4-dihydropyrimidine (**159**; R = Ph).[78]

The epoxyisonitrile [**164**; R = $(CH_2)_6Me$] upon treatment with Bu^tOK in Bu^tOH yielded the α, β-unsaturated ketone [**165**; R = $(CH_2)_6Me$], the mechanism of formation of which (Scheme 14) plausibly involving the intermediacy of the 5,6-dihydro-4*H*-1,3-oxazine [**166**; R = $(CH_2)_6Me$].[79]

A theoretical study of the reaction of water and methanol with HNCO has led to a prediction of a four-centred transition state for both reactions.[80] The interactions of water[81] and of alcohols[82] with alkyl isocyanates have been the subject of both experimental and theoretical study. In the case of hydration, evidence for initial interaction of water and water clusters (n = 1–3) across the N=C bond of the alkyl isocyanate



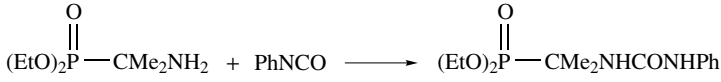
SCHEME 14



rather than the C=O bond was adduced by *ab initio* methods, both in the gas phase and in aqueous solution. The C=O bond of the alkyl isocyanate thus remains intact in the first-formed intermediate, the carbamic acid (**168**), but this rapidly breaks down to CO_2 and an amine, which reacts with a further molecule of isocyanate to give the 1,3-disubstituted urea (**169**).[81] By contrast, alcohol addition to an alkyl isocyanate yields a

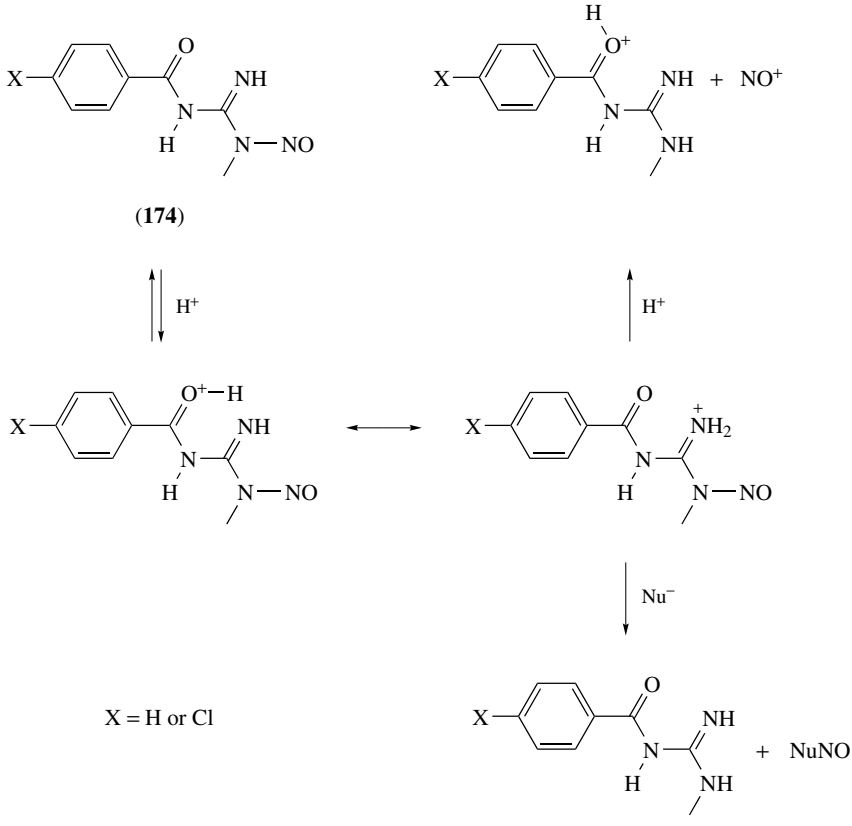
stable carbamate (**170**). The experimental study of this reaction, which was undertaken employing propan-2-ol and cyclohexanol in low and high concentrations, suggested that either two or three molecules of alcohol are involved in the initial interaction with the isocyanate; like the hydration reaction, the addition of alcohol occurs in a concerted way across the N=C bond of the isocyanate, rather than the C=O bond.[82]

A study of the kinetics of the reaction between *O,O*-diethyl 1-amino-1-methylethanephosphonate (**171**) and phenyl isocyanate (**172**) has been reported. The product of the adduction (**173**) is considered to have an autocatalytic effect on the reaction.[83]

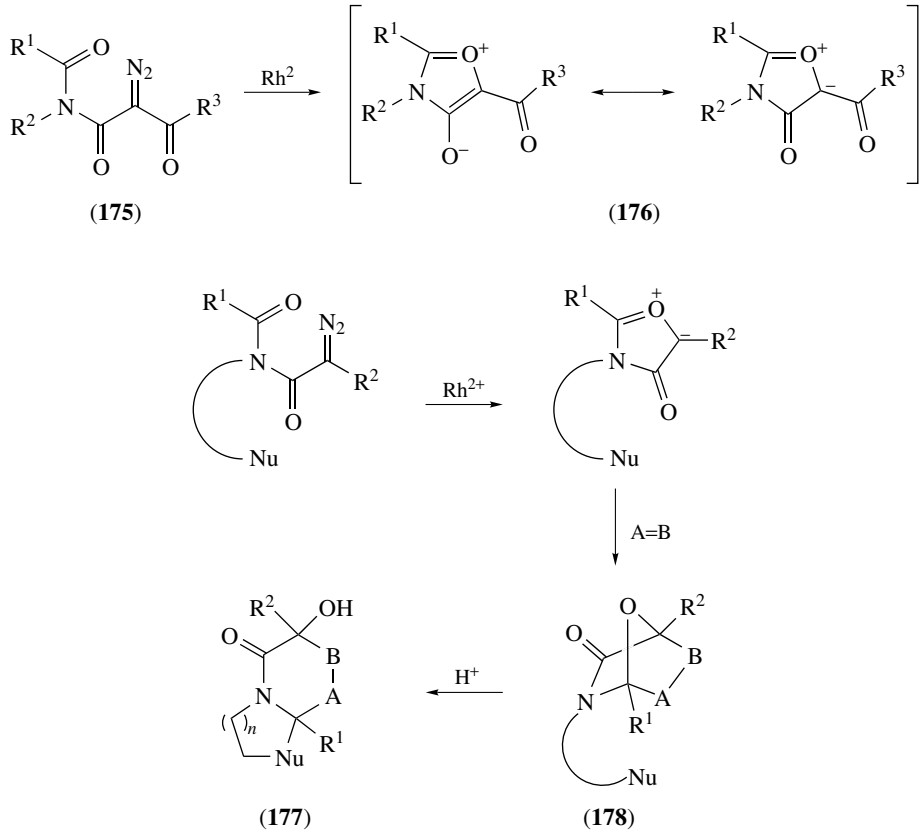


(**171**) (**172**) (**173**)

1-Methyl-1-nitroso-3-benzoylguanidine (**174**; X = H) undergoes denitrosation by two parallel pathways (Scheme 15). One involves a slow nucleophilic attack concerted



SCHEME 15



(**175**) (**176**)

(**177**) (**178**)

SCHEME 16

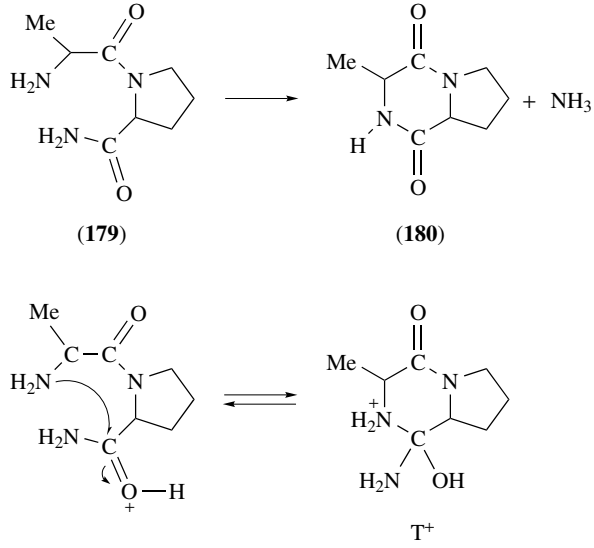
with an intramolecular proton transfer, and the other a slow concerted denitrosation, where a second proton transfer and NO^+ expulsion are simultaneous.[84]

A domino carbenoid cyclization/4 + 2-cycloaddition/cationic π-cyclization protocol as a method for construction of complex nitrogen heterocycles such as lycopine and aspidospermine indole alkaloids has been reviewed.[85] The constructs for this process are diazoimides (**175**), which upon treatment with a rhodium(II) catalyst yield 1,3-oxazolium 4-oxides (isomunchones) (**176**). As cyclic equivalents of carbonyl ylides, the isomunchones (**176**) readily undergo 4 + 2-cycloaddition with electron-rich or electron-deficient dipolarophiles. By incorporating an internal nucleophile on a tether, annulation of the original cycloadduct (**178**) allows for the construction of more complex nitrogen heterocyclic systems, e.g. (**177**); see Scheme 16.[85]

(i) *Other heterocyclic nitrogen centres*

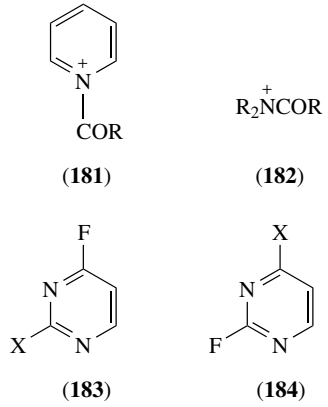
2,5-Dioxopiperazines are products of sometimes unwanted cyclizations of the *N*-terminal residues of di- and oligo-peptides and proteins. As a model for this process,

in which the nitrogen atom of the *N*-terminal deprotonated amino group attacks the C=O group of the second residue, the cyclization of H-Ala-Pro-NH_2 (**179**) to the bicyclic 2,5-dioxopiperazine (**180**) has been studied.[86] At low pH, the protonated amide carbonyl undergoes attack by the free amino group to give T^+ (Scheme 17). At high pH the pH–rate profile levels off, and this is interpreted as a *trans* → *cis* isomerization of the Ala-Pro peptide bond, rendering the cyclization unattainable.[86]



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

SCHEME 17



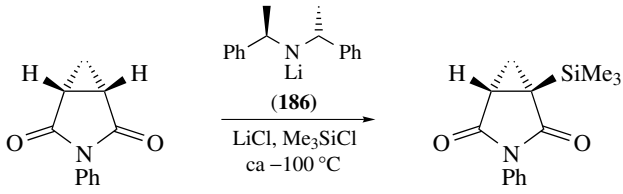
(**181**) (**182**)

(**183**) (**184**)

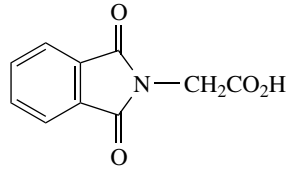
The general chemistry of acylpyridinium salts (**181**) and their role in the nucleophilic catalysis by pyridine of carbonyl substitution reactions have been reviewed and compared with the role of acylammonium salts (**182**).[87]

The rates of alkaline hydrolysis of a series of amino derivatives of 4-fluoro-(**183**; X = NH_2) and 2-fluoro-pyrimidines (**184**; X = NH_2) have been compared, revealing that the former hydrolyse more rapidly.[88] Some difluoro analogues (**184**; X = F) with amino and alkyl substituents were also studied, the 4-fluoro substituent departing the more readily.

The desymmetrization of the *N*-phenylcyclopropylsuccinimide (**185**) has been effected by its reaction at low temperature with a chiral base (**186**) and an *in situ* electrophile, trimethylsilyl chloride. The silylated product (**187**) was obtained in 80% yield and 95% *ee* (Scheme 18).[89]



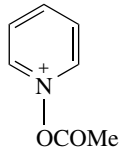
SCHEME 18



(**188**)

Kinetic evidence has been obtained for ion-pair formation when the effects of inorganic salts on the alkaline hydrolysis of *N*-phthaloylglycine (**188**) were investigated.[90]

Kinetic studies have been reported of acetyl transfer in acetonitrile from *N*-acetyloxypyridinium cations (**189**) to 4-(4′-*N,N*-dimethylaminostyryl)pyridine *N*-oxide (**190**), pyridine *N*-oxide (**191**) and 4-dimethylaminopyridine (**192**).[91] In a follow-up



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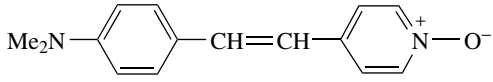
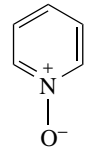


(**190**)



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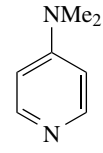
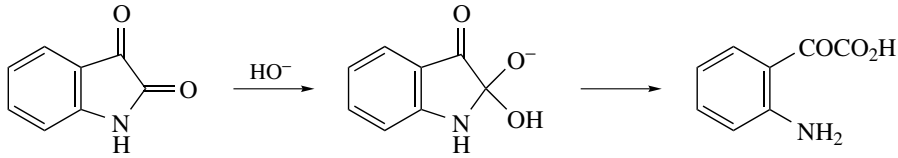


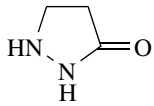
(**192**)

study,[92] methoxycarbonyl transfer to and from similar and analogous reactants have been reported. Generally, it was found that the methoxycarbonyl transfer was a concerted process and reactivity depended on the ionization potential of the nucleophile and the electron affinity of the acylonium salt.[92]

Solvent effects have been investigated in isatin (**193**) hydrolysis.[93] Results from ethanol–water and acetonitrile–water mixtures revealed that for alkaline hydrolysis log k was correlated with the reciprocal of the dielectric constant. A tetrahedral intermediate (**194**) is involved, which breaks down to yield the ring-opened amino acid (**195**).[93] A comparison has been made of the lability of isatin (**193**) towards diethylamine and hydroxide ion, the latter showing the greater effect.[94]



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

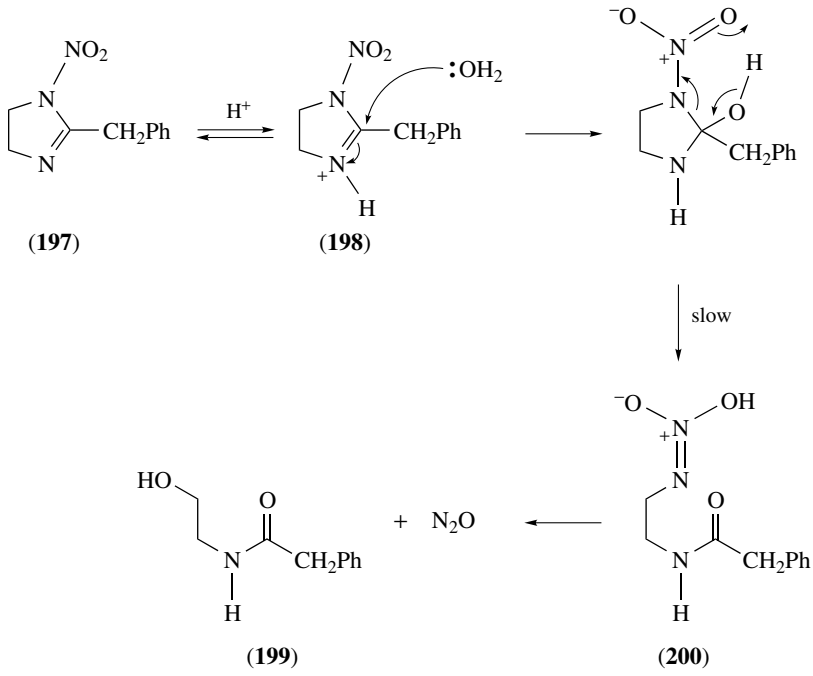


(**196**)

A complete study of the basic hydrolysis of pyrazolidinone (**196**) by *ab initio* calculations at RHF/6–31+G*//RHF/6–31+G* and MP2/6–31+G*//MP2/6–31+G* levels has been carried out. The alkaline hydrolysis has been studied through a $B_{AC}2$ mechanism, characterized by a nucleophilic attack of the hydroxyl group on the carbonyl of the γ-lactam ring, formation of the tetrahedral intermediate, and cleavage of the C(2)–N(3) bond to yield the final reaction product.[95]

Studies of the acid-catalysed kinetics of a simple cyclic N-nitroamidine have been reported.[96] N-Nitrotolazoline (**197**) (i.e. N-nitro-2-benzyl-4,5-dihydro-1H-imidazole), which was formed from the α-adrenergic blocking agent, tolazoline (**197**; H for NO_2) by treatment with N_2O_4, undergoes acid-catalysed hydrolysis to form N-(2-hydroxyethyl)phenylacetamide (**199**). The proposed mechanism involves rapid water attack of a protonated intermediate (**198**) followed by a slow, intramolecular rearrangement involving proton transfer to yield a zwitterion (**200**), which eliminates N_2O to yield the product (**199**) (Scheme 19).[96]

3-(Dimethylamino)propanol (**201**; R = H) is known to be acetylated by N-acetylimidazole (**206**) by a mechanism that involves intramolecular general base

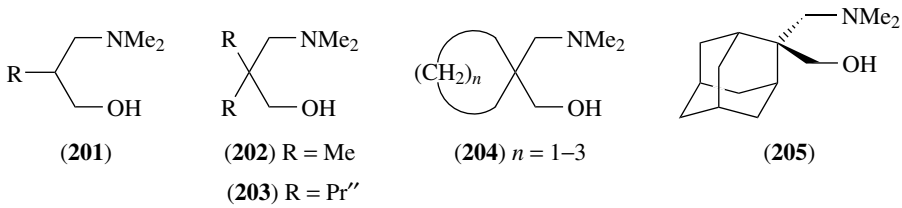


(**197**) (**198**) (**199**) (**200**)

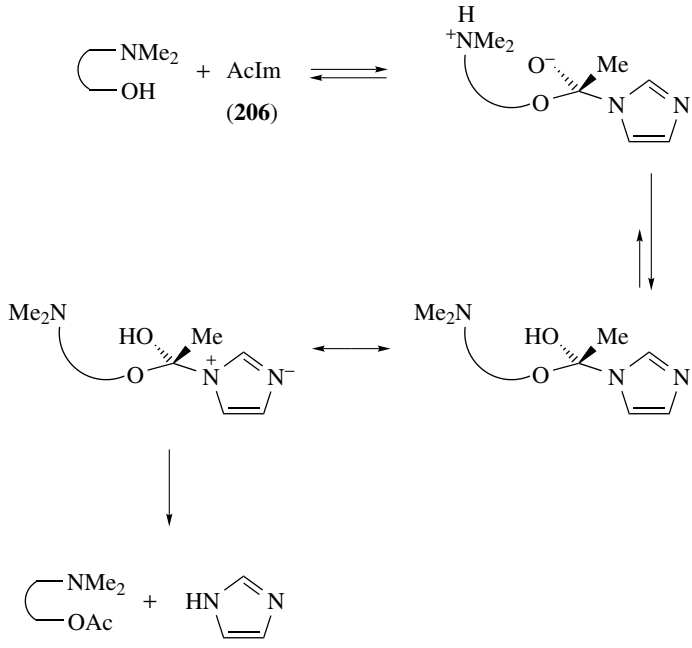
SCHEME 19

catalysis (Scheme 20). Now a study of the rates of acetylation of 2-alkyl (**201**; R = Bu^t) and 2,2-dialkyl analogues (**202**)–(**205**) by *N*-acetylimidazole (**206**) in MeCN have been reported.[97] Only a modest increase in acetylation rate was detected for the series, the highest rate being seen with the adamantyl compound (**205**), where the magnitude of the internal bond angle at the 2-position, $\alpha = 107°$, was the smallest. Effective molarities were estimated to be 13–14 M.[197]

An electron-withdrawing group (EWG) on the nitrogen of a pyrrole of the type (**210**) is thought to suppress the formation of a highly electrophilic azafulvenium species (**208**) in nucleophilic substitution reactions (Scheme 21). In the absence of such deactivation, the analogous pyrroles (**207**) readily react with a nucleophile, via the postulated azafulvene intermediate (**208**) to give products of the type (**209**). If the EWG is an *N*-protected α-aminoacyl group, e.g. (**212**), then it is feasible that *in vivo* esteratic removal of the EWG could lead to a reactive azafulvene (**208**) which would be capable of inactivating the enzyme by alkylation (Scheme 21, where Nu^- is an amino acid in the enzyme's active site). Such a latent reactive inhibitor of serine proteases has been developed in which the EWG is *N*-phthalylleucinyl, i.e. (**212a**).[98] Now studies of the fate of each of the ^{2}H-labelled hydrogens of the methylene group of (**212a**) in which (**212b**) and (**212c**) were base-hydrolysed in the presence of an external nucleophile, (+)-*sec*-butylamine (**215**), have shown that



(**201**) (**202**) R = Me (**203**) R = Pr″ (**204**) *n* = 1–3 (**205**)

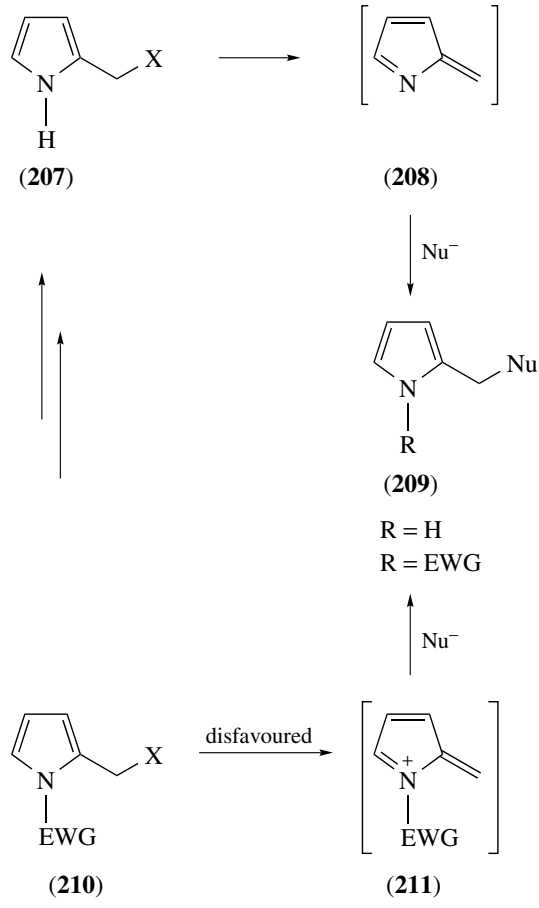


SCHEME 20

the reaction proceeds by an initial intramolecular *N*- to *O*-acyl transfer to yield (**214**) (pathway *a*, Scheme 22), which upon deacylation yields an azafulvene (**213**). Evidence for the intervention of the azafulvene (**213**) was the isolation of the (*S*)- and (*R*)-*sec*-butylamino[^{2}H]methylpyrroles (**216**; R = D) formed by its reaction with (+)-*sec*-butylamine (**215**) (pathway *b*).[98]

Reactions in Aprotic Solvents

Several reactions that have been conducted in aprotic solvents have been dealt with earlier; see references 1, 2, 19, 25, 31, 39, 43, 44, 51, 52, 91, 92 and 97. The following references ahead also deal with reactions in aprotic solvents: 101, 113, 139, 165–167, and 179–181.



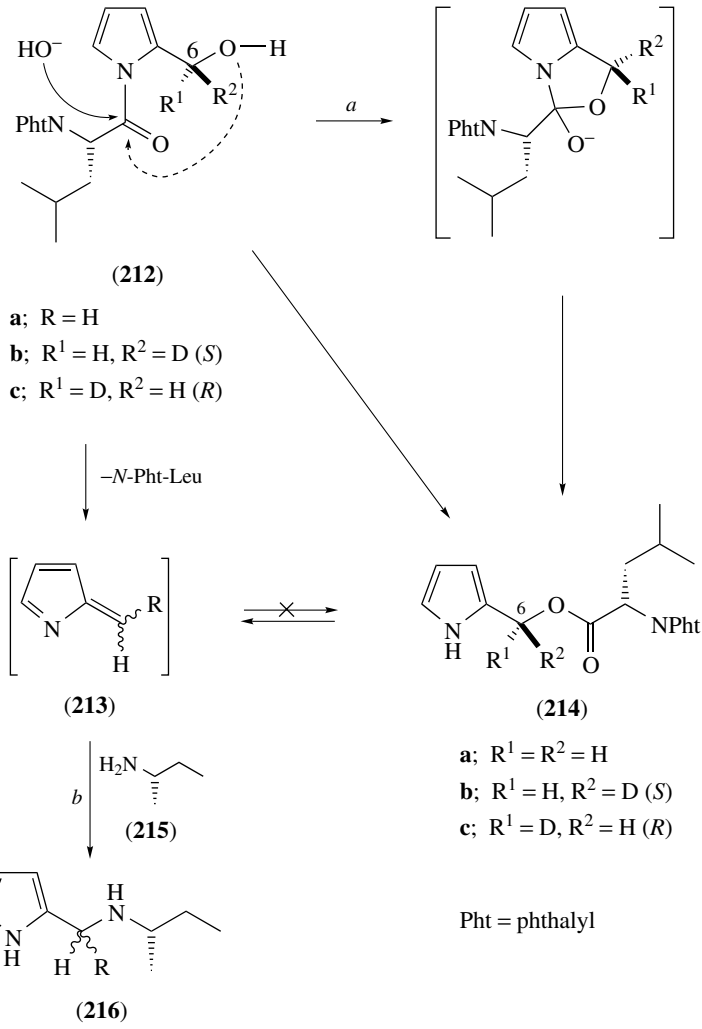
EWG = electron-withdrawing group

SCHEME 21

Intramolecular Catalysis and Neighbouring-group Participation

Neighbouring-group participation in the hydrolysis of esters and amides has been reviewed.[99] The effects of urea, Na^+ and Li^+ on the intramolecular general-base-catalysed glycolysis of phenyl salicylate (**217**) in glycol–acetonitrile solvent at constant water concentration have been reported.[100]

The stereoisomeric bicyclic amino alcohols (**218**) and (**219**) each undergo in tetrahydrofuran solvent ready acetylation with acetyl chloride and ready mesylation with methanesulfonyl chloride. Reaction of the *endo* isomer (**219**) very probably proceeds via the intramolecular 5-*exo-Trig* pathway, similar intermediates being formed in

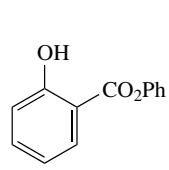


SCHEME 22

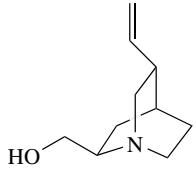
both acetylation (Scheme 23) and mesylation (Scheme 24).[101] However, although not discussed by the authors, the *exo* isomer (**218**) cannot react in a similar way, and intermolecular catalysis presumably occurs.

Association-prefaced Catalysis

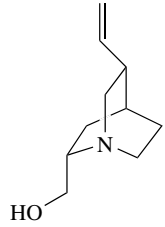
Hydrolysis of substituted phenyl acetates is catalysed by the Zn(II) complex of 1,5,9-triazacyclododecane (**220**). The results support the mechanism in which the ester is first complexed to the metal centre, and then water or hydroxide ion makes a nucleophilic attack at the complexed ester.[102]



(**217**)



(**218**)



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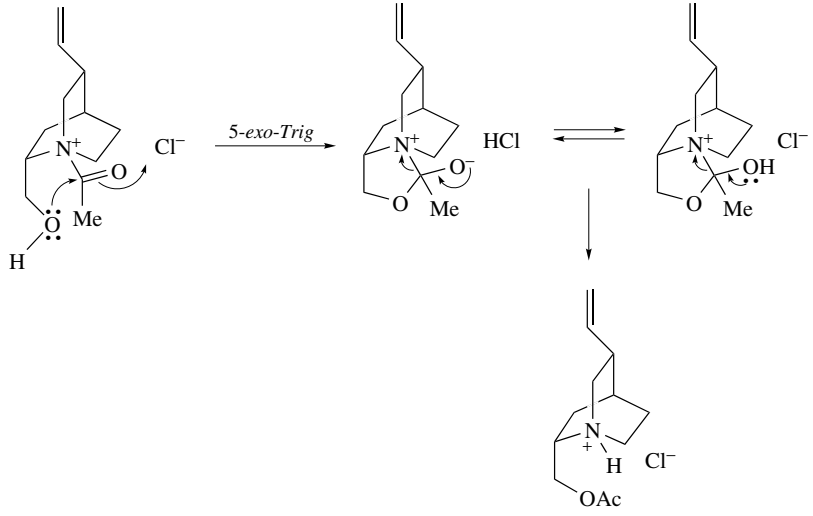
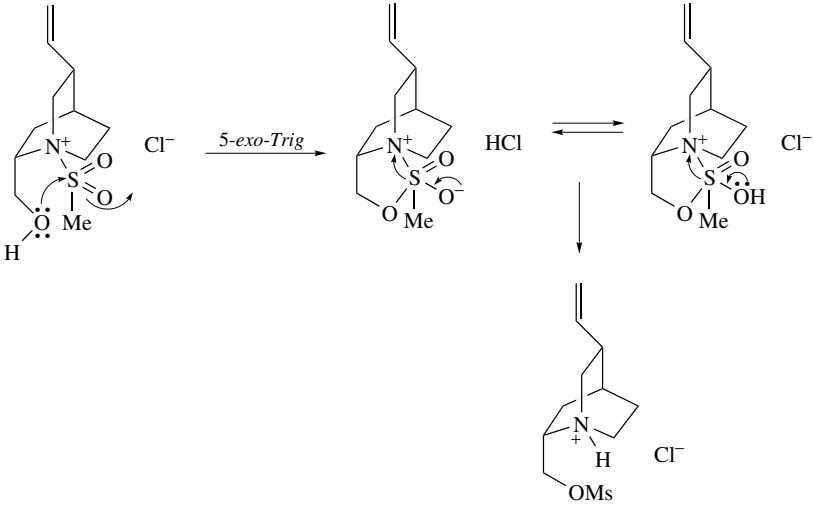
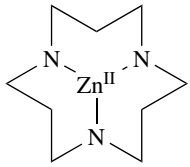


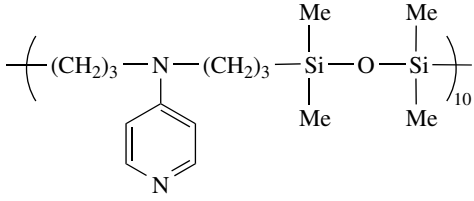
SCHEME 23



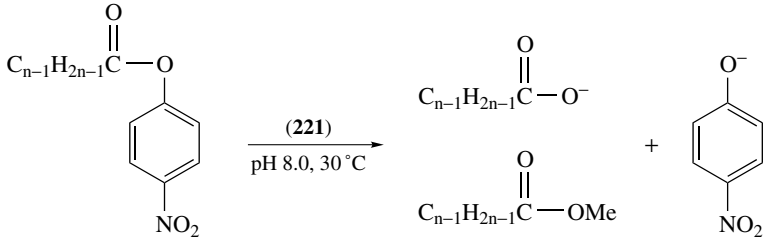
SCHEME 24



(**220**)



(**221**)



(**222**)

$n = 2, 4, 6, 8, 10, 12, 14, 16, 18$

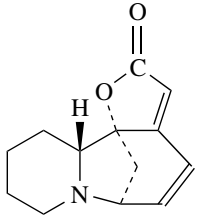
The substrate specificity in solvolysis reactions of *p*-nitrophenyl alkanoates (**222**; $n = 2–18$) catalysed by 4-(dialkylamino)pyridine-functionalized polymer (**221**) can be controlled by the concentration of (**221**) in 50:50 (v/v) methanol–aqueous phosphate buffer solution at pH 8.0 and 30 °C. Below 1.0×10^{-5} unit mol l^{-1}, macromolecule (**221**) exhibits substrate specificity for (**222**; $n = 14$). As the concentration of (**221**) increases to 2.5×10^{-5} unit mol l^{-1}, the substrate preference changes from (**222**; $n = 14$) to (**222**; $n = 12$). The substrate specificity changes again from (**222**; $n = 12$) to (**222**; $n = 10$) when the concentration of (**222**) increases further to 7.5×10^{-5} unit mol l^{-1}. The control of substrate specificity by polymer catalyst concentration is claimed to be unprecedented for catalysis of ester solvolysis.[103]

The cleavage of *p*-nitrophenyl alkanoates (**222**; $n = 1–8$) at high pH is modestly catalysed by micelles formed from cetyltrimethylammonium bromide (CTAB) in aqueous solution. Rate constants exhibit saturation behaviour with respect to [CTAB], consistent with substrate binding in the micelles. The strength of substrate binding and transition state binding to the micelles increases monotonically with the acyl chain length, and with exactly the same sensitivity. As a result, the extent of acceleration

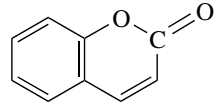
(or catalytic ratio) is independent of the ester chain. These and earlier results are consistent with the reaction centre being located in the Stern layer of the micelle, with the acyl chain of the ester being directed into the hydrophobic micellar interior.[104]

Complexation with caffeine and theophylline-7-acetate depresses the rate of alkaline hydrolysis of substituted phenyl benzoates and is consistent with the formation of molecular complexes with 1:1 stoichiometry between the hosts and esters; stacking of the xanthines is excluded as an explanation in the range of concentrations studied. Inhibition of hydrolysis is attributed to repulsion of the hydroxide ion from the host–ester complex by the extra hydrophobicity engendered by the xanthine host, as well as by the weaker binding of the transition state to the host compared with that in the host–ester complex.[105]

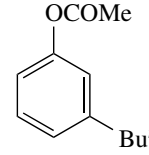
The effects of micelles of cetyltrimethylammonium bromide (CTABr), tetradecyltrimethylammonium bromide (TTABr) and sodium dodecyl sulfate (SDS) on the rates of alkaline hydrolysis of securinine (**223**) were studied at a constant [HO^-] (0.05 M). An increase in the total concentrations of CTABr, TTABr and SDS from 0.0 to 0.2 M causes a decrease in the observed pseudo-first-order rate constants (k_{obs}) by factors of ca 2.5, 3, and 7, respectively. The observed data are explained in terms of pseudophase and pseudophase ion-exchange (PIE) models of micelles.[106] Cationic micelles of CTABr speed attack of hydroxide ion upon coumarin (**224**) twofold owing to a concentration effect.[107]



(**223**)



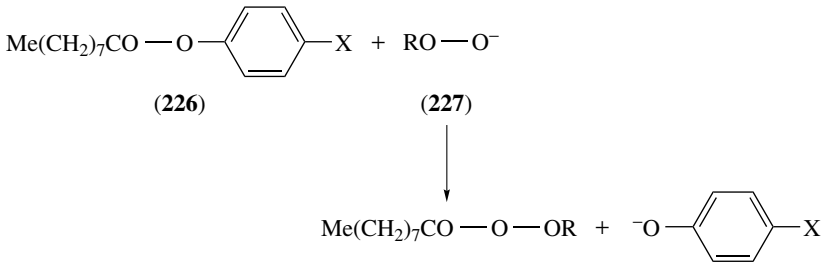
(**224**)



(**225**)

Molecular dynamics free-energy perturbation simulations utilizing the empirical valence bond model have been used to study the catalytic action of β-cyclodextrin in ester hydrolysis. Reaction routes for nucleophilic attack on *m-t*-butylphenyl acetate (**225**) by the secondary alkoxide ions $O(2)^-$ and $O(3)^-$ of cyclodextrin giving the *R* and *S* stereoisomers of ester tetrahedral intermediate were examined. Only the reaction path leading to the *S* isomer at O(2) shows an activation barrier that is lower (by about 3 kcal mol^{-1}) than the barrier for the corresponding reference reaction in water. The calculated rate acceleration was in excellent agreement with experimental data.[108]

The micellar kinetics of the acyl transfer from *n*-nonanoyloxybenzenesulfonate (**226**; X = SO_3^-) and phenyl nonanoate (**226**; X = H) to hydrogen peroxide (**227**; R = H) and pernonanoic acid [**227**; R = $Me(CH_2)_7CO$] have been reported. The



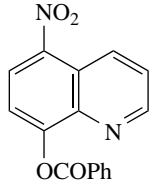
(**226**) (**227**)

micellar association constant of phenyl nonanoate with SDS is four orders of magnitude greater than that of *n*-nonanoyloxybenzenesulfonate owing to the absence of the negatively charged sulfonate group, whilst the apparent micellar association constant of the transition state for its reaction with pernonanoate is more than an order of magnitude less.[14]

Metal-ion Catalysis

Ruthenium(III) catalyses the oxidative decarboxylation of butanoic and 2-methylpropanoic acid in aqueous sulfuric acid.[109] Studies of alkaline earth (Ba, Sr) metal alkoxides in amide ethanolysis[68] and of alkali metal alkoxide clusters as highly effective transesterification catalysts[8] were covered earlier. Kinetic studies of the ethanolysis of 5-nitroquinol-8-yl benzoate (**228**) in the presence of lithium, sodium, or potassium ethoxide revealed that the highest catalytic activity is observed with Na^+.[110]

In the hydrolysis of methyl (**229**; X = OMe) and ethyl esters of α-amino acids (**229**; X = OEt) the catalytic effectiveness of Ce(III) and Nd(III) was the highest for a set of 20 lanthanide ions; Ln(III) and Yb(III) were the least effective. For the hydrolysis of amides of α-amino acids (**229**; X = NH_2), however, the Ce(IV) ion is much more active than any of the lanthanide(III) ions.[111]



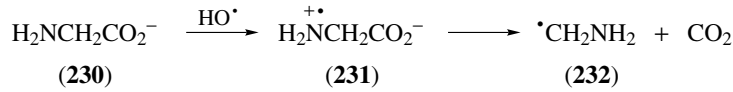
(**228**)

$RCH(NH_2)COX$

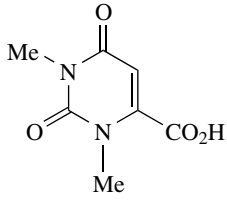
(**229**)

Decarboxylation

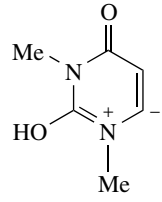
Glycine anion (**230**) is decarboxylated when exposed to hydroxyl radicals. The major initial product is an amino radical cation (**231**), which suffers rapid ($\leqslant$100 ns) fragmentation into CO_2 and a carbon-centred radical (**232**).[112] Oxidative decarboxylation



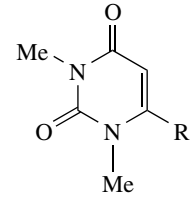
(**230**) (**231**) (**232**)



(**233**)

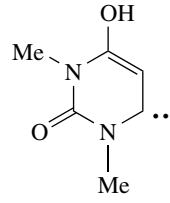


(**234**)



(**235**) R = H

(**236**) R = CH_2Ph



(**237**)

of butanoic and 2-methylpropanoic acid in aqueous sulfuric acid is catalysed by ruthenium(III).[109]

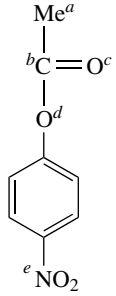
When 1,3-dimethylorotic acid (**233**) was heated at 198 °C in benzyl bromide for 3 h, 6-benzyl-1,3-dimethyluracil (**236**) was formed in 10% yield together with the product of decarboxylation, 1,3-dimethyluracil (**235**). This finding supports the involvement of a carbon-6-centred nucleophilic intermediate in the decarboxylation reaction; a carbanion (**234**) could be involved or a carbene (**237**).[113]

Oxalic acid, tartaric acid, and other hydroxylated di- and tricarboxylic acids are decarboxylated to varying extents by radical pathways when reacted at 25 °C with Ce(IV) in 1 M sulfuric acid solution.[114]

Enzymic Catalysis

General

Isotope effects have been measured for the reaction of *p*-nitrophenyl acetate with chymotrypsin, papain and an acid protease and the results compared with data from its uncatalysed reactions with oxygen and sulfur nucleophiles. The isotope effects, which were measured by the competitive method and are therefore effects on *V/K,* were determined at the β-deuterium (^{D}k), carbonyl carbon (^{13}k), carbonyl oxygen ($^{18}k_{C}{=}O$), leaving-group phenolic oxygen ($^{18}k_{lg}$) and leaving-group nitrogen (^{15}k) positions (see Scheme 25).[115] All of the enzymatic reactions showed isotope effects consistent with a concerted mechanism like that seen in uncatalysed aqueous reactions, but exhibited



(**a**) $^{D}(V/K)$

(**b**) $^{13}(V/K)$

(**c**) $^{18}(V/K)_{carbonyl}$

(**d**) $^{18}(V/K)_{lg}$

(**e**) $^{15}(V/K)$

SCHEME 25

smaller inverse β-deuterium effects than seen in the non-enzymatic reactions. This phenomenon may be explained by greater hydrogen bonding or electrostatic interaction with the ester carbonyl group in enzymatic transition states relative to non-enzymatic aqueous transition sates.[115]

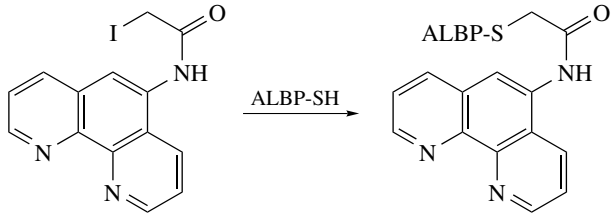
A new, more general, way to combine *ab initio* quantum mechanical calculations with classical mechanical free-energy perturbation approach (QM/FE approach) to calculate the energetics of enzyme-catalysed reactions and the same reaction in solution has been reported.[116] The calculated free energies were in fairly good agreement with the experimental data for the activation energies of the first test case, amide hydrolysis in trypsin and in aqueous solution.[116]

β-Lactamases

The mechanism of catalysis and the inhibition of β-lactamases have been reviewed (75 references).[117]

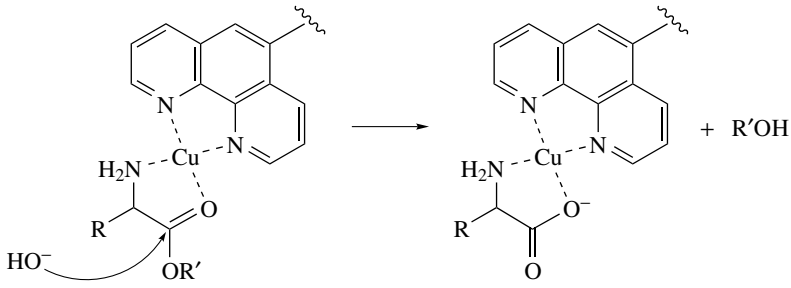
Other Enzymes

A semi-synthetic metalloenzyme that catalyses the enantioselective hydrolysis of simple amino acid esters has been reported.[118] Iodoacetamido-1,10-phenanthroline (**238**) was interacted with a cysteine residue in adipocyte lipid binding protein (ALBP) to produce the conjugate ALBP–Phen (**239**), which was converted into its Cu(II) complex. The ALBP–Phen–Cu(II) was found to catalyse the enantioselective



(**238**) (**239**) (ALBP-Phen)

hydrolysis of several amino acid esters under mild conditions (pH 6.1, 25 °C) at rates 30–250-fold above the spontaneous rate. A possible mechanism involves the positioning of the amino acid ester around the copper such that the C=O group is activated towards attack by water or hydroxide ion (see Scheme 26).[118]



SCHEME 26

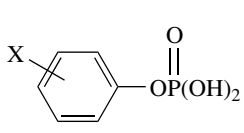
NON-CARBOXYLIC ACIDS

Phosphorus-containing Acids

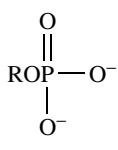
Phosphates and Phosphonates

Solvolysis studies of *meta*- and *para*-substituted phenyl phosphates (**240**) in anhydrous Bu^{t}OH and in Am^{t}OH have revealed that generally reactions of dianions are much faster in alcohols than in water. For example, the dianion of *p*-nitrophenyl phosphate (**240**; $X = 4\text{-}NO_2$) reacts 7500- and 8750-fold faster in Bu^{t}OH and Am^{t}OH, respectively, than in water.[119] The results of a theoretical study of the reactivity of phosphate monoester anions in aqueous solution do not support the generally accepted view that Brønsted coefficients $\beta_{lg} = -1.23$ and $\beta_{nuc} = 0.13$ determined more than 30 years ago for the uncatalysed reaction of water and a monophosphate dianion (**241**) represent conclusive evidence for the dissociative mechanism. It is suggested that, instead, the observed LFERs could correspond to a late transition state in the associative mechanism.[120]

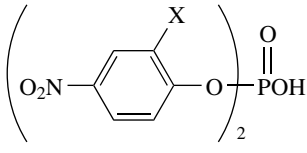
An aquahydroxy complex of Co(III) with 1,4,7,10-tetraazacyclododecane (**243**) has been shown to be an effective catalyst for the hydrolysis of *p*-nitrophenyl phosphate (**240**; $X = 4\text{-}NO_2$), bis(*p*-nitrophenyl) phosphate (**242**; X = H) and bis(2,4-dinitrophenyl) phosphate (**242**; $X = NO_2$).[121] Whereas Th^{4+} had no effect, Ce^{4+}



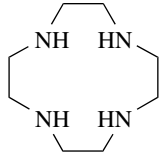
(**240**)



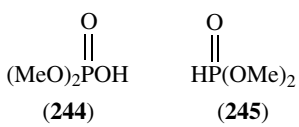
(**241**)



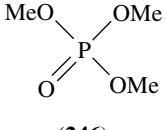
(**242**)

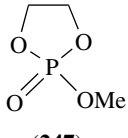


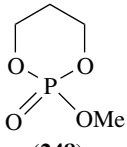
(**243**)


(**244**)

(**245**)


(**246**)


(**247**)

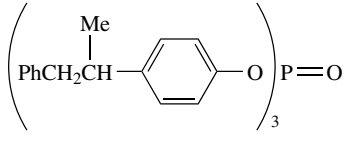

(**248**)

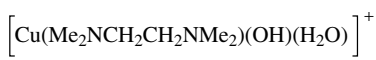
caused an acceleration of 2×10^8-fold in the acid hydrolysis of dimethyl phosphate (**244**). The mechanism of the catalytic process is uncertain and is undergoing investigation.[122]

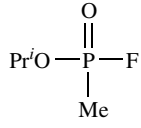
Quantitative ^{31}P NMR examination of the hydrolysis of dimethyl phosphonate (**245**) using ^{18}O-enriched water under base-catalysed conditions supports a mechanism involving P−O rather than C−O bond cleavage.[123]

Ab initio calculations to map out the gas-phase activation free energy profiles of the reactions of trimethyl phosphate (TMP) (**246**) with three nucleophiles, HO^-, MeO^- and F^- have been carried out. The calculations revealed, *inter alia,* a novel activation free-energy pathway for HO^- attack on TMP in the gas phase in which initial addition at phosphorus is followed by pseudorotation and subsequent elimination with *simultaneous* intramolecular proton transfer.[124] *Ab initio* calculations and continuum dielectric methods have been employed to map out the lowest activation free-energy profiles for the alkaline hydrolysis of a five-membered cyclic phosphate, methyl ethylene phosphate (**247**), its acyclic analogue, trimethyl phosphate (**246**), and its six-membered ring counterpart, methyl propylene phosphate (**248**). The rate-limiting step for the three reactions was found to be hydroxyl ion attack at the phosphorus atom of the triester.[125]

The kinetics and mechanism of the acid hydrolysis of tris[4-(2′-phenylisopropyl) phenyl] phosphate (**249**) have been reported.[126]

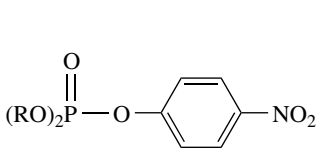

(**249**)


(**250**)

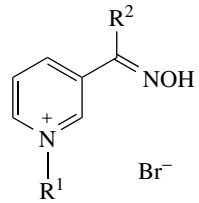

(**251**)

A hydroxoaqua copper complex containing *N*, *N*, *N*′, *N*′-tetramethyl-1,2-diaminoethane (**250**) is an excellent catalyst for the hydrolysis of sarin, *O*-isopropyl methylphosphonofluoridate (**251**), and diethyl *p*-nitrophenyl phosphate (**252**; R = Et). The mechanism of the reaction probably involves bound hydroxide attacking the phosphoryl group with concomitant electrophilic catalysis by copper.[127]

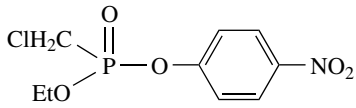
Two types of amphiphilic quaternary 3-pyridinium ketoximes (**253a**, **b**) with different positioning of the hydrophobic alkyl chain have been synthesized and tested as hydrolytic micellar catalysts. A considerable positive deviation from the expected first-order curve was observed in the absorbance vs time plot when *p*-nitrophenyl diphenyl phosphate (**252**; R = Ph) and *p*-nitrophenyl diethyl phosphate



(**252**)



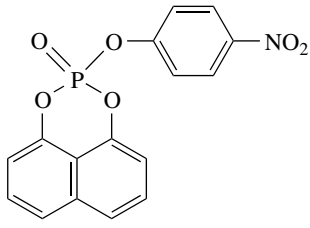
(**253**)



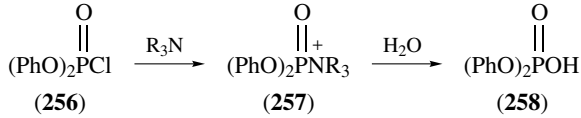
(**254**)

	R^1	R^2
(**a**)	$C_{12}H_{25}$	Me
(**b**)	Me	$C_{12}H_{25}$

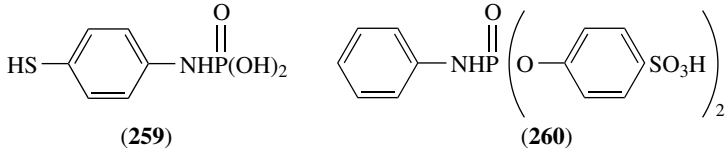
(**252**; R = Et) were hydrolysed in micellar solutions of the prepared ketoximes under pseudo-first-order reaction conditions.[128] In the alkaline hydrolysis of *p*-nitrophenyl ethyl chloromethylphosphonate (**254**), micellar catalysis by cetylpyridinium bromide is much reduced when KCl and KBr are present.[129]



(**255**)



(**256**) (**257**) (**258**)



(**259**) (**260**)

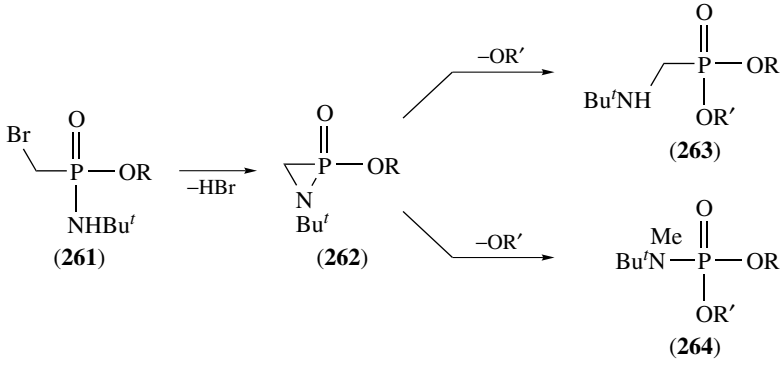
p-Nitrophenyl 1,8-naphthyl phosphate (**255**) is 1–2 orders of magnitude more reactive than *p*-nitrophenyl diphenyl phosphate (**252**; R = Ph) towards nucleophilic attack. An X-ray crystal structure of (**255**) revealed that the O(2)–P–O(3) bond angle is 105.8° and is therefore 'unstrained.' If a trigonal bipyramidal intermediate is formed, some strain will be engendered in attaining an O–P–O bond angle of 120°, but

the principal source of the higher reactivity of (**255**) over (**252**; R = Ph) is probably due to the easy access of the nucleophile to the phosphoryl centre.[130] Tertiary amines, pyridine, and imidazoles catalyse the hydrolysis, in aqueous acetonitrile, of diphenyl phosphochloridate (**256**) by attacking the phosphorus and displacing the chloro substituent to yield a cationic intermediate (**257**), which hydrolyses to diphenyl phosphate (**258**).[131]

Phosphorus–Nitrogen Centres

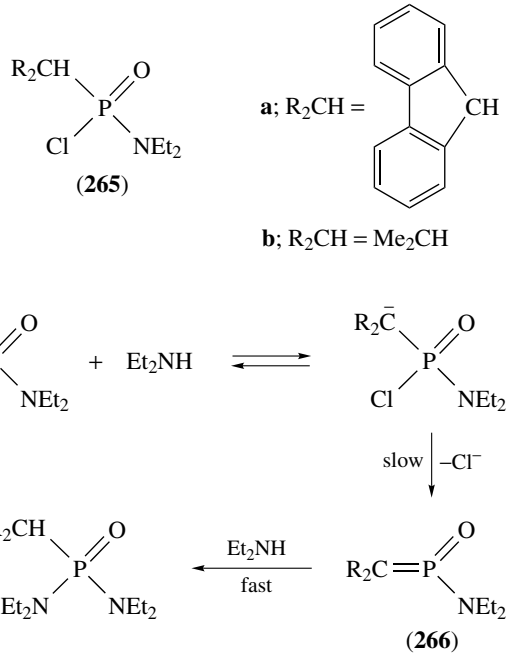
Kinetic studies have been reported of the acid hydrolysis of *N*-(*p*-sulfophenyl)phosphoramidic acid (**259**)[132] and of bis(*p*-sulfonyl) *N*-phenylphosphoramidate (**260**).[133]

Methyl *P*-bromomethyl *N*-*t*-butylphosphonamidate (**261**; R = Me) rearranges with methoxide, giving dimethyl-*t*-butylaminomethylphosphonate (**263**; R = R′ = Me) and dimethyl-*t*-butyl-*N*-methylphosphoramidate (**264**; R = R′ = Me) in comparable amounts. These products are derived from the (postulated) azaphosphiridine oxide intermediate (**262**; R = Me) by nucleophilic attack at phosphorus and cleavage at the P−N or P−C bond (Scheme 27). Increased bulk in the alkyl group of the alkoxy ligand (R = methyl < cyclohexyl < *t*-butyl < menthyl) or the alkoxide nucleophile (methoxide < *t*-butoxide) increases P−N bond cleavage at the expense of P−C cleavage.[134]

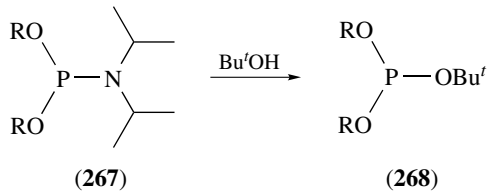


SCHEME 27

Compared with *N,N*-diethyl isopropylphosphonochloridate (**265b**), the corresponding fluorenyl compound (**265a**) shows remarkably high reactivity in nucleophilic substitution with Et_2NH. Substitution is catalysed by base {1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)} and shows little discrimination between competing Me_2NH and Et_2NH. These characteristics point to an elimination–addition (*EA*) mechanism with a reactive phosphene intermediate (**266**; Scheme 28). When Et_2ND is the nucleophile, H–D exchange at the α-carbon atom occurs much more quickly than substitution. This suggests that the elimination stage of the *EA* mechanism is reversible *E1cB*.[135]



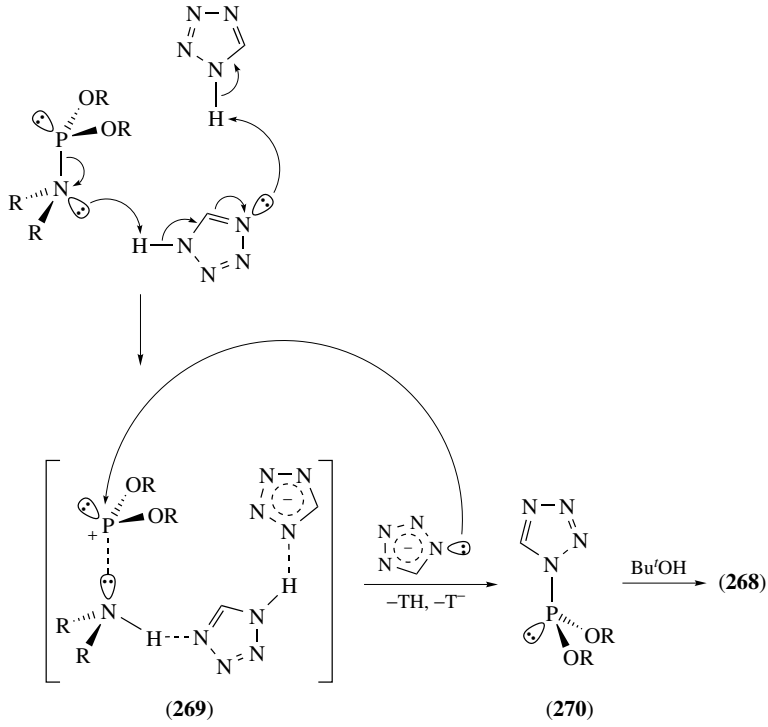
SCHEME 28



The tetrazole-catalysed alcoholysis of simple dialkylphosphoramidates (**267**) in THF to yield trialkylphosphites (**268**) occurs via nucleophilic catalysis (Scheme 29). The proposed mechanism sees tetrazole acting first as an acid catalyst to give the protonated intermediate (**269**), which then reacts with tetrazolide anion to yield the tetrazolylphosphite (**270**); alcoholysis of the latter (**270**) then yields the final product, the trialkylphosphite (**268**).[136]

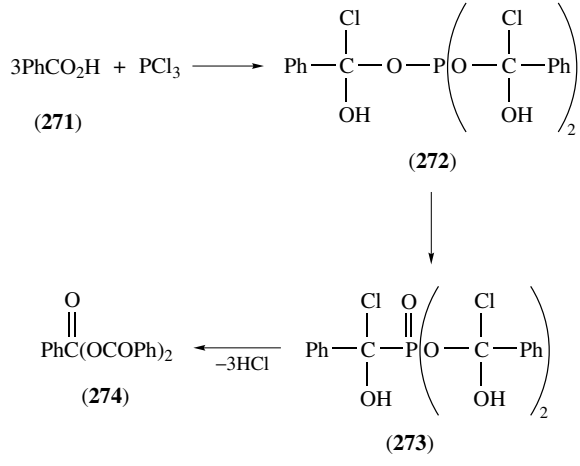
Phosphorus–Oxygen and Phosphorus–Sulfur Centres

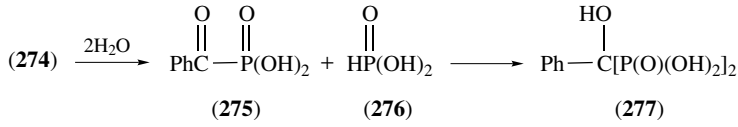
Benzoic acid (**271**) when reacted with PCl_3 yielded an adduct (**272**) which underwent an Arbuzov rearrangement to the phosphoryl compound (**273**), which eliminated 3HCl to give benzoylphosphonic anhydride (**274**). Addition of water to the reaction mixture converted the anhydride (**274**) into benzoylphosphonic acid (**275**), which underwent



SCHEME 29

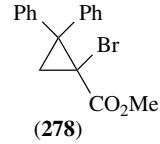
an addition reaction at its C=O group with the product of PCl_3 hydrolysis, phosphinic acid (**276**), to yield as the ultimate product phenylhydroxymethanediphosphinic acid (**277**). This pathway excludes the formation of benzoyl chloride, presumed hitherto to be the precursor which is phosphorylated to yield the diphosphinic acid (**277**).[137]

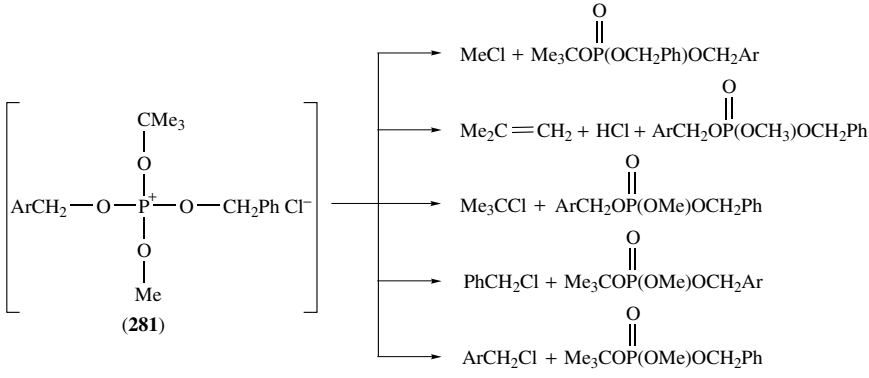




The reaction of $R_2P{-}O^-$ and $R_2P{-}S^-$ with methyl 1-bromo-2,2-diphenylcyclopropanecarboxylate (**278**) proceeds by the initial displacement of bromide ion, and thence gives rise to a complex mixture of products.[138]

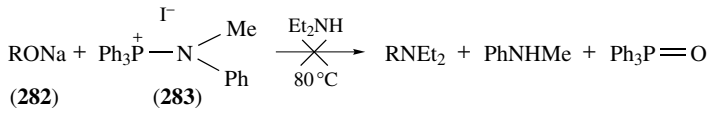
Benzyl methyl Y-substituted benzyl phosphites (**280**) react in CCl_4 at low temperature (−20 to 40 °C) with *t*-butyl hypochlorite (**279**) to give a complex mixture of products. Tetraalkoxyphosphonium chlorides (**281**; At = YC_6H_4) are the key intermediates, and it is proposed that they can undergo heterocyclic fragmentation in five different ways (Scheme 30).[139]



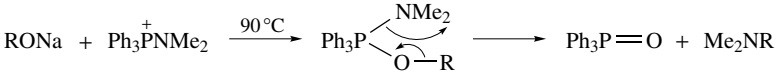


SCHEME 30

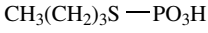
A thorough investigation has shown that the Tanigawa amination of alcohols, in which the corresponding alkoxide (**282**) is treated in DMF with *N*-methyl-*N*-phenylaminotriphenylphosphonium iodide (**283**) and a secondary amine at 80 °C, does not proceed at this temperature. *In situ* generation of the *N,N*-dimethylamino analogue (**284**) by reaction of (**283**) with dimethylamine, however, does lead to a smooth reaction at 90 °C. The proposed mechanism involves a pentacoordinated intermediate (**285**).[140]



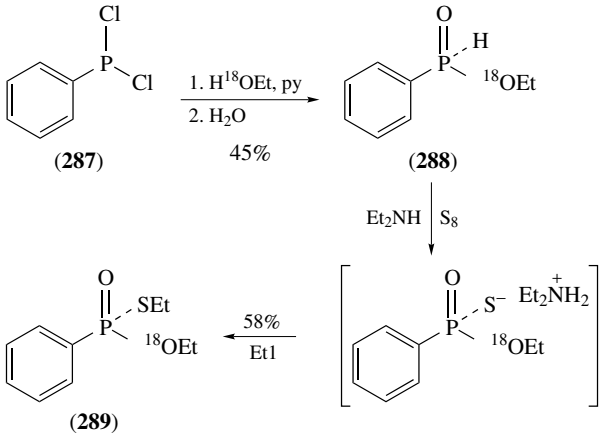
(**282**) (**283**)



(**284**) (**285**)

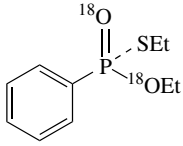


(**286**)



(**287**) (**288**) (**289**)

SCHEME 31



(**290**)

Mechanistic studies of the acid hydrolysis of *S*-butyl phosphorothioate (**286**) have been reported.[141]

The synthesis of ^{18}O-labelled phenylphosphonothioate (**289**) (Scheme 31) was achieved by reaction of dichlorophenylphosphine (**287**) with Et^{18}OH followed by addition of water to give (**288**). Oxidation with elemental sulfur in the presence of diethylamine then gave the salt of the *O*-ethylphenylphosphonothioate, which was alkylated with ethyl iodide to give the ^{18}O-labelled *O,S*-diethyl

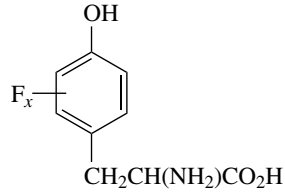
phenylphosphonothioate (**289**).[171] However, analysis by MS showed that some of the doubly labelled product (**290**) had also been formed. The authors suggest that it arose from the reaction of the dichlorophosphine (**287**) with $Et^{18}OH$, followed by partial hydrolysis of that product with $H_2{}^{18}O$ that had been formed concurrently by dehydration of the $Et^{18}OH$.[142]

Biologically Important Reactions

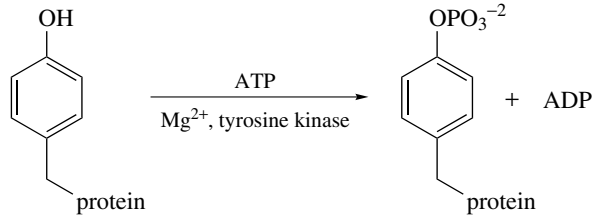
A series of synthetic fluorotyrosine-containing heptapeptides (**291**; X = fluorotyrosine) has been used to probe the nature of the transition state in a protein tyrosine kinase, a class of enzyme which catalyses the transfer of the γ-phosphoryl group from ATP to tyrosine residues in proteins (Scheme 32).[143] Indeed, both of the monofluoro, all four of the difluoro-, both of the trifluoro- and the tetrafluoro-tyrosines (**292**), which had been biosynthesized in gram quantities by incubating the corresponding fluorophenols with a recombinant enzyme tyrosine phenol-lyase in the presence of pyruvate and ammonia, were incorporated into the heptapeptides (**291**; X = fluorotyrosine) by automated solid-phase peptide synthesis. 2-Fluorotyrosine has $pK_a = 9.0$ and 2,3,5,6-tetrafluorotyrosine has $pK_a = 5.2$, with the di- and tri-fluoro analogues possessing values in between, and this range of substrates was used to show that (i) the substrate tyrosine phenol must be neutral to be enzymically active and (ii) a dissociative (path *b*), rather than associative (path *a*), transition state is indicated for phosphoryl transfer (Scheme 33).[143]

H_2N—Glu—Asp—Asn—Glu—X—Thr—Ala—CO_2H

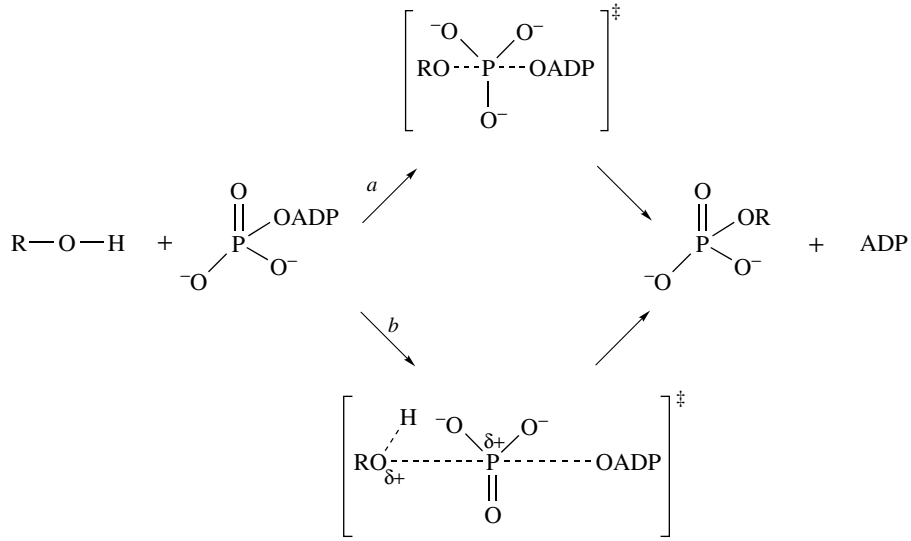
(**291**)



(**292**)

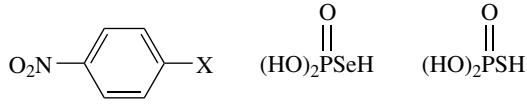


SCHEME 32



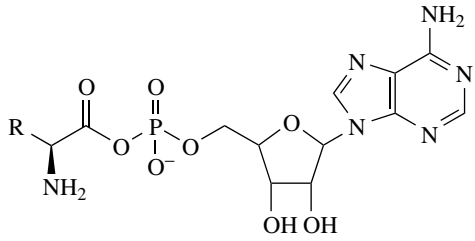
SCHEME 33

In a reverse micellar system prepared by dissolving sodium bis(2-ethylhexyl)sulfosuccinate in isooctane, the pK_a of 4-nitrophenol (**293**; X = OH) depends on the degree of hydration of the system. Such a system is claimed to be a good mimic of membrane-bound enzymes. Human placental alkaline phosphatase, known to be membrane-bound, has been deployed in this reverse micellar system with varying degrees of hydration, to study the enzymic hydrolysis of 4-nitrophenyl phosphate (**293**; X = OPO_3H). The pK_a of 4-nitrophenol (**293**; X = OH) was found to range between 9.2 and 10.8 for degrees of hydration ([H_2O]/[detergent]) between 40 and 4.44, and this allowed Brønsted constants to be determined for $k_{cat}(\beta_{lg} = -0.47)$ and for $k_{cat}/k_m(\beta_{lg} = -1.03)$. These model results were considered as support for phosphorylation being the rate-determining step in membrane-bound alkaline phosphatase, whereas in aqueous solution, dissociation of non-covalently bound phosphate is the rate-determining step.[144]



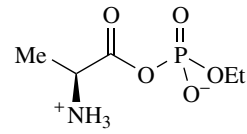
(**293**) (**294**) (**295**)

The hydrolysis, alcoholysis, and aminolysis of monoselenophosphate (**294**) have been reported for the first time; (**294**) is the labile selenium donor compound required for the synthesis of Se-dependent enzymes and seleno-tRNAs, and is formed from ATP and selenide, HSe^-. The rate of hydrolysis of monoselenophosphate (**294**) is



Aminoacyl adenylate

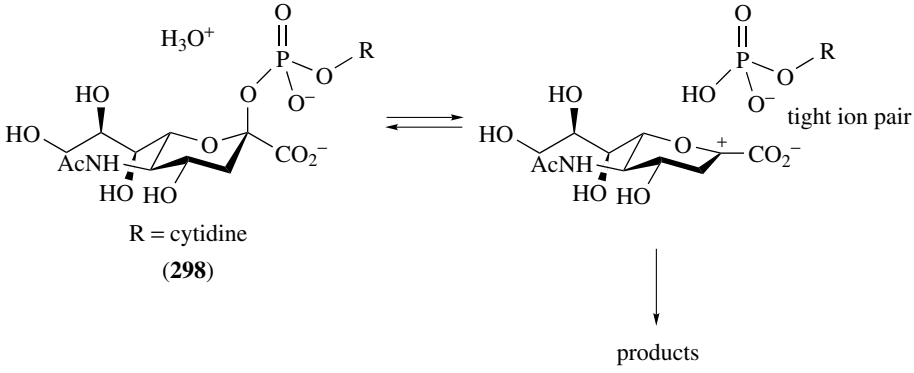
(**296**)



(**297**)

maximal at about pH 7, in contrast to that of monothiophosphate (**295**), which is maximal at pH 3. This suggests that the dianion of monoselenophosphate (**294**) is the species that reacts the fastest. From all the results obtained, the authors suggest that the mechanism of hydrolysis of monoselenophosphate (**294**) is dissociative in nature, involving a monomeric metaphosphate-like transition state.[145]

Aminoacyl adenylates (**296**), which are formed from protein amino acids and ATP, act as acylating agents towards t-RNAs, acylating their terminal 3′-hydroxy groups. These 'charged' tRNAs are then used in protein synthesis. Little is known about the reactivity of aminoacyl adenylates (**296**), and studies are now reported of a model compound, alanyl ethyl phosphate (**297**). As expected, hydrolysis in both acid and base involves attack at the C=O group of (**297**) with departure of ethyl phosphate. Metal ions (Cu^{2+}, Zn^{2+}) were found to act as catalysts of the hydrolysis.[146]



R = cytidine

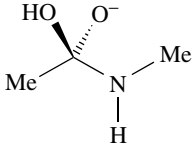
(**298**)

products

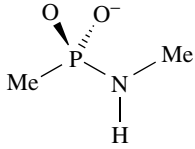
SCHEME 34

Cytidine 5′-phospho-*N*-acetylneuraminate (**298**), the coenzyme of sialyltransferases, is a sugar–nucleotide in which the leaving group is a nucleotidyl monophosphate that contains a carboxylate group directly attached to the anomeric centre. Studies of its hydrolysis reveal that at pH 5 specific acid catalysis occurs (Scheme 34) to yield a glycosyl carbocation as a tight ion pair, the lifetime of which was estimated

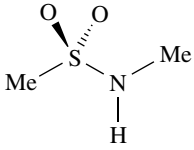
from trapping studies with azide ion to be $\geqslant 3 \times 10^{-11}$s. Generally, the carboxylate group was a spectator of the reaction, no evidence for its direct involvement being obtained.[147]



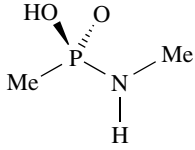
(**299**)



(**300**)



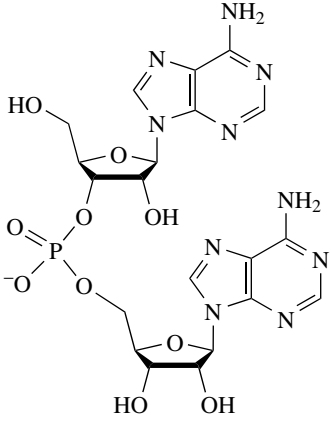
(**301**)



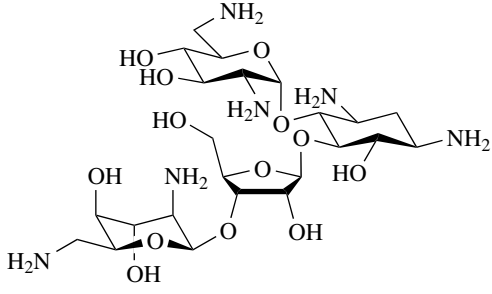
(**302**)

A theoretical investigation of *N*-methylmethanephosphonamidate (**300**), *N*-methylmethanephosphamide (**302**), and *N*-methylmethanesulfonamide (**301**) as protease transition-state isosteres has revealed that the anionic phosphonamidate (**300**) is the best mimic of the tetrahedral intermediate for base-catalysed *N*-methylacetamide (**299**) hydrolysis.[148]

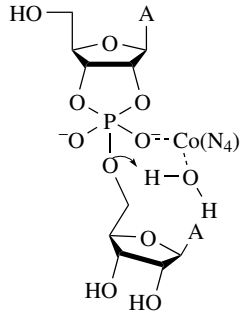
(**303**)



(**304**)



(**307**)



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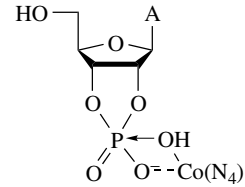
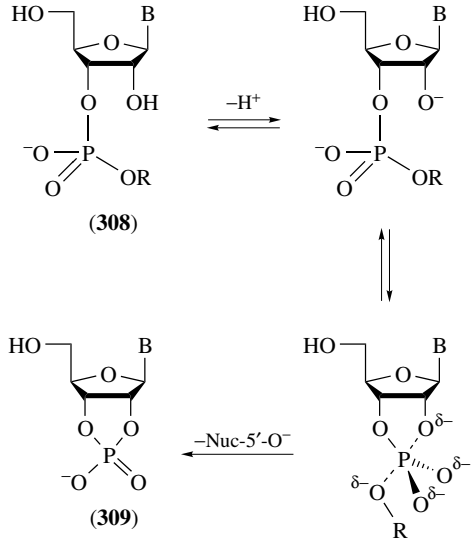


(**306**)

A series of diaquatetraaza cobalt(III) complexes accelerated the hydrolysis of adenylyl(3′–5′)adenosine (ApA) (**304**), an enhancement of 10^5-fold being observed with the triethylenetetramine complex (**303**) at pH 7. The pentacoordinated intermediate (**305**), which is formed with the complex initially acting as an electrophilic catalyst, then suffers general acid catalysis by the coordination water on the Co(III) ion to yield the complexed 1,2-cyclic phosphate (**306**), the hydrolysis of which occurs via intracomplex nucleophilic attack by the metal-bound hydroxide ion on the phosphorus atom.[149] Neomycin B (**307**) has also been shown to accelerate the phosphodiester hydrolysis of ApA (**304**) more effectively than a simple unstructured diamine.[150]

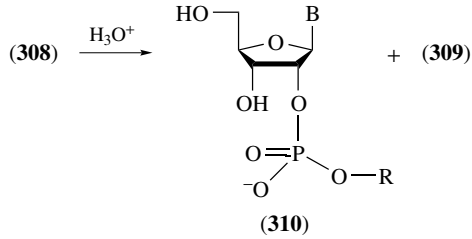
A series of uridine 3′-alkylphosphates (**308**) undergo in alkaline solution a hydroxide-ion catalysed reaction to give the 2′,3′-cyclic monophosphates (**309**) via phosphorane-type intermediates (Scheme 35). The alkyl groups ranged from ethyl



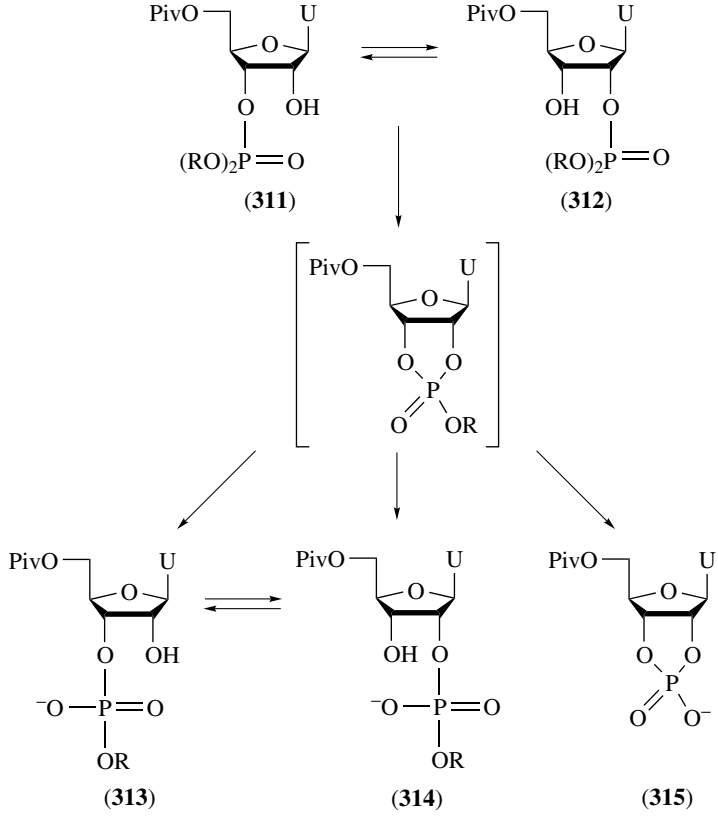
(**308**)

(**309**)

SCHEME 35



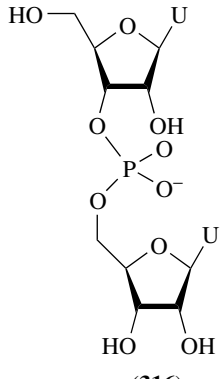
to 1,1,1-trichloroethyl, permitting the determination of a β_{lg} for the reaction of -1.28 ± 0.05, and this was interpreted as evidence for a mechanism lying on the borderline between a concerted and a stepwise mechanism. By contrast, in aqueous acid (**308**) undergo concurrent isomerization to 2′-alkylphosphates (**310**) and cleavage to 2′, 3′-cyclic phosphates (**309**) both processes being fairly insensitive to the electron-withdrawing ability of the alkyl group with β and β_{lg} values being -0.18 ± 0.02 and -0.12 ± 0.05, respectively.[151] The same group[152] has studied the acid hydrolysis of uridine 3′-dialkyl phosphates (**311**) (with protection of the 5′-hydroxyl group with a



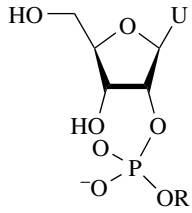
SCHEME 36

pivaloyl group), and they observed two parallel reactions: isomerization to 2′-dialkyl phosphates (**312**) and cleavage to a mixture of 2′- (**313**) and 3′-monalkyl phosphates (**314**) and a 2′, 3′-cyclic phosphate (**315**). The latter reaction presumably proceeded via the 2′, 3′-cyclic triester, which was too unstable to be detected (Scheme 36).[152]

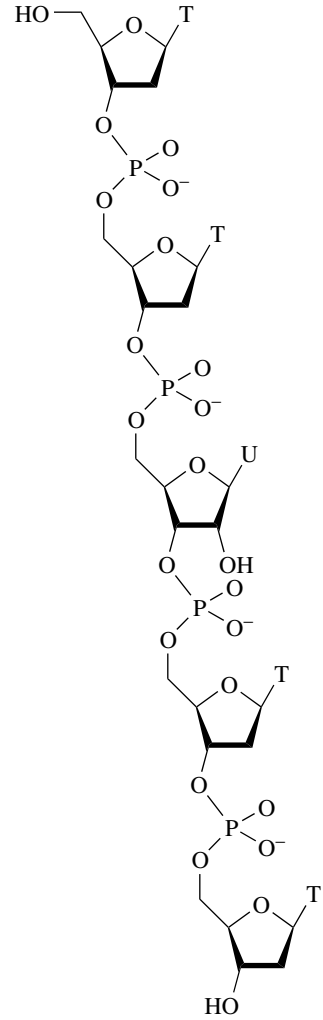
Measurements of medium and ionic strength effects on the rates of hydrolysis and isomerization of the dinucleoside monophosphate (3′, 5″-UpU) (**316**) in 0.1–0.7 M imidazole–imidazolium (Im/ImH$^+$) buffers have been reported.[153] The hydrolysis of (**316**) is catalysed both by Im and, less effectively, by ImH$^+$, whereas the isomerization to 2′, 5″-UpU (**317**; R = 5′-uridyl) is catalysed only by ImH$^+$. As a better model for RNA, the chimaeric oligonucleotide TTUTT (**318**), which undergoes the same



(**316**)

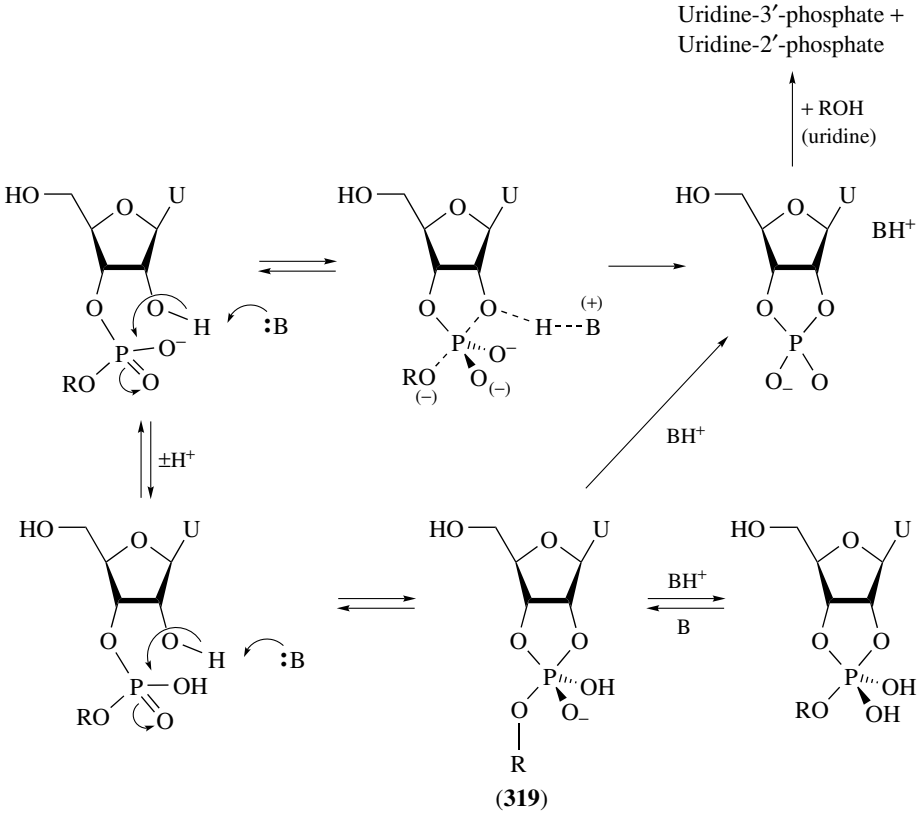


(**317**)



(**318**)

reactions at the unique in-chain uridylyl residue, was also studied. The isomerization reaction of TTUTT, was, like 3,5″-UpU, catalysed only by ImH^+, but the hydrolysis of TTUTT was catalysed more effectively by ImH^+ than by Im, in contradistinction to the results with 3′, 5″-UpU. From all the results obtained, it was concluded that the hydrolysis of the internucleoside bond in these phosphodiesters involves two parallel pathways: a more or less concerted general-base-catalysed reaction and a two-step process, involving the rate-determining general acid-catalysed breakdown of a phosphorane monoanion intermediate (**319**) (Scheme 37).[153]

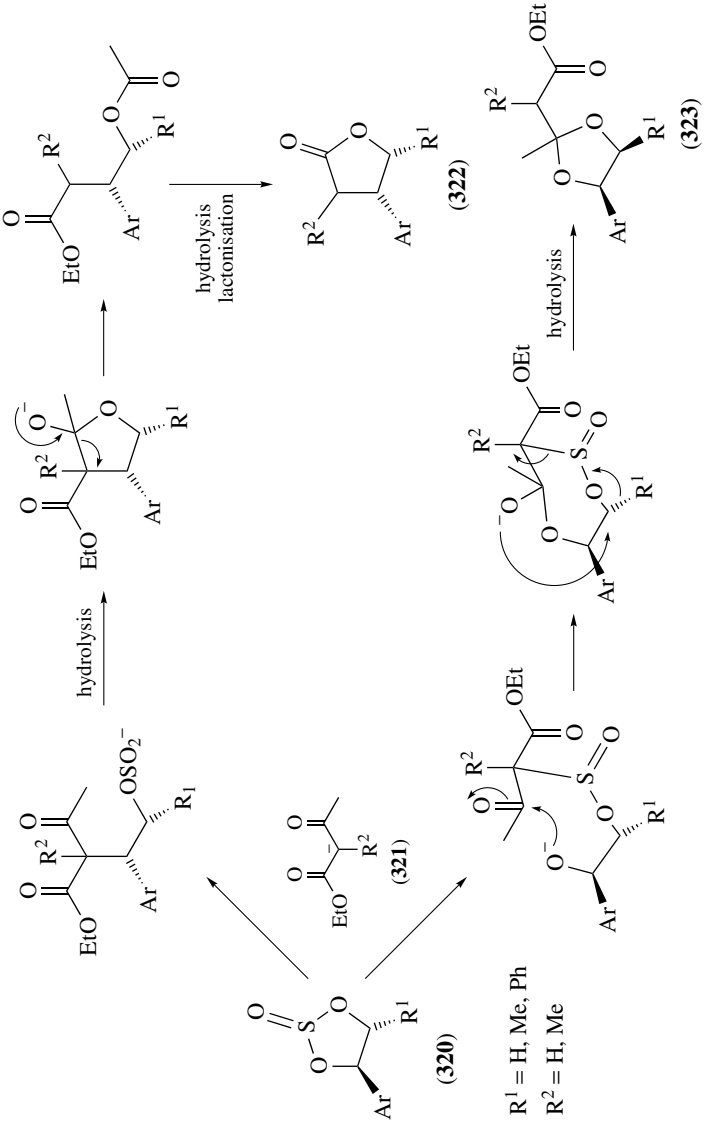


SCHEME 37

Sulfur-containing Acids

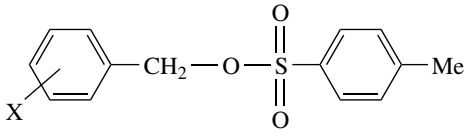
Sulfur–Oxygen Compounds

1,2-Cyclic sulfites (**320**) have been shown to react with sodium acetoacetate (**321**; $R^2 = H$) either by S_N2 attack at carbon to give γ-lactones (**322**) or by attack at the S=O group to give acetals (**323**) (Scheme 38).[154]

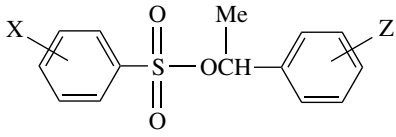

hydrolysis
hydrolysis
lactonisation
hydrolysis
(320)
(321)
(322)
(323)
R1 = H, Me, Ph
R2 = H, Me

SCHEME 38

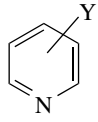
The specific rates of solvolysis of benzyl *p*-toluenesulfonate and nine benzylic-ring-substituted derivatives (**324**) have been satisfactorily correlated using N_T and Y_{OTs} scales within the extended Grunwald–Winstein equation.[155] The reactions of Z-phenylethyl X-benzenesulfonates (**325**) with Y-pyridines (**326**) in acetonitrile at 60 °C have been studied at high pressures. The results indicated that the mechanism of the reaction moves from a dissociative S_N2 to an early-type concerted S_N2 with increasing pressure.[156]



(**324**)

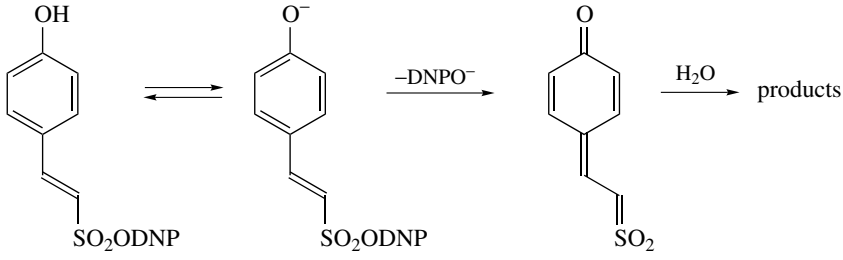


(**325**)



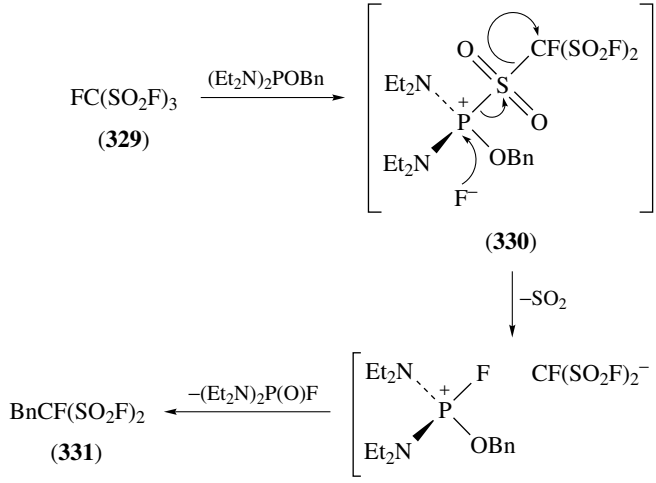
(**326**)

In strongly alkaline solution, 2,4-dinitrophenyl 4-hydroxy-β-styrenesulfonate (**327**) hydrolyses via a dissociation ($E1cB$) mechanism with the probable intervention of an extended 'sulfoquinone' intermediate (**328**).[157]

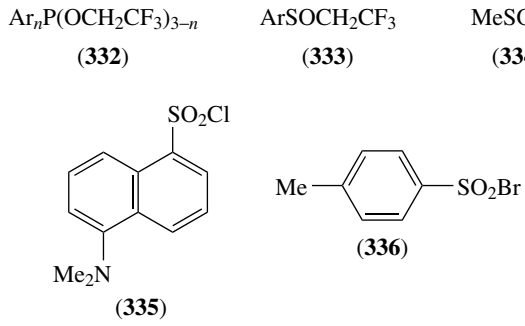


(**327**) (**328**)

Tris(fluorosulfuroyl)fluoromethane (**329**) reacted with bis(diethylamido)benzyl phosphite to yield an intermediate (**330**) which extruded a molecule of SO_2 to give as final product the bis(fluorosulfonyl) compound (**331**).[158] The kinetics and mechanism of the reaction of fluorinated tricoordinate phosphorus compounds (**332**) and aryl 2,2,2-trifluoroethyl sulfenates (**333**) have been reviewed.[159]

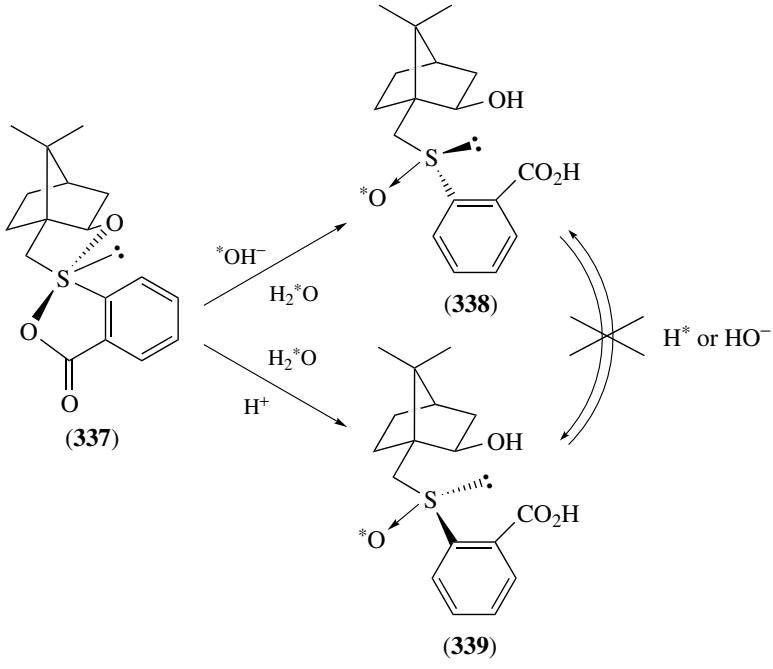


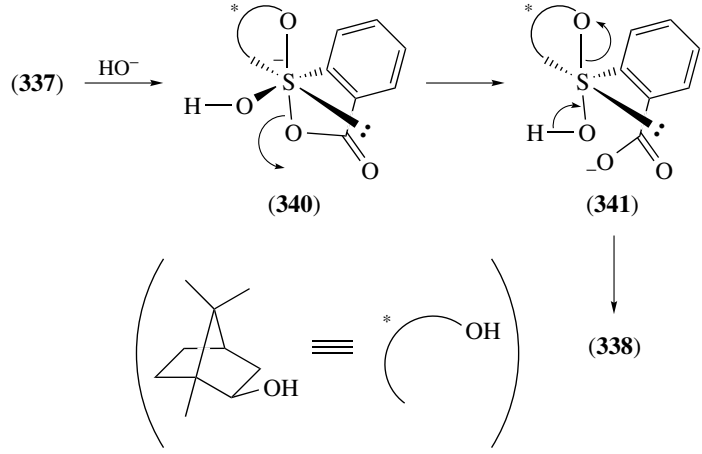
Ab initio SCRF/MO methods have been applied to the hydrolysis and methanolysis of methanesulfonyl chloride (**334**).[160] The aminolysis by aromatic amines of sulfonyl and acyl chlorides has been examined in terms of solvent parameters, the former being the more solvent-dependent process.[161] Solvent effects on the reactions of dansyl chloride (**335**) with substituted pyridines in MeOH–MeCN were studied using two parameters of Taft's solvatochromatic correlation and four parameters of the Kirkwood–Onsager, Parker, Marcus and Hildebrand equations. MeCN solvent molecules accelerate charge separation of the reactants and stabilize the transition state.[162]



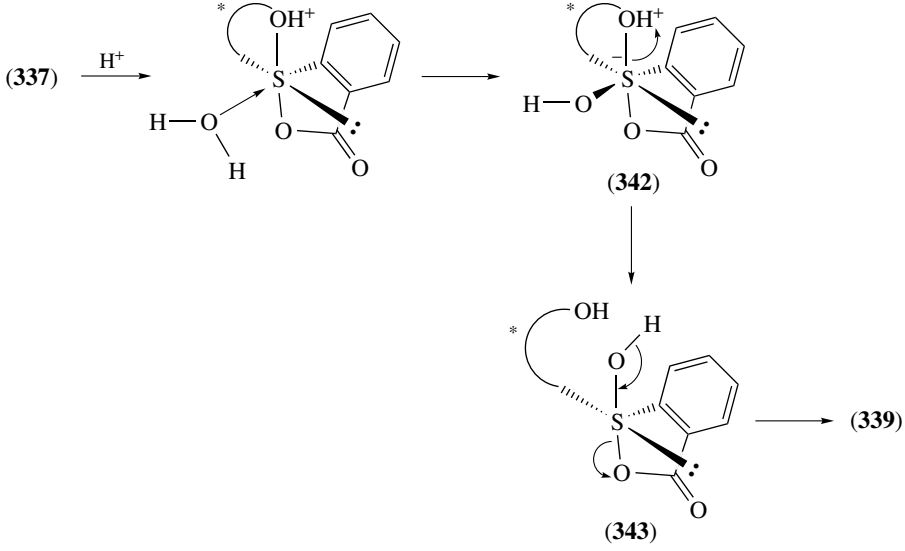
The activation parameters of the hydrolysis in aqueous dioxane of *p*-toluenesulfonyl bromide (**336**) pass through maxima at dioxane mole fractions of 0.01 and 0.12, which correspond to the range of stabilization of the solvent structure.[163]

The chiral spiro-λ_4-sulfurane (**337**) is easily hydrolysed under basic conditions (1 M NaOH) to give optically pure sulfoxide (**338**) as a single diastereomer. In contrast, hydrolysis of spiro sulfurane (**337**) under acidic conditions (1 M HCl) gave sulfoxide (**339**), also as a single diastereomer but with an opposite absolute configuration at the sulfur atom. The proposed mechanism of these reactions is as follows: hydrolysis under basic conditions may proceed through the attack of hydroxide ion on the central sulfur atom to give an intermediate (**340**) (Scheme 39). Cleavage of the S−O(acyloxy) bond and isomerization around the sulfur centre generates the pentacoordinate intermediate (**341**) with the hydroxyl group at the apical position. Then, deprotonation and tandem breaking of the S−O(alkoxy) bond takes place to give the highly diastereoselective formation of the sulfoxide (**338**) with *R* absolute configuration. Under the acidic conditions, the reaction may proceed through the initial protonation of the spirosulfurane at the oxygen of alkoxy, then attack by H_2O at the sulfur atom takes place and a hexacoordinate sulfur intermediate (**342**) is formed (Scheme 40). Cleavage of the S−O(alkoxy) bond of the intermediate (**342**) and isomerization around the sulfur centre produce an intermediate (**343**) with the hydroxyl group at the apical position. Final deprotonation and consecutive breaking of the S−O(acyloxy) bond gave sulfoxide (**339**) with *S* absolute configuration at the sulfur atom.[164]





SCHEME 39



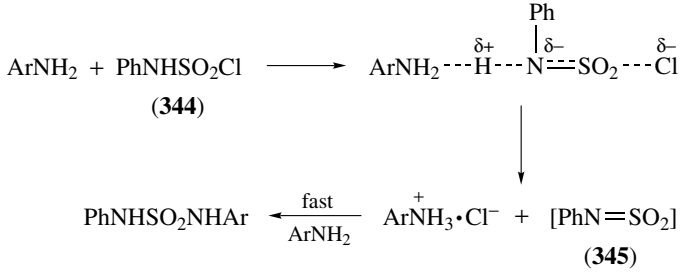
SCHEME 40

Sulfur–Nitrogen Compounds

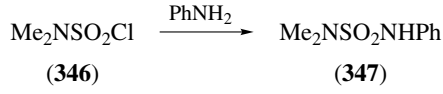
Detailed studies of the anilinolysis of *N*-phenylsulfamoyl chloride (**344**) (and related compounds) in chloroform support the operation of an *E2*-type mechanism in which an *N*-sulfonylamine (**345**) is formed in the rate-determining step (Scheme 41).[165] Lacking a proton on nitrogen, the corresponding *N,N*-dimethylsulfamoyl chloride (**346**) (and its congeners) cannot undergo an elimination of HCl, and instead attack by aniline occurs at the sulfur of the sulfamoyl group to yield *N,N*-dimethyl-*N′*-phenylsulfamide

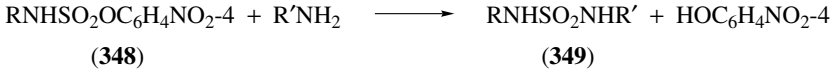
(**347**). This is a very much slower reaction and proceeds at rates 10^6-fold slower than the elimination pathway.[165] The same group has studied the aminolysis in chloroform of the corresponding *p*-nitrophenyl *N*-alkyl- or *N*-phenyl-sulfamates (**348**) which also yield sulfamides (**349**). Reaction with 2-substituted imidazoles, it was concluded,[166] probably proceeds via an *ElcB* mechanism (Scheme 42) involving extensive S−O bond cleavage with the formation of an *N*-sulfonylamine. Extending these aminolysis studies to a set of *p*-nitrophenyl *N*-*X*-phenyl sulfamates (**348**) using piperidine and a set of five pyridines, Brønsted β_{nuc} values have been determined which support *E2* mechanisms for these bases, although the data indicate that those reactants with the larger β_{nuc} values probably veer towards the *ElcB* pathway somewhat.[167]

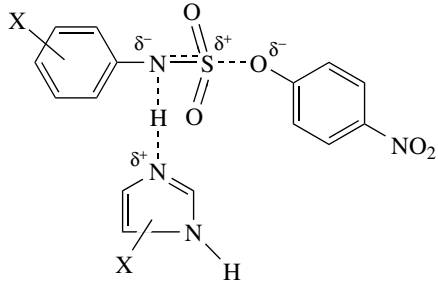
Kinetic studies of the hydrolysis of aryl *N*-(methoxycarbonyl)sulfamates (**350**) are reported for the first time.[168] The compounds are fairly strong acids with pK_a = 0.5–2.4, and in acid both S−O and C−O bond cleavages occur (Scheme 43). From an



SCHEME 41



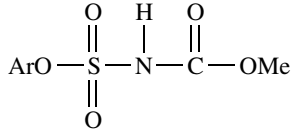




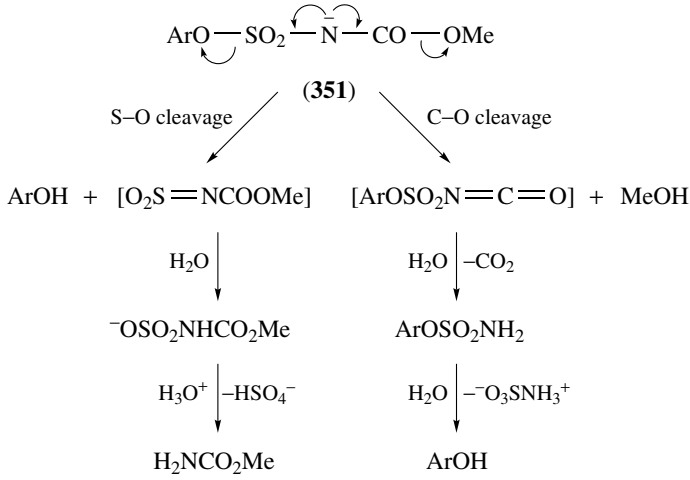
SCHEME 42

analysis of β_{lg}, solvent isotope effects, and solvent isotopic labelling of products, it was concluded that the S−O cleavage reaction involves either an intra- or inter-molecular general-acid-catalysed decomposition of the parent compound (**350**) or its ionized form (**351**) and the C−O cleavage reaction involves protonation of the leaving-group methanol and its expulsion from the dipolar intermediate (Scheme 43).[168]

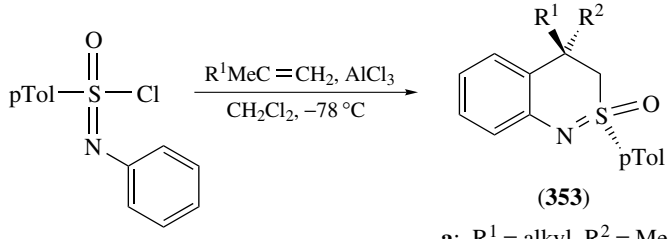
The Lewis acid-mediated reaction of *N*-phenyl-*S*-(4-methylphenyl)sulfonimidoyl chloride (**352**) with 1,1-disubstituted alkenes yields benzothiazines (**353**) with low stereoselectivity in moderate yields (33–57%).[169]



(**350**)



SCHEME 43

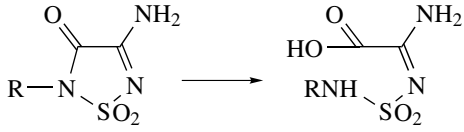


(**352**)

(**353**)

a; R^1 = alkyl, R^2 = Me

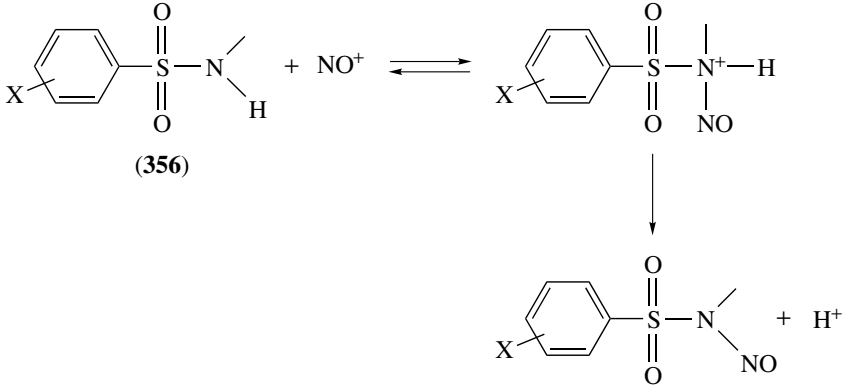
b; R^1 = Me, R^2 = alkyl



(**354**) (**355**)

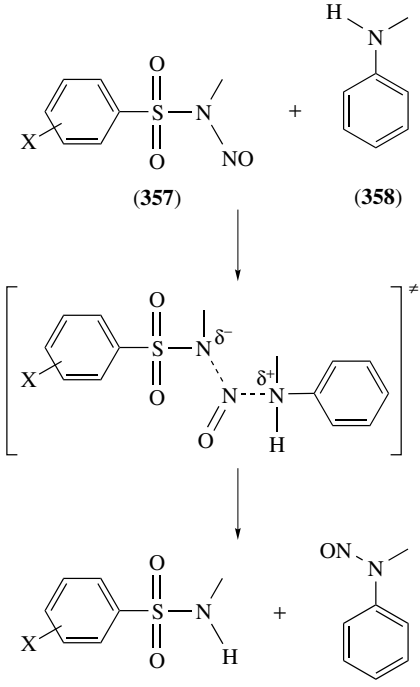
The kinetics of the hydrolysis reactions of 4-amino-2-phenethyl- (**354**; R = $PhCH_2CH_2$) and 4-amino-2-cyclohexyl-2,3-dihydro-3-oxo-1,2,5-thiadiazole 1,1-dioxide (**354**; R = C_6H_{11}) have been investigated in the pH range 1–10 at 24–73 °C. The products are the corresponding new compounds: 2-amino-2-[(*N*-substituted-sulfamoyl)imino]acetic acid salts (**355**; R = $PhCH_2CH_2$ or C_6H_{11}) which hydrolyse further, in a slow reaction, to the sulfamide and oxalic acid derivatives.[170]

Studies of the kinetics of the nitrosation of a series of 4-substituted *N*-methylbenzenesulfonamides (**356**) have revealed that electron-withdrawing groups retard the process. The mechanism probably involves a fast nitrosation pre-equilibrium followed by a slow proton transfer to the medium (Scheme 44).[171] The de-nitrosation reaction, which was also studied, is general acid catalysed and proceeds via a rate-determining proton transfer.[171] The same group determined the hydrolytic stability and efficiency as nitrosating agents of a small set of acyl-substituted *N*-methyl-*N*-nitrosobenzenesulfonamides (**357**; X = 2, 4, 6-Me_3, 4-OMe, 4-Cl and 4-NO_2). The nitrosating reactivity was measured by reaction of each with *N*-methylaniline (**358**), which reacts via a transition state with zwitterionic character (Scheme 45).[172] The acid and base hydrolysis of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (**357**; X = 4-Me) in micellar media have been reported.[173,174] 1-Methyl-1-nitroso-3-*p*-tolylsulfonylguanidine (**359**) undergoes a denitrosation reaction in acid medium which is probably concerted (Scheme 46).[84]



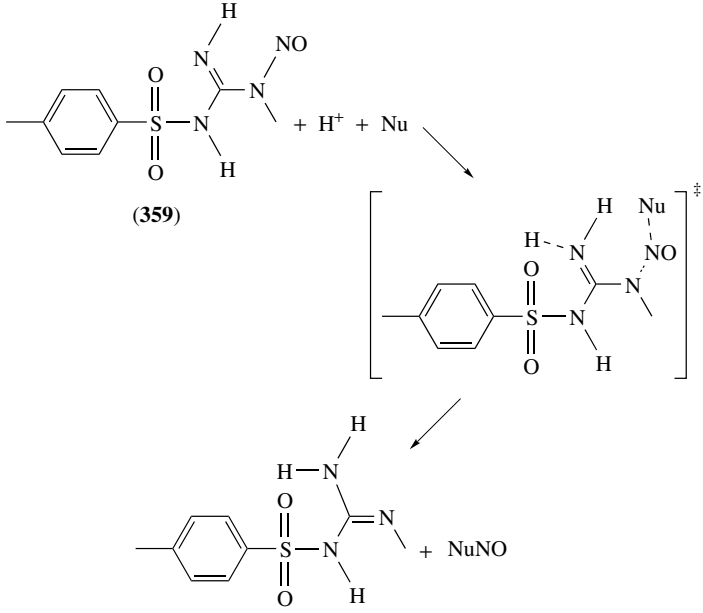
(**356**)

SCHEME 44



(**357**) (**358**)

SCHEME 45



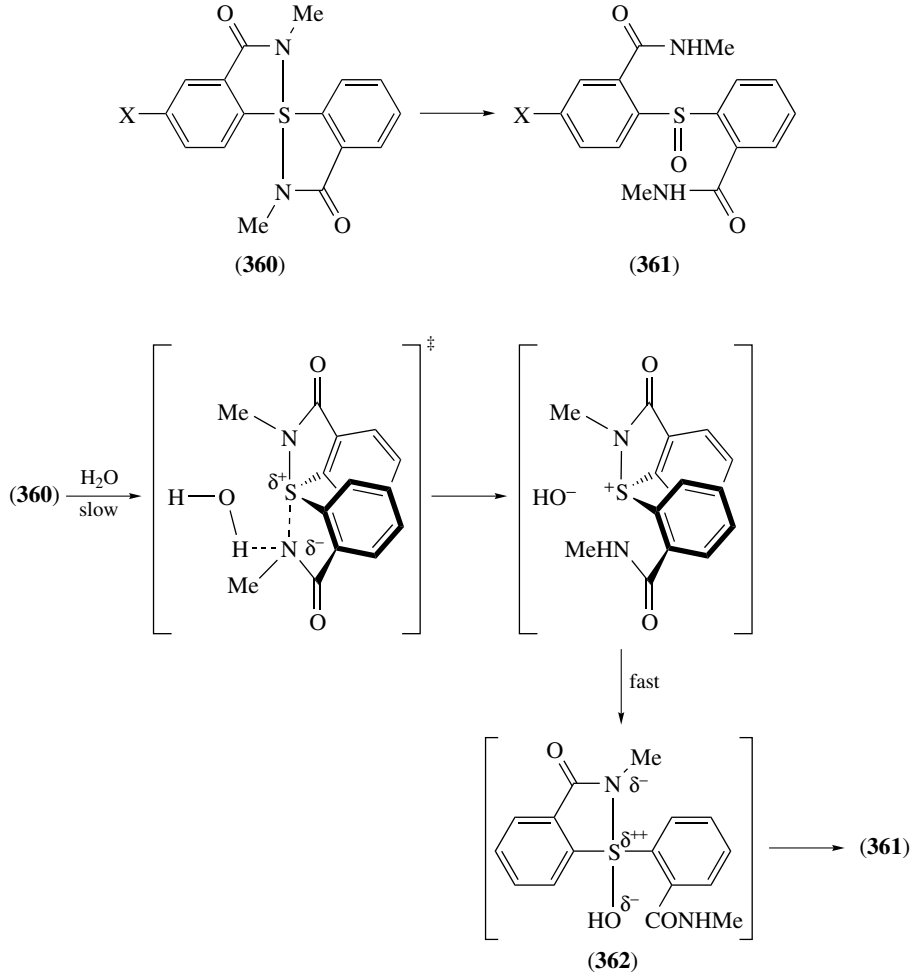
(**359**)

SCHEME 46

The parent compound and a set of monosubstituted bis(acylamino)diarylspiro-λ_4-sulfanes (**360**; X = H, Me, MeO, Cl, NO_2) undergo hydrolysis to the corresponding sulfoxides (**361**). The probable mechanism involves rate-determining cleavage of one of the S−N hypervalent bonds in the spiro ring with simultaneous proton transfer to the nitrogen atom. The hydroxide ion which is formed thereby then attacks the sulfur atom in a fast step to form a diaryl(acylamino)hydroxy-λ_4-sulfane (**362**), which is converted into the sulfoxide (**361**) (Scheme 47).[175]

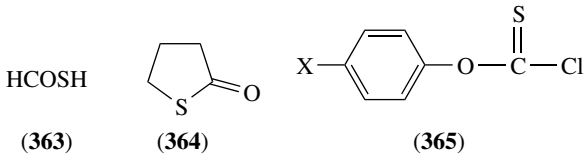
Sulfur–Carbon Compounds and Other Sulfur-containing Functionalities

An *ab initio* study of the unimolecular pyrolysis mechanisms of monothioformic acid (**363**) has yielded activation energies for dehydrogenation and dehydrosulfidation.[176]

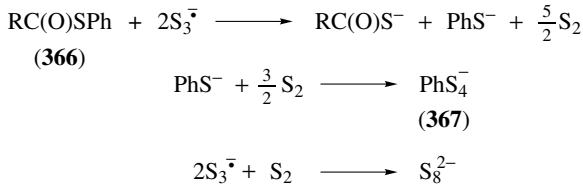


SCHEME 47

Enthalpy barriers for the decarbonylation and dethiocarboxylation of γ-thiobutyrolactone (**364**) have been calculated as 378 and 404 kJ mol^{-1}, respectively, which accords with the experimental results which saw CO as the major and COS as the minor thermal degradation products.[177] Phenyl and 4-nitrophenyl chlorothionoformates (**365**; X = H, NO_2) reacted with phenolates in aqueous dioxane with $\beta_{nuc} = 0.55$ and 0.47, respectively, from which it was concluded that a concerted mechanism prevailed.[178]



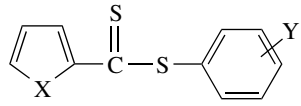
(**363**) (**364**) (**365**)



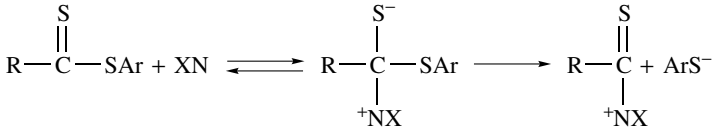
(**366**) (**367**)

SCHEME 48

S-Thiophenyl acetates (**366**; R = Me) and propionates (**366**; R = Et) react with electrogenerated polysulfide ions $S_3^{\bullet-}$ in DMF to yield thiocarboxylate ions, thiolate ions, and phenyl tetrasulfanide (**367**), the last deriving from the reaction of thiolate ions with sulfur (Scheme 48).[179] Studies of the aminolysis by a set of substituted anilines of Y-aryl dithio-2-thiophenates (**368**; X = S) and dithio-2-furoates (**368**; X = O) in acetonitrile have shown that the rate-determining step in these reactions is the departure of the thiophenolate ion from the zwitterionic tetrahedral intermediate $T^{\pm}$ (Scheme 49). Experiments with deuteriated anilines yielded k_H/k_D values of 1.7–1.9,

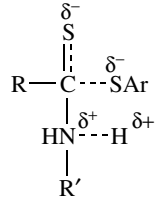


(**368**)



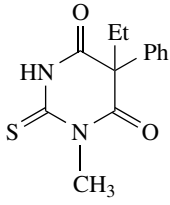
SCHEME 49

and these results are considered to favour a four-centre-type transition state (**369**).[180] Similar studies of the aminolysis of *O*-ethyl *S*-aryl dithiocarbonates point to an analogous mechanism (Scheme 49; R = EtO) involving a four-centre transition state (**369**; R = EtO).[181]

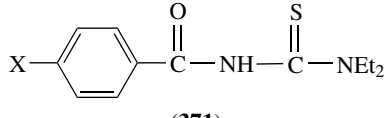


(**369**)

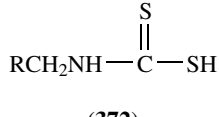
The kinetics of the alkaline hydrolysis of 5-ethyl-1-methyl-5-phenyl-2-thioxo-4,6-(*1H,3H,5H*)-pyrimidinedione (2-thioprominal) (**370**) have been reported.[182] Hammett plots of pK_a values were linear for a series of *N*-*X*-benzoyl *N*′, *N*′-diethylthioureas (**371**).[183]



(**370**)

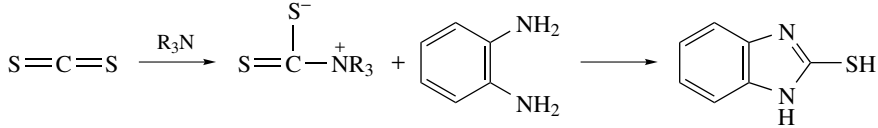


(**371**)



(**372**)

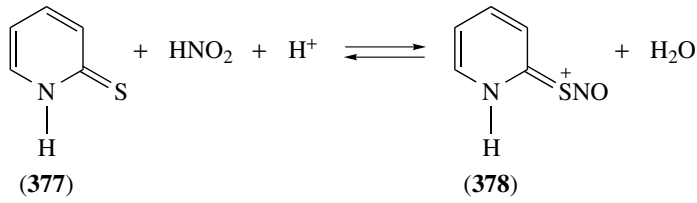
Kinetic studies of the acid hydrolysis of *N*-alkyl dithiocarbamates (**372**) have been reported.[184] The tertiary amine-catalysed addition of CS_2 (**373**) to 1,2-diaminobenzene (**375**) involves initial formation of the zwitterionic adduct (**374**), which then reacts with the diamine (**375**) to yield 2-mercaptobenzimidazole (**376**).[185]



(**373**) (**374**) (**375**) (**376**)

2-Mercaptopyridine (**377**) reacts rapidly with nitrous acid in mildly acid aqueous solution (via the thione tautomer) to give an unstable *S*-nitroso ion (**378**) in a reversible

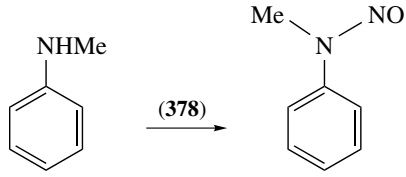
process with an equilibrium constant (K_N) of ca 1×10^5 dm^6mol^{-2}. SNO^+ is readily detected by two peaks in the UV spectrum at 295 and 240 nm with molar absorptivities of 9600 and 9300 $dm^3mol^{-1}cm^{-1}$, respectively; (**377**) is regenerated when the solution is made alkaline. In acidic solution, SNO^+ decomposed to the disulfide (2,2′-dipyridyl disulfide) and NO. There was clear evidence that SNO^+ can act as an efficient nitrosating species: addition of the thiol *N*-acetylcysteine (**379**) resulted in the almost instantaneous decomposition of SNO^+; addition of *N*-methylaniline (**380**) to an acidified solution of SNO^+ resulted in quantitative *N*-methyl-*N*-nitrosoaniline (**381**) formation.[186]



(**377**) (**378**)

$MeCONHCH(CO_2H)CH_2SH$

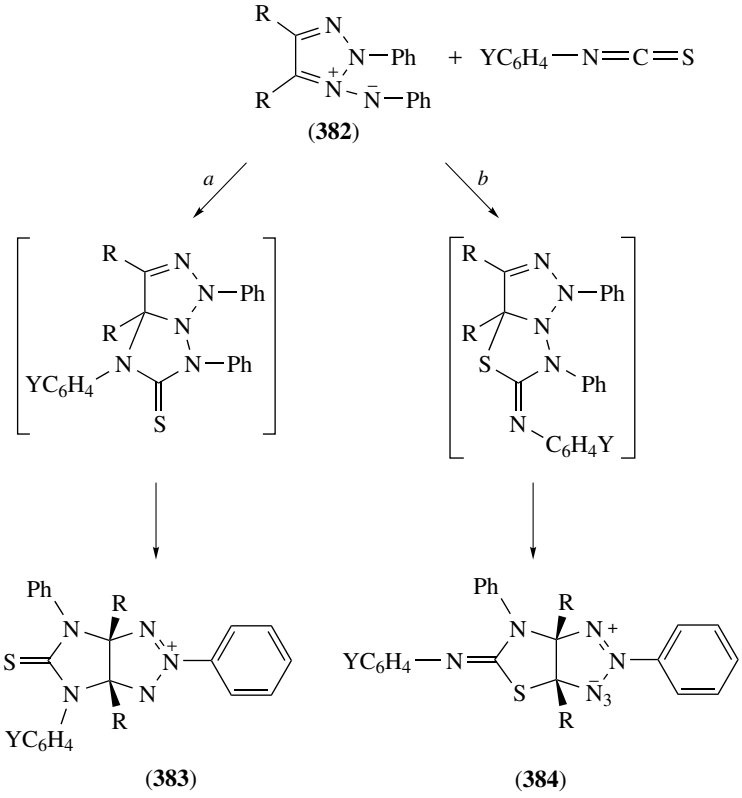
(**379**)



(**380**) (**381**)

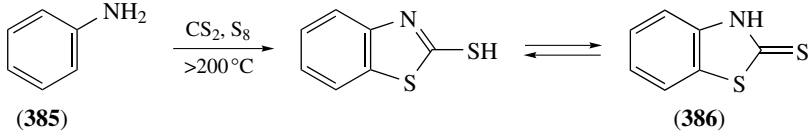
Substituted 1,2,3-triazolium-1-aminide 1,3-dipoles (**382**) react with aryl isothiocyanates at both the N=C (path *a*) and C=S (path *b*) sites to give mixtures of substituted imidazolo[4,5-*d*][1,2,3]triazoles (**383**) and new thiazolo[4,5-*d*][1,2,3]-triazoles (**384**) including tricyclic derivatives with the C(3a) and C(6a) bridgeheads linked via $(CH_2)_4$ and phenanthro groups (Scheme 50). The product distribution is controlled by the *para*-substituent of the aryl isothiocyanate. Theoretical calculations at the 3–21G* and 6–31G* levels suggest that linear triple-bonded canonical forms of the aryl isothiocyanate system play a key role in the ambident reactivity of these systems.[187]

The formation of benzothiazole-2-thiol (**386**) from aniline (**385**), carbon disulfide, and sulfur at 230 °C has been shown to occur by a sequence of three principal steps. Labelling experiments confirmed that both sulfur atoms originated from carbon disulfide. An initial polar reaction to form thiocarbanilide (**389**) via phenylcarbamic acid



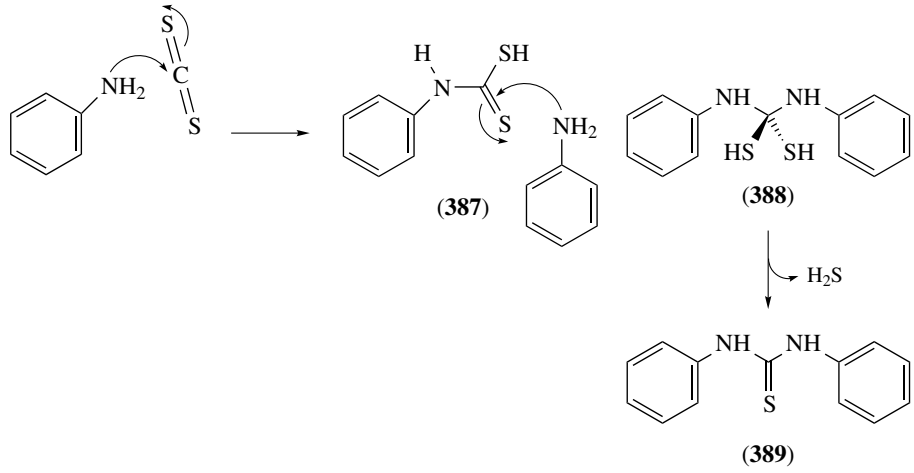
SCHEME 50

(**387**) and a tetrahedral intermediate (**388**) (Scheme 51) is followed by radical cyclization of these to benzothiazole (**386**) and 2-phenylaminobenzothiazole (**390**); the latter is converted into the desired product (**386**) by a polar displacement of aniline by H_2S (Scheme 52).[188]

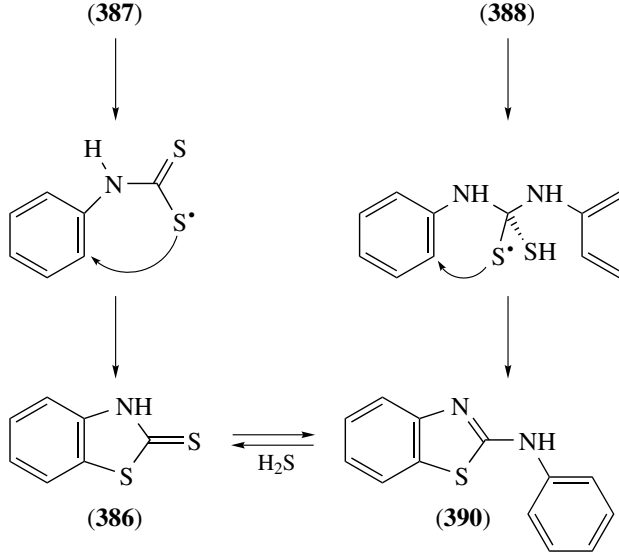


Other Acids

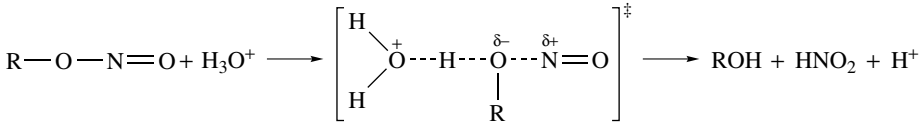
The acid hydrolysis of alkyl nitrites (Scheme 53) is inhibited by the presence of β-cyclodextrin (CD) owing to the formation of 1:1 inclusion complexes that are unreactive or much less reactive than the RONO not complexed. The degree of inhibition



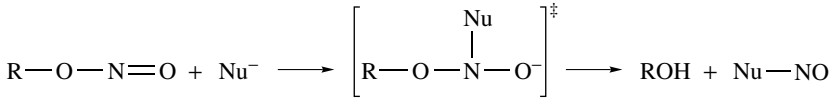
SCHEME 51



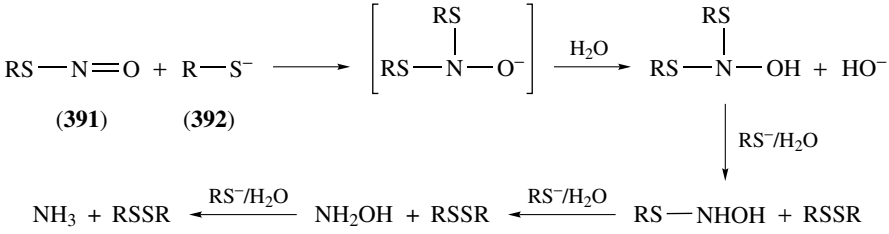
SCHEME 52



SCHEME 53



SCHEME 54



SCHEME 55

increases with increase in the association of the alkyl nitrite to CD: those with aromatic substituents interact more efficiently with the apolar CD cavity than do aliphatic alkyl nitrites. However, the basic hydrolysis of alkyl nitrites (Scheme 54) at pH values higher than the pK_a of β-cyclodextrin is powerfully catalysed by the presence of β-cyclodextrin because the nucleophilic reaction of alkyl nitrite by an ionized secondary hydroxy group of CD is faster than the reaction with HO^-, i.e. the reaction rate of the complex is faster than that of the RONO not complexed.[189]

Reactions of *S*-nitrosothiols (**391**) with their corresponding thiols (**392**) present in a large excess (>20-fold) proceed readily to give the disulfide. Ammonia is formed together with some nitrite anion, and these constitute >90% of the 'nitrogen' products. This is in marked contrast with the reaction at low thiol concentration, where nitric oxide is the major initial 'nitrogen' product, which is rapidly converted in the presence of oxygen in water into nitrite anion. The ammonia-forming reaction (Scheme 55) involves initial rate-determining attack of RS^- (**392**) at the nitrogen atom of the *S*-nitrosothiol (**391**), which is followed by other reactions of RS^- at the sulfur atom and various proton transfers, leading to the formation of hydroxylamine, then ammonia. For *S*-nitrosocysteine [**391**; R = $H_2NCH(CO_2)CH_2$], this pathway accounts for 80% of the total reaction at 25 mM cysteine [**392**; R = $H_2NCH(CO_2H)CH_2$]. The mechanism of the NO-producing reaction is to be the subject of a subsequent study, and could be either a homo- or hetero-lytic process.[190]

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CHAPTER 3

Radical Reactions: Part 1

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Introduction

Free-radical chemistry continues to be a focus for research, a number of reviews being published in 1998. In particular, mechanistic considerations have attracted significant interest, with an increasing number of theoretical papers appearing. These theoretical papers have dealt with all aspects of radical chemistry, including the modelling of mechanisms and kinetics of radical processes ranging from biologically relevant radical reactions to those of importance in the atmosphere and in combustion.

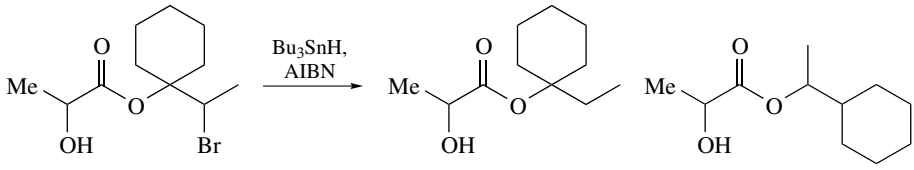
At least 10 reviews on peroxyl radicals and their reactions have appeared, ranging in subject from their reactions in the gas phase and in the atmosphere to their ESR spectra and rate constants for formation[1–10] (for more details of these papers, see the *Peroxyl Radicals* section of this chapter). The chemistry of aromatic systems has also attracted attention. Comparative quantitative structure–activity relationships (QSAR) for the reactions of a range of radicals with aromatic compounds have been reported.[11] This review includes reactions relevant to biological and atmospheric systems as well as conventional organic chemistry. Both the electron-transfer (ET) mechanisms for nitration of aromatics by $^{\bullet}NO_2$, and $^{\bullet}NO_3$ as well as the radical-coupling reactions between phenoxy radicals and nitrogen dioxide have also been reviewed.[12,13] Radical and radical-ionic migrations and fragmentation reactions have been reviewed. The discussion concentrates in particular upon the reactions of β-(acyloxy)alkyl and β-(phosphatoxy)alkyl radicals.[14] In addition, another paper comparing the reactivity of a range of radicals and radical cations has appeared.[15]

Turning to the application of radical chemistry in organic synthesis, a review dealing with the cyclization of carbon radicals on to unsaturated CN bonds and the cyclization of a range of nitrogen-centred radicals has appeared.[16] In addition, new synthetic methods utilizing photo-induced single-electron transfer[17] and all aspects of the solution structure, reactivity, and chemistry of carbon-centred fluorine-containing free radicals have been reviewed.[18] The development of asymmetric radical reactions continues with a review appearing on stereoselectivity of hydrogen- and allyl-transfer reactions in acyclic systems.[19] Homolytic substitution reactions have also been reviewed.[20]

Rearrangements

Group Migration

The chemistry and rearrangement reactions of β-(acyloxy)alkyl and β-(phosphatoxy)alkyl radicals have been reviewed.[14] The review incorporates both rearrangement and fragmentation reactions as well as addressing mechanistic considerations. It also addresses QSAR, ESR, and computational aspects of this class of reaction. Rate enhancements of acyloxy rearrangements (**1**) to (**3**) have been observed if the reactions are carried out in the presence of a stoichiometric quantities of Lewis acid (Scheme 1).[21] Based upon recent calculations, it was postulated that this acceleration upon complexation was due to favouring of the three-electron three-centred shift mechanism for rearrangement. The 1,5-migration of aryl groups from



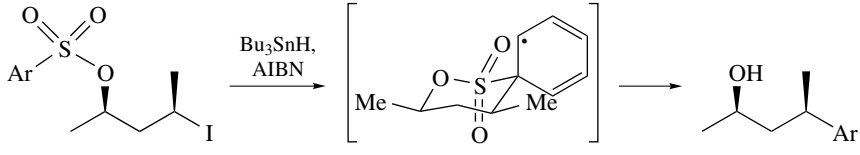
(**1**) (**2**) (**3**)

no additive: ratio (**2**):(**3**) = 99:1
$Sc(OTf)_3$, 2,6-lutidine: ratio (**2**):(**3**) = 7:93

SCHEME 1

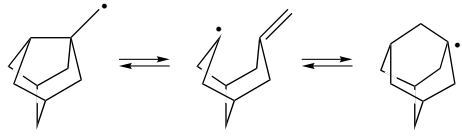
sulfur [in a range of arylsulfonates, e.g. (**4**)] to carbon have been investigated.[22] In particular, the stereochemical outcome of these migrations has been studied. Reaction of (**4**) with Bu_3SnH under standard conditions gave (**6**) in 76% yield as a 13:1 mixture of diastereomers (Scheme 2). Effective 1,2-stereochemical induction was also observed in the reactions. The observations were explained due to the chair-like transition state arising from *ipso* cyclization via the cyclohexadienyl radical (**5**).

The chemical vapour disposition (CVD) of diamond is an important process but little information is available on the mechanistic reactions taking place at the surface.[23] Both chemical trapping studies, as well as calculations on model systems for the surface radicals [interconversion of 3-methylenebicyclo[3.3.1]nonan-7-yl (**7**), (3-noradamantyl)methyl (**8**), and 1-adamantyl (**9**) radicals], have been used to investigate the process in more detail (Scheme 3). The thermal isomerization of homoazulene, which involves a ground-state di-π-methane radical rearrangement, has been studied using semiempirical AM1 methods. The activation energies and geometries of each step in the pathway have been calculated.[24]



(**4**) (**5**) (**6**)

SCHEME 2



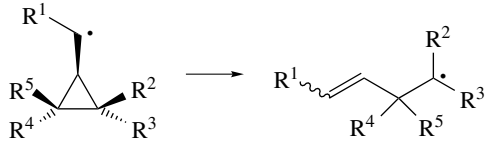
(**7**) (**8**) (**9**)

SCHEME 3

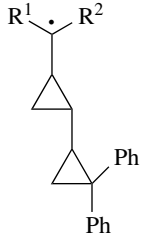
β-Scission (Ring Opening)

Newcomb and co-workers have explored the ring opening of variously-substituted cyclopropylcarbinyl radicals.[25–27] The electronic effects on the kinetics of cyclopropylcarbinyl radical ring opening have been probed by *ab initio* methods at a range of levels of theory. Whereas vinyl and methoxy substituents on the ring (R^2, R^3, R^4, R^5 in Scheme 4) reduce the activation barriers due to conjugation and hyperconjugation, respectively, when these substituents are at the radical centre (R^1) they raise the barrier.[25] Theoretical calculations were in good agreement with experimental data. In addition, ring openings of cyclopropyl groups containing reporter groups have been measured using laser flash photolysis (LFP) methods.[27] Three reporter groups were studied, each of which rearranges on the nanosecond time-scale to give UV-detectable benzylic radicals. Interestingly, alkyl radicals (**10a**, **b**) displayed no kinetic solvent effect whereas the ester-substituted radicals (**10c**, **d**) did. High levels of theory have also been used to investigate the ring opening of the related hetero-substituted compounds (Scheme 5).[28] It was found that the CBS-RAD procedure gave good agreement with experimental thermochemical data. While hetero substitution at the 1-position had little effect on the rate of ring opening, substitution at the 2-position caused a significant rate enhancement. In related work, the fast ring openings of the secondary and tertiary *trans*-2-phenylcyclopropylcarbinyl radicals (**11**) have been determined to be three orders of magnitude faster than those of the corresponding series (**12**).[26]

Ring opening of four-membered rings has also been investigated. 2-Oxetanon-4-ylcarbinyl radicals (**13**) undergo a facile ring opening with cleavage of the C–O

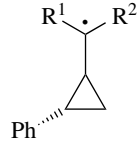


SCHEME 4

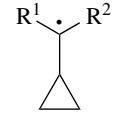


(**10**)

a; $R^1 = R^2 = H$
b; R^1 = Me, $R^2 = H$
c; $R^1 = CO_2Et$, $R^2 = H$
d; $R^1 = CO_2Et$, R^2 = Me

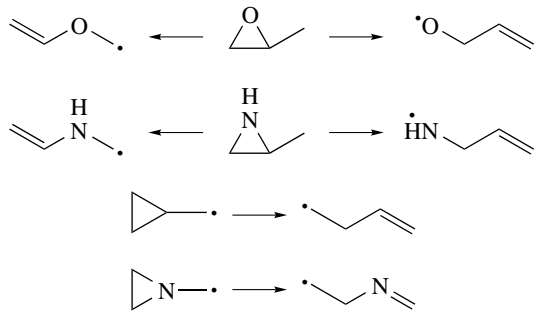


(**11**)

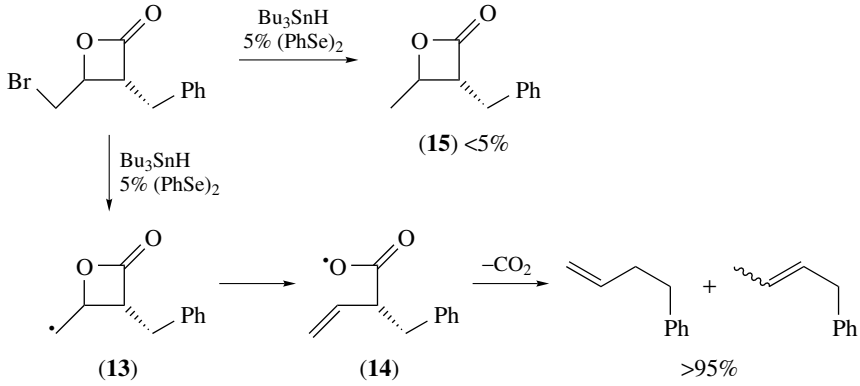


(**12**)

a; $R^1 = H$, R^2 = Me
b; $R^1 = R^2$ = Me

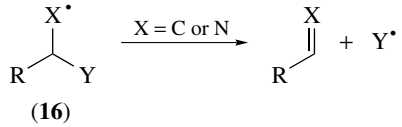


SCHEME 5



SCHEME 6

bond to give initially 3-butenoyl radicals (**14**), which, after loss of CO_2, give allyl radicals. Using conventional Bu_3SnH/AIBN procedures, low yields were obtained owing to poor chain propagation; however, the inclusion of catalytic Ph_2Se_2 gave much cleaner reactions owing to the better H-donor ability of the PhSeH formed *in situ* (Scheme 6). In the presence of a stoichiometric quantity of PhSeH, the reduced product (**15**) was trapped in 80% yield.[29] β-Elimination in acyclic systems is also possible. The relative rates of elimination from a number of carbon- and nitrogen-centred radicals (**16**) have been measured. For carbon radicals the order was found to be Y = Br > PhSe > PhS > $PhSO_2$ > Cl, whereas for nitrogen-centred radicals the order PhSe > $PhSO_2$ > PhS ≈ Br was observed (Scheme 7).[30] The effect of solvent upon the rate of β-scission of the *t*-butoxy radical has been determined by LFP.[31] It was concluded that both the solvent polarity and its ability for hydrogen bonding accelerated the rate of β-scission. The aqueous kinetics of the succinimidyl radical have been examined in the presence of a range of oxidizable substrates and oxygen.[32] A rapid equilibrium between the succinimidyl radical and its ring-opened analogue [the β-(isocyanatocarbonyl)ethyl radical] was observed and the equilibrium constant measured.

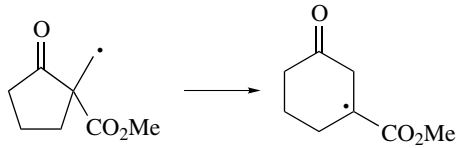


(**16**)

SCHEME 7

Ring Expansion

The one-carbon ring expansion of (**17**) to (**18**) has been accurately measured and proposed as an alternative radical clock to the 5-hexenyl radical to help determine rates in the middle regions of the kinetic scale (Scheme 8).[33] *Ab initio* calculations have indicated that the isomerization of the 3-oxocyclopentylmethyl radical to the 3-oxocyclohexyl radical is energetically more favourable than the process leading to the ring-opened 5-hexenoyl radical.[34]



(**17**) (**18**)

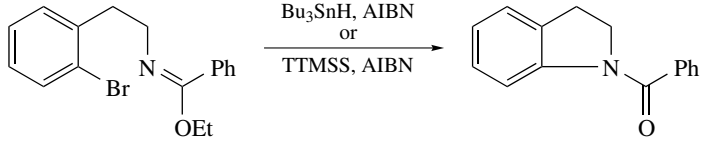
SCHEME 8

Intramolecular Addition

Cyclization

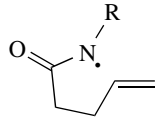
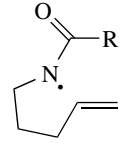
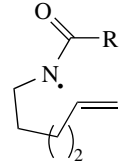
Free-radical cyclization on to unsaturated CN bonds and also the cyclization of a range of nitrogen-centred radicals have continued to attract interest and have been reviewed.[16] Aryl radicals, generated from Bu_3SnH- or TTMSS-mediated homolytic cleavage of aryl–bromide bonds, have been shown to cyclize on to the nitrogen atom of imidate esters in the 5-*exo* mode (Scheme 9).[35] Loss of an ethyl radical leads to the observed *N*-acylindolines. No cyclization in the 6-*endo* mode was detected.

Cyclizations of amidyl radicals have been studied both synthetically and kinetically. A detailed study on the rates of a variety of amidyl radical reactions was determined by both LFP and indirect competition methods (Table 1).[36] In addition, the rate constants for reactions with Bu_3SnH and PhSH were also reported (thus giving a range of simple amidyl radical clocks). The results obtained will be useful in synthetic sequence-planning involving amidyl radicals.



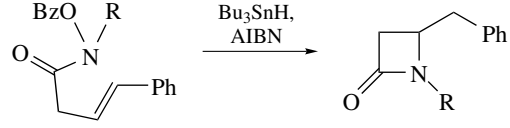
SCHEME 9

TABLE 1

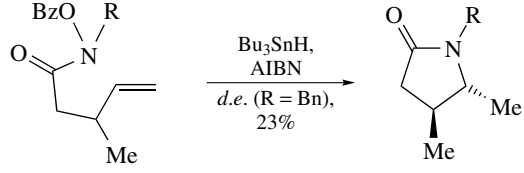
Radical	$k_c(s^{-1})$	$k_T(Bu_3SnH)$ $(l\,mol^{-1}s^{-1})$
	2×10^9	1.3×10^9
	5×10^8	1.3×10^9
	1×10^7	1.3×10^9

In synthetic work, amidyl radicals, prepared by Bu_3SnH/AIBN-mediated homolysis of *O*-benzoylhydroxamic acid derivatives, have been shown to cyclize in a 4-*exo* fashion to give β-lactams (Scheme 10).[37] In addition, radicals generated in this way have also been reported to undergo 5-*exo* cyclization to give mixtures of *cis*- and *trans*-pyrrolidinones with the steric nature of the *N*-substituent having little effect on the stereochemical outcome (Scheme 11).[38] The major products detected were those predicted by application of the 'Beckwith rule.'

The cyclization of a range of fluorinated radicals has attracted interest.[39,40] The rate constants for the 5-*exo* cyclization of a range of fluorinated 5-hexenyl radicals have been studied as a function of the position and number of fluorine substituents. For fluorine substituents at or close to the alkene there is little effect on the rate, whereas

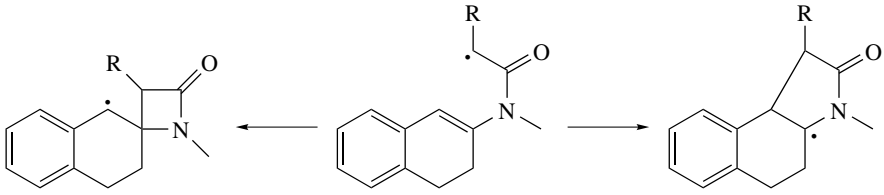


SCHEME 10



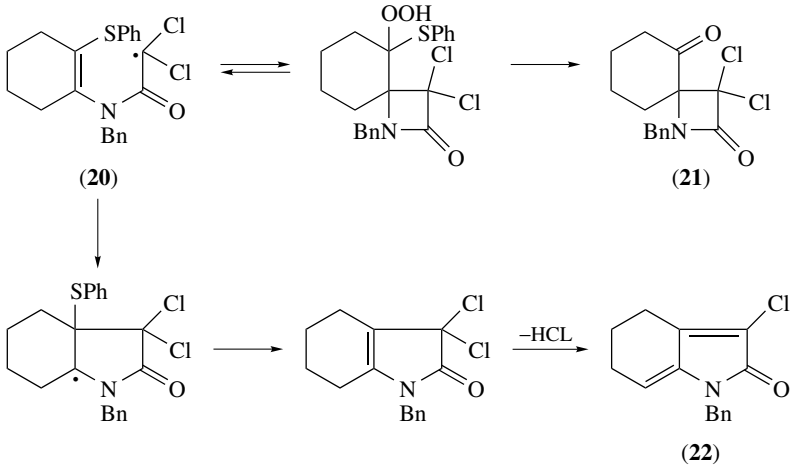
SCHEME 11

fluorine near to the radical centre has a great effect on both the rate and the regioselectivity. These effects were ascribed to both polar and pyrimidalization effects.[39] The rate constant for cyclization in the 6-*exo* mode of the 1,1,2,2,3,3,4,4-octafluorohept-6-enyl radical has also been reported and was found to be 3700 times greater than that of the parent hept-6-enyl system. It was also found to be faster than the 5-*exo* cyclization of its fluorinated analogue.[40] The competition between cyclization in the 4-*exo* and 5-*endo* modes of amide derivatives has been investigated by a number of groups. The effect of the radical substituent R in the Bu_3SnH-mediated cyclization of a range of *N*-vinyl-α-haloamides (**19**) has been reported (Scheme 12).[41] Radical-stabilizing groups (such as Ph and Me) furnish 5-*endo* products, whereas when R = H, the β-lactams are formed. The results were explained based upon the reversibility of the 4-*exo* cyclization leading to the thermodynamic products when R was radical stabilizing. The temperature dependence indicated that lower temperatures favoured the kinetic products. In related work, the cyclization of di-or tri-halo-substituted *N*-vinylamides proceeded to give either 5-*endo* or 4-*exo* products depending on the temperature.[42] Thus, cyclization of (**20**) at low temperature with $Bu_3SnH/Et_3B/O_2$ preferentially occurred in a 4-*exo* fashion (kinetic control) to give (**21**) after trapping with O_2; at reflux, however, the 5-*endo* product (**22**) was obtained via an irreversible



(**19**)

SCHEME 12



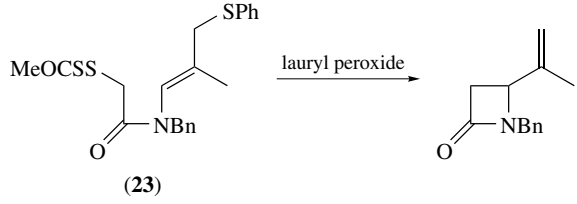
(**20**) (**21**) (**22**)

SCHEME 13

elimination of PhS•. Xanthate derivatives of *N*-ethenylacetamides (**23**) undergo efficient radical cyclization to give β-lactams (Scheme 14).[43]

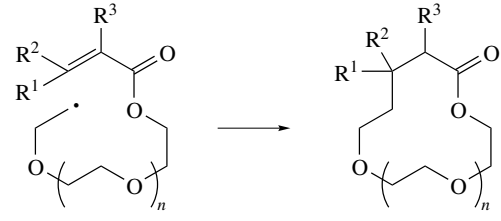
Cyclization to give larger ring sizes has been reported to be mediated by Bu_3SnH.[44] The effects of chain length (12-, 15-, 18-, 21- and 24-membered rings) and the substituents present on the chain on the outcome of the reactions and the effect of solvent were evaluated (Scheme 15). The rate constants determined for cyclization at 80 °C in benzene for a variety of chain lengths were shown to be 10–30 times greater than those for the cyclization of the corresponding parent alkenyl species, presumably owing to the decrease in strain energy in the transition state.

The absolute rate constants for a variety of cyclizations have been measured. In particular, the rates of decarbonylation of a variety of alkoxycarbonyl radicals have been obtained by LFP studies on PTOC oxalates.[45] From these data, rate constants for the reduction of alkoxycarbonyl radicals with Bu_3SnH and their 5-*exo* cyclizations were determined. Whereas cyclizations were slightly faster than the analogous alkyl radical 5-*exo* cyclizations, their reactions with Bu_3SnH were 10 times slower, indicating that cyclization processes should be synthetically useful. The rate constants for the cyclization of a number of variously substituted α-amide radicals have been determined together with their relative reactivities towards reduction using Bu_3SnH (Scheme 16).[46] Cyclizations of secondary-based radicals were found to be similar to the corresponding alkyl-substituted radicals. In addition, the rate constants were subject to minor electronic

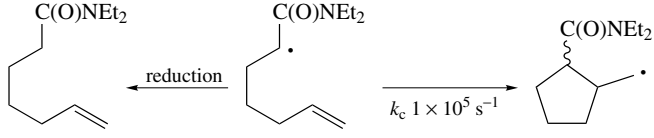


(**23**)

SCHEME 14



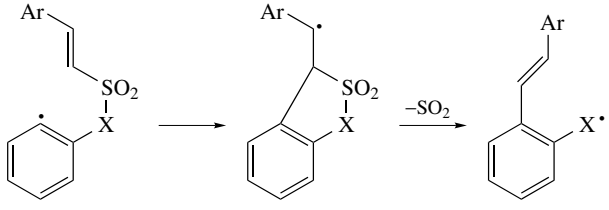
SCHEME 15



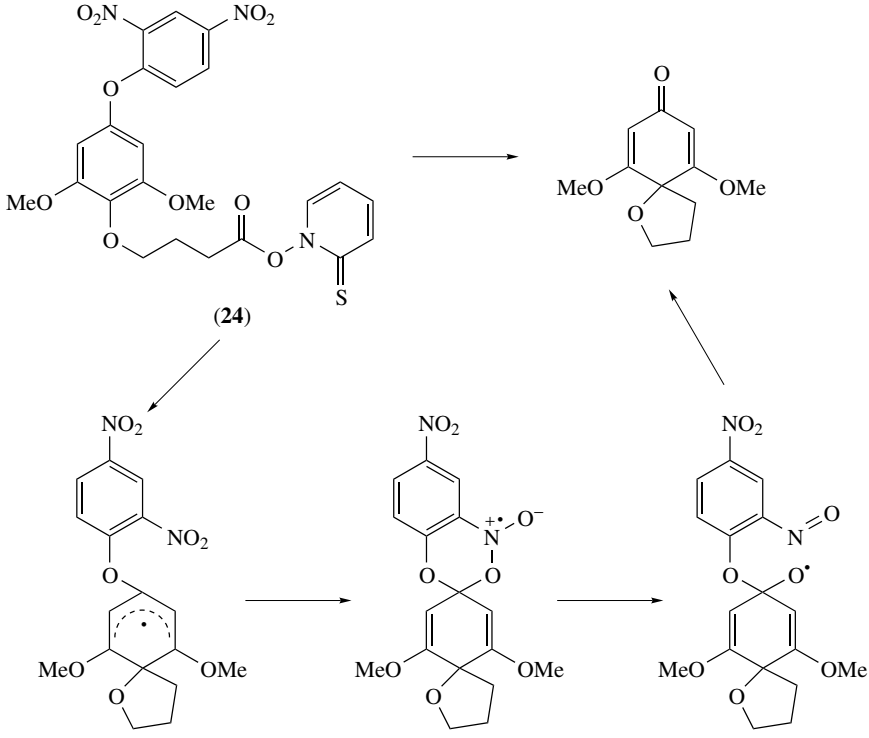
SCHEME 16

effects (as in the case of α-ester radicals) but steric effects led to reductions in rates far greater than those observed in other electron-deficient radical cyclizations.

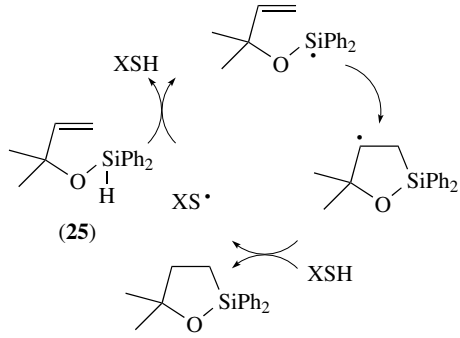
A model radical-reaction system has been used to probe the postulated radical rearrangement/cyclization mechanism proposed for the growth of diamond by chemical vapour deposition.[23] The results of these model studies agree with low-level calculations used to model a large section of the diamond surface. Unsymmetrical stilbene derivatives have been prepared by 5-*exo* cyclization of aryl radicals on to vinyl sulfonamides and sulfonates followed by elimination of SO_2 (Scheme 17).[47] The mechanism of the spiro-cyclization of (**24**) has been investigated. On the basis of isotopic labelling studies, it was proposed that oxygen transfer from an NO_2 group to a cyclohexadienyl radical was the most likely process (Scheme 18).[48]



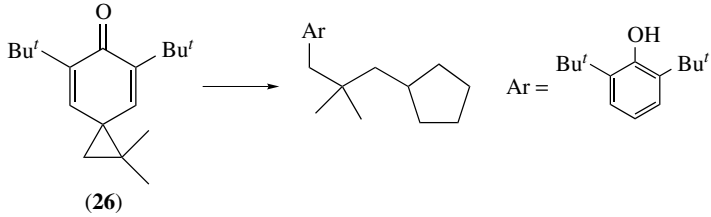
SCHEME 17



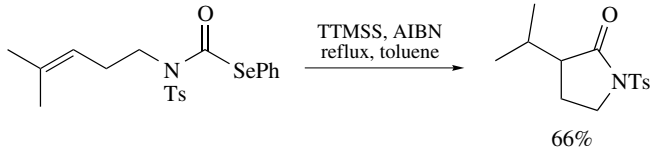
SCHEME 18



SCHEME 19



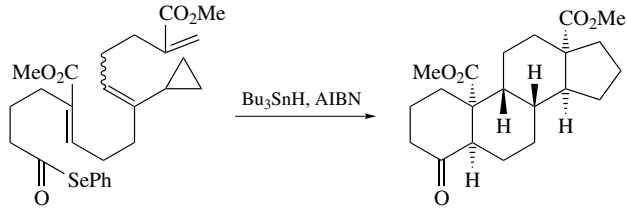
SCHEME 20



SCHEME 21

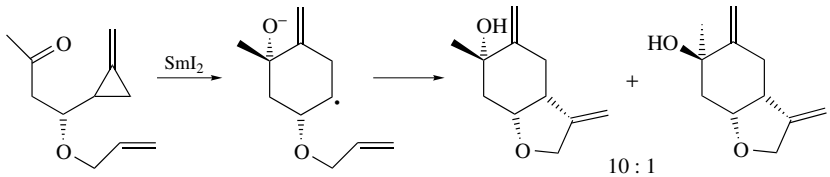
Radical-chain cyclization of alkenyloxysilanes using thiol catalysts give five-membered ring products (via a 5-*endo* cyclization) in the case of allyloxysilanes (**25**) (Scheme 19).[49] Homoallyloxysilanes gave a mixture of five- and six-membered rings, but the intermediate silyl radical underwent predominantly 6-*endo* cyclization. Pentenyloxysilane gave the 7-*endo* product only. The stereochemistry of these reactions was found to be determined by steric effects, even in the presence of chiral thiol catalysts. The structures of the radical intermediates were studied by EPR.

The radical-ion probe (**26**) has been used mechanistically to investigate the addition of Grignard reagents to conjugated carbonyl compounds (Scheme 20).[50] Reaction of (**26**) with 5-hexenylmagnesium bromide indicated that cyclization occurred mainly by a polar process; however, the detection of products arising from reaction via a cyclopentylcarbinyl rearrangement indicated freely diffusing paramagnetic intermediates. Carbamoyl radicals derived from *Se*-phenyl selenocarbamates undergo efficient intramolecular addition to alkenes (Scheme 21).[51] Substituent effects for the regioselectivity of cyclization of vinyl radicals on to aromatic rings have been reported.[52]

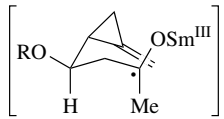


(**27**) (**28**)

SCHEME 22



(**29**) (**30**)



(**31**)

SCHEME 23

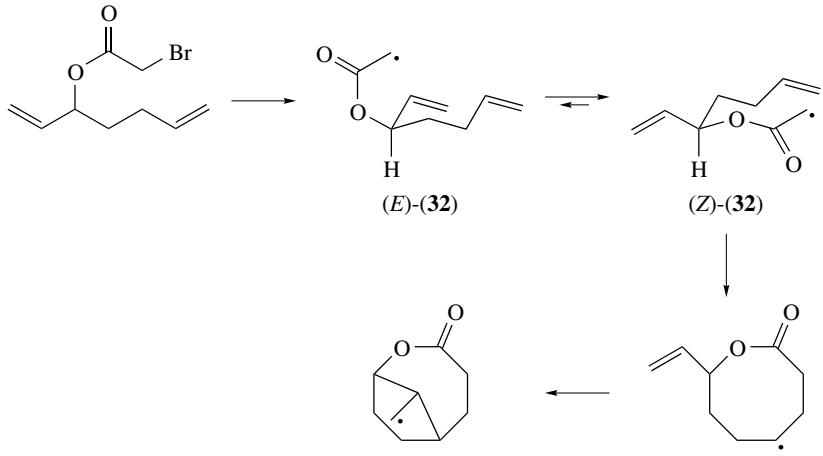
Tandem Reactions

The ability to sequence radical reactions continues to be a great advantage in the use of radical chemistry in synthesis. For example, the controlled sequencing of five different reactions leads to the formation of the steroidal skeleton (**28**).[53] Thus, two 6-*endo* cyclizations followed by a cyclopropyl ring opening/9-*endo*-trig/transannular cyclization furnishes (**28**) from (**27**) in 45% yield (Scheme 22). The ring opening of cyclopropyl radicals has also been utilized in a cascade process leading to bicyclic systems.[54] Thus, SmI_2-mediated reaction of the methyl 2-cyclopropylethyl ketone (**29**) to give ethers (**30**) proceeds with high stereoselectivity (Scheme 23). The stereoselectivity was dependent on the presence of additives (HMPA, 10:1 mixture, DMPU 1.5:1, no additive 1:1.3). Cyclization via the transition state (**31**) was postulated to explain the stereoselectivity.

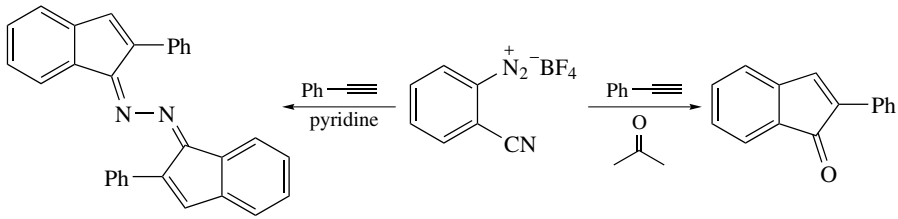
The tandem 8-*endo*/5-*exo* cyclization of the (alkoxycarbonyl)methyl radical (**32**) has indicated that 8-*endo* cyclization is favoured over 5-*exo* cyclization in this system (Scheme 24).[55] *Ab initio* studies indicated that this was due to the initial radical favouring a (*Z*)-(**32**) over an (*E*)-(**32**) conformation.

Radical Annulation

A novel [3 + 2] radical annulation of *o*-cyano-substituted aryl radicals with alkynes has been reported.[56] The reactions occur by addition of the aryl radical to the alkynes



SCHEME 24



SCHEME 25

followed by cyclization of the resulting vinyl radical on to the cyano group to give an imine radical. The fate of this radical is then determined by the reaction conditions (Scheme 25).

Fragmentation, Recombination, and Homolysis

Radical-recombination reactions play an important role in combustion and atmospheric processes. Reactions that have no energy barrier along the reaction coordinate have become increasingly studied theoretically. For example, canonical flexible transition-state theory (CFTST) has been used to determine the temperature dependences of the self-recombination of $Me^{\bullet}$, $F_3C^{\bullet}$ and $Cl_3C^{\bullet}$ radicals.[57] There was found to be good agreement between theoretical data and experiment. Both the combination reactions of $Me^{\bullet}$ with ethane and of $Me^{\bullet}$ and $H^{\bullet}$ with methane have been examined theoretically at high temperatures and pressures.[58,59] For both processes the combination was best described by the formation of a weakly-bound intermediate with the contribution of a strongly bound complex for the $Me^{\bullet}$ recombination being one order of magnitude smaller. For the $CH_3 \cdots H$ complex, the contribution involving a strongly bound complex was dependent on temperature. The recombination of peroxyl radicals in the gas phase has been reviewed.[2] The review concentrates on both kinetic and mechanistic

aspects. Key reactions that underpin new non-bromine-containing fire-extinguishing methods have been studies theoretically (MP2, QCISD, B3LYP, GAUSSIAN-1 and -2).[60] In particular, the reactions between $^{\bullet}CF_3$ and both $HO^{\bullet}$ and $H^{\bullet}$ have been probed. The recombination reactions of methyl radicals ($^{\bullet}CH_3$, $^{\bullet}CH_2D$ and $^{\bullet}CHD_2$) with $D^{\bullet}$ have been studied at low pressures.[61] At 1 Torr the initially formed methane complex was found not to be stabilized.

Ab initio methods have been used to locate the potential-energy surface and transition states for a series of hydrogenolysis reactions in order to determine whether the Marcus equation could be extended to atom-transfer reactions.[62] It was concluded that there was not good agreement with the Marcus equation owing to the latter's neglect of Pauli repulsion. If the Pauli repulsion terms were considered, then an equation that fits the data can be constructed. This indicated that the repulsions were important and should be considered in atom-transfer or ligand-transfer reactions. The homolytic bond-dissociation enthalpies of the C−H bonds adjacent to a variety of hydrocarbon, allylic and benzylic radicals have been calculated using the *ab initio* CBS-4 method.[63] Calculations suggested that radical centres typically weaken the neighbouring C−H bond strength by about 50–70 kcal mol^{-1}. In other theoretical work the thermochemistry of the reactions between $HSCH_2^{\bullet}$ and O_2, NO, and NO_2 have been calculated by HF, MP2, DFT, CBS-4, CBS-Q and G2MP2 methods.[64]

Hydrogen abstraction from propan-2-ol and propan-2-ol-d_7 by hydrogen and deuterium atoms has been studied by pulsed radiolysis FT-ESR.[65] A secondary kinetic isotope effect was observed for $H^{\bullet}(D^{\bullet})$ abstraction from the C−H (C−D) bonds. The results were compared with *ab initio* data. In similar work, the kinetic isotope effects in $H^{\bullet}$ and $D^{\bullet}$ abstraction from a variety of other alcohols in aqueous solvents have been measured.[66] It was found that, compared with the gas phase, the reactions exhibit higher activation energies in agreement with the ability of solvation to decrease the dipole moment from the reactant alcohol to the transition state.

The pressure dependence of the reaction between butane-1-thiol and hydrogen atoms at 133, 266, 532, 2660, and 5320 Pa, using two types of fast-flow discharge reactors, have been studied.[67] Butane and but-1-ene were the main products. Pressure dependence indicated decomposition through vibrationally activated species.

Bromine-atom atomic resonance absorption spectrometry (ARAS) has been applied to measure the thermal decomposition rate constants of CF_3Br in Kr over the temperature range 1222–1624 K.[68] The results were found to be consistent with recently published theory. The formation of cyclopent[*a*]indene and acenaphthylene from alkyl esters of biphenyl-mono- and -di-carboxylic acids has been observed in flash vacuum pyrolyses at 1000–1100 °C.[69] The kinetics and mechanisms of free-radical generation in the ternary system containing styrene epoxide, *p*-TsOH, and *i*-PrOH have been examined in both the presence and absence of O_2.[70]

Atom Abstraction Reactions

Hydrogen Abstraction by Carbon-centred Radicals

Hydrogen abstraction by fluorinated and chlorinated radicals has attracted a good deal of attention.[71–73] The rates of H-abstraction by both the perfluoroisopropyl and *t*-butyl

radicals have been measured and compared with those for non-fluorinated analogues.[71] The rate constants of 3.6×10^6 and $2.4 \times 10^8\,l\,mol^{-1}\,s^{-1}$ were much higher than for their respective non-fluorinated analogues. In the case of t-$C_4F_9^{\bullet}$ it was found to be more reactive than the highly electrophilic $(Me)_3CO^{\bullet}$ radical. The kinetics of hydrogen abstraction by the $CF_3CO-C(C_2F_5)_2$ radical have been studied by ESR and a reaction mechanism proposed.[72] Hydrogen abstraction from a range of cycloalkanols by $Cl_3C^{\bullet}$ has been studied.[73] The authors proposed that under specific conditions the reactivity of the C−H bonds is controlled by hyperconjugation of neighbouring C−H bonds, rather than I-strain or radical stability.

In theoretical work, the initial steps in the polymerization of 1,1-dicyano-, 1,1-difluoro-, and 1,1-dimethyl-cyclopropanes by reaction with $H^{\bullet}$, $^{\bullet}OH$, and $Me^{\bullet}$ have been modelled by *ab initio* methods.[74] Other *ab initio* MO calculations for the reactions of $H^{\bullet}$, $Me^{\bullet}$, $Et^{\bullet}$, i-$Pr^{\bullet}$, and t-$Bu^{\bullet}$ with a variety of silanes and germanes have been carried out.[75] The results indicate that the attacking and leaving radicals adopt an almost co-linear arrangement. Bond distances and energy barriers were predicted for the reactions studied.

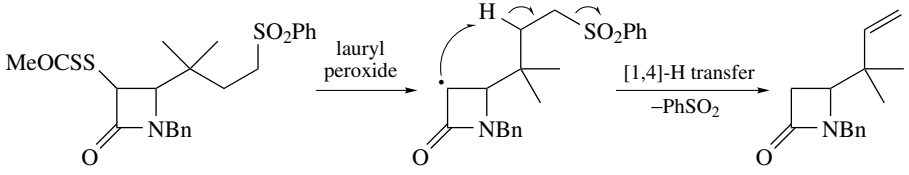
In kinetic studies, the abstraction of $F^{\bullet}$ from CF_3CH_2OH by $ArN_2^+BF_4^-$ was shown to be an ionic process, whereas abstraction of an α-H atom from CH_3CH_2OH was determined to be a radical process.[76] In other kinetic work, the expansion of cyclopentanones has been used to measure the kinetics of hydrogen-atom abstraction reactions for a range of hydrogen donors in benzene including $(MeO)_2P(O)H(1.2 \times 10^5\,l\,mol^{-1}\,s^{-1})$ and $(MeS)_3SiH(3.9 \times 10^5\,l\,mol^{-1}\,s^{-1})$.[33]

The feasibility of hydrogen abstraction at the peptidyl α-carbon hydrogen bond by 1,4-aryl diradicals has been determined by examining a model reaction, i.e. abstraction of deuterium from dideuterioglycine by aryl radicals.[77] The results have biological implications for the reactivity of the enediyne anti-tumour antibiotics with proteins. The non-Arrhenius behaviour of hydrogen-abstraction reactions by radicals has been investigated.[78] For a number of reactions studied the enthalpy of activation was found either to increase or to decrease as a function of temperature.

An example of the relatively rare 1,4-hydrogen-atom transfer has been invoked in the reaction of (**34**) to give (**35**); see Scheme 26.[43]

Hydrogen Abstraction by Heteroatom-centred Radicals

Abstraction reactions in biological systems, in particular the site of radical attack in proteins (oxidative damage), continue to be a matter of great interest, primarily owing



(**34**) (**35**)

SCHEME 26

to their implicated role in ageing and other disorders. In the light of this interest, *ab initio* studies have been used to calculate bond-dissociation energies and transition states for hydrogen-atom abstraction by thiyl radicals [B3LYP/6–31G(D)] in both cysteine and model peptides.[79] In addition, implications for the radical-induced strand cleavage of DNA have been examined by observing the racemization of the model tetrahydrofurfuryl acetate under a range of conditions.[80] Whereas the presence of alkanethiols was ineffective in promoting racemization, those containing electron-withdrawing *S*-alkyl groups (1-thio-β-D-glucopyranose and 2,2,2-trifluoroethanethiol) acted as good promoters of radical racemization via 'polarity reversal catalysis.' The mechanism of 'polarity reversal catalysis' has been probed using a variety of theoretical methods to examine the hydrogen-atom transfer reaction between silane and the methylthiyl radical.[81] At the highest level of theory, CCSD(T)/aug-cc-pVDZ/MP2/aug-cc-pVDZ calculations predict the abstraction to proceed with an energy barrier of 34.0 kJ mol^{-1} while being endothermic by 18.3–34.0 kJ mol^{-1}. These calculations indicate that sustainable chain reactions are certainly possible by invoking the traditional explanation for the origin of the 'polarity reversal catalysis.'

Hydrogen abstraction by halogens has attracted much study, in particular the abstraction by Cl$^{\bullet}$. H-atom abstraction from propane by Cl$^{\bullet}$ has been studied using VUV synchrotron radiation in a crossed molecular beam.[82] The rate coefficients for the abstraction of H$^{\bullet}$ from methane, ethane, propane, and butane by Cl$^{\bullet}$ have been measured by pulsed-laser photolysis resonance fluorescence.[83] The laser flash photolysis fluorescence technique has also been used to investigate the kinetics and mechanism of the reaction between Cl$^{\bullet}$ and MeI as a function of temperature (218–694 K).[84] Above 364 K, the rates were found to be independent of pressure and a significant H/D kinetic isotope effect was measured, indicating that hydrogen transfer was the dominant pathway; on the other hand, at temperatures lower than 250 K, rates were pressure dependent; at temperatures between 263 and 309 K reversible addition was observed. In theoretical work, *ab initio* calculations have been performed for reactions involving channel hydrogen abstraction from methanol by Cl$^{\bullet}$, Br$^{\bullet}$, and F$^{\bullet}$.[85,86] The calculations showed that all three reactions proceed via formation of intermediate complexes. Rate-constant calculations were found to be in good agreement with experimental data.

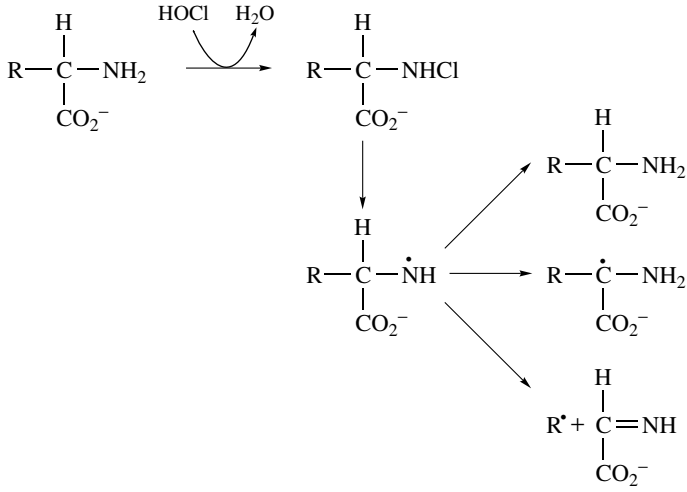
Hydrofluoro ethers have been proposed as a new generation of CFC alternatives. The absolute rate constants for the abstraction of a hydrogen atom by Cl$^{\bullet}$ with several hydrofluoro ethers have been examined using VLPR monitored by quadrupole MS.[87] The rate parameters for abstraction were found to correlate well with the theoretical C–H bond strengths determined by *ab initio* calculations.

Reactions mediated by F$^{\bullet}$ have also been investigated. The absolute rate constants for hydrogen-atom abstraction from CHF_3, $CHClF_2$, $CHCl_2F$ and $CHCl_3$ by fluorine atoms have been reported.[88] Using a pulsed-radiolysis UV–vis absorption system, the rate constants for reaction of F$^{\bullet}$ with MeCHO and of O_2 with MeCO have been measured at 295 K at 1000 mbar.[89] The two possible H-abstraction reactions of CHF_2CH_3 with F$^{\bullet}$ atoms were studied through theoretical calculations and were found to be in good agreement with experimental values.[90] The same authors have also measured the rate constants and kinetic isotope effects (1.4 ± 0.2) for direct hydrogen abstraction

by $Cl^{\bullet}$ from butane and butane-*d* using both the relative-rate method (GC-FID) and resonance fluorescence (FFDS).[91] Both methods were in good agreement.

Hydrogen-atom abstraction from a range of alkyl-substituted aromatics by peroxyl radicals has been examined by statistical analysis based upon MINDO/3 calculations. The role of various structural factors in the regioselectivity of abstraction was examined and discussed.[92] A range of theoretical methods, ranging from DFT to *ab initio* methods, have been used to examine hydrogen abstraction from ethane by the hydrogen atom and conclusions as to the best systems to employ were discussed.[93] Comments upon the Roberts and Steel and Zavitsas methods for calculating energies of activation of hydrogen-atom abstractions have appeared, and the limitations of both approaches highlighted.[94] The Zavitsas approach has been used to calculate the $H^{18}O-H/HO^{\bullet}$ identity reaction in the light of recent experimental results.

The reaction of amino acids with HOCl was studied using EPR spin trapping and UV–vis spectroscopy.[95] Some nitrogen-centred radicals, which then undergo a variety of abstraction, rearrangement, and fragmentation reactions, were detected (Scheme 27).



SCHEME 27

Halogen Abstraction

Halogen abstraction by $Bu_3Sn^{\bullet}$ has been studied by a number of groups. The activation energies for halogen abstraction from a range of aliphatic, benzylic, and aromatic halides have been measured and the results compared with the bond-dissociation energies of the C–X bond.[96] In addition, the absolute rate constants for the abstraction of bromine from a range of aromatic bromides by $Bu_3Sn^{\bullet}$ has been reported.[97] For the particularly hindered 2,4,6-tri-*t*-butylbromobenzene, the rate was found to be unusually fast, presumably owing to steric acceleration. *Ab initio* calculations at various levels of theory have been used to investigate the hydrogen-atom transfer of

various ω-halo-l-alkyl radicals. It was found that, for 1,5- to 1,7-halogen transfer, the reaction took place via C_2 or C_s symmetric transition states. No 9-X-2 intermediates were located in the study.[98] In other theoretical work, halogen abstraction from CF_4, CF_3Cl, CF_3Br, and CF_3I by $Me^{\bullet}$ has been studied theoretically at HF/6–31G(d) and MP2 = full/6–31G(d) levels of theory.[99] Transition states, energy barriers and rate constants were calculated (298–2500 K range). The computed results were accurate to $\pm 61\,kJ\,mol^{-1}$ over the 360–500 K range. Conclusions were drawn with respect to flame-suppression chemistry.

A range of traditional *ab initio* methods (HF, MP2, MP4) have been compared with DFT methods (B3LYP, BLYP) in the Cl-abstraction reactions of MeCl, CH_2Cl_2, and $CHCl_3$ by the silyl ($H_3Si^{\bullet}$) and trichlorosilyl ($Cl_3Si^{\bullet}$) radicals, respectively.[100] While HF, MP2, and MP4 largely over-estimated the activation barrier, DFT approaches gave results in good agreement with experiment (B3LYP being the best).

The relative importance of bromine-atom abstraction, relative to hydrogen abstraction, in the reactions of C_3H_7Br, C_4H_9Br, s-C_3H_7Br, and s-C_4H_9Br with the hydrogen atom have been estimated by bond-energy bond-order (BEPO) calculations.[101] The rate coefficients for the reactions were determined by experiment in a discharge flow reactor and good agreement with predictive information was achieved. The reaction of thiolate ions with a range of 2,2,2-trifluoroethyl halides under UV irradiation at room temperature has been investigated.[102] These reactions led to the generation of the trifluoroethyl radical (detected by ESR), indicating that the processes were proceeding via an S_{RN} 1 reaction.

Halogenation

The chlorination of alkanes has been investigated in supercritical CO_2 ($SC-CO_2$).[103] The chlorine-atom cage effect was used to probe the effect of viscosity and solvent clusters on reactivity and cage lifetimes. No evidence was found for an enhanced cage effect. Chlorine-atom selectivities were found to be intermediate between the gas and liquid phases. The lower viscosity of $SC-CO_2$, compared with conventional solvents, allows absolute rate constants to exceed $10^{10}\,l\,mol^{-1}\,s^{-1}$ and the tuneable solvent properties allow a means of controlling both reactivity and selectivity. The free-radical chlorination of alkanes has also been examined in a range of chlorinated solvents.[104] The results indicate that $Cl^{\bullet}$ forms a complex with halogenated solvents, with the selectivity of hydrogen abstraction decreasing with increasing Cl content of the solvent (i.e. increasing ionization potential of the solvent).

The mechanism of addition of Cl_2 and $Cl^{\bullet}$ to both alkynes[105] and alkenes[106,107] has been reported. Theoretical calculations have shown that the addition of Cl_2 to C_2H_2 proceeds through a free-radical mechanism, the initial step being the generation of $Cl^{\bullet}$ and $C_2H_2Cl^{\bullet}$ radicals.[105] In a reply to comments on previously reported work[106] on the inverse kinetic isotope effect observed for the addition of $Cl^{\bullet}$ to C_2H_4 and C_2D_4, it was highlighted that, owing to the large standard deviation in the experiment (27%) and limited number of experiments conducted in He, deriving values for the third-body efficiency of N_2 versus He was not appropriate. However, it was also pointed

out that this would not affect the ultimate conclusion that there was an inverse kinetic isotope effect of about 3 for the reactions examined.[107]

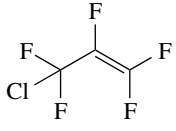
The kinetics of the reactions of photo-generated $^{\bullet}CH_2Cl$, $^{\bullet}CHBrCl$, $^{\bullet}CCl_3$, and $CH_3C^{\bullet}Cl_2$ radicals with Cl_2 have been measured. In addition, the transition states for the four reactions were localized and optimized at the MP2/6–31G(d,p) level of theory. The kinetics were found to be controlled by the electronic nature of the substituents.[108]

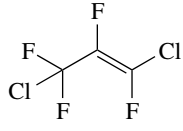
Addition Reactions

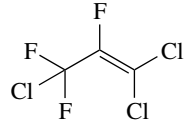
Addition to Carbon–Carbon Multiple Bonds

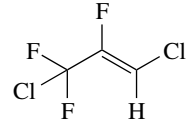
The regioselectivity of the addition of nucleophilic radicals, derived from alcohols and ethers, to a range of chlorofluoropropenes (**36a–d**) have indicated that selectivity is dependent on the number of chlorine atoms on the alkene.[109] Thus, addition to (**36c**) proceeds in an anti-Kharash mode while the rates of addition decreased with increasing chlorine substitution. In theoretical work, the regioselectivity of addition of the methyl radical to fluoroethanes has been studied using quantum-mechanical calculations.[110] While the Hartree–Fock (B3LYP) method is reliable in calculating activation energies and reaction enthalpies, it fails to predict accurately the regioselectivity of addition. Coupled cluster calculations were found to be far more reliable. Similar calculations on the addition of $Me^{\bullet}$ to alkenes using DFT methods have shown that, in comparison with $^{\bullet}CH_2OH$, $Me^{\bullet}$ does not behave as a nucleophile.[111] The addition of other carbon radicals to alkenes has also been investigated by *ab initio* calculations at a variety of levels of theory. Closest agreement with experimental barriers was found with the use of the CBS-RAD procedure.[112] In other theoretical work, molecular-orbital calculations have been used to study the addition of a range of free radicals to alkenes.[113] High levels of theory were required to obtain useful data. Polar effects were found to be important for the addition of $^{\bullet}CH_2OH$, $^{\bullet}CH_2CN$, and $Me_3C^{\bullet}$ radicals.

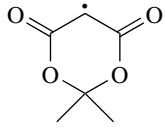
The addition of a range of perfluoro-*n*-alkyl radicals to both $CH_2{=}CHCH_2C_4F_9$ and $CH_2{=}CHC_4F_9$ have been studied and the rate constants determined as 1.15×10^6 and $2.6 \times 10^5\,l\,mol^{-1}\,s^{-1}$, respectively, at 298 K.[114] The mechanism for the addition of both $Me^{\bullet}$ and $^{\bullet}CF_3$ to fluoroethylene has also attracted attention.[115] The results

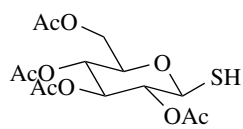

(**36a**)


(**36b**)


(**36c**)


(**36d**)


(**37**)


(**38**)

indicated that, regardless of fluoro substitution, the alkenes acted as electron donors whereas the radicals acted as electron acceptors. The anomaly in the regioselectivity found for the addition of both $Me^{\bullet}$ and $^{\bullet}CF_3$ radicals to trifluoroethylene was explained in electrostatic terms. The radical addition to a series of cyclopentenones and cyclohexenones was found to occur primarily at the 3-position (kinetic product) at lower temperatures, but at higher temperatures or with a hindered 3-position addition occurred at the oxygen atom.[116]

The absolute rate constants for the addition of the cyclic malonyl radical (**37**) and the di(*t*-butyl)malonyl radical to over 26 different alkenes have been measured by time-resolved ESR spectroscopy.[117] Rate constants range from $1.1 \times 10^5\,l\,mol^{-1}\,s^{-1}$ (acrolein) to $2.41 \times 10^6\,l\,mol^{-1}\,s^{-1}$ (1,1-diphenylethene) with activation energies ranging from $12.9\,kJ\,mol^{-1}$ (1,1-diphenylethene) to $21.7\,kJ\,mol^{-1}$ (acrylonitrile). Correlation with alkene ionization potential and reaction enthalpy was observed. No correlation between the activation energy and the alkene electron affinities was found.

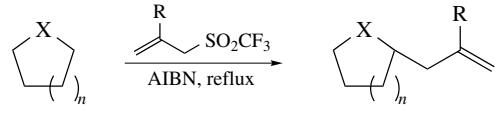
In atmospheric chemistry, reactions between pure nitric oxide and a range of activated alkenes have been examined. However, no addition products were observed.[118] Only in the presence of NO_2 was addition to give β-nitroalkyl radicals, followed by trapping to β-nitronitroso compounds, observed. These final products can also trap other radicals to give aminoxyl radicals.

In order to determine the fate of $^{\bullet}NO_3$ at night in the troposphere, an *ab initio* study on the mechanism of the reaction of $^{\bullet}NO_3$ with ethene has been reported.[119] The theoretical data show that, out of the three possible reaction channels to give oxirane, ethanol, or nitric acid, the formation of oxirane is kinetically favoured at low pressures. In other atmospheric-chemistry studies, there is increasing evidence that suggests that brominated compounds play a significant role in ozone chemistry, and this has prompted interest in studying the low-pressure (0.5–2.0 Torr) reaction between bromine atoms and propene (233–320 K) using mass spectrometric discharge flow methods.[120] Both the abstraction and addition pathways were observed and Arrhenius expressions obtained.

The rate constants for the addition of a range of carbohydrate and *myo*-inositol-based radicals to acrylic acid have been measured using EPR spectroscopy.[121] The addition of α-keto radicals to allylsilanes has been reported and is heavily dependent on the substitution, size, and electronic properties of substituents attached to the silicon atom. Thus, electron-donating groups promote the additions but increased steric demand at silicon retards them.[122] Radicals derived from α-halo esters in the presence of Ph_3SiH were found to add efficiently to electron-rich alkenes in the presence of thiols as polarity-reversal catalysts.[123] The use of optically active thiols such as the glucose derivative (**38**) proceeds to give adducts with induced enantioselectivity. Thiols have also been shown to catalyse the addition of primary aldehydes to terminal alkenes to give ketone adducts in moderate yields.[124] The hydroacylation reaction was effective for electron-rich, neutral, and electron-deficient alkenes, with the former being the most efficient reactions. Triorganosilanethiols also function as catalysts. The role of the thiol was postulated to be that of a polarity-reversal catalyst which promoted hydrogen-atom transfer from the aldehyde to the carbon-centred radical produced by addition of the acyl radical to the alkene.

The ability to conduct radical reactions without the use of tin reagents is important. Allylic triflones have been used to conduct allylation reactions on a range of substrates (**39**) as a replacement for allyltributylstannane (Scheme 28).[125] The main limitation was that unactivated or trisubstituted triflones failed to undergo reactions. In other non-tin radical methods, arenesulfonyl halides have been used as functional initiators in the CuCl/4, 4′-dinonyl-2, 2′-bipyridine-catalysed 'living' atom-transfer polymerization of styrenes, methacrylates, and acrylates.[126] The kinetics of initiation and propagation were examined with a range of substituted arylsulfonyl halides with initiator efficiency measured at 100%.

A range of addition reactions of $(TMS)_3GeH$ with alkynes, alkenes, ketones, azines, and quinones has been studied using EPR.[127] In addition, synthetic studies of hydrogermylation of alkynes have shown that the reaction proceeds regio- and stereoselectively, whereas reactions with alkenes do not take place (presumably owing to the reversibility of the germyl radical addition) (Scheme 29).

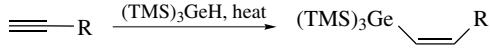


(**39**) (**40**)

X = O, C
n = 1, 2

R = Ph, CN, CO_2Me

SCHEME 28

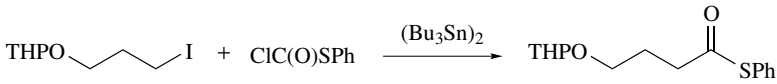


SCHEME 29

The reactions of *N*-phenyl α-*t*-butyl nitrone (PBN) with maleimides, maleic anhydride, and diethyl maleate have been studied by EPR and two types of spin adduct detected. They arise from the reductive addition of PBN to the alkenes and the degradation product of DBN (2-methyl-2-nitropropane).[128] The deuterium and muonium kinetic isotope effects for the addition of the hydrogen atom to a variety of alkenes have been determined experimentally and theoretically.[129]

Addition to Oxygen-containing Multiple Bonds

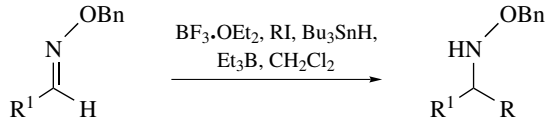
A new free-radical carbonylation strategy, employing *S*-phenyl chlorothioformates and alkyl halides, has been developed.[130] Reaction with $(Bu_3Sn)_2$ furnishes the corresponding *S*-phenyl esters in moderate yields (Scheme 30).



SCHEME 30

Addition to Nitrogen-containing Multiple Bonds

Muon spin relaxation (μSR) has been employed in determining the rate constants and Arrhenius parameters for the addition of the ethyl radical and the *t*-butyl radical to NO.[131] 5-*exo*-Cyclization of aryl radicals on to the nitrogen atom of imidate esters has been reported.[35] Intermolecular radical addition to a wide range of aldoxime ethers, using Et_3B as an initiator, to give the corresponding benzyloximines has been studied (Scheme 31). The reaction was accelerated by the addition of $BF_3.OEt_2$.[132]



SCHEME 31

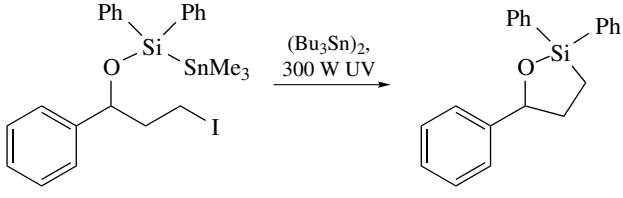
Homolytic Substitution

Aromatic Substitution

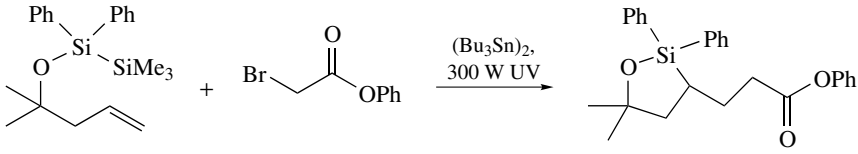
The reactions of bromine and chlorine atoms (generated in aqueous solution) with binuclear and trinuclear aza-arenes have been reported.[133] In addition to products arising from substitution of a hydrogen atom by a halogen, oxidation products similar to those found in reactions with hydroxyl radicals were also detected. The detection of aryl radicals in several hydrodediazonization reactions has been observed when iodoacetic acid was used as an aryl-radical trapping agent. All hydrodediazonizations studied were found to proceed through radical intermediates irrespective of whether they were initiated or not.[134]

S_H2 and Related Reactions

Homolytic substitution reactions including homolytic allylation, radical [2,3]-migrations and stereochemical reactions been reviewed. The review also highlights the possible applications of homolytic substitution reactions.[20] S_Hi reactions at silicon (by carbon-centred radicals in the α-position of stannylated silyl ethers) are efficient UMCT reactions producing cyclized alkoxysilanes. Bimolecular reactions can also be facilitated in good yield (Schemes 32 and 33).[135]



SCHEME 32



SCHEME 33

Reactivity Effects

Polarity and Philicity

Substituent effects for the regioselectivity of cyclization of vinyl radicals on to aromatic rings have been investigated and the nature of the polar effects suggests that vinyl radicals have slight electrophilic character.[136] The cyclizations of a range of fluorinated radicals have been studied. When the fluorine was substituted near to the radical centre, great effects on both the rate and the regioselectivity of the process were observed.[39] These effects were ascribed to both polar and pyrimidalization effects. An assessment of the nucleophilicity and electrophilicity of radicals, and the polar effects on radical addition reactions, have been determined using principal component analysis (PCA).[137] The results indicated that the hydroxymethyl radical was strongly nucleophilic, the methyl radical moderately nucleophilic, the *t*-butoxycarbonyl and cyanomethyl radicals mildly nucleophilic, and the phenylsulfonyl and tosyl radicals moderately electrophilic.

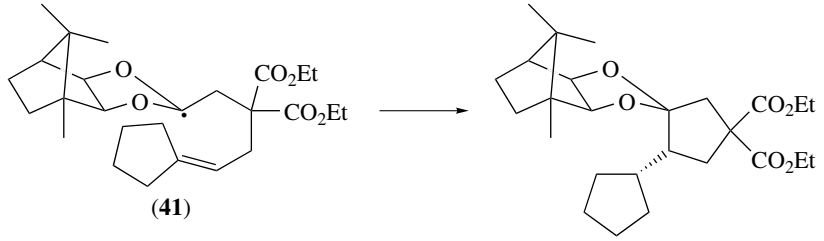
Stability of Radicals

The kinetics of hydrogen abstraction by the $CF_3COC(C_2F_5)_2$ radical have been studied by ESR with the degree of delocalization calculated using the MNDO/PM3 method.[72] All aspects of the solution structure, stability, and chemistry of carbon-centred fluorine-containing free radicals have been discussed.[138]

Stereoselectivity in Radical Reactions

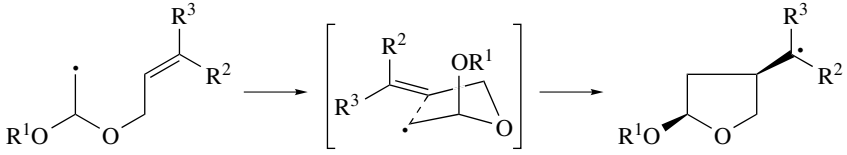
Stereoselectivity in Cyclization

Almost complete stereoselectivity was obtained in the cyclization of the constrained 1,3-dioxabicyclo[4.3.0]nonan-2-yl radical (**41**) (Scheme 34).[139] Locking the 1,3-dioxolanyl unit into an envelope conformation was found to be important in controlling such 5-*exo* cyclizations. Radical-chain cyclization of alkenyloxysilanes using thiols has been studied.[49] The stereochemistry of these reactions was determined by steric effects, even in the presence of chiral thiol catalysts. Cyclization of a range of acetals proceeds to give *cis* isomers preferentially, indicating that cyclization takes place via a chair-like transition state with the substituent alkoxy group in the pseudo-axial position (Scheme 35).[140] This unusual stereochemical outcome was postulated to arise due to the anomeric effect. The 5-*exo* oxygen-radical cyclization of (**42**) to (**43**) has been reported. This gives rise to 2,3-*trans*-disubstituted THFs caused by high levels of

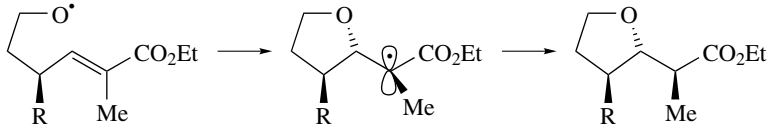


(**41**)

SCHEME 34

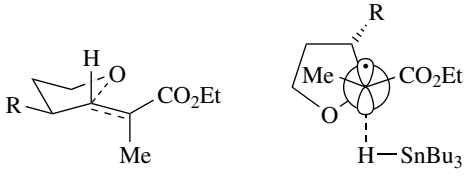


SCHEME 35



(**42**) (**43**)

SCHEME 36

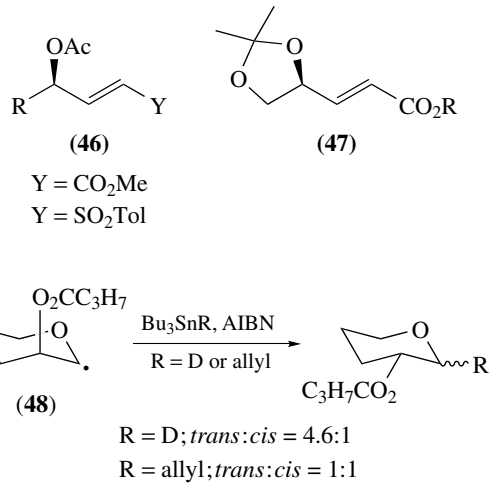


(**44**) (**45**)

1,2-induction in both steps (Scheme 36).[141] The steric nature of R was investigated for its effect upon the stereochemical outcome of the reaction. Transition states for both cyclization (**44**) and reduction (**45**) were postulated to explain the stereoselectivity.

Stereoselectivity in Addition Reactions

High *anti*-asymmetric induction in the additions of the 1-hydroxy-1-methylethyl radical to (*E*)-γ-hydroxy-α, β-unsaturated esters and sulfones (**46**) has been observed.[142] Selectivity was greatest with bulkier R groups. In contrast, the *Z*-isomer led to the *syn*-isomers exclusively. This is in contrast to recent work on the addition to



SCHEME 37

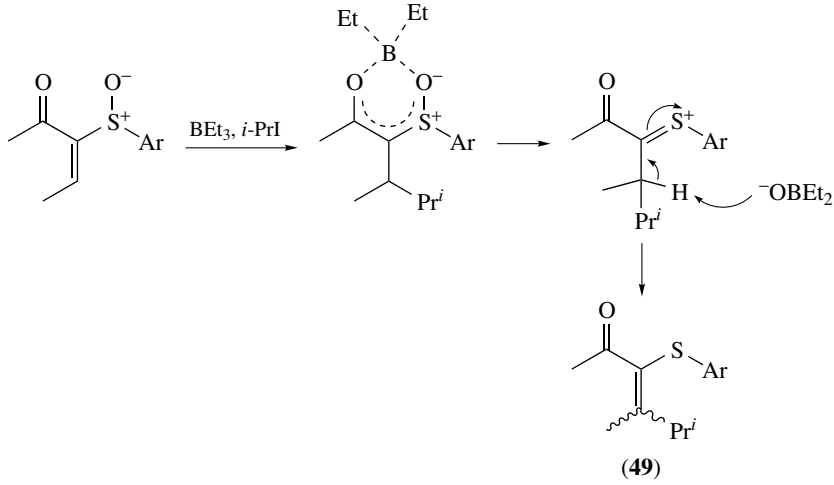
(*E*)-(**47**) which gives *syn*-isomers as the major products. Observations based on X-ray and NMR analysis and MNDO/PM3 calculations indicated that selectivity arises from attack at the least-hindered side (opposite to the R group in the *E*-compounds) from the conformation with the acetoxy group 'inside' the double bond. For the (*Z*)-alkenes, the same was true but from a conformation with the acetoxy group located 'outside' the alkene.

The influence of the classical anomeric effect and quasi-anomeric effect on the reactivity of various radicals has been probed.[143] The isomer distribution for the deuteriation of radical (**48**) was found to be selective whereas allylation was non-selective (Scheme 37). The results were explained by invoking a later transition state in the allylation, thus increasing the significance of thermodynamic control in the later reactions. Radical addition to a range of α-(arylsulfonyl)enones has been reported to give unexpected Pummerer rearrangement products (**49**) (Scheme 38).[144] A mechanism has been postulated proceeding via the boron enolate followed by elimination of Et_2BO^- anion.

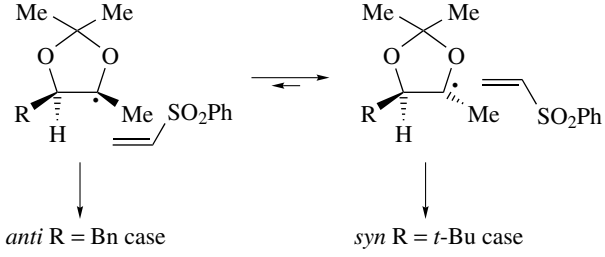
The stereochemical outcome for addition of *t*-1,3-dioxolan-4-yl and oxiranyl radicals to phenyl vinyl sulfone has been probed. The results indicated that the *syn*:*anti* selectivity could be altered by changing the group next to the radical in the dioxolanyl case but not in the oxiranyl case (bulky groups had a large *syn*-directing effect) (Scheme 39).[145] Several alkenyl-lactones and -lactams have been subjected to hydrosilylation conditions using carbohydrate-derived thiols as homochiral polarity reversal catalysts (yields 25–96%; *ee* 5–95%).[146]

Stereoselectivity in Atom Transfer

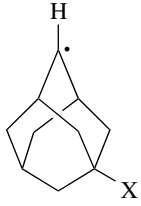
A review on asymmetric induction in hydrogen-transfer and allylation reactions of a range of chiral ester derivatives has highlighted both structural and electronic roles



SCHEME 38

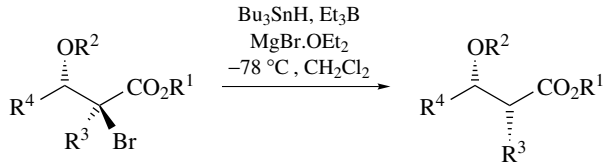


SCHEME 39



X	*anti*:*syn*
F	25:75
Br	34:66
$SnMe_3$	66:34

in controlling selectivity.[19] Diastereoselectivity in D-atom and halogen-atom abstraction reactions mediated by 5-substituted 2-adamantyl radicals (**50**) was shown to be dependent on the electronic character of the 5-substituent.[147] These observations are in accord with both the Cieplak transition-state hyperconjugation model and also the possibility of an early reactant-like TS. The reductions of a range of α-bromo-β-alkoxy esters under chelation-controlled conditions (using $MgBr_2.OEt_2$ and Bu_3SnH) have been shown to give rise to *syn* products.[148] The effects of substituents at positions

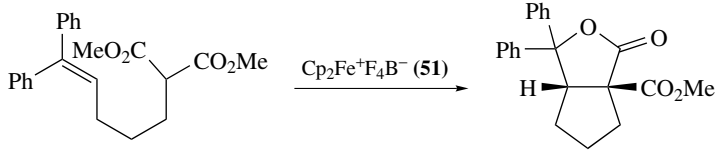


SCHEME 40

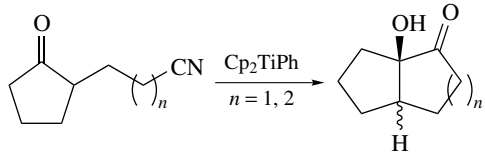
2 and 3, and the role of the ester substituents, were probed and it was found that they had little effect on the stereochemical outcome (Scheme 40). Work by the same authors has shown that the diastereoselectivity of hydrogen-atom transfer in the reactions of acyclic free radicals can be enhanced using a strategy employing bifunctional protecting groups (taking advantage of the 'exocyclic effect').[149]

Redox Reactions

Various transition metals have been used in redox processes. For example, tandem sequences of cyclization have been initiated from malonate enolates by electron-transfer-induced oxidation with ferricenium ion Cp_2Fe^+ (**51**) followed by cyclization and either radical or cationic termination (Scheme 41).[150] Titanium, in the form of Cp_2TiPh, has been used to initiate reductive radical cyclizations to give γ- and δ-cyano esters in a 5- or 6-*exo* manner, respectively (Scheme 42). The Ti(III) reagent coordinates both to the C=O and CN groups and cyclization proceeds irreversibly without formation of iminyl radical intermediates.[151] The oxidation of benzylic and allylic alcohols in a two-phase system in the presence of *t*-butyl hydroperoxide, a copper catalyst, and a phase-transfer catalyst has been examined.[152] The reactions were shown to proceed via a heterolytic mechanism; however, the oxidations of related active methylene compounds (without the alcohol functionality) were determined to be free-radical processes.



SCHEME 41



SCHEME 42

Radical Ions

Anion Radicals

Analysis and calculation of features that govern nucleophilic reactivity in $S_{RN}1$ processes have been studied, focusing upon the addition of anions to Ph$^{\bullet}$. In this addition step, electron transfer to give the radical anion is concerted with bond formation. The extra electron is located in the π^* orbital of the aromatic group.[153]

Cation Radicals

A review on the nitration of aromatics (using a range of species including $^{\bullet}NO_2$ and $^{\bullet}NO_3$) has appeared.[12] Evidence for electron-transfer mechanisms via radical cations has been reviewed. In addition, another review comparing the reactivity of a range of radicals and radical cations has appeared.[15] While radicals prefer to add to the carbon of CN triple bonds, radical cations were found to prefer addition at the N atom. *Ab initio* calculations were performed to rationalize this behaviour.

The generation of radical cations by photo-induced SET processes has been reviewed.[154] The reaction between a variety of aromatic compounds and some common halogenating reagents (ICl, Cl_2, Br_2, I_2, NBS, and NCS) in 1,1,1,3,3,3-hexafluoropropan-2-ol has been investigated using EPR.[155] The results indicated that the reactions followed an ET mechanism, where the initial step produces a mixture of $ArH^{+\bullet}$ and the halide ion, which slowly react to give the observed halogenated aromatics. The fluorinated solvent favours the mechanism by both increasing the oxidative power of the halogen source as well as deactivating the nucleophile.

An SET photo-sensitization technique has been employed to generate and study the decay of anilinium radicals derived by one-electron oxidation of α-anilinocarboxylates, β-anilino alcohols and α-anilinosilanes. In particular, the effects of the electrofugal group, reaction medium, and substituents upon the outcome of the reactions (desilylation, decarboxylation, and retro-aldol cleavage) were studied.[156] Irradiation using sunlight of a TiO_2/MeCN suspension containing 4-methoxybenzyl(trimethyl)silane and maleic anhydride generates a benzyl radical, formed initially from a radical cation derived from the silane.[157]

Peroxides, Peroxyl, and Hydroxyl Radicals

Peroxides

The abstraction ability from cyclohexane of radicals derived from dialkyl peroxides has been reported.[158] The experiments were performed with and without the trapping agent MSD (α-methylstyrene dimer), the abstracting species being alkoxy radicals derived from the peroxides. However, some dehydro dimer yields indicated that abstraction was also occurring by alkyl radicals.

The radical chemistry of *t*-butyl hydroperoxide in the oxidation of activated hydrocarbons has been reported.[159]

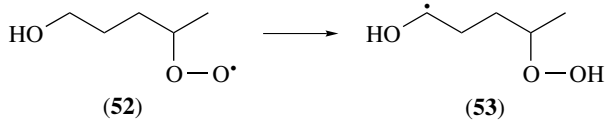
Peroxyl Radicals

A review of peroxyl radicals, including rate constants for their formation, solvent effects, and other relevant information, has appeared.[1] In addition, other reviews encompassing the recombination of peroxyl radicals,[2] their reactions in (a) the gas phase,[3] (b) aqueous solution,[4] (c) mixed-solvent systems[5] and (d) organic solvents[6] have appeared. Further reviews have dealt with the ESR spectra of peroxyl radicals,[7] the atmospheric chemistry of peroxyl radicals,[8] the chemistry of heteroatom peroxyl radicals such as trioxyl, *S*-peroxyl and *N*-peroxyl radicals,[9] and the reactions of hydroperoxyl radicals with organic and inorganic compounds in aqueous media.[10]

H-abstractions by peroxyl radicals have been studied.[92] Thus, the regioselectivity of hydrogen-atom abstraction from a range of alkyl-substituted aromatics by the α,α-dimethylbenzylperoxyl radical has been examined using MINDO/3 calculations.[92] The activation energies of intramolecular H-abstraction (1,5-translocation) by the oxygen atom in peroxides have been studied theoretically using density-functional molecular-orbital methods. The results were compared with experimental data and conclusions drawn.[160] An early-transition-state model with charge transfer has been proposed for the reaction of some C−H bonds with peroxyl radicals.[161] The rate constant for the isomerization of (**52**) to (**53**) (an important reaction in atmospheric pollution and low-temperature combustion processes) has been determined [463–523 K; $A(\mathrm{H}) = 3.2 \times 10^{10}\,\mathrm{s}^{-1}$; $E_a = 16.9\,\mathrm{kcal\,mol}^{-1}$) (Scheme 43).[162]

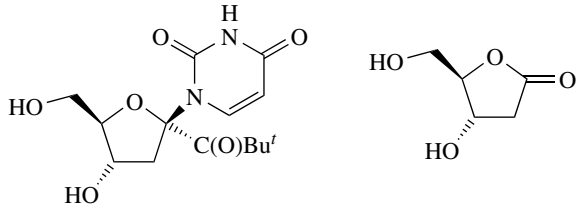
The reactivity of a range of alkenes in addition reactions of peroxyl radicals has been reported.[163] Parameters that described the relationship between the activation energy and enthalpy were calculated. An activation energy of $82\,\mathrm{kJ\,mol}^{-1}$ was determined for the addition of alkylperoxy radicals to isolated C=C bonds, rising by $8.5\,\mathrm{kJ\,mol}^{-1}$ when the alkene was conjugated with an aromatic substituent.

The process of oxidative DNA cleavage has been modelled through irradiation of the compound (**54**). Hence, in the presence of O_2, H_2O, and photolyzing conditions, (**54**) gave uracil, lactone (**55**), and starting material in a 0.15:0.15:1 ratio.[164]



(**52**) (**53**)

SCHEME 43



(**54**) (**55**)

Hydroxyl Radical

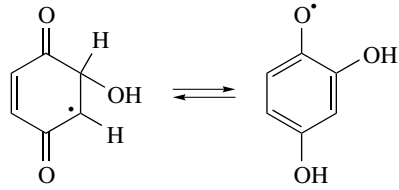
The role of •OH in ozone chemistry continues to be an important area of research. Thus, one of the first pathways in the production of ozone by hydrocarbons in the troposphere is their reaction with •OH. This reaction has been studied theoretically with a range of simple alkanes, and activation energies were found to increase as one goes from tertiary to secondary to primary hydrocarbons.[165] The competing role of orbital overlap and energy difference on the delocalization energy of the transition state for the reactions of the hydroxyl radical with ethane, propane, and cyclopropane has been examined by both experimental and theoretical analysis.[166] In other studies on the reactivity of •OH with various functional groups, the absolute rate constants for the reaction of •OH with acetone, butan-2-one, and three other ketones have been measured using pulsed-laser photolysis-induced fluorescence at 243–372 K.[167] Using relative-rate methods, the rate constants for the reaction between •OH and a range of methyl esters,[168] dibasic esters,[169] and alcohols[170] (hexan-1-ol, 1-methoxypropan-2-ol, butan-1-ol, 2-butoxyethanol, pentan-1-ol, ethane-1,2-diol, and propane-1,2-diol) have been measured. The tropospheric lifetimes were then estimated and the mechanisms of the reactions discussed in light of the current understanding of atmospheric oxygenated chemistry.[171]

The oxidative degradations of binuclear azaarenes (quinoline, isoquinoline, and benzodrazines) by hydroxyl and sulfate radicals[172] and halogen radicals[133] have been studied under both photochemical and dark-reaction conditions. A shift from oxidation of the benzene moiety to the pyridine moiety was observed in the quinoline and isoquinoline systems upon changing the reaction from the dark to photochemical conditions. The results were interpreted using frontier-orbital calculations. The reaction of •OH with the dye 3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-(1,8)(2*H*,5*H*)-acridinedione has been studied, and the transient absorption bands assigned in neutral solution.[173] The redox potential (and also the pK_a of the transient species) was determined. Hydroxyl radicals have been found to react with thioanisole via both electron transfer to give radical cations (73%) and OH-adduct formation (23%). The bimolecular rate constant was determined (3.5×10^9 l mol^{-1} s^{-1}).[174]

The reaction of •OH with HFCs has attracted interest. The temperature dependence of the fast initial H• abstraction by HO• in HFCs has been calculated using *ab initio* methods.[175] Rate constants calculated using HF and MP2(G–31G(d)) were found to be substantially greater than those determined experimentally. In other work investigating reactions of •OH with HFCs, rate constants for its reactions with HFC-245cb ($MeCF_2CF_3$) and other fluoroalkenes have been determined.[176]

Pulsed radiolysis in NO-saturated aqueous solution at a variety of wavelengths has been used to generate hydroxyl radicals and measure the rate of addition to 1,4-benzoquinones. Mechanistically, the kinetic data indicated that the first-formed adduct undergoes a rapid keto–enol tautomerism to give (**56**).[177]

In biological chemistry, the reaction of the glycine anion $H_2NCH_2CO_2^-$ with HO• has been investigated by pulse radiolysis. The major pathway was found to be loss of



(**56**)

SCHEME 44

CO_2 via initial •OH-induced oxidation to both $H_2N^{+\bullet}CH_2CO_2^-$ and $H\dot{N}CH_2CO_2^-$ in 63 and 37% yields, respectively. The fragmentation of the radical cation to CO_2 and $^{\bullet}CH_2NH_2$ was found to be fairly fast (<100 ns).[178]

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CHAPTER 4

Radical Reactions: Part 2

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Structure and Stability

Carbon-centred Radicals

The Whiffen effect in EPR spectroscopy and the relevant aspects of the H−C and M−C (M = metal) hyperconjugation in radicals and spin-paired molecules has been reviewed.[1] A paper on the resonance structures of benzoid conjugated radicals has been published. The number of resonance structures (SC) in radical benzoid hydrocarbons is larger than the numbers of resonance structures in Kekuléan (closed-shell) benzoid hydrocarbons. Analytical expressions for the SC of benzoid radicals have been derived.[2] Enthalpies of formation of 20 cyclic and conjugated hydrocarbon radicals were calculated.[3] Proton and electron affinities were calculated for a series of aliphatic and alicyclic carbanions and radicals using MP2/6−31 and B3LYP methods. Structural and electronic factors that control anion and radical stabilization were examined by natural bond orbital analysis. Structural analyses of several systems showed the importance of C−H and C−C hyperconjugation effects in both radicals and anions. No correlations between the % *s*-character of ionizing C−H bonds and proton affinity existed.[4] The mechanisms of decomposition of primary arsines and dialkyl R_2E,

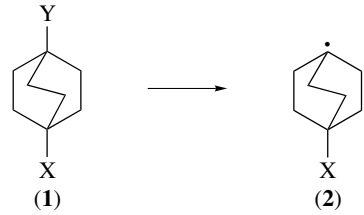
where E = S, Se, Te, as precursors for metal organic vapour-phase epitaxy has been reviewed.[5]

A CAS-MCSCF and CCSD(T) theoretical study on the mesolytic dissociations of methyl- and silyl-cyclopropenyl radical cations and anions has shown that the radical cations dissociate into *c*-$C_3H_3^+$ and $XH_3^\bullet$ (X = C, Si). The radical anions fragment into *c*-$C_3H_3^\bullet$ and XH_3^- (X = C, Si).[6] The cleavage reactions of but-1-ene and 4,4-dimethyl pent-1-ene molecules and their cations to form neutral and charged hydrocarbon products were investigated using Hartree–Fock/density-functional theory. For the radicals studied, the isotropic coupling constants are reported and are comparable to experimental data. It was found that the experimental hyperfine properties of the but-1-ene cation could be explained by rotational averaging caused by the flat potential surface for the rotation about the C(2)–C(3) bond.[7]

Ab initio MO and B3LYP hybrid Hartree–Fock/density-functional (HF/DF) calculations of benzene and toluene nitrosation confirm that nitrosation proceeds through initial formation of intermediate electron-acceptor π-complexes.[8] Transformation of (benzene–NO)$^+$ and (toluene–NO)$^+$ π-complexes into *N*-protonated nitroso derivatives in B3LYP and MP2 calculations occur by a novel migratory insertion of nitrogen into the aromatic C–H bond. The IMOMO (integrated MO + MO) method has been used to calculate single-bond dissociation energies for the C–H bond of benzene, the C–F bond of fluorobenzene, the C–CH_3 bond of toluene, the Si–H bond of phenylsilane, the O–H bond of *n*-propanol, isopropanol, *n*-butanol and *t*-butanol, the C–S bond of $PhCH_2$-SCH_2, and the O–O bond of SF_5O–OSF_3.[9] The PM3 method has been used to study the 'breakage mechanism' of N–NO_2 and the 'cleavage mechanism' of C-NO_2 for the decomposition of *o*-nitroazidobenzene.[10] *Ab initio* calculations on the gas-phase decomposition of nitroethylene have revealed that the first stage involved the formation of a four-membered cyclic intermediate, the decomposition of which to H_2CO and HCNO proceeds via a biradical intermediate.[11] A coupled-cluster analysis of the electronic states of 4-aminobenzonitrile and 4-(*N*,*N*-dimethylamino)benzonitrile has been reported.[12]

Polarity reversal catalysis by tri-*t*-butoxysilanethiol has been applied to promote radical-chain epimerization selectively at carbon centres of the type $R^1R^2C^*HOR$.[13] B3LYP and post-HF computations performed on α-substituted carbocations $CH_3\overset{+}{C}HR$, (R = H, CH_3, CH=CH_2, C≡CH, F, and Cl) revealed that the substituents stabilize the cations compared with R = H in the order CH=CH_2 > CH_2 > C≡CH > Cl > F.[14]

The interactions of acetone with liquid sulfuric acid solutions have been described.[15] A theoretical analysis of the reaction of H with C_2H_5 has shown three barrierless pathways, two leading to association and one for abstraction.[16] Similarly, the reaction H + CH_2CO → CH_3 + CO has been studied at high temperatures and pressures.[17] An ESR study of the radical species formed by pyrrole reaction with cyanoacetylene in the system KOH–DMSO was carried out.[18] The effect of bridgehead substituents on the stability of 1-norbornyl radical (**2**) generated by electrochemical reduction of a series 4-X-substituted bicyclo[2.2.1]heptan-1-yl bromides and iodides (**1**) (X = H, F, Cl, Br, I, $SnMe_3$) has been investigated by cyclic voltammetry.[19] The variations in the peak reduction can be translated to values for the weakening of the C–Br and C–I bond dissociation energies upon replacement of X = H by all the substituents



(**1**) (**2**)

X = H, F, Cl, Br, I, $SnMe_3$

Y = Br, I

X, using dissociative electron-transfer theory. A through-space stabilizing interaction (homohyperconjugation) in the 4-X-substituted bicyclo[2.2.1]heptane radical species has been shown to exist.

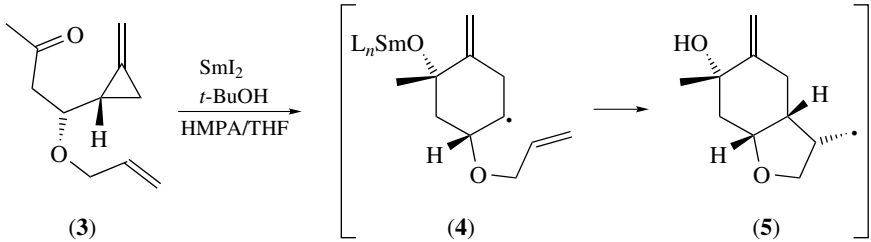
The reactions of sodium dimethyl and diisopropyl phosphite with 4-nitrobenzyl chloride, 9-chlorofluorene, and diphenylchloromethane provided information that supported the proposed reaction mechanism. The R_2PO^- anion acts towards an arylmethyl chloride as a base and abstracts a proton to form a carbanion, which can then participate in single-electron transfer processes to produce carbon-centred radicals.[20]

The 2-glycyl radical $H_2N\dot{C}HCO_2H$ has been generated by collisional neutralization of the stable 2-glycyl cation ($H_2N\overset{+}{C}HCO_2H$) and is stable on the microsecond timescale.[21] Losses of CO, water, and an amine hydrogen were calculated to be the lowest energy dissociations by combined density-functional theory and *ab initio* calculations. The authors concluded that depletion of the glycyl radicals in biological systems most likely occur via a bimolecular reaction.

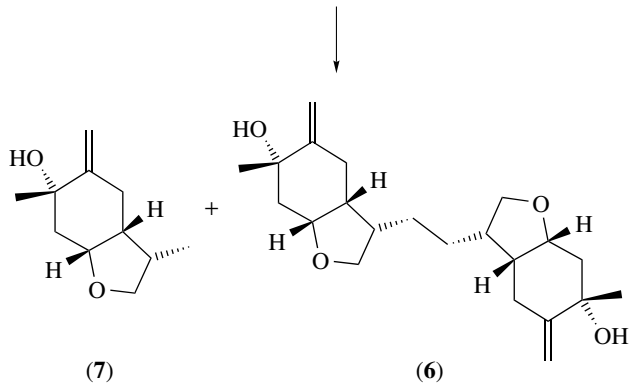
A samarium(II) iodide-mediated cascade sequence, that leads to a highly stereoselective dimerization, has been reported. This sequence begins with an SmI_2-mediated formation of a ketyl radical and leads to an alkyl radical which appears to be partially protected from further reduction to the organosamarium by ligation to the ketyl oxygen-bound samarium. This radical instead undergoes dimerization (**6**) and reduction to a smaller extent (**7**).[22] The cyclization of the initially formed ketyl radical may proceed via a chair-like transition state to give the intermediate radical as a single diastereoisomer which then cyclizes to give the alkyl radical.

ω-Iodo-aldehydes (**8**) or -ketones in the presence of triethylborane as a radical initiator and in the presence of oxygen or light as terminator undergo 5-*exo*-trig cyclization to give (**9**).[23] In these conditions a 5-*exo*-trig cyclization on an aldehyde is faster than on an alkene. The high reactivity of carbonyl derivatives may be attributed to the Lewis acidity of triethylborane.

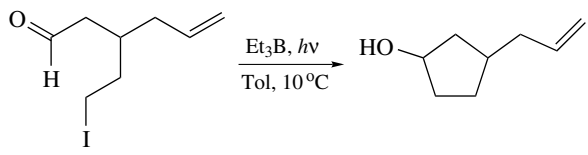
The kinetics of the reaction of 2′-deoxyuridin-1′-yl radicals (**11**) with thiols, with superoxide release from the peroxyl radical (**13**) generated, have been reported.[24] Radical (**11**) is produced by photolysis of precursor (**10**). When the radical is produced in the presence of thiols, (**12**) is formed. Second-order kinetics were found for the reactions with thiols. Peroxyl radical (**13**) is formed in the presence of oxygen. This undergoes heterolytic fragmentation to the superoxide anion $O_2^{\bullet-}$ and cation (**14**), which ultimately leads to 2-deoxyribonolactone (**15**).



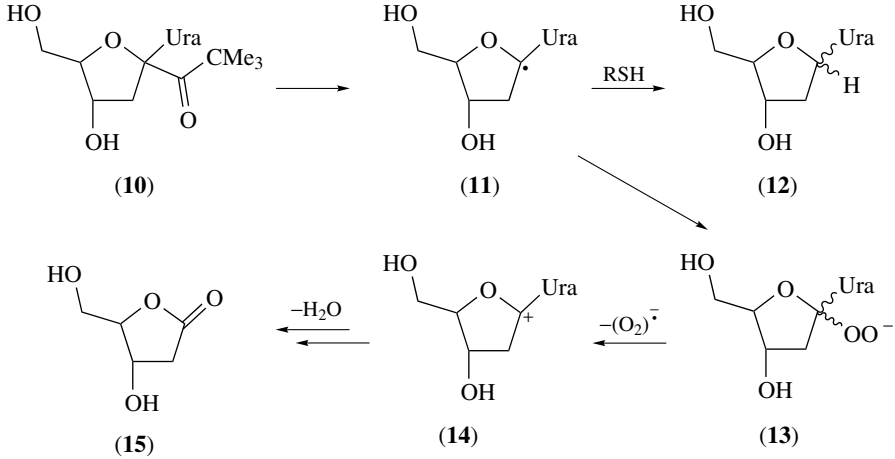
(**3**) (**4**) (**5**)



(**7**) (**6**)



(**8**) (**9**)



(**10**) (**11**) (**12**) (**13**) (**14**) (**15**)

A kinetic and mechanistic study of the reaction between toluidine blue (TB) and sulfite has shown a first-order dependence on both reactants, a stoichiometric ratio of 1:1 and pH dependence.[25] The reactive species are TB^+ and SO_3^{2-} ions and Cu(II) acted as a promoter by facilitating the formation of a ternary complex with TB^+ and SO_3^{2-}.

Miscellaneous Radicals

The spin-density distribution in carbon-based peroxyl radicals was studied by density-functional theory at the B3LYP level. Electronegative substitution at the carbon α to the peroxyl group results in an increase of terminal hyperfine coupling and spin-density shortening of the C−O bond and lengthening of the O−O bond. In cases of steric hindrance, the C−O bond-shortening was prevented. Thiyl peroxyl radicals were reinvestigated and it was confirmed that the addition of an electron-pair donor (hydroxide) to $CH_3SOO^\bullet$ alters the spin-density contribution in the peroxyl group.[26]

The reaction of $HO^\bullet$ radical with a number of dialkyl sulfides was reported to be affected by the pH, the nature of the functional group, and the chain length.[27] The presence of the CH_2CH_2OH group results in the formation of α-thio radicals and dimer radical cation in neutral and acidic conditions. In the case of the $CH_2CH_2CH_2OH$ group, an intramolecular radical cation, with *p*-orbital overlap between oxidized sulfur and O, is observed that forms a five-membered ring. The reaction with 2,2′-thiodiethanoyl chloride leads to the formation of α-thio radicals in neutral conditions and in acidic conditions an intramolecular cation forms a four-membered ring between the oxidized sulfur and chlorine. The hydroxyl radical-induced decomposition of 2′-deoxycytidine has been reported and the products were identified.[28] An explanation of the decomposition mechanism was provided. The Bell–Evans–Polanyi principle and CASSCF wavefunctions were used to locate transition structures for the unimolecular decomposition of methyldioxirane into $MeCH(O^\bullet)_2$ and of $MeCH(O^\bullet)_2$ into AcOH, HCO_2Ac, and $CO_2 + CH_4$.[29] Semiempirical UHF/PM3 calculations examined three possible mechanisms for the diphenylcarbonyl oxide (Ph_2COO) bimolecular decay.[30] The 'head-to-tail' interaction of two Ph_2COO molecules has been found to be the most favourable pathway.

A report considers the reactions of 1-butoxy and 1-pentoxy radicals with oxygen (eqs 1 and 2) and of their isomerizations by 1,5-H-shift (eqs 3 and 4) using direct and time-resolved monitoring of the formation of NO_2 and HO radicals in the laser flash-initiated oxidation of 1-butyl and 1-pentyl radicals.[31]

$$CH_3CH_2CH_2CH_2O + O_2 \longrightarrow CH_3CH_2CH_2CHO + HO_2 \quad (1)$$

$$CH_3CH_2CH_2O + O_2 \longrightarrow CH_3CH_2CHO + HO_2 \quad (2)$$

$$CH_3CH_2CH_2CH_2O \longrightarrow CH_2CH_2CH_2CHOH \quad (3)$$

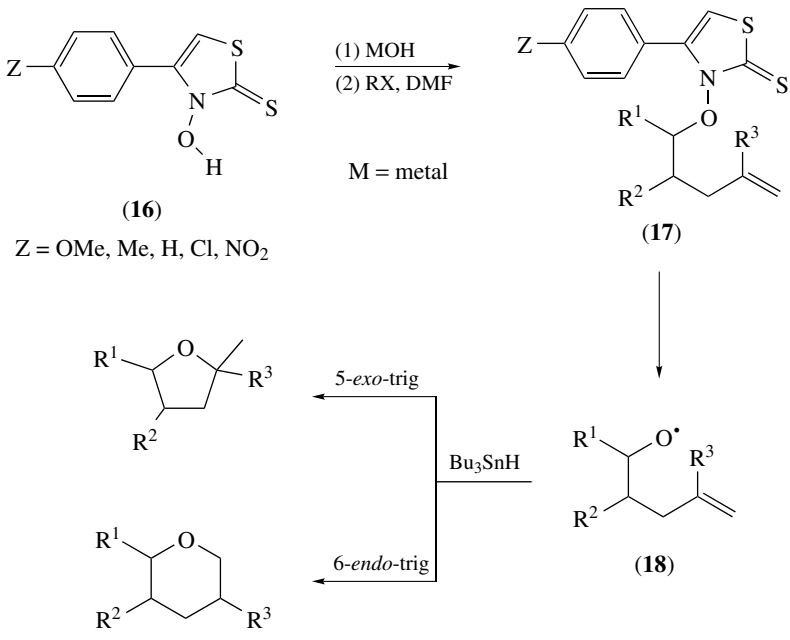
$$CH_3CH_2CH_2CH_2O \longrightarrow CH_3CHCH_2CHOH \quad (4)$$

Their rate coefficients were determined and showed that the primary alkoxy radicals have slightly higher rate coefficients for the reaction with O_2 than the secondary

radicals and the isomerizations abstracting H atoms from CH_2 group are faster than those which abstract the H-atom from a methyl group.

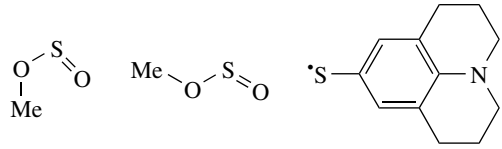
Highly stable 4-(benzimidazol-2-yl)-2,6-di-*t*-butylphenoxyl radicals have been synthesized. Their hydrogen-bonding functionality offers prospects for use in molecular magnetic materials.[32]

p-Chlorophenyl derivatives of *N*-alkoxy-4-arylthiazolethiones (**16**) were selected for precursors of oxygen-centred radicals after a study of their physical and chemical properties. Thiazolethiones (**17**) efficiently liberate free alkoxy radicals (**18**) upon irradiation or heating in the presence of Bu_3SnH as a radical trap. These reactive intermediates (**18**) undergo intramolecular cyclization by selective 5-*exo*-trig or 6-*endo*-trig pathways to the olefinic bonds to afford tetrahydrofurans or tetrahydropyrans as the major products in good yields.[33]



The thermochemistry of sulfur radicals in the gas phase has been reviewed.[34] Methylsulfonyl radicals and cations have been produced by femtosecond collisional electron transfer in the gas phase.[35] When formed by vertical collisional electron transfer from cation $CH_3SO_2^+$, radical $CH_3SO_2^{\bullet}$ dissociates to $CH_3^{\bullet}$ and SO_2. Radical $CH_3OSO^{\bullet}$ exists as a mixture of *syn* (**19a**) and *anti* (**19b**) isomers which are stable when formed by collisional electron transfer to the corresponding cation. Dissociation of both isomers of $CH_3OSO^{\bullet}$ formed $CH_3^{\bullet}$ and SO_2 via isomerization to methylsulfonyl radical. An *ab initio* study on the formation of the thiyl peroxyl radical has also been reported.[36] Julolidylthiyl radicals (**20**) were formed by femtosecond photo-dissociation of the corresponding disulfide and have been observed

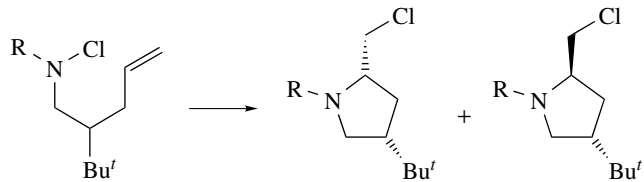
with pumb/supercontinuum probe spectroscopy.[37] Two forms of the radical were distinguished by their kinetics and by their spectra. Semiempirical calculations predict a radical doublet state D_2, optically dark, close to bright and a more polar ground state D_0.



(**19a**) (**19b**) (**20**)

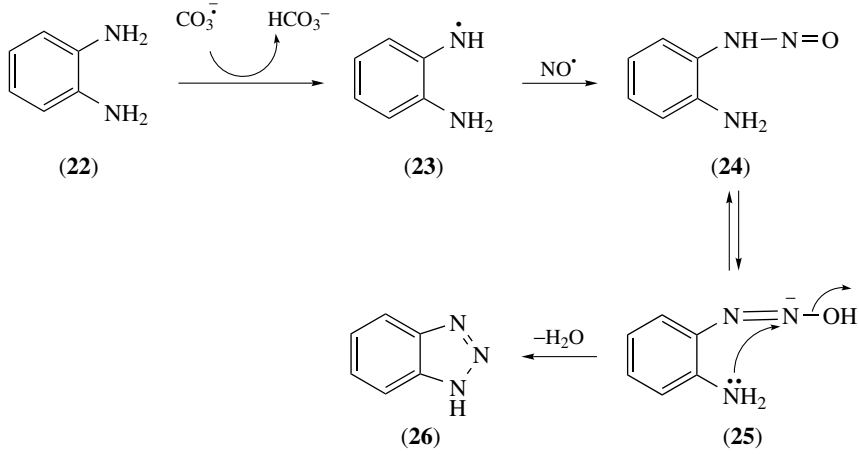
Tin hydrides containing one or two pyridyl groups have shown selective reactivity towards organic iodides, bromides, and chlorides. Those containing one pyridyl group smoothly reduce primary alkyl bromides but were completely inactive towards primary and secondary alkyl or aromatic chlorides. Tin hydrides with two pyridyl groups reduced iodides easily, bromides much more slowly, and were unreactive towards organic chlorides. This selective reactivity has been attributed to the intramolecular coordination of the tin to the pyridyl group.[38]

Stable thioaminyl radicals have been studied by ESR, X-ray crystallography and magnetic resonance.[39] Cationic aminyl radicals produced from *N*-chloroalkenylamines (**21**) by using Lewis acids ($CuCl:CuCl_2$, $FeCl_2:FeCl_3$, and $TiCl_3:TiCl_4$) underwent intramolecular cyclization to give pyrrolidines in excellent diastereoselectivity (depending on the type of *N*-substituent and Lewis acid).[40]

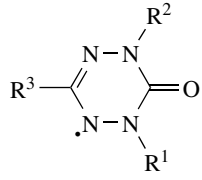


(**21**)

A free-radical mechanism has been suggested for the nitrosation of 1,2-phenylenediamine (**22**) by peroxynitrite PN/CO_2.[41] 1,2,3-Benzotriazole (**26**) was formed as a result of an intramolecular nucleophilic displacement on the diazo hydroxide (**25**) by the neighbouring amine group. The authors suggest that the mechanism involves an initial H-atom abstraction or one-electron oxidation from (**22**) by $CO_3^{\bullet-}$, followed by the reaction of the product (**23**) with $NO^{\bullet}$. The inhibitory effects of azide support a free-radical mechanism of the reaction.



A study of the HeI photoelectron spectroscopy (PES) on the electronic structure of the $(CH_3)_2N$ radical, which was produced through the pyrolysis of $(CH_3)_2NNO$, has been reported. The PES bands were assigned using density functional theory calculations based on the Amsterdam density function program.[42] A triphenylamine triradical containing three *N*-*t*-butyl-*N*-oxylamino radical groups in the *para* position has been found to contain a doublet ground state, as shown by ESR and magnetic susceptibility measurements.[43] This was supported by MO calculations. The structure, conformational behaviour, and magnetic properties of the oxoverdazyl radical (**27**) and of the biradical obtained by joining two identical units have been investigated by hybrid HF/DFT electronic method.[44] A non-planar structure is predicted for the biradical *in vacuo* and in solution and a planar conformation in the solid state which is ascribed to the packing effect.

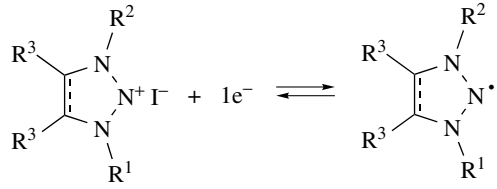


(**27**)

The 3-picolyl and 2,5-lutidyl radicals were isolated and studied by mass-resolved and fluorescence excitation. The 3-picolyl radical has a much shorter D1 life (9 ns) compared with that of 2,5-lutidyl radical (245 ns). The addition of a CH_3 group to the picolyl radical to form lutidyl suggests that the presence of the CH_3 group alters or eliminates a non-radiative pathway in the picolyl radical. *Ab initio* calculations suggest that ring expansion through a seven-membered radical ring could account for

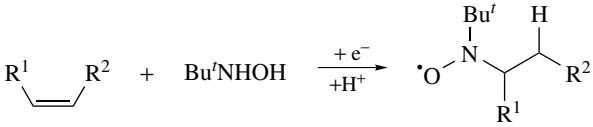
the missing 2- and 4-picolyl radicals and lutidyl counterparts if the D1 lifetimes for the excited-state species are short.[45]

A paper has reported that nitrogen-centred radicals (**29**) have been generated by one-electron reduction (at carbon or metal electrodes) of stable nitrenium ions of the general structure (**28**). The reactivity of the radicals is influenced by the substituents attached to the two nitrogen atoms that are directly linked to the ion nitrenium centre.[46]



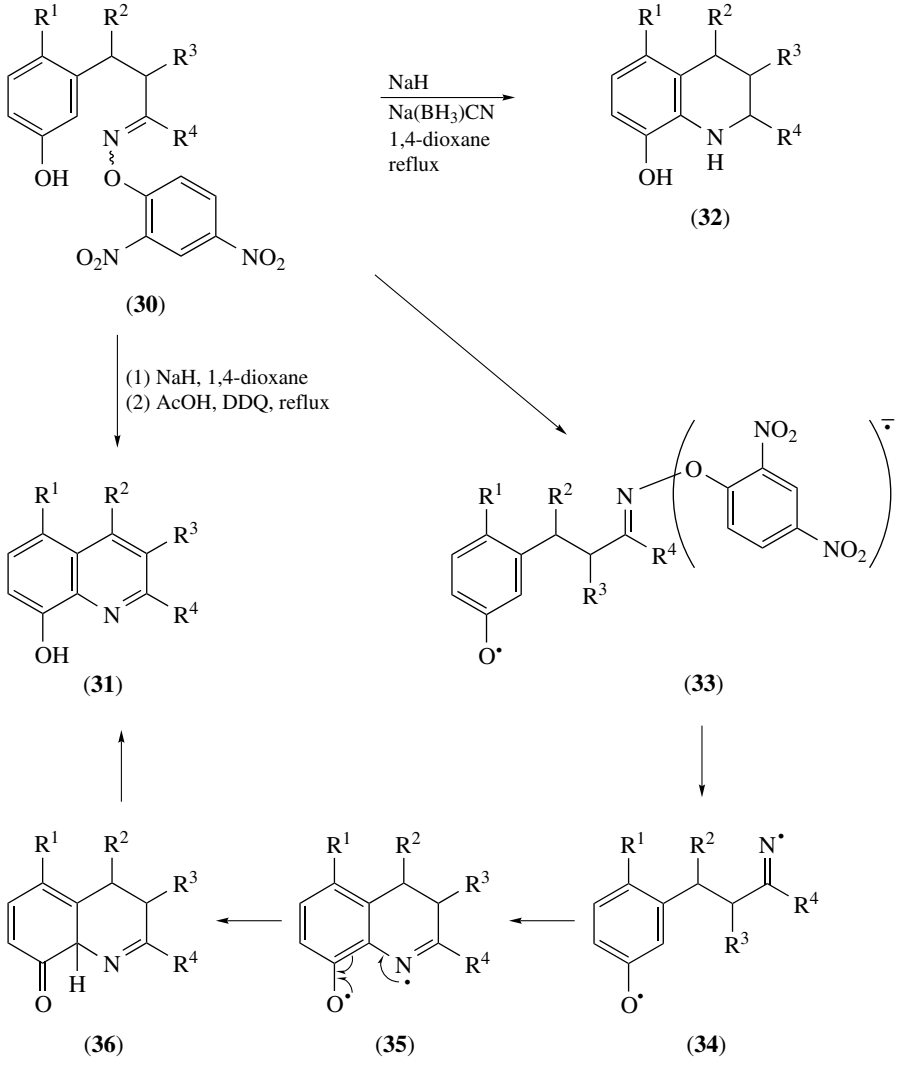
(**28**) (**29**)

Quinolin-8-ols (**31**) and 1,2,3,4-tetrahydroquinolin-8-ols (**32**) were synthesized from 2-(3-hydroxyphenyl)ethyl ketone *o*-2,4-dinitrophenyloximes (**30**).[47] Treatment with NaH and then DDQ and acetic acid afforded quinolin-8-ols (**31**). When the reaction was carried out in the presence of $Na[BH_3(CN)]$, 1,2,3,4-tetrahydroquinolin-8-ols (**32**) were obtained. The cyclization proceeds via alkylideneaminyl radical intermediates generated by single electron transfer between the 3-hydroxyphenyl and 2,4-dinitrophenyl moieties to generate an anion radical intermediate (**33**). The nitrogen–oxygen bond of the oxime cleaves to provide an alkylideneaminyl radical (**34**). Intramolecular coupling of biradical (**34**) gave (**31**) after isomerization. The magnetic properties of terpyridine-like ligands bearing appended nitronyl nitroxide or imino nitroxide radicals have been studied.[48] An EPR study of the behaviour of stable β-phosphorylated cyclic aminoxyl radicals in the presence of SDS micelles has been reported.[49] The radicals, except in the case of strongly hydrophilic radicals, were found to exchange between water and micelles. Their partition coefficients were evaluated from computer stimulations of the EPR spectra. *N*-*t*-Butylhydroxylamine reacted with an acceptor alkene, substituted by at least one conjugatively electron-withdrawing group, in the presence of *t*-BuNO as an oxidant to give aminoxyls identical with those formed in the thermal or photochemical reaction between the alkene and α-phenyl *N*-*t*-butyl nitrone (Scheme 1).[50]



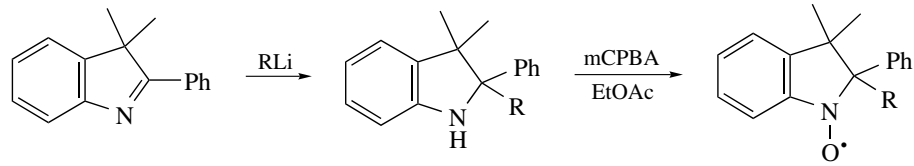
R^1 and R^2 = electron-withdrawing groups

SCHEME 1



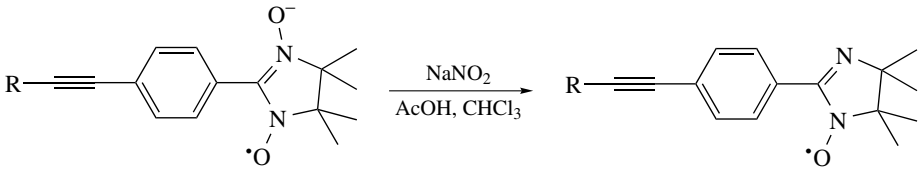
1,2-Organolithium additions to 2-phenyl-3,3-dimethyl-3*H*-indole (**37**), followed by oxidation of indolines (**38**) with *m*-chloroperoxybenzoic acid, gave indolinic aminoxyls (**39**) in 20–30% yield.[51] The organolithium addition does not occur when groups other than phenyl are present at C(2). Attempts to synthesize suitable precursors such as 1,2-dihydro-2-phenyl-2-alkylbenzothiazole, 1,2-dihydro-2-phenyl-2-alkylbenzoxazole, and 1,2-dihydro-2-phenyl-2-alkyl-4*H*-3,1-benzoxazin-4-one for other new aminoxyls failed.

A report was concerned with the ability of nitroxyl radicals, such as TEMPO and other related structures, to act as catalysts in the asymmetric oxidation of alcohols. Cyclic voltammetry was used to measure the oxidation potentials of the nitroxyl



(**37**) (**38**) (**39**)

radicals and provided information on the stability of the *N*-oxo ammonium salts. Those with the lowest redox potentials and with half-lives greater than a few minutes were the best catalysts.[52] Aryl(heteroaryl)ethynylphenyl-2-imidazoline nitronyl nitroxyl (**40**) radical and imino nitroxyl (**41**) radicals have been synthesized. The *g* tensor and HFI components for imidazoline-1-oxyl were found to depend on the properties of the substituents at the 2-position.[53]



(**40**) (**41**)

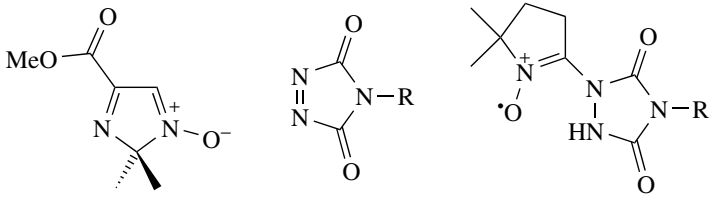
Nitroxides and Spin Trapping

In situ radiolysis time-resolved ESR was used to measure the reaction rate constants of the nitrone spin trap 5,5-dimethyl-1-pyrrolidine–*N*-oxide (DMPO) with a number of small alkyl and σ parent radicals in dilute aqueous solution. Electron-releasing α-hydroxyalkyl radicals reacted more rapidly than the unsubstituted radicals while the electron-withdrawing carboxymethyl radical was slower. σ-Radicals such as sulfite anion and carboxyl anion were trapped rapidly. Polar effects and steric considerations only weakly influence spin adduct formation. The reaction rates of alkyl and hydroxyalkyl radicals with DMPO are similar whether electron-withdrawing or electron-releasing substituents are present. The measured trapping rate constants with DMPO are slower than the corresponding rates with a nitroso spin trap MNR. This is due to the weakly nucleophilic character of DMPO, the strongly electrophilic character of MNP and the unfavourable steric factors in the DMPO–radical encounter complex.[54] The formation of the hydroxy radical spin adduct, HO–DMPO•, has been studied by EPR spectroscopy under conditions where the hydroxy radical is not involved. One method was the photo-sensitized oxidation of DMPO to its radical cation followed by reaction with water using quinines as sensitizers. A second method involved nucleophilic addition of water to DMPO followed by reaction of the intermediate hydroxylamine by mild oxidants such as quinones and Fe(III). The observation of HO–DMPO• was dependent on the acidity of the medium and decreased

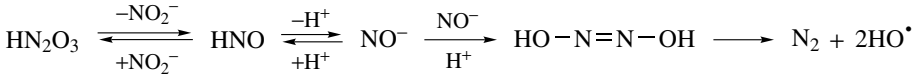
by increasing acidity. Use of buffered neutral or slightly alkaline solutions or ethyl acetate increased the formation of the adduct.[55]

A series of 2*H*-imidazole-1-oxides, isoquinoline-*N*-oxides and pyrrolidine-*N*-oxides were investigated as to their specificity and efficiency at spin trapping $HO^{\bullet}$ and $O_2^{\bullet-}$ as well as the stability of the corresponding spin-trapped adducts.[56] 2,2-Dimethyl-4-methoxycarbonyl-2*H*-imidazole (**42**) has been found to be the most selective of the spin traps investigated for the *in vivo*, *in situ* detection of $HO^{\bullet}$ at the expense of $O_2^{\bullet-}$.

The reaction of two 4-R-triazolinediones (**43**) (RTAD; R = Me and Ph) with DMPO was investigated by UV–visible, FT-IR, ^1H and ^{13}C NMR and EPR spectroscopy.[57] The reaction sequence involved the spin-adduct formation via a modified version of the Forrester–Hepburn mechanism and the rate-determining step was the oxidation of the spin adduct by RTAD, leading to the final product (**44**). An ESR spin-trapping study of the decomposition of sodium trioxodinitrate (Angeli's salt) in the presence of 5,5′-dimethyl-1′-pyrrolidine *N*-oxide (DMPO) suggest that its hydrolysis is associated with the generation of OH radicals.[58] The hydrolysis of AS in the presence of either ethanol or DMSO produces 1-hydroxyethyl and methyl radicals which add to DMPO to give ESR spectra of the DMPO/hydroxyethyl and DMPO/$Me^{\bullet}$ nitroxides. It is anticipated that NO^- generated by the decomposition of AS dimerizes to *cis*-hyponitrous acid which is unstable and decomposes via an azo-type homolytic fission (Scheme 2).

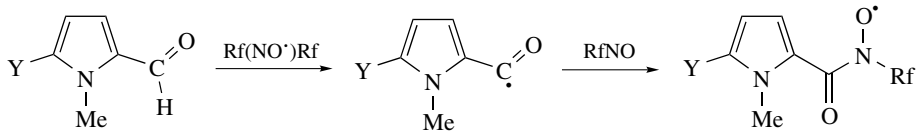


(**42**) (**43**) (**44**)

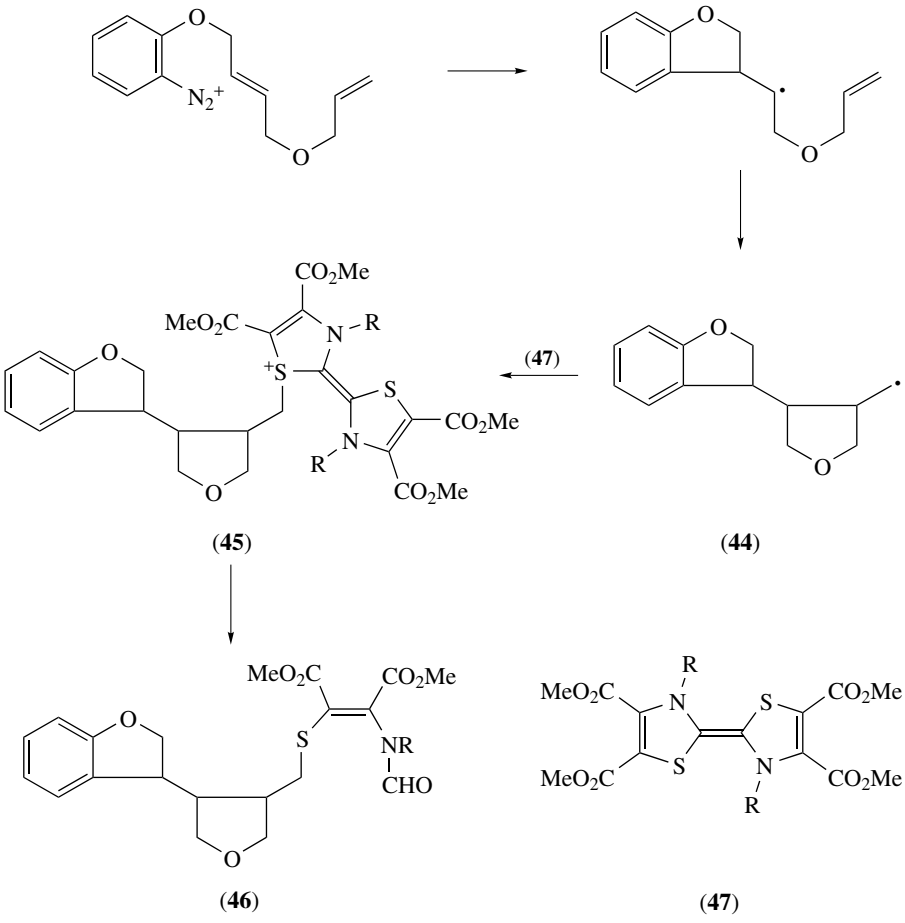


SCHEME 2

1-Methyl-2-substituted-5-pyrrolylcarbonyl fluorinated nitroxides, generated by the H-abstraction/spin-trapping reaction of 1-methyl-2-substituted-pyrrole-5-carbaldehydes with the H-abstracting agent [Rf($NO^{\bullet}$)Rf] and the spin trapping agent RfNO, were studied by EPR.[59] The a_N values (hyperfine splitting constants) were affected by the polar effect of the 2-substituent and the spin-delocalization effect also existed (Scheme 3).



SCHEME 3



The radical cations of diathazadithafulvalenes DDTF (**47**) trap primary carbon radicals and afford isolable products.[60] These products feature cleavage of the DDTF ring system. Their radical cations couple more slowly with secondary carbon radicals allowing a second cyclization affording the final radical (**44**). This primary radical reacts with the radical cation of DDTF to afford (**45**), which after cleavage of the ring gives formamide (**46**).

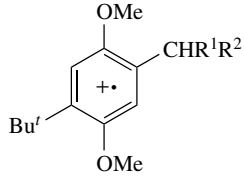
The copolymerization of styrene and maleic anhydride was studied by the spin-trapping technique using 2-methyl-2-nitrosopropane as a spin trap. Four types of ESR spectra were obtained, of which three corresponded to trapping of the growing polymer chain at a centre originating from the styrene part or from two centres originating from the maleic anhydride part. The fourth EPR spectrum may be due to a cyclic five-membered aminoxyl or a six-membered 1,2-oxazine radical cation.[61]

Oxidation and Reduction

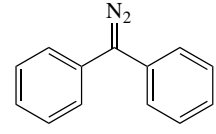
Perturbation theory was utilized to predetermine the regioselectivity of free-radical benzylic and allyl oxidation reactions of unconjugated π-systems.[62]

The chemistry of radical cations generated via cerium(IV) ammonium nitrate (CAN) oxidation of cyclopropylarenes and their potential as ion probes have been investigated. Oxidation of cyclopropylbenzene and 1- and 2-cyclopropylnaphthalenes leads to cyclopropane ring-opened products whereas 9-cyclopropylanthracene yields a radical cation that does not undergo cyclopropane ring opening. The results suggest that the cyclopropylarene radicals cannot be utilized as single-electron transfer probes because the cyclopropane ring opening does not occur at an appreciable rate.[63] Radical cations of 2-alkyl-5-*t*-butyl-1,4-dimethoxybenzene (**48**; 2-alkyl = Me, Et, *i*-Pr, and $PhCH_2$) were generated in one-electron oxidation of their parent compounds by pentafluorobenzoyl peroxide or cerium(IV) sulfate.[64] These radical cations were shown to collapse through two competitive pathways i.e deprotonation and de-*t*-butylation. The deprotonation was confirmed by EPR observation of the corresponding benzyl radicals. The relative importance of the two pathways is greatly dependent on the structure of the alkyl substituents, the nature of solvents, and the reaction temperature. For deprotonation, the reactivity order is found to be Me > $PHCH_2$ > Et $\gg$ *i*-Pr.

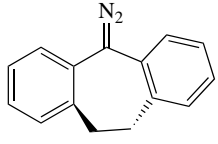
Small changes in the solvent or in the conditions of oxidation can lead to changes in the electronic and molecular structure of aryldiazo radical cations, from a linear allylic π- to a bent σ-radical state.[65] Both states have been observed in the radical cations of diphenyldiazomethane (**49**) and 5-diazo-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene



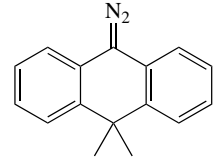
(**48**)



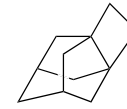
(**49**)



(**50**)



(**51**)



(**52**)

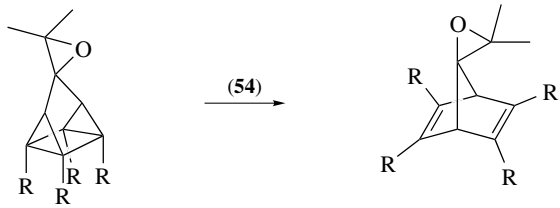
(**50**) whereas only the π-radical state could be formed in the radical cation of 9-diazo-9,10-dihydro-10,10-dimethylanthracene (**51**) in which the two phenyl rings are forced into a position coplanar with the $(C_{ipso})_2{-}CN_2$ plane. Quantum-chemical calculations have shown that observed small energy differences between the π- and σ-radical states of aryldiazo radical cations are due to solvent and/or counterion effects (see above).

The oxidation of 3,6-dehydrohomoadamantane (**52**) with $NO^+BF_4^-$, photo-excited tetracyanobenzene, and under anodic conditions has been found to involve a common radical cation intermediate. The study has shown that the activation of propellane σ_{C-C} bonds with strong oxidizing electrophiles occurs by a sequence of single-electron transfer steps. These findings are supported by *ab initio* computations showing that the isomeric radical cations can equilibrate with low barriers and lead to a common product.[66]

Chiral 2-imidazoline dianions undergo one-electron oxidation in the presence of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) to form a radical anion that is either trapped stereoselectively by TEMPO or undergoes dimerization.[67] Oxidation of bis-diazene oxides leads to novel *O*-stabilized 4N/3e radical cations and 4N/2e dications. These were detected by ESR spectroscopy and cyclic voltammetry. B3LYR/6–31G calculations confirmed the nature of the 4N/3e and 4N/2e systems.[68]

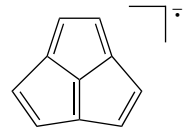
The oxidation of isopropylidenequadricyclane (**53**) with the electron-transfer catalyst tris(*p*-tolyl)aminium hexafluoroantimonate, $TTA^{+\bullet}SbF_6^-$ (**54**), gave the bicycloheptatriene (**55**). Epoxidation of the isopropylidene group (**56**) changes the reactivity of the quadricyclane and oxidation with $TTA^{+\bullet}SbF_6^-$ produces the norbornadiene (**57**).[69] A histidine radical cation and a histidine peroxy radical were formed by oxidation of histidine with the Ti^{3+}/H_2O_2 Fenton system. Isotropic hyperfine coupling constants of β-protons and three ring protons and two nitrogen nuclei have been determined.[70] The radical anion of acepentalene (**58**) was generated by photo-oxidation of the acepentalene dianion.[71] The spin population appears to be evenly distributed over the

(**53**) (**55**)



(**56**) (**57**)

nine-membered perimeter due to a rapid interconversion between two bowl-shaped C_s forms and a relative low-lying planar C_{2v} transition structure.

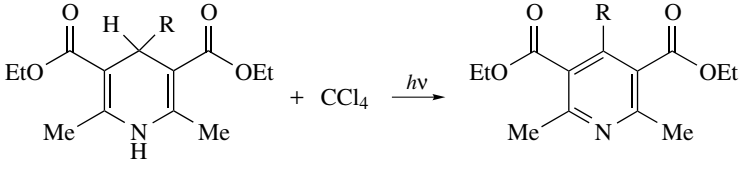


(**58**)

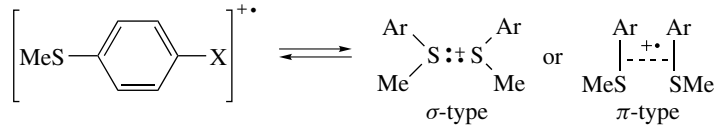
Oxidation of benzyl alcohol catalysed by chloroperoxidase exhibits a very high prochiral selectivity involving only the cleavage of the *pro-S* C−H bond.[72] The reaction mechanism involved the transfer of a hydrogen atom to the ferryl oxygen of the iron-oxo complex. An α-hydroxy-carbon radical and the iron-hydroxy complex P−Fe^{IV}−OH form. They may lead to the hydrated benzaldehyde or stepwise with the formation of the intermediate α-hydroxy cation.

Hantzsch 1,4-dihydropyridines were oxidized quantitatively to give the corresponding pyridine derivatives by irradiation in CCl_4. A photo-induced electron-transfer mechanism is involved. The critical step in this mechanism is the fast dechlorination of CCl_4 (Scheme 4).[73]

In the photochemical one-electron oxidation of aromatic sulfides, dimer radical cations were formed in rapid equilibrium with monomeric radical cation (**59**). The complex formation of σ- and π-types has been shown to be sensitive to the steric and electronic influence of substituent. For the case of *p*-(methylthio)anisole the formation of π-type dimer was shown to be reduced due to steric hindrance of two methyl groups. No formation of dimer radical cation was observed for *p*-(methoxy)thioanisole and diphenyl disulfide where the corresponding monomer radical cations are stabilized by the delocalization of positive charge on the sulfur atom. Density-functional calculations supported the experimental results. The intramolecular formation of similar radical



SCHEME 4

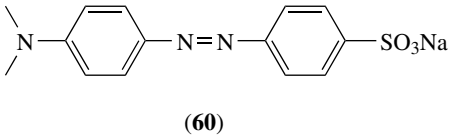


(**59**)

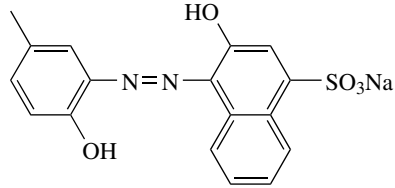
ion π and σ complexes for the 1,*n*-bis(phenylthio)alkanes with $n = 3$ and 4 was reported.[74]

Br-atom initiated oxidation of dimethyl sulfide (DMS) in a large-volume reaction chamber gave SO_2, CH_3SBr, and DMSO.[75] A rapid addition of Br atoms to DMS takes place, forming an adduct that mainly reforms reactants but also decomposes unimolecularly to form CH_3SBr and CH_3 radicals. DMSO is formed from the reaction of BrO radicals with DMS. The reaction $CH_3O_2 + Br \rightarrow CH_3O + BrO$ is postulated as the source of BrO radicals.

The HO-initiated oxidation of isoprene[62] and propene in the presence of nitrogen oxides has been the subject of two reports. Oxidation of isoprene in the presence of NO and O_2, and regeneration of the OH radicals by the reaction of isoprene-based peroxy radicals with NO, were measured and compared with simulations of the kinetics of this system.[76] CH_2O and CH_3CHO were produced from the oxidation of propene.[77] Reaction of the β-hydroxypropylperoxy radicals with NO leads to the formation of chemically activated β-hydroxypropoxy radicals which, according to theoretical calculations, decompose to CH_2O and CH_3CHO. The most stable conformations of the oxy radicals are found to contain intramolecular hydrogen bonds. Similarly, the hydroxyl radical oxidations of the azo dyes methyl orange (**60**) and calmagite (**61**) were found to be extremely fast with second-order rate constants. Methyl orange reacted with the hydroxyl radical by one-electron reduction at the nitrogen centre forming the anilino cation radical. Hydroxyl radicals reacted with calmagite by addition to the benzene ring producing hydroxycyclohexadienyl radicals, which rapidly decomposed to phenoxyl-type radicals by water elimination.[78]

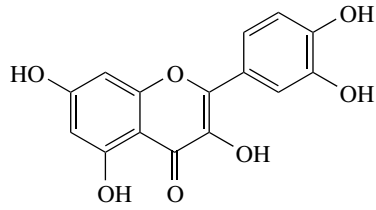


(**60**)



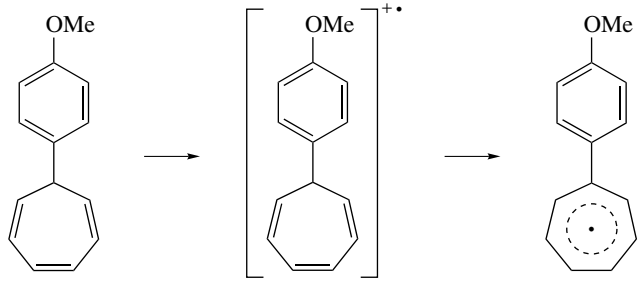
(**61**)

A one-electron oxidation study of quercetin (see structure below) and quercetin derivatives (rutin) by DPBH, CAN, or dioxygen in protic and aprotic solvents has shown that quercetin radicals quickly disproportionate to generate quercetin and produce a quinone.[79] This quinone adds water molecules and is then degraded. Oligomerization might be a minor route in media of low water content. Oxidation of quercetin–serum albumin complex retarded water to the quercetin quinone. The role of the quercetin 3-OH was established as follows: (1) allows the formation of *p*-quinonoid compounds, quickly converted into solvent adducts which still react with one-electron oxidants, and (2) in its deprotonated form stabilizes radicals, allowing autoxidation to proceed under mild conditions.



quercetin

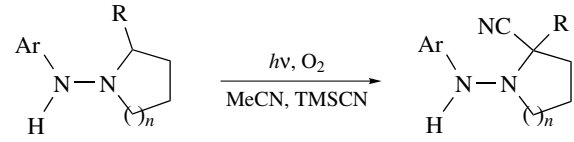
The photo-oxidation of the aryl-substituted cycloheptatrienes 7-(*p*-methoxyphenyl)cycloheptatriene and 7-, 1- and 3-(*p*-dimethylaminophenyl)cycloheptatrienes to the corresponding radical cations in de-aerated acetonitrile solution was accomplished by electron transfer to the electronically excited acceptors 9,10-dicyanoanthracene, *N*-methylquinolinium perchlorate, *N*-methylacridinium perchlorate and 1,1′-dimethyl-4,4-bipyridinium dichloride.[80] In the case of 7-(*p*-methoxyphenyl)cycloheptatriene (**62**), deprotonation of the radical cation occurs successfully, compared with back electron transfer, to give a cycloheptatrienyl radical (**63**) which undergoes a self-reaction forming a bitropyl. If the photo-oxidation is done in air-saturated acetonitrile solution containing HBF_4 and one of the acceptors, the tropylium cation is formed. Back electron transfer dominates in the *p*-dimethylaminocycloheptatrienes and the formation of the cycloheptatrienyl radical is prevented.



(**62**) (**63**)

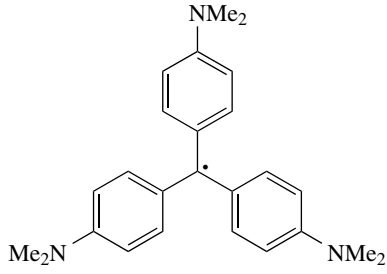
Photo-oxidation of 1,1-dialkyl-2-arylhydrazines by single-electron transfer with trimethylsilyl cyanide (TMSCN) as cyanide ion source leads to regio- and stereoselective α-hydrazino nitriles.[81] This stereoselective cyanation of hydrazines takes place on the more substituted carbon atom compared with the results obtained with tertiary amines (Scheme 5).

The reductive dehalogenation of polyfluoroarenes by zinc in aqueous ammonia gave products derived from the removal of one or two halogen atoms.[82] A radical anion is suggested to form initially by direct electron transfer from the zinc to substrate which then fragments. C_{60} undergoes single-electron reduction by the electron-rich,



R = H, Me; n = 1,2

SCHEME 5

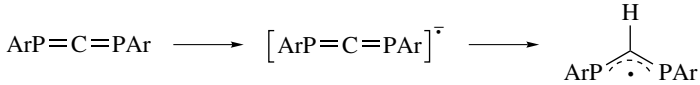


(**64**)

sterically hindered Crystal Violet radical (**64**) leading to a carbocation–carbanion salt $(\mathbf{64})^{+}(C_{60})^{\bullet-}$ which is stable in solution and in the solid state.[83]

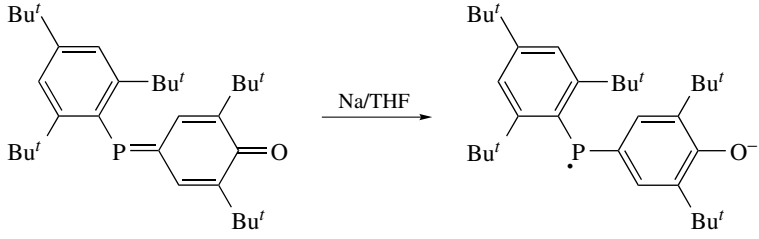
First-order kinetics have been found for the reductions of pinacolone by borane-dimethyl sulfide in THF, which proceeds via a monoalkoxyborane complex.[84] In contrast, the kinetics were second order for the reduction with catecholborane and the reactive species was found to be a catecholborane dimer present in small concentrations.

The reduction of several phosphaallenes has attracted a lot of attention. Bis(2,4,6-tri-*t*-butylphenyl)-1,3-diphoshaallene (**65**) was electrochemically reduced in THF to give diphosphaallyl radical (**67**), which would originate through protonation of the radical anion (**66**) immediately after its formation. The radical (**67**) was identified by EPR spectroscopy and was supported by DFT calculations.[85] Monophosphaallene $ArP{=}C{=}C(C_6H_5)_2$ (Ar = 2,4,6-*t*-$Bu_3C_6H_2$) underwent irreversible reduction to the neutral monophosphaallylic radical Ar-$\dot{P}$-CH=CPh_2 as shown by EPR. Comparison of the hyperfine tensors with those obtained from *ab initio* calculations for the radical anion $(HP{=}C{=}CH_2)^{\bullet-}$ and the monophosphaallylic radical $(H\dot{P}{-}CH{=}CH_2) \leftrightarrow (HP{=}CH{-}\dot{C}H_2)$ indicate that the species observed by EPR is the monophosphaallylic radical Ar$-\dot{P}-$CH=CPh_2.[86] The radical anion of *p*-phosphaquinone was successfully



(**65**) (**66**) (**67**)

generated *in situ* by reduction with Na in THF (Scheme 6). Comparison of the isotropic and anisotropic coupling constants of the radical anion with those of the phosphorus atoms suggest that about 2% and 64% of the unpaired electron are localized on the 3*s* and 3*p* orbitals of phosphorus, respectively.[87]



SCHEME 6

The reductive cleavage of iodobenzene and 3-methyliodobenzene was studied by cyclic voltammetry in both DMF and acetonitrile at 21 and 56 °C at different scan rates and has shown that there is a transition between stepwise and concerted mechanisms at lower scan rates. 1-Iodonaphthalene undergoes a stepwise reductive cleavage with mixed kinetic control by electron transfer and follow-up bond breaking, whatever the scan rate.[88]

The kinetics of hydride and organometallic additions to benzaldehyde-H and -D were determined at −78 °C using a variety of hydride reagents, Grignard reagents and organolithiums.[89] The additions of hydride, methyl-Grignard reagents, and methyl- and phenyl-lithiums showed an inverse deuterium kinetic isotope effect. Little effect was observed was observed with phenyl-Grignard and *n*-butyl- and *t*−butyl-lithium. Allyl-Grignard and allyllithium showed a normal secondary deuterium effect. The results showed that the rate-determining single-electron transfer occurs with allyl reagents but direct nucleophilic reaction occurs with all other reagents. The extent of bond formation is dependent on the reactivity of the reagent.

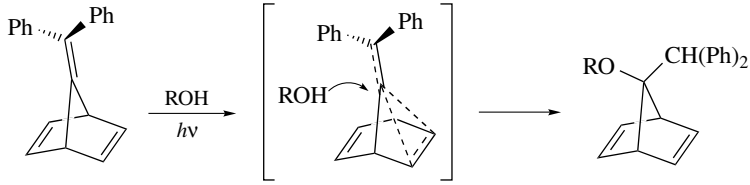
Electron-transfer Reactions

Photo-induced Electron Transfers

Photo-induced electron-transfer decarboxylation reactions have been reviewed.[90] A variety of methyl- and methoxy-substituted phenol radical cations have been generated by either photo-induced electron transfer or photo-ionization in dry solvents such as acetonitrile.[91] In the presence of small amounts of water the radical cations are not detected and the phenoxyl radical is the only transient species observed. The 2-methoxyphenol radical cation was found to be more reactive than the 4-methoxy radical cation.

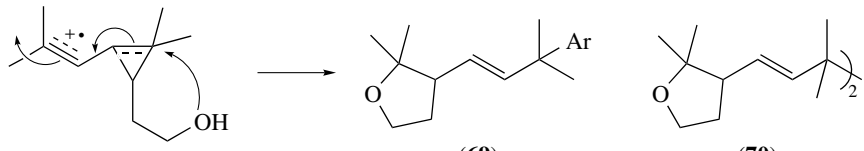
The reactivity and π-facial selectivity of CH_3OH and H_2O additions to the radical cations of 7-benzhydrylidenenorbornene derivatives (**68**), generated by photo-induced

electron transfer, were investigated. It was found that, amongst the $\pi-\pi$ interactions in the radical cations of 7-benzhydrylidenenorbornene derivatives, the interaction between the 7-benzhydrylidene group and the *endo* alkene induces efficient nucleophilic capture of a radical cation at the benzhydrylidene group with the *anti* selectivity at the *endo* alkene.[92]



(**68**)

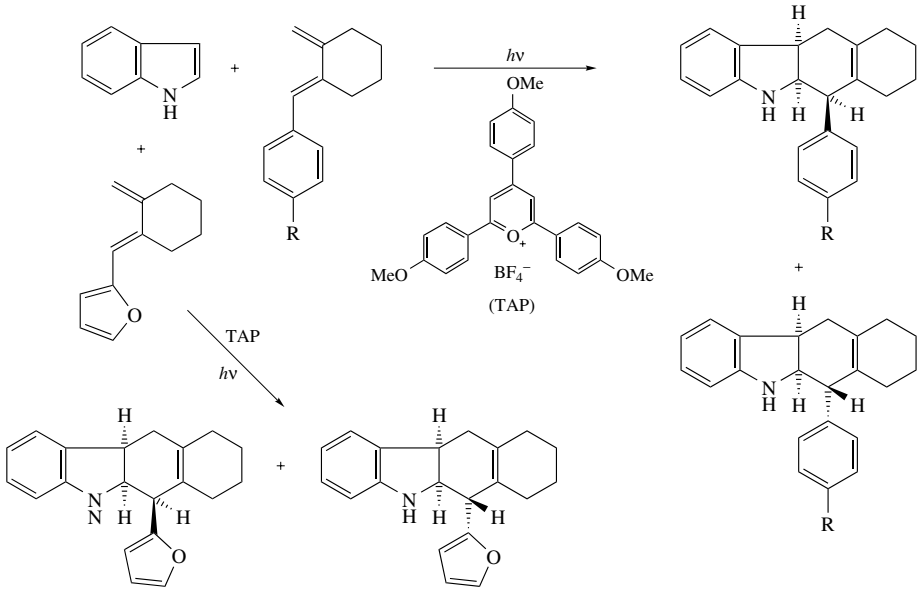
The electron-transfer-induced cyclization of homochrysanthemol proceeds via a five-membered transition state, from intramolecular substitution at the quaternary cyclopropane carbon, to generate the five-membered cyclic ethers (**69**) and (**70**).[93] In contrast, the intramolecular photo-induced cyclization of chrysanthemol goes via a six–membered transition state involving attack at the terminal vinyl carbon.



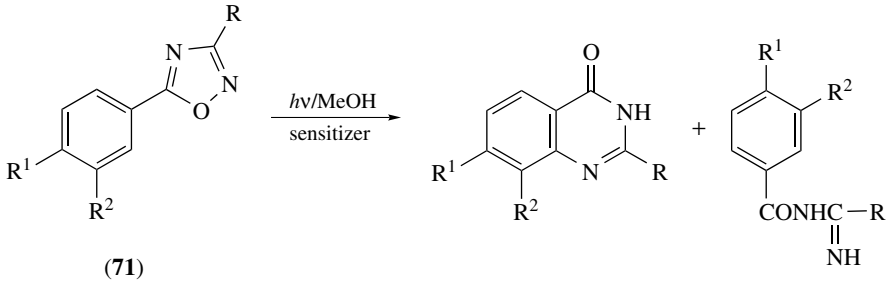
(**69**) (**70**)

Photo-induced electron-transfer radical-cation Diels–Alder reactions of indole with aromatic or heteroaromatic substituted exocyclic dienes using tris(4-methoxyphenyl)pyrylium tetrafluoroborate as a catalyst proceed with complete regioselectivity to form [*b*]-annelated tetrahydrocarbazoles (Scheme 7). The regio- and diastereo-selectivities were rationalized using potential energy surface calculations. The mechanism and the potential energy hypersurface of the radical-cation Diels–Alder reaction was investigated using quantum chemical methods. The potential surface demonstrates non-synchronous and non-concerted reaction pathways. The energies of the different long-bond intermediates have been calculated with semiempirical molecular and density-functional methods.[94]

A photo-induced electron transfer (from either the sensitizer in its excited state to the oxadiazole in its ground state or from the electron-donor reagent such as triethylamine to the excited oxadiazole) has been suggested as an explanation for the breaking of the O–N bond of 5-aryl-3-methoxy-(or 5-aryl-3-phenyl-)-1,2,4-oxadiazoles (**71**) upon irradiation.[95] The resulting oxadiazole radical anion underwent either a heterocyclization to give quinazolin-4-ones or reduction to give open-chain products.



SCHEME 7



(**71**)

Other Electron Transfers

The kinetic isotope effect in the one-electron transfer from 1-benzyl-1,4-dihydronicotinamide to 9-fluorenylidenemalononitrile was studied and the rate constants of the reactions were calculated.[96] The electron affinities (EA) for a series of methyl benzoates, acetophenones, benzaldehydes, and benzophenones were determined by applying the electron-transfer equilibrium method in the gas phase.[97] The substituent effect on the stability of aromatic radical anions has been analysed.

ESR, IR and Raman spectroscopic studies on the $^{14}N/^{15}N$ and $^{12}C/^{13}C$ equilibrium isotope effects on the electron-transfer reaction between *N*-methylphenothiazine and the radical cation of its ^{15}N- and/or *N*-^{13}C-methyl-substituted analogues have been reported.[98] ^{15}N and ^{13}C substitution of methylphenothiazine increases the ionization potential of the molecule, making it difficult to lose an electron to form the corresponding radical cation.

Evidence of a single transfer process from the nucleophile to the aromatic substrate has been found for the nucleophilic aromatic substitution (S_NAr) reaction of different polynitrobenzenes with nucleophiles such as alkoxides, thiolates, and tertiary amines.[99] The two radical species that are generated within the solvent cage have been detected by EPR spectroscopy. *Ab initio* calculations have been performed in the investigation of the electron transfer reaction between biphenyl radical anion and neutral biphenyl.[100] Aromatic compounds substituted with an electron-donating group, such as methoxy, hydroxy, or amino, were regioselectively iodinated with iodine in the presence of tetrabutylammonium peroxodisulfate in CH_3CN via an electron-transfer mechanism.[101] The *p*-positions of methoxybenzenes and phenols were exclusively iodinated whereas *o*-iodination only occurred when the *p*-position was blocked.

Chlorides RMe_2CCH_2Cl [(a) R = Me, R = Ph and (b) R = CH_2Ph] reacted with diphenylphosphide ions in liquid ammonia, via a proposed $S_{RN}1$ mechanism and their reactivities were measured. The higher reactivity of (a) has been attributed to efficient intramolecular electron transfer from the phenyl ring to the C−Cl σ^* bond (intra-ET catalysis). The lower reactivity of (b) is ascribed to a decrease in the rate of the intra-ET by elongation of the bridge by one methylene unit. The relative reactivity of (a) versus (b) is proposed to indicate the ratio of the intra-ET rates of the radical anions of both compounds.[102]

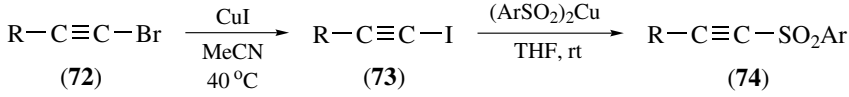
Chloride dioxide (ClO_2) forms red charge-transfer complexes with piperidine and imidazoline nitroxyl radicals that slowly transform into oxoammonium salts.[103]

The aminium salt-induced cyclodimerization of stilbenes in 1,1,1,3,3,3-hexafluoropropanol gave mixtures of indane and tetrahydronapthalenes. The solvent effects are consistent with an electron-transfer mechanism via a radical cation.[104]

The Patterno–Buchi coupling of various stilbenes (S) with chloroanil (Q) to yield *trans*-oxetanes is achieved by the specific charge-transfer photo-activation of the electron donor–acceptor complexes (SQ). Time-resolved spectroscopy revealed the (singlet) ion–radical pair[$S^{+\bullet}$, $Q^{\bar{\bullet}}$] to be the primary reaction intermediate and established the electron-transfer pathway for this Patterno–Büchi transformation. Carbonyl quinone activation leads to the same oxetane products with identical isomer ratios. Thus, an analogous mechanism is applied which includes an initial transfer quenching of the photo-activated (triplet) quinone acceptor by the stilbene donors resulting in triplet ion–radical pairs.[105]

The electron-transfer reactions between the β-cyclodextrin (β-CD) *N*-substituted phenothiazine derivatives and β-CD.ATPO (4-acetoxy-2,2,6,6-tetramethyl-1-oxopiperidinium hexachloroantimonate) were found to be influenced by the conformations of the phenothiazine derivatives restricted by the β-CD cavity. *N*-Phenylphenothiazine (PPT) and *N*-phenylethylphenothiazine (PEPT), included by β-CD, can transfer an electron to the β-CD.ATP complex. No electron transfer was observed between the β-CD.*N*-benzylphenothiazine (β-CD.BPT) complex under the same conditions. The conformation of the β-CD.BPT complex is such that the oxidation centre was shielded by the β-CD wall and the substituent. However, electron-transfer reactions between γ-CD.BPT and β-CD.ATP and nitric acid occurred.[106]

Copper iodide acts as an efficient reagent for the nucleophilic displacement of 1-haloalkynes. It transforms 1-bromoalkynes (**72**) into 1-iodoalkynes (**73**) which, on further treatment with copper(II) bis(arenesulfinate), are converted into the corresponding alkynyl aryl sulfones (**74**).[107] An electron transfer between 1-haloalkynes and copper(I) salts is believed to take place for the copper-assisted halogen-exchange reaction at the acetylenic carbon atom.

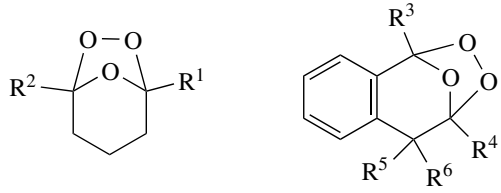


(**72**) (**73**) (**74**)

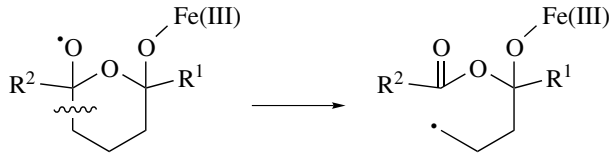
Substituent effects on the electron-transfer processes between pyrrolidinofullerenes and tetrakis(dimethylamino)ethylene (TDAE) were studied in both the ground state and excited triplet state.[108] Equilibrium constants and rate constants for forward and backward electron-transfer processes in the ground state, in addition to rate constants of the forward electron transfer in the excited triplet state were measured.

An inner-sphere electron reduction has been proposed as a possible mechanism for the Fe(II)-induced decomposition of 1,2,4-trioxolanes (ozonides) (**75**) and (**76**).[109] Benzoic acid was found to be the major product. The nucleophilic Fe(II) species attack the ozonide from the less hindered side of the electrophilic O—O σ^* orbital to generate exclusively the Fe(III) oxy-complexed radical (inner-sphere electron transfer). After selective scission of the C—C bond, the resulting carbon-centred radical produced the observed product. The substituent effect determine the regioselective generation of one of the two possible Fe(III)-complexed oxy radicals. The bond scission shown will occur if R^2 is bulkier than R^1.

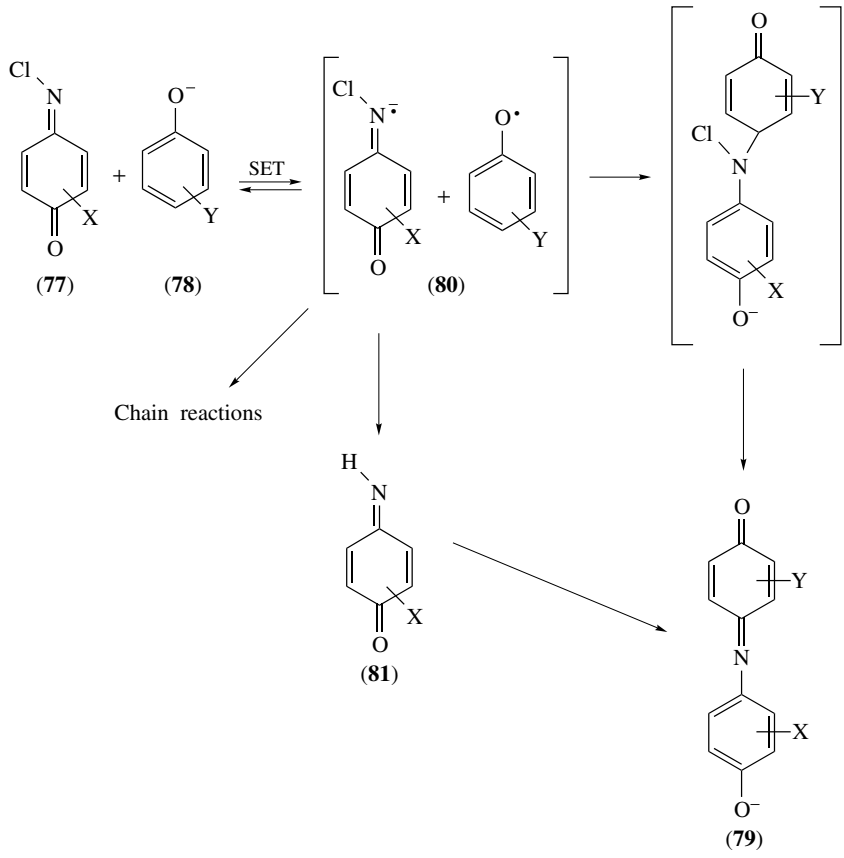
The mechanism of the Gibbs reaction has been investigated.[110] It has been concluded that *N*-chloroimine radical anion (**80**), generated in a single-electron transfer



(**75**) (**76**)



from the anion of phenol (**78**) to *N*-chloroimine (**77**), can produce indophenol dye (**79**) in three distinct routes. For more reactive reagents/substrates, a fast combination of the radical pair in the solvent cage is involved. For less reactive reagents, the *N*-chloroimine radical anion (**80**) escapes the solvent cage to initiate a chain reaction. The mechanism of the chain reactions has been termed $S_{RN}2$. In the case where the anion of (**80**) is less active, a competitive reaction along a third route can proceed in which the haloimine radical anion (**80**) yields a benzoquinone imine (**81**) by elimination of halide and the abstraction of an H-atom from the medium. Compound (**81**) could also give indophenol.



Radical Cations

A review considering the generation and characterization of radical ions, their reactions, formation of species with three-electron bonds, and radical cations of strained systems has been published.[111] The redox and acidity properties of a number of substituted benzene radical cations were studied by pulse radiolysis.[112]

Radical cations of toluene, *p*-, *o*-, and *m*-xylene and their deuteriated analogues, generated in $CFCl_3$ and CF_3CCl_3 matrices by X-irradiation, have been investigated by ESR and high-resolution ENDOR spectroscopy.[113] The ESR and ENDOR spectra are dominated by large axially symmetric hyperfine splitting due to methyl group protons. The hyperfine coupling constants of methyl and ring protons for toluene and *p*-xylene were accurately measured by ENDOR spectroscopy. Theoretical calculations of the isotropic and dipolar hyperfine coupling constants were in agreement with experiment. From spin-density calculations, the methyl-substituted benzenes were classified in two groups: toluene and *p*-xylene are of the $^2B_{2g}$ and *o*- and *m*-xylene are of the $^2B_{1g}$ type. The hybrid density-functional method B3LYP and the cc-pVDZ basis set have demonstrated that the naphthalene radical cation isomerizes to azulene radical cation via the Dewar–Becker mechanism at energies lower than its dissociation limit for acetylene elimination. The hydrogen-shifted naphthalene isomer is a proper intermediate whereas the norcadiene isomer of the Dewar–Becker mechanism was found to be a transition structure in the ionic system.[114]

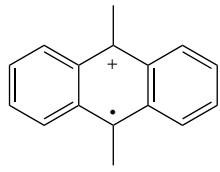
Ab initio calculations have been used to determine the parameters that govern the rate of spin-forbidden interconversion of the triplet and singlet states of a series of *p*-X-substituted aryl cations (X = H, CN, CH_3, F, OH, NH_2). The cations, where X = H, CN, CH_3 and F, were found to be ground-state singlets; X = NH_2 has a triplet ground state and the OH derivatives were almost isoenergetic. The minimum-energy crossing points between the two surfaces were found to lie very little above the higher of the minima in all cases and spin–orbit coupling was significant at these points. Therefore, it is expected that aryl cations will rapidly convert into their most stable spin states, and in the case of near degeneracy, such as for *p*-$HOC_6H_4^+$, the states may interconvert rapidly enough to be accessible in thermal reactions.[115]

The regio- and diastereo-selectivities in the rearrangement or strained cyclopentane-1,3-diyl radical cations, generated by electron transfer, and the mechanism of this novel 1,2-migration have been reviewed.[116] A different theoretical study of the 1,2-rearrangement of housane radical cations suggested that the ground-state potential-energy surface of the housane radical cations is centred around a conical intersection at a planar, symmetric cyclopentane-1,3-diyl symmetry.[117] The computations show that the reaction proceeds in two steps: breakage of the one-electron bond of the reactants, which produces the asymmetric, quasi-planar intermediate, and subsequent 1,2-rearrangement, which is essentially barrierless. The reaction results in the selective 1,2-migration of the original *endo* substituent of the reactant.

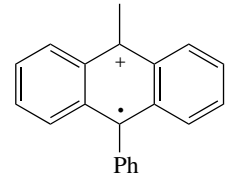
A number of papers have reported studies on pyrimidine radical cations. 1-Methylthymine radical cations generated via a triplet-sensitized electron transfer to anthraquinone-2,6-disulfonic acid were detected by Fourier transform electron paramagnetic resonance (FTEPR). The parent 1-methylthymine radical cation, and its transformation to the N(3)-deprotonated radical cation, were observed. Radical cations formed by addition of HO^- and PO_3^- at C(6) were also detected depending on the pH.[118] Similarly, pyrimidine radical cations deprotonated at N(1) and C(5)-OH were detected from the reaction of $SO_4^{\bullet-}$ with various methylated pyrimidines.[119] These radicals are derived from the initial $SO_4^{\bullet-}$ adducts of the pyrimidines. Radical cations of methylated uracils and thymines, generated by electron transfer to parent ions of

solvents such as *n*-butyl chloride and acetone, have also been detected. They show a transient tautomerism and exist in *n*-butyl chloride in the lactam and in acetone in the lactim form.[120] A kinetic study of the proton-transfer reactions between methylarene radical cations (**82**) and (**83**) and pyrimidine bases implicated a mechanism in which a complex is first formed that then undergoes proton transfer, followed by separation of the product.[121]

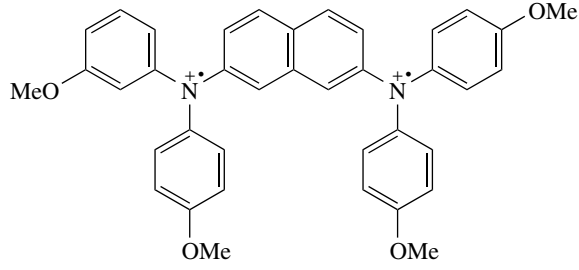
2,7-Diaminonapthalene radical dications (**84**) and (**85**) were prepared by oxidation of the equivalent amines.[122] Oxidation with thianthrenium perchlorate yielded ESR-active solutions. The ESR studies and effective magnetic moment measurements suggest a triplet ground state for ($\mathbf{84}^{2+}$) whereas ($\mathbf{85}^{2+}$) has a possible singlet ground state in $CDCl_3$ at 30 K. The thianthrene cation radical perchlorate ($Th^{+\bullet}ClO_4^-$) adds to



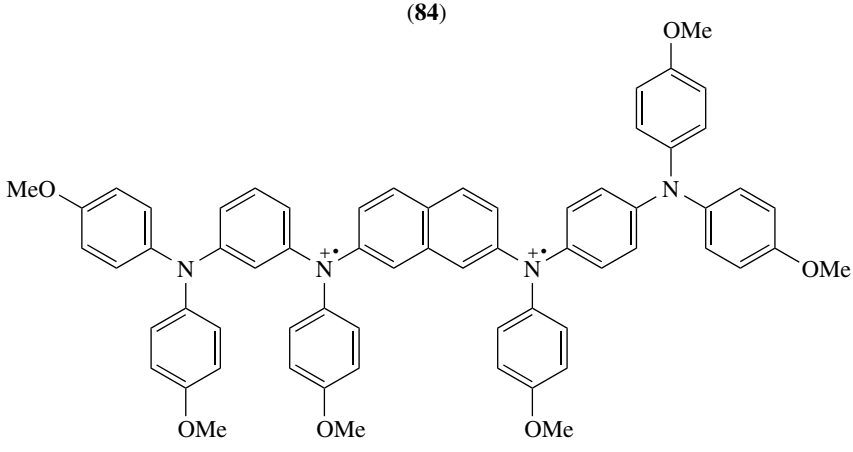
(**82**)



(**83**)



(**84**)



(**85**)

cyclostomes to give the monadic 1,2-(5,10-thianthrenium-diyl)cyclostomes. Addition of $Th^{+\bullet}ClO_4^-$ to cyclopentene and cycloheptene gave mixtures of mono- and bis-adducts, the monoadduct to a small extent for the former (17%) and a large extent (50%) for the latter.[123]

The tricyclopropylamine radical cation has been generated by γ-irradiation of cyclopropylamine in a mobile $CF_2ClCFCl_2$ matrix and was studied by EPR.[124] A planar geometry at the nitrogen atom has been revealed. The minimum-energy geometry has a C_{3h} symmetry with the three cyclopropyl groups in the bisected orientation. The geometries of the radical cations of cyclopropyldiisopropylamine, di-*t*-butylcyclopropylamine, dicyclopropylisopropylamine, and tricyclopropylamine were examined by ESR spectroscopy. All the radical cations were shown to be planar. Amines that have cyclopropyl substituents assume a perpendicular conformation in the neutral amines and a bisected orientation in the corresponding radical cations.[125]

Exposure of dilute solutions of triethylamine–boron hydride (Me_3N-BH_3) in Freon ($CFCl_3$) to ionizing radiation gave a radical cation whose EPR spectrum was that of the radical cation ($Me_3N-BH_3^{+\bullet}$). Electron loss from B–H bonds is clearly favoured over loss from the N–B bond.[126] The gas-phase reactions of the methylamine radical cation with mono- and di-haloethenes occur by substitution of one halogen substituent and by formal hydride abstraction yielding the ion $(H_2CNH_2)^+$ and a halogenated ethyl radical as products.[127] High-level *ab initio* calculations were carried out to establish the minimum-energy path of the reaction of methylamine radical cation and chloroethene along both reaction channels. EPR spectra have been obtained for the radical cations of a series of fluorinated ethylenes and propenes that were generated by irradiation with γ-rays in solid halocarbon matrices.[128] The spectra consist of a hyperfine structure with a nearly axial symmetry due to fluorine nuclei. The trifluoroalkene cations $CF_2{=}CFX^+$ ($X = H$, CH_3) have a planar structure. For the mono- and di-fluoroalkene radical cations the optimized geometry was calculated by an *ab initio* MO method. The results show that fluorinated ethene and propene cations have planar structures.

Ab initio molecular-orbital calculation on the isomerization of $[C_3H_5N]^{+\bullet}$ radical cation reveal that acetonitrile-*N*-methyl $[CH_3-CN-CH_2]^{+\bullet}$ and *N*-methylketenimine $[CH_3-NC-CH_2]^{+\bullet}$ are the most stable species among the 15 isomers considered.[129] The study revealed that the two isomers constituted distinct species in the gas phase and that isomerization takes place prior to dissociation during high-energy CID experiments. Methoxy isothiocyanate $(CH_3ON{=}C{=}S)^{+\bullet}$ and methyl cyanate *N*-sulfite ($CH_3OCN^+-S^-$) radical cations, derived from dissociative ionization of heterocyclic precursors, have been fully characterized by mass spectrometric methods in the gas phase.[130]

The effects of temperature on the shape of intervalence charge-transfer bands for the radical cations of bis(2-*t*-butyl-2,3-diazabicyclo[2.2.2]oct-3-yl)hydrazines that are bridged by 2,5-xylene-1,4-diyl, durene-1,4-diyl, naphthalene-1,4-diyl, biphenyl-4,4-diyl and 9,9-dimethylfluorene-2,7-diyl aromatic rings were studied by ESR.[131]

The X-ray crystal structure of the hexafluoroantimonate salt of 1,4-diithin radical cation stabilized by bicyclo[2.2.2]octane annelation revealed a planar ring and was in agreement with theoretical calculations.[132] Tertiary aminium radical cations underwent facile 5-*exo*-cyclization to give distonic 2-substituted pyrrolidinium radical cations.[133]

These can be further oxidized to 1,3-dications and trapped by nucleophiles such as water, alcohols, or chloride ion.

The metastable dimethoxyethane radical cation $[CH_3OCH_2CH_2OCH_3]^{+\bullet}$ eliminates methanol to give a $[C_3H_6O]^{+\bullet}$ fragment.[134] The reaction involves a sequence of 1,4-H shift, leading finally to the radical cation $[CH_3\overset{+}{O}(H)CH_2\dot{C}HOCH_3]$, which eliminates methanol to give $[CH_2CHOCH_3]^{+\bullet}$.

The radical cation of 2,5-dimethylhexa-2,4-diene was generated and some of the Raman spectrum bands were assigned using theoretical methods such as UHF, CASSCF, UBLYP and UB3LYP procedures. A small amount of the less stable *gauche* conformer of the radical cation was identified and its bands assigned.[135] *Ab initio* calculations on the isomerization of butene and pentene radical cations indicate that the lowest barrier for a rearrangement to the most stable ion structure is below the dissociation limit.[136] The linear butene radical cation isomerizes to the isobutene via the $(CH_3CC_2H_5)^{+\bullet}$ structure, whereas in the pentene case the isomerizations proceeds via the 1,2-dimethycyclopropane radical cation.

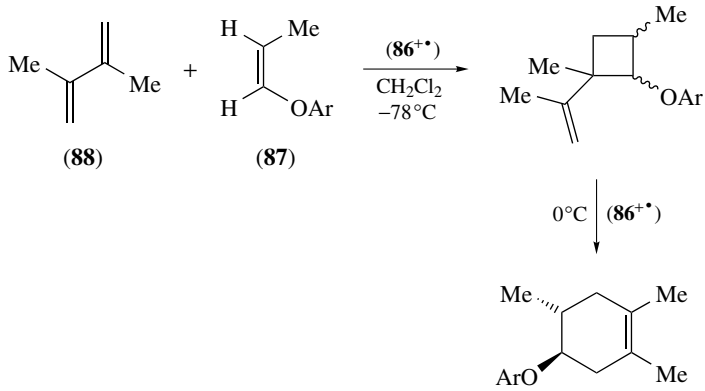
The gaseous dichlorocarbene radical cation reacted with alkyl halides via a fast electrophilic addition to form a covalently bonded intermediate $(Cl_2C{-}X{-}R)^{+\bullet}$ in a Fourier transform ion cyclotron resonance mass spectrometer.[137] This intermediate fragments either homolytically or heterolytically to produce net halogen atom or halogen ion transfer product. Addition of carbonyls to the carbene ion is followed by homolytic cleavage of the C−O bond to yield a new carbene radical cation.

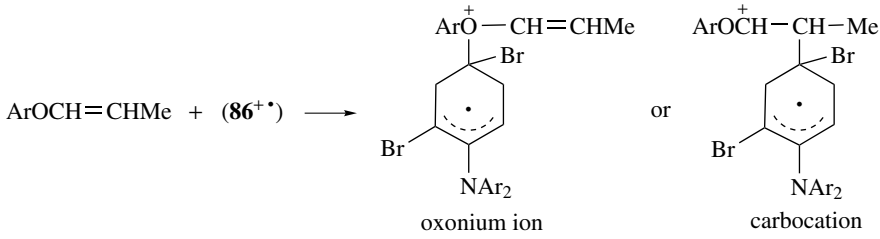
The solvent effects on the ring opening of the cyclobutene radical cation by implementation of the polarizable continuum model have been studied.[138] The authors concluded that the reaction leads directly to *trans*-butadiene radical cation via a cyclopropenyl-carbinyl type of radical cation, in contrast to expectations of a normal 'electrocyclic' pathway leading to *cis*-butadiene radical cation. MO and DFT calculations on the 2 + 2-cycloreversion reaction of the cyclobutane radical cation have revealed three distinct but energetically similar structures for the radical cation: a parallelogram that corresponds to the minimum, on the Jahn–Teller surface, a rhombus, corresponding to a transition structure connecting two parallelograms, and a rectangle that is a second-order saddle point. The reaction was shown to proceed in a concerted fashion, and is not consistent with a putative acyclic intermediate, but the two ethylene fragments are brought relative to each other. The transition structure connects the product complex to the parallelogram structure of the cyclobutane radical cation.[139]

Reaction pathways for the addition of ethylene to butadiene radical cation involving H-shifts have been investigated at the coupled cluster UCCSD(T)/DZP//UMP2(fc)/DZP + ZPE level of theory.[140] Several rearrangement reactions have been found to occur below the energy limit of separated ethylene and butadiene radical cation. The cyclopentenyl cation $(C_5H_7)^+$ in the gas phase may originate from various pathways.

The Diels–Alder reaction of either *m*- or *p*-substituted aryl *cis*-prop-1-enyl ethers (**87**) with 2,3-dimethylbutadiene (**88**) catalysed by tris(2,4-dibromophenyl)aminium hexachloroantimonate (**86**$^{+\bullet}$) at 0 °C are non-stereospecific and occur via an indirect Diels–Alder reaction.[141] When the reaction is carried out at −78 °C, the vinylcyclobutane adducts are observed and these are efficiently converted into the

Diels–alder adducts at 0 °C. This cation radical–vinylcyclobutane rearrangement is non-stereospecific, thus accounting for the formation of a *cis–trans* mixture of Diels–Alder adducts. Kinetic studies revealed (Scheme 8) that the ionization of these ethers involves an inner-sphere electron-transfer mechanism involving strong covalent (electrophilic) attachment to the substrate via oxygen (oxonium ion) or carbon (carbocation).

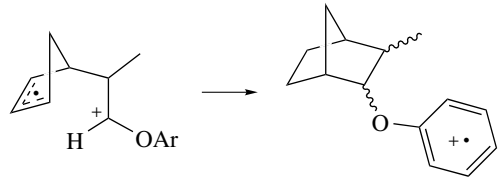




SCHEME 8

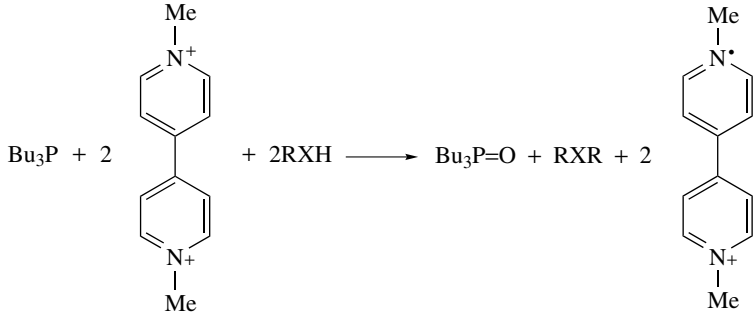
The cation radical Diels–Alder cycloadditions of *cis*- and *trans*-prop-1-enyl aryl ethers to cyclopenta-1,3-diene catalysed by tris(4-bromophenyl)aminium hexachloroantimonate are stepwise processes involving an intermediate distonic cation radical in which the carbocationic site is stabilized by the electron-donating functionality (Scheme 9).[142]

A cation radical chain cycloaddition–polymerization catalysed by tris(4-bromophenyl)aminium hexachloroantimonate has been reported to afford polymers with an average molecular weight up to 150 000. Both cyclobutanation and Diels–Alder polymers were obtained.[143] The reactivity of the phospine radical cation towards nucleophiles was studied. Tributylphosphine reacted with 1,1-dimethyl-4,4-bipyridinium (methyl viologen, MV) in the presence of an alcohol or thiol (RXH; X = O, S), which resulted in the gradual formation of the one-electron reduced form



SCHEME 9

of the MV (Scheme 10). Tributylphosphine was oxidized to the tributylphospine oxide. The increase in the amount of the MV^+, which was followed spectrophotochemically and with tributylphosphine and RXH in excess, did not follow first-order kinetics. A single-electron transfer takes place from tributylphosphine to MV, to generate tributylphospine radical cation and MV^+. The resulting phosphine radical cation undergoes ionic reaction with RXH and back electron transfer from MV^+ with comparable efficiency. The kinetic data show that the reaction of the tributylphosphine radical cation with nucleophile RXH is governed by both electronic and steric factors.[144]



SCHEME 10

Transformations of the radical cations of 2,3- and 2,5-dihydrofuran (DHF), radiolytically generated in Freon matrices, were investigated by low-temperature EPR. The 2,3-$DHF^{+\bullet}$ radical cation is stable at 77 K but at higher temperatures is transformed into dihydrofuryl radical, $DHF^{\bullet}$. The oxygen-centred radical cation 2,5-$DHF^{+\bullet}$ is unstable at 77 K and transforms via an intramolecular H-shift into a transient distonic radical cation 2,4-$DHF^{+\bullet}$ which at higher temperatures yields the $DHF^{\bullet}$ radical.[145]

Radical Anions

EPR was used for the determination of equilibrium constants K_1 for

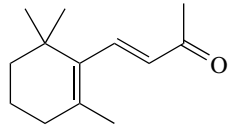
$$Q + QH_2 \rightleftharpoons Q^{-\bullet} + Q^{-\bullet} + 2H^+$$

from a steady-state concentration of semiquinones ($Q^{\bullet -}$) in mixtures of 11 alkyl-, methoxy-, and chloro-substituted 1,4-benzoquinones and 1,4-naphthaquinone (Q) and hydroquinones (QH_2).[146]

Rate constants K_H for proton transfer from a series of substituted phenols to anthracene and phenanthrene radical anions formed in DMF have been measured by the voltammetric method. The homolytic bond dissociation energy D for $ArH^{\bullet} \rightarrow Ar + H^{\bullet}$ was evaluated and the values were in agreement with experiment.[147] Cyclic voltammetry and EPR spectroscopy have shown that the stability of the anion radicals of dialkylbenzene-1,3-dicarboxylates, dialkyl pyridine-2,6-dicarboxylates, and their corresponding dithio-*S*, *S*−diesters is due to a reversible dimerization mechanism. The EPS data confirmed the existence of relatively stable anion radicals formed from one-electron reduction of the diesters, the simple spectra of which suggested that the radicals responsible were the primary anions.[148] The solvent-induced intramolecular electron-exchange (IEE) reaction within the conjugated 1,4-dinitrobenzene radical anion has been studied in linear alcohols.[149] The rate constants were determined from alternating line-broadening effects in EPR spectra and were found to be smaller than the rate constants for the 1,3-dinitrobenzene radical anion due to the conjugation of the nitro groups. A semiempirical AM1 study of the fragmentation of the radical anions of *o*-, *m*-, and *p*-halonitrobenzenes and some alkyl-substituted derivatives in relation to their $\sigma-\pi$ orbital isomerism and the energy of their interconversion was reported.[150]

The solvent effects on the C−Cl bond cleavage in the aromatic radical anions of 9-chloroanthracene, 3-nitrobenzyl chloride, and 3-chloroacetophenone were described by applying the Savéant model.[151] The results showed that the bond dissociation energy is not strongly solvent dependent.

An EPR and AM1 molecular modelling study of the structure of the radical anion of β-ionone (**89**) was carried out to investigate the structure and magnetic properties of one-electron transfer reactions of carotenoids. The temperature dependence of the EPR spectrum of the radical anion helped to reassign the coupling constant of 16 G from the 7-*H* to the 4-*H* proton in the axial orientation. The previous assignment failed to account for the rate of the cyclohexene ring inversion. The EPR showed that the coupling for the 7-*H* proton is approximately 9.5 G. The rate of cyclohexene ring inversion in the radical anion was estimated.[152]



(**89**)

The stability of radical anions of disulfides $[RS-SR]^{\bullet -}$ and their ease of dissociation into thiolate anions and thiyl radical were studied as a function of pH with alkyl substituents of different structures:[153]

$$RS^{\bullet} + RS^{-} \rightleftharpoons [RS-SR]^{\bullet -}$$

The radical anion stability increased when protonated amino groups were present and rose with their proximity to the S−S group. The presence of electron-donating methyl groups on the α-carbon caused a small reduction in stability. Ionized CO_2^- groups on the β-carbon reduced the stability significantly. In the absence of protonated amino groups, the strength of the $(S-S)^-$ bond increased with the electron-withdrawing ability of the groups attached to S atoms.

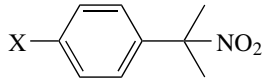
A series of alkoxycyclooctatetraene radical anions was synthesized by lithium reduction of the corresponding ethers in hexamethylphosphoramide. The radical anions of *n*-propoxycyclooctatetraene and ibuprofoxycyclooctatetraene exhibit a small splitting for the γ-proton on the sp^3-hybridized carbon connected to the oxygen atom. The EPR pattern is consistent with a homohyperconjugative interaction involving overlap of the σ-bond to the γ-hydrogen and the π-system of the conjugated cyclooctatetraene ring.[154]

The EPR spectra of electrolytically produced anion radicals of α-aminoanthraquinones were measured in DMF and DMSO. The isotropic hyperfine coupling constants were assigned by comparison with the EPS spectra of dihydroxy-substituted antraquinones and molecular-orbital calculations.[155] Isomerically pure phenylcarbene anion ($PhCH^{\bar{\bullet}}$) has been generated in the gas phase by dissociative electron ionization of phenyldiazirine.[156] $PhCH^{\bar{\bullet}}$ has strong base and nucleophilic character. It abstracts an S atom from CS_2^- and OCS, an N atom from N_2O, and an H atom from $(CH_3)_2NH$, propene, and $(CH_3)_2S$. Nucleophilic displacement of Cl^- from CH_3Cl occurs at a 41% collision rate. It also exchanges both the carbene hydrogen and a hydrogen in the phenyl ring upon reaction with ND_3 and D_2O. The rate constants for the H-atom abstraction reactions of the dichloride radical anion ($Cl_2^{\bar{\bullet}}$) with oxygenated hydrocarbons, ethanol, methanol, propanol, formaldehyde, diethyl ether, tetrahydrofuran, and acetone in dilute aqueous solutions were determined by the laser flash photolysis–long-path laser absorption technique.[157]

Comparison of the standard potentials of the radical anion of three α-nitrocumenes (α-nitrocumene, *p*-cyano-α-nitrocumene and *p*-nitro-α-nitrocumene) revealed that the nitroallyl portion occurs in (**90a**) and (**90b**), while in (**90c**) the electron is added to the nitrophenyl group. It was concluded that homolytic cleavage takes place for the radical anions of (**90a**) and (**90b**) to give nitrite and the cumyl radical whereas the cleavage of radical anion (**90c**) is heterolytic.[158]

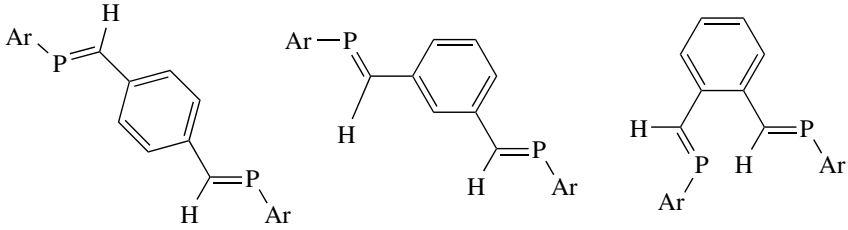
The radical anions of various phenyldiphosphaalkenes (Scheme 11) were studied by EPR.[159] Their reduction is easier than that of monophosphaalkenes and is dependent on the nature of the isomer. Both EPR spectra and DFT calculations showed that in the radical anion the unpaired electron belongs to a π^* orbital and that its delocalization is dependent on the relative position of the two phosphaalkene moieties and on the nature of the bridging group. The spin density on the phosphaalkene carbon is higher for the *meta* compound than for the *ortho* and *para* compounds.

Radical anions of acyclic vicinal oligo-ketones with up to five CO units, generated by reduction of the parent compounds with potassium in the presence of Kryptofix 222, were shown to be extended π-systems by ESR measurements.[160]



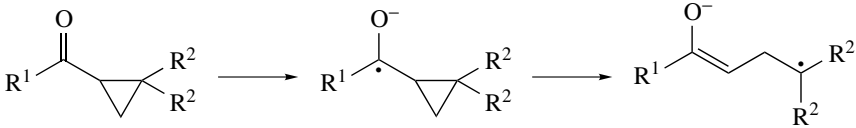
(**90**)

a; X = H
b; X = CN
c; X = NO_2



SCHEME 11

The kinetics of the rearrangement of radical anions derived from aliphatic cyclopropyl ketones (**91**) have been studied by homogeneous redox catalysis and compared with the neutral radicals. For radical anions (**92**), rearrangement is actually faster than that of the free radicals.[161] Placement of a phenyl group on the α-carbon of either a neutral radical or radical anion retards the rate of rearrangement because of delocalization of spin. For the radical ion the delocalization of charge is also important. In the ring-opened form (**93**), the negative charge no longer enjoys the stabilization afforded by the aromatic ring and the radical anion rearrangement is three orders of magnitude slower than that of the neutral radicals. In summary, the delocalization of spin affects the rates of rearrangement, and for radical anions charge plays an important role.



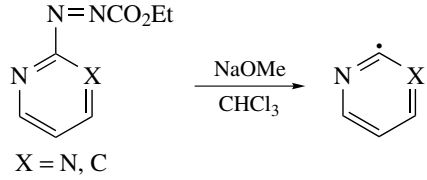
(**91**) (**92**) (**93**)

Biradicals

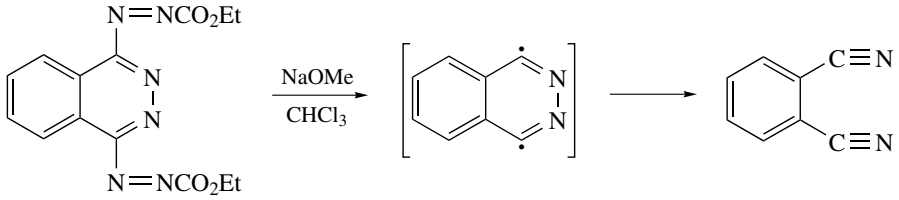
The matrix isolation and spectroscopic characterization of *m*- and *p*-benzynes and their derivatives have been reported.[162] Fourier transform ion cyclotron resonance mass spectrometry has been employed to investigate the reactivity of *m*-benzyne biradical with a pyridinium charge site in the 5-position.[163] The chemical properties of *m*-benzyne in the gas phase differ from those of the monoradical and

o-benzyne. *m*-Benzyne undergoes radical and addition reactions characteristic of *o*-benzyne but is less reactive. This reduced reactivity is rationalized by the strong coupling of the unpaired electrons, which results in a reduced thermodynamic force and increased barrier for radical reactions. The greater distance between the reactive centres in *m*-benzyne hinders alkyne-type addition reactions characteristic of *o*-benzyne.

Aromatic diradicals have attracted a lot of interest since the discovery that 1,4-diradicals are likely to be the key intermediates in the biological action of the enediyne group of anti-tumour antibiotics. A series of heteroaromatic arylazo esters with different numbers of ring nitrogens adjacent to the azo ester have been synthesized and their methanolysis in chloroform has been studied by EPR spectroscopy in order to investigate whether radical intermediates play an essential role in DNA cleavage.[164] Evidence from EPR spectroscopy shows that radicals are formed by methanolysis of the monoazo esters (Scheme 12). Methanolysis of 1,4-bisazo esters has also been studied in an effort to generate a diradical similar to that produced by enediynes. No EPR signal was observed. A diradical has been proposed as an intermediate (Scheme 13). These diradicals have been shown to be unstable and undergo retro-Bergman cyclization to form nitriles. The decomposition product 1,2-dicyanobenzene was isolated in 25% yield and is consistent with a diradical intermediate.



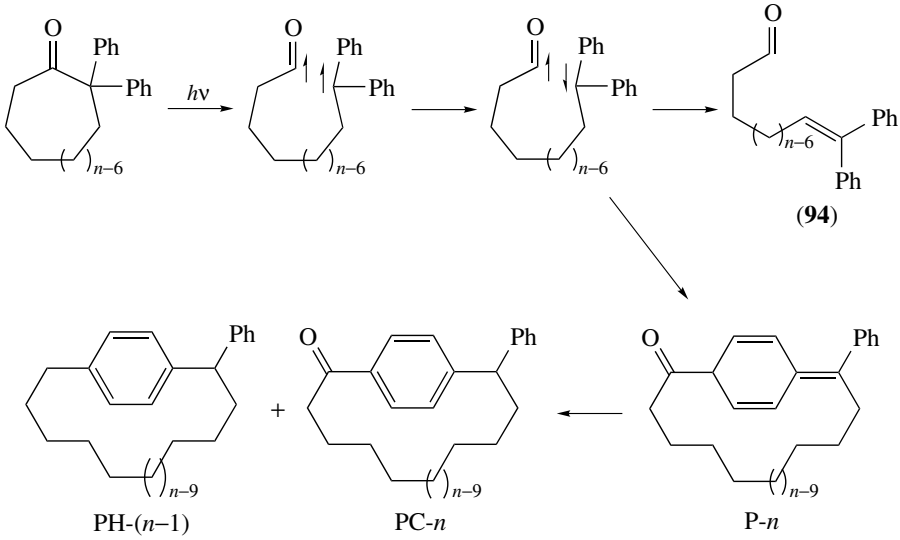
SCHEME 12



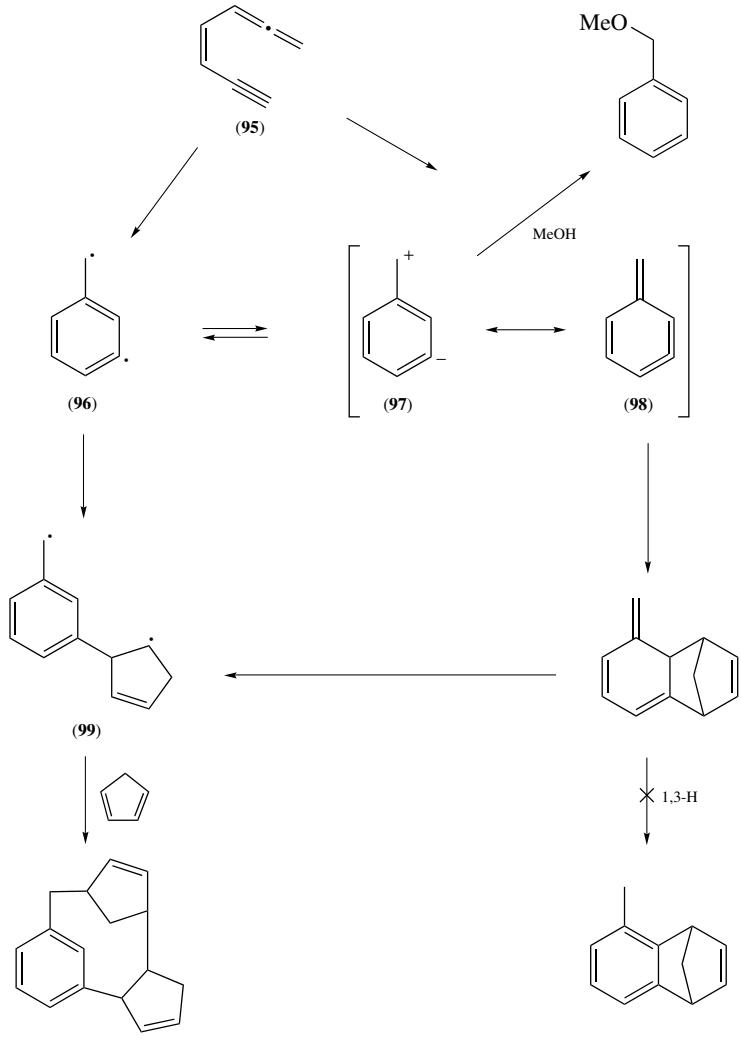
SCHEME 13

The behaviour of triplet acyl–diphenylmethyl biradicals $O{=}C^{\uparrow}{-}(CH_2)_{n-2}{-}C^{\uparrow}Ph_2$, generated from the Norrish type-I reaction of 2,2-diphenylcycloalkanones $(CK)_n$ with various ring sizes, $n = 6$, 7, 9, 11, 12, 13, was the subject of a study. For 2,2-diphenylcycloalkanones where $n = 6$ and 7 an intramolecular disproportionation takes place giving rise to a diphenylalkenal (**94**). The primary products in the photolysis

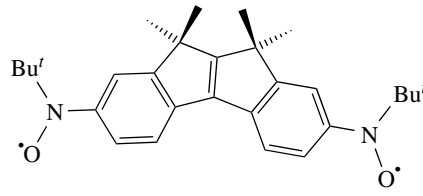
of $(CK)_n$ ($n \geqslant 9$) are the *para*-coupling products of biradicals, 4-methylenecyclohexa-2,5-denienyl ketone $(P)_n$, which are converted thermally into $(PC)_n$ (for $n = 11-13$) or photolysed to give decarbonylation products upon prolonged irradiation $(PH)_{n-1}$.[165]



The Myers–Saito cycloaromatization of enynallenes has been proposed to consist of two parallel mechanisms, one involving a biradical and the other with dipolar character.[166] The competitive trapping experiments with cyclohexa-1,4-diene and cyclopentadiene are incompatible with a single-intermediate mechanism and suggest that there two parallel pathways for the cycloaromatization of (**95**). One pathway involves a biradical (**96**) but the nature of the intermediate is uncertain. MCSCF calculations suggest that a cyclic allene (**98**) is the more likely intermediate. Attempts to trap this cyclic allene with dienes, such as cyclopentadiene, butadiene, and cyclohexadiene, did not give the Diels–Alder cycloadduct. A reaction of one molecule of (**95**) with two molecules of diene was observed. The obvious mechanism involves the sequential reaction of the biradical intermediate with two equivalents of diene to close the macrocycle. It is possible, though, that a Diels–Alder reaction occurred but the bond homolysis in the cycloadduct could lead to the diradical (**99**) that reacted with a second molecule of cyclopentadiene. The zwitterions could be the second intermediate. The solvent effects on the product ratio in more non-polar reaction media support a more polar intermediate but the calculated energies indicate that (**97**) would not be energetically competitive with the biradical (**96**). The authors concluded that the cyclic allene is the most likely second intermediate.



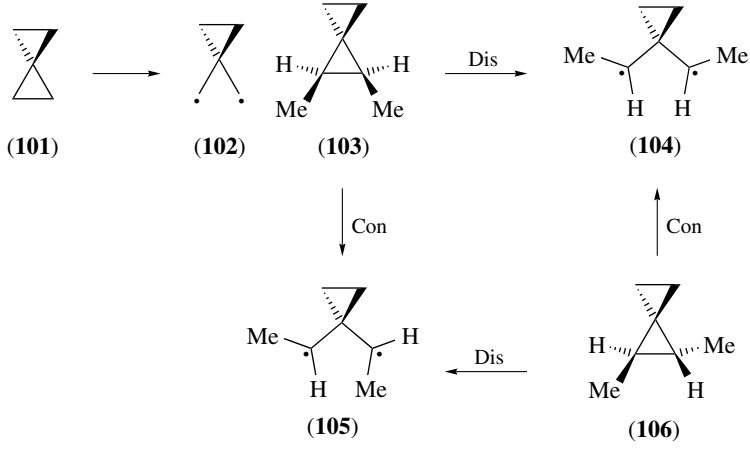
Several trimethylenemethane-type (TMM) dinitroxide diradicals have been prepared that differ in *t*-butylaminoxylphenyl ring-torsion angles by virtue of different steric demands of their 'spin-protecting groups.'[167] A TMM-type dinitroxide (**100**) having a planar π-system was synthesized. EPR spectral characterization revealed that neither N- nor H-hfcc varied. This indicated that there is no apparent relationship between N- or H-hfccs and conformation. All the biradicals, apart from one, exhibited linear Curie plots that are consistent with both triplet ground states and singlet–triplet degeneracies.



(**100**)

4,6-Bis(trifluoromethyl)-*N*,*N*′-di-*t*-butyl-1,3-phenylenebis(aminoxyl) biradical, upon quenching in 2-methyltetrahydrofuran from ambient temperature to 5 K or below, produced the biradical in its singlet state, which slowly converts at low temperatures into the triplet ground state.[168] *Ab initio* calculations on the lowest singlet and triplet states of 2,2-disilylcyclopentane-1,3-diyl indicated the singlet lies well below the triplet.[169] Density-functional calculations indicated that the ground state of the tetramethyleneethane (TME) diradical in the gas phase is the singlet, whereas the triplet state should be metastable. In the vibrational spectra of the two states of TME the symmetric scissoring vibrations have the same frequencies as the vibrational modes of the photoelectron spectrum of the $(TME)^-$ anion.[170]

Ab initio calculations on spiropentane (**101**) and *cis*- and *trans*-1,2-dimethylspiropentanes (**103**) and (**106**) have shown that, in the diradicals (**102**), (**104**), and (**105**) which are formed by the cleavage of the peripheral bond between C(1) and C(2) in the spiropentanes, the weakly electron-donating cyclopropane ring results in conrotation as the preferred pathway for ring opening of (**101**), (**103**), and (**106**),[171] in agreement with experimental results. The calculations indicated that the *s*-*cis*-methyl conformation in diradical (**105**) is lower in energy than the *s*-*trans*-methyl conformation in diradical (**104**). A long-range attraction between *s*-*cis*-methyl group at C(1) and the non-bonding *p*-π AO at C(3) in (**105**) contributes to stabilizing the diradical.



(**101**) (**102**) (**103**) (**104**) (**105**) (**106**)

Similarly, *ab initio* calculations on the thermal reaction of propene forming methylcyclopentane suggested a three-step biradical reaction with 1,4-biradical and 1,5-biradical as intermediates.[172] Quantum-chemical calculations have been carried out for the cyclization of the neocarzinostatin chromophore cyclonona-1,2,3,5-tetraen-7-yne to 1,5-didehydroindene biradical.[173] The degree of stereoselectivity of the Diels–Alder reaction of 2-methylfuran and maleic acid in water has been found to reduce significantly in the presence of heavy atoms. Taking into account the relatively low concentration (3.5–7 M) of heavy-atoms, and the rapid fall off of the heavy-atom effect with distance, these results show that a large portion of the Diels–Alder reaction occurs via diradical intermediates.[174]

The relative stabilities of singlet and triplet electronic states of three different oxyallyl systems and the closed form of cyclopropanone, bicyclo[1.1.0]butanone, and bicyclo[2.1.0]pentan-5-one have been studied by density-functional calculations (B3LYP/6–31 G*). The results of these calculations are in good agreement with predictions of calculations based on multi-determinant methods.[175]

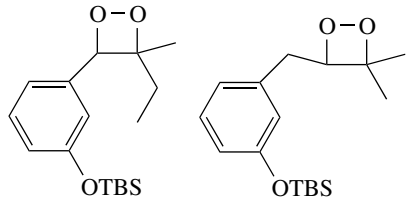
Pyrolysis and Thermolysis

The mechanism of the thermal $S_{RN}1$ reaction, using 4-nitrocumyl chloride and 2-nitropropanate ion as a model has been investigated. The results provided unambiguous evidence that a decrease in driving force is able to change the mechanism of homogeneous reductive cleavage reactions from stepwise to concerted.[176]

The thermolysis of a variety of 1,2,4-trioxanes in methanol has been followed by mass spectrometry and provided evidence of the corresponding products.[177] A study of the thermal decomposition of 3,6-diphenyl-1,2,4,5-tetroxane in toluene and methanol revealed a significant solvent effect that supported a homolytic stepwise mechanism instead of a concerted process.[178]

Ab initio calculations were carried out to elucidate the possible mechanism for decomposition reactions of dioxetane and dioxetanone and related species. The computational results indicate that endothermic O–O cleavages, followed by charge transfers, are operative for the chemiluminescence reactions of these peroxides with several anion species such as phenols, indoles, and luficerins. The chemically initiated electron-exchange luminescence mechanism requires complete one-electron transfer for the formation of excited carbonyl fragments.[179] Another theoretical study of the thermal decomposition of 1,2-dioxetane has re-examined the singlet/triplet surface-crossing regions and computed the spin–orbit coupling and energetics.[180] The barrier to O–O cleavage on the ground-state surface has been found to lie at nearly the same energy as the transition structure for the C–C biradical cleavage on the triplet energy surface. The computational results indicate that the singlet and triplet surfaces do not cross along the minimum-energy path between the ground state O–O cleavage and the singlet biradical. The authors have evidence for a singlet/triplet crossing 'line' that spans the ground-state O–O cleavage valley and lies a few kcal mol^{-1} higher in energy. The computed spin–orbit coupling between the ground state and triplet $^3(3\pi)$ surfaces is larger throughout the crossing region. It has been suggested that facile intersystem crossing from the ground state to the triplet state can occur anywhere

along the minimum-energy path, which could lead to a $^{\bullet}OCHCH_2O^{\bullet}$ triplet biradical. This could either fragment to form triplet products or undergo intersystem crossing back to the ground-state surface. Along these lines *m*-silyloxyphenolate-substituted 1,2-dioxatenes (see below) containing the substituent directly attached to the peroxidic ring or separated by a methylene group were treated with fluoride. The released phenolate anion acts as an intramolecular electron donor to the dioxetane moiety, inducing dioxetane cleavage and formation of an electronically excited singlet state, which emits fluorescence.[181]



The thermal unimolecular decomposition of ethoxy radicals ($C_2H_5O^{\bullet}$) was investigated at different temperatures and pressures. Under these conditions the β-C−C scission $CH_3CH_2O^{\bullet} + M \rightarrow CH_2O + CH_3^{\bullet} + M$ is the dominant decomposition channel. Excellent agreement between the experimental and calculated rate constants has been found.[182]

A number of reports on the thermal decomposition of peroxides have been published. The thermal decompositions of *t*-butyl peroxyacetate and *t*-butyl peroxypivalate,[183] of HCOH[184] and a kinetic study of the acid-induced decomposition of di-*t*-butyl peroxide[185] in *n*-heptane at high temperatures and pressures have been reported. Thermolysis of substituted *t*-butyl (2-phenylprop-2-yl) peroxides gave acetophenone as the major product, formed via fragmentation of intermediate alkoxy radicals $RCH_2C(Ph)(Me)O^{\bullet}$.[186] A study of the thermolysis mechanism of di-*t*-butyl and di-*t*-amyl peroxide by ESR and spin-trapping techniques has been reported.[187] The di-*t*-amyloxy radical has been trapped for the first time. β-Scission reaction is much faster in di-*t*-amyloxyl radicals than in *t*-butoxyl radicals. The radicals derived from di-*t*-butyl peroxide are more reactive towards hydrogen abstraction from toluene than those derived from di-*t*-amyl peroxide.

The flash vacuum pyrolysis of alkynes, arynes, and aryl radicals has been reviewed. A discussion of secondary reactions and rearrangements is included.[188] The pyrolysis of cyclopentadienes has also been examined.[189] The rates for the initial C−H bond fission and the decomposition of *c*-C_5H_5 have been calculated. A single-pulse shock study on the thermal decomposition of 1-pentyl radicals found alkene products that are formed by radical isomerization through 1,4- and 1,3-hydrogen migration to form 2- and 3-pentyl radicals.[190] The pyrrolysis of *t*-butylbenzene in supercritical water was the subject of a report.[191]

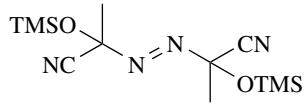
The kinetics of the thermal isomerization of methylcyclopropane to four isomeric butanes have been determined from rate-constant measurements over a wide range of temperatures 695–1154 K. The kinetic parameters are consistent with the formation

of the two but-2-enes through a diradical intermediate. Kinetic data for but-1-ene and 2-methylpropene formation are also presented. The higher activation energy for the formation of but-1-ene and of *cis*- and *trans*-but-2-ene is due to the higher energy required to break the C(2)-C(3) bond compared with the methyl-substituted C(1)−C(2) bond.[192]

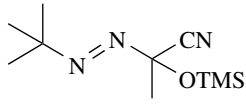
An *ab initio* RHF/3−21 G study has shown that the decomposition of 3-hydroxy-3-methylbutan-2-one is a concerted process with hydrogen transfer and bond breaking via a five-membered cyclic transition state.[193] AM1 and PM3 methods using UHF calculations were applied to study the thermolysis of 2-cyanofuroxan.[194] The reaction proceeds via a two-step pathway in which the second step is rate determining. The effect of solvent in the thermal decomposition reaction of *trans*-3,3-dimethyl-5,6-tetramethylene-1,2,4-trioxacyclohexane was studied.[195]

The kinetics of the pyrolysis of CF_3CHFCF_3 in a single-pulse shock tube over the temperature range 1200−1500 K have been studied. The most important products detected were C_2F_6, $CF_2{=}CHF$, C_2F_4, C_3F_6, cyclo-C_3F_6, and CF_3CHFCF_2H. Traces of CF_3H, CF_4, C_2F_5H, C_3F_8, and C_4F_6 were identified. Modelling results showed that the major initiation step was the C−C bond-fission reaction. The abstraction of a secondary H atom by F atoms was predicted to be important, whereas 1,2-HF elimination was slower.[196] New completely fluorinated intermediates have been identified from spectroscopic studies of thermal reactions of perfluorinated alkenes, carbocycles and oxiranes in the gas phase.[197] A theoretical study of the thermal decomposition mechanism of fluoromethanethiol (FCH_2SH) and of CH_3SF at the G2(MP2) level of theory has shown that the most energetically favourable channel is the formation of HF and CH_2S via a four-centre elimination mechanism for both molecules.[198]

The thermal decomposition of azoalkanes bearing geminal α-cyano and α-trimethylsiloxy groups has been the subject of a report.[199] The symmetrical compound (**107**) decomposes near room temperature to afford entirely C−C dimers, whereas the unsymmetrical azoalkane (**108**) requires heating to 75 °C. A ^{13}C NMR product study of photolysed (**107**) in the presence of TEMPO showed that the fate of caged *t*-butyl-1-trimethylsiloxy-1-cyanoethyl radical pairs is disproportionation (17%), cage recombination (20%), and cage escape (63%).



(**107**)



(**108**)

The kinetics and mechanism of pyrrole pyrolysis were investigated by *ab initio* quantum-chemical calculations. It was revealed that pyrrole undergoes tautomerization to form 2*H*- and 3*H*-pyrroles prior to any thermal decomposition. It has been shown that the major product, HCN, arises from a hydrogen migration in pyrrole to form a cyclic carbene with the NH bond intact. Ring scission of the carbene leads to an allenic imine of HCN and propyne which is the lowest energy pathway. The 2*H*-pyrrole

undergoes CN fission to form an open-chain biradical species which leads to *cis*- and *trans*-crotononitrile and allyl cyanide. The biradical can also undergo facile H-fission to form cyanoallyl radical that leads to acetylene, acetonitrile, acrylonitrile, and H_2.[200]

A similar study using density-functional B3LYP theory and *ab initio* calculations was done by other researchers.[201] The pyrrole was found to tautomerize to 2*H*-pyrrole which, via 1,2-hydrogen migration, yields 3*H*-pyrrole; 3*H*-pyrrole can rearrange to *cis*-isocyanocrotonitrile via a concerted transition state of C(2)−C(3) bond cleavage and 1,2-hydrogen migration from C(2) to C(3). *cis*-Isocyanocrotonitrile isomerized to *cis*-crotonitrile. Allyl cyanide was proposed to form from 2*H*-pyrrole through a concerted transition state of C−N bond cleavage and 1,2-migration. This study failed to identify a decomposition pathway for HCN generation.

The thermolysis of 2-methoxyphenol in the presence of cumene as a radical scavenger occurs via two possible pathways. A homolytic cleavage of the methoxyl O−C bond leads to methane and 1,2-dihydroxybenzene whereas an induced route starting with abstraction of the phenolic hydrogen by cumyl radicals leads, after a cascade of reactions, to phenol, 2-hydroxybenzaldehyde, and 2-hydroxybenzyl alcohol.[202]

A gas-phase study of the decomposition mechanisms of nitromethane (CH_3NO_2), methyl nitrite (CH_3ONO), dimethylnitramine, and 1,3,3-trinitroazetidine [$(NO_2)_2C_3H_4NNO_2$] revealed that, after the initial bond fission, several reaction centres develop when very active radicals such as CH_3, H, NO, OH, HCO, and HNO combine to form the final mixture of products.[203] CH_3ONO decomposition gives large amounts of NO_2 and CH_3OH which are not produced in the CH_3NO_2 decomposition. The results indicate that the nitro–nitrite isomerization is minimal for the CH_3NO_2 system. The thermal decomposition of nitromethane in shock tubes (Scheme 14) has been analysed and the rate constants for the reactions (*a*) and (*b*) below (Scheme 14) were re-examined.[204] The rate constants for reaction (*b*) decreased slightly with temperature.

$$CH_3NO_2 \overset{a}{\rightleftharpoons} CH_3 + NO_2 \qquad CH_3 + NO_2 \overset{b}{\rightleftharpoons} CH_3O + NO$$

SCHEME 14

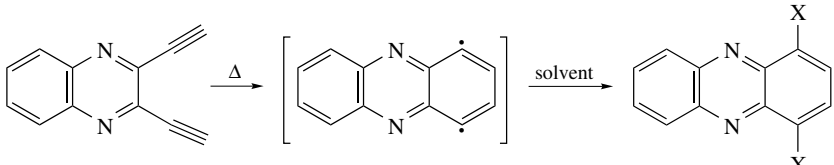
A kinetic modelling study on the decomposition of benzene near 1000 K revealed that the presence of CH_4 product and the enhanced yields of H_2 above the predicted values could only be explained by invoking the reaction with 0.1% toluene impurity. The decomposition reaction is dominated by the unimolecular dissociation of C_6H_6 followed $H + C_6H_6 = C_6H_5 + H_2$ and $C_6H_5 + C_6H_6 = C_{12}H_{10} + H_2$ by the short chain process which results in the dehydrogenation of C_6H_6 producing $C_{12}H_{10} + H_2$.[205]

Propyne pyrolysis was studied in a flow reactor at 1210 K and 1 atm. Pressure-dependent rate coefficients of several reaction steps in propyne and allene pyrolysis were determined by *ab initio* calculations. The reactions include the mutual isomerization of propyne and allene, the chemically activated reactions with the H atom and of acetylene with methyl on C_3H_5 potential-energy surface. The reaction mechanism predicts the acetylene and methane production rates determined in the flow reactor.[206]

The pyrolysis of acetonitrile in a single-pulse shock tube over the temperature range 1400–2100 K was investigated. The major products detected were HCN, C_2H_2,

CH_4, and H_2 while minor products such as HCCCN, $H_2C{=}CHCN$, C_2H_4 and C_4H_2 were also detected. *Ab initio* chemical calculations revealed that the pyrolysis of acetonitrile is initiated by CH bond fission, forming a cyanomethyl radical. Products such as HCCN and $H_2C{=}CHCN$ have been shown to arise from the decomposition of succinonitrile, that forms by the recombination of two cyanomethyl radicals.[207]

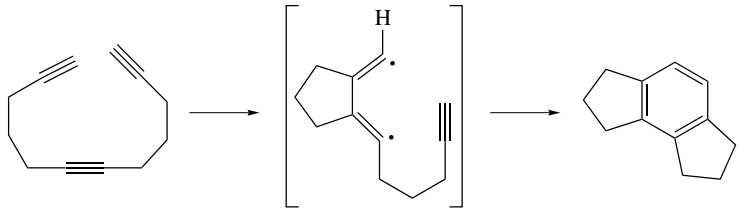
The kinetics of thermocyclization of 2,3-diethynylquinoxaline (**109**) (Bergman cyclization) have been studied in various solvents. Non-polar solvents give shorter half-lives and better yields. The cyclization rates observed were found to be solvent dependent.[208]



(**109**)

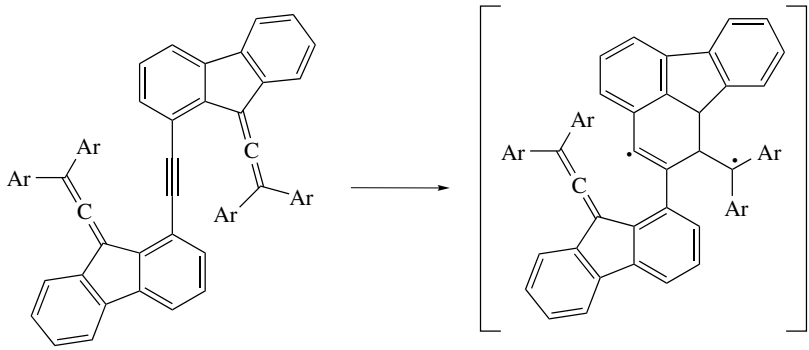
Other researchers have reported that the cyclization step is believed to be rate determining in the cycloaromatization (Bergman) reaction of aliphatic enediynes.[209] It has been found that the rate-limiting step is hydrogen abstraction by benzannelation. This effect should be attributable to the faster rate of retro-Bergman cyclization from the aromatic ring-condensed 1,4-didehydrobenzene diradicals and/or the slower rate of hydrogen abstraction by them.

The intramolecular thermal cyclotrimerization of dodeca-1,6,11-triyne (**110**) at 450–600 °C afforded 1,2,3,6,7,8-hexahydro[*a*5]indacene (**112**) and dehydro derivatives. An exothermic cycloaromatization mechanism has been proposed. An initial formation of a single bond gives diradical (**111**) which is then trapped by an alkyne.[210]

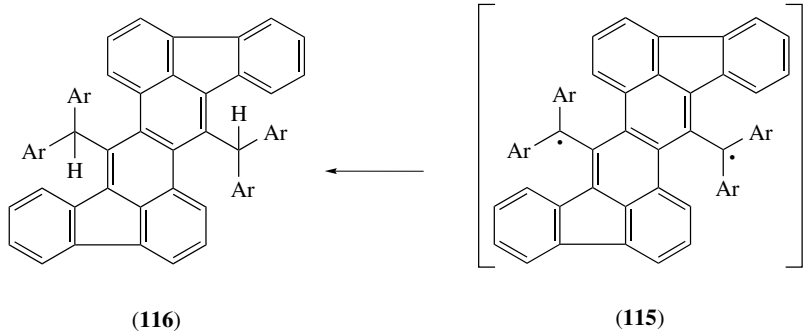


(**110**) (**111**) (**112**)

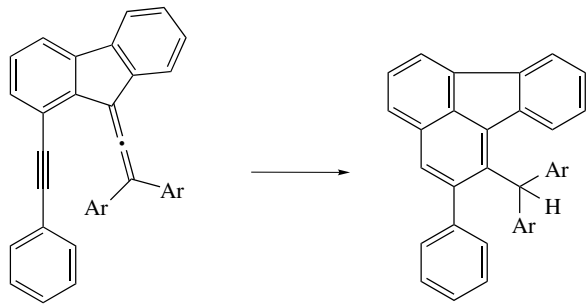
Thermolysis of benzoenyneallene (**113**) in cyclohexadiene at 75 °C produced the cycloaromatized adduct (**116**) in 22% yield. A biradical is believed to form through a cascade sequence involving an initial Myers cyclization. Trapping of the aryl radical centre in (**114**) with the tetrarylallenic moiety intramolecularly affords (**115**), having two triaryl radical centres. Hydrogen abstraction from cyclohexa-1,4-diene by (**115**)



(**113**) (**114**)

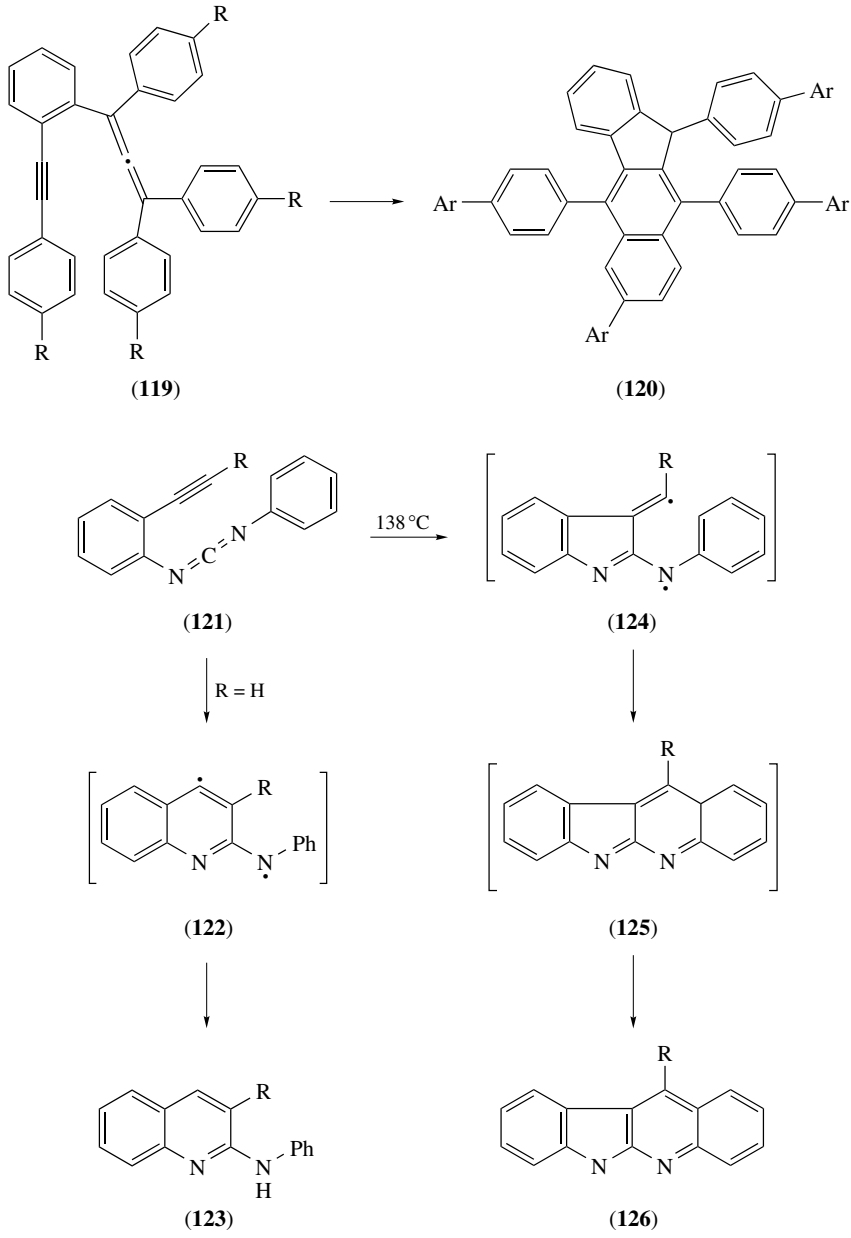


(**116**) (**115**)



(**117**) (**118**)

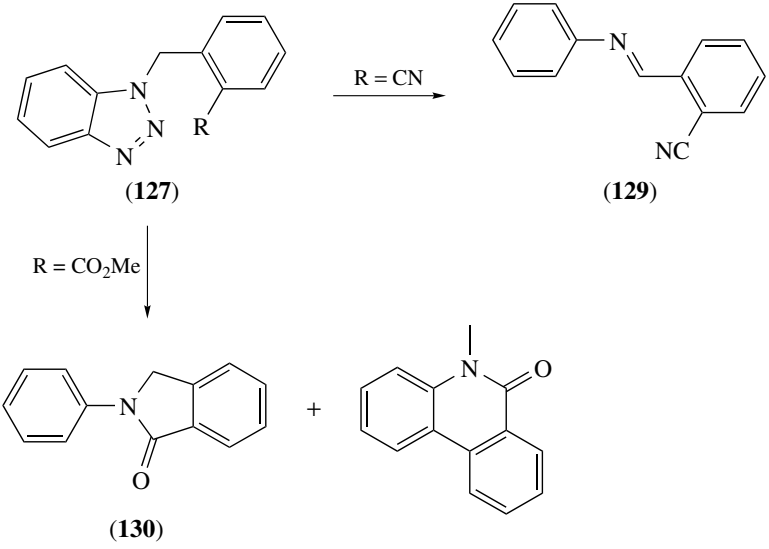
gives (**116**). Thermolysis of benzoenyneallene (**117**) furnished fluoroanthenes (**118**). The presence of the five-membered ring in (**113**) and (**117**) is essential to direct the initial biradical-forming step towards the Myers cyclization reaction. Without the five-membered ring, as in (**119**), the C(2)–C(6) cyclization reaction becomes the preferred pathway leading to benzofluorenes (**120**).[211]



In a similar way, thermolysis of *N*-[2-(1-alkynyl)phenyl]-*N*′-phenylcarbodiimides (**121**) provides a new route for the synthesis of 6*H*-indolo[2,3-*b*]quinolines.[212] Thermolysis of (**121**) for R = H, in γ-terpinene at 138 °C produced (2-phenylamino)quinoline (**123**; 49%) and 6*H*-indolo[2,3-*b*]quinoline (**126**; 16%); (**123**) was produced via biradical (**122**) followed by hydrogen abstraction from γ-terpinene.

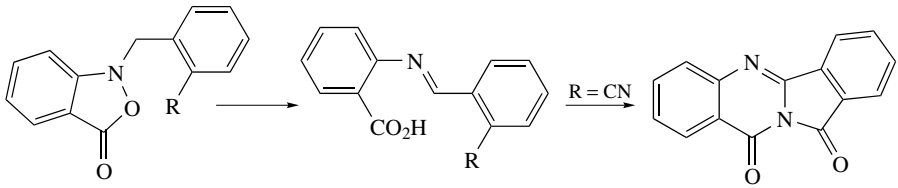
A two-step biradical pathway through (**124**) or one-step intramolecular Diels–Alder reaction could furnish (**125**), which underwent tautomerization to give (**126**). For R = TMS, Me, Pr, *t*-Bu, and Ph, 6*H*-indolo[2,3-*b*]quinolines (**126**) were obtained exclusively and in high yields.

The flash vacuum pyrolysis of *N*-benzylbenzotriazoles (**127**), [(2-benzotriazol-1-ylmethyl)benzonitrile and methyl 2-(benzotriazol-1-ylmethylbenzene)] and the corresponding *N*-benzylisoxazolones (**128**) has been studied.[213] The benzotriazoles lose nitrogen to give diradicals which undergo intramolecular hydrogen-atom transfer to give the benzaldehyde *N*-phenylimine when R = CN (**129**), or undergo cyclization (**130**, R = CO_2Me). The benzisoxazolones (**128**) rearrange initially to the corresponding benzaldehyde *N*-(2-carboxyphenyl)imines (**131**), which then undergo subsequent intramolecular addition reactions.

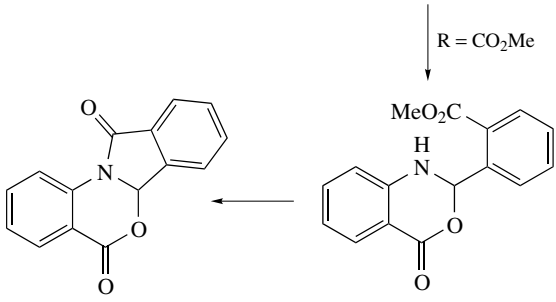


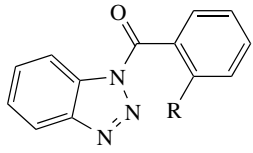
(**127**) (**129**) (**130**)

The same researchers have also studied the flash vacuum pyrolysis of *N*-acylbenzotriazoles (**132**) and of the corresponding *N*-acylbenziisoxazolones (**133**).[214] The benzotriazole derivatives gave compounds whose origin suggests a triplet diradical intermediate (**134**) formed by loss of N_2. The benzotriazole derivatives R = CO_2Me and R = CN gave benzoxazoles and the isoindolo[1,2,3,5]benzotetraazepine (**135**) for R = CN. For R = CH_2Cl, acrinidine was the only product. At lower temperatures the benzisoxazolones gave benzoxazole products, consistent with a singlet carbene intermediate. Thus, at low temperatures indolo[1,2*b*]benzoxazole is the major pyrolysis product, but this had triplet diradical properties at higher temperatures leading to the formation of acrinidine for the chloromethyl compound.



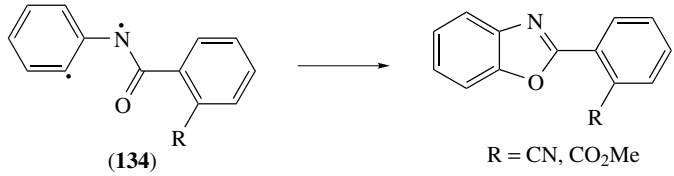
(**128**) (**131**)



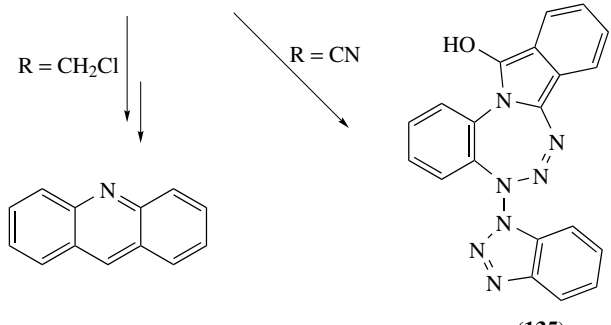


(**132**)

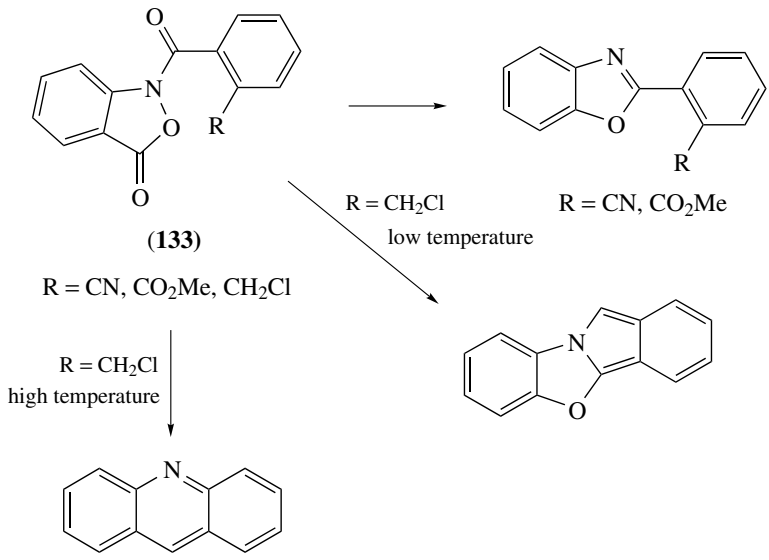
R = CN, CO_2Me, CH_2Cl



(**134**) R = CN, CO_2Me



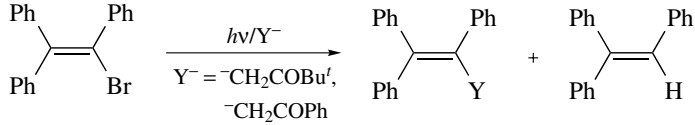
(**135**)



Photolysis

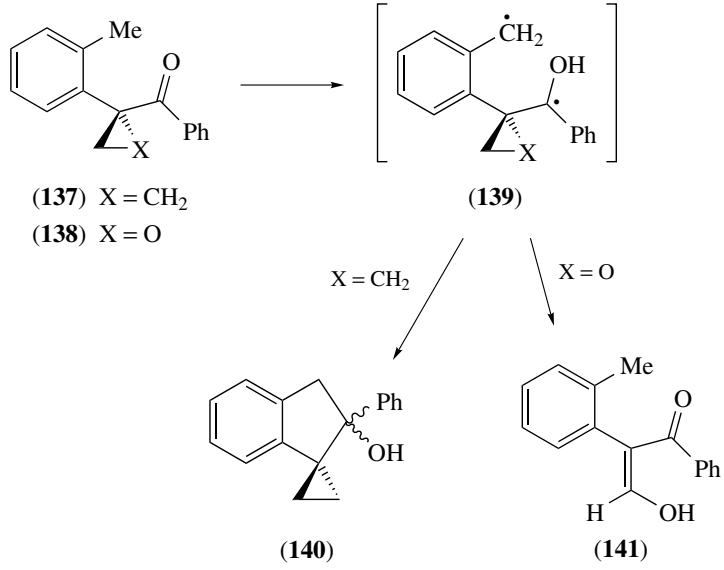
Two examples of enone/alkene photo-cycloaddition involving a rearrangement of the intermediate 1,4-diradical have been reported.[215] The photo-Fries rearrangement of 1-naphthyl acetate in aqueous solution of the novel antenna polyelectrolyte poly(sodium styrenesulfonate-co-2-vinylfluorene) (PSSS-VF) was studied. Three copolymers of different fluorine chromophores were synthesized. It was demonstrated that electronic excitation energy could migrate along the polymer chain before being transferred to the solubilized molecule. The reaction of naphthyl acetate is sensitized by light absorbed by the polymeric fluorine chromophores. The product contribution was dependent on the content of fluorine in the copolymer. The reaction in aqueous solution of PSSS-VF rich in fluorine chromophores occurs with high sensitivity to form the caged product, 2-naphthol, in 95% yield whereas sensitizers with low fluorine content gave 90% yield of the non-caged product, 1-naphthol.[216]

Photolysis of vinyl halides can induce both heterolysis of the C−X bond, thereby generating vinyl cations, and homolysis giving vinyl radicals. This competition between the two mechanisms was studied for 3-vinyl halides, 1,2,2-triphenylbromoethane (**136**) and 1-phenyl-2,2-bis(*o*-methoxyphenyl)-1-bromoethene and β-styrene.[217] Incursion of the photo-induced $S_{RN}1$ process, through the intermediate vinyl radical, is verified in the presence of reducing nucleophiles, such as the enolate ions of ketones and in part with $(EtO)_2PO^-$. Incursion of the heterolytic pathway and the intermediacy of the radical cation, occurs in the presence of weak electron-donor anions, such as NO_2^-, N_3^- and Cl^-. The vinyl cation of β-styrene gives phenylacetylene via an $E1$-type elimination.



(**136**)

Photolysis of 1-(*o*-tolyl)-1-benzoylcyclopropane (**137**) and 1-(*o*-tolyl)-1-benzoyloxirane (**138**) resulted in hydrogen-transfer reaction to produce a 1,5-biradical intermediate (**139**). The biradical from (**137**) cyclized before cyclopropyl ring opening to give spiroindanol (**140**). However, with the biradical derived from (**138**), the oxiranyl ring opens up immediately after the initial hydrogen abstraction to give (**141**).[218]

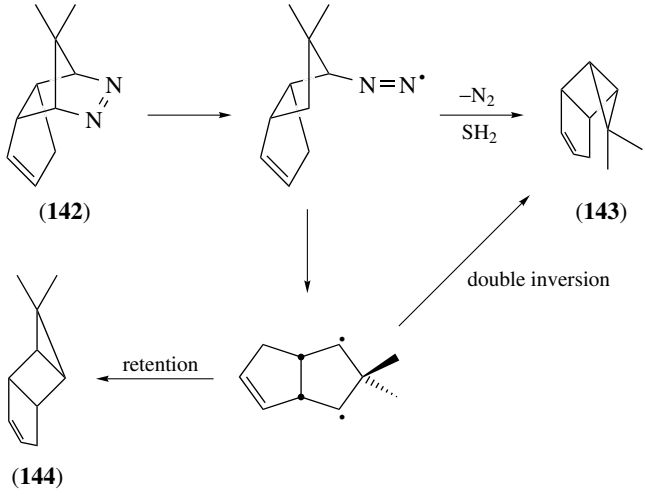


(**137**) X = CH_2
(**138**) X = O

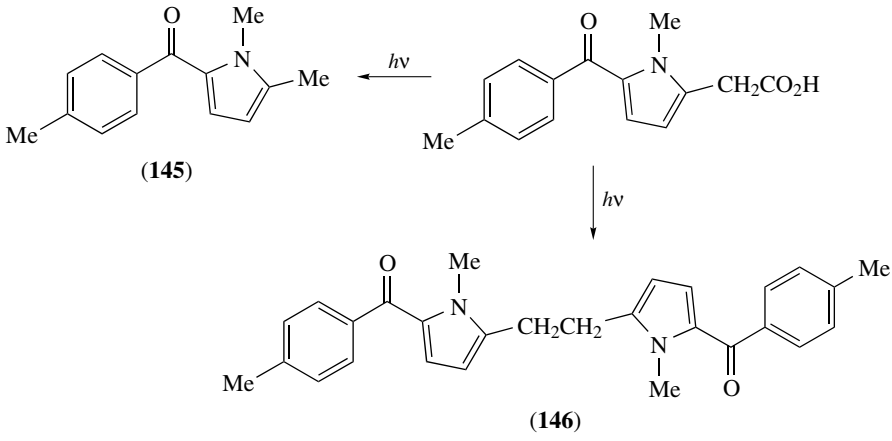
(**139**)

(**140**) (**141**)

The photolysis of the diazobicyclo[2.2.2]heptene derivative (**142**) was studied at different temperatures and was found to give mixtures of *syn* (**143**) and *anti* (**144**) products.[219] The experimental data support the homolytic (S_H2) pathway as the prevalent reaction channel at elevated temperatures for the generation of the sterically encumbered *syn* product, whereas at low temperatures the triplet pathway operates and loss of the *syn* selectivity is observed. The loss of *syn* selectivity at low temperatures is due to efficient intersystem crossing in the singlet-excited azoalkane to afford the planar, nitrogen-free triplet diradical which unselectively ring closes.

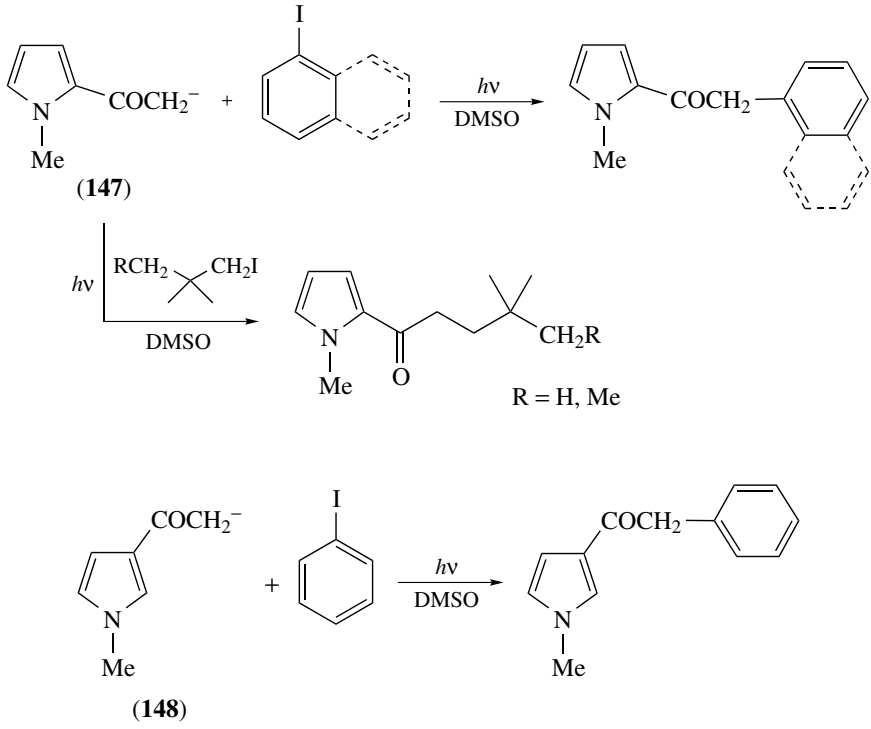


Copper(II), at very low concentrations, modulates the distribution of tolmetin stable photo-products (**145**) and (**146**), as well as inhibiting the DNA cleavage photo-induced by the drug. An electron-transfer process from the triplet carbanion (generated in the tolmetin photolysis) to the copper is involved.[220]



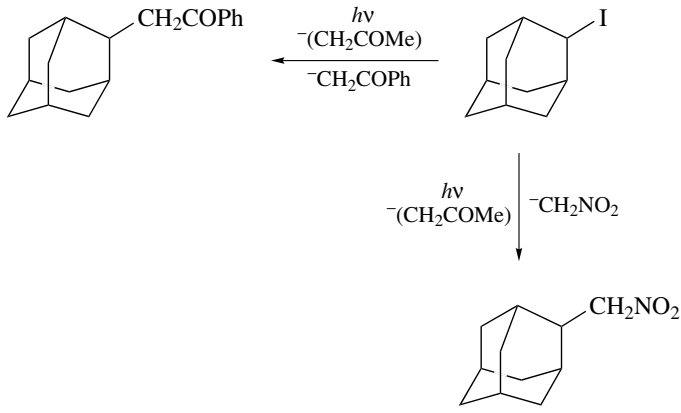
Radioloysis

A review of aromatic substitution by the $S_{RN}1$ reaction has been published.[221] The reactions of enolate ions of 2-acetyl-(**147**) and 3-acetyl-1-methylpyrroles (**148**) with aryl iodides and neopentyl iodides under irradiation conditions afforded good yields of substitution products by $S_{RN}1$ mechanisms, without the need for initiator.[222] These

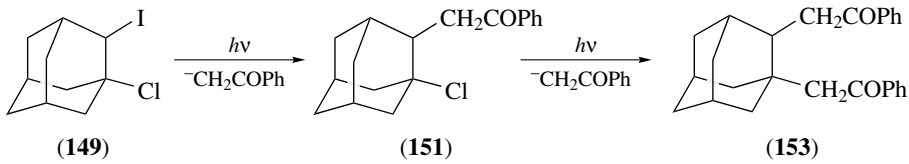


anions were found to be more reactive than the enolate ion of acetophenone and are able to participate in initiation in contrast to the enolate ions of the five-membered ring analogues 2-acetylthiophene and 2-acetylfuran. The reactions of 2-iodo- and 1,2-dihalo-adamantanes with carbanions under $S_{RN}1$ conditions have been reviewed.[223] The reactions of 2-iodoadamantane with two carbanions ($^{-}CH_2COPh$) and ($^{-}CH_2NO_2$) by the $S_{RN}1$ mechanism under irradiation by entrainment with the enolate ion of acetone or by induction with $FeBr_2$ have been examined (Scheme 15). A decrease in reactivity of 2-adamantyl radicals with bulky carbanions (such as anthrone and 2-naphthyl methyl ketone) and with less-reactive nucleophiles has been observed.

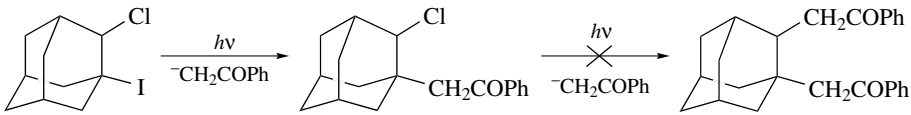
Chloroadamantanes (**149**) and (**150**) reacted with $^{-}CH_2COPh$ to afford the monosubstitution products (**151**) and (**152**) as intermediates, the intramolecular electron-transfer reaction of the radical anion intermediate being a slow process. Product (**151**) with chlorine in the 1-position reacted further to give (**153**), whereas (**152**) with chlorine in the 2-position is unreactive, showing that the 1-position is the more reactive. 1,2-Diiodoadamantane (**154**) reacted with $^{-}CH_2NO_2$ to give the monosubstitution products (**155**) and (**156**). This implies that the intramolecular electron-transfer reaction of the radical anion is a slow process. The fact that (**155**) was formed as major product and (**156**) was the minor product shows that, when (**154**) accepts an electron, fragmentation occurs faster at the 1-position than the 2-position.



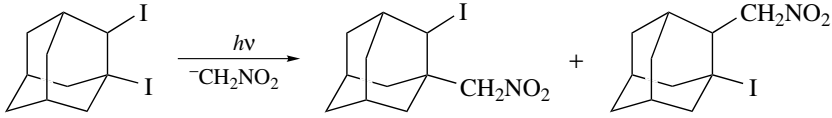
SCHEME 15



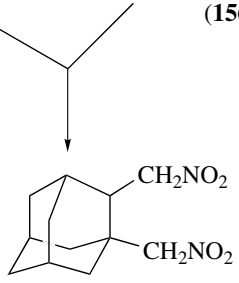
(**149**) (**151**) (**153**)



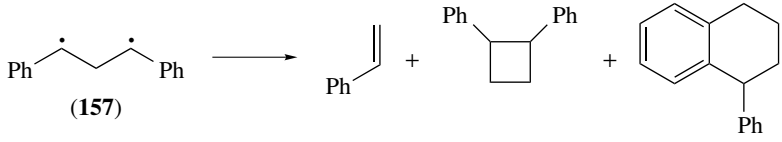
(**150**) (**152**)



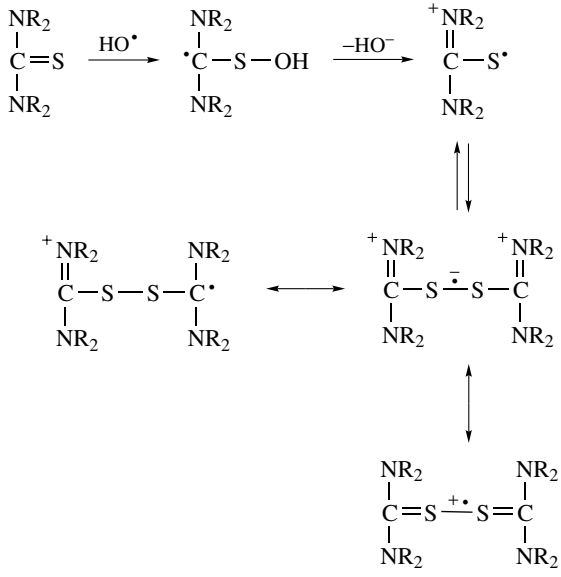
(**154**) (**155**) (**156**)



The 1,4-diphenylbutane-1,4-diyl biradical (**157**) was generated from 1,4-dichloro-1,4-diphenylbutane or 2,5-diphenylcyclopentanone under irradiation conditions giving rise to styrene, 1,2-diphenylcyclobutane, and 1-phenyl-1,2,3,4-tetrahydronaphthalene.[224] Tetrahydronaphthalene forms from 1,4-biradicals that have a phenyl group attached to one of the radical centres. Irradiation of 2-phenylcyclopentanone resulted in the formation of tetrahydronaphthalene.

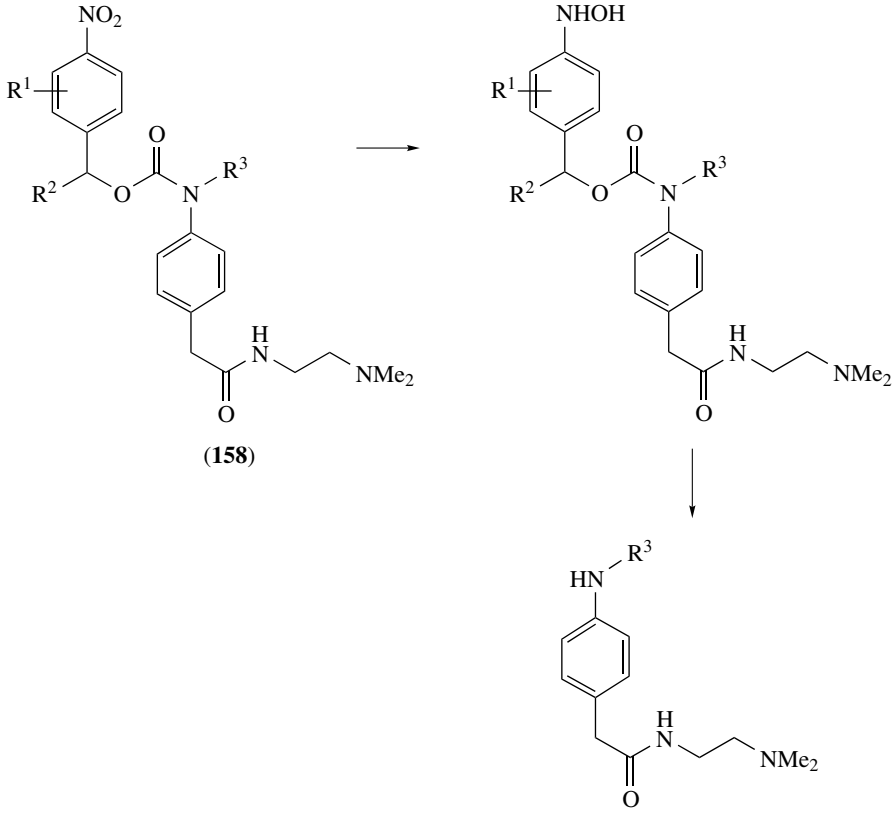


Hydroxyl radicals were generated radiolytically in N_2O-saturated aqueous solutions of thiourea and tetramethylthiourea.[225] Conductometric detection showed that HO^- and a dimeric radical cation were produced. The dimeric radical cation is formed by addition of a primary radical to a molecule of thiourea. In basic solution, the dimeric radical cation decays rapidly to a dimeric radical anion, which is formed via neutralization of the cation and subsequent deprotonation of the neutral dimeric radical (Scheme 16). This was not observed in tetramethylurea. These dimeric radical cations of thiourea and tetramethylurea are strong oxidants and readily oxidize the superoxide radical, phenolate ion, and azide ion.



SCHEME 16

The nature and redox properties of the transient species formed on pulse radiolysis of aqueous solutions of 2-(phenylthio)ethanol have been reported.[226] Radiolytic reduction has been used to study the substituent effect on nitrobenzyl carbamate fragmentation designed as triggers for bioreductve prodrugs. A series of 2,3- and α-substituted 4-[*N*-methyl-*N*-(4-nitrobenzyloxycarbonyl)amino]phenylacetamides (**158**) were studied. The hydroxylamines were generated by ^{60}Co γ-irradiation of the nitro compounds in aqueous phosphate-buffered propan-2-ol. Electron-donating substituents in the 2-position of the benzyl ring accelerated fragmentation of the hydroxylamines.[227]



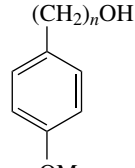
(**158**)

The solute benzene radical cation was formed on pulse radiolysis of an acidic aqueous solution of benzene. The transient optical absorption bands ($\lambda_{max} = 310$, 350–500 nm) were assigned to the solute benzene radical cation which is formed on acid-catalysed dehydration of the OH adduct. The radical cation is able to undergo an electron-transfer reaction with Br^- and was found to be a strong electron oxidant.[228]

Pulse radiolysis has been used to study the complex reaction that follows electron addition to hydroxybenzophenones (HOBPs).[229] The various radical species involved have been characterized spectrally and their pK_a values evaluated. The differences

observed for *p*-, *o*-, and *m*-derivatives have been explained. Reduction of hydroxybenzophenone was also studied using dimethyl ketyl radicals as reductants in mixed water–acetone–propanol solvents. These radicals have been found to react via adduct formation with the HOBPs, whereas H-atom transfer reaction have been identified in the reactions with $^{-}$OBPs.

A pulse radiolysis study of the reactivity of the radical cations generated from 2-, 3- and 4-(4-methoxyphenyl)alkanols (**159**), where the OH group is separated from the aromatic ring by an increased number (from 2 to 4) of carbon atoms, has shown that the cations react with HO^{-} forming products of $C_{\alpha}-C_{\beta}$ bond cleavage. Either O–H deprotonation is coupled to C–C bond cleavage or a radical zwitterion is first formed which undergoes intramolecular electron transfer coupled to C–C bond cleavage. An oxyl radical intermediate is suggested for the base-catalysed decay of 3-(4-methoxyphenyl)propanol radical cation. This radical undergoes 1,2-H atom shift leading to the formation of 3-(4-methoxyphenyl)propanal. The oxygen acidity disappears when four carbon atoms are interposed between the OH group and the aromatic ring. These systems behave as carbon acids both in acidic and aqueous solutions.[230]

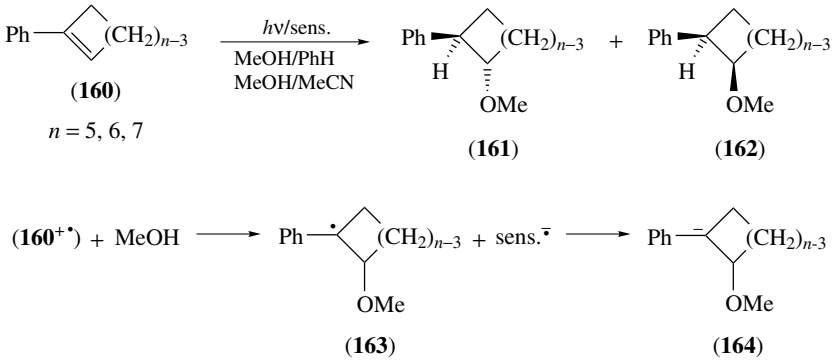


(**159**)

$n = 2, 3, 4$

A similar kinetic and product study of the side-fragmentation reactions of a series of radical cations [4-$MeOC_6H_4CH(OH)R^{+\bullet}$] has also been carried out in acidic and basic solution.[231] At pH 4, the radical cations undergo C_{α}-H deprotonation for R = H, Me and Et and $C_{\alpha}-C_{\beta}$ bond cleavage for R = *t*-Bu, CH(OH)Me and CH(OMe)Me. Both types of cleavage are observed for R = *i*-Pr. Hydrogen bonding of the α-OH group with the solvent stabilizes the transition state of the C–C bond fragmentation but not of the deprotonation process. In the presence of $^{-}$OH the 1-arylalkanol radical cations become oxygen acids and deprotonation involves the alcoholic C_{α}-OH bond. The proton is transferred to the base to give the benzyloxy radical either via radical zwitterions (which undergo intramolecular electron transfer) or directly (electron transfer coupled with deprotonation.) The benzyloxy radical can then undergo a β-C–C bond cleavage to form 4-methoxybenzaldehyde and $R^{\bullet}$ or a formal 1,2-H shift to form an α-type radical.

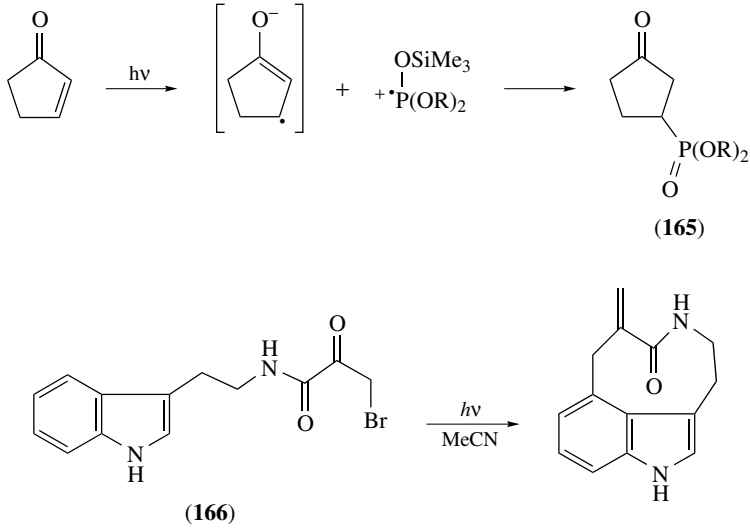
Irradiation of 1-phenylcycloalkenes (**160**) with cyano-aromatics electron-accepting sensitizers in MeCN and benzene containing 1 M methanol gave *trans*-(**161**) and *cis*-isomers (**162**) of anti-Markovnikov adducts.[232] The (**161**)/(**162**) isomer ratio was found to depend on the ring size of 1-phenylcycloalkene but not on the sensitizer used. The mechanism of the reactions was studied by semiempirical MO calculations.



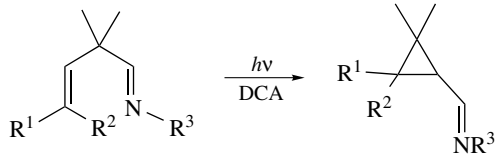
The stereoselectivity of anti-Markovnikov adducts (**161**) and (**162**) produced through photo-induced electron-transfer reaction of (**160**) with MeOH in MeCN depends on the optimum structures and stabilities of the corresponding radical and carbanion intermediates (**163**) and (**164**). In PhH, steric hindrance in an exciplex, comprising an excited singlet sensitizer and (**160**), forced *cis* addition of MeOH to (**160**) to give *trans*-isomer (**161**) as the major addition product.

Photochemical irradiation of α,β-unsaturated ketones in the presence of $Me_3SiOP(OR)_2$ (R = Me, Et) gave phosphonosilylation products of 1,4-conjugate additions which are hydrolysed to the phosphono ketones (**165**).[233] The envisaged initiation step is electron transfer to the triplet excited state of the enone to generate a radical ion pair.

Photo-irradiation of the tryptamine (**166**) produces an intermediate diradical cation that leads to the formation of an azonino[*cd*]indole.[234] This is the first example of a vinylogous Witkop cyclization.



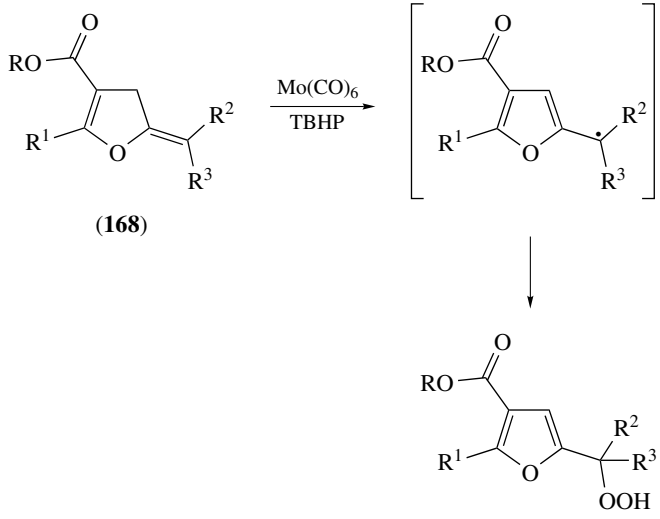
N-Substituted-1-aza-1,4-dienes (**167**) undergo the di-π-methane rearrangement to give cyclopropane derivatives when irradiated in the presence of 9,10-dicyanoanthracene (DCA) as an electron transfer sensitizer. It is the second example of a rearrangement of the di-π-methane type that takes place in the ground state of the radical cation intermediate.[235]



(**167**)

Autoxidation

The $Mo(CO)_6$–TBHP system promoted autoxidation of 5-alkylidenene-4,5-dihydrofurans (**168**) under mild conditions, allowing the preparation of primary, secondary and tertiary furyl hydroperoxides.[236] A radical mechanism has been proposed and was supported by the experimental data.



(**168**)

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CHAPTER 5

Oxidation and Reduction

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Oxidation by Metal Ions and Related Species

Chromium, Manganese, and Nickel

Chromium(III) catalyses the cerium(IV) oxidation of primary and secondary alcohols in a mixture of H_2SO_4 and $HClO_4$.[1] Kinetic results have been interpreted in terms of the formation of chromium(IV) in a reversible equilibrium, which forms a complex with the alcohol. Internal oxidation–reduction occurs in a rate-determining step to give aldehyde or ketone and regenerate the catalyst in the +3 state. The oxidation of ethanol under similar conditions has also been studied.[2]

The oxidation of alkyl aryl sulfides to sulfoxides with oxochromium(V) complexes is first order in oxidant and in substrate.[3] The better correlation of log k with σ^+ rather than σ and the low magnitude of ρ^+ value (-1.19) were interpreted as evidence for a rate-determining single-electron-transfer mechanism. This was further supported by good correlation in the plots of log k versus oxidation potential/ionization energy.

The kinetics of the oxidation of oxalic acid with chromium(VI) have been studied in acidic and neutral media.[4] In the absence of an acidic medium, a mechanism with an intermediate open-chain ester is proposed. H_2SO_4 and $HClO_4$ were found to decrease the reaction rate and $MeCO_2H$ increased it; this is accounted for by a mechanism in which $HOCrO_2OC(O)Me$ and $MeCO_2CrO_2OC(O)Me$ are intermediates when acetic acid is present. The oxidation of dimethyl sulfoxide by chromium(VI) involves nucleophilic attack of the sulfur of DMSO on chromium, leading to a DMSO–chromate ester, $Me_2S(O^-)-Cr(=O)_2X$ (where $X = ClO_4$ or HSO_4 for reactions in $HClO_4$ or H_2SO_4, respectively), which subsequently decomposes to chromium(IV) and dimethyl sulfone.[5] This reaction is promoted by picolinic acid (PA), which, acting as a bidentate ligand, forms a complex with chromium in a pre-equilibrium step.[6] Nucleophilic attack of the sulfur of DMSO on the Cr(VI)–PA complex leads to the build-up of positive charge on sulfur, accounting for the rate acceleration observed upon addition of the anionic surfactant sodium dodecyl sulfate and the retardation induced by the cationic surfactant cetyl pyridinium chloride. The oxidation of 2-pyridinecarboxaldehyde by dichromate has an unusual mixed fourth-order rate law: first order each in $[H^+]$ and [Cr(VI)] and second order in [aldehyde].[7] In the oxidation of pyridoxal by dichromate, the reduction of Cr(VI) to Cr(III) proceeds through a Cr(V) intermediate complex that was detected by ESR.[8] A polar transition state involving electron transfer from sulfur to Cr(VI) is proposed in the oxidation of dialkyl and alkyl phenyl sulfides.[9] A ternary complex is proposed in the oxidation of substituted *S*-phenylmercaptoacetic acids by chromic acid.[10]

Kinetic studies of the oxidation of some α-hydroxy acids with pyridinium dichromate (PDC) are consistent with a mechanism involving the loss of H_2O from the protonated substrate in the rate-determining step.[11] The oxidation of 8-hydroxyquinoline (oxine) by PDC has been studied.[12] The intermediacy of an acetochromate ion in the oxidation of some acetophenone oximes with PDC is suggested.[13]

The pyridinium chlorochromate (PCC) oxidations of pentaamine cobalt(III)-bound and unbound mandelic and lactic acids have been studied and found to proceed at similar rates.[14] Free-energy relationships in the oxidation of aromatic anils by PCC have been studied.[15] Solvent effects in the oxidation of methionine by PCC[16] and pyridinium bromochromate (PBC)[17] have been investigated; the reaction leads to the formation of the corresponding sulfoxide and mechanisms have been proposed. The major product of the acid-catalysed oxidation of a range of diols by PBC is the hydroxyaldehyde. The reaction is first order with respect to the diol and exhibits a substantial primary kinetic isotope effect.[18] Proposed acid-dependent and acid-independent mechanisms involve the rapid formation of a chromate ester in a pre-equilibrium step, followed by rate-determining hydride ion transfer via a cyclic intermediate. PBC oxidation of thio acids has been studied.[19]

Correlation of structure and reactivity in the oxidation of substituted aromatic anils by pyridinium fluorochromate (PFC) has been attempted using Grunwald–Winstein and Hammett equations.[20] The stoichiometry between the substrate and oxidant is 1:2 in the oxidation of cyclic ketones by PFC to 1,2-diketones.[21] PFC oxidation of secondary alcohols has been investigated.[22]

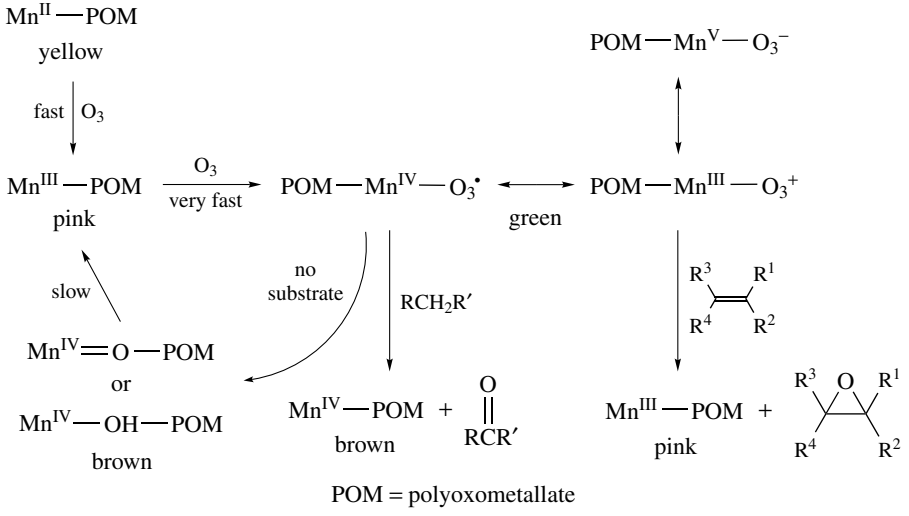
Following earlier studies of the oxidation of formic and oxalic acids by pyridinium fluoro-, chloro-, and bromo-chromates, Banerji and co-workers have studied the kinetics of oxidation of these acids by 2, 2′-bipyridinium chlorochromate (BPCC) to CO_2.[23] The formation constant of the initially formed BPCC–formic acid complex shows little dependence on the solvent, whilst a more variable rate constant for its decomposition to products correlates well with the cation-solvating power. This indicates the formation of an electron-deficient carbon centre in the transition state, possibly due to hydride transfer in an anhydride intermediate HCOO–Cr(=O)(OH)(Cl)–O–bpyH. A cyclic intermediate complex, in which oxalic acid acts as a bidentate ligand, is proposed to account for the unfavourable entropy term observed in the oxidation of this acid.

Quinolinium dichromate (QDC) oxidations of primary[24] and secondary[25] alcohols both proceed via a cyclic chromate ester. Acrylonitrile polymerization was observed in the oxidation of several *para*- and *meta*-substituted benzaldehydes to the corresponding benzoic acids by quinolinium chlorochromate (QCC).[26] QCC oxidations of diphenacyl sulfide[27] and of aromatic anils[28] have been studied.

Steric effects dominate in the oxidation of dialkyl, alkyl phenyl and benzal methyl phenyl sulfides to their sulfoxides by quinolinium fluorochromate (QFC) in aqueous acetic acid.[29] QFC oxidation of phenoxyacetic acids has been studied.[30] Imidazolium dichromate oxidations of α-hydroxy acids have been studied.[31,32]

The kinetics of the manganese(II)- and cerium(III)-catalysed Belusov–Zhabotinsky (BZ) oscillatory reactions were studied with mixed organic acid–ketone substrates.[33] In this mixed substrate system, mandelic acid derivatives are oxidized by the metal, whilst the ketone is brominated and has minimal interaction with the metal. Ketone enolization is shown to be the rate-determining step. Manganese(II) and $[Fe(phen)_3]^{2+}$ are employed as coupled catalysts in a BZ-type reaction with amino acids or peptides as organic substrates.[34] Both components are required for oscillations: manganese(II) catalyses the oxidation of the substrate by BrO_3^- to produce intermediates which reduce bromine to bromide, catalysed by $[Fe(phen)_3]^{2+}$. Manganous sulfate [Mn(II)] and cerium(IV) sulfate were employed as catalysts in a BZ system with 4-methoxy-3-hydroxybenzaldehyde (vanillin) as the substrate.[35] Measurement of the potential for the oxidation of vanillin in the presence of catalyst and acidic potassium bromate shows a two-phase oscillatory system in which the first phase has a greater frequency than the second. The second phase begins when sufficient vanillic acid (the oxidation product) is present. A survey of experimental data on spiral waves in the BZ reaction has been made[36] and compared with several models and numerical simulations. The inhibition of the manganese(II)-catalysed, oscillating Briggs–Raucher reaction by bromide ion is accounted for by the formation of IBr through the reaction of bromide and HOI. IBr competes with I_2 in the iodination of the substrate, malonic acid. Thus the growth of iodide ion, and hence the oscillations, is prevented.[37]

The oxidative stability of polyoxometallates and analogues substituted with transition metals has allowed them to be studied in place of metalloporphyrins in catalysed oxidations, for example with ozone.[38] Alkanes have been oxidized with high selectivity to ketones using $Li_{12}[Mn^{II}{}_2{-}ZnW(ZnW_9O_{34})_2]$ in *t*-butanol–water with ozone as the terminal oxidant. For example, ethylbenzene is oxidized to acetophenone, with only a small amount of 1-phenylethanol formed (85:15; 82% conversion). This selectivity is contrary to manganese porphyrin hydroxylations with ozone, where the alcohol is the major product. The use of lithium cations circumvents the problem of self-oxidation of the quaternary ammonium cations that are normally used to transfer polyoxometallates into organic solvents. The mechanism of the reaction has been investigated using UV–visible and ESR spectroscopy. Coupled with the observations that cumene gives acetophenone and *cis*-decalin forms *trans*-decalol as the major product, the results have been interpreted in terms of the mechanism summarized in Scheme 1. The key intermediate, a green compound, is postulated to be a manganese ozonide complex, and the ESR spectrum is attributed to this species formulated as $POM{-}Mn^{IV}{-}O{-}O{-}O^{\bullet}$. Epoxidation of alkenes also occurs under these conditions with retention of stereochemistry, which is explained in terms of reaction of the ozonide ($POM{-}Mn^{III}{-}O{-}O{-}O^{+}$ canonical form) as an electrophile with the nucleophilic alkene.



SCHEME 1

Kinetic studies on the oxidation of glutamate by manganese(III) in aqueous sulfuric acid, acetic acid, and pyrophosphate suggest different mechanisms for each case.[39] In all cases there is evidence for the involvement of free radicals and in the case of acetic acid and pyrophosphate media a chelated intermediate is postulated. Simultaneous Mn(III)/Mn(IV)-mediated reaction is observed in the oxidation of formaldehyde by

aquamanganese(III) ions.[40] The kinetics of the oxidation of neutral amino acids by manganese(III) ions in pyrophosphate solution have been studied.[41]

Electronic effects modulate *ee* in salen–Mn(III) alkene epoxidations. As a result of an excellent study, it has been suggested by Jacobsen and co-workers that more electron-donating substituents stabilize the Mn(V)oxo species relative to the Mn(IV) radical intermediate resulting in a later, more product-like transition state which gives greater enantioselectivity.[42] This suggestion was convincingly supported by linear Hammett plots of enantioselectivity versus σ_p and secondary isotope effects correlating k_H/k_D at C_β with enantioselectivity. Interestingly, Jacobsen and co-workers comment that the importance of transition state timing 'is quite reasonable in retrospect, but it could hardly have been anticipated in the initial design of these systems.' The generality of this discovery is that it might be usefully extended to many systems that, like Mn(III) epoxidations, do not involve substrate pre-arrangement. Mn(III), Co(II), and Ni(II)-salen complexes based on Schiff bases of (+)- or (−)-1,2-diamino-1,2-diphenylethane and benzaldehydes catalysed the asymmetric epoxidation of styrene by sodium hypochlorite.[43]

Oxidation of L-alanine by alkaline permanganate is first order in [permanganate] and fractional order in [L-alanine] and [alkali]. The proposed mechanism involves oxidation via two paths: the slow oxidation of L-alanine by permanganate to yield products and reaction of alkali and permanganate ion to give manganate.[44] A kinetic study of the oxidation of DL-alanine by acidic permanganate catalysed by silver(I) ion indicates a mechanism involving a rate-determining proton abstraction by water.[45] The kinetics of oxidation of alkyl cinnamates[46] using acetyltrimethylammonium permanganate have been studied and a mechanism involving a cyclic manganate(V) diester intermediate is proposed. Investigation of the kinetics of the oxidation of benzene and alkylbenzenes by permanganate in aqueous perchloric acid solution has indicated that the MnO_3^+ species attacks the aromatic ring.[47] The oxidation of dimethyl and diphenyl sulfoxides by MnO_4^- in aqueous acetic acid has been found to be first order in [substrate] and [MnO_4^-].[48] Permanganate oxidizes benzyl alcohols and ethers to benzaldehyde and benzoate esters, respectively. In both cases, the rates respond in an identical way to substitution in the ring, suggesting that oxidation proceeds by the same mechanism.[49] The proposed mechanism involves an initial interaction between the HOMO of the reductant (oxygen $2p$ orbital) with the LUMO of the oxidant (manganese two-electron antibonding orbital), followed by rate-limiting hydrogen transfer. Under strongly alkaline conditions (pH>12), the stable reduction product of permanganate ion is the manganate ion MnO_4^{2-}.[50] The oxidation of mandelic acid by permanganate has been investigated under these conditions, revealing a stoichiometry of 1:2. Kinetic data suggest that an alkali–metal permanganate complex, formed in an initial equilibrium, reacts with the substrate to give another complex, $[PhCH(OH)C(O)O-Mn(=O)_2O_2]^{2-}$, which decomposes in a slow step with loss of CO_2 to give a free-radical intermediate $PhCH(OH)^\bullet$, corresponding to decarboxylated mandelic acid. This reacts with hydroxide ion and a second equivalent of permanganate to yield the final product, benzaldehyde. Oxidation of L-phenylalanine by alkaline permanganate proceeds via the formation of a complex between L-phenylalanine and

permanganate, which decomposes to the free radical of L-phenylalanine which reacts with another molecule of permanganate.[51]

A good fit between previously observed linear free Hammett plots and those based on a simple 3 + 2 FMO-based calculation fit well and therefore support a 3 + 2 mechanism for the addition of permanganate to a C=C double bond.[52] A scaling factor allowed the lateness or earliness of the transition state to be adjusted, and thus allowed adjustments that are consistent with the ability of MnO_4^{2-} to dihydroxylate both electron-rich and electron-poor alkenes.

Phenylhydrazones were oxidized by NiO_2 at 0 °C via a radical mechanism to afford C−C and C−N dimers.[53]

Silver, Copper, and Gold

The oxidation of 2-carboxyphenylacetic acid by peroxodisulfate ion is catalysed by Ag(I).[54] The kinetics of the oxidation of tetrahydrofurfuryl alcohol by ditelluratocuprate(III)[55] and by ditelluratoargentate(III)[56] in alkaline media have been studied.

The kinetics of the oxidation of isopropylamine by diperiodatocuprate(III) complex ion have been studied and the results are consistent with a mechanism in which dissociation of one of the periodate ligands is followed by an adduct formation between $[Cu(HIO_6)]^-$ and isopropylamine. Polymerization of acrylamide indicated the participation of free radicals.[57] The kinetics of the oxidation of several diols by diperiodatocuprate(III) (DPC) in aqueous alkaline media have been studied.[58]

The oxidation of glycolaldehyde by tetrachloroaurate[59] was carried out in acetic acid–sodium acetate buffer and found to be first order in [Au(III)] and [glycolaldehyde]. H^+ and Cl^- both retarded the reaction. A compatible mechanism was proposed, which involves a one-step, rate-determining, two-electron transfer and the involvement of three gold species, $AuCl_4^-$, $AuCl_3(OH_2)$, and $AuCl_3(OH)^-$, the last being the most active.

Cerium, Titanium, Cobalt, Vanadium, Tungsten, Rhenium, Palladium, Platinum, and Iridium

Homogeneous oxidations of alkanes by electrophilic late transition metals have been reviewed.[60]

The CO_2/Ce(IV) stoichiometry in Ce(IV) oxidation of 10 organic acids has been measured under aerobic and anaerobic conditions.[61] The various results are explained by possible mechanisms in which the initially formed radical either (i) recombines giving no CO_2, (ii) recombines giving an unstable product from which either one or two molecules of CO_2 splits off, giving a stoichiometry of 0.5 or 1, (iii) loses CO_2 itself giving a stoichiometry of 1, or (iv) under aerobic conditions, adds O_2 followed by combination of two peroxy radicals giving either zero or one molecule of CO_2 and a stoichiometry of zero or 0.5. The mechanism of the oxidation of anisole derivatives by Ce(IV) in $HClO_4$ solution has been reviewed.[62] Calculations of the electron and spin densities of corresponding radicals and radical cations have been used to discuss the oxidation of tetrafluorobenzene derivatives with cerium(IV) perchlorate.[63] A single-electron transfer is proposed in the oxidation of α-amino-4-imidazolepropionic acid

by cerium(IV) perchlorate.[64] The oxidation of the amino-acids Asp, Phe, and Ser by Ce(IV) to aldehydes, NH_3, and CO_2 is pseudo-first order whereas the oxidation of Met is second order.[65] The kinetics of the oxidation of benzyl alcohol to benzaldehyde by ceric sulfate have been studied.[66]

Non-linear effects (NLEs) between *ee* of reagent or ligand and product *ee* indicate the differential participation or non-participation of diastereomeric species.[67] Kagan and co-workers have suggested these as potential fingerprints of asymmetric processes using the example of asymmetric sulfoxidation by $Ti(i\text{-}PrO)_4$–tartrate–peroxide systems to highlight remarkable complexity in observed NLEs even with minor system modifications.[67] Asymmetric oxidations of alkyl azaheterocyclic sulfides using a TADDOL system incorporating a 1,4-diol ligand, titanium tetraisopropoxide, and *t*-butyl hydroperoxide give sulfoxides which are moderately enriched in the *S*-enantiomer.[68] The system displays linear chiral induction, suggesting an active species that contains only one TADDOL ligand. A model is proposed for the intermediate in which the peroxide is chelated to titanium and the substrate is axially bound such that the terminal peroxy oxygen, the titanium and the sulfur are coplanar. Titanium-catalysed, asymmetric sulfoxidation of alkyl aryl sulfides with chiral hydroperoxides has been studied, with (*S*)-(−)-1-phenylethylhydroperoxide being most effective.[69] Detailed mechanistic studies showed that the enantioselectivity results from a combination of a low selectivity (*ee* <20%) induction and then kinetic resolution (*ee* 80–85%) of the sulfoxide to sulfone. The over-oxidation (and better stereoselectivity) is attributed to preferential sulfoxide coordination to titanium.

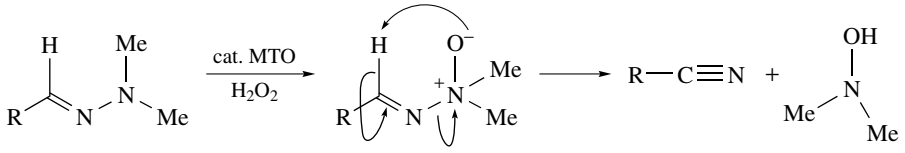
The oxidation of thioglycolic, thiomalic, and thiolactic acids in DMSO is first-order in tetrabutylammonium-12-tungstocobaltate(III) ion.[70]

The first example of the catalytic asymmetric oxidation of *t*-butyl disulfide to thiosulfinate has been described.[71] The use of a chiral Schiff base ligand, stoichiometric H_2O_2, and 0.25 mol% $VO(acac)_2$ gave the product in 91% *ee* and 92% yield. Good nucleophiles displace the *t*-BuS in the thiosulfinate with inversion of configuration as a ready route to various enantio-rich sulfinyl compounds. The oxidation of tartaric acid by vanadium(V), with and without control of ionic strength, has been investigated and a mechanism proposed for both cases. Comparison with published data on maleic and tartaric acid reveal that electron-withdrawing groups at the α-position of the substrate increase the oxidation rate.[72] A high negative ρ value (−3.64) was obtained in the oxidation of (phenylthio)acetic acids by vanadium(V) to corresponding diphenyl disulfide.[73]

The kinetics of the catalytic oxidation of cyclopentene to glutaraldehyde by aqueous hydrogen peroxide and tungstic acid have been studied and a compatible mechanism was proposed, which proceeds via cyclopentene oxide and β-hydroxycyclopentenyl hydroperoxide.[74] Monosubstituted heteropolytungstate-catalysed oxidation of alkenes by *t*-butyl hydroperoxide, iodosobenzene, and dioxygen have been studied; a radical mechanism was proved for the reaction of alkenes with *t*-BuOOH and O_2, but alkene epoxidation by iodosobenzene proceeds via oxidant coordination to the catalyst and has a heterolytic mechanism.[75]

Methyltrioxorhenium (MTO) is now well established as a catalyst in a number of oxidations employing hydrogen peroxide. Two groups have now reported,

independently, that this combination can be used for the oxidative transformation of *N*,*N*-dimethylhydrazones derived from aldehydes into nitriles.[76,77] The reaction has wide scope (aliphatic, unsaturated, aromatic, and heterocyclic aldehydes have all been used successfully), proceeds in high yields, and is selective over epoxidation of C=C bonds elsewhere in the substrate. It is suggested that the oxidation proceeds via the *N*-oxide (Scheme 2) which undergoes a Cope-type elimination of dimethylhydroxylamine to generate the nitrile. The former is further oxidized by a second equivalent of H_2O_2 to generate a nitrone, which has been detected by NMR. Stankovic and Espenson[76] reported that the optimum medium is acetonitrile–acetic acid–pyridine (94.5:5:0.5), the acid purportedly required to inhibit deactivation of MTO to perrhenate, and the pyridine to prevent hydrolysis to the parent aldehyde. However, Rudler and Denise[77] obtained comparable yields using ethanol alone as the solvent.



MTO = MeRe(=O)$_3$

SCHEME 2

Cerium(IV) oxidations of organic substrates are often catalysed by transition metal ions. The oxidation of formaldehyde to formic acid by cerium(IV) has been shown to be catalysed by iridium(III).[78] The observed kinetics can be explained in terms of an outer-sphere association of the oxidant, substrate, and catalyst in a pre-equilibrium, followed by electron transfer, to generate $Ce^{III}(S)Ir^{IV}$, where S is the hydrated form of formaldehyde $H_2C(OH)_2$. This is followed by electron transfer from S to Ir(IV) and loss of H^+ to generate the $H_2C(OH)O^{\bullet}$ radical, which is then oxidized by Ce(IV) in a fast step to the products. Ir(III) catalyses the *N*-bromobenzamide oxidation of mandelic acid[79] and *N*-bromosuccinimide oxidation of cycloheptanol in acidic solutions.[80]

The aerobic oxidation of terminal alkenes to alkan-2-ones is normally catalysed by an aqueous solution of palladium(II) and copper(II) salts under Wacker conditions. The copper(II) serves to mediate the re-oxidation of Pd(0) to Pd(II); addition of HCl is also necessary to inhibit clustering of atomic palladium, but this has drawbacks including reduction of catalytic activity, formation of chlorinated by-products and isomerization in the case of higher alkenes. Sheldon and co-workers, as part of a series of investigations of catalytic conversions in water, have shown that water-soluble palladium complexes with chelating diamines are able to catalyse such reactions efficiently, without the need for copper ions, chloride ions, or an organic solvent.[81] Bathophenanthroline disulfonate as ligand gave the best results; for example, hex-1-ene underwent 48% conversion into hexan-2-one in >99% selectivity. The catalyst could be recycled with only modest loss of activity, provided that sodium acetate was added, the role of which is probably to inhibit the formation of palladium clusters. Palladium(II) has been found to catalyse the oxidation of allyl alcohol by alkaline periodate.[82] The rate

increased upon addition of chloride ions, and the kinetic data were interpreted in terms of complex formation between the catalyst and substrate. The complex is oxidised by $H_2IO_6^{3-}$ in a rate-determining step to generate the $CH_2{=}CH\dot{C}HOH$ radical, which is then oxidized in a fast step to the product acrolein. It is proposed that the complex is a four-coordinate π-complex, in which the allyl alcohol acts as a bidentate ligand to palladium, binding through the alcohol and via the C=C double bond, the remaining sites being occupied by chloride and OH.

In the oxidation of glycolaldehyde in alkali, a two-electron-transfer process is proposed for Pt(IV) but a one-electron-transfer process for Ir(IV).[83]

Group VIII Metals

The mechanistic distinction between the iron–*t*-butyl hydroperoxide (TBHP) and the so-called Gif systems (iron salts and hydrogen peroxide) lies in the solely radical nature of the former, whereas in the Gif system, after initial formation of a carbon–iron bond, two manifolds exist, one involving Fe(III)–Fe(V) in which no radical is formed and the other involving Fe(II)–Fe(IV) in which fragmentation of the Fe(IV) species may give Fe(III) and a carbon radical in some cases. In radical chemistry, cyclooctane is more reactive than cyclohexane, while the reverse is true in Gif reactions. Furthermore, in Gif chemistry, saturated hydrocarbons are oxidized in the presence of alcohols without significant reaction of the latter. Competitive oxidations involving combinations of the above cycloalkanes and cyclooctanol, cyclohexanol, or 3-pentanol reveal product ratios consistent with a mechanism for the Gif reaction in which there is no initiation by oxygen radicals.[84] A review of Gif chemistry in 1998 by the late Sir Derek Barton, the originator, reinforces these conclusions.[85] The key observation is that the selective oxidation of saturated hydrocarbons in the presence of reductants such as H_2S or PhSeH is not compatible with radical chemistry, as has been suggested by others.

The Belusov–Zhabotinsky (BZ) reaction is catalyzed by a different mechanism when low-reduction-potential couples such as $[Fe(phen)_3]^{3+}/[Fe(phen)_3]^{2+}$ are employed. Experimental results for the BZ reaction with this couple in aerated conditions are compared with satisfactory agreement to a model calculation based on an 18-step skeleton mechanism, which includes reactions of organic radicals and molecular oxygen.[86]

Various metallo-phthalocyanines (Pht) and metallo-tetraphenylporphyrins (TTP) have been tested as catalysts for the oxidation of sulfides into sulfones by hydrogen peroxide.[87] TPPFe(III)Cl in ethanol was the only catalyst tested to give 100% conversion into sulfones in under 5 min; sulfoxides were identified as intermediates. PhtFe(III) gave sulfoxides in 100% yield and PhtMn(III) and TPPMn(III)Cl gave the sulfoxides in up to 70% yields. The absence of any by-product, in particular disulfide, suggests that a sulfenium radical cation is not an active intermediate in this process. The active metallic species is thought to be the oxene, $Por{-}\overset{+\bullet}{M}{=}O$; the mechanism is discussed in terms of the competing reactions of this species and the superior performance of the Fe(III) over the Mn(III) system is attributed to the faster oxygen transfer from the oxene to the sulfide or sulfoxide.

The oxidative behaviour of glycolaldehyde towards hexacyanoferrate(III) in alkaline media has been investigated and a mechanism proposed, which involves an intermediate alkoxide ion.[88] Reactions of tetranitromethane with the luminol and luminol-peroxide radical anions have been shown to contribute substantially to the tetranitromethane reduction in luminol oxidation with hexacyanoferrate(III) in aerated aqueous alkali solutions.[89] The retarding effect of crown ethers on the oxidation of triethylamine by hexacyanoferrate(III) ion has been noted.[90] The influence of ionic strength on the rate constant of oxidation of ascorbic acid by hexacyanoferrate(III) in acidic media has been investigated.[91] The oxidations of CH_2=CHX (where X = CN, $CONH_2$, and CO_2^-) by alkaline hexacyanoferrate(III) to diols have been studied.[92]

The kinetics of the oxidation of 1,4-thioxane by potassium ferrate have been studied and a mechanism involving the reaction of thioxane and protonated ferrate as the rate-determining step is proposed.[93] An iron–carboxylate complex immobilized on a modified silica surface is able to catalyse the aerobic oxidation of hexane to a mixture of hexan-1-ol, -2-ol, and -3-ol, with no ketone formation.[94] Reaction does not proceed in the absence of a thiol (propane-1,3-dithiol) and yields and rates were greatly increased by added triphenylphosphine and acetic acid. A mechanism has been put forward in which reduction of Fe(III) to Fe(II) by the thiol initiates the reaction and the alkyl disulfide formed reacts with Ph_3P to form a thioalkoxyphosphonium cation intermediate. Oxygen-18 labelling studies suggest that this intermediate is attacked by a dioxygen–metal adduct to generate Ph_3PO and an iron-oxo species from which oxygen is transferred to the substrate. Parallels are drawn with reactions in cytochrome P-450 model studies.

Ruthenium(III) catalyses the oxidative decarboxylation of *n*-butyric acid and isobutyric acid by ceric sulfate in aqueous acid.[95] A mechanism for the Ru(III)-catalysed oxidation of *o*-hydroxybenzoic acid by an acidic solution of bromamine-B ($PhSO_2$-NNaBr, BAB) has been proposed based on a kinetic study.[96] An ionic mechanism is suggested for the ruthenium(III) analogue of the Udenfriend-type system Ru(III)–EDTA–ascorbate–O_2, for the selective oxygen-atom transfer to saturated and unsaturated hydrocarbons.[97] The kinetics of the oxidation of p-$XC_6H_4CHPhOH$(X = H, Cl, Br, NO_2, Me, MeO) by bromamine-B, catalysed in the presence of HCl in 30% aqueous methanol by $RuCl_3$ have been studied and a biphasic Hammett σ-relationship derived.[98] A kinetic study of the ruthenium(III)-catalysed oxidation of aliphatic primary amines by sodium *N*-bromo-*p*-toluenesulfonamide (bromamine-T, BAT) in hydrochloric acid medium has been undertaken and the mechanism of the reaction discussed.[99] A concerted hydrogen-atom transfer one-electron transfer mechanism is proposed for the ruthenium(III)-catalysed oxidation of 2-methylpentane-2,4-diol by alkaline hexacyanoferrate(III).[100] The kinetics of the oxidation of propane-1,3-diol under the same conditions have been studied.[101] Ruthenium(III) catalyses the oxidation of primary alcohols by bromamine-B. A Taft LFE reaction constant of $\rho^* = -0.77$ indicates the development of positive charge in the transition state.[102]

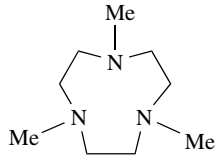
In the presence of ruthenium trichloride, alkaline sodium hypochlorite is able to oxidize methylbenzenes to benzoic acids under phase-transfer conditions at room temperature. In a recent development, selective oxidation of xylenes to toluic acids has

been achieved.[103] The selectivity for oxidation of just one of the two methyl groups lies in the fact that the monobenzoic acid, once formed, is immediately extracted into the aqueous phase. Electron-withdrawing substituents in the ring which have lone pairs of electrons (e.g. Cl or Br) direct the oxidation to the methyl group *ortho* or *para* to it, whereas for those with no unshared pairs of electrons (e.g. nitro, sulfonate, or carboxylate), the methyl group in the *meta* position is oxidised. This is rationalised in terms of the ability of the substituent to stabilise the carbocation formed by hydride abstraction from the substrate by RuO_4. Electron-donating substituents also favour ring chlorination.

A kinetic study of the oxidation of secondary alcohols by *N*-methylmorpholine-*N*-oxide (NMO) catalysed by the *trans*-dioxo-ruthenium(VI) complex, $[PPh_3(CH_2Ph)]^+[Ru(O)_2OAcCl_2]^-$, or tetrapropylammonium perruthenate indicates that the first step of the mechanism is the formation of a complex between the catalyst and substrate.[104] The oxidations of a series of benzydrols by *trans*-$[(TMC)Ru(VI)(O)_2]^{2+}$ (TMC = 1,4,8,11-tetramethyl-1,4,8,11-tetraazocyclotetradecane) are correlated by a Hammett σ plot indicating that a carbocation-type intermediate is not involved. A primary deuterium isotope effect for the α-proton and absence of an O–D isotope effect suggest that α-C–H bond cleavage is rate-limiting. Two mechanisms are proposed:[105] one is a 2 + 2(C–H + Ru=O) addition involving an organometallic intermediate in which the new ligand is attached through carbon; the other involves the formation of an intermediate ruthenate ester, in which the oxygen-bound ligand undergoes a cyclic transfer of hydrogen to Ru=O, thereby being released from the metal. Molecular-orbital considerations favour the second theory.

A mechanistic investigation of four Schiff base–Ru(IV) complexes in asymmetric epoxidation has been conducted.[106] The observation of inverse kinetic isotope effects for the oxidation of β-d_2-styrene due to rehybridization and its absence in the α-deuteriostyrene oxidations discount a rate-limiting formation of a metallooxetane or a concerted oxene insertion mechanism. A linear-free-energy relationship between log k and total substituent effects for the ruthenium oxidation of *para*-substituted styrenes suggests a rate-limiting formation of a benzylic radical intermediate. Moderate enantioselectivities were observed because the acyclic carbon-centred radical intermediate undergoes collapse (*cis*) or rotation–collapse (*trans*) processes before the epoxide-forming ring closure.

Complex (**1**) is a catalyst for selective oxidation of benzylic, allylic alcohols to aldehydes, and secondary alcohols to ketones using *t*-butyl hydroperoxide.[107] Primary aliphatic alcohol oxidation failed. The use of cumyl hydroperoxide as radical probe discounted the involvement of *t*-BuO$^\bullet$/*t*-BuOO$^\bullet$. Hammett studies ($\rho = -0.47$) and kinetic isotope effects ($k_H/k_D = 4.8$) have been interpreted as suggesting an Ru–OO–Bu-*t* intermediate oxidant.



$Ru^{III}(CF_3CO_2^-)_3$

(**1**)

The kinetics of osmium(VIII)-catalysed oxidation of dimethyl sulfoxide by diperiodatonickelate(IV) in aqueous alkaline medium have been investigated.[108] Monoperiodatonickelate(IV) and $[OsO_4(OH)_2]^{2-}$ were the suggested active species of oxidant and catalyst, respectively. The kinetics of oxidation of cycloheptanol by hexacyanoferrate(III) in the presence of Os(VIII) have been investigated; a low [Os(VIII)] allows its continuous regeneration by hexacyanoferrate(III) ions.[109] Oxidation of propanal by potassium hexacyanoferrate(III) catalysed by osmium tetraoxide in alkaline media is zero order with respect to oxidant and first order with respect to catalyst.[110] The kinetics of the oxidation of reducing sugars by osmium tetraoxide in alkaline medium suggest the formation of an activated complex between enediol and osmium tetraoxide, which slowly disproportionates to give an osmium(VI) species and the intermediate products. Key changes are mainly due to the known Lobry de Bruyn–Van Ekenstein reaction.[111] Os(VIII) catalyses the oxidation of glutamic acid by chloramine-T.[112] In the oxidation of glycolaldehyde in alkali, a two-electron-transfer process is proposed for Os(VIII).[83]

Oxidation by Compounds of Non-Metallic Elements

Nitrogen, Sulfur, and Tellurium

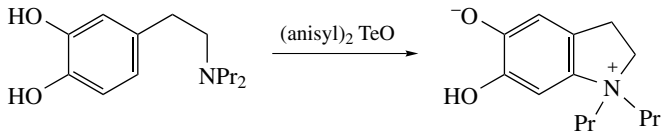
Many oxaziridines are oxidants. 2-*t*-Butyl-3-phenyloxaziridine, hitherto thought to be inactive as an oxidant owing to thermal rearrangement to *N*-*t*-butyl-α-phenyl nitrone, has now been shown to be effective in oxidizing sulfides to sulfoxides, provided that very high pressures are employed.[113] At 800 MPa, methyl phenyl sulfide was oxidized to methyl phenyl sulfoxide, the other major product being *N*-*t*-butylbenzaldimine (from the oxaziridine). At a lower pressure of 400 MPa, in contrast, the major product was *N*-*t*-butyl-α-phenyl nitrone. These results are interpreted in terms of competition between oxaziridine ring rearrangement and sulfide oxidation. Both processes release strain in the oxaziridine, but the latter requires the close approach of the two reactants, which is excessively hindered at all but very high pressures by the bulkiness of the substituents. Davis and co-workers have studied the oxidation of enolates of 1,3-dicarbonyl compounds using (camphorylsulfonyl)oxaziridine as a source of electrophilic oxygen to give an α-alkoxide that, upon work-up, gives an α-hydroxy product or undergoes Baeyer–Villiger-type rearrangement via the attack of O^- on the neighbouring C=O.[114] Only when the keto group was part of six-membered rings were useful *ee*s observed.

Nitrosoalkanes $Me_2C(CH_2X)NO$ are oxidized by NO_2 in CCl_4 much more rapidly than nitrosoarenes. Using stopped-flow techniques, Arrhenius parameters have been determined for several X substituents, revealing that electron-withdrawing substituents significantly decrease the rates, an observation that has been discussed in terms of the atomic charges at the nitrogen atom as calculated by the TNDO/2 method.[115] L-Ascorbate reduces substituted nitrosobenzenes giving the corresponding phenylhydroxylamines.[116] A Hammett σ^+ relationship and a primary kinetic deuterium isotope effect suggest that the reaction proceeds via a rate-determining cyclic transition state in which the transfer of the 2-H proton of ascorbate and the electron transfer from the anionic ascorbate oxygen are concerted.

Peroxynitrous acid, which has an estimated lifetime of 1–3 s at neutral pH, has been studied through *ab initio* calculations that suggest that peroxynitrous acid, peroxyformic acid, and dimethyldioxirane have, despite diverse O–O bond energies, similar activation energies for oxygen-atom transfer.[117] The transition-state structures for the epoxidation of ethene and propene with peroxynitrous acid are symmetrical with equal or almost equal bond distances between the spiro oxygen and the carbons of the double bond.

The kinetics of oxidation of several *para*-substituted anilines[118] and aliphatic acetals[119] by peroxomonosulfate in aqueous acetic acid have been investigated. In the oxidation of sulfides to sulfoxides by peroxymonosulfate (Oxone), the observed increase in second-order rate constants with increasing concentration of H_2SO_4 has been shown to be due to the increasing polarity of the medium, rather than to acid catalysis.[120] Similar conclusions were arrived at for the oxidation of aryl thiobenzoates and thiol-phosphorus(V) esters.

Dianisyltellurium oxide (DAT) is a mild and selective oxidant for quinone formation.[121] Treatment of the *N*,*N*-di-*n*-propyldopamine (**2**) with DAT leads to the betaine (**3**), which is identical with the product of oxidation by the enzyme tyrosinase both of (**2**) and of the monohydric phenol *N*,*N*-dimethyltyramine. The implications and relevance to the mode of action of tyrosinases have been discussed.



(**2**) (**3**)

Halogens

The oxidations of secondary alcohols and sulfides by halamine polymers produce ketones and sulfoxides, respectively, with some sulfones and chlorosulfoxides produced in the latter case. A mechanism is proposed based on the oxidation kinetics.[122] A review of the oxidation of haloalkanes with halogens and their derivatives has appeared.[123]

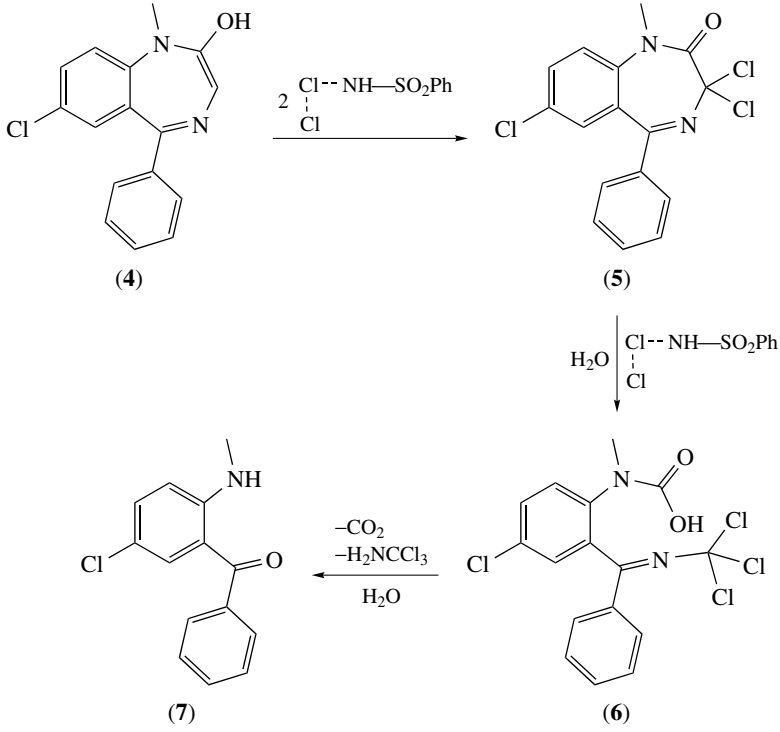
In the oxidation of aliphatic amines by aqueous chlorine, the key rate-limiting step is the transfer of chlorine from HOCl to the amino group N with probable involvement in the transition state of water molecules.[124]

The oxidation of formaldehyde by chlorite, ClO_2^-, has been studied in aqueous solution.[125] In the presence of excess chlorite, formaldehyde was oxidized to CO_2, with ClO_2 also being formed. This compound was also obtained as an oxidation product when HCHO was in excess, in which case the latter was oxidized only as far as formic acid. The first step of the reaction produces HOCl, which acts as an autocatalyst, catalysing the formation of ClO_2 and the further oxidation of HCO_2H to CO_2. The build-up of ClO_2 is due to the fact that HOCl reacts much more rapidly

with ClO_2^- than with the other reductants, and also to the relative unreactivity of ClO_2 towards HCHO and HCO_2H.

Kinetic studies on the oxidation of amino acids by chloramine-B (CAB, $PhSO_2NNaCl$) in acidic aqueous methanol reveals a dependence of the mechanism on the solvent composition and pH; a two-pathway mechanism is therefore proposed with substrate-dependent and independent paths.[126] The oxidation of diazepam by chloramine-B in aqueous hydrochloric acid medium was studied and found to exhibit first-order kinetics in the oxidant and fractional orders in HCl and diazepam. The overall reaction was found to involve a six-electron change. In acidic solution, chloramine-B exists in equilibrium between a variety of species; kinetic studies showed $PhSO_2NHCl$ to be the effective oxidizing species. A mechanism (Scheme 3) was proposed[127] in which $PhSO_2NHCl$ is protonated and forms an ion pair with chloride ion. This intermediate then reacts with the substrate in the enol form (**4**) giving an intermediate, which reacts with a second molecule of the oxidant to give the dichloro species (**5**). A final reaction of the oxidant with simultaneous hydrolysis gives (**6**) which, after decomposition in the presence of water, gives the product (5-chloro-2-methylaminophenyl)phenylmethanone (**7**).

It is suggested that oxidative degradation of D-mannosamine, D-galactosamine, and D-glucosamine by CAB involves attack of an anomeric alkoxide on CAB as a source of Cl^+ followed by elimination to lactone.[128]



The kinetics of the oxidation of metol [4-(methylamino)phenol sulfate] with chloramine-T (sodium *N*-chloro-*p*-toluenesulfonamide) have been studied, and possible mechanisms in which $ArSO_2NHCl$ was the reactive species have been discussed.[129] The kinetics of oxidation of some substituted piperidin-4-ols by chloramine-T have been studied and a compatible mechanism proposed.[130] The kinetics of oxidation of D-mannosamine by chloramine-T in alkaline medium are consistent with a stepwise mechanism in which the reaction of the enol-anion of the sugar with the oxidant is rate limiting.[131] A mechanism involving the aldo-enolic anions of pentoses and keto-enolic anions of hexoses is suggested for the oxidation of *erythro*-series pentoses and hexoses by chloramine-T.[132] Tetracyclines are oxidized by chloramine-T in aqueous acetic acid with concomitant decarboxylation.[133] The kinetics of oxidation of amino acids (leucine, serine, asparagine, glutamine, glutamic acid, and proline) by chloramine-T have been investigated.[134] The kinetics of chloramine-T oxidation of triethanolamine in alkaline media have been investigated.[135]

Mechanisms involving glycol bond fission have been proposed for the oxidation of vicinal diols, and hydride transfer for other diols in the oxidation of diols by bromine in acid solution.[136] The kinetics of oxidation of some five-ring heterocyclic aldehydes by acidic bromate have been studied.[137] The reaction of phenothiazin-5-ium 3-amino-7-dimethylamino-2-methyl chloride (toluidine blue) with acidic bromate has been studied.[138] Kinetic studies revealed an initial induction period before the rapid consumption of substrate and this is accounted for by a mechanism in which bromide ion is converted into the active bromate and hyperbromous acid during induction and the substrate is converted into the demethylated sulfoxide.

A primary kinetic isotope effect ($k_H/k_D = 6.03$ at 298 K) was observed for the oxidation of formic and oxalic acids by benzyltrimethylammonium tribromide (BTMAB) to carbon dioxide.[139] The kinetics of oxidation of pyridoxine to pyridoxal by bromamine-T and bromamine-B[140] and caffeine by bromamine-B[141] have been investigated.

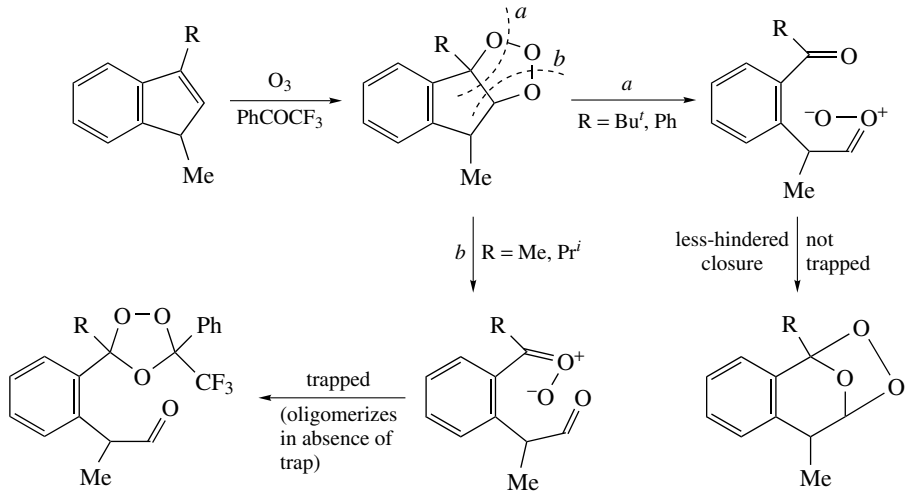
Kinetic studies of the oxidation of aspirin by bromamine-T, *N*-bromosuccinimide (NBS), and *N*-bromophthalimide (NBP) support a mechanism in which the unprotonated oxidant is the active species.[142] The ultimate product of the reaction is 2,4,6-tribromophenol, which arises through decarboxylation, bromination and loss of acetic acid. The NBP and NBS oxidations of α-hydroxy acids are found to be similar in mechanism.[143]

The effect of pH on the periodate oxidation of seven anilines has been investigated.[144] The kinetics of periodate oxidation of aromatic amines have been studied.[145,146] Periodate oxidation of oxalic acid is catalysed by Mn(II).[147] The reaction of ethane-1,2-diol with periodate has been investigated under a variety of conditions and the results compared with those of earlier work and analogous studies on pinacol.[148] The IO_4^- ion is the primary reactant, with H_5IO_6 as a secondary reactant; the reverse is true for pinacol. The complex observed in previous work is shown not to be an intermediate, but rather to deactivate the reactants.

Ozonolysis and Ozonation

Solvent effects on relative stability and electronic and molecular structure of carbonyl oxide (Criegee) intermediates in ozonolysis have been analysed by *ab initio*

calculations and revealed that stability was enhanced by favouring the zwitterionic form of carbonyl oxide.[149] A theoretical study of the electronic structures of oxygenated dipoles in relation to concerted and biradical mechanisms of 1,3-dipolar additions and ozonolyses in the gas phase has been published.[150] Ozonolyses of 3-alkyl-substituted 1-methylindenes and cyclopentenes suggest that collapse of the primary ozonide is influenced by the bulk of the substituent R (Scheme 3).[151] The nature of the resulting carbonyl oxide–carbonyl pair then influences the success of secondary ozonide formation.



SCHEME 3

Ozonolysis of styrene and ethylidenecyclohexane in the presence of [^{17}O]benzaldehyde yields stable secondary ozonides incorporating ^{17}O. ^{17}O NMR showed that labelled oxygen appeared as the ether oxygen, not the peroxo bridge, thus confirming the Criegee mechanism as opposed to the so-called unified concept.[152]

Gas-phase oxidations by ozone are important in atmospheric chemistry. A detailed study of the ozone oxidation of ethene at atmospheric pressure has been carried out using FTIR spectroscopy to monitor product formation and reactions of the Criegee intermediate, in the presence of hydroxy and carbonyl compounds.[153] A detailed kinetic analysis for reaction of 2,3-dimethylbut-2-ene has also been reported.[154] The mechanism of ozonolysis of methyl vinyl ketone, methacrolein, methacrylic acid, and acrylic acid in the gas phase have been investigated, and in particular the fate of the Criegee intermediate or carbonyl oxide was addressed.[155] Rate constants for the gas-phase ozonolysis of a range of unsaturated oxygenates were measured and compared with literature data. The results were discussed in terms of reactivity towards ozone as a function of the nature, number, and position of oxygen-containing substituents.[156] OH radicals were detected in reactions of ozone with alkenes in the gas phase by the use of hydrocarbon OH 'tracer' compounds.[157]

Ozone also reacts with *ethane* in the gas phase at room temperature. Rather than a direct molecular reaction, however, evidence points to the initiation of radical-chain reactions by the very small O-atom concentrations present in ozone at room temperature.[158] Added oxygen scavenges the radicals and slows the build-up, leading to induction periods which may be in excess of 3 h. Recent advances in mechanistic investigations of gas-phase ozonolysis of alkanes have been reviewed.[159] Oligomeric peroxides dominate the products of oxidation of nitrotoluenes with ozone in acetic acid.[160]

Peracids and Peroxides

Peracids *m*-CPBA and CF_3CO_3H have been used in epoxidations of substrates with two tunable allylic directing groups expected to direct the peracids to opposite faces of the alkene. Control of face selectivity was observed and attributed to the different binding abilities of the two peracids to the various allylic functionalities, carbamate on one side of the alkene and alcohol, methyl ester, acetate, trifluoroacetate, or TBS-ether on the other.[161] The conversion of *N*-mono-protected and *N*-di-protected cyclopent-3-enylamines to corresponding cyclopentene oxides using *m*-CPBA gave *cis*-epoxides and *trans*-epoxides, respectively. Amines protected with sterically small sulfonamides and carbamates gave the best *cis* selectivity; this is explained by hydrogen bonding between the *m*-CPBA and the NH for *N*-mono-protected amines, whereas *trans*-epoxides result from purely steric effects.[162] *Ab initio* calculations for the epoxidation of allyl alcohols with peroxyformic acid have revealed that the directing effect of the hydroxyl group is due to hydrogen bonding between the carbonyl oxygen of the peroxy acid and the allylic OH.[163]

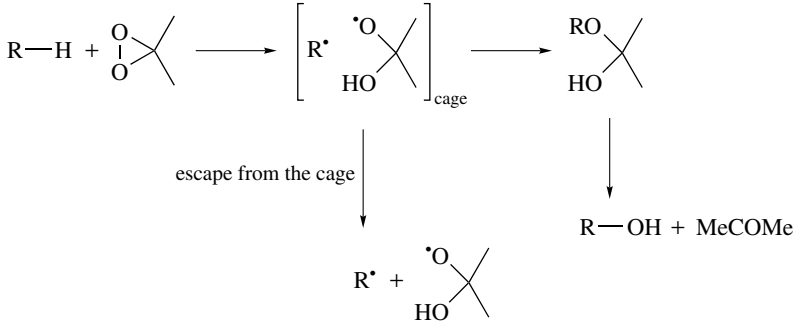
The oxidation of sulfoxides by aliphatic peroxy acids is first order in both reactants; the solvent effects have also been investigated.[164] Thiosulfinates are oxidized by peroxy acids to thiosulfonates and not disulfoxides. It had previously been proposed that the disulfoxides are formed first but homolytically cleave and recombine to give thiosulfonates. A series of *ab initio* calculations were performed (at the 3–21G* and 6–31G* levels) which indicate little difference in the rate of oxidation of S over S(O) in the gas phase but faster S(O) oxidation in a reaction cluster.[165]

The use and investigation of dioxiranes continues to expand rapidly. In low-conversion mono-epoxidations of allylic alcohols with (trifluoromethyl)methyldioxirane (TFDO) and dimethyldioxirane (DMDO), the less nucleophilic 2,3-double bond of geraniol is rendered more reactive by a hydrogen-bond-stabilized transition state when less polar aprotic solvents are used, although the effect is more pronounced with DMDO.[166] In chiral allylic alcohols, intramolecular hydrogen bonding controls the diastereoselectivity. In TFDO epoxidations of cyclic allylic alcohols, no enone formation is seen, as it is with DMDO. Kinetic data for the epoxidation of *cis*-alkenes and cycloalkenes with DMDO in acetone are consistent with a mechanism involving a spiro transition state.[167] DFT at the B3LYP/6–31 G* level, using a model solvent dielectric $\varepsilon = 20$, for the DMDO-mediated epoxidation of 2-methylbut-2-ene allowed enthalpies of activation to be calculated similar to those determined experimentally in acetone.[168] The system also showed substantially decreased activation barriers

when hydrogen-bonding substituents were present due to hydrogen bonding and not due to inductive effects. An even more significant lowering was observed when hydrogen bonding to methanol as a model protic solvent and this can understandably account for lowered selectivities in such solvents. 6–31 G*-level calculations for alkene epoxidation using dioxiranes predict a symmetrical spiro-butterfly transition state with two identical C—O forming bond lengths[169] and support hydrogen-bonding interactions (<25 kJ mol^{-1}) in the epoxidations of allylic alcohols with dioxiranes.[170]

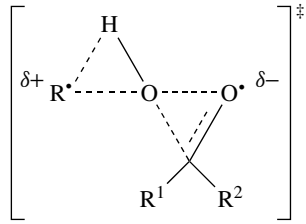
In situ-generated *N*-oxides have been shown to react with DMDO or TFDO reverting to the corresponding amines and singlet oxygen, $^1O_2$. In the case of nucleophilic, heteroaromatic *N*-oxides, the decomposition of the dioxirane by the *N*-oxide is slow compared with the oxidation, and the *N*-oxide predominates.[171] As discussed in *Organic Reaction Mechanisms 1997*, the mechanisms of many oxidations by dimethyldioxirane have been the subject of some controversy. Increasingly, evidence points to an electrophilic S_N2 mechanism (e.g. for epoxidation and alkene-insertion reactions), but other studies have suggested the involvement of bis(oxyl) radicals. The oxidation of a series of *N*,*N*-dimethylanilines by DMDO (to the *N*-oxides) has been investigated with respect to sensitivity to *para* substituents, and compared with analogous oxidations by *t*-butyl hydroperoxide (TBHP) (where a homolytic pathway is thought to be involved) and benzoyl peroxide (electrophilic mechanism).[172] Reactivity decreased in the order MeO > H > Cl > NO_2 for oxidations by DMDO and $(PhCOO)_2$, in line with an electrophilic mechanism, whereas the TBHP reactions were less susceptible to changes in substituent, as expected for a non-electrophilic reaction. Further analysis showed no evidence for free radicals or electron transfer in the DMDO oxidation.

Similarly, an interesting and somewhat controversial discourse has developed as to the mechanism of DMDO-mediated alkene oxidation: is it concerted oxygen insertion or radical? Although the former is more widely accepted, Minisci and co-workers have presented evidence that supports a radical mechanism.[173] Trapping products and the effect of oxygen suggested a molecule-induced homolysis of DMDO by alkanes, ethers, and aldehydes through hydrogen abstraction. The oxidation then occurs through cross-coupling of the radical pair in the solvent cage (rebound), while radicals escaping from the cage can initiate chains (Scheme 4). Less evidence exists for the subsequent suggestion by the authors that alkene epoxidation by analogy also proceeds in this way.



SCHEME 4

DMDO hydroxylation of a hypersensitive radical probe, *trans*-(2-ethylcyclopropyl)benzene, supports evidence for an oxygen-atom-insertion pathway over radical-pair formation.[174] Unrearranged and rearranged products are possible in this reaction, the latter arising from the ring opening of the radical formed by hydrogen abstraction from the cyclopropylcarbinyl position of the probe; a large predominance of unrearranged products was observed, indicating that the lifetime of the radical, if present, is too short for radical-pair formation. High-level *ab initio* calculations lend strong support to the generally accepted concerted electrophilic oxygen-insertion mechanism for the oxidation of alkanes to alcohols with dioxiranes under typical preparative conditions.[175] As part of this debate, *ab initio* calculations suggest a new mechanism of the dioxirane oxidation of aliphatic C−H bonds, which reconciles the apparently contradictory data.[176] A common transition state is suggested: the C−H bond is partially broken, the O−H bond is essentially completely formed, and the O−O bond is substantially broken (see structure). This is followed by either concerted transfer of the OH group to the carbon atom or separation into an α-hydroxyalkoxyl radical and an alkyl radical. These calculations reproduced the observed selectivity of the dioxirane oxidation of the C−H bonds in hydrocarbons, alcohols, and 1,2-diols. A very similar transition state was independently determined by Houk and co-workers.[177]

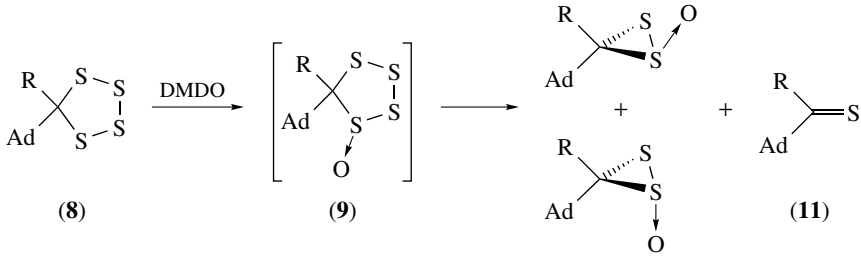


Kinetics of the dimethyldioxirane oxidation of adamantane in an oxygen atmosphere support a radical mechanism.[178] The kinetics of the oxidation of 2-methylbutane by DMDO in acetone solution have been studied and the mechanisms of the reaction and of inhibition of the reaction by O_2 were discussed.[179]

Oxidation of tetrathiolanes (**8**) with DMDO gave mixtures of dithiirane 1-oxides (**10**) and thioketones (**11**) (Scheme 5). The existence of the intermediate tetrathiolane 1-oxides (**9**) was verified by NMR of the cooled and evaporated reaction mixture.[180]

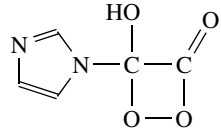
The relative reactivity of a wide series of nucleophiles towards dioxirane, dimethyldioxirane, carbonyl oxide, and dimethylcarbonyl oxide has been examined at various levels of theory.[181] The general trend in reactivity for oxidation by dioxirane was $R_2S \approx R_2SO$, $R_3P > R_3N$ in the gas phase, and $R_2S \approx R_2SO$, $R_3N \approx R_3P(R = Me)$ in solution. A theoretical study of the first oxidation step of [3.2.1]-bridged bicyclic disulfides highlights a highly oriented reaction path was probably responsible for stereoselective attack on the *exo* face.[182]

The existence of an intermediate species in the dioxygen transfer from 4a-hydroperoxyflavin anion to phenolate and indole anions has previously been shown and *ab initio* and semiempirical MO calculations have been used to examine possible candidates for



SCHEME 5

the intermediate;[183] two dioxetane species were identified as probable intermediates. Stopped-flow kinetics have been used to investigate the imidazole-catalysed peroxyoxalate chemiluminescence reaction of bis(2,4,6-trichlorophenyl) oxalate.[184] The failure of other amine bases suggests a role for imidazole as a nucleophilic catalyst. The results are consistent with an intermediate oxalyldiimidazole that reacts to form a monoperacid which in turn forms a high-energy light-generating intermediate (**12**).

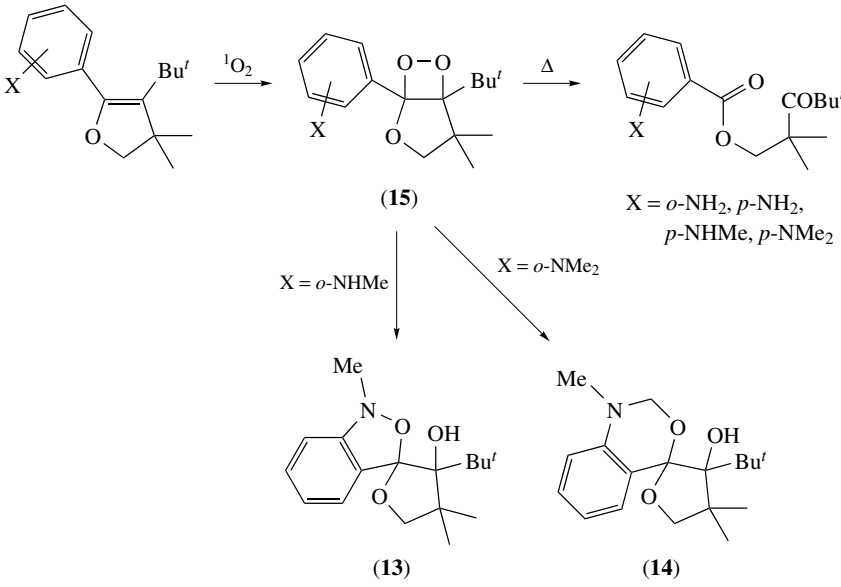


(**12**)

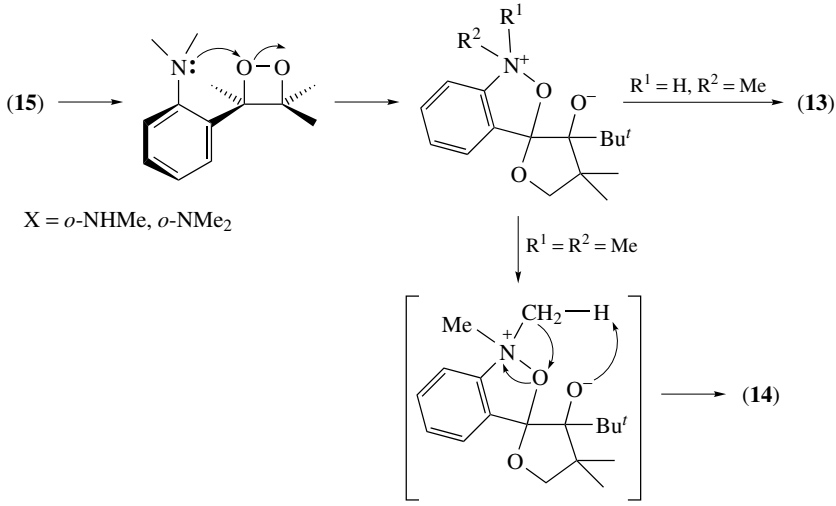
Although thermal decomposition of 1,2-dioxetanes normally leads to two carbonyl products, dioxetanes bearing a phenyl group substituted with an *N*-methylamino or *N*,*N*-dimethylamino group at the *ortho* position have been found to undergo a different and unusual decomposition pathway leading to heterocycles (**13**) and (**14**), despite the fact that the unsubstituted *o*- and *p*-amino analogues decompose in the normal fashion to carbonyl products (Scheme 6).[185] This interesting competitive pathway has been rationalized in terms of intramolecular nucleophilic attack of the *N*-methylamino group at the O−O moiety of the dioxetane and O−O bond fission, followed by proton exchange in the intermediate zwitterion (Scheme 7).

Hexamethylbenzene reacts with DMDO via three pathways: (i) to an arene oxide, which rapidly rearranges to an oxepin tautomer that then is oxidized to a *cis*-diepoxide and then to a *cis, cis,trans*-triepoxide; (ii) a methyl group migrates in the first epoxide to give a cyclohexadienone, which then reacts to give a *trans*-diepoxide; (iii) C−H insertion to give the benzyl alcohol and then the corresponding benzoic acid.[186]

Wang and Shi have published a detailed study of their fructose-based dioxirane epoxidation catalyst system with hydroxyalkene substrates.[187] The *ee*s obtained were highly pH dependent. The lower enantioselectivity obtained at low pH is attributed to the substantial contribution of direct epoxidation by Oxone. The results obtained with



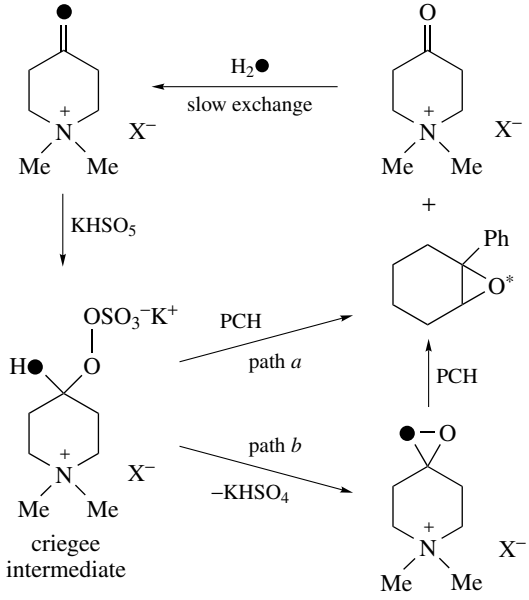
SCHEME 6



SCHEME 7

the corresponding TBS ethers strongly suggest that the epoxidation by Oxone was facilitated by the hydroxyl group in the substrate perhaps due to enhanced intramolecular epoxidation through hydrogen bonding or enhancing the aqueous solubility of the substrate.

Denmark and Wu have suggested[188] discrepancies in previous [^{18}O]dioxirane labelling experiments[189,190] and disclosed their results as shown in Scheme 8; 34% incorporation

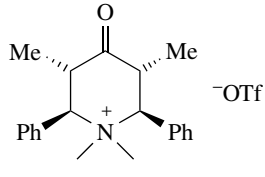


PCH = 1-phenylcyclohexene
● = ^{18}O (90% ^{18}O)
X = TfO

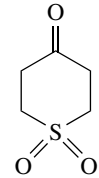
SCHEME 8

of ^{18}O into epoxide was observed. The disparity between 34% and the theoretically expected 43% (50% of the 86% present in the labelled water used) was attributed to the slow exchange of ketone O in $H_2{}^{18}O$. This was confirmed by increasing the number of ketone equivalents to 5, which gave increased (39%) incorporation. They suggest that the problem with previous ketone systems was that there was no mechanistically significant, ketone-catalysed pathway in those cases owing to the insolubility of the ketone in the aqueous phase, and that this explains the lack of ^{18}O incorporation observed in those previous cases.

By exploiting electrostatic field effects (unfavourable through-space charge–dipole repulsion) to increase the nucleophilic susceptibility of cyclohexanones, more efficient catalysts (**16**) and (**17**) for epoxidation through *in situ* dioxirane formation have been designed.[191]

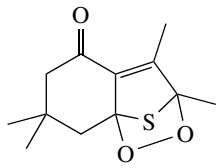


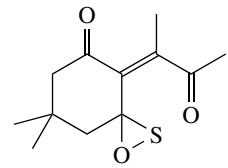
(**16**)

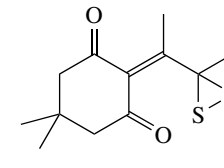


(**17**)

The thiophene endoperoxide (**18**) is a powerful episulfidation reagent.[192] The stereospecific transformation of *cis*- or *trans*-cyclooctene suggests a concerted process. First-order consumption kinetics have now shown that (**18**) is not itself the active *S*-transfer reagent: two such intermediates are proposed, possibly oxathiiranes such as (**19**) or (**20**), based on similarities in the trends for epoxidations of the same substrate by DMDO.[193]


(**18**)

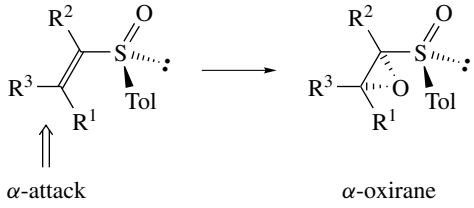

(**19**)


(**20**)

Pinene hydroperoxide (PHP) when compared with *t*-butyl hydroperoxide has been proposed as an excellent mechanistic probe in metal-catalysed oxidations.[194] If intermolecular oxygen transfer from a peroxometal species to the substrate is rate limiting, the bulky PHP is unreactive, but for reaction of an oxometal species as the rate-limiting step, little or no difference is observed and only small differences in reactivity are observed when re-oxidation of the catalyst by ROOH to an active oxometal species is the rate-limiting step.

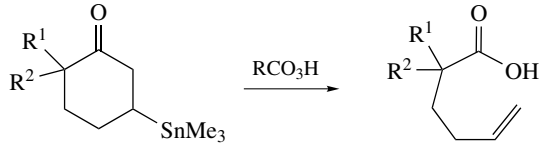
t-Butyl and cumene hydroperoxide allow hydroxylation of nitroarenes by vicarious nucleophilic substitution (nucleophilic addition of alkyl hydroperoxide anion followed by base-induced *E*2 β-elimination of ROH).[195] Stereoselective nucleophilic epoxidation of simple vinyl and dienyl sulfoxides with $NaOOBu^t$ or $KOOBu^t$ has been rationalized by initial nucleophilic addition to the α-face of the reactive conformation shown in Scheme 9 followed by epoxide ring closure.[196] It is likely that steric hindrance by the bulky tolyl group is a key factor. Interestingly, the diastereoselectivity of the epoxidation of (1*E*)-2-sulfinyl dienes can be altered by a simple change in the metal cation from Li^+ to Na^+.

Ab initio calculations of the transition-state energies in the epoxidation of alkenes by hydrogen peroxide catalysed by titanosilicates have been carried out.[197] They indicate a markedly lower energy barrier for attack of the alkene by the oxygen atom of the titanium(IV) hydroperoxide intermediate that is closer to the metal centre.



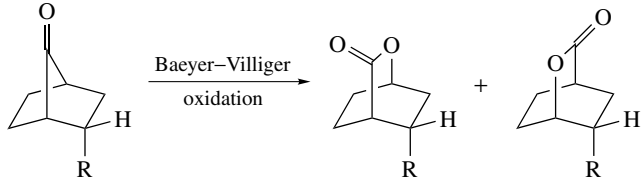
SCHEME 9

The Baeyer–Villiger (BV) oxidation of ketones to esters involves the migration of one of the groups flanking the carbonyl to the adjacent electron-deficient oxygen atom. For unsymmetrical ketones, the migratory aptitudes of the groups is determined by their relative abilities to support the developing positive charge in the transition state. It is well known that substituents of Group 14 (Si, Ge, and Sn) are able to stabilize positive charge at the β-position, and that a β-silicon atom does, indeed, enhance the migratory aptitude of groups in the BV reaction. A study of the BV reaction of β-stannyl cyclohexanones has now revealed that a β-trimethylstannyl substituent raises the migratory ability of a primary carbon to above that of a tertiary carbon (in the absence of other activation); thus, compounds (**21**)–(**23**) gave the acyclic alkene acids (**24**)–(**26**), either via the corresponding lactones or possibly a concerted breakdown of the initially formed tetrahedral intermediate.[198] A separate study on the BV oxidation of norbornan-7-ones has revealed a remarkable effect of distal 2-*endo*-substituents on migratory ability and hence on the regioselectivity of the reaction (Scheme 10).[199] Electron-withdrawing substituents at the C(2)-*endo* position reduce



(**21**) $R^1 = R^2 = H$
(**22**) $R^1 = H$, $R^2 = Me$
(**23**) $R^1 = R^2 = Me$

(**24**) $R^1 = R^2 = H$
(**25**) $R^1 = H$, $R^2 = Me$
(**26**) $R^1 = R^2 = Me$



A B

R	A:B product ratio
CN	100:0
CO_2Me	>90:10
OMe	77:23
Ph	51:49
C_6H_4OMe-*p*	39:61
OC_6H_4F-*p*	52:48
$C_6H_4NO_2$-*o*	70:30
$C_6H_4NO_2$-*p*	75:25

SCHEME 10

the propensity of the C(1)−C(7) bond to migrate compared with the C(4)−C(7); for R = CN, the effect is so large that migration of the latter occurs exclusively to give a single product. Thus, the strong inductive effect of such substituents is relayed to the C(1)−C(7) bond through the C(1)−C(2) bond. On the other hand, an aryl group at C(2) incorporating an electron-donating methoxy substituent leads to a reversal in regioselectivity. For a simple phenyl group (R = Ph), the inductive electron withdrawal is probably counterbalanced by through-space π-donation into the C(1)−C(2), leading to the absence of any migratory preference in this case.

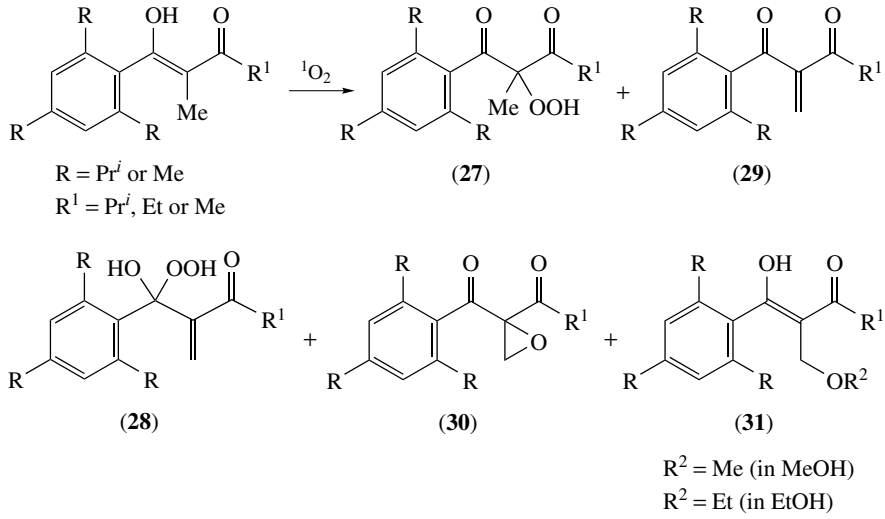
Some evidence for stereoelectronic effects in peroxide rearrangements, such as Criegee and Baeyer–Villiger rearrangements, has been determined.[200] Certain hydroperoxides display highly unusual reactivity patterns under conditions for effecting Criegee rearrangement. The bond conformation revealed in corresponding crystal structures suggests that the bond antiperiplanar to the dissociating peroxide bond is always and exclusively the bond that migrates, even when electronically disfavoured from doing so.

Fenton-type reagents [H_2O_2 or *t*-butyl hydroperoxide (TBHP) with Fe/Co/Cu catalysts] are of increasing interest as more benign, catalytic alternatives to the use of stoichiometric chromium-based oxidants in benzylic and allylic oxidations. In a study employing TBHP and copper salts under phase-transfer conditions, π-activated methylene groups are oxidized to *t*-butyl peroxides, e.g. 1,2,3,4-tetrahydronaphthalene (tetralin) is oxidized to 1-*t*-butylperoxytetralin.[201] The reaction proceeds according to a classic Kochi free-radical mechanism involving *t*-BuO radicals and Cu(II)−OOBu-*t*. Secondary allylic and benzylic alcohols are oxidized under the same conditions to ketones. In this case, however, observations including a very large kinetic isotope effect ($k_H/k_D = 12.9$) for PhCH(OH)Me compared with PhCD(OH)Me indicate that the rate-determining step involves breakage of the benzylic C−H bond and that reaction proceeds via a heterolytic mechanism, the copper catalyst being transformed to Cu(OH)Cl which enters the organic phase. The co-existence of two distinct reaction pathways in the same medium has been attributed to H-bonding of the alcohol substrate with the TBHP oxidant, which lessens the free-radical, peroxidic hydrogen abstraction by the *t*-butyloxy radical. A review on recent progress in the study of oxidation with hydrogen peroxide in organic synthesis has appeared.[202]

Photo-Oxygenation, Singlet Oxygen, and Superoxide

A type I one-electron photo-oxidation of methionine–methionine-containing peptides by triplet carboxybenzophenone in air-saturated aqueous solution has been reported; the $S^{+\bullet}$ radical cation that is formed then reacts with the other Met-S to form an S−S three-electron complex which reacts with superoxide radical anion before hydrolysis to Met(=O)−Met(=O) bis-sulfoxide.[203] Alternatively, cyclization of the *N*-terminal NH_2 on to the S can occur to give a three-electron S−N complex which can react with superoxide radical anion to give a cyclic sulfonium intermediate.

Whilst reactions of α,β-unsaturated carbonyl compounds with $^1O_2$ have been the subject of a number of studies, the corresponding reactions of their enolic tautomers have received little attention. Reaction of the β-hydroxy-α,β-unsaturated ketones

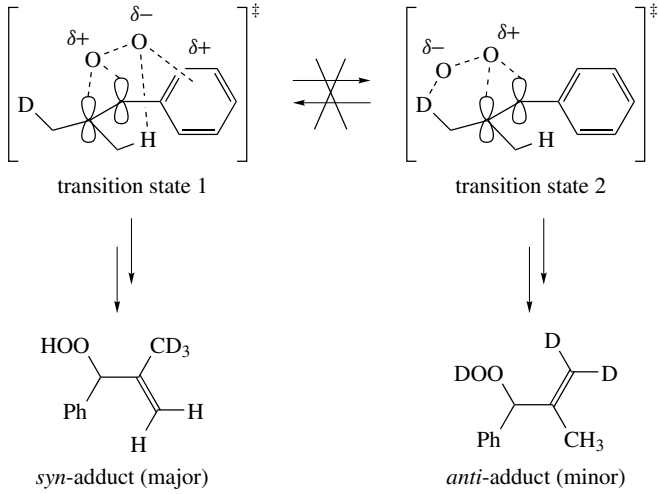


SCHEME 11

in Scheme 11 led to the products shown.[204] The photo-oxidation probably involves an ene reaction with $^1O_2$, in which the oxygen abstracts hydrogen either from the enolic hydroxy group, to generate (**27**), or from the 2-methyl group, leading to (**28**). Decomposition of (**28**) by loss of hydrogen peroxide leads to the major enedione product (**29**), which can subsequently react with the H_2O_2 liberated to give (**30**). In alcoholic solvents, compounds of the form (**31**) predominate, and are probably formed by conjugate addition of the alcohol on the enedione. Epoxidation to give (**30**) is reduced by bulky substituents in the ring *ortho* positions and at the terminal carbonyl, and favoured when all substituents are methyl. It has been shown that the phenyl ring of styrene substrates can dictate the *syn*/*anti* stereochemistry in ene reactions with singlet oxygen and triazolinediones, perhaps through a favourable interaction of the enophile with the phenyl ring (Scheme 12).[205]

Ab initio calculations of the transition structures for the Schenck reaction of singlet oxygen suggest that Me substitution makes the transition structure earlier and more stable and that the transition-state geometry is sensitive to the position of Me substituents.[206]

Tyrosine hydroxylase catalyses the formation of DOPA from tyrosine using molecular oxygen and tetrahydropterin as a co-factor. There are no primary deuterium or solvent kinetic isotope effects; however an ^{18}O isotope effect of 1.0175 ($\pm$0.0019) measured through the isolation of remaining O_2 has been recorded.[207] The results support a rate-limiting reductive activation of molecular oxygen via a one-electron transfer from the tetrahydropterin to from superoxide anion as a key reactive intermediate. *Ab initio* calculations suggest that an *S*-hydroperoxysulfonium ylid is an important intermediate in the $^1O_2$ oxidation of sulfides.[208] This ylid intermediate can rearrange to either an α-hydroperoxide or to a protonated sulfone ylid and then to the sulfone product. Similar results were obtained from an almost parallel study.[209]



SCHEME 12

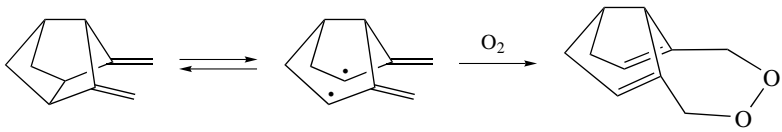
Atomic Oxygen, Triplet Oxygen, and Autoxidation

Under oxidative conditions, *p*-benzoquinone is primarily consumed via thermal dissociation at lower temperatures, whereas hydrogen-abstraction reactions with the O/H radical pool lead to OC_6H_3O and C_6H_3O at higher temperatures.[210] This shift occurs at lower temperatures with a higher oxygen concentration. The oxidation of isobutene in O_2 was studied in a continuous-flow stirred-tank reactor and shock tube.[211] Comparison of the partial-pressure profiles of various products of the reaction fit reasonably well with theoretical data obtained with CHEMKIN II software. The kinetics of the oxidation of dimethyl ether in a jet-stirred reactor and shock tube have been studied[212] and product and intermediate distributions compare well with calculations using a numerical model consisting of 336 reactions. The major products detected were CO, CO_2, H_2, H_2CO, and CH_4. The thermal gas-phase oxidation of tetrachloroethene by molecular oxygen in the presence of trifluoromethyl hypofluorite (CF_3OF) has been studied and a detailed mechanism was presented.[213] The application of a system of computer-aided design of kinetic models of oxidation and combustion to previously obtained results for the oxidation of *n*-octane and *n*-decane has been performed with satisfactory fitting of the conversion and distribution of products formed.[214] The oxidation of methanol over a wide range of temperature and pressure is sensitive to the kinetics of the hydroperoxyl radical through a branching mechanism involving hydrogen peroxide ($H_2O_2 \rightarrow 2OH$) at low temperature and a terminating mechanism ($H_2O_2 \rightarrow H_2O + O_2$) at high temperature.[215]

In order to model the oxygenation of vitamin K in its hydroquinone form, a naphthohydroquinone derivative with a 1-hydroxy group and 4-ethyl ether was prepared and its alkoxide subjected to oxidation with molecular oxygen.[216] Products consistent with two possible mechanisms were isolated, the epoxy-quinone which must derive from a peroxy anion intermediate at the 4-position, and a 2-hydroxy product which

could arise from a 2-peroxy anion intermediate. The liquid-phase oxidation of 1- and 2-isopropenylnaphthalene with pure oxygen in PhCl solution in the presence of cumene and cumene hydroperoxide at 75–125 °C has been investigated.[217]

The Cope rearrangement of the highly strained diene (**32**) (Scheme 13) is shown to proceed by a non-concerted mechanism involving the diradical (**33**), which may be trapped by oxygen to give the peroxide (**34**). A full kinetic study confirms the intermediacy of the diradical.[218]



(**32**) (**33**) (**34**)

SCHEME 13

The use of O(3P) atoms produced by microwave irradiation of He–O_2 mixtures has shown that alkenes react with atomic oxygen in solution or neat to give predominantly epoxides.[219] Unlike reactions in the gas phase, at low temperature these produce useful product yields and distributions. Similar yields suggest that epoxide formation and 1,2-H/1,2-C shifts/ring contractions compete.

Other Oxidations

The stereoselectivity of enzymatic primary carbon hydroxylation has been reviewed.[220] The phthalimide *N*-oxyl radical (PINO), which may be formed from *N*-hydroxyphthalimide (NHPI), has been shown to catalyse the oxygenation of alkynes to α, β-acetylenic ketones with dioxygen under mild conditions, in the presence of a transition metal catalyst, e.g. $Co(acac)_2$.[221] The subsequent introduction of oxygen into the prop-2-ynylic C–H bond is presumed to occur by a free-radical process involving hydrogen-atom abstraction at the energetically favourable prop-2-ynylic position. EPR analysis suggests that, in order for the PINO radical to be formed from NHPI, the alkynyl substrate must be present, in addition to O_2. The mechanism of the synergistic oxidation of cyclohexane with H_2S and O_2 has been investigated by addition of PhSeSePh; the results rule out the involvement of carbon and oxygen radicals.[222] The pyrolysis and oxidation of formaldehyde at high temperatures have been investigated by monitoring the progress of the reaction by laser absorption of CO molecules.[223] A detailed kinetic analysis led to a new reaction model giving good agreement with the experimental data.

Human type II inosine monophosphate dehydrogenase catalyses NAD-dependent conversion of inosine monophosphate (IMP) into xanthosine monophosphate (XMP); measurements of the primary kinetic isotope effect using [^{2}H]IMP suggest that both substrates (IMP and NAD) can dissociate from the enzyme–substrate complex; therefore, the kinetic mechanism is not ordered. NMR studies indicate hydride transfer to the B or *pro-S* face of the nicotinamide ring of NAD, while kinetic studies suggest

that this is a kinetically significant step, although the rate-limiting step occurs at a later stage in the mechanism.[224]

The one-electron oxidation of *N*-benzylphenothiazine by nitric acid occurs in the presence of β-cyclodextrin, which stabilizes the radical cation by incorporation into its cavity. The reaction is inhibited by adamantane, which preferentially occupies the cavity.[225] Novel Pummerer-type rearrangements of *p*-sulfinylphenyl derivatives, yielding *p*-quinones and protected dihydroquinones, and highly enantioselective Pummerer-type rearrangements of chiral, non-racemic sulfoxides have been reviewed.[226] A comprehensive study has demonstrated that the redox potential for 7- and 8-substituted flavins is linearly correlated with Hammett σ values.[227] DFT calculations in [3.3.*n*]propellanes highlight low ionization potentials that favour SET oxidative cleavage of the strained central C−C bond rather than direct C−H or C−C bond attack.[228] Oxidations and reductions in water have been reviewed.[229]

Reduction by Complex Metal Hydrides

The applications of sodium acyloxyborohydrides, formed from sodium borohydrides in carboxylic acid media, are reviewed.[230] Useful reviews of the stereoselective reduction of endocyclic C=N compounds[231] and of the enantioselective reduction of ketones have appeared.[232]

A nice analysis of non-linear effects in Rh−chiral diamine-catalysed transfer hydrogenation has been performed that reinforces the need to consider the kinetics of all of the steps in reaction manifolds (e.g. reversible formation of diastereomeric precursors and their subsequent interaction with achiral reactants).[233]

Some further examples of the reduction of adamantanones have highlighted that increasing the positive dipole on the C=O using Lewis acids, or placing charged substituents at C(5) within the adamantyl framework, enhances face selectivities in borohydride and aluminium hydride reductions due to Cieplak effects.[234]

Other Reductions

The reduction of (2,3)-α- and (2,3)-β-methylenepenam β-sulfoxides to the corresponding sulfides using potassium iodide and trifluoroacetic anhydride (TFAA) is found to be much faster than for bicyclic β-lactam β-sulfoxides.[235] In the proposed mechanism, initial attack of the sulfoxide oxygen on TFAA is followed by rate-limiting, nucleophilic displacement of trifluoroacetate by iodide ion; nucleophilic attack of iodide on the iodine atom then yields the sulfide and iodine. The rate enhancement is accounted for by the stabilization of the transition state in the rate-limiting step by interaction of the *p*-like orbital of sulfur and the cyclopropane σ^* orbital.

The results of kinetic studies on the reaction between iodide and *N*-chloro compounds support a mechanism in which the rate-determining transfer of Cl^+ from the *N*-chloramine to iodide gives an ICl intermediate which rapidly reacts with excess iodide to give triiodide ions.[236]

The mechanisms of electrochemical reduction of 9-chloroanthracene, 3-nitrobenzyl chloride, and 3-chloroacetophenone have been investigated by means of cyclic voltammetry.[237] The effect of different aprotic solvents was studied and, in the case of

9-chloroanthracene and 3-nitrobenzyl chloride, the rate of the reaction was found to depend on the electrophilic properties of the solvent as defined by Gutmann acceptor and donor numbers, respectively; 3-chloroacetophenone showed no linear dependence on solvent properties.

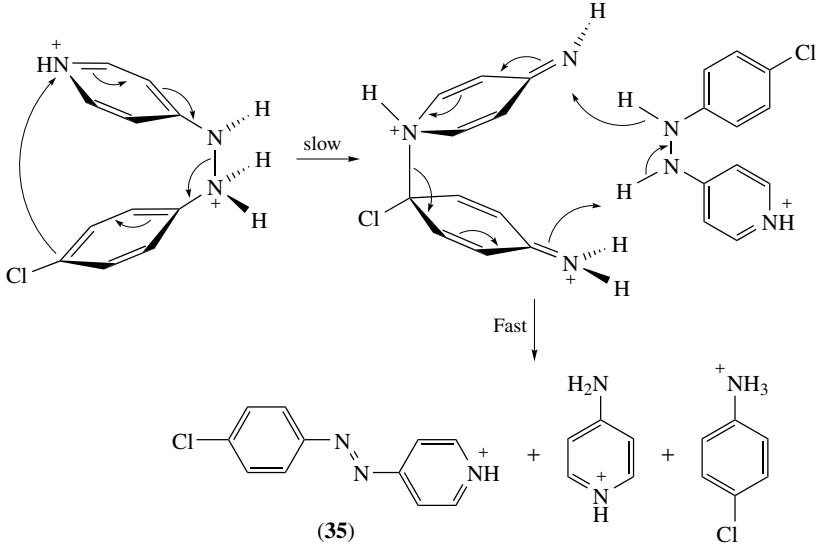
Atomic charges, effective charges at reacting centres, and HOMO and LUMO energies have been calculated for nitrobenzene, nitrosobenzene, *N*-phenylhydrazine, diphenyldiazine, *N*,*N*′-diphenyldiazine-*N*-oxide, and *N*,*N*′-diphenylhydrazine, compared with kinetic data for the hydrogenation of these compounds, and used to propose a mechanism for the hydrogenation of nitrobenzene.[238]

Reduction of *N*-arylmaleimides with sodium dithionate gives monomeric and dimeric products; a mechanism has been proposed.[239]

The kinetics of the reduction of 2,6-dichlorophenolindolphenol (DCPI), a common dye used for analysing ascorbic acid, by Fe^{2+} and oxalate have been studied and indicate the rapid formation of an intermediate complex of Fe^{2+} and $C_2O_4^{2-}$, predominantly FeC_2O_4, prior to the reduction of DCPI.[240]

Disproportionations

The disproportionation reactions of 4-(4-chlorophenylazo)pyridine and 4-(4-chlorophenylhydrazo)pyridine in acidic media have been studied. The hydrazo compound disproportionates to give 1 mol of the azo compound (**35**) and 1 mol each of the reduced products 4-chloroaniline and 4-aminopyridine. The azo compound also undergoes a slower hydroxylation reaction giving a variety of products. A proposed mechanism for the disproportionation of 4-(4-chlorophenylhydrazo)pyridine consistent with observed first-order kinetics involves a rate-determining electrocyclic rearrangement of the diprotonated species (Scheme 14).[241]



SCHEME 14

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CHAPTER 6

Carbenes and Nitrenes

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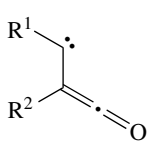
Reviews

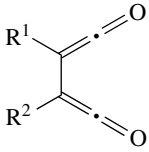
The rearrangements, mechanisms, and conformations of alkylcarbenes have been reviewed.[1] A review of Shpolskii matrix-isolated aromatic carbenes, the study of their conformational isomerism, and the determination of the zero-field splitting parameters of their excited triplet states has appeared.[2] Reviews have also appeared on laser flash photolysis of carbonyl carbenes,[3] 1,2-hydrogen migration of singlet carbenes and the mechanistic issues involved in the use of diazirine precursors,[4] the insertion of carbenes to give compounds containing bridgehead double bonds,[5] asymmetric carbene transformations,[6] mechanisms and applications of 1,4-addition reactions of carbenes to dienes,[7] stereoselective intramolecular C−H insertion reactions of metal carbenes,[8] the formation and reactions of donor-substituted carbenes,[9] and the thermally induced isomerizations of vinylsilanes.[10]

Structure and Reactivity

At the HF/6−31G* level, ketenyl carbenes (**1**) were calculated to be intermediates in the decarbonylation of 1,2-bisketenes (**2**) to form cyclopropenones.[11] At the MP2/6−31G* and B3LYP levels, however, decarbonylation was predicted to form the cyclopropenones directly. The *anti*-ketenyl carbenes were found to be 2.2−5.4 kcal mol^{-1} higher in energy than the *syn* isomers (**1**). The mechanism of reaction of [1.1.1]propellane with singlet dihalocarbene has been reported.[12]



(**1**)



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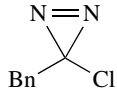

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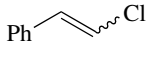
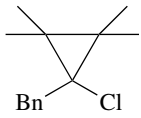


(**4**)



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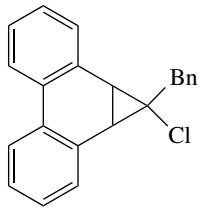


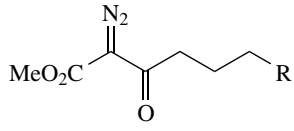
(**6**)

F_2C**:**, formed in the initial pyrolysis of perfluoro(methylcyclopropane), is proposed to recombine to form biradicaloid $C_2F_4{}^*$.[13] Time-resolved electron paramagnetic resonance spectroscopy has been used to study the lowest excited triplet state of Ph_2C**:**, generated by photolysis of the corresponding diazo compound at low temperature.[14] The zero-field splitting parameters $|D|(-0.142\,cm^{-1})$ and $|E|(-0.0033\,cm^{-1})$ were obtained.

Photolysis of benzylchlorodiazirine (**3**) in the presence of tetramethylethylene (TME) is known to produce (*E*)- and (*Z*)-β-chlorostyrene (**4**) and the cyclopropane (**5**). Plots of [**5**]/[**4**] vs [TME] are curved, consistent with the existence of two pathways for the formation of the alkenes (**4**). Benzylchlorocarbene (BnClC**:**) was generated by laser flash photolysis of the phenanthrene (**6**) in the presence of TME.[15] In this case, plots of [**5**]/[**4**] vs [TME] are linear, ruling out the possibility that the second pathway to the alkenes (**4**) involves reaction of a carbene–alkene complex. Time-resolved IR spectroscopy revealed that diazirine (**3**) rearranges to the corresponding diazo compound, but this process is too inefficient to account for the curvatures. It is proposed that the second pathway to alkene formation involves the excited state of the diazirine.

In contrast to 2-alkylarylcarbenes, triplet carbonyl carbenes do not abstract H from δ- or ε-CH bonds.[16] Photolysis of diazo compounds (**7**) in methanol gave products due to Wolff rearrangement (**8**) and O–H insertion (**9**). Sensitized photolysis led, in addition, to the H-abstraction product (**10**). Analysis of the results indicated that a large proportion of the insertion product (**9**) arises from the excited diazo compound and that spin inversion of the triplet carbene is faster than H-abstraction from the solvent. Intersystem crossing to the singlet state is a major reaction of all triplet carbonyl carbenes that are not rapidly scavenged intramolecularly.

The absolute rate constants for reaction of *p*-tolyl(trifluoromethyl)carbene, generated by laser flash photolysis of the corresponding diazirine, with pyridine ($4 \times 10^8\,l\,mol^{-1}\,s^{-1}$ in Freon-113), ketones [$(1.5–9.8) \times 10^8\,l\,mol^{-1}\,s^{-1}$ in hexafluorobenzene], and quenchers of biological interest have been obtained.[17] The results support a triplet ground state with a small ($0.5–1.5\,kcal\,mol^{-1}$) singlet–triplet energy gap.



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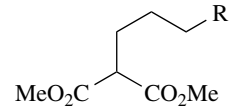

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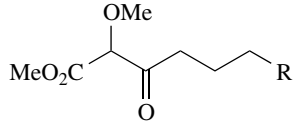

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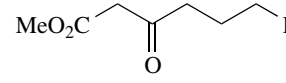
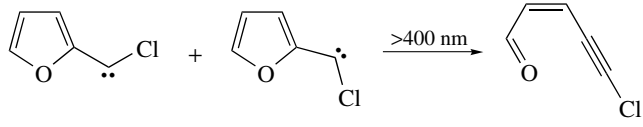


(**10**)

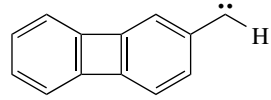
2-Furylchorocarbene (**11**), generated by irradiation of the corresponding diazirine in a nitrogen matrix at 8 K, was characterized by IR spectroscopy, which revealed two species, one of which was destroyed on irradiation to form the aldehyde (**12**).[18] The experimental and calculated spectra were in accord with two conformations of the carbene, one of which decomposes to the aldehyde.

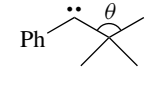
Irradiation of 2-diazomethylbiphenylene gives the carbene (**13**), which possesses an antiaromatic ring.[19] Insertion into the C−H bond of cyclohexane and addition to alkenes with retention of stereochemistry suggest reactions via the singlet state. ESR spectroscopy allowed the estimation of zero-field splitting parameters of the two conformational isomers of (**13**). Both were $S = 1$ species displaying slightly more delocalization than the corresponding naphthylcarbenes.

t-Butylphenylmethylene (**14**) is calculated to have a singlet–triplet gap of 5–6 kcal mol^{-1} with a triplet ground state.[20] The larger angle at the carbene carbon in the triplet (138.5°) compared with the singlet (119.3°) reduces steric interactions and allows the phenyl ring to adopt a position in which maximum overlap with the carbene *p*-orbital can occur. The Me−C$_\alpha$−C$_{carbene}$ angle θ is 101°, indicating some stabilization of the carbene by the adjacent C−C σ-bond. The barriers for 1,3-CH insertion and C−C migration were calculated to be 1.8 and 3.8 kcal mol^{-1}, respectively, in good agreement with the experimentally determined ratio of these processes.

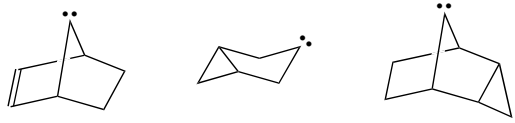


(**11**) (**12**)





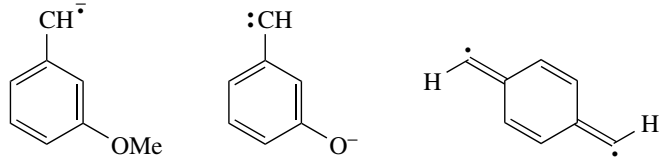
(**13**) (**14**)



(**15**) (**16**) (**17**)

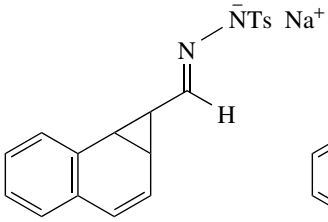
Calculations at the B3LYP/6−31G*//B3LYP/6−31G* level were used to evaluate the stabilization energy of the singlet carbene (**15**) as 15.56 kcal mol^{-1}.[21] Similar calculations on singlet 3-carbenabicyclohexane (**16**) and the tricyclooctane (**17**) gave values of 3.27 and 14.06 kcal mol^{-1}, respectively. The calculated geometries of (**15**) and (**17**) showed a significant leaning of the carbenic carbon over the π system or cyclopropane. This distortion was absent in the triplet structures, which were found to lie well above the singlets (by 27.82 and 25.74 kcal mol^{-1}, respectively). Singlet carbenes (**15**) and (**17**) appear to be strongly homoaromatic, whereas (**16**) is only weakly so.

Abstraction of H_2^+ from 3-methylanisole, generated in a flowing afterglow triple quadrupole apparatus, gives the radical anion (**18**). This species undergoes electron transfer to F_2 followed by attack of fluoride ion at the methoxy methyl group to give the distonic carbene ion (**19**).[22] Carbene (**19**) displays reactivity characteristic of a singlet species and calculations at the B3LYP/cc-pVTZ level predict a singlet ground state with singlet−triplet gap of 3 kcal mol^{-1}. Kinetic protonation on oxygen is predicted to give a ground-state triplet. *C*-protonation is predicted to give a triplet biradical 22.6 kcal mol^{-1} more stable than the *O*-protonated form. Insight into the origin of spin−orbit coupling in carbenes and the heavy atom effect of substituents was gained by calculations on **:**CH_2, **:**CHF, **:**CHCl, and **:**CHBr.[23] Photolysis of 1,4-bis(diazomethylbenzene) in an N_2 matrix at 10 K produced a species attributed by IR and UV−Visible spectroscopy to *p*-phenylenebismethylene as its biradical (**20**).[24] The biscarbene (**20**) was trapped by HCl to form 1,4-di(chloromethyl)benzene and by oxygen to form the bis(carbonyl *O*-oxide).



(**18**) (**19**) (**20**)

Both thermal (120 °C at 0.005τ) and photochemical decomposition of the tosylhydrazone salt (**21**) were proposed to proceed by initial formation of the cyclopropylcarbene followed by fragmentation to biradicals (**22**) and (**23**), which proceeded to 1- and 2-vinylnaphthalene and benzobarrelene (**24**).[25]



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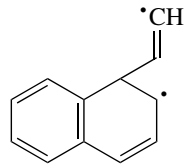

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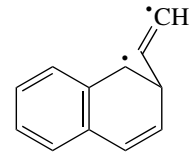

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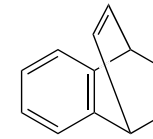
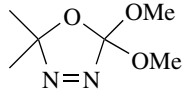


(**24**)

Thermolysis of the oxadiazoline (**25**) in the gas phase using a CO_2 laser as directed heat source gives products including acetone, tetramethoxyethene, and dimethyl oxalate.[26] Subtraction of the photoelectron spectra of these species from the spectrum of the product mixture leaves a simple photoelectron spectrum attributed to dimethoxycarbene in the W conformation (**26**). Photoelectron spectra for two stable carbenes (**27**; R = Et and R = ^{i}Pr) have been recorded.[27] The first ionization potentials were found to be 7.71 and 7.56 eV, respectively. Calculations of the first adiabatic ionization potentials of eight electronically diverse carbenes were performed using a variety of levels of theory. Calculations using the CBS-4 model and those using B3LYP/6−31 + G* were shown to give good agreement with experiment.



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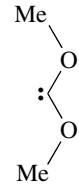

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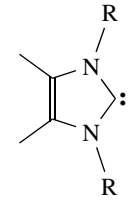
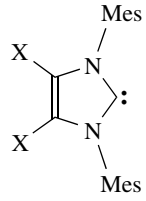


(**27**)

1,3-Dimesitylimidazol-2-ylidene (**28**; X = H) reacts with CCl_4 to give carbene (**28**; X = Cl), which showed enhanced stability towards air, moisture, and acidic halogenated solvents.[28] An X-ray crystal-structure determination was obtained. Both carbenes (**28**; X = H or Cl) react with tellurium to give the corresponding tellurone. The strong σ electron-withdrawing effect of the chlorine atoms is evidenced by the very downfield ^{125}Te resonance of this species (−4 ppm compared with −150 ppm for the non-chlorinated tellurone).

Proton abstraction from the imidazolium chloride (**29**) by KO^{t}Bu gave the carbene (**30**) originally postulated, but not isolated, by Wanzlick.[29] An X-ray structure determination of the carbene (**30**) showed the expected near-planarity of the imidazole ring and an NCN angle of 102.1°, characteristic of a singlet carbene.



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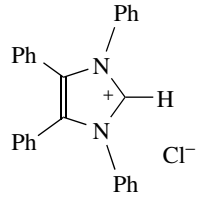

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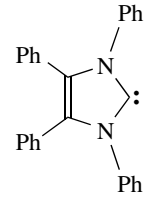
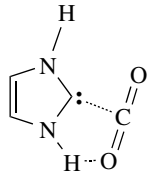


(**30**)

Irradiation of matrix-isolated imidazole-2-carboxylic acid gave the 2,3-dihydro-imidazol-2-ylidene–CO_2 complex (**31**) characterized by IR spectroscopy and calculated to lie 15.9 kcal mol^{-1} above the starting material.[30] A series of non-aromatic nucleophilic carbenes (**32**) were prepared by desulfurization of the corresponding thiones by molten potassium in boiling THF.[31] The most hindered of the series (**32**; R = ^{t}Bu) is stable indefinitely under exclusion of air and water and can be distilled without decomposition. The less hindered carbenes slowly dimerize to the corresponding alkenes. Stable aminoxy- and aminothiocarbenes (**33**; X = O, S) were prepared by deprotonation of iminium salts with lithium amide bases.[32] The carbene carbon resonance appears at 260–297 ppm in the ^{13}C NMR spectrum and an X-ray structure determination of an aminooxycarbene indicated that electron donation from the nitrogen is more important than that from oxygen. These carbenes do not dimerize.

The observed IR spectrum of the initial product of irradiation of *p*-diazidobenzene in an argon matrix at 12 K was in excellent agreement with that calculated for the bisnitrene (**34**).[33] Calculations indicated that (**34**) has a singlet ground state and small singlet–triplet gap. The decay of (**34**) gave rise to a species assigned as (**35**) which, in turn, fragmented to acetylene and the alkene (**36**).



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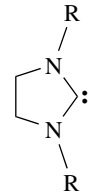

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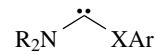

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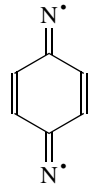

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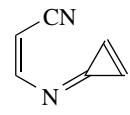

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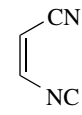
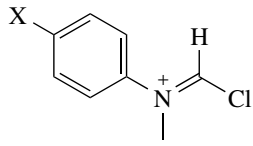


(**36**)

Generation

Extrusion of F_2C**:** from the CF_3 group adjacent to the radical centre of an initially formed biradicaloid isomer in the pyrolysis of hexafluoropropylene was proposed.[34] The activation energy for this extrusion was 30 ± 2.5 kcal mol^{-1} and $(F_3C)FC$**:** was not observed. Thermal decomposition of $CHCl_3$ in krypton was found to proceed by elimination to form HCl and Cl_2C**:** in a laser Schlieren density gradient study.[35] Chlorine atom formation is entirely due to the thermal reactivity of Cl_2C**:**. MNDO calculations have been used to study the reaction of CCl_4 with magnesium to form Cl_2C**:**.[36]

Deprotonation of Vilsmeier reagents (**37**) by tertiary amine bases has been proposed to give nucleophilic aminochlorocarbenes (**38**), which react with (**37**) to produce the observed enediamine products (**39**).[37]



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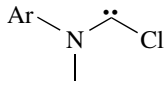

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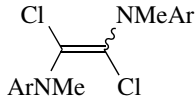

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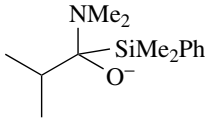

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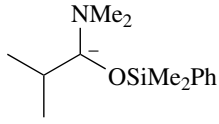

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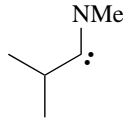
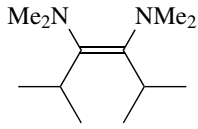


(**42**)



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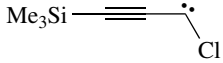
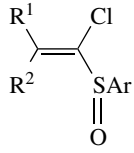


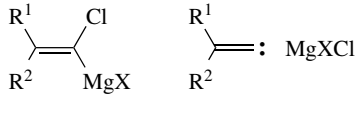
(**44**)



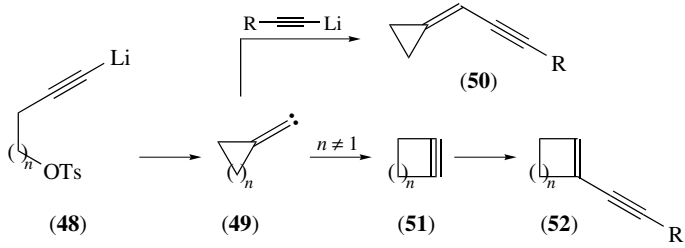
(**45**)

Reaction of an amide with $PhMe_2SiLi$ was proposed to proceed via addition to the carbonyl (**40**), Brook rearrangement to (**41**), and loss of $PhMe_2SiO^-$ to give the carbene (**42**), which dimerizes to the enediamine product (**43**).[38] The carbene could be trapped by a second equivalent of silyl lithium reagent to give $R(Me_2N)CLi(SiMe_2Ph)$.

Chloro(trimethylsilylethynyl)carbene (**44**) was formed by α-elimination of HCl from trimethylsilylethynyldichloromethane with KO^{t}Bu.[39] Cycloaddition to alkenes gave the corresponding cyclopropanes. Treatment of 1-halovinyl sulfoxides (**45**) with EtMgX gave rise to the corresponding magnesium alkylidene carbenoids (**46**), which could be trapped by electrophiles to give vinyl chlorides.[40] Carbenoids (**46**) were



(**46**) (**47**)

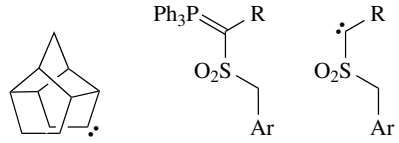


(**48**) (**49**) (**51**) (**52**) (**50**)

configurationally unstable and exchanged Cl with Br on magnesium, suggesting an equilibrium with the alkylidene carbene–magnesium halide complex (**47**).

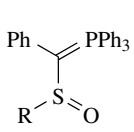
An *exo*-type cyclization, proceeding through a cycloalkylidene carbene (**49**; $n = 1$, 3, 4), was proposed to explain the formation of enynes (**50**) and (**52**) from alkynyl lithium species (**48**).[41] The proposed carbene (**49**) could be trapped by addition to cyclohexene and the cycloalkyne intermediate (**51**) was trapped by Diels–Alder reaction with 1,3-diphenylisobenzofuran.

The reactivity of cage-annulated carbene (**53**) was found to depend markedly on the method of its formation.[42] Pyrolysis of the corresponding tosylhydrazone sodium salt gave products of intramolecular CH insertion or H-abstraction. Photolysis of a diazirine precursor gave only azine products by reaction of the carbene with the precursor or diazo compound. Treatment of the *gem*-dibromoalkane with BuLi gave products due to intermolecular insertion of the carbene into CH bonds of the solvent.

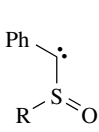


(**53**) (**54**) (**55**)

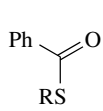
Flash vacuum pyrolysis (600 °C) of arylmethylsulfonyl-stabilized phosphorus ylides (**54**) gave products resulting from initial extrusion of Ph_3P to form the sulfonyl carbene (**55**) followed by 1,2-, 1,3-, or 1,5-CH insertion and loss of SO_2.[43] 1,3-Insertion gives a thiirane dioxide, which loses SO_2 to produce an alkene ArCH=CHR. Flash vacuum pyrolysis of alkane sulfinyl ylides (**56**; R = alkyl) gave thioesters (**58**) by extrusion of Ph_3P to give the α-sulfinyl carbenes (**57**) followed by 1,2-oxygen transfer.[44] The corresponding arylsulfinyl ylides (**56**; R = aryl) give, in addition, ketones (**60**) via



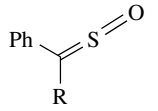
(**56**)



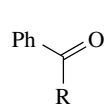
(**57**)



(**58**)

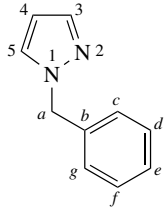


(**59**)

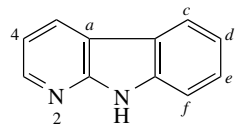


(**60**)

(**61**)



(**62**)



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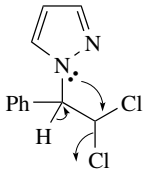

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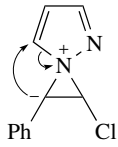
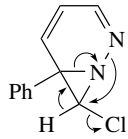
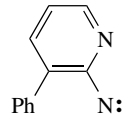


(**65**)



(**66**)



(**67**)

Wolff-like rearrangement of the carbenes (**57**) to the sulfines (**59**), which rearrange with loss of sulfur. The remaining minor products were postulated to arise by loss of Ph_3PO to give the sulfenyl carbene RS(Ph)C**:**.

Phenyliodonium ylides (**61**; Z = CO_2R, SO_2Ph, COR) react in the presence of Rh(II) catalysts with the same selectivity in cyclopropanations as the corresponding diazo compounds and intramolecular CH insertions occur with identical enantioselectivities.[45] This strongly suggests the intermediacy of Rh carbenoids in reactions of the ylides. Copper(I)-catalysed cyclopropanation of alkenes with diphenylsulfoniumethoxycarbonylmethylide also gave *cis:trans* ratios and *ee*s identical with those formed using ethyl diazoacetate. $Rh_2(OAc)_4$-catalysed alkene aziridination using NsN=IPh(Ns = *N*-*p*-nitrobenzenesulfonyl) is stereospecific, CH insertions occur with retention of stereochemistry, chiral ligands on rhodium give enantio-enriched products, and no ring opening is observed in the CH insertion reactions of alkylcyclopropanes.[46] A single-step mechanism involving a metal-complexed nitrene is proposed for both reactions.

A series of substituted or ^{13}C- or ^{15}N-labelled 1-arylmethylpyrazoles (**62**) were used to identify the origin of the atoms in the α-carboline (**63**) formed by pyrolysis in the presence of chloroform.[47] The proposed mechanism involves insertion of dichlorocarbene into a benzylic CH bond to give (**64**). Loss of HCl gives (**65**), which undergoes a Stevens-type rearrangement to (**66**) followed by rearrangement to the nitrene (**67**), which closes on to the phenyl ring to give the α-carboline (**63**).

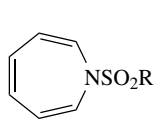
Treatment of sulfonylamide tetrabutylammonium salts $RSO_2NH^-Bu_4N^+$ in benzene with XeF_2 gives the corresponding *N*-sulfonylazepines (**68**) via a proposed sulfonyl nitrene intermediate.[48]

Addition

Ab initio and RRKM calculations indicate that the reactions of C, CH, and $^1(H_2C{:})$ with acetylene occur with no barrier.[49] Laser flash photolysis of the cyclopropanes (**69**) and (**70**) was used to generate the corresponding dihalocarbenes.[50] The absolute rate constant for the formation of a pyridine ylide from $Br_2C{:}$ was $(4-11) \times 10^{-9}\,l\,mol^{-1}\,s^{-1}$. The rates of additions of these carbenes to alkenes were measured by competition with pyridine ylide formation and the reactivity of BrClC**:** was found to resemble that of $Br_2C{:}$ rather than $Cl_2C{:}$.

Theoretical studies on the cyclopropanation of ethene with lithium carbenoid and zinc carbenoid (Simmons–Smith reagent) revealed that both methylene-transfer and carbometallation pathways are fast for lithium whereas only the former is fast enough to be experimentally observed for the zinc carbenoid.[51] Treatment of trimethyl orthoformate with Me_3SiCl and zinc amalgam in the presence of alkenes gave rise to the corresponding alkoxycyclopropanes (**71**) via a postulated zinc carbenoid (**72**).[52] The reaction showed a preference for electron-rich alkenes, proceeded with retention of configuration on the alkene, and gave predominantly the more hindered *endo* isomer (**71**).

7-Norbornylidene carbene (**73**) was generated by treatment of the corresponding dibromomethylene species with butyllithium.[53] The carbene reacted with alkenes with retention of configuration, a characteristic of singlet carbenes. No evidence of 1,2-C shift to the corresponding alkyne was seen. Similar observations were made with the heptacyclic analogue (**74**).



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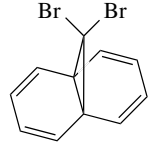
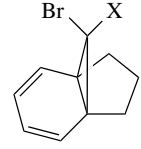
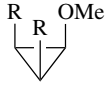


(**69**)

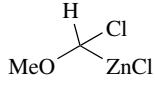


(**70**)

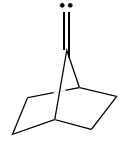
X = Br, Cl



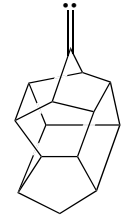
(**71**)



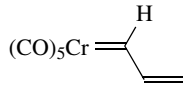
(**72**)



(**73**)



(**74**)



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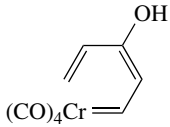
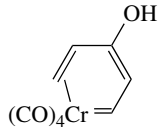


(**76**)



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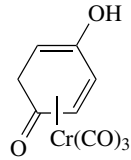


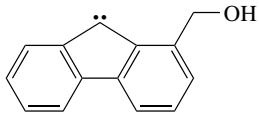
(**78**)

Density functional calculations on the Dötz reaction leading from chromium carbene (**75**) with acetylene to give the phenol (**78**) suggested a new mechanism involving the formation of a chromahexatriene complex (**77**) from the initially formed vinylallylidene complex (**76**).[54] Complex (**77**) then collapses to the phenol complex (**78**).

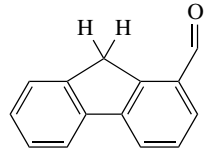
Insertion and Abstraction

Laser flash photolysis of phenylchlorodiazirine was used to measure the absolute rate constants for intermolecular insertion of phenylchlorocarbene into CH bonds of a variety of co-reactants.[55] Selective stabilization of the carbene ground state by π-complexation to benzene was proposed to explain the slower insertions observed in this solvent in comparison with those in pentane. Insertion into the secondary CH bond of cyclohexane showed a primary kinetic isotope effect $k_H k_D$ of 3.8. 1-Hydroxymethyl-9-fluorenylidene (**79**), generated by photolysis of the corresponding diazo compound, gave aldehyde (**80**) in benzene or acetonitrile via intramolecular H-transfer.[56] In methanol, the major product was the ether, formed by insertion of the carbene into the MeO−H bond, and the aldehyde (**80**) was formed in minor amounts through H-transfer from the triplet carbene to give a triplet diradical which can relax to the enol.

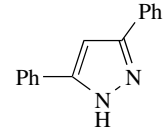
Flash vacuum pyrolysis of 3,5-diphenylpyrazole (**81**) gave rise to products of intramolecular CH insertion of the resulting vinylcarbene (**82**).[57] The barrier to nitrogen extrusion is $20 \pm 3\,\mathrm{kJ\,mol^{-1}}$ and $\log A = 13.1 \pm 0.1\,\mathrm{s^{-1}}$.



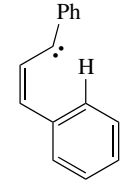
(**79**)



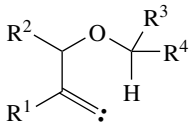
(**80**)



(**81**)



(**82**)



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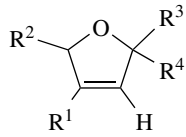
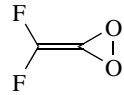


(**84**)

(**85**)



(**86**)

1,5-CH insertion of vinylidenecarbenes (**83**), generated from the corresponding ketones by treatment with lithio(trimethylsilyl)diazomethane, gave rise to 2,5-dihydrofurans (**84**).[58] The use of aldehydes ($R^1 = H$) gave rise to alkynes by 1,2-H shift in the corresponding carbenes. Matrix-isolated difluorovinylidene (**85**) was generated by photo-induced 1,2-F shift from difluoroacetylene.[59] The reaction of vinylidene (**85**) with CO_2 leads, by electrophilic attack on the oxygen of CO_2, to difluoroketene and CO. The reaction of (**85**) with molecular dioxygen produces F_2C**:** and CO_2 and is postulated to proceed via difluoromethlene dioxirane (**86**).

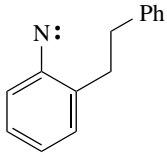
The deuterium kinetic isotope effect for intramolecular CH insertion of the nitrene (**87**), generated by photolysis of the corresponding azide, is 14.7 ± 0.3 at 20 °C and is consistent with the H-abstraction–recombination mechanism from the triplet state.[60] The temperature dependence of the kinetic isotope effect suggests that quantum mechanical tunnelling is important in this process.

Rearrangement

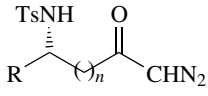
A density functional study has been made of the competition between Wolff rearrangement and [1,2]-H shift in β-oxy-α-diazocarbonyl compounds.[61] Silver-catalysed decomposition of α-diazoketones (**88**; $n = 0$), derived from *N*-tosyl α-amino acids in methanol, gave rise to mixtures of products of Wolff rearrangement (**89**) and direct insertion of the carbene into the NH bond (**90**).[62] The β-amino acid derived species (**88**; $n = 1$) gave rise to products of Wolff rearrangement.

Dimethylcarbene and dimethylcarbene-d_6 were generated by laser flash photolysis of the corresponding diazirines.[63] In perfluorohexane, the carbenes decay by rearrangement to propene with barriers of 2.56 ± 0.05 and 5.63 ± 0.03 kcal mol^{-1}, respectively. The results, in comparison with calculations, indicate that quantum mechanical tunnelling is significant for dimethylcarbene, but makes only a minor contribution for dimethylcarbene-d_6.

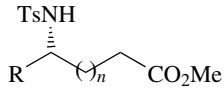
A detailed reinvestigation of the products and kinetics of reactions of benzylchlorocarbene, generated by photolysis of the corresponding diazirine, indicated that the



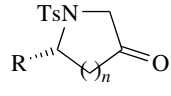
(**87**)



(**88**)



(**89**)



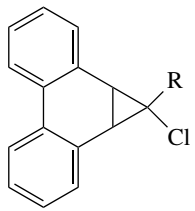
(**90**)

curvature observed in the Arrhenius plots ($\ln k$ vs $1/T$) for the rate constants of 1,2-H shift in hydrocarbon solvents is mainly due to competitive intermolecular reactions (azine formation and solvent insertion) down to $-70\,^{\circ}C$.[64] The barrier to [1,2]-H shift is ca $4.8\,kcal\,mol^{-1}$ in hydrocarbons and ca $3.2\,kcal\,mol^{-1}$ in polar solvents (e.g. tetrachloroethane). Quantum mechanical tunnelling does not appear to play a major role in the [1,2]-H shift of benzylchlorocarbene at ambient temperature in solution.

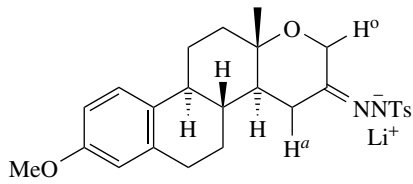
Previous studies of the photochemistry of alkylchlorodiazirines have shown that the yield of trappable carbene is sensitive to the alkylcarbene structure. A laser flash photolysis study of phenanthridenes (**91**), precursors of alkylchlorocarbenes, in the presence of pyridine, has ruled out the intermediacy of a carbene–pyridine complex which partitions between pyridine–ylide formation and [1,2]-H shift.[65]

Substituent effects at the migration origin on the rate of rearrangement of several alkylchlorocarbenes have been studied at the B3LYP/6–311G**//B3LYP/6–31G* level.[66] [1,2]-H shifts are accelerated in the order Ph > Me > F > Cl > H. The exclusive [1,2]-H shift observed in Bn(Cl)C**:** is not due to a migratory preference of H over Ph, but is the result of the greater acceleration of [1,2]-H shift by the Ph group than of the [1,2]-Ph shift by an adjacent H. The relative effect of ring-alkyl vs ring-oxygen on the [1,2]-migration of hydrogen (H^a vs H^o, respectively) to the steroidal carbene formed by thermal or photochemical decomposition of the *N*-tosylhydrazone lithium salt (**92**) showed that ring-oxygen is a more powerful activator than ring-alkyl by a factor of 12:1 in thermolysis at 170 °C and by 14:1 in photolysis at $-70\,^{\circ}C$.[67]

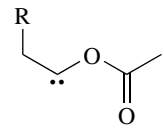
A study of the absolute rate constants for [1,2]-H and [1,2]-acyl shifts in a series of alkylacetoxycarbenes (**93**), generated by photolysis of the corresponding diazirines, showed that an α-methyl group is ca 12 times more effective at promoting [1,2]-H shift than an α-Ph group.[68]



(**91**)



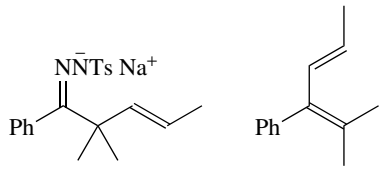
(**92**)



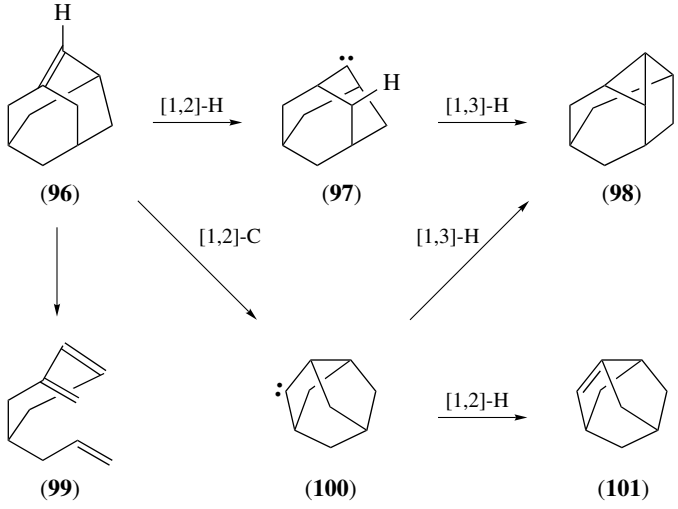
(**93**)

Photolysis of the tosylhydrazone sodium salt (**94**) in diglyme gave, as the major product, 1,3-diene (**95**) by [1,2]-vinyl shift in the intermediate carbene.[69] Vinyl migration occurs with retention of configuration and is postulated to occur in the singlet manifold.

B3LYP calculations indicated that 2-adamantene (**96**) is $17.4\,kcal\,mol^{-1}$ more stable than $^1A_1$-adamantylidene (**97**).[70] The barrier to interconversion of (**96**) to (**97**) by [1,2]-H shift is $69.1\,kcal\,mol^{-1}$, much higher than that for [1,2]-C migration



(**94**) (**95**)

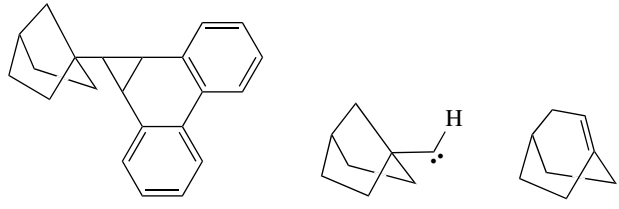


(**96**) (**97**) (**98**)

(**99**) (**100**) (**101**)

to 4-propoadamantylidene (**100**) (30.3 kcal mol^{-1}) or for retro-Diels–Alder reaction (20.5 kcal mol^{-1}) to form the triene (**99**). The singlet carbene (**100**) rearranges via [1,3]-H and [1,2]-H shifts with identical barriers (8.8 kcal mol^{-1}). The predicted distribution of products (**99**) $\gg$ (**98**) $\approx$ (**101**) is in agreement with experiment.

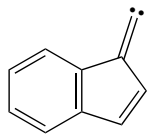
The non-nitrogenous carbene precursor (**102**) was used for the photochemical generation of the carbene (**103**) without complications due to reactions of diazirine or diazo species.[71] In the presence of alkenes, carbene (**103**) gave rise to cyclopropanes and in the absence of alkenes was proposed to undergo [1,2]-C shift to form (**104**), which suffered retro-Diels–Alder reaction to give a triene.



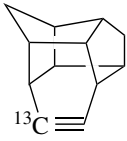
(**102**) (**103**) (**104**)

Calculations at the BLYP/6–311G** level were found to give a good estimate of the barrier (33.2 kcal mol^{-1}) of the benzyne to cyclopentadienylidenecarbene (CPDC) rearrangement.[72] Similar calculations on polycyclic arynes (e.g. naphthalynes) identified three distinct types of rearrangement. Only type I, e.g. of 1,2-naphthalyne, to produce relatively stable CPDCs [such as (**105**)] with aromatic conjugation unaffected by the cyclopentadienylidene moiety are observed experimentally.

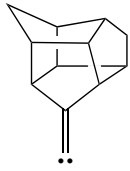
The ^{13}C-labelled cycloalkyne (**106**) generated by treatment of the corresponding vinyl bromide with a strong base (LDA), was proposed to undergo [1,2]-C rearrangement to the vinylidenecarbene (**107**) in which the label is scrambled between the two sp^2 carbons. Carbene (**107**) was trapped by cycloadditions to alkenes.[73] The reverse process, rearrangement of vinylidenecarbene (**107**) to the cycloalkyne (**106**), was shown not to occur because formation of (**107**) from the corresponding ^{13}C-labelled dibromomethylene precursor (**108**) gave products in which no scrambling of the label was observed. The cycloalkyne was calculated to lie 8.3 kcal mol^{-1} above the carbene.



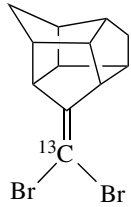
(**105**)



(**106**)



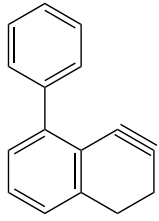
(**107**)



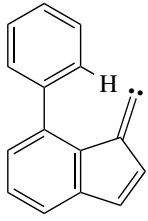
(**108**)

The cyclodehydration of 1-phenylnaphthalene has been studied by BLYP/6–311G** calculations.[74] A minor pathway involving two consecutive losses of H to give the naphthalyne (**109**), which rearranges to the CPDC (**110**) (with a barrier of 30.3 kcal mol^{-1}), that can insert into the *ortho*-H of the phenyl ring (barrier 3.0 kcal mol^{-1}) was identified.

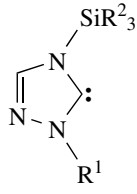
Attempted formation of the 4-silyl-substituted nucleophilic carbene (**111**) by deprotonation of the corresponding triazolium salt with KH led to the triazole (**112**), the product of apparent [1,2]-Si migration.[75] A crossover experiment indicated that silyl transfer is intermolecular.



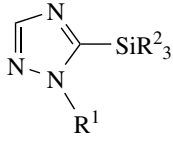
(**109**)



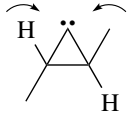
(**110**)



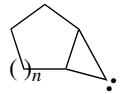
(**111**)



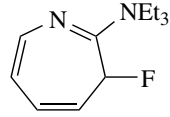
(**112**)



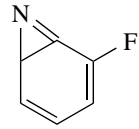
(**113**)



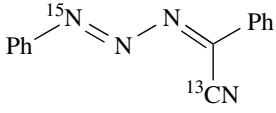
(**114**)



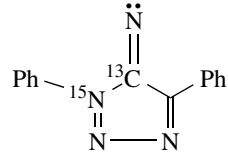
(**115**)



(**116**)



(**117**)



(**118**)

Calculations on the ring opening of *trans*-cyclopropylidene (**113**) to 1,3-dimethylallene predicted a barrier of 4.2 kcal mol^{-1} via initial disrotatory motion of the substituents followed by a change to conrotatory motion.[76] The *cis*-cyclopropylidene rearrangement is barrierless and, in agreement with the elusive nature of 1,2-cycloheptadiene, the barrier to ring opening of bicyclic cyclopropylidene (**114**; $n = 2$) cannot be overcome at low temperatures.

Irradiation of *o*-fluorophenyl azide in the presence of diethylamine gives the single azepine (**115**), suggesting that the ring closure of *o*-fluorophenylnitrene occurs away from the substituent to give azirine (**116**).[77] Only in azides bearing two *ortho*-fluorine substituents is ring expansion sufficiently retarded to allow the singlet nitrene to react with diethylamine.

Thermal decomposition of a doubly labelled azidotriazole gave rise to the open-chain triazine (**117**) in which the labels were not scrambled.[78] Laser flash photolysis of the triazole leads to (**117**) within 20 ns with no observable intermediate. *Ab initio* calculations indicate that a dynamic equilibrium between the open-chain triazine (**117**) and a cyctic nitrene (**118**), as originally proposed,[79] is highly disfavoured.

Nitrenium ions

Calculations of the singlet–triplet energy gaps of a series of nitrenium ions [X(H)N**:**]$^+$ in the gas phase and in solution indicate that the gap decreases in the order X = H > CN > F as a result of stabilization of the singlet state by π-donation from the substituent. For strong π-donors (Cl, F), the singlet state is more stable than the triplet.[80]

Calculations on the isoelectronic series Me(Ph)B$^-$, Me(Ph)C**:**, and [Me(Ph)N**:**]$^+$ show that the singlet-state geometries are different, reflecting differences in the orbital interactions between the hypovalent atom and the π-system.[81] The high calculated barrier (21.5 kcal mol^{-1}) for [1,2]-H shift in the nitrenium ion is the result of migration using the orbital which is conjugated with the π-system.

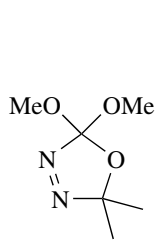
Nucleophiles and Electrophiles

The yields of CO production in the reaction of BrFC**:** with substituted benzaldehydes are dependent on the electronic effects of *para* substituents.[82] Carbonyl ylide intermediates were trapped with dimethyl acetylenedicarboxylate. Sterically hindered tetraphenylcyclopentadienone gave a high yield of CO and no ylide could be trapped in this case.

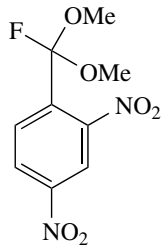
The absolute rate constants for oxygen and sulfur transfer to a range of carbenes (dialkyl, cycloalkylidene, alkylchloro, diaryl, arylchloro, arylalkoxy, and dialkoxy), generated by laser flash photolysis of diazirine or oxadiazoline precursors, were determined.[83] No evidence was seen for ylide formation and a concerted mechanism via an ylide-like transition state was proposed.

Ab initio and density functional calculations indicate that the first step of the abnormal Reimer–Tiemann reaction involves barrierless formation of an intermediate by nucleophilic attack on **:**CCl_2 of the β-carbon of pyrrole anion.[84] This is followed by a single, concerted step to give the product, 3-chloropyridine.

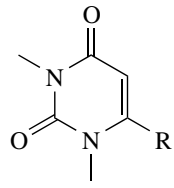
Dimethoxycarbene $(MeO)_2C$**:**, generated by thermolysis of the oxadiazoline (**119**), was found to effect nucleophilic substitution on highly electron-deficient aryl fluorides.[85] Reaction with Sanger's reagent (2,4-dinitrofluorobenzene) gave rise to (**120**) by attack on the fluorine-bearing carbon followed by [1,2]-F shift. Thermal decarboxylation of 1,3-dimethylorotic acid (**121**; R = CO_2H) in refluxing benzyl bromide give rise to the 6-benzyluracil (**121**; R = Bn).[86] This process involves a C(6)nucleophile, either a zwitterion or the carbene (**122**).



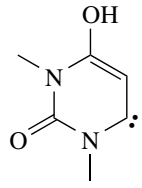
(**119**)



(**120**)



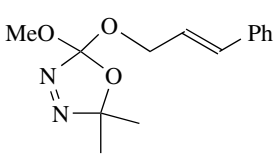
(**121**)



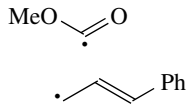
(**122**)

Thermolysis of the oxadiazoline (**123**) gives rise to the corresponding dialkoxycarbene, which can be trapped by reaction with *t*-butanol to form orthoesters.[87] The formation of a regioisomeric mixture of esters was explained by fragmentation of the carbene to radicals (**124**) which recombine at either end of the allyl system.

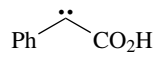
Flash photolysis of 2-diazophenylacetic acid in ^{18}O-labelled water gives mandelic acid (**127**) labelled in the carbonyl oxygen, thus ruling out a mechanism involving Wolff rearrangement of the carbene (**125**) to give a hydroxyphenylketene.[88] The results were consistent with direct conjugate addition of water to the carbene (**125**) to form the enol (**126**).



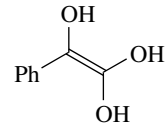
(**123**)



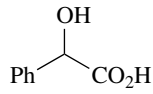
(**124**)



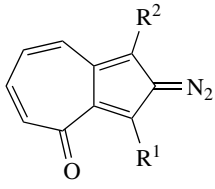
(**125**)



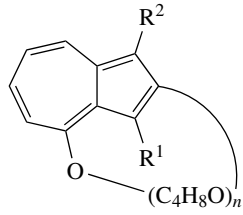
(**126**)



(**127**)



(**128**)



(**129**)

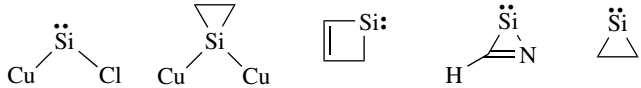
Insertion of the carbenes, via a low-lying singlet state close to the ground-state triplet, generated by photolysis of the diazo compounds (**128**), into the CO bond of cyclic ether solvents (THF, THP, dioxane) gave rise to polyether-bridged azulenes such as (**129**).[89]

$FeCl_2$ has been used to catalyse nitrene transfer from *t*-butyloxycarbonyl azide to sulfoxides (to form sulfoximides), sulfides (to give sulfimides), and a ketene acetal (to form an α-amino ester).[90]

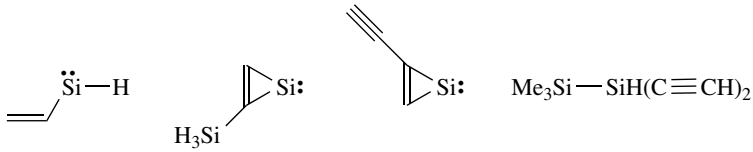
Silylenes

Silylene (H_2Si**:**) and methylene were used to develop a general procedure for calculation of spin–orbit coupling of triplet states of organic biradicals with their singlet states.[91] The silylene (**130**) was invoked to explain the formation of ethyldichlorosilane from the reaction of metallic silicon with HCl and ethene in the presence of a CuCl catalyst.[92] Initial reaction to form the silacyclopropane (**131**) followed by reaction with 2 mol of HCl was proposed. The rate constant for insertion of Cl_2Si**:** into the CH bond of methane has been determined as $13.41\,mol^{-1}\,s^{-1}$ at 921 K.[93] The decomposition of the methyldichlorosilane product is proposed to involve elimination of methane to form Cl_2Si**:** with a rate constant of $(1.5 \pm 0.2) \times 10^{-3}\,s^{-1}$ at 905 K. The results of a study of the thermal decomposition of Cl_3SiH, Cl_2SiH_2, and $ClSiH_3$ are consistent with molecular elimination reactions to give silylene intermediates (Cl_2Si**:**, Cl_2Si**:**, and HClSi**:**, respectively).[94]

An attempt to investigate the possible photochemical rearrangement of silacyclobutenylidene (**132**) to give silacyclobutadiene produced seven silylene species in the



(**130**) (**131**) (**132**) (**133**) (**134**)



(**135**) (**136**) (**137**) (**138**)

C_3H_4Si manifold, none of which proved to be the silacyclobutadiene.[95] Silicon atoms, generated thermally, were co-condensed in an argon matrix with HCN. The initial product **:**CH−N=Si**:** is rapidly converted into (**133**) and **:**SiH−C ≡ N.[96] The silylene (**133**) is converted into **:**SiH−N=C**:** on further irradiation and this then isomerizes to radical species.

Thermally generated silicon atoms react in an argon matrix with acetylene to give silacyclopropenylidene and in a similar way with ethylene to give silacyclopropylidene (**134**).[97] Subsequent irradiation gives the *anti*-conformer of vinylsilylene (**135**) and then a species assigned as 1-silaallene ($H_2Si{=}C{=}CH_2$). Pulsed flash photolysis of three different precursors led to matrix-isolated silacyclopropenylidene (**136**), which was converted by further irradiation into the isomeric silylenes $H_3SiC \equiv C{-}(H)Si$**:** and $H_3Si(H{-}C \equiv C)Si$**:**.[98] Calculations on five C_4H_2Si species identified the silacyclopropenylidene (**137**) as the most stable isomer.[99] Flash pyrolysis of disilane (**138**) gave rise to (**137**), which was trapped in an argon matrix at 10 K.

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CHAPTER 7

Nucleophilic Aromatic Substitution

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General

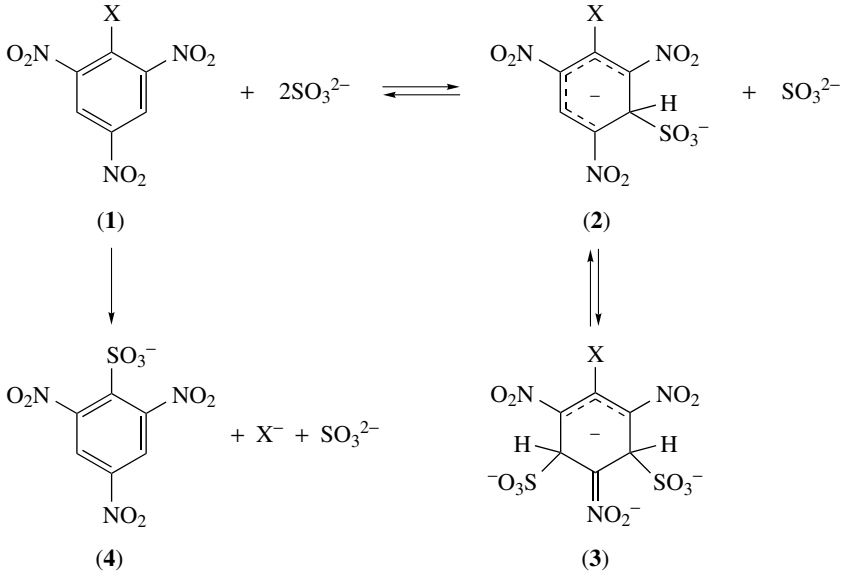
The dediazoniation of arenediazonium ions may occur by heterolytic or homolytic pathways. In a new study of the decomposition of 4-methylbenzenediazonium tetrafluoroborate in aqueous solution, the concentrations of the products, *p*-cresol with a small amount of 4-chlorotoluene, and also the unreacted diazonium salt were simultaneously monitored. The results are in accord with the heterolytic mechanism involving a highly reactive aryl cation which shows little discrimination for water or chloride ions.[1] The dediazoniation of 2,4,6-trimethylbenzenediazonium ions in concentrated aqueous solutions of acetamide, *N*-methylacetamide and *N,N*-dimethylacetamide also involves heterolysis; the aryl cation intermediate may be trapped by the oxygen or nitrogen atoms of the amides as well as by water. This approach provides a possible new method for obtaining information on the topologies and orientations of aggregate-bound polypeptides.[2]

The radical-chain $S_{RN}1$ reaction is a useful method for the formation of new carbon–carbon bonds; reactions of the enolate ions of 2-acetylthiophene and 2-acetylfuran with aryl halides have been investigated using photo-initiation and also iron(II) initiation.[3]

The S_NAr Mechanism

Sulfite is an extremely good nucleophile for activated aromatic systems and reaction with 1-substituted-2,4,6-trinitrobenzenes (**1**) may result in σ-adduct formation or in displacement of the 1-substituent as shown in Scheme 1. When X = OEt or SEt, adducts (**2**) and (**3**) formed by reaction at unsubstituted positions are long-lived.

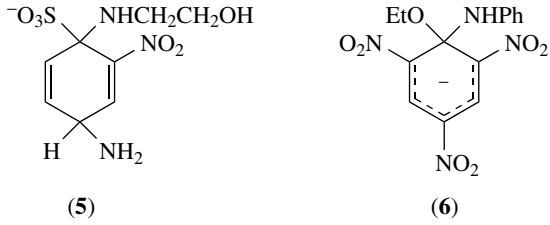
However when X = OPh or SPh, the substitution product (**4**) is eventually produced reflecting the better leaving-group ability of the phenyl compared to the alkyl derivatives.[4] The intermediate (**5**) has been postulated[5] in the catalysis by sulfite of the displacement by ammonia of the hydroxyethylamino group in 1-hydroxyethylamino-2-nitro-4-aminobenzene.



X = OEt, SEt, OPh, SPh

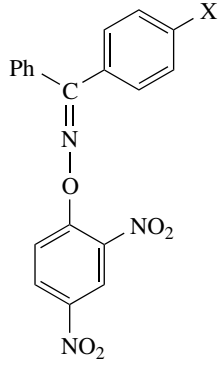
SCHEME 1

The reaction of ethyl 2,4,6-trinitrophenyl ether with aniline in dimethyl sulfoxide (DMSO) in the presence of Dabco occurs in two stages via the intermediate (**6**). Kinetic studies show that proton transfer is rate-limiting both in the formation of the intermediate and in the subsequent acid-catalysed decomposition to give 2,4,6-trinitrodiphenylamine. Phenoxide is a considerably better leaving group than ethoxide so that substitutions of phenyl 2,4,6-trinitrophenyl ethers and phenyl 2,4-dinitronaphthyl ether with aniline occur without the accumulation of intermediates. Both uncatalysed and base-catalysed pathways are involved.[6]



The $^{18}F/^{19}F$ kinetic isotope effect (KIE) has been measured in the reactions of 2,4-dinitrofluorobenzene with 2- and 4-methylaniline in DMSO. The large KIE for 2-methylaniline suggests rate-limiting expulsion of fluoride with this sterically hindered nucleophile whereas the low KIE for 4-methylaniline is consistent with rate-limiting nucleophilic attack.[7] The role of 2(1*H*)-pyridones as bifunctional catalysts has been investigated in the substitution reaction of 2-cyano-4-nitrofluorobenzene with piperidine in chloroform.[8] There has been a kinetic study of the reactions of 2-nitrofluorobenzene with aliphatic amines in DMSO and in toluene.[9]

In non-polar solvents many aminolysis reactions show a third-order dependence on the amine, B. This may be explained by catalysis of leaving-group departure by hydrogen-bonded homoconjugates, BH^+B. Evidence for this pathway has been adduced from studies of the reactions of some nitro-activated *O*-aryl oximes (**7**) with pyrrolidine in benzene, chlorobenzene, and dioxane,[10] and with piperidine and hexylamine in cyclohexane.[11] The third-order dependence on amine of the reaction of 2,6-dinitroanisole with butylamine in toluene and toluene–octanol mixtures has been interpreted in terms of a mechanism involving attack by dimers of the nucleophile.[12]



(**7**)

The reaction of aliphatic amines with *sym*-trichlorotrinitrobenzene results in substitution of chlorine and, in the case of ammonia and monoalkylamines, the formation of di- and tri-substituted products is facilitated by monosubstitution. This has been attributed to hydrogen bonding between an amino hydrogen and an *ortho*-nitro group which helps to relieve steric strain so that nitro groups may more nearly achieve coplanarity with the aromatic ring.[13] Nitranions, formed from aryl and heteroaryl amines and sodium hydride, may replace chlorine in 4-chloronitrobenzene to yield diarylamines; reactivity is higher in DMSO than in toluene owing to ion-pair formation in the latter solvent.[14] Microwave irradiation has been found to speed reaction, compared with conventional reflux, in the substitution of halogens by piperidine or potassium *t*-butoxide in DMSO or in dimethylformamide (DMF).[15]

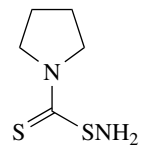
A spectrochemical study has been reported[16] of the reactions in dimethylacetamide of benzyl thiolate, RS^-, and disulfide, RS_2^-, ions with nitrobenzenes, $XC_6H_4NO_2$,

activated by a second electron-withdrawing group. Nitro group displacement is observed yielding unsymmetrical monosulfides, XC_6H_4SR, or (poly)sulfide anions, $XC_6H_4S_y^-$ ($y = 1, 2$). Reaction of 4-bromophenoxide ions with 3-substituted or 3,5-disubstituted nitrobenzenes in DMF may also result in displacement of the nitro group, and a correlation has been established between reactivity and σ_M substituent constants.[17] It is reported that reaction in DMSO or DMF of 1-nitro-4-chloroanthraquinone with thiophenolate ions results in nitro group displacement; however, with phenolate ions chlorine is preferentially substituted.[18] A kinetic study of the formation of 1,2,3,4-tetrachlorodibenzo-*p*-dioxin in DMSO indicates a rate-limiting step involving nucleophilic attack by a pyrocatechol anion on hexachlorobenzene.[19]

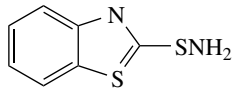
An unusually facile hydroxydemethoxylation reaction has been reported for 1-benzoyl-4-methoxynaphthalene. The use of ^{18}O-enriched hydroxide confirmed that reaction occurs by the S_NAr pathway rather than by cleavage of the oxygen to methyl bond. A related reaction is observed in 3-(4-methoxy-1-naphthoyl)indole derivatives. These results indicate the possibility of S_NAr activation by a 4-carbonyl group; the reaction is facilitated by use of a naphthyl ketone as substrate and DMSO as solvent.[20]

The vicarious nucleophilic substitution (VNS) of hydrogen is an important method of replacement of ring hydrogen atoms. It is termed vicarious since it involves departure of an anion from the incoming nucleophile rather than hydride ion from the aromatic ring. A short review[21] has summarized studies of the mechanism and the orientation of substitution in VNS reactions. The synthesis of a hexasubstituted benzene has been reported by VNS reaction of 2-chloro-3,5-dinitro-4-methylbenzene with the anion of chloromethyl *p*-tolyl sulfone.[22] VNS reaction of nitroarenes with the anion of 1-cyano-2,2-diethoxycarbonyl cyclopropane proceeds by σ-adduct formation and base-induced elimination which results in cleavage of the cyclopropane ring; reaction *ortho* to the nitro group may eventually yield substituted *N*-hydroxyindoles.[23]

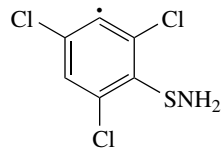
Full reports have appeared, following preliminary communications, of both the amination and hydroxylation of nitroarenes. Amination may be achieved by use of sulfenamides as nucleophiles. The mechanism is analogous to VNS with thiolates as leaving groups. Use of the sulfenamide (**8**) results in amination *para* to the nitro group, while (**9**) and (**10**) allow reaction at the *ortho* position.[24] The amination of dinitroarenes by this procedure is not satisfactory and S_NAr substitution of nitro groups may occur. Hydroxylation of nitroarenes may be observed following reaction with the anions of *t*-butyl or cumyl hydroperoxides;[25] again VNS is involved with base-induced elimination of the alcohol occurring by an *E*2-type mechanism.



(**8**)

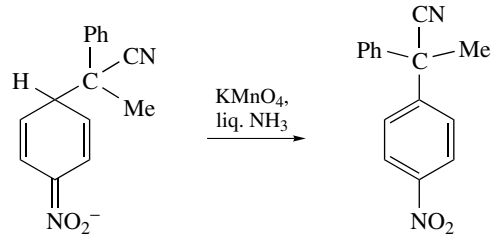


(**9**)

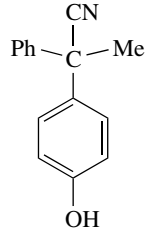


(**10**)

There have been several studies of the oxidative substitution of hydrogen by carbanions. Reaction of the carbanion of 2-phenylpropionitrile with nitroarenes in liquid ammonia yields σ-adducts (**11**), which may be oxidized with potassium permanganate to yield the neutral products (**12**). Addition of methyl iodide to a 1:1 carbanion–nitroarene mixture indicates the presence of little free carbanion, showing that formation of the initial σ-adduct goes almost to completion.[26] The value of 9.8 found for the isotope effect k_H/k_D measured by comparison of the rates of reaction of nitrobenzene and [4 − ^{2}H]nitrobenzene confirms that carbon–hydrogen bond breaking is rate limiting in the oxidation process.[27] Studies with related phenylacetonitrile derivatives PhCHRCN [R = Et, $n - C_5H_{11}$, Bn, MeO, PhO, NMe_2, Ph, CH(Me)Ph and $CHPh_2$] show that σ-adduct formation at the 4-position of nitroarenes is the norm; when suitable leaving groups, R = MeO, PhO, are present in the carbanion then VNS may compete with oxidation of the adducts.[28] Interestingly, in the reaction of 2-phenylpropionitrile with nitroarenes the use of dimethyldioxirane as the oxidant rather than permanganate results in nitro group displacement to yield substituted phenols (**13**); it is likely that a dienone intermediate is involved.[29] Kinetic studies of substituent effects on the reaction in alcohols as solvents of substituted nitrobenzenes with the anion of phenylacetonitrile show that initial complexation may be rate limiting; the eventual products are 2,1-benzisoxazoles.[30] Mass spectrometry has been used to identify 3-methylbenz-1,2-isoxazole as a decomposition product formed from substituted 1-phenylethanone oximes on electron ionization. A mechanism was proposed involving intramolecular attack of the oxime hydroxyl group followed by a 1,2-elimination of the *ortho*-substituent and the hydrogen of the hydroxyl group.[31]



(**11**) (**12**)



(**13**)

The reaction of the carbanion derived from diethyl methylphosphonate with perhalogenated aromatics may result in substitution of halide to yield perhaloaryl(hetaryl)methylphosphonates, which can be converted into tris- or bis-(perhaloaryl)methanes.[32] Displacement of fluoride ion has been reported in the reaction of dimethoxycarbene with 1-fluoro-2,4-dinitrobenzene and with hexafluorobenzene.[33] The hydrodehalogenation of halogenated aryl ketones may be facilitated using hydrogen over a Pt/C catalyst.[34]

There has been a useful review of phase-transfer catalysis in nucleophilic aromatic substitution.[35] A comparison has been reported of the reactions with nucleophiles of 1-chloro-2,4-dinitrobenzene (substitution) and 4-nitrophenyl diphenyl phosphate (dephosphorylation) in neutral micelles of dodecyl (10) and (23) polyoxyethylene glycol. In the substitution reaction considerable amounts of ether may be formed by reaction with alkoxide ions at the micellar surface. Differences in reactivity of the two substrates are probably due to differences in their location in the micellar structures.[36]

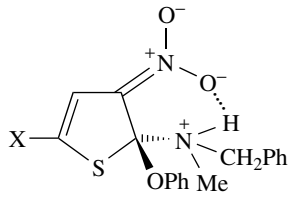
It has been shown that when nucleophilic aromatic photo-substitution reactions are carried out in non-deoxygenated solutions of aprotic solvents, such as DMSO and acetonitrile, destructive superoxide anions may be formed from aromatic radical anions. Such solvents are best avoided.[37] There has been a review of mechanistic aspects of photo-substitutions of the cyano group in aromatic compounds.[38]

A kinetic study has been reported[39] of the nucleophilic exchange reaction of the radionuclide ^{131}I with 15-(4-iodophenyl)pentadecanoic acid in the presence of Cu(I). The activation of arenes to nucleophilic attack by complexation with transition metal ligands is well known. It is reported that potassium hydride will react with $Cr(CO)_3$–aryltrimethylsilanes to generate aryl anions which can further react with electrophiles.[40] Several new rhodium(III) complexes have been synthesized and shown to be efficient catalysts for methoxydefluorination reactions of fluoroarenes.[41] The transition metal-catalysed reactions of nitrogen, oxygen, sulfur, and phosphorus nucleophiles with aromatic and with heteroaromatic compounds have been reviewed; palladium or nickel complexes containing phosphine ligands are often used and inter- and intra-molecular substitutions may occur.[42] It has been reported that arene–chromium complexes may be used effectively as supporting ligands in the palladium-catalysed amination reactions of both electron-rich and electron-deficient aryl bromides with secondary amines.[43] A new co-catalysed cyanation reaction involving Pd(0) catalysis has been reported, providing an efficient synthetic route to aryl nitriles. Thus the CuI–$Pd(PPh_3)_4$ system allows conversion of aryl halides and triflates into the corresponding nitrile derivatives using sodium or potassium cyanide.[44]

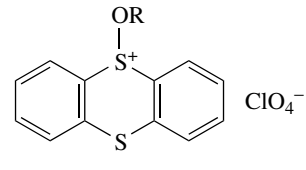
Heterocyclic Systems

A kinetic study has been reported of substituent effects on the reactions of 2-phenoxy- and 2-(4-nitrophenoxy)-3-nitro-5-X-thiophenes with benzylamine and with *N*-methylbenzylamine in benzene as solvent. The intramolecularly hydrogen-bonded intermediate (**14**) is postulated. Reactions of the 5-unsubstituted thiophenes (X = H) are not base-catalysed, indicating that nucleophilic attack is rate limiting, and the more basic secondary amine shows higher reactivity than the primary

amine. The introduction of electron-withdrawing groups at the 5-position results in a weakening of the hyper-*ortho* interaction between the reaction centre and the 3-nitro group, so that the strength of the intramolecular hydrogen bond is reduced. A consequence of this is that reversal of the intermediate to reactants is facilitated and with *N*-methylbenzylamine base catalysis, probably by the SB–GA mechanism, is observed.[45]



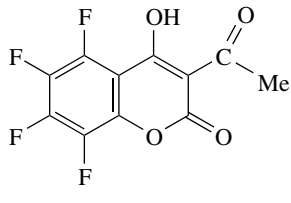
(**14**)



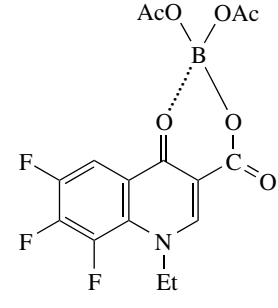
(**15**)

Some 5-(alkyloxy)thianthrenium perchlorates (**15**) have been prepared in which the alkyl group may be primary or secondary. Reaction with iodide ions may result in S_N2 reaction at the alkyl group or S_NAr reaction at the sulfonium sulfur atom leading to the formation of thianthrene.[46]

2,4,6-Tribromo-3,5-difluoropyridine may be prepared by reaction of pentafluoropyridine with a mixture of hydrogen bromide and aluminium tribromide. Surprisingly, reaction with hard nucleophiles, such as methoxide in methanol or aqueous ammonia, resulted in exclusive displacement of fluoride whereas reaction with softer nucleophiles, such as sodium thiophenolate, gave exclusive displacement of bromide.[47] Fluoride displacement at the 7-position is observed in the reaction of 3-acetyl-5,6,7,8-tetrafluoro-4-hydroxycoumarin (**16**) with ammonia or morpholine in DMSO; however, reaction with ammonia in water, alcohol, or glyme results in attack at the acetyl group to yield the corresponding 3-(1-iminoethyl) derivative.[48] It is reported[49] that the rate of nucleophilic displacement of halogens at the 7-position in halogenated derivatives of *N*-substituted 4-oxo-1,4-dihydroquinoline-3-carboxylic acid may be enhanced by the formation of boron chelates such as (**17**). Acceleration of the alkaline



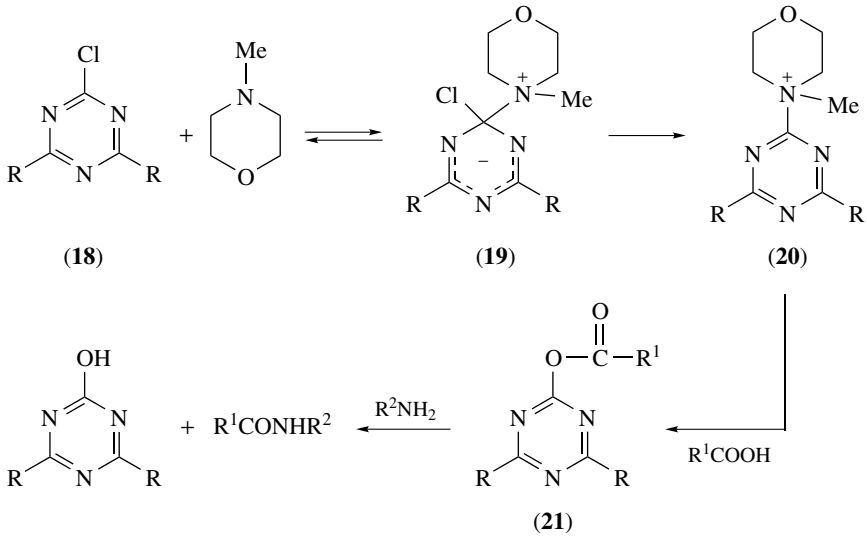
(**16**)



(**17**)

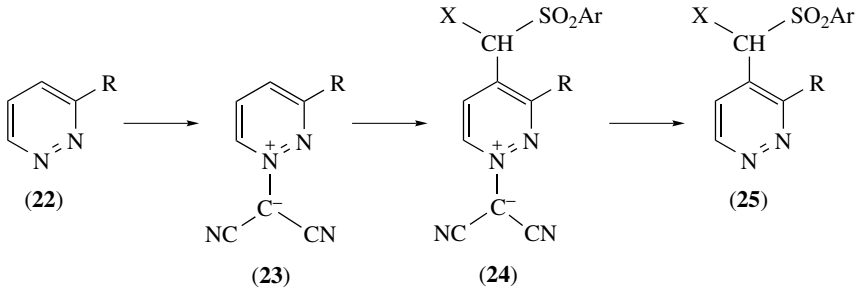
hydrolysis of 2-phenoxyquinoxaline has been found in micelles of cetyltrialkylammonium hydroxides and in related cationic micelles; increases in rate constants with increasing size of the head group were attributed to exclusion of water from the micellar surface.[50]

There has been a study of the mechanism of the activation of carboxylic acids to peptide formation by chloro-*s*-triazines in combination with tertiary amines. The first step, exemplified in Scheme 2 by the reaction of 2-chloro-4,6-disubstituted-1,3,5-triazines (**18**) with *N*-methylmorpholine, is formation of a quaternary triazinylammonium salt (**20**). Here there is ^{1}H NMR evidence for the formation at $-50\,^{\circ}$C of the intermediate (**19**), showing that the substitution involves the two-step S_NAr mechanism rather than a synchronous pathway. The subsequent reaction of (**20**) with a carboxylic acid yields the 2-acyloxy derivative (**21**), which carries an excellent leaving group for the amide-forming step.[51]

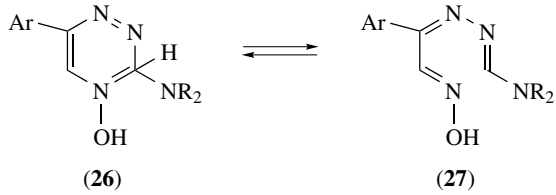


SCHEME 2

The nucleophilic substitution of hydrogen in pyridazines (**22**) may be achieved by vicarious substitution in the dicyanomethylide derivatives.[52] As outlined in Scheme 3, treatment with tetracyanoethylene oxide gives the *N*-dicyanomethylide (**23**) which will react under VNS conditions to give (**24**); the dicyanomethylene group may be eliminated by a radical pathway to yield the 4-substituted pyridazine (**25**). The replacement of ring hydrogen and of good leaving groups has been compared in a review of the reactions of 1,2,4-triazines with carbon nucleophiles including cyanide ions.[53] The reaction of 6-aryl-1,2,4-triazine-4-oxides with secondary amines in alcohol yields σ-adducts (**26**), which form isolable ring-opened intermediates (**27**); oxidative aromatisation with permanganate allows the isolation of 1,2,4-triazines substituted in the 3-position.[54] The reaction of 3-amino- or 3-methylthio-1,2,4-triazine with electron-rich



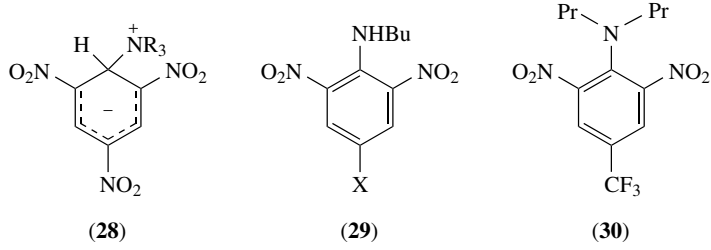
SCHEME 3



arenes, such as 2,6-dimethylphenol, resorcinol, or indole, may result in the formation of 4,5-dihydro derivatives.[55]

Meisenheimer and Related Adducts

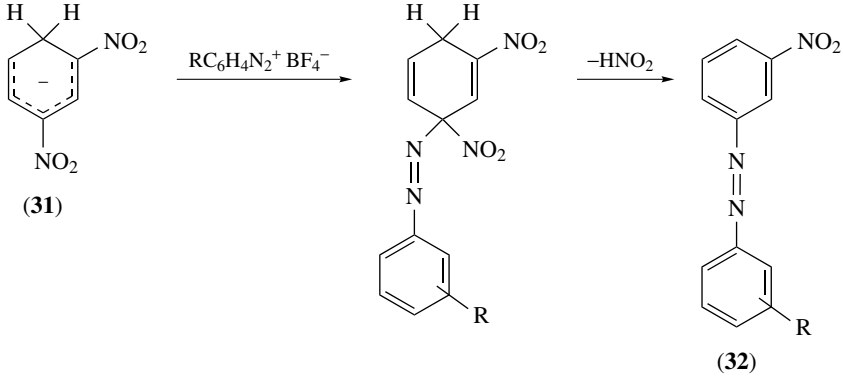
A kinetic study of the formation of zwitterionic adducts (**28**) from 1,3,5-trinitrobenzene and diazabicyclo derivatives indicates that reactions are surprisingly slow, with rate constants many orders of magnitude lower than those for related reactions with primary or secondary amines.[56] The use of rapid-scan spectrophotometry was necessary to study the kinetics of reaction of 4-substituted-2,6-dinitro-*N*-*n*-butylanilines (**29**) with *n*-butylamine in DMSO; the two processes observed were identified as rapid deprotonation to give the conjugate base and competitive σ-adduct formation at the 3-position.[57] The reactions of *N,N*-di-*n*-propyl-2,6-dinitro-4-trifluoromethylaniline (**30**), the herbicide trifluralin, and its *N*-ethyl-*N*-*n*-butyl analogue with deuteroxide ions and with sulfite ions in [$^2H_6$]DMSO–D_2O have been investigated by ^{1}H NMR spectroscopy. With deuteroxide σ-adduct formation at the 3-position is followed by



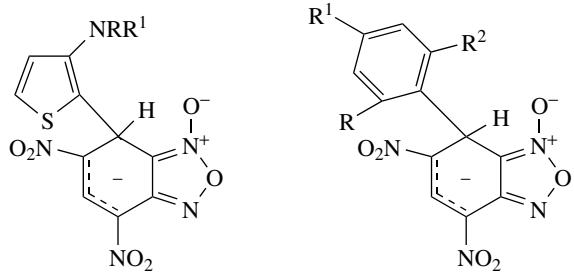
nucleophilic displacement of the *N,N*-dialkyl substituents, while in the case of sulfite attack at the 3-position is followed by the formation of isomeric *cis*- and *trans*-diadducts resulting from addition at the 3- and 1-positions. The reactions with deuteroxide are accompanied by slow aryl H–D exchange.[58] Note that σ-adducts have also been observed during the reactions with sulfite of 1-substituted-2,4,6-trinitrobenzenes.[4]

Hydride adducts (**31**) may be formed by the reaction of 1,3-dinitrobenzene with potassium borohydride; their treatment[59] with phenyldiazonium salts leads to nitro group displacement yielding azo-coupled products (**32**).

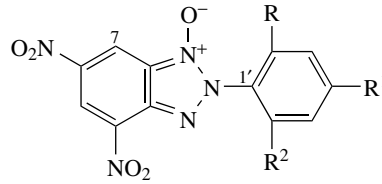
The super-electrophile 4,6-dinitrobenzofuroxan (DNBF) has been used to probe the reactivity of 3-aminothiophenes; their ready formation of adducts (**33**) by reaction at the 2-position indicates their strongly enaminic nature.[60] Mixing DNBF and hydroxy- and methoxy-substituted benzenes in DMSO yields adducts (**34**; R, R^1, R^2 = OH, OMe). In the reaction with 1,3,5-trimethoxybenzene an isotope effect, k_H/k_D, of 3.71 is observed, indicating that in the reaction, viewed as an S_EAr substitution, proton transfer of ring hydrogen is partially rate limiting.[61] The highly electrophilic benzotriazole derivative (**35**), in which R, R^1 and R^2 may include one, two, or three nitro groups, has been used to monitor reactivities of sterically hindered phenoxide ions. NMR studies show that for both 2,6-di-*t*-butylphenoxide, acting as a carbon nucleophile, and 3,5-di-*t*-butylphenoxide, acting as an oxygen nucleophile, the propensity



(**31**) (**32**)



(**33**) (**34**)



(**35**)

for reaction at the 1′-position of (**35**) relative to the 7-position increases with nitro substitution.[62]

Benzyne and Related Intermediates

It has been shown that, in the presence of lithium diethylamide at −70 °C, bromobenzoic acids form arynes which may react with arylacetonitriles to yield, predominantly, 2-cyanobenzoic acids.[63] The reaction of alkyl and aryl isocyanides with benzyne may yield benzamide derivatives, showing their ability to act as charge-reversed equivalents to isocyanates.[64] The generation and cyclization of a benzyne-tethered alkyllithium have been reported, and lead to a convenient synthetic route for 4-substituted indans.[65]

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CHAPTER 8

Electrophilic Aromatic Substitution

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General

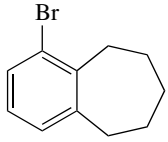
Methyl cation affinities of benzene and some substituted benzenes have been calculated. These follow a simple additivity rule and the value for benzene shows good agreement with the experimental estimate. Conclusive evidence is presented that these values are linearly related to the corresponding proton affinities.[1] The competition between deuteriation and alkylation in the reaction of radiolytically formed perdeuterio ethyl cations with *N*-methylpyrrole and with thiophene has been studied. Deuteriation, the Brønsted acid pathway, predominates and intramolecular selectivities have been determined for each reaction.[2]

Examples have been given where high and unusual reactivity with electrophiles is seen when simple, monocyclic benzene rings are bent by short bridges into a boat-shaped conformation, as in small para- and meta-cyclophanes.[3] For example, bromination of [5]metacyclophane occurs at $-75\,^{\circ}C$ without a catalyst to give the bromobenzocycloheptene (**1**). *Ab initio* calculations suggest[4] that chloro and bromo substituents deactivate a benzene ring to electrophilic substitution not, as commonly quoted, by the inductive effect but because the energy levels of the valence *p*-orbitals of these elements, are higher than that of the π-molecular orbital (π_1) of benzene. For chlorobenzene, π_1 is then at a lower energy and electron density at the 4-position is significantly reduced, causing deactivation.

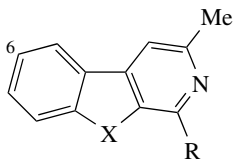
Changes in intramolecular selectivity in the bromination and nitration of alkylbenzenes in acidic media have been attributed[5] to changes in medium polarity or changes in electrophile solvation. Mass spectrometric studies of the first stage in the gas-phase reactions of halobenzenes, furan, thiophene and pyrrole with alkyl cations have been rationalized in terms of co-existing σ- and π-complexes.[6] The extent of

π-complex formation decreases as the capability of the aromatic to donate electron density increases. Alkyl group isomerization can occur within the lifetime of the π-complex. Complete isomerization occurs in the loosely bound π-complexes formed between halobenzenes and carbenium ions.

Electrophilic substitution in benzo[*b*]thieno- and benzo[*b*]furo-[2,3-*c*]pyridines (**2**) occurs mainly at the 6-position, although when this position is blocked by Cl in a related structure 5-,7-, and 8-substituted products are formed.[7] The usefulness of trifluoromethanesulfonic acid as a new solvent with $CFCl_3$ for the reaction of fluorine with aromatics has been explored.[8] Fluorobenzene gives 1,4-difluorobenzene (31%) and 1,2-difluorobenzene (7%) instead of the addition products mainly observed when the acid is absent; 1,2- and 1,3- but not 1,4-difluorobenzene undergo further substitution at appropriate acidity.

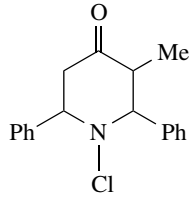


(**1**)



(**2**)

X = S, R = Et
X = O, R = Me



(**3**)

Halogenation

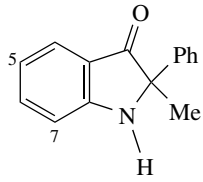
Kinetic results on the chlorination of aniline by *N*-chloro-3-methyl-2,6-diphenylpiperidin-4-one (**3**) suggest that the protonated reagent is reactive and that the initial site of attack is at the amino nitrogen.[9] The effects of substituents in the aniline have been analysed but product studies were not reported. Zinc bromide supported on acid-activated montmorillonite K-10 or mesoporous silica (100 Å) has been demonstrated[10] to be a fast, selective catalyst for the regioselective *para*-bromination of activated and mildly deactivated aromatics in hydrocarbon solvents at 25 °C. For example, bromobenzene yields around 90% of dibromobenzenes with an *ortho*/*para* ratio of ~0.12.

The regioselectivity of chlorination and bromination of *N,N*-dialkylbenzamides in aqueous acetic acid is strongly influenced by the alkyl groups.[11] *Ortho* and *para* orientation results fairly selectively from substrates with large alkyl substituents. For example, *N,N*-diisopropylbenzamide gives *o*-, *m*- and *p*-chloro derivatives in the proportion 47:11:42.

Kinetic studies of the iodination of benzene and acetanilide by iodine, diiodine pentoxide, and sulfuric acid in acetic acid indicate that benzene is involved in an equilibrium reaction prior to the rate-limiting σ-complex formation.[12] It is proposed that this equilibrium involves the formation of a π-complex between iodine adsorbed on diiodine pentoxide and the benzene as it is adsorbed. In the case of acetanilide the σ-complex is formed directly with activated iodine adsorbed on the diiodine pentoxide.

The kinetics of iodination of aniline and *p*-toluidine by iodine in acidified aqueous methanol have been determined[13] at various solvent compositions and temperatures. It was deduced that HOI was the effective electrophile under the reaction conditions.

1,2-Dihydro-2-methyl-2-phenyl-3*H*-indol-3-one [the indoxyl (**4**)] gives 5- and/or 7-sub-stitution on reaction with *N*-chlorosuccinimide, *N*-bromosuccinimide, or *N*-chlorobenzotriazole.[14] Reactions either involved conventional electrophilic substitution or the intermediate formation of the *N*-haloindoxyl, which then rearranged via a nitrenium ion.



(**4**)

Nitration

An authoritative review[15] on homogeneous nitration reactions involving NO^+, $NO_2^\bullet$, $NO_3^\bullet$ and N_2O_5 has appeared. Evidence on the electron-transfer reaction mechanism under thermal conditions for nitrous acid-catalysed nitration, on nitration by $NO_2^\bullet/N_2O_4$ in organic solvents, on nitration by N_2O_5 and on ozone-mediated $NO_2^\bullet/N_2O_4$ nitration is assembled. There has also been a comprehensive review of the last of these systems, kyodai nitration.[16] Theoretical studies[17] of the NO_2^+–NO electron transfer and related systems show that the activity of NO_2^+ as an oxidizing reagent in aromatic nitration is lowered owing to a high activation barrier resulting mainly from the change in the ONO bond angle. Nitrous acid and 4-fluorophenol react in trifluoroacetic acid to form 4-fluoro-2-nitrophenol by a mechanism involving reaction of an intermediate phenoxy radical with $NO_2^\bullet$ such as that occurring for similar substrates in media of lower acidity.[18] A review[19] covering reactions of phenols with nitrogen dioxide also describes reactions of nitrodienones, which may be intermediates under other nitration conditions.

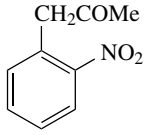
Vanadium(V) oxytrinitrate [$VO(NO_3)_3$] has been established as a powerful but moisture-sensitive reagent which nitrates a range of substituted aromatic compounds in good yield in dichloromethane at room temperature.[20] The hydrated triflates $Hf(OTf)_4$ and $Zr(OTf)_4$ are excellent recyclable catalysts for the mononitration of *o*-nitrotoluene with 1 equiv. of concentrated nitric acid.[21]

Examples of the so-called chaperon effect involving interaction between the electrophile and an appropriate substituent at the α-position in an alkyl chain prior to ring substitution at the *ortho*-position have been explored in nitrations involving dilute solutions of nitric acid in dichloromethane.[22] Aldehydic or ketonic carbonyl groups are most effective, but carboxyl, alkoxycarboxyl, and amide groups also work well. 1-Phenylpropan-2-one, for example, forms 85% of 1-(2-nitrophenyl)propan-2-one (**5**).

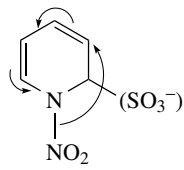
Interestingly enhanced *para* substitution results from the nitration of 3-phenylpropanenitrile. It is suggested that in these dilute solutions the NO_2^+ donor is some adduct of lower reactivity than free NO_2^+.

Although the intermolecular selectivity of the nitration of alkylbenzenes by nitric acid in trifluoroacetic acid is controlled by both electronic and steric factors, it is argued[23] that intramolecular selectivity is controlled by steric effects on transition state solvation.

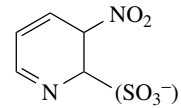
The formation of 3-nitropyridines by reaction of *N*-nitropyridinium nitrates with aqueous sodium hydrogen sulfite solution has been further studied[24] with particular attention to the rearrangement of 1,2-dihydropyridines [e.g. (**6**) from pyridine]. The activation parameters, response to medium effects, and regiospecificity of the rearrangement here and with related compounds are better explained by a [1,5]-sigmatropic shift, (**6**) → (**7**), than by formation of a radical pair intermediate. In contrast to the reaction with nitric acid, 3-phenyloxetane (**8**) reacts with dinitrogen pentoxide in dichloromethane to yield quantitatively 3-(2-nitrophenyl)oxetane (10%) and 3-(4-nitrophenyl)oxetane (90%), with oxetane-ring opening occurring subsequent to the aromatic nitration.[25]



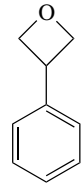
(**5**)



(**6**)



(**7**)



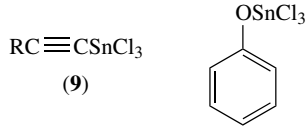
(**8**)

Alkylation, Acylation, and Related Reactions

The lifetimes of typical ion–neutral complexes $CH_3C_6H_5.C_2Y_4X^+$(X = H, Y = D; X = D, Y = H) in the alternative mechanism of gas-phase electrophilic alkylation which has been reported over the last 3 years (*Organic Reaction Mechanisms 1995*, p. 252, ref. 31; *1996*, p. 168, ref. 40; *1997* p. 259, ref. 3) have been estimated ($\sim 10^{-11}$ s at 393 K) by a kinetic approach which uses the rate of H/D scrambling in $C_2H_4D^+$ or $C_2HD_4^+$ as an internal clock.[26] The addition of various promoters (Br_2, C_2H_5Cl, CCl_4, Ph_3CCl) to aluminium chloride or aluminium chloride–silica in the alkylation of benzene with pentane and 2-methylbutane gives a 1.5–4.4-fold increase in alkylbenzene yield.[27]

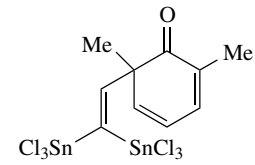
A continuous procedure for the alkylation of mesitylene and anisole with supercritical propene, or propan-2-ol in supercritical carbon dioxide, with a heterogeneous polysiloxane-supported solid acid Deloxan® catalyst has been reported[28] giving 100% selectivity for monoalkylation of mesitylene with 50% conversion at 250 °C and 150 bar by propan-2-ol in supercritical carbon dioxide. *p*-Toluenesulfonic acid monohydrate has been demonstrated as an efficient catalyst for the clean alkylation of aromatics using activated alkyl halides, alkenes or tosylates under mild conditions.[29] Cyclohexene, for example, reacts with toluene to give 100% cyclohexyltoluenes (*o*:*m*:*p*-29:18:53) under these circumstances.

Various phenols with electron-donating or -withdrawing substituents were vinylated at the *ortho*-position with ethyne using an $SnCl_4$–Bu_3N reagent.[30] Trichlorostannylethynes (**9**) and phenoxytins [e.g. (**10**)] are suggested as intermediates, the latter then undergoing electrophilic substitution by attack of the β-carbon of the former. *Ortho* attack is much favoured and 2,6-dimethylphenol reacts via the *ipso* cyclohexadienone intermediate (**11**). The results from hydroxymethylation of monocyclic aromatics with formaldehyde in benzene–aqueous sulfuric acid depend[31] on the phase-transfer catalyst, sodium tetraperfluorophenylborate, $(C_6F_5)_4B^-Na^+$, or dimethylstearyltaurobetaine, $C_{18}H_{37}(CH_3)_2N^+CH_2CH_2SO_2^-$, being studied. Results are interpreted in terms of an 'early' transition state for reactions with the former reagent and a 'late' transition state for the latter.



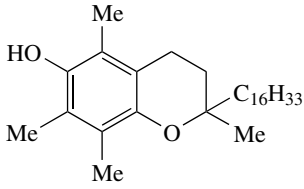
(**9**)

(**10**)

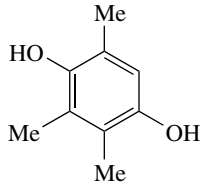


(**11**)

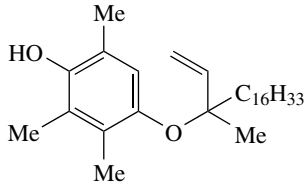
A review has appeared[32] of the mechanism of synthesis of α-tocopherol (**12**) from trimethylhydroquinone (**13**). This suggests that the reaction in the presence of a Lewis acid differs from that in the presence of Brønsted acids and involves intermediate formation of an ether (**14**), which undergoes Claisen rearrangement and then ring closure. The stereoselectivity of reaction of *N*-arylsulfonimidoyl chlorides (**15**) with alkenes (**16**) to form benzothiazines (**17**) has been investigated.[33] With trisubstituted alkenes steric effects seem definitely to cause a reaction pathway involving a carbocationic intermediate which may also precede σ-complex formation. The ionic liquid system 1-methyl-3-ethylimidazolium (**18**) chloride–aluminium(III) chloride is an excellent medium for the acetylation using acetyl chloride of a range of aromatic substrates.[34] Excellent yields and selectivities are observed. In the case of anthracene the reaction is reversible and the 9-acetylanthracene initially formed undergoes a slow disproportionation to anthracene and mainly 1,5-diacetylanthracene. The acetylation of 2-methylnaphthalene by acetyl chloride with various catalysts has been studied, changing solvent, mode of addition, concentration and the catalyst.[35] Under appropriate conditions the formation of mainly either 1-acetyl-2-methyl- or 2-acetyl-6-methyl-naphthalene can be achieved, accompanied by other minor products.



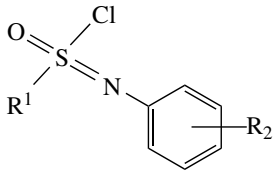
(**12**)



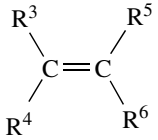
(**13**)



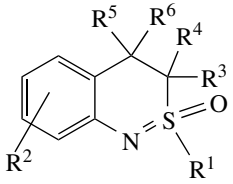
(**14**)



(**15**)



(**16**)



(**17**)

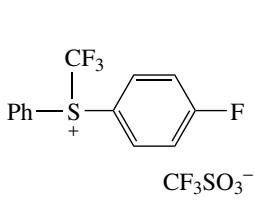
(**18**)

Other Reactions

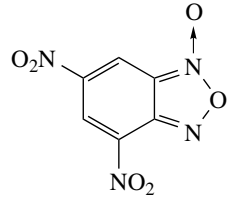
Ab initio calculations have been performed on the *ipso* protonation of toluene and mainly disubstituted derivatives and suggest[36] that a simple scheme of additivity of substituent effects is operative. The results suggest that protonation *ipso* to methyl is not thermodynamically the most favourable pathway provided that there is a single unsubstituted position on the ring. Radiolytic studies[37] of H/D exchange between substituted arenium ions and various bases together with NMR analysis provide information about the site of protonation. This is found to involve the most basic ring positions *ortho/para* for alkyl substituents and *ortho/meta* for electron-withdrawing substituents.

The kinetics of the diazo coupling of aryldiazo phenyl sulfides with 2-naphthol in acidic media have been reported and indicate that the sulfides are fully protonated in a pre-equilibrium stage of the reaction.[38] Synthetic routes to four stable trifluoromethylating agents have been established.[39] These reagents, substituted *S*-(trifluoromethyl)diphenylsulfonium triflates [e.g. (**19**)], react with a range of reactive aromatics to give, for example, 2- and 4-trifluoromethylaniline from aniline. The ability of these reagents to transfer a CF_3 group is enhanced by electron withdrawal in the phenyl groups. Rates of reaction of 4,6-dinitrobenzofuroxan (**20**) with a series of activated substituted benzenes have been reported;[40] (**20**) is more reactive and less selective than H_3O^+ towards these substrates. In the case of 1,3,5-trimethoxybenzene

a primary kinetic isotope effect is observed, indicating that reversion to reactants and proton loss from the Wheland intermediate occur at comparable rates. The compound (**20**) reacts with 3-methoxythiophene but here the first step is rate limiting.[41] The solvent effect suggests a highly polar transition state where the development of negative charge on the dinitrobenzofuroxan moeity and of a partial positive change on the thiophene ring occur together. The results allow the estimation of the carbon basicity of the thiophene and support the view that it exhibits some vinyl ether behaviour. The aluminium chloride and antimony pentafluoride-catalysed reaction of *p*-toluenesulfonyl chloride with benzene and toluene in dichloromethane gave higher toluene/benzene rate ratios and proportions of *meta* sulfone products than in the literature.[42] The probable electrophile for the former reactions is a molecular complex between *p*-toluenesulphonyl chloride and aluminium chloride with coordination through oxygen. The reaction of benzene and substituted benzenes with the Baylis–Hillman adducts of *N*-tosylimine derivatives [e.g. (**21**)] in the presence of sulfuric acid gives stereochemically defined substituted benzylalkenes [e.g. (**22**)] in moderate yields, the stereochemistry depending on the electron-withdrawing group present in the adduct.[43] *Ab initio* calculations on the intramolecular nucleophilic displacement of a protonated oxime oxygen with an aryl ring to give a spiro intermediate demonstrated that the substitution on the sp^2 nitrogen atom is a low-energy process.[44] Experimental results on the effects of changing the acid catalyst on such a reaction of (**23**) and the competing Beckmann rearrangement were reported.



(**19**)



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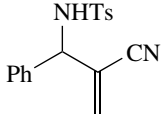

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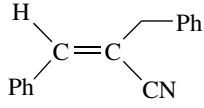

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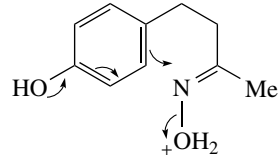
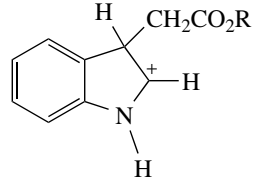


(**23**)

The formation of 2-(indolin-2-yl)indole dimers from indole-3-acetic acid and its propyl ester in trifluoroacetic acid and phosphoric acid has been studied.[45] The reaction involves electrophilic attack of the protonated species (**24**) on the free substituted indole to give the *trans* stereochemistry at the C(2)–C(3) bond.



(**24**)

R = H, Pr

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CHAPTER 9

Carbocations

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Introduction

A recently published book on vinyl cations and related species[1] contains several relevant reviews, which will be detailed below. A comprehensive review of the interactions between carbocations and anions which take place in crystals has been published,[2] and a review commentary concerning the heterolytic bond dissociation energies of the weak carbon–carbon σ-bonds in species which dissociate to stabilized carbocations and stabilized carbanions has appeared.[3] Another review wonders whether or not acid catalysis via organic cations and electron-transfer catalysis via cation radicals are distinctive mechanisms in alkene isomerization processes, and suggests that rigorous experimental evidence be obtained before assigning one of these mechanisms.[4] A computational study suggests that interaction with π systems can considerably stabilize carbocations, for instance in the complexation of methyl cation with benzene which occurs in the gas phase.[5]

Simple Carbocations

Hydrogen–deuterium exchange processes occur during the reaction of methyl cation with methane to give ethyl cation and molecular hydrogen in the gas phase, and the exchanged products do not quite have a statistical H/D distribution.[6] The reaction of [$^3H_3$]methyl cations with *sec*-butylmethylamine in the gas phase mainly gives primary and secondary amines, but that of [^{3}H]butyl cations with dimethylamine mostly results in the substrate becoming labelled.[7] A high-level calculation concerning the elimination of molecular hydrogen from ethyl cation has been performed.[8] The reaction of perdeuteriated ethyl cations, formed radiolytically, with thiophene and *N*-methylpyrrole in the gas phase leads to exchanged and alkylated products, and the conclusion was reached that ethyl cations are Brønsted acids more than they are Lewis acids.[9]

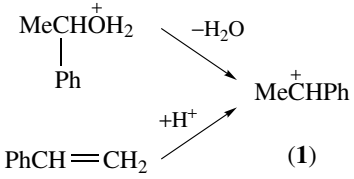
Calculations suggest that in the gas phase the 2-propyl cation forms ion pairs with FBH_3^- and LiH_2^- anions, in which the geometry of the 2-propyl cation is somewhat different from that which it adopts in the free state,[10] and that even in solution the 2-propyl cation exists mostly in the ion-paired form, as suggested by *ab initio* calculations of its ^{13}C NMR spectrum.[11] The $C_3H_9^+$ (protonated propane) cation is not an H-proponium species but has an energy-minimum structure with a proton located essentially equidistant between two carbons; however, the van der Waals complex between 2-propyl cation and molecular hydrogen is only 0.3 kcal mol^{-1} higher in energy.[12] An *ab initio* study of the rearrangements of pentacoordinated carbonium ions suggests that products formed in superacid or zeolite media result from the protonation of accessible C–H bonds rather than the inner C–C bonds of alkanes.[13]

The gas-phase dissociation processes of the butyl cation have been the subject of an experimental and theoretical study.[14] Most butyl and isobutyl species give a mixture of *s*- and *t*-$C_4H_9^+$ in the mass spectrometer; these may decompose to methane and a $C_3H_5^+$ species with the prop-2-enyl cation structure (not allyl), but metastable $C_4H_9^+$ can give ethylene and a non-classical ethyl cation with a proton bridging the two carbons.[14] In Friedel–Crafts reactions, 2-*t*-butyl-1-tosylaziridines give a variety of products resulting from two-step 1,2-shift processes and recombinations in the intermediate carbenium ions.[15] Thermally, *N*-nitroamines apparently decompose by way of a carbocation intermediate,[16] a different mechanism from that found in the acid-catalysed solvolyses of these substrates.[17]

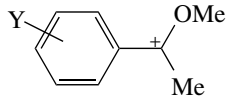
Benzyl Cations

The α-methylbenzyl cation (**1**) can be approached from the alcohol dehydration direction or the alkene protonation direction, as shown, and both of these processes have been the subject of *ab initio* molecular orbital calculations.[18] It was found that the alcohol dehydration has a transition state about half way between the two structures shown, with the transition state and the carbocation having about the same amount of π-orbital overlap. However, the alkene protonation has an earlier transition state with less effective π-orbital overlap than that in the cation. This is held to explain the different Yukawa–Tsuno r^+ values found for the two processes, 0.7–1.1 for alkene

hydrations and 1.0–1.4 for solvolyses.[18] Semiempirical studies of the α-methoxy-α-methylbenzyl cations (**2**) have enabled the twist angle between the ring and the substituents on the carbocation centre to be calculated as a measure of the resonance interaction in these species.[19] The stabilities of the *o*-, *m*-, and *p*-tolyl cations, and the tropylium ion, relative to the benzyl cation have been calculated and found to be $o < m < p$.[20] An AM1 MO study of the bond dissociation energies in a number of different benzene and toluene derivatives (R–Y, with R = Ar and $ArCH_2$) has been carried out in order to see how well the principle of maximum hardness applies to them.[21] Modern molecular mechanics calculations on a number of benzylic and cyclic delocalized cations have been shown to agree well with *ab initio* calculations on the same species.[22]



(**1**)



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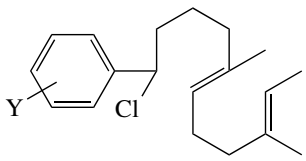

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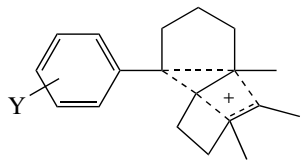
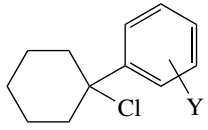


(**4**)

Hammett ρ^+ values referring to the formation of the intermediate (or transition state) (**4**) during the solvolysis of (**3**) have been measured to be between −1.5 and −1.8, the same as those observed for benzylic squalane derivatives; these are typical values for biomimetic cyclizations of this type.[23] Solvolysis of (**5**) in MeOH–MeCN mixtures leads to H/D isotope effects, activation parameters and ρ^+ values typical for S_N1 solvolysis processes; an observed Winstein–Grunwald *m* value of >1 is held to suggest positive charge delocalization on to the ring.[24] The decomposition of (**6**) leads to a nitrogen-separated benzyl cation–benzoate ion pair, and the benzyl cation behaves as an essentially free species, useful, for instance, in the direct alkylation of acid-sensitive heterocyclic compounds.[25] The ionization of α-chlorobenzyl alkyl ethers gives contact and solvent-separated ion pairs with great ease, as compared with the thermal decomposition to benzaldehyde and alkyl chloride that can also occur with these molecules.[26] The topomerization of these substrates was studied.[26] Hydride ion can attack the crowded cation (**7**) from either side, and the steric influence of the Y substituents on the reaction of these with hydrosilanes and sodium borohydride has been investigated.[27]



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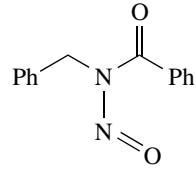
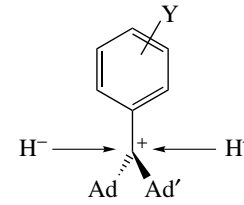


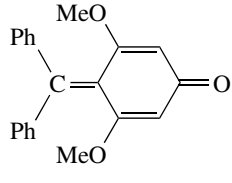
(**6**)



(**7**)

Trityl, Fluorenyl, and Related Cations

Triarylmethylamines (Ar_3CNH_2) deaminate to trityl cations in dilute aqueous perchloric acid; the rates of this process have been studied and pK values in aqueous MeCN determined.[28] The reaction was studied in more detail for the 4,4′-dimethoxytrityl cation and the kinetics of its formation, equilibria, and deuterium isotope effects were determined.[29] Ion-pair formation may occur in this system.[29] The hydride affinities of 45 trityl cations have been measured in MeCN and DMSO; the resulting free energies are a linear function of the pK_{R^+} values.[30] Bis- and tris-(2,4,6-trimethoxyphenyl)carbenium ion salts (called Φ_2CHX and Φ_3CX, X being an anion) have been found to have unusual stabilities and reactivities.[31] For instance $\Phi_2CH^+ClO_4^-$ is recrystallizable from hot methanol; $\Phi_2CH^+Cl^-$ and $\Phi_2CH^+NO_3^-$ decompose to Φ_3CH in aqueous HCl or methanol, or can be reduced to Φ_2CH_2 in primary or secondary alcohol solvents. In aqueous NaOH, (**8**) is formed.[31]



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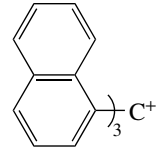

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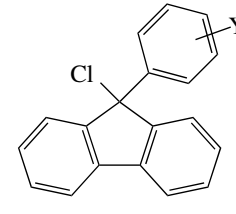
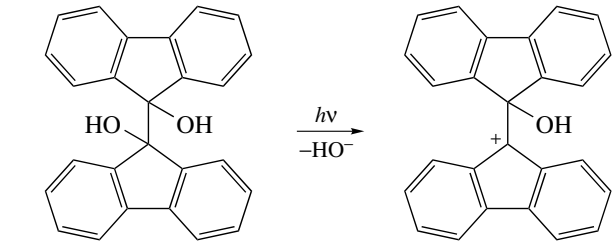


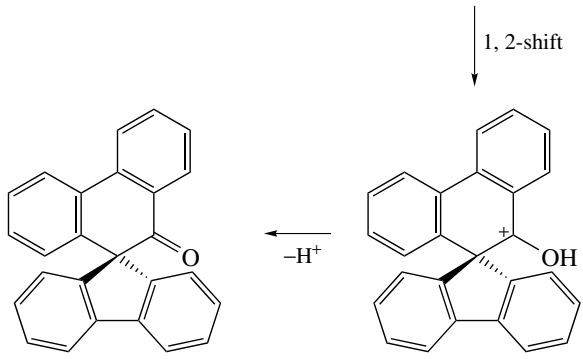
(**10**)

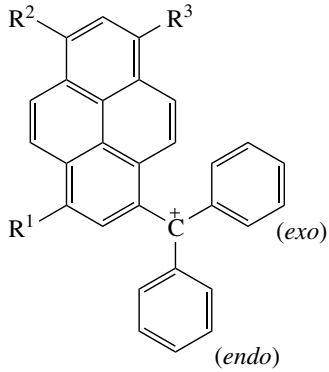
The highly crowded tris(1-naphthyl) and tris(2-naphthyl) cations, e.g. (**9**), can be prepared by treating the alcohol precursors with $FSO_3H–SO_2ClF$ between −78 and −20 °C.[32] 9-Aryl-9-chlorofluorenes (**10**) give the corresponding fluorenyl cations as solvolysis intermediates; a linear plot of the logarithm of solvolysis rate constants against σ^+ was found, but a good Winstein–Grunwald correlation was not observed.[33] The experimental evidence and the results of theoretical calculations were interpreted in favour of the fluorenyl cation behaving much like the diphenylmethyl and trityl cations.[33] An interesting photochemical pinacol rearrangement involving the fluorenyl cation (**11**) has been observed.[34]

The reduction of xanthylium cations by BNAH apparently involves rate-determining electron transfer followed by fast hydrogen atom abstraction.[35] Conformational studies



(**11**)

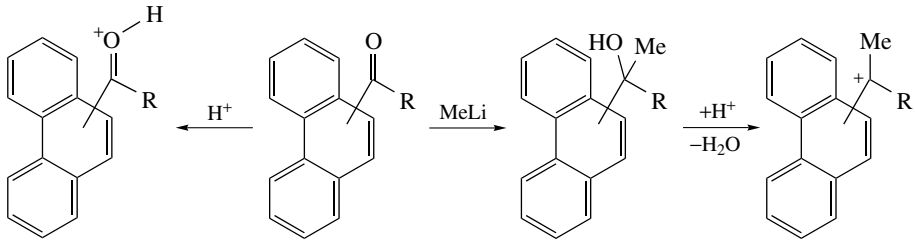




(**12**)

$R^1 = R^2 = R^3 = H$
$R^1 = R^3 = H$, $R^2 = {}^+CPh_2$
$R^1 = R^3 = Br$, $R^2 = {}^+CPh_2$
$R^1 = R^2 = H$, $R^3 = {}^+CPh_2$
$R^1 = R^2 = Br$, $R^3 = {}^+CPh_2$

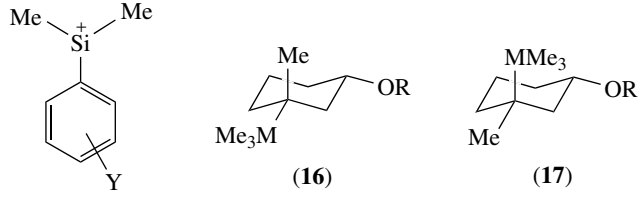
on the pyrenyl carbocations (**12**) have been carried out by means of semiempirical calculations and by NMR investigation under stable-ion conditions.[36] These fairly stable crowded species are twisted, and there is a high enough barrier to rotation that *exo*- and *endo*-phenyl groups can be distinguished by NMR. The most extensive charge delocalization was found in (**12**; $R^1 = R^2 = R^3 = H$).[36] Charge delocalization in the phenanthrene species (**14**) is much more extensive than it is in (**13**); some of the *O*-protonated species (**13**) do not readily undergo cisoid–transoid rotations.[37]



(**13**) (R = Me, Ph) (**14**)

Carbocations Containing Silicon, Tin, etc.

Several review articles on different aspects of this topic have appeared. A comprehensive review covers carbenium ions stabilized by heteroatoms,[38] and the chemistry of R_3Si^+ as a bridge between organic and inorganic chemistry is discussed.[39] A more specialized article reviews attempts at the isolation and detection of silyl and germyl cations.[40] A calculational study of the tropylium, silatropylium, and germatropylium cations shows that for $C_7H_7^+$ the tropylium ion structure is the global minimum and that the benzyl cation structure is fairly close to it in energy, but that the opposite is true for $C_6H_7Ge^+$.[41] For $C_6H_7Si^+$ all of the isomeric structures were found to be very close in energy.[41] In the gas phase the relative stabilities of a series of cations (**15**) have been compared with that of the parent ion (Y = H) by being allowed to equilibrate with it.[42] The ρ and r^+ values found were significantly smaller than those found for the carbon analogue, and it is surmised that there is no significant π-delocalization of positive charge into the ring in (**15**).[42] In a study of the γ-effect it was found that the unimolecular solvolysis of (**16**) takes place more than 10^4 times faster than does that of (**17**), and that the C–O bond in (**16**) is lengthened with respect to that in (**17**).[43]

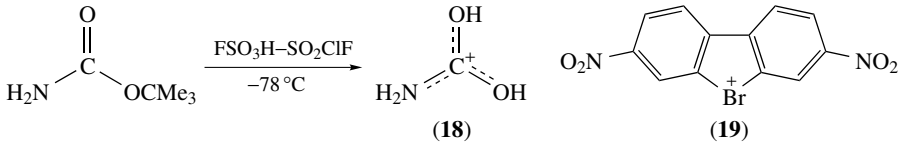


(**15**) M = Si, Sn; R = $SO_2C_6H_4NO_2$-*p*, $COC_6H_4NO_2$-*p* (**16**) (**17**)

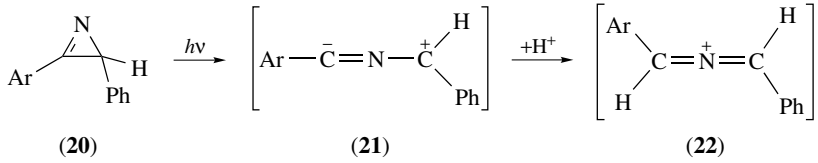
Carbocations Containing Other Heteroatoms

The recent preparation and characterization of the simple acylium systems $H-\overset{+}{C}=O$ and $F-\overset{+}{C}=O$ has been reviewed.[44] A study of the cations $R\overset{+}{C}Me_2$ (R = H, Me, Cl) has shown that α-substitution by Cl provides about as much stabilization as

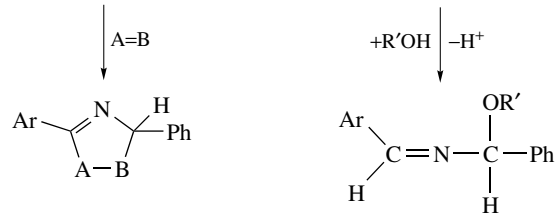
does substitution by Me in these species.[45] An experimental and theoretical study of the addition of the cations and radical cations of carbon to nitriles shows that addition takes place on the nitrogen; for instance, Me^+ adds to MeCN to give ($Me-C\equiv\overset{+}{N}-Me \leftrightarrow Me-\overset{+}{C}=N-Me$).[46] In the gas phase the 2-bromobutane cation $C_4H_9Br^+$ may lose Br to give *sec*-butyl ($C_4H_9^+$) or, at slightly lower ion energies, lose HBr to give a butenyl cation by a concerted process which may involve tunnelling.[47] Some heats of formation at 0 K were also determined.[47] Protonated carbamic acid (**18**) has been studied theoretically and by ^1H, ^{13}C and ^{15}N NMR spectroscopy.[48]



(**18**) (**19**)



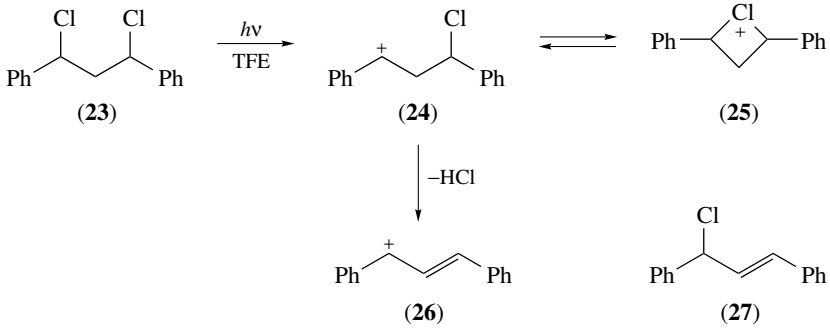
(**20**) (**21**) (**22**)

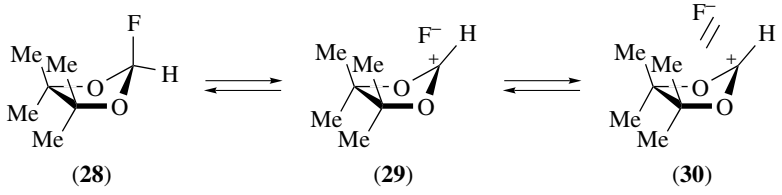


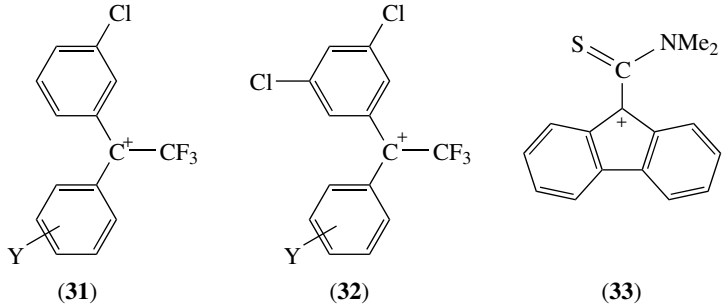
The ethylene bromonium and 1-bromoethyl cations and their neutral and anionic counterparts have been the subject of a tandem mass spectrometric study of dissociation and gas-phase redox reactions.[49] IR and Raman studies of the bioactive bromonium cation (**19**), as its hydrogensulfate salt, agree with the results of an X-ray structure determination, and theoretical calculations are also in agreement, except for the details of the NO_2 groups.[50] The azaallenium ion (**22**) is an intermediate in the photolysis of (**20**); (**21**) and (**22**) could both be seen.[51] Flash photolysis of (**23**) leads to (**24**), (**25**), and (**26**), all of which could be trapped by nucleophiles; (**27**) was not an intermediate.[52] NMR lineshape analysis of the spectrum of (**28**) leads to reaction rate constants of formation for both the intimate ion pair (**29**) and the solvent-separated ion pair (**30**).[53]

Destabilized Carbocations

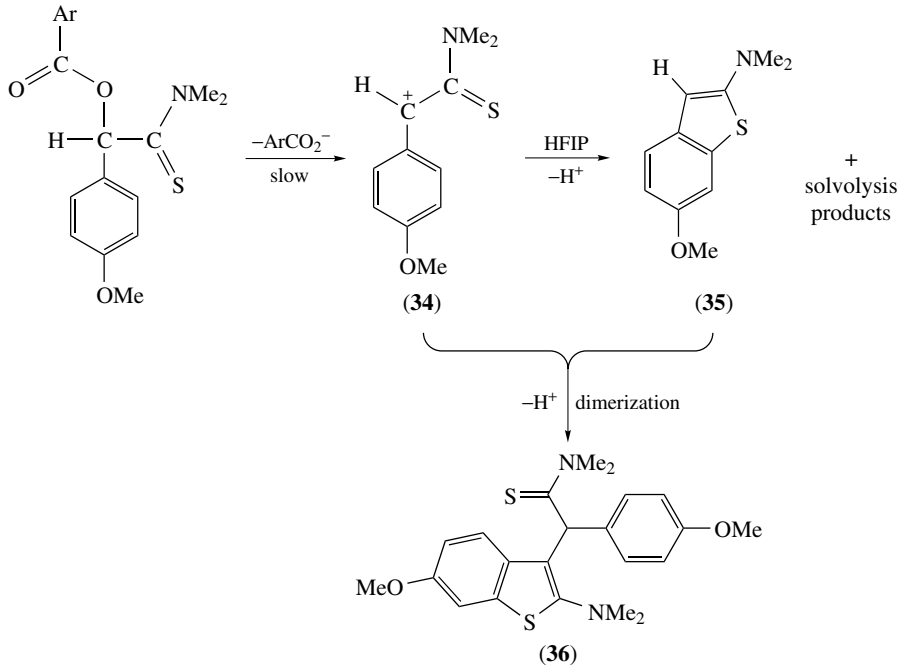
These are carbocations with formally electron-withdrawing groups situated α to the positive charge centre. The presence of the α-CF_3 group in (**31**) and (**32**) causes



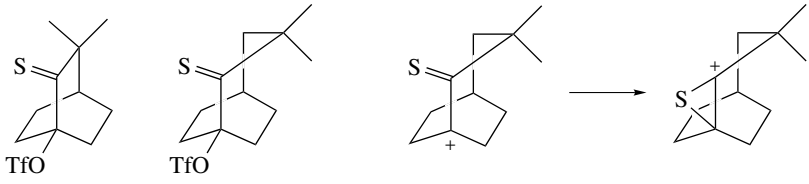




Yukawa–Tsuno plots of the logarithm of the solvolysis rate constants of the corresponding tosylates (in 80% aqueous ethanol at 25 °C) to be bilinear, owing to the changing coplanarity with substituent of the two aryl π-systems with varying electron demand.[54] The $C_2H_4NS^+$ and $C_2H_4NO^+$ potential-energy surfaces have been compared.[55] For the thioformamidylmethyl cation an *S*-bridged species was found to be lowest in energy, but for the formamidylmethyl cation itself the low-energy structure is a solvated $H_2C{=}\overset{+}{N}H_2 \cdots CO$.[55] Benzylic α-chlorothioamides solvolyse via intermediate carbocations such as (**33**); species such as this apparently do not have carbonyl conjugation as a cation stabilization feature.[56] The α-thioamide-substituted benzyl cation (**34**) has been studied under solvolysis conditions; one of the reaction products is (**35**), and this undergoes a unique dimerization by reacting with another (**34**) to give (**36**), the mechanism of which has been worked out.[57] In another study (**34**) has been found to be fairly reactive, only π-nucleophiles with nucleophilicity

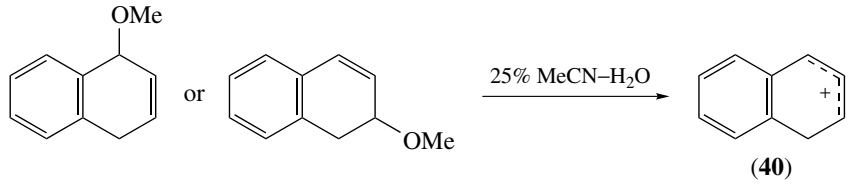


parameters >6 being able to capture it during solvolysis.[58] The presence of the α-sulfur in (**37**) reduces its reactivity relative to the molecule without it by a factor of $10^{-6.2}$, but the reactivity reduction for (**38**) is only $10^{-2.5}$.[59] This difference is attributed to stabilization by sulfur bridging as in (**39**), possible in the latter case but not the former.[59]

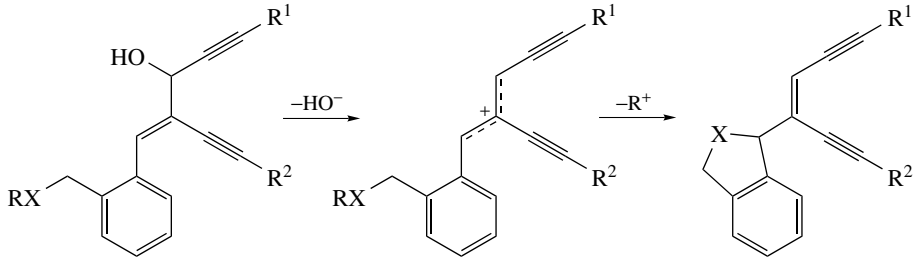


Allylic Systems

The allylic cation (**40**), formed in a specific acid-catalysed process, is relatively stable thermodynamically, stable enough towards trapping by nucleophiles that the reaction product obtained is almost invariably the naphthalene elimination product.[60] *cis*-Enediynes (**42**) are formed regiospecifically when the allylic cation (**41**) is trapped as shown.[61] The 'walking' of methanol around optically active 1-methyl-3-ethylallyl



(**40**)

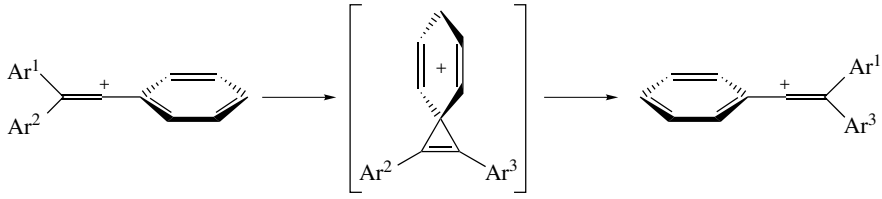


(X = O, S; R = Bu^{t}Me$_2$Si, H) (**41**) (**42**)

cations can be seen in the gas phase, leading to distinct hydrogen-bonded complexes; the kinetics and mechanisms of the various racemization and regio isomerization processes observable are reported.[62] The products are (*S*)-*trans*-hex-4-en-3-ol and (*R*)-*trans*-hex-3-en-2-ol.[62] Some stable allylic [60]fullerene carbocations, $C_{60}Ar_5^+$, have been observed.[63]

Vinyl, Aryl, and Related Cations

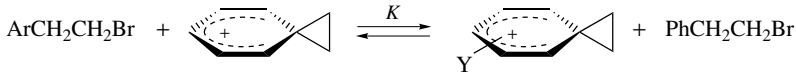
Many valuable reviews of the chemistry of these species are given in the new book *Dicoordinated Carbocations*.[1] An introduction by Grob[64] is followed by reviews of various theoretical studies of vinyl cations,[65] their gas-phase chemistry,[66] their generation by nuclear decay,[67] and their NMR spectroscopic characterization.[68] Vinyl cation production by addition to acetylenes and allenes,[69] by solvolysis,[70] and photolytically[71] are covered, together with the chemistry of the species generated in these various ways. The next chapter deals with the synthetic applications of vinyl cations,[72] and alkynyl and aryl cations are covered in the last chapter.[73] A review of the NMR spectroscopic and quantum-chemical investigation of vinyl cations in superacid media (also of dienyl and 1-cyclopropylvinyl cations) is published separately,[74] as is a review of alkynylcarbenium ions, e.g. $[R^1R^2\overset{+}{C}-C\equiv C-R^3 \leftrightarrow R^1R^2C=C=\overset{+}{C}-R^3]$, and related unsaturated species.[75] The structural sensitivity of 1,2-aryl rearrangements in triarylvinyl cations has been examined; (**44**) may be an intermediate or a transition state in the interconversion of (**43**) and (**45**), depending on the substituents present, and it may be chiral or achiral depending on the bulk of the ring substituents.[76] The gas-phase chemistry of dehydrobenzoyl cations has been examined; these are distonic ions with dual free radical and acylium ion reactivity.[77]



(**43**) (**44**) (**45**)

Arenium Ions

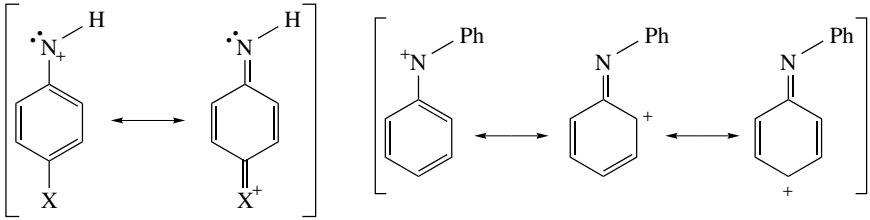
The thermodynamic stabilities of phenonium ions relative to the parent have been determined in the gas phase by measuring the position of the equilibrium between (**46**) and (**47**).[78] The results followed a Yukawa–Tsuno relationship with a ρ value of -12.6 and an r^+ value of 0.62, the general behaviour being more like benzenium ions than benzyl cations, with π-delocalization less effective than in benzyl cations.[78] A theoretical study of the elimination of molecular H_2 from the benzenium ion $C_6H_7^+$ shows that the barrier to this process appears to be very small.[79] The gas-phase Friedel–Crafts alkylation reaction of $CF_3C_6L_6^+$ (L = H or D) with C_2L_4 is accompanied by isotopic scrambling, which has been used to elucidate the mechanism of this process.[80] A theoretical calculation shows that the lifetime of triplet phenyl cation must be very short.[81]



(**46**) (**47**)

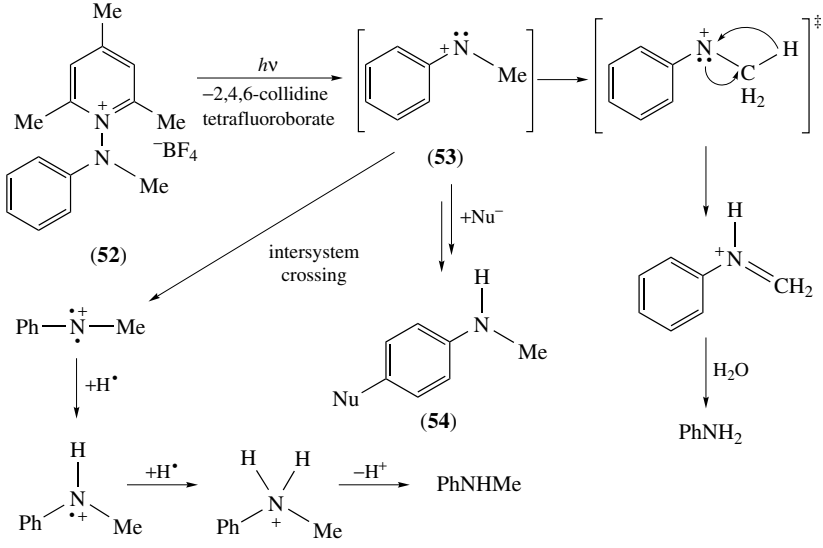
Nitrenium Ions

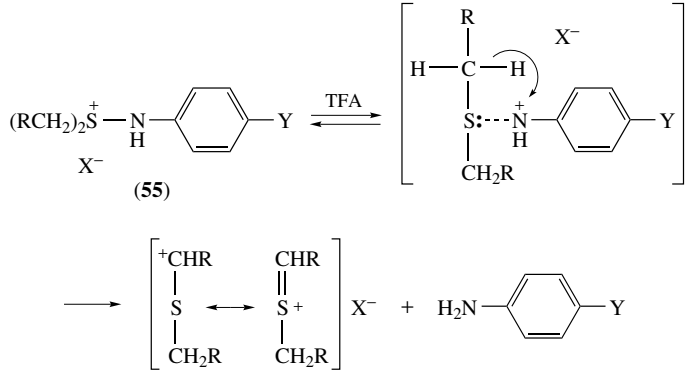
The nitrenium ion $^+NH_2$ has been the subject of a detailed, comprehensive calculation.[82] Calculations on (**48**) with 15 different X substituents reveal a large substituent sensitivity, and also that aqueous solvation preferentially stabilizes the singlet state.[83] This substituent sensitivity agrees with the results of a time-resolved IR study of the diphenylnitrenium ion (**49**), which shows that resonance contributors such as (**50**) and (**51**) are very important to the overall structure.[84] Substituted 4-biphenyl nitrenium ions



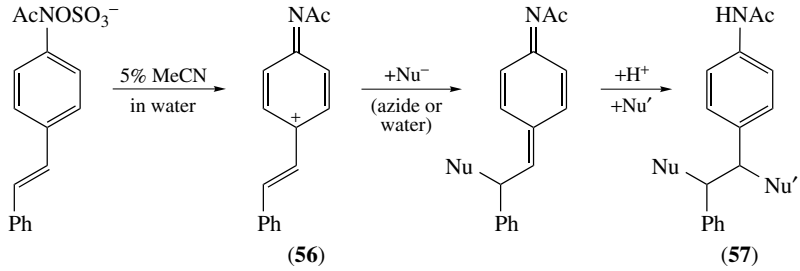
(**48**) (**49**) (**50**) (**51**)

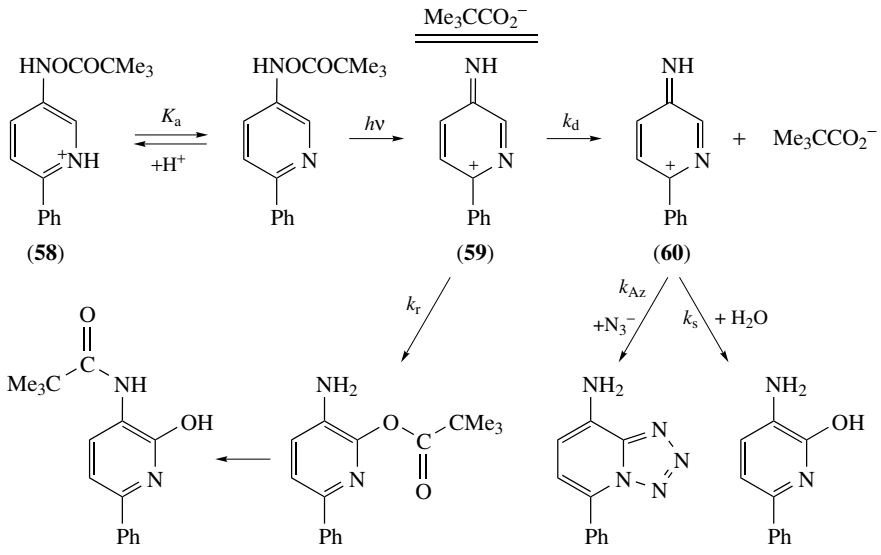
(**48**; X = C_6H_4Y) have lifetimes of 0.6 ms (Y = 4-OMe) to 26 ns (Y = 4-CF_3).[85] They are quenched by azide ion at the diffusion limit. The Yukawa–Tsuno r^+ value for these is 2.8, also consistent with a large amount of resonance delocalization.[85] Photolysis of (**52**) results in the *N*-methyl-*N*-phenylnitrenium ion (**53**), which presumably gives the observed products (**54**), aniline and *N*-methylaniline as shown.[86]





A different method of generating a nitrenium ion has been demonstrated; the sulfur–nitrogen bond in (**55**) cleaves and then a novel intramolecular hydride shift to the arylnitrenium ion centre takes place.[87] The nitrenium species (**56**) undergoes two nucleophilic additions to the double bond to give the product (**57**).[88] Two studies concerning the physiological effects of nitrenium ions *in vivo* are reported.[89,90] Products are formed from both the ion-paired nitrenium ion (**59**) and the free ion (**60**)

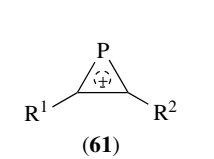




during the reaction of (**58**); the kinetics of these processes were studied.[89] The *N*-acetyl-*N*-(2-fluorenyl)nitrenium ion readily adds to monomeric 2′-deoxyguanosine.[90]

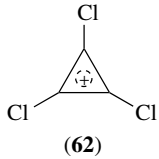
Aromatic Systems

The phosphirenylium cation (**61**) can form when the halogenated precursor is treated with liquid SO_2.[91] High-level theoretical calculations show that the aromatic character is due to a three-centre two-electron π-type bond; the resonance energy is fairly high at $\sim$38 kcal mol^{-1}.[91] The trichlorocyclopropyl cation (**62**) is substantially more stable than are the *t*-butyl or adamantyl cations, according to a theoretical study and some FTICR experimental measurements.[92] Trinaphthophenalenium trifluoroacetate (**63**) is a dark-violet solid; the cation represents a new $n = 7$ aromatic system.[93] The tropylium ion, $C_7H_7^+$, is the subject of a recent theoretical calculation; the spectral assignments were updated.[94] The substituted tropylium ion (**64**) rearranges to (**65**) on heating.[95] $C_7Ph_7^+$, the heptaphenyl tropylium ion (**66**), is not planar but has a seven-bladed propeller structure.[96] According to theoretical calculations (**67**) has the positive charge

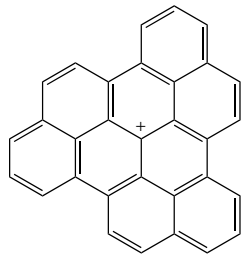


(**61**)

R^1, R^2 = H, Me, SiH_3, CN, NH_2, OH

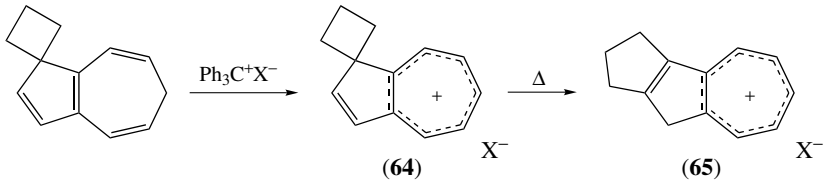


(**62**)

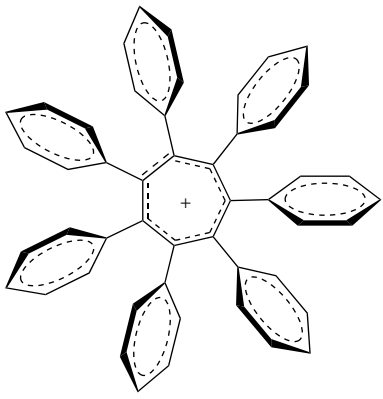


$CF_3CO_2^-$

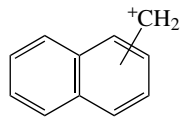
(**63**)



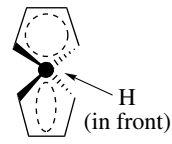
(**64**) (**65**)



(**66**)



(**67**)

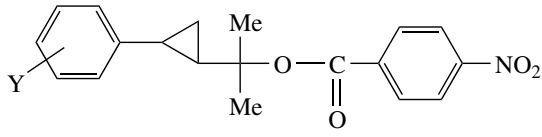


(**68**)

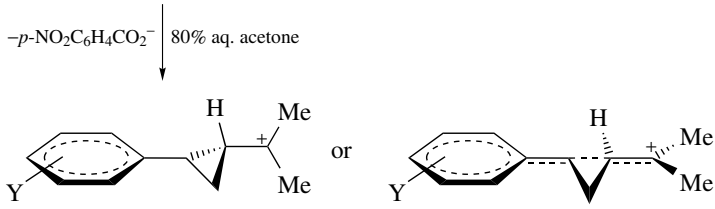
delocalized over the whole molecule if the substituent is in the 2-position, but in the 1-position delocalization is partly limited to the first ring.[97] Monocyclic $(CH)_9^+$, which is difficult to draw but an attempt is given as (**68**), is an aromatic Heilbronner Möbius [4*n*]annulene.[98]

Cyclic Systems

Molecular mechanics and *ab initio* calculations on the cyclopentadienyl cation have been carried out; an allylic structure is favoured.[99] Calculations referring to the initiation of polymerization of 1,1-disubstituted cyclopropanes by cations (also neutrals and anions) are reported.[100] Rate constants for the solvolyses of (**69**) show reasonable Yukawa–Tsuno correlations, interpreted in terms of the less reactive substituents



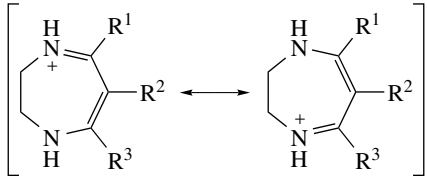
(**69**)



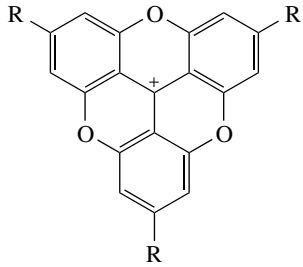
(**70**) (**71**)

preferring the cyclopropylmethyl cation pathway (**70**), and the more reactive ones preferring to react by way of the allylic cation species (**71**).[101]

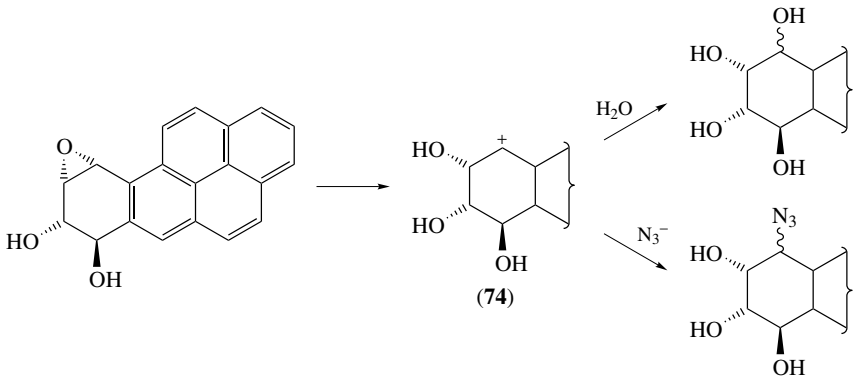
The salts of the diazepines (**72**; $R^1 = R^3 = H$, $R^2 = Ph$) and (**72**; $R^2 = H$, $R^1 = R^3 = Ph$) have been compared; Ph in the 6-position has less conjugative interaction than it does in the other positions, but electrophilic substitution still occurs readily in both molecules.[102] Crystal structures of the 2,3-cyclohexano derivatives, as the picrates, are reported.[102] The crystal and molecular structures of the 2,3-dihydro derivatives have also been determined.[103] The very interesting 2,6,10-tris(dialkylamino)trioxatriangulenium ions (**73**; R = diethylamino) and (**73**; R = *N*-pyrrolidinyl) are reported.[104] The X-ray structure of the latter shows that the ion is planar, and the former is so stable that its pK_{R^+} value of 19.7 is 10 orders of magnitude higher than that of any other reported carbocation, and has to be measured in strong base media.[104] Stereospecific ring opening in buffer media of the diol epoxide precursor gives the cation (**74**), which can be trapped as shown; the ring opening becomes reversible in more basic amine buffers.[105] The 2-deoxyglucosyl oxocarbenium ion is not solvent-equilibrated in water, hydrolysis of the α- and β-anomers not involving a common intermediate.[106]



(**72**)

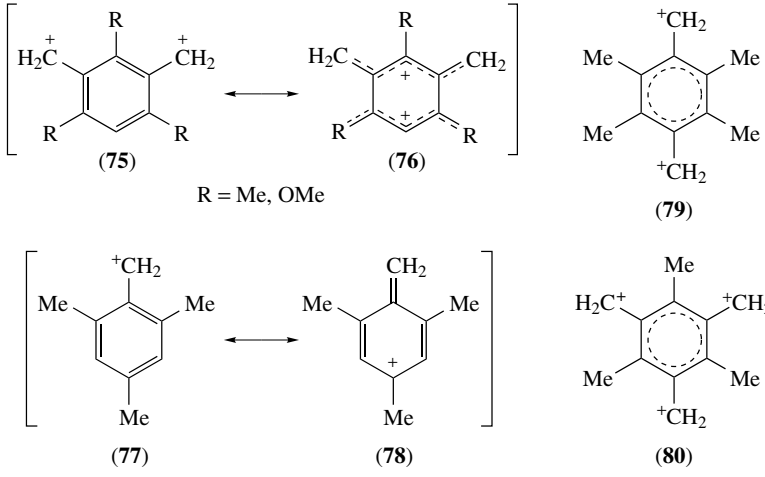


(**73**)

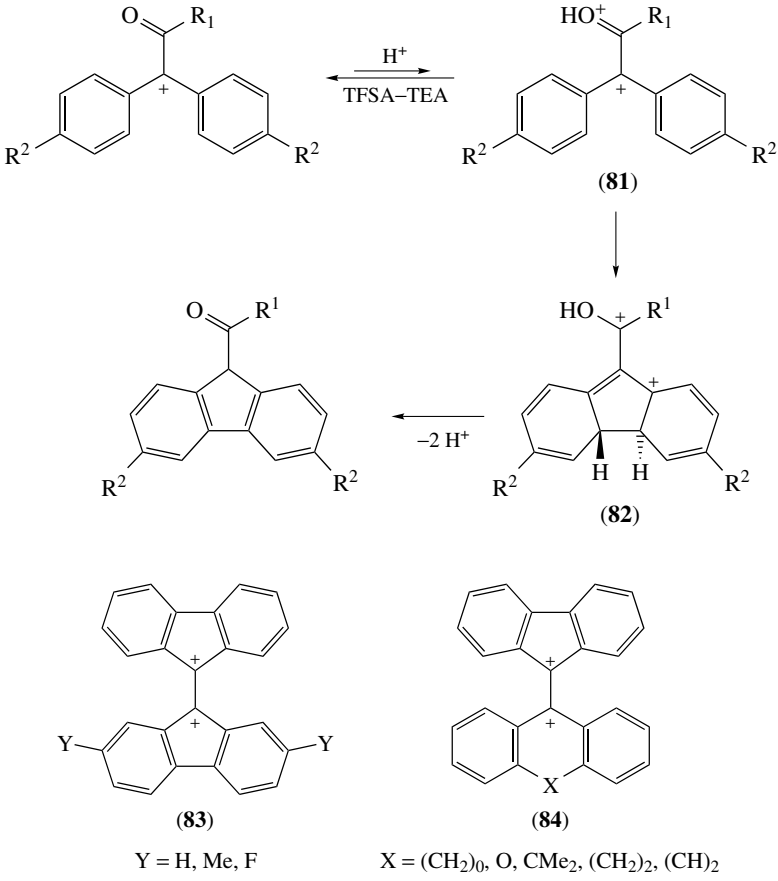


Dications

Some benzylic mono- and di-cations have been studied by the ^{13}C NMR/DFT/IGLO technique.[107] Of the stable dications, the trimethyl species (**76**; R = Me) was found to be the major resonance contributor to the structure of (**75**), and the same was found to be true for the trimethoxy derivative. In the related monocations, for (**77**) the major resonance contributor was (**78**), and this was also the case for the pentamethyl and 2,5-dimethyl-4-*t*-butyl compounds.[107] The dication (**79**) and the trication (**80**),



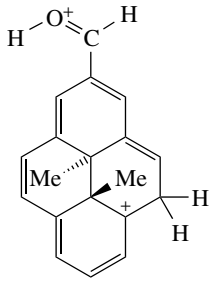
however, could not be prepared.[107] Treatment of the aldehyde precursor with the strong acid system trifluoromethanesulfonic acid–trifluoroacetic acid causes a monocation–dication equilibrium to be set up, and (**81**) ring closes to give the fluorene via dication (**82**).[108] A strange-looking dication derived from hexakis(methylthio)benzene is proposed as a possible reaction intermediate in a Pummerer-type rearrangement.[109]



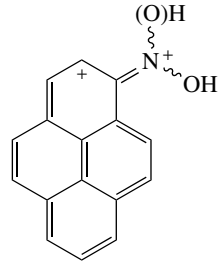
The difluorenyl dication (**83**) results when the parent fluorenylidene is treated with SbF_5 in SO_2ClF.[110] The two ring systems are at right-angles to one another, and the significant paratropicity observed is attributed to an antiaromatic ring current.[110] The related systems (**84**) behave similarly; substituent effects are held to be transmitted by cross-hyperconjugation.[111] The parent aldehyde, with chemical shifts for the 15,16-methyl groups being −3.91 and −3.90, is monoprotonated on the carbonyl group in FSO_3H in SO_2ClF, chemical shifts −1.95 and −1.87, and diprotonated to (**85**) in FSO_3H–SbF_5 (4:1) in SO_2ClF, with methyl chemical shifts of +0.48 and +0.10.[112] This was typical of several compounds studied.[112] Similarly, nitropyrene gives (**86**) in 1:1 FSO_3H–SbF_5.[113] With SbF_5 in SO_2ClF at −30 °C several benzoanthracene derivatives give delocalized dications, e.g. (**87**).[114]

Adamantyl Systems

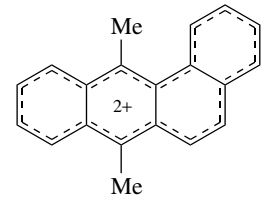
The X-ray structure of the bridged chloronium cation (**88**) is reported; it is described as being 'unsymmetrical' and 'non-classical.'[115] It shows distinctive electrophilic



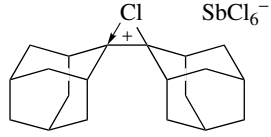
(**85**)



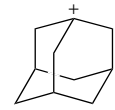
(**86**)



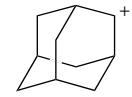
(**87**)



(**88**)

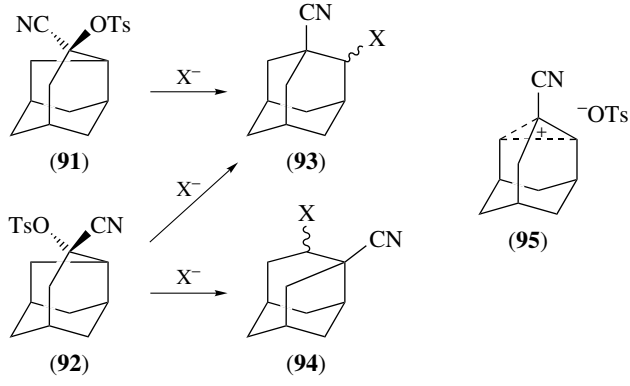


(**89**)

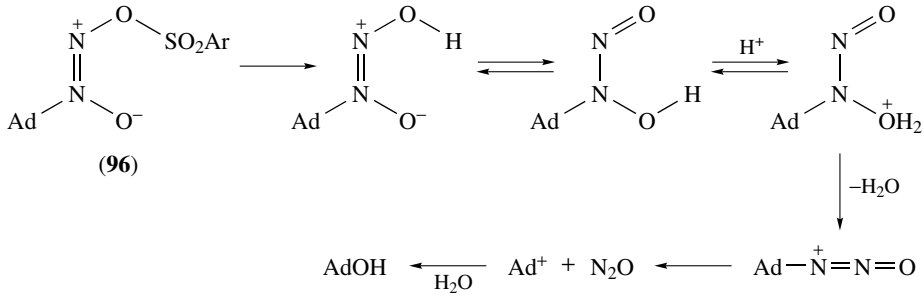


(**90**)

chlorination reactivity compared with singly bonded chloroarenium cations.[115] The 1-adamantyl (**89**) and 2-adamantyl (**90**) cations have had their gas-phase heats of formation determined; they are 152 ± 3 and 171 ± 3 kcal mol^{-1}, respectively.[116] The stereoselectivities of the destabilized 1-cyano-2-adamantyl and 3-cyano-4-protoadamantyl carbocations have been examined; (**91**) gives only (**93**), but (**92**) gives both (**93**) and (**94**).[117] The *endo* selectivity found previously for (**95**) was not observed.[117] The mechanism of solvolysis of 2-adamantyl azoxytosylate (**96**) has been determined to be as shown, primarily from isotopic labelling and medium-effect studies.[118] The observed *m* value was only 0.46, one of the lowest observed for an unambiguous S_N1 mechanism.[118] Solvation effects in the heterolysis of some adamantyl and alicyclic substrates have been studied,[119] and salt effects in the S_N1 solvolysis of adamantyl tosylates have been investigated.[120]



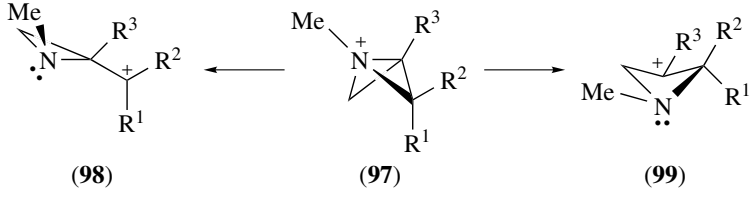
(**91**) (**93**) (**92**) (**94**) (**95**)



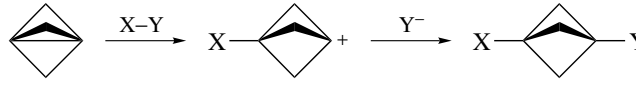
(**96**)

Bicyclic Systems

An *ab initio* study of the 1-azabicyclo[1.1.0]butyl cation (**97**) and its isomers shows that (**98**) and (**99**) are much less stable than (**97**), and that the transition states between (**97**), (**98**), and (**99**) are too high in energy to allow (**99**) to form.[121] The 3-halobicyclo[1.1.1]pent-1-yl cation (**101**) has been shown to be an intermediate in the addition of halogens to (**100**).[122] The only product observed was (**102**); no rearranged products were detected.[122] The Diels–Alder-type reaction of (**103**) to give (**104**) is said to involve several carbenium ion intermediates.[123]

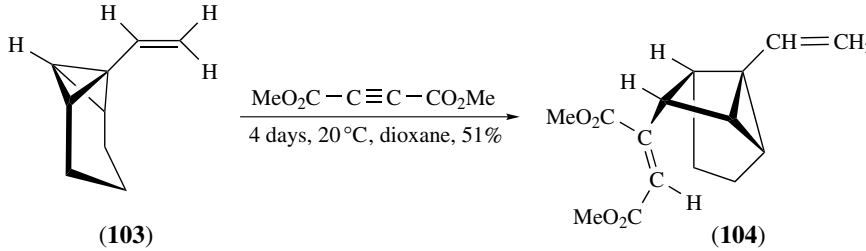


(**98**) (**97**) (**99**)

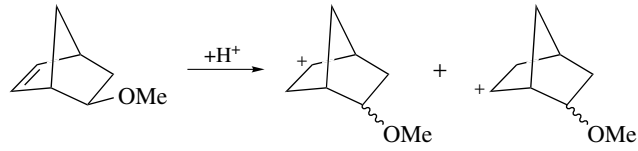


(**100**) (**101**) (**102**)

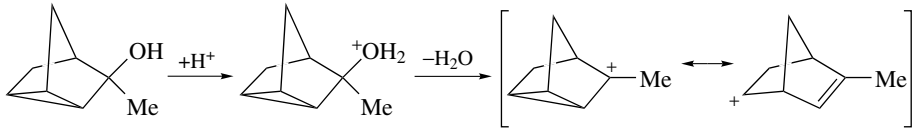
X or Y = I, Br, Cl



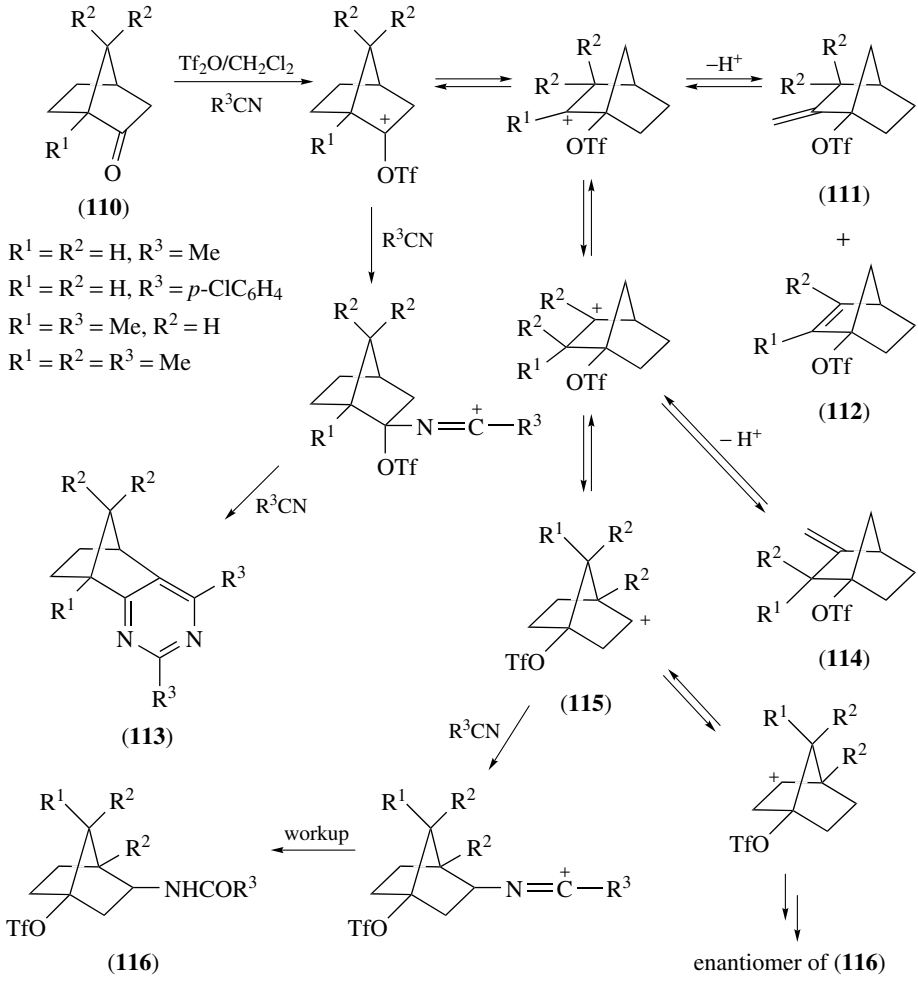
(**103**) (**104**)



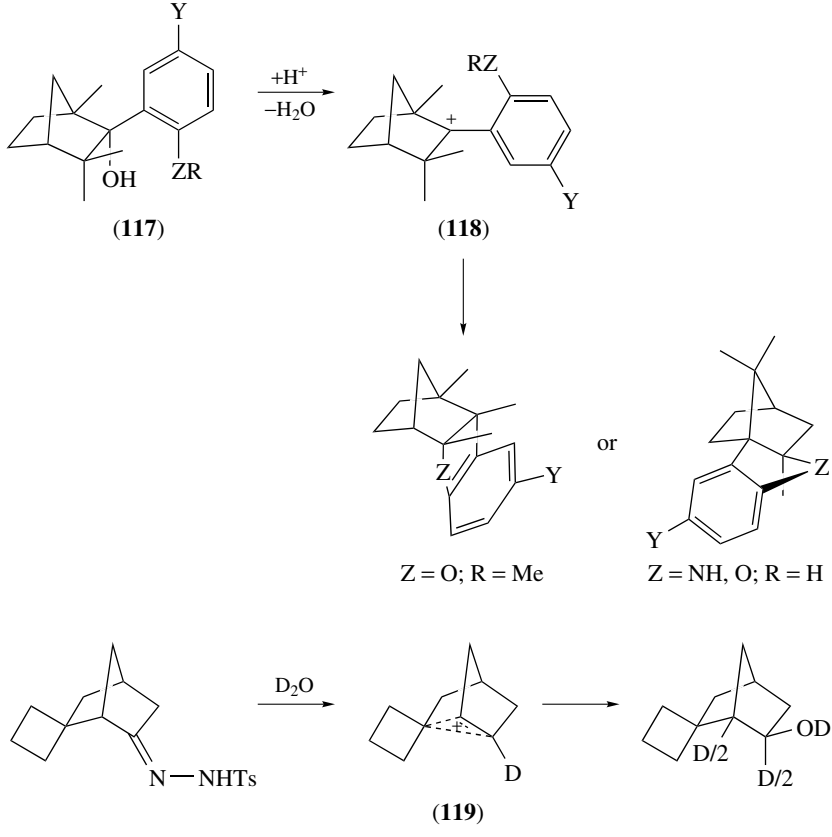
(**105**) (**106**) (**107**)



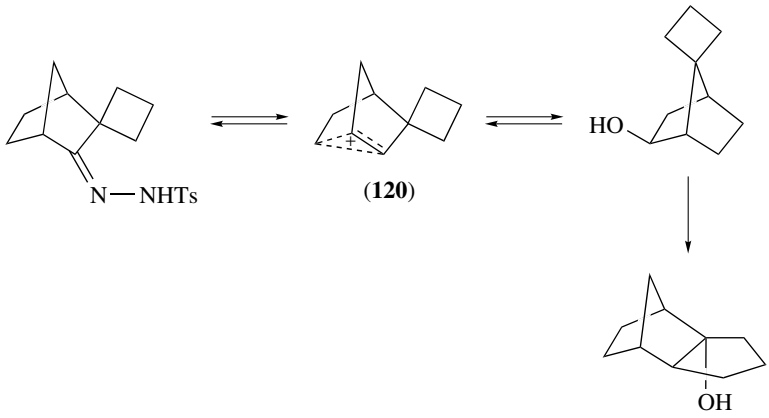
(**108**) (**109**)



The kinetics of the hydration of *exo*- and *endo*-5-methoxy-2-norbornene and 3-methoxynortricyclane in aqueous perchloric acid have been subjected to an excess acidity analysis.[124] For instance, the hydrolysis mechanism of (**105**) probably involves the intermediacy of the cations (**106**) and (**107**).[124] A similar kinetic analysis shows that the resonance-stabilized cation (**109**) is a likely intermediate in the acid-catalysed hydrolysis of 3-methyl-2-nortricyclanol (**108**).[125] The complex series of rearrangements, hydride shifts, proton eliminations and cation trappings that take place when the norbornyl ketone (**110**) is treated with triflic anhydride in nitrile solvents has been examined.[126] The primary products are (**111**), (**112**), (**113**), (**114**) and (**116**), the last in two isomeric forms, the relative amounts formed depending on the fate of the cation (**115**). The different possibilities are in delicate balance and the product mix actually observed depends on the substitution pattern, among other factors.[126] The effect of *ortho* substituents on the direction of 1,2-migration in the rearrangement of the 2-*exo*-arylfenchyl alcohols (**117**) has been examined; cation (**118**) is the common intermediate and the observed product again depends on the substituents present.[127] Spirocyclobutane-substituted cations (**119**) and (**120**) mostly give products in which



the spirocyclobutane ring is retained, much less ring expansion being observed than in the equivalent cyclopropane analogues.[128]



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CHAPTER 10

Nucleophilic Aliphatic Substitution

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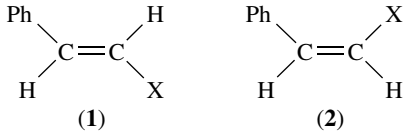
Vinylic Systems

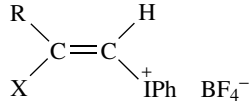
Rappoport and co-workers' work has continued in a study of the substitution of (*E*)- and (*Z*)-β-bromo- or chloro-styrenes, (**1**) and (**2**), by MeS^- in DMSO-d_6 (sometimes in admixture with CD_3OD) as solvent.[1] Product studies indicated retention stereochemistry; rate measurements found only a small Br/Cl element effect, slower reactions of the *p*-OMe bromo compounds, and retardation by CD_3OD. These results are consistent with Tiecco's suggestion in 1983 that even this system, activated by only a single phenyl group, reacts through the nucleophilic addition–elimination multistep route.

Ochiai's group has continued work on the nucleophilic vinylic substitutions of alkenyl(phenyl)iodonium salts. (The leaving-group ability of the phenyliodonio group is about 10^6 times greater than that of triflate.)[2–4] Reactions of (*Z*)-(β-chloroalkenyl)- and (*Z*)-(β-bromoalkenyl)-iodonium tetrafluroroborates (**3**) with sodium benzenesulfinate in THF yielded the (*Z*)-1,2-bis(benzenesulfonyl)alkene (**4**) stereoselectively with retention of configuration.[2] Intermediate formation of (*Z*)-[β-(benzenesulfonyl)alkenyl]



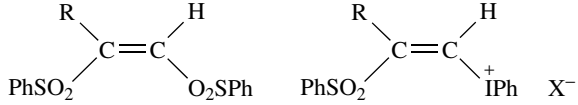
(**1**) (**2**)

X = Br or Cl

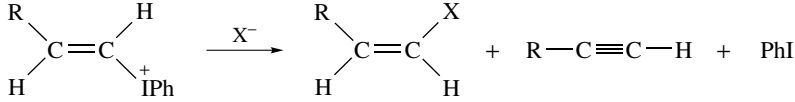


(**3**)

R = *n*-C_8H_{17} X = Br or Cl



(**4**) (**5**)



(**6a**) (**6b**) (**6c**) (**6d**)

R = *n*-C_8H_{17} X = Cl, Br, I, F

iodonium salt (**5**) was shown by PMR experiments in $CDCl_3$. The formation of (**5**) involves a hitherto unobserved Michael addition of benzenesulfinate anion to the alkenyliodonium salts at the β-C, followed by extrusion of halogen.

Reactions of (*E*)-1-decenyl(phenyl)iodonium salt (**6a**) with halide ions have been examined under various conditions.[3] The products are those of substitution and elimination, usually (*Z*)-1-halodec-1-ene (**6b**) and dec-1-yne (**6c**), as well as iodobenzene (**6d**), but F^- gives exclusively elimination. In kinetic studies of secondary kinetic isotope effects, leaving-group substituent effects, and pressure effects on the rate, the results are compatible with the in-plane vinylic mechanism for substitution with inversion. The reactions of four (*E*)-β-alkylvinyl(phenyl)iodonium salts with Cl^- in MeCN and other solvents at 25 °C have been examined.[4] Substitution with inversion is usually in competition with elimination to form the alk-1-yne.

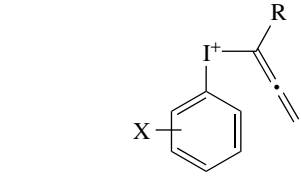
Allylic and Other Unsaturated Systems

The work of Ochiai's group on nucleophilic vinylic substitution of phenyliodonium salts (see previous section) has been extended to examining the behaviour of allenyl (aryl)iodine(III).[5] Ratios of nucleophilic substitution to [3,3]-sigmatropic rearrangement for the collapse of allenyl(aryl)iodine(III), generated from the reactions of aryliodanes

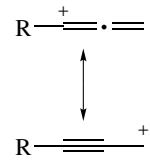
with propargylsilanes in the presence of BF_3-Et_2O in alcohols, have been determined. A suggested mechanism involves generation of propargyl cations (**8**), via a unimolecular pathway from the allenyl(aryl)iodonium ion (**7**).

The regio- and stereo-chemistry of the nucleophilic attack of (*S*)-*trans*-hex-3-en-2-ol and (*S*)-*trans*-hex-4-en-3-ol on the corresponding *O*-protonated or -methylated derivatives have been examined in the gas phase at 40 °C and 720 Torr.[6] Firm evidence of various kinds was obtained for the concerted S_N2' pathway accompanying the classical S_N2 mechanism. Competition between the two processes is essentially governed by the orienting properties of the oxonium intermediate towards the approaching nucleophile. Many other details were elucidated.

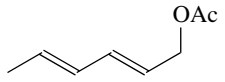
The substitution reaction of Cl^- with methyl chloride, 2-chloroethyl radical, and allyl chloride has been treated by several different *ab initio* theoretical models.[7] Depending on the method, the intrinsic barrier for the S_N2' process in allyl chloride is 7–11 kcal mol^{-1} higher than the barrier for the S_N2 reaction of methyl chloride. The reaction of Cl^- with the 2-chloroethyl radical involves an intermediate complex, which is best described as an ethylene fragment flanked by a resonating chloride anion–chloride radical pair. There are many other points of interest.



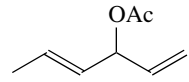
(**7**)



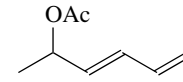
(**8**)



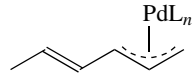
(**9**)



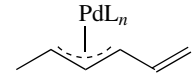
(**10**)



(**11**)



(**12**)



(**13**)

The effect of the nature of ion pairs as nucleophiles in a metal-catalysed substitution reaction has been investigated by determining product ratios for the Pd-catalysed allylic alkylations of substrates (**9**)–(**11**) under various conditions, particularly with respect to catalyst ligands, nucleophiles, and counterions.[8] Each dienyl acetate ionizes to form initially the vinyl (π-allyl)–Pd intermediate corresponding most closely to the leaving group, i.e. (**12**) from (**9**), (**13**) from (**11**), but (**12**) and (**13**) from (**10**). The initial intermediate can then either be trapped by the nucleophile or it can begin to equilibrate to some mixture of vinyl π-allyl intermediates. If nucleophilic addition occurs before full equilibration, the product ratio is different for each substrate; if

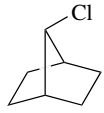
equilibrium is reached from all three substrates prior to nucleophilic addition, then the product ratio is the same for each substrate. This unified mechanism provides the framework for interpreting the effects of ligands, nucleophiles, and counterions. Any role for S_N2' processes is at present discounted.

The specific acid-catalysed solvolysis of 1-methoxy-1,4-dihydronaphthalene or 2-methoxy-1,2-dihydronaphthalene has been subjected to kinetic and product studies.[9] The elimination product, naphthalene, predominates.

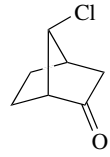
The *C*-glycosylation of pentose glycals with silylacetylenes or allylsilanes through oxocarbenium ion intermediates proceeds with high regio- and stereo-selectivity, giving the 1,4-*anti* compounds as the main products.[10]

Norbornyl and Closely Related Systems

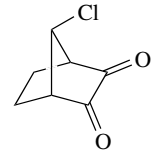
The well-known low reactivity for the displacement of a nucleofuge from the C(7) position of norbornane has been illuminated by *ab initio* and natural bond orbital (NBO) calculations on the ground states of a series of 7-chloronorbornanes, e.g. (**14**)–(**16**).[11] MO calculations were also performed on the corresponding S_N2 transition states. The value of $\Delta H^{\ddagger}$ for the parent compound (**14**) is 22.4 kcal mol^{-1}, but it drops to 18.2 kcal mol^{-1} when a carbonyl group is present at C(2), and further to 10.1 kcal mol^{-1} when a second such group is present at C(3). The NBO analysis shows that this striking effect is due to the strong electric field of the substituent. Calculations for C−F and C=S gave similar results.



(**14**)



(**15**)



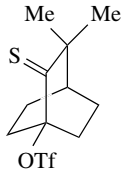
(**16**)

The rates of ethanolysis of 3,3-dimethyl-2-thioxobicyclo[2.2.2]oct-1-yl triflate (**17**) and 3,3-dimethyl-2-thioxobicyclo[3.2.2]non-1-yl triflate (**19**) relative to their corresponding parent compounds, (**18**) and (**20**), are $10^{-6.2}$ and $10^{-2.5}$, respectively, at 25 °C.[12] The smaller retarding effect of the thioxo group when introduced into the more flexible system supports the applicability of the authors' methodology to change the conjugative ability of bridgehead carbocations.

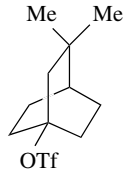
In the hydrolysis of the tosylate (**21a**) the predominance of *exo* isomers (**21b**) relative to *endo* isomers indicated the importance of steric hindrance of the C(1) Me group to *endo* attack by the nucleophile.[13] An analogous result was found for the products of bromination (**21d**) of the corresponding iodides (**21c**).

Epoxide Reactions

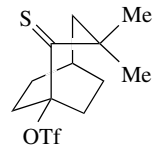
The ring opening of glycidic acids and their derivatives by reactants such as the sodium salt of malonic ester has been reviewed in Russian.[14]



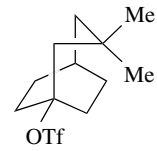
(**17**)



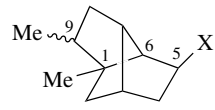
(**18**)



(**19**)



(**20**)



(**21**)

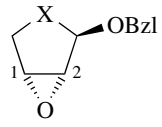
a; X = OTs
b; X = OH
c; X = I
d; X = Br

Crotti and co-workers' work on regiochemical control of ring opening of epoxides by means of chelating agents has continued.[15] Under standard conditions the regioisomeric C(1) derivatives are the sole products from the *trans* epoxides (**22a**) and (**22b**) and are the predominant products from the *cis* epoxides (**23a**) and (**23b**). Under chelating conditions the *cis* epoxides unexpectedly show a consistent increase in C(2) selectivity. The results are discussed in terms of electronic and steric effects.

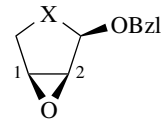
Mechanisms and stereochemistry have been investigated for the acid-induced ring opening of optically active 1, 2-propene oxides in gaseous CH_4 and CH_3F at 720 Torr and in the presence of H_2O or CH_3OH as nucleophile.[16] Two reaction pathways are possible, both proceeding through complete inversion of configuration at the reaction centre.

In the reactions of styrene oxide and butadiene monoxide with ester carbanions, attack takes place at both primary and secondary epoxy carbon atoms.[17] The findings provide evidence for the participation of the conjugative effect in the ring opening of these epoxides.

A model system consisting of methyloxirane, formate, and formic acid has been used to study the nucleophile-catalysed and nucleophile- and acid-catalysed opening of an epoxide ring by applying *ab initio* quantum mechanical calculations [up to the MP4(SDQ)/6−31+G**//MP2/6−31+G** level] and also density functional theory



(**22**)

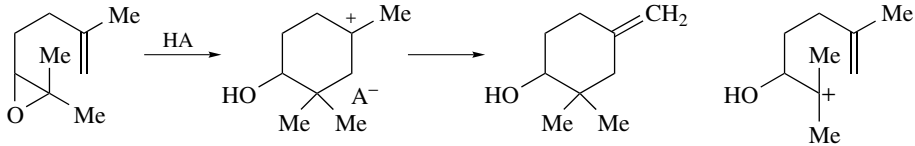


(**23**)

a; X = CH_2 *b*; X = O

calculations [Becke 3LYP/6–31 + G**).[18] This system is intended to serve as a model for the covalent binding of the epoxide inhibitor to the active site of glycosidase. Solvation effects were estimated by using the isodensity surface-polarized continuum model. The ring opening takes place preferentially between the epoxide oxygen and the less substituted carbon, and both the nucleophile and the acid–base catalyst are needed for the process to occur efficiently.

Theoretical evidence [Hartree–Fock (RHF) calculations and density functional theory] has been obtained for a concerted mechanism of oxirane cleavage and A-ring formation in oxidosqualene cyclization.[19] A common concerted mechanistic pathway has been demonstrated for the acid-catalysed cyclization of 5,6-unsaturated oxiranes in chemical and enzymic systems.[20] For example, the conversion of (**24**) into (**26**) proceeds via (**25**) and not via a discrete carbocation (**27**). Kinetic studies and other evidence are presented for various systems.



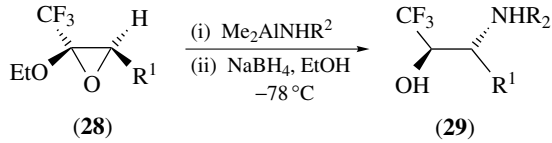
(**24**) (**25**) (**26**) (**27**)

The transition structures for the intramolecular reactions of protonated *cis*- and *trans*-3,4-epoxypentan-1-ol, which result in the formation of protonated *cis*- and *trans*-2-methylfuran-3-ol with inversion and with retention, have been determined at the *ab initio* MP2/6–31G* and hybrid density functional B3LYP/6–31G* levels of theory.[21] Intramolecular attack with inversion occurs in concert with ring opening. The retention transition structures are too high in energy to afford credible reaction pathways. A further contribution from the same research group is a detailed kinetic study of general acid-catalysed benzo[*a*]pyrene diol epoxide hydrolysis.[22] Buffer solutions containing primary amines whose pK_a values span the range 5.4–10.7 were used, and a change in rate-limiting step was detected when amines of pK_a values in the neighbourhood of 8 were employed.

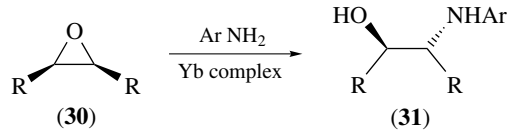
In the tetracyanoethylene-catalysed methanolysis of some steroidal hydroxyepoxides, an adjacent *cis*-5-hydroxy group changes the regio- and stereo-chemistry from *trans* diaxial to diequatorial cleavage.[23] The regioselective ring-opening halogenation of some epoxides by elementary iodine and bromine has been studied.[24] A series of new synthetic macrocyclic diamides and also dibenzo-18-crown-6, 18-crown-6, and aza-18-crown-6 acted as catalysts under mild reaction conditions in various aprotic solvents. Halohydrins were formed in high yields with more than 95% regioselectivity. The macrocyclic catalysts are considered to generate nucleophilic halogen species X_3^-.

anti-(Trifluoromethyl) β-amino-alcohols (**29**) have been prepared in good yields and with 90% diastereoisomeric excess through a reaction of 1-(trifluoromethyl) epoxy ethers (**28**) with dimethylaluminium amide, followed by *in situ* chelation-controlled stereoselective reduction of the intermediate amino ketone.[25] Depending on R^1 the

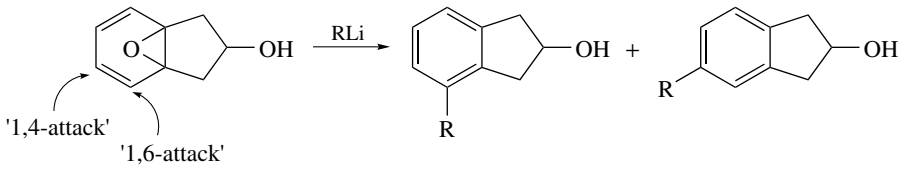
anti:syn ratio of the product ranged from 97:3 (Ph) to 73:27 (CH_2-cyclohexyl), for the reagent with R^2 = benzyl. Chiral β-amino alcohols (**31**) have been prepared by desymmetric ring opening of *meso*-epoxides (**30**) with anilines, the catalyst being a chiral Yb triflate complex.[26] Upto 80.1% *ee* was obtained, depending on R and Ar.



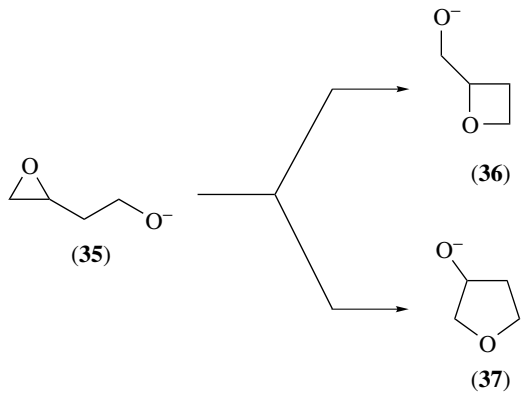
(**28**) (**29**)



(**30**) (**31**)



(**32**) (**33**) (**34**)



(**35**) (**36**) (**37**)

The rare 4- and 5-alkylindan-2-ols (**33**) and (**34**) have been prepared in 62–72% yields by formal 1,6- and 1,4-nucleophilic ring opening of the 2-hydroxyindan-3a, 7a-oxide (**32**), respectively.[27] In a comparison of gas-phase and condensed-phase S_Ni reactions, the competitive four- and five-centre cyclizations [yielding (**36**) and (**37**), respectively] of the 3,4-epoxybutoxide anion (**35**) have been subjected to both experimental and theoretical study.[28] In the gas phase, the barriers to the transition

states are comparable, but the tetrahydrofuran-3-ol product (**37**) is much more stable. Base treatment of (**35**) in two different solvent systems yielded the same two products as observed in the gas phase, but (**37**) is the kinetic product in both solvent systems.

Highly regioselective cyclizations of 3,4-, 4,5- and 5,6-unsaturated alcohols to yield tetrahydrofuranols and tetrahydropyranols have been carried out with the TS-1–H_2O_2 system[29] (this is a titanium silicate molecular sieve–H_2O_2 complex.) The reactions involve the intermediate formation of epoxides and their S_Ni ring opening.

Other Small Rings

In a long series on geminal substituent effects, the authors address the question: 'Do alkoxycarbonyl substituents stabilize small cycloalkane rings?'[30] This article is essentially thermochemical. It is concluded that *gem*-alkoxycarbonyl substituents provide only weak stabilization of small cycloalkane rings. Accordingly, high rates of S_Ni ring closure to *gem*-dialkoxycarbonyl cyclopropanes are not attributable to a stabilizing effect resulting from conjugation between alkoxycarbonyl substituents and the cyclopropane ring, as has been suggested. A Thorpe–Ingold or *gem*-dimethyl-type effect offers a more satisfactory interpretation.

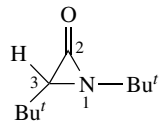
Reaction rates and product composition have been studied for the solvolysis of 1-[*trans*-2-(*m*- or *p*-substituted phenyl)cyclopropyl]-1-methylethyl *p*-nitrobenzoates in 80% aqueous acetone.[31] For the less reactive substrates (those with *m*-Br, *m*-Cl, or *m*-CF_3), the solvolysis products were the corresponding 2-(2-arylcyclopropyl)propan-2-ol, indicating a cyclopropylmethyl cation intermediate. The ring-opened products increased as the electron-donating ability of the substituents increased. Evidence is adduced that in such cases there is a homoallylic cation intermediate.

In the acid-catalysed ring opening of *N*-(3,4-dihydro-4-oxoquinazolin-3-yl)-substituted aziridines, participation by the quinazolinone carbonyl oxygen brings about ring opening with retention of configuration.[32] Monochiral *N*-diphenylphosphinylaziridines undergo ring-opening reactions with a variety of nucleophiles in good yield.[33]

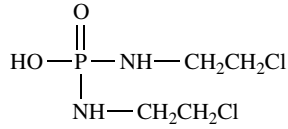
Competing modes of ring opening of 1,3-di-*t*-butylaziridinone (**38**) and similar aziridinones by a variety of *N, O, S*, and Hal nucleophiles do not give proportions of products in agreement with simple guidelines in the literature.[34] For example, (**38**) reacts with aromatic amines by 1,3-cleavage exclusively, as expected, but with aliphatic and saturated cyclic amines, various behaviour is found, including exclusive 1,2-cleavage.

The mechanism of bisalkylation by isophosphoramide mustard (**39**) has been studied.[35] The $\beta, \beta, \beta', \beta'$-$d_4$ derivative was used to demonstrate bisalkylation through sequential aziridinyl intermediates.

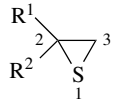
Novel S_N2 ring-opening reactions of 2- and 2,2-substituted thiiranes (**40**) with thiols, using as catalyst Na^+-exchanged X-type zeolite or triethylamine in methanol, have been examined;[36] (**40a**) and (**40b**) undergo ring opening regiospecifically at C(3), but for (**40c**) the reaction is not regiospecific, ring opening at both C(3) and C(2) occurring in various proportions, depending on catalyst and other conditions.



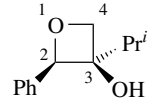
(**38**)



(**39**)

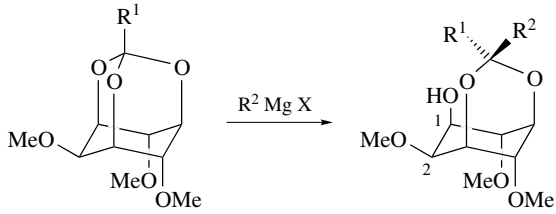


(**40**)



(**41**)

	R^1	R^2
a;	H	Me
b;	Me	Me
c;	H	Ph



(**42**) (**43**)

R^1 = H or Ph

R^2 = Me

X = I or Br

The ring opening of 3-isopropyl-2-phenyl-3-oxetanol (**41**) by different nucleophiles has been studied.[37] In the presence of BF_3-Et_2O, various nucleophiles RLi reacted regiospecifically at C(4), and the corresponding 1,2-diols were isolated in diastereomerically pure form. Other interesting details are provided.

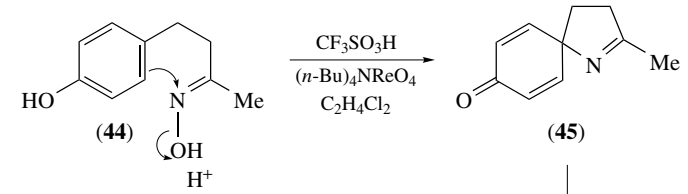
Reactions of orthoesters of *myo*-inositol (**42**) with 1–2 equiv. of Grignard reagent in benzene yield regio- and stereo-selectively ring-opened products (**43**) having a free hydroxy group at C(1).[38] The regioselectivity is attributed to the OMe at C(2) forming a chelation complex with magnesium.

Substitution at Elements Other than Carbon

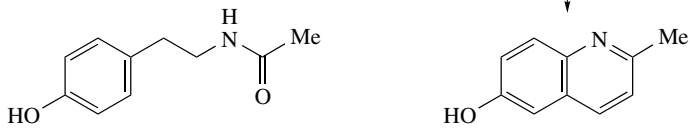
Experimental and theoretical evidence has been obtained for an S_N2-type mechanism in dissociation of B–N coordinate bonds in 2,6-bis[(dimethylamino)methyl]phenylborane derivatives.[39] *Ab initio* calculations were carried out for the system of NH_3 and BH_3.

An acid–rhenium catalyst mixture acts on (*E*)-4-(4-hydroxyphenyl)butan-2-one oxime (**44**) to produce a high yield of the spiro compound (**45**), which then rearranges to the substituted quinoline (**46**).[40] The Beckmann rearrangement product (**47**)

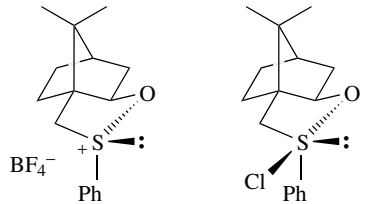
is scarcely produced. The formation of (**45**) is essentially an intramolecular S_N2 process (the electron-rich aryl group being the nucleophile) on the sp^2 nitrogen of protonated oxime. Post-Hartree–Fock *ab initio* calculations indicate that the reaction pathways leading to (**45**) and (**47**) are of comparable energies and should be in effective competition. Experimental studies found considerable amounts of Beckmann product under various other conditions.



(**44**) (**45**)



(**47**) (**46**)



(**48**) (**49**)

The isolation and stereochemical studies of a cyclic alkoxysulfonium salt (**48**) have been reported.[41] Such a species has previously been proposed as an intermediate in the hydrolysis of the chlorosulfurane (**49**).

Intramolecular Substitution

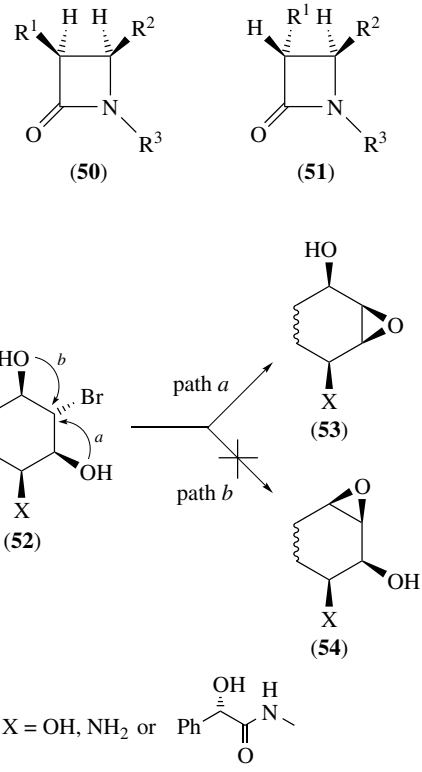
Three-membered ring-forming processes involving $^{-}X-CH_2-CH_2-F$ or $^{-}CH_2-C(Y)-CH_2F$ ($X = CH_2$, O, or S and $Y = O$ or S) in the gas phase have been treated by the *ab initio* MO method with a 6–31+G* basis set.[42] When electron correlation effects were considered, the activation ($\Delta G^{\ddagger}$) and reaction (ΔG°) free energies were lowered by about 10 kcal mol^{-1}, indicating the importance of electron correlation in these reactions. The contribution of entropy of activation ($-T\Delta S^{\ddagger}$) at 298 K to $\Delta G^{\ddagger}$ is very small; the reactions are enthalpy controlled.

Ab initio calculations at the MP2/6–31+G(d,p)//MP2/6–31+G(d) level have been used to investigate the cyclizations of a series of stabilized 3-chlorocarbanions

$ClCH_2CH_2CHZ^-$ [Z = C(O)H, CCH, or CN] to cyclopropane derivatives.[43] In each case the cyclization barrier is lower than the S_N2 barrier of an analogous acyclic system, despite the cyclization being over 25 kcal mol^{-1} less exothermic. The surprisingly small enthalpic barrier to the cyclizations is due to the nucleophile being held in close proximity to the electrophilic site in the substrate, and this destabilizes the ground state.

Density functional theory calculations (B3LYP/6–31G* level) have provided an explanation for the stereodivergent outcome of the Staudinger reaction between acyl chlorides and imines to form 2-azetidinones (β-lactams).[44] When ketene is formed prior to cycloaddition, preferential or exclusive formation of *cis*-β-lactam (**50**) is predicted. If, however, the imine reacts directly with the acid chloride, the step that determines the stereochemical outcome is an intramolecular S_N2 displacement, and preferential or exclusive formation of *trans* isomer (**51**) is predicted. These predictions agree well with the experimental evidence regarding the stereochemical outcome for various reactants and reaction conditions.

Bromocyclopentitols and amino(or amido)bromocyclopentitols having a C−Br bond *trans* to two vicinal hydroxy groups show selectivity in base-promoted epoxide formation, e.g. (**52**) gives (**53**) by path *a*, rather than (**54**) by path *b*.[45]

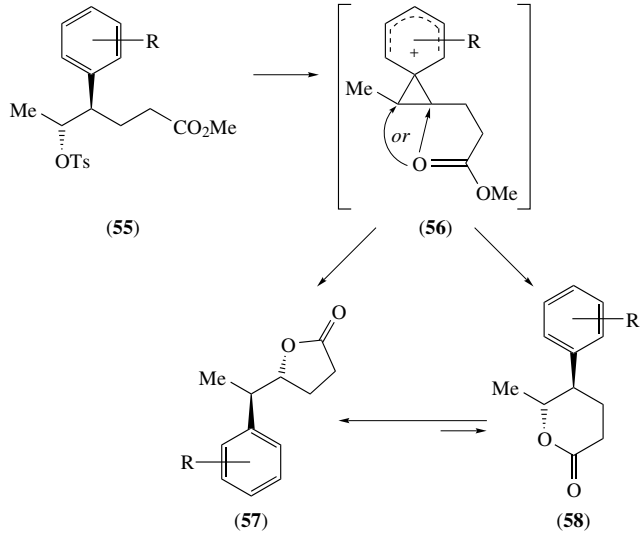


The hydrolysis of *o*-nitrobenzyl tosylate in 1:1 MeCN–H_2O gives *o*-nitrobenzyl alcohol and *o*-nitrosobenzaldehyde in a ratio of 1.8:1.[46] The formation of the aldehyde indicates that the nitro group participates in the expulsion of the tosylate group to give a cyclic intermediate, which then undergoes ring opening to *o*-nitrobenzaldehyde. *o*-Nitrosobenzaldehyde reacts with benzylamine to form 3-(*N*-benzylamino)anthranil (or its tautomer) as a major product.

Ab initio MO theory, mainly at the 3–21+G level, has been applied to intramolecular S_N2 methyl transfer between two oxygen atoms confined within a rigid template.[47] This is found to proceed exclusively by a high-energy retention mechanism when the oxygens are separated by three or four bonds, and by high-energy inversion when the oxygens are separated by six bonds. The mechanisms compete when the oxygen atoms are separated by five bonds. The CH_3/CD_3 kinetic isotope effects are normal (1.21–1.34) in retention and inverse (0.66–0.81) in inversion. The same group has pursued a further study of alkyl transfer with retention or inversion of configuration in re-examining the thermal rearrangement of 2-alkoxypyridine-1-oxides to 1-alkoxy-2-pyridones, a putative intramolecular [1s, 4s] sigmatropic migration of the alkyl group.[48] An alternative mechanism involving intermolecular alkyl transfer is now put forward.

It has been suggested that the Tanigawa reaction involves the decomposition of an intermediate by an intramolecular S_N2 process.[49]

The study of lactonization via an intermediate phenonium ion has been further pursued for several methyl 4-aryl-5-tosylhexanoates (**55**) as substrates.[50] The intermediate phenonium ion (**56**) has two possibilities for ring closure, yielding products (**57**) or (**58**). In all the substrates, Ar contained one or two methoxy groups and sometimes also a methyl group. The effects of reaction medium, temperature, and time on the product ratios were examined. It was concluded that substrates (**55**) give γ-lactone (**57**) selectively under thermodynamic conditions, but δ-lactone (**58**) under kinetic conditions. Substituents in Ar influence the selectivity through their electronic effects.



Ambident Nucleophiles

The structures of lithium and sodium cyanates and isocyanates and their related ion-pair S_N2 reactions have been examined by using quantum mechanics at the Hartree–Fock (HF)/6–31G**//HF/6–31G** level.[51] (The cyanate ion is NCO^-; the isocyanate ion is CNO^-.) The isocyanate ion pairs are the most stable monomeric forms; the lowest energy dimers are planar eight-membered rings. For the ionic S_N2 reaction of cyanate ion with MeF or MeCl, methyl isocyanate is the predicted major product. Predictions about the S_N2 reactions of the ion pairs were also made.

Alpha Effect

Second-order rate constants have been measured for the S_N2 reactions of benzyl bromide and *p*-nitrobenzyl bromide with hydroxy nucleophiles.[52] The values of $k(HOO^-)/k(HO^-)$ are very small (1.3 and 1.2, respectively) for the two substrates. Thus the α-effect is very small and it is suggested that this may be due to the lack of tight σ-bond formation at the transition state.

Isotope Effects

Westaway and co-workers' work on kinetic isotope effects (KIEs) has continued.[53–55]

In a long series on isotope effects in nucleophilic substitution reactions, the effect of changing the nucleophilic atom on ion pairing in an S_N2 reaction has been examined.[53] When the nucleophile is sodium thiophenoxide, ion pairing markedly alters the secondary α-deuterium KIE and the effect of changing the *p*-substituent on the nucleophile. In the case of sodium phenoxide, ion pairing does not significantly affect the secondary α-deuterium or the chlorine leaving-group KIEs or the effects of changing a *p*-substituent on the nucleophile or the substrate.

The $^{11}C/^{14}C$ incoming-group and secondary α-deuterium KIEs have been used to determine how a change in leaving group alters the structure of the transition state of the S_N2 reactions between *m*-chlorobenzyl *p*-substituted benzenesulfonates and cyanide ion.[54] The results suggest that the reactions occur by way of an unsymmetrical, product-like transition state.

Two methods were used to measure the chlorine leaving-group KIE for the S_N2 reduction of benzyl chloride to toluene by sodium borohydride in DMSO at 30 °C.[55] One procedure involved the classical IRMS technique. The second method was a new technique in which the ratio of the chlorine isotopes was obtained by fast atom bombardment mass spectrometry on silver chloride recovered from the reaction. The KIE values k^{35}/k^{37} found by the two methods were 1.007 and 1.008, respectively, identical within experimental error. This large KIE indicates considerable C–Cl bond rupture in the transition state.

Gas-phase Reactions

The dynamics and mechanism of nucleophilic displacements involving ions in the gas phase have been reviewed.[56] The article covers aspects of kinetics (especially the

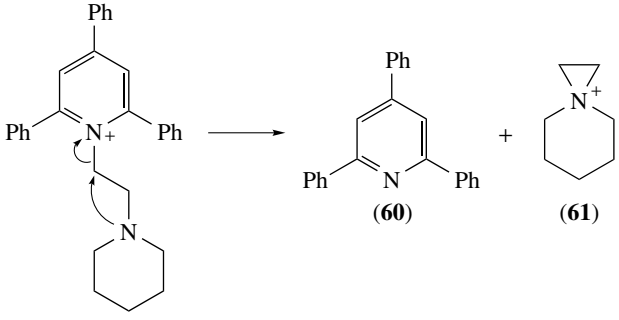
applicability of statistical reaction rate theory), the relation of structure and reactivity, and the effects on the reactions of introducing small numbers of solvent molecules. The behaviour of the ionic reaction in the gas phase is compared with that in solution.

In studies of ion–molecule reactions in the gas phase, the influence of collision energy on competitive S_N2 and S_Ni reactions has been examined for reactions of epimeric indan-1,2-diols with the NH_3–NH_4^+ system.[57] Stereospecific S_N2 and S_Ni pathways operate for the *cis* and *trans* derivatives, respectively.

Hase and co-workers' work has continued[58–60] with a review of computational and experimental studies of the dynamics of gas-phase S_N2 reactions of the type $X^- + RY \rightarrow XR + Y^-$, in particular for R = Me, X = Cl, and Y = Cl or Br.[58] The computational studies involve classical trajectory simulations on analytical potential energy functions derived from *ab initio* electronic structure calculations. *Ab initio* calculations at different levels of theory are considered. Among the topics studied are the dynamics of the $X^- + RY$ association process, a direct mechanism for $X^- + RY \rightarrow XR + Y^-$, and energy partitioning for the $XR + Y^-$ products. The series on trajectory studies of S_N2 processes has continued with an examination of the role of translational activation in the $Cl^- + CH_3Cl$ reaction[59] and in the $F^- + CH_3Cl$ reaction.[60] In the former the reactive trajectories are direct, with negligible trapping in the ion–dipole complexes, whereas in the latter there is evidence for the formation of ion–molecule complexes at lower energies.

Studies of gas-phase S_N2 reactions at sp^3 carbon have been made by Fourier transform ion cyclotron resonance mass spectrometry (FTICRMS) and complemented by both semiempirical and *ab initio* MO calculations.[61] The particular processes of interest involved intramolecular reactions in which neutral nucleophiles displace neutral leaving groups within cationic substrates, e.g. *N*-(2-piperidinoethyl)-2,4,6-triphenylpyridinium cation (**59**), in which the piperidino moiety is the nucleophile and 2,4,6-triphenylpyridine (**60**) is the leaving group. No evidence has been obtained for any intermolecular gas-phase S_N2 reaction involving a pyridine moiety as a leaving group. The quantum mechanical treatments account for the intramolecular preference.

An *ab initio* MO study has been carried out on a linear relationship between free energies of activation of Menshutkin reactions and the proton affinities of the nitrogen bases used as nucleophiles.[62] The relationship had been discovered some



(**59**) (**60**) (**61**)

years ago. Different lines were obtained for sp^2 and sp^3 bases, and the calculations at the MP2/6–31+G*//RHF/6–31+G* level explain why this occurs. The relationship has now been extended to activation energies.

The $HO^- + CH_2F_2$ reaction has been studied by selected ion flow tube (SIFT) experiments and *ab initio* calculations.[63] SIFT experiments at 300 K showed that a bimolecular process [leading to CHF_2^- (86%), F^- (11%), and HF_2^- (3%)] competes with a three-body association leading to $HO^-.CH_2F_2$. The bimolecular rate coefficient has an upper limit of about 2.4×10^{-12}cm^{3}molecule^{-1}s^{-1} and shows a small negative temperature dependence, suggesting that reaction proceeds via an ion complex intermediate. The results were rationalized by the MO calculations.

The nature of the neutral or acidic hydrolysis of CH_2Cl_2 has been examined from ambient temperature to supercritical conditions (600 °C at 246 bar).[64] Rate measurements were made and the results show major deviations from the simple behaviour expressed by the Arrhenius equation. The rate decreases at higher temperatures and relatively little hydrolysis occurs under supercritical conditions. The observed behaviour is explained by a combination of Kirkwood dielectric theory and *ab initio* modelling.

Gas-phase nucleophilic substitution reactions of Y-benzyl chlorides and X-phenoxide or X-thiophenoxide nucleophiles have been investigated by using the PM3 semiempirical MO method.[65] The structure of the transition state was examined. The values of the gas-phase Hammett constants ρ_X and ρ_Y are much greater than for the solution reactions, but a theoretical cross-interaction constant ρ_{XY} (ca −0.60 for both phenoxides and thiophenoxides) agrees well with an experimental value of −0.62 for the thiophenoxide reactions in MeOH at 20 °C. Other work by the same group has involved theoretical studies of competitive gas-phase S_N2 and $E2$ reactions of $NCCH_2CH_2Cl$ with HO^- and HS^-.[66] An *ab initio* method at the 6–31+G* level was used, with electron correlation at the MP2 level. $E2$ is preferred to S_N2 for both HO^- and HS^-.

Ab initio MO calculations have been carried out for two carbocation-generating reactions: the S_N1 reaction of protonated 1-phenylethanol (H_2O leaving group) and the acid-catalysed hydration of styrene.[67] Optimizations were done at the MP2/6–31G* level. The S_N1 transition state lies half way between the reactant and the product with respect to the bond lengths, charge distribution, and secondary deuterium isotope effects.

An *ab initio* study of elimination and substitution has been done for the gas-phase reaction of F^- with chlorocyclopropane.[68] Among various findings it emerged that at the MP2/6–31(+)G*//HF/6–31(+)G* level, the S_N2 pathway has a lower activation barrier by 7.3 kcal mol^{-1} compared with the $E2$(*anti*) pathway.

The S_N2 reactions of the radical anions ($CHCl^{\cdot}$ and $CHBr^{\cdot}$) and the closed-shell anions (CH_2Cl^- and CH_2Br^-) with CH_3Cl and CH_3Br have been studied by using density functional theory.[69] The closed-shell anions were found to be more reactive than the radical anions, in agreement with experiment. Other details of the systems were also elucidated. *Ab initio* and semiempirical (AM1) methods were used to study the gas-phase S_N2 reactions between methyl nitrate and various nucleophiles.[70]

Radical Processes

The stereochemistry of the nucleophilic reaction of the enolate ion of 1,4-dihydro-4-methoxycarbonyl-1-methylpyridine with (*R*)-(−)- and (*S*)-(+)-2-bromobutane has been investigated.[71] The reaction proceeds with 99.7% inversion of configuration. Thus, even though the inner-sphere stabilization of this reaction is small, there is no sign of the outer-sphere electron-transfer (ET) process, which would lead to racemization.

By means of diastereomeric probes, it has been demonstrated that the vicinal nucleophilic displacement of a diethylphosphate group from a β-(phosphatoxy)alkyl radical may occur through backside or frontside attack, depending on steric constraints.[72]

The competition between ET and S_N2 processes in the reaction between radical anions of various aromatic compounds, e.g. anthracene, pyrene, (*E*)-stilbene, and *m*- and *p*-cyanotoluene, and substrates such as RHal (where R = Me, Et, Bu, 2-Bu, neopentyl, and 1-adamantyl) or various methanesulfonates has been studied in DMF as solvent.[73] The reaction mechanism could be characterized electrochemically in many of the systems indicated above. The presence of an S_N2 component is related not only to the steric requirements of the substrate, but also to the magnitude of the driving force for the ET process.

2,2,2-Trifluoroethyl chloride, bromide, and iodide (but not fluoride) react with thiolate ions in DMF under laboratory illumination at 30–50 °C to give high yields of 2,2,2-trifluoroethyl thiol derivatives.[74] Various features of the reactions show that they occur by the $S_{RN}1$ mechanism. The initiation may be spontaneous or thermal electron transfer between thiolate and halides, because the reactions can occur in the dark.

The two-electron reduction product of terephthalodinitrile reacts with alkyl halides in liquid ammonia to yield 4-alkylbenzonitriles and 2-alkylterephthalodinitriles.[75] The product ratio strongly depends on the alkyl halide and changes in favour of the *ipso* product, 4-alkylbenzonitrile, on going from tertiary alkyl to primary and from iodide to chloride. This change is the result of increased contribution of the S_N mechanism relative to the ET mechanism.

Medium Effects

Palm's group has continued to develop statistical procedures for treating solvent effects.[76] In a previous paper, a set of nine basic solvent parameter scales was proposed. Six of them were then 'purified' via subtraction of contributions dependent on other scales. This set of solvent parameters has now been applied to an extended compilation of experimental data for solvent effects on individual processes. Overall, the new procedure gives a significantly better fit than the well-known equations of Kamlet, Abboud, and Taft, or Koppel and Palm.

Kinetics of the solvolysis of acyl chlorides and alkyl chlorides in hydroxylic solvent mixtures have been measured conductimetrically at various temperatures and pressures.[77] The activation parameters $\Delta V^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ were calculated from the rate constants. The authors appear to have been interested mainly in acyl chlorides, but conclude that, whereas *p*-methylbenzoyl chloride reacts via a dissociative

S_N2 mechanism, *p*-methylbenzyl chloride reacts via an ion-pair mechanism of a unimolecular reaction.

Correlation analysis of solvent effects on the heterolysis of *p*-methoxyneophyl tosylate has been performed by using the Koppel–Palm and Kamlet–Taft equations.[78] The reaction rate is satisfactorily described by the electrophilicity and polarity parameters of solvents, but a possible role for polarizability or nucleophilicity parameters was also examined.

Heterolysis rates of *t*-butyl bromide, 1-bromo-1-methylcyclohexane, and 2-bromo-2-methyladamantane increase in the order of solvents MeCN < γ-butyrolactone < sulfolane, but heterolysis rates of 2-bromo-2-phenyladamantane decrease in the same order of solvents.[79] The observed effects are considered to be caused by superposition of dipolar and electrophilic solvations.

Studies of 'dimensiosolvatic' effects have continued with an attempt to quantify them for solvolyses of 2-bromoadamantane in water–alcohol mixtures.[80] Product selectivities $S = k(\text{ether})/k(\text{alcohol})$ were measured at various concentrations of water in an alcohol and at various temperatures. The reciprocals of the averages of S values for 1.0:0.8 alcohol–water mixtures at all the experimental temperatures (120–150 °C) were proposed 'as measures D of dimensiosolvatic effects when a solvent molecule intervenes into contact ion pair to form solvent-separated ion pair.' The scale runs from $D = 1.0$ (by definition) to $D = 10.0$ for *t*-butyl alcohol and is essentially a measure of the bulkiness of solvent molecules.

Kevill and co-workers' work on solvolysis rates has continued.[81–83] The specific rates of solvolysis of the benzylmethylphenylsulfonium ion and five benzylic ring-substituted derivatives can be satisfactorily correlated using N_T solvent nucleophilicity scales.[81] Addition of a secondary term, governed by the aromatic ring parameter (I), shows the sensitivities towards changes in this parameter to fall and those towards changes in N_T to rise with increasing electron-withdrawing ability of the substituent. The specific rates of solvolysis of benzyl *p*-toluenesulfonate and nine benzylic-ring-substituted derivatives are satisfactorily correlated by using N_T and Y_{OTs} scales in the extended Grunwald–Winstein equation.[82] Addition of a third term involving the aromatic ring parameter I is statistically significant. Electron-withdrawing substituents increase the sensitivity towards changes in N_T, whereas they decrease the sensitivity towards changes in Y_{OTs} and I. The trend of sensitivities towards N_T can be very nicely shown, with very precise correlations, by using an internally generated scale of Y values. However, such a procedure has no overall advantage if it is desired ultimately to make a comparison with sensitivity values generated by using an external scale of Y values. Solvent effects on the rate coefficients of solvolysis of 4-chloro-2,2,4,6,6-pentamethylheptane and 3,3-dimethyl-1-neopentylbutyl mesylate (whose molecules are extremely crowded), previously analysed by using the extended Grunwald–Winstein equation incorporating N_T and Y_X values, are better correlated by using a combination of Y_X and I values.[83]

Liu and co-workers' work on solvolysis rates has continued.[84–88] Rate coefficients of solvolysis of four 1-R-1-chloro-1-(4-methyl)phenylmethanes (R = Me, Et, Pr^i, or Bu^t) were measured in aqueous-acetone, -ethanol, and -methanol, and in ethanol-trifluoroethanol mixtures.[84] Grunwald–Winstein type correlation analysis using the

Y_{BnCl} scale suggests significant nucleophilic solvent intervention for the substrate with R = Me. Increasing bulkiness of R resulted in a gradual change to limiting S_N1 mechanisms. The superiority of employing the Y_{BnCl} scale over the combination of Y_{Cl} and I (aromatic ring parameter) scales in the mechanistic study was observed. Rate coefficients in various solvents have been measured for a series of 1-aryl-1-*t*-butylmethyl chlorides.[85] Correlation analysis with a single-parameter Grunwald–Winstein equation incorporating Y_{BnCl} was excellent in every case. Substituent effects were treated in terms of the Hammett equation (Brown–Okamoto σ^+ constants) and the Yukawa–Tsuno equation. Solvolysis rates have been measured for α-*t*-butyl(2-naphthyl)methyl chloride, 9-fluorenyl chloride, and a series of monosubstituted benzhydryl chlorides in a wide range of solvents.[86] These substrates were selected because the corresponding carbocations all show extended charge delocalization. The application of Y_{BnCl}, with or without the inclusion of a solvent nucleophilicity parameter, did not give fully satisfactory correlations, so a new scale of solvent ionizing power Y_{xBnCl} for the correlation of solvolytic reactivities of benzylic chlorides with extended charge delocalization was based on the results for α-*t*-butyl(2-naphthyl)methyl chloride. Applications of Y_{BnCl} or Y_{xBnCl} were held to give a better understanding of reaction mechanisms than those of Y_{Cl} combined with I. Further work from Liu's group has involved 'B-strain and solvolytic reactivity revisited. Nucleophilic solvent participation and abnormal rate ratios for tertiary chloroalkanes.'[87] The 'abnormal rate ratios' are those involving introducing Pr^i, and are considered due to competition between B strain and nucleophilic solvent participation. In presenting solvolytic studies of 4-methoxybenzyl chloride and bromide, and of 1-(4-methoxyphenyl)ethyl chloride, further opportunity was taken to criticize the introduction and use of the aromatic ring parameter I.[88]

Rate constants and products have been reported for solvolysis of benzhydryl chloride and *p*-methoxybenzyl chloride in 2,2,2-trifluoroethanol (TFE)–water and–ethanol, along with additional kinetic data for solvolysis of *t*-butyl and other alkyl halides in 97% TFE and 97% hexafluoropropan-2-ol.[89] The results are discussed in terms of solvent ionizing power Y and nucleophilicity N, and contributions from other solvation effects are considered. Comparisons with other S_N1 reactions show that the solvolyses of benzhydryl chloride in TFE mixtures are unexpectedly fast; an additional solvation effect influences solvolysis leading to delocalized cations.

Solvolysis rates of substituted 2-aryl-1, 1-dimethylethyl bromides have been determined in various binary solvent mixtures, particularly aqueous–organic mixtures.[90] Grunwald–Winstein treatments gave mixed results. They were reasonably successful for aryl = Ph or p-MeC_6H_4, but aryl = p-$MeOC_6H_4$ failed to give a single linear correlation against either Y or Y_{Cl}. It did, however, give fairly good linearity against Y_Δ, defined from the solvolysis of 4-methoxyneophyl tosylate.

Rates of solvolysis of 2-adamantyl azoxytosylate were measured over a range of temperatures in ethanoic acid, methanoic acid, and various mixed solvents.[91] For comparison solvolysis rates of 2-adamantyl tosylate were measured in several of the same solvents. The m value for 2-adamantyl azoxytosylate solvolysis is only 0.46, one of the lowest observed values for a reaction that is unambiguously S_N1.

Aqueous ethanolyses of adamantylideneadamantyl halides show Grunwald–Winstein sensitivity parameters (m) of 0.74 (±0.06), 0.90 (±0.01), and 0.88 (±0.03) for the chloride, bromide, and iodide compounds, respectively.[92] All reaction products are formed with retention of both the ring structure and the stereochemistry of the reaction centre. Observed common-ion rate depressions are consistent with a reaction pathway via a free solvated homoallylic carbenium ion.

Rate constants have been determined for solvolyses of 2-bromo- (or -chloro-) -2-methylbutane and 3-chloro-3-methylpentane in 10 diols at 298.15 K.[93] By combining kinetic data with thermodynamic data, transfer Gibbs energies of the reactants (initial state) and of the activated complex (transition state) were obtained, which allowed the solvent effects on both states to be quantitatively analysed.

The solvation and nucleophilic reactivity (towards ethyl iodide) of the 1,2,4-triazolate ion have been investigated in MeCN–MeOH mixtures.[94] Various correlations of thermodynamic and kinetic functions are presented.

The specific rates of hydrolysis of five organic halides in three water-based liquid mixtures near their respective equilibrium consolute points have been observed to be suppressed.[95] The systems studied included *t*-amyl chloride in isobutyric acid + water (upper consolute temperature), and 3-chloro-3-methylpentane in 2-butoxyethanol + water (lower consolute temperature). The slowing effect occurred within a few tenths of a degree on either side of the consolute temperature.

Ab initio MO calculations were carried out on the hydrolysis of CH_3Cl, with explicit consideration of up to 13 water solvent molecules.[96] The treatments were at the HF/3–21G, HF/6–31G, HF/6–31+G* or MP2/6–31+G* levels. For $n \geqslant 3$ three important stationary points were detected in the course of the reaction. Calculations for $n = 13$ at the HF/6–31+G* level reproduced the experimental activation enthalpy and the secondary deuterium KIE. The proton transfer from the attacking water to the water cluster occurs after the transition state, in which O–C is 1.975 Å and C–Cl is 2.500 Å.

The nature of salt effects in monomolecular heterolysis has been reviewed.[97] The experimental work of the same group on salt effects has continued with a study of the negative salt effect of lithium perchlorate on the heterolysis of 1-iodoadamantane in γ-butyrolactone.[98] It is assumed that the salt effect of lithium perchlorate is caused by the salt action on the solvent-separated ion pair of the substrate.

Extensive studies have been carried out on the concentrated salt effects on the solvolysis reaction rates of aliphatic halides and related compounds in acetone–water mixed solvents.[99] The main outcome of the complicated results presented appears to be that 'It is proposed that one could simply distinguish S_N1 from S_N2 reactions merely by observing a substantial increase in the solvolysis rate constant at 1.0 mol dm^{-3} $LiClO_4$ in aqueous mixed solvents.'

Phase-transfer Catalysis and Other Intermolecular Effects

Kinetic studies have been carried out for reactions of triphenylphosphine with substituted benzyl halides in various two-phase organic solvent–water media.[100] The effects of water, agitation, organic solvent, reactant and temperature were investigated. The order of relative reactivity for solvents was $CHCl_3 > CH_2Cl_2 \gg C_6H_6$.

Nucleophilic substitution on methyl *p*-nitrobenzenesulfonate in CH_2Cl_2 has been studied with a series of chloride salts with different structures and solvations: Bu_4NCl, PPNCl [bis(triphenylphosphoranylidene)ammonium chloride], KCl complexed by 18-crown-6 or Kryptofix 2,2,2, and for comparison PPNBr.[101] Rate constants and activation parameters are in accordance with an S_N2 mechanism. The results were treated by the Acree equation. There are two reaction paths: the first, involving the chloride ion, has the same rate for all the salts, whereas the second slower path, involving the ion pair, has a rate related to the dissociation constant of the salt.

A new transition-state-searching algorithm was used to determine the mechanism for methanol condensation to form dimethyl ether within the microporous environment of the zeolite, chabazite, using periodic boundary conditions and density functional theory.[102] An acid site in the zeolite produces $MeOH_2^+$ for nucleophilic attack by a second adsorbed MeOH molecule.

Structural Effects

The number of references for this section has fallen greatly, and it now seems unnecessary to use sub-headings.

A methodology that can classify reactions by using similarity measures has recently been introduced and has now been extended to include a steric similarity index.[103] Both substitution and elimination reactions are included.

The rate constants for methanolysis of alkyl *p*-toluenesulfonates conform to a two-parameter equation of the Hammett–Taft type, the governing structural factor being steric hindrance.[104] However, the alcoholysis rates of alkenyl and alkynyl *p*-toluenesulfonates do not obey this relation, probably because the multiple bonds stabilize the reaction intermediate.

Solvolysis of 1-(X-phenyl)-1-cyclohexyl chlorides in MeOH–MeCN mixtures was studied at 30.0 and 40.0 °C.[105] The ρ_x^+ values, −4.67 to −4.81 at 30.0 °C, are within the range for secondary and tertiary compounds which are believed to react by an S_N1 mechanism. The Grunwald–Winstein *m* values (plots using $Y_{1-AdOTs}$) are $\geqslant 1.0$, and these relatively large values suggest that the positive charge developed in the transition state is considerable and is delocalized on to the aromatic ring. The kinetics and mechanism of nucleophilic substitution reactions of *exo*- and *endo*-2-norbornyl arenesulfonates with anilines have been investigated in MeOH–MeCN mixtures at 60.0 °C.[106] Rate constants for three distinct competing processes were separately determined: solvolysis k_s, unimolecular k_1, and bimolecular k_2. The Hammett equation with cross-terms was applied to the effects of substituents X in the nucleophile and Z in the leaving group on the analysed rate constants, but in most cases the ρ_{XZ} term was negligible. The Hammett equation with cross-terms has also been applied to the reactions of Z-substituted benzyl X-benzenesulfonates with Y-substituted thiobenzamides in acetone at 45 °C.[107] The findings $\rho_Z < 0$ and $\rho_{YZ} > \rho_{XZ}$ indicate that this reaction proceeds by a dissociative S_N2 mechanism.

Isoparametricity has been experimentally verified as occurring in the reactions of Y-substituted benzyl bromides with X-substituted anilines in dioxane and in 2, 3, and 5 M DMSO solutions in dioxane at 40 °C.[108] The phenomenon is interpreted on

the basis of structural variation of the transition state of the S_N2 reaction. The same author studied the kinetics of the reactions of benzyl bromides with imidazoles and pyridines in nitrobenzene at 40 °C.[109,110] Cross-correlation analysis was applied.[109] The reactivities of imidazoles towards benzyl bromides are considerably less than those of pyridines of equal basicity.

Solvolysis rates of 2,2,2,-trifluoro-1-(3-chlorophenyl)-1-(substituted phenyl)ethyl and 2,2,2-trifluoro-1-(3,5-dichlorophenyl)-1-(substituted phenyl)ethyl tosylates or bromides have been measured conductimetrically at 25.0 °C in 80% aqueous ethanol.[111] The former reaction series showed a bilinear Yukawa–Tsuno correlation with $\rho = -4.81$ and $r = 1.41$ for substituents more deactivating than 3,5-dimethyl, and with $\rho = -6.19$ and $r = 1.57$ for the substituent range more activating than 4-methyl. The bilinear correlation was interpreted in terms of the changing coplanarity of the two aryl rings. The 3,5-dichlorophenyl-fixed substrates showed an excellent Yukawa–Tsuno correlation for the substituent range 4-MeO to 4-Cl, with $\rho = -5.95$ and $r = 1.69$. The variable aryl rings in this series show the largest extent of resonance interaction in the transition state with a carbenium ion centre that is highly deactivated by α-CF_3 and α-(3,5-dichlorophenyl).

Rate data for the Menshutkin reaction between strongly activated Z-substituted benzyl *p*-toluenesulfonates and Y-substituted *N,N*-dimethylanilines in MeCN at 35 °C fit the equation $k_{obs} = k_1 + k_2$ [DMA], which is consistent with concurrent first- and second-order processes.[112] The S_N1 constant k_1 is unaffected by changing the nucleophile and conforms to Yukawa–Tsuno treatment with $\rho = -5.2$ and $r = 1.3$. The S_N2 constant k_2 was increased by electron-donating substituents in the nucleophile and showed upward curvature when subjected to the Brown σ^+ treatment.

Studies on the reactions of MeBr and EtBr with KOH in absolute or aqueous MeOH showed that the main products are Me_2O and EtOMe, respectively.[113] The rates are the same whether KOH or KOMe is used to provide the nucleophile because the equilibrium $HO^- + MeOH \leftrightarrows MeO^- + H_2O$ lies very much to the right.

Miscellaneous S_N2 Reactions

In studies of onio-assisted S_N2 reactions, the behaviour of substrates such as $[Ph_3AsCH_2OTf]^+TfO^-$ has been examined.[114] This contains a 1,1-biselectrophilic sp^3 carbon centre. With neutral nucleophiles (Nu^1) under mild conditions a series of 1,1-bis-onium salts $[Ph_3AsCH_2Nu^1]^{2+}2TfO^-$ was obtained in good yields. Under more stringent conditions the triphenylarsonio function can act as a nucleofuge in a subsequent reaction with a second nucleophile Nu^2, yielding a series of unsymmetrical 1,1-bis-onium salts $[Nu^2CH_2Nu^1]^{2+}2TfO^-$.

The reaction of 1-alkoxypolyfluoroalkyl sulfonates with lithium tetraalkyl aluminates yields stereospecifically alkylated products with a high degree of inversion.[115] However, the reaction with trialkylaluminium reagents is considerably less stereospecific.

A series of imidate esters derived from secondary alcohols has been found to react with potassium benzoate or potassium phthalimide to give products of S_N2 substitution in excellent yields and with clean inversion of stereochemistry.[116]

Molecular dynamics simulations of ground and transition states have been carried out for the S_N2 displacement of chloride ion from 1,2-dichloroethane by the Asp 124–CO_2^- at the active site of *Xanthobacter autotrophicus* haloalkane dehalogenase.[117]

Detailed theoretical studies have been made for the S_N2 reaction of methyl bromide with $Me_2CuLi.LiCl$, with particular attention to solvent and cluster effects.[118]

A long series on stereochemistry has continued in a study of the acetolysis of triterpenoid *p*-toluenesulfonates in the presence of NaOAc.[119] Both substitution and elimination products were formed. Substitution could be accounted for by bimolecular processes (S_N2 on carbon, S_AN on sulfur). Some confirmation of this was obtained by kinetic studies.

Miscellaneous Kinetic Studies

Kinetic studies of various systems have been carried out as follows: the reaction of 2, 2′-dichlorodiethyl sulfide and of 2-chloroethyl ethyl sulfide with diethylenetriamine and triethylamine in 2-methoxyethanol;[120] the catalysed reactions of substituted phenols with epichlorohydrin;[121] the reactions of *para*-substituted benzyl bromides with isoquinoline under high pressure;[122] the reactions of *O*-alkylisoureas with OH-acidic compounds [the actual system was *N*, *N*′-dicyclohexyl-*O*-(1-methylheptyl)isourea with acetic acid];[123] and the ring opening of isatin in aqueous binary mixtures of methanol and acetonitrile cosolvents.[124]

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CHAPTER 11

Carbanions and Electrophilic Aliphatic Substitution

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Carbanion Structure and Stability

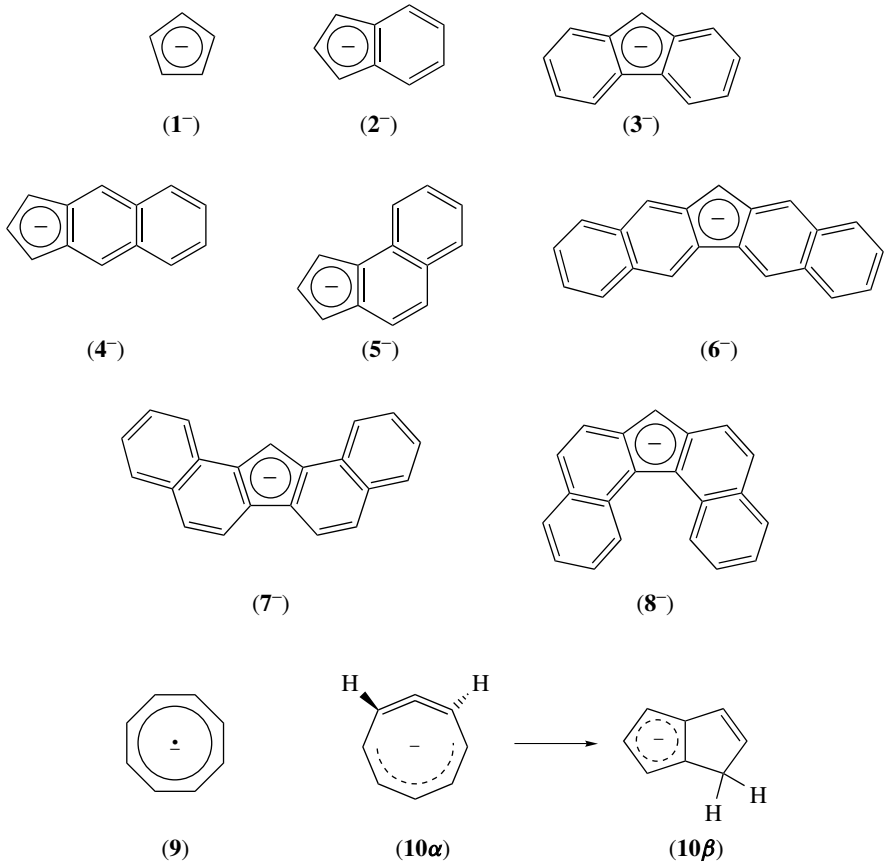
MO Calculations

Regular trends in gas-phase C−H acidity have been interpreted by considering the conversion of a neutral molecule into a hydrocarbon carbanion to occur in two steps, each contributing to ΔE_{deprot}.[1] Initial C−H cleavage, to form the hypothetical carbanion with all nuclei in the same position as in the parent hydrocarbon [characterized by the $^1J(^{13}\text{CH})$ coupling constant], is followed by reorganization (E_{relax}) to achieve optimal distribution of electron density. The AM1 approximation has been used to calculate the CH deprotonation energies, and the relaxation energies and correlations between ΔE_{deprot} and $^1J(^{13}\text{CH})$ and E_{relax} have been obtained. For strained ring systems the principal contribution to ΔE_{deprot} is derived from the first process.

Very high level *ab initio* [CCSD(T)//MCSF] calculations have been applied to singlet and triplet cyclopropenyl anion and cyclopropenyl radical. The anion ground state, a singlet with C_s symmetry, is destabilized relative to cyclopropyl anion as expected for an antiaromatic structure; it is stabilized, with respect to its conjugate acid and the corresponding radical, by electron-withdrawing substituents such that 1,2,3-tricyanopropene has a predicted pK_a of 10–15.[2]

Ionization potentials calculated for cyclopentadienide ions ($\mathbf{1}^- - \mathbf{8}^-$) by a semi-empirical molecular-orbital method (AM1) correlate with the observed electron

affinities for (**1**•), (**2**•), and (**3**•) in the gas phase; the stability increases in the order ($\mathbf{1}^- < \mathbf{2}^- < \mathbf{4}^- < \mathbf{3}^- < \mathbf{5}^- \approx \mathbf{6}^- < \mathbf{7}^- < \mathbf{8}^-$), in broad correlation with the number of condensed aromatic rings present and the consequent charge delocalization.[3] However, the stability for single-electron oxidation in DMSO increases in the sequence ($\mathbf{4}^- < \mathbf{3}^- < \mathbf{6}^- < \mathbf{2}^- < \mathbf{5}^- < \mathbf{7}^- < \mathbf{1}^- < \mathbf{8}^-$), there being no simple correlation with structure. It has been concluded that charge delocalization on to the larger cyclopentadienide ions may decrease the stabilizing solvation effects; however, frontier orbital considerations reveal that the essential stability of each cyclopentadienide ion depends on the structure itself.



(**1**$^-$) (**2**$^-$) (**3**$^-$)

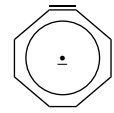
(**4**$^-$) (**5**$^-$) (**6**$^-$)

(**7**$^-$) (**8**$^-$)

(**9**) (**10**α) (**10**β)

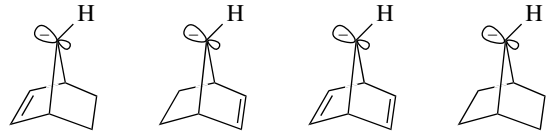
Deprotonation energies for 9-substituted fluorenes, calculated using AM1 semiempirical MO theory, correlate linearly with acidities determined experimentally for these heteroatom-substituted compounds.[4]

Anions (**9**), (**10**α) and (**11**) derived from cycloctatetraene have been studied using the selected ion flow tube technique and MO calculations, as a continuation of previous work on the structures and energetics of eight-membered-ring species, C_8H_n and



(**11**)

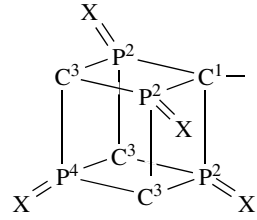
$C_8H_n^-$ ($n = 6, 7, 8$).[5] A novel collision-induced isomerization of $C_8H_7^-$ (**10α**), which has a strained allenic bond, to (**10β**) has been reported to occur upon SIFT injection of (**10α**) at elevated kinetic energies (KE) and collision with helium. In contrast, radical anions (**9**) and (**11**) undergo electron detachment upon collisional excitation with helium. Bimolecular reactions of the ions with NO, NO_2, SO_2, COS, CS_2, and O_2 have been examined. The remarkable formation of CN^- on reaction of (**11**) with NO has been attributed to cycloaddition of NO to the triple bond followed by eliminative rearrangement.



(**12**) (**13**) (**14**) (**15**)

High-level *ab initio* calculations have provided more precise structural details, and relative stability estimates, for members of the 7-norbornyl anion series (**12–15**).[6] Far from being classical carbanions, each of the ions is stabilized by delocalization of the negative charge into accessible LUMOs of anti-parallel C−C bonds of the molecular framework and each is more stable than methyl carbanion. Consequently, it is unlikely that solution studies of the unsaturated systems will reveal any bishomo-antiaromatic character.

Computational estimates of the gas-phase deprotonation energies of tetraphosphacubane (**16a**) and its tetraoxide (**16b**) and tetrasulfide (**16c**) at MP2/6–31 +



(**16**)

a; X = lone pair
b; X = O
c; X = S

$G^*//MP2/6-31+G^*$ levels have been reported.[7] Upon deprotonation, the distance between the carbon formally carrying the negative charge [C(1)] and the neighbouring P atom shortens dramatically and changes in the angles suggest increased strain in the molecules. However, P−O and P−S distances, including those distant from C(1), are longer in the anions than in the neutrals and suggest that charge is delocalized from C to P in (**16a**) and on to O and S in (**16b**) and (**16c**), respectively. For (**16a–c**) the DPEs calculated (382.8, 320.2, and 328.9 kcal mol^{-1}, respectively) are remarkably small and compare with respective values for methanol, *p*-nitrobenzoic acid and HBr. Thus, DPE for phosphacubane (**16a**) is 21 kcal mol^{-1} less than for cubane as a consequence of the high *s* character of the hybrid orbital on C, combined with significant charge delocalization on to each P atom. A through-space interaction between the anionic centre and the P, P=O or P=S across the cube transfers electron density to the remote acceptor, as reflected in the contraction of this body diagonal distance which is most pronounced in the case of the oxide.

The semiempirical AM1 MO method has been used to calculate heats of formation of a series of *m*- and *p*-substituted benzene and toluene derivatives ArY and $ArCH_2Y$, and their phenyl or benzyl cations, anions, and radicals;[8] heterolytic and homolytic bond dissociation energies (BDEs) and electron transfer energies for the ions have also been calculated and the relationship $\Delta H_{het} = \Delta H_{ET} + \Delta H_{homo}$ has been confirmed (it being noted that ΔH_{homo} is insensitive to ring substituents). The linear relationship found between ΔH_{het} and the appropriate HOMO or LUMO energies of phenyl, benzyl or Y ions is in keeping with the principle of maximum hardness.

MP2 perturbation theory applied in a theoretical study of C_2H_3OLi, CH_2=CH(OLi), CH_3(C=O)Li and CH_2=C(OH)Li (a model of unsaturated α-lithio ether) has revealed that mutation between the three different isomer types is almost impossible.[9]

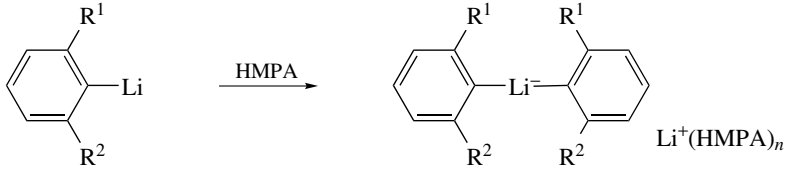
Organolithiums

The lithium ion pair pK scale has been extended to 25 indicators with a pK range of 9.7–24.4 and compared with the corresponding caesium scale and with ionic pKs in DMSO and aqueous DMSO.[10] Caesium ion pair acidities measured for several sulfones reveal that cyclopropyl phenyl sulfone is less acidic than isopropyl phenyl sulfone and that the sulfone group prevents significant delocalization of carbanion charge into the phenyl ring on ionization of substituted methyl phenyl sulfones.[11]

The caesium enolate of *p*-phenylisobutyrophenone (CsPhIBP) in THF has been found to be more highly aggregated and much more basic than the corresponding lithium ion pair; the average aggregation number of CsPhIBP at 10^{-3} M is now estimated to be 3.2, much greater than the value of 2.2 reported earlier.[12] Previous interpretations of alkylation kinetics have consequently been revised in favour of ion pair monomer rather than free enolate ion reactions. The rate laws for alkylation reactions of LiPhIBP at 25 °C in THF at concentrations of 10^{-3}–10^{-2} M are of order 0.5–0.3 in the formal lithium enolate concentration but of first order in monomer, which remains the reactive species even though tetramer contact ion pairs have been found to dominate the equilibrium.[13]

Millimetre/submillimetre spectroscopy has been used to determine the geometric parameters of highly reactive, solvent-free, monomeric CH_3Li for the first time.[14] The isotopomers $^{12}C^1H_3{}^7Li$, $^{12}C^2H_3{}^7Li$, and $^{12}C^1H_3{}^6Li$, were also studied so as to determine independently values for C−M and C−H bond lengths and HCH bond angle θ. The C−Li distance (1.959 Å) and C−Na distance (2.299 Å) are the shortest known for organolithium and organosodiums, and the respective small HCH angles (106.2 and 107.3°) agree with results of *ab initio* calculations.

A variety of localized lithiated carbanions, such as aryllithiums and sulfur- and silicon-substituted alkyllithiums, have been found, by application of ^{13}C, ^6Li, and ^7Li NMR techniques, to form triple ions in THF–HMPA solution.[15] Thus, change to triple ion structures (**18a–g**) could be discerned as HMPA (2–5 equiv.) was added to solutions of monomeric structures (**17a–g**) in 4:1 THF–diethylether. The amount of triple ion is sensitive to *ortho* substitution; monomeric (**17a**) and (**17b**) form 65–80% triple ion in presence of 1–3 equiv. HMPA whereas (**17c**) and (**17e**) form less than 20% at 5 equiv. HMPA. Pyridylthio-substituted carbanion (**19**) forms bis-chelated triple ion (**20**).

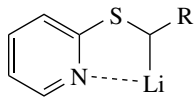


(**17**)

a; $R^1 = R^2 = Pr^i$
b; $R^1 = R^2 = Me$
c; $R^1 = R^2 = H$

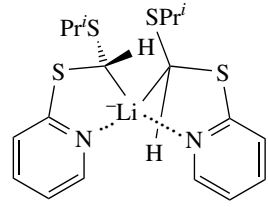
(**18**)

d; $R^1 = R^2 = OMe$
e; $R^1 = Me$, $R^2 = H$
f; $R^1 = OMe$, $R^2 = H$
g; $R^1 = OCH_2OMe$, $R^2 = H$



(**19**)

a; $R = SPr^i$
b; R = H
c; R = SMe
d; R = SPh
e; $R = SC_6H_3\text{-}3,5(CF_3)_2$



(**20**)

$Li^+(HMPA)_4$

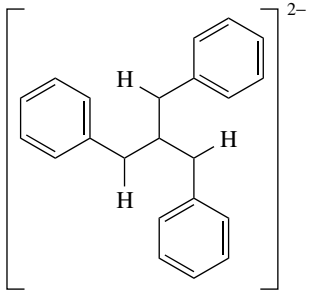
A further study of the aggregation state of PhLi in etheral solvents has resolved signals for the *ipso* carbon which firmly establish the tetramer and dimer structures in diethylether, and the dimer and monomer structures in THF.[16] The effects of polar additives such as THF, DME, dioxolane, 2,5-dimethyltetrahydrofuran, TMEDA, PMDTA, HMTTA, HMPA, DMPU, and 12-crown-6 to solutions of PhLi in diethylether and/or THF have been studied by low-temperature multinuclear techniques.

1,2- versus 1,4-regioselectivity of lithiated phenylacetonitrile towards α,β-unsaturated carbonyl compounds has been interpreted in terms of monomer–dimer equilibria (dependent on solvent dielectric constant) between ion pairs in solution.[17,42] The lithiated monomer is believed to have a lithium bridged structure, as evidenced by IR and ^{13}C NMR and supported by *ab initio* calculations.[17]

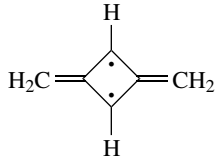
The crystal and solution structures of a range of *N*-lithio-α-aminonitrile anions have been characterized and the effects of association on the transition state for 1,4-addition of enantiopure lithiated α-aminonitriles to Michael acceptors have been discussed.[18]

Aromatic and Other Delocalized Anions

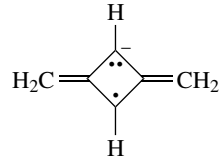
NMR study of tribenzylidenemethane dianion (**21**) (and its derivative having *m*,*m*′-dimethyl substitution on one ring) has established that the benzylic positions are ca $sp^{2.5}$ hybridized and that only ca 50% of the net charge (2−) remains on the Y-frame carbons.[19] Thus, the benzylic bonds have gained double bond character due to $p-\pi$ conjugation and charge delocalization on to the rings. Rotation about the Y-bonds is fast on the NMR time-scale and it has been reasoned that the Y-bonds are weaker than the benzylic bonds; this is therefore inconsistent with a through-the-center delocalization of Y-shaped dianions. Minimization of electrostatic repulsions between the three lone pairs by distribution of the extra charge to the 'corners' seems to be the origin of the remarkable stability of trimethylenemethane dianion and its derivatives.



(**21**)



(**22**)



(**23**)

The solid aromatic dianion salt of 1,2-di-[^{13}C][8]annulene has not been found to scramble the ^{13}Cs even on heating to over 600 °C for 2 hs.[20] This behaviour of the cyclooctatetraene dianion is in contrast with that of neutral aromatic systems, which readily automerize in the gas phase. Apparently, when sufficient energy is applied

to overcome the lattice energy of the dianion, the expected carbene intermediate is formed but the larger electron–electron repulsion energy of the contracted ring induces electron transfer back to the metal.

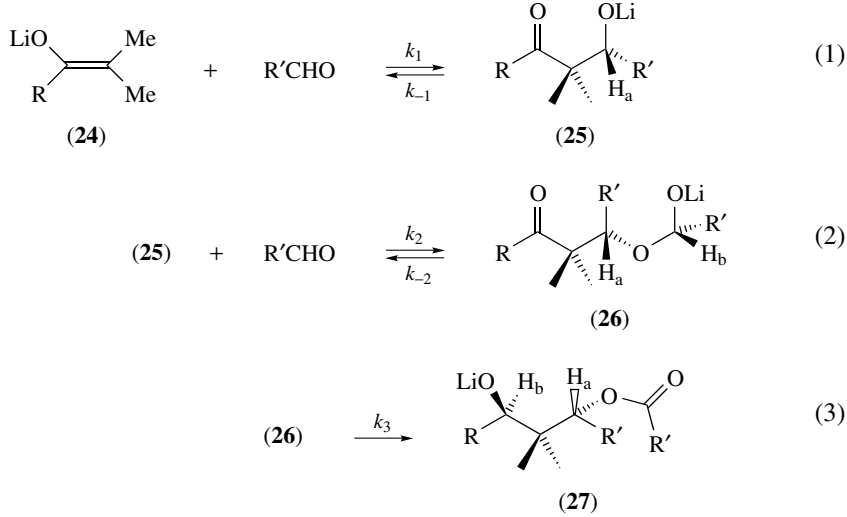
The non-Kekulé-benzene negative ion (**23**), generated in the gas phase, has been found to display characteristic radical- and carbanion-type reactivity including adduct formation with NO, COS, and CO_2, S-atom abstraction from CS_2, and thiomethyl group abstraction from CH_3SSCH_3.[21] Results of density functional calculations of the structures and energies of (**23**) and the corresponding biradical (**22**) carried out at the B3LYP/6–31+G* level are in good agreement with results of experimental and theoretical thermochemistry.

Carbanion Reactions

Enolates and Related Species

Catalysed enantioselective aldol additions of latent enolate equivalents have been reviewed[22] and electronic effects of the aldehyde component on such reactions of trichlorosilylenolates of cyclopentanone and cycloheptanone, catalysed by chiral phosphoramides, have been interpreted[23] in terms of initial aldehyde coordination to the trichlorosilyl enolate and aldolization via a six-membered boat-like transition state.

The mechanism of the aldol–Tishchenko reaction has been probed by determination of kinetics and isotope effects for formation of diol–monoester on reaction between the lithium enolate of *p*-(phenylsulfonyl)isobutyrophenone (LiSIBP) and two molecules of benzaldehyde.[24]. The results are consistent with the formation of an initial lithium aldolate (**25**) followed by reaction with a second aldehyde to form an acetal (**26**), and finally a rate-limiting intramolecular hydride transfer (Tishchenko



(1)

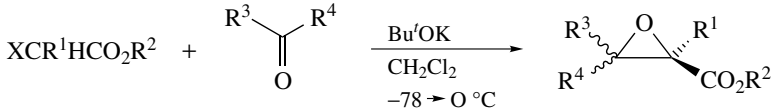
(2)

(3)

SCHEME 1

reaction). Theoretical kinetic and equilibrium isotope effects, based on *ab initio* molecular orbital calculations, are in agreement with those determined experimentally using benzaldehyde-*d*, for which $KIE_{ob} = 2.0$ reflects both the true KIE of eq. 3 and the equilibrium isotope effect of eq. 1 and 2.

Darzens reaction of (−)-8-phenylmethyl α-chloroacetate (and α-bromoacetate) with various ketones (Scheme 2) yields *cis*-glycidic esters (**28**) with high geometric and diastereofacial selectivity which can be explained in terms of both open-chain or non-chelated antiperiplanar transition state models for the initial aldol-type reaction; the ketone approaches the *Si*-face of the *Z*-enolate such that the phenyl ring of the chiral auxiliary and the enolate portion are face-to-face.[25] Aza-Darzens condensation reaction of *N*-benzylideneaniline has also been studied. Kinetically controlled base-promoted lithiation of 3,3-diphenylpropiomesitylene results in *E* : *Z* enolate ratios in the range 94:6 (lithium diisopropylamide) to 50:50 (BuLi), depending on the choice of solvent and temperature.[26]



(**28**)

SCHEME 2

The mechanism of reaction between barbiturate and 1,3-dimethylbarbiturate ions with *o*-nitro-, *p*-nitro-, and 2,4-dinitrobenzaldehyde has been explored;[27] rate dependence on solvent viscosity is indicative of involvement of a diffusion-controlled proton transfer in the rate-determining step at pH 2–4. Unexpected values of Brønsted α for the acid-catalysed process have been explained.

The relative reactivities of the enolate ions of acetophenone and 2-acetylnaphthalene towards phenyl radicals have been explored in order to determine their suitability as electron donor initiators of $S_{RN}1$ reactions of enolate ions of 2-acetylthiophene and 2-acetylfuran with aryl halides PhI.[28]

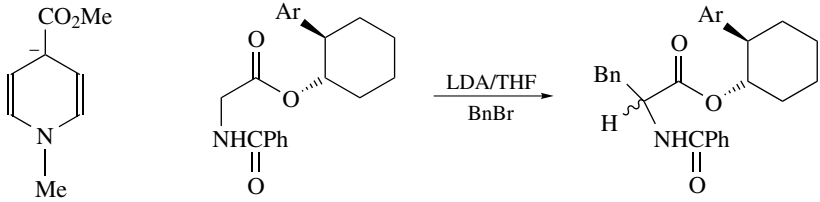
A chair-like amino–zinc–enolate transition state has been used to explain how substituents on the ring affect the diastereoselective and enantioselective formation of polysubstituted pyrrolidines during intramolecular amino–zinc–enolate carbometallation reactions.[29]

Products of ethylation and methylation of enolates of cycloalkane-1,3-diones with ring sizes 7–10 have been studied under a variety of alkylating reagent–solvent systems.[30] Decrease in the *O*/*C* alkylation ratios with increase in ring size is believed to be a consequence of greater steric strain in the conjugated enolate resonance contributor and consequent diminution in the proportion of *O*-attack.

Fluorination of the sodium enolate of 2-methyl-1-tetralone by (−)-*N*-fluoro-2,10-(3,3-dichlorocamphorsultam) gives (*S*)-(+)-2-fluoro-2-methyl-1-tetralone in 70% *ee*, which corresponds to the opposite asymmetric induction to that achieved using non-racemic (camphorsulfonyl)oxaziridines as closely related hydroxylation reagents.[31]

The mechanism of nitrosation of $MeCOCH_2^-Na^+$ with MeONO to give MeCOCH=NOH has been studied by HF and MP3 *ab initio* methods;[32] pericyclic rearrangement of first-formed adduct gives an intermediate complex, $[MeCOCH_2NO(OMe)]^-\ Na^+$, from which the product is obtained by antiperiplanar elimination of MeOH.

It has been shown that a complete shift in stereochemistry of the nucleophilic reactions of (**29**), with alkyl halides such as 2-bromobutane or *cis*-2-bromomethoxycyclohexane, from racemization to complete inversion, is induced by increase in the inner-sphere stabilization of the transition state from 0 to 3 kcal mol^{-1}.[33] This has been ascribed to competition between inner-sphere S_N2 and outer-sphere electron-transfer processes; the former being extremely sensitive towards inner-sphere stabilization.



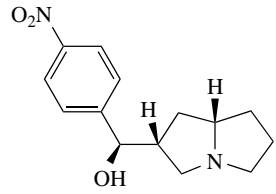
(**29**) (**30**) (**31**)

A further attempt has been made to develop a predictive model for chirality transfer achieved through alkylation reactions of ester enolates which feature chiral auxiliaries.[34] Hippurate esters (**30**) derived from (1*R**,2*S**)-*trans*-2-(*p*-substituted phenyl)cyclohexanols were found, on reaction with benzyl bromide, to give (**31**) with predominantly the *S** configuration at the alkylation centre but with no correlation between the degree of stereoselectivity (20–98%) and the electron density on the aromatic ring.

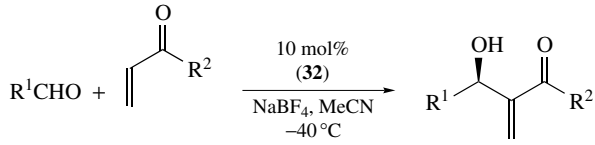
Diastereoselectivity in the aldol and the conjugate additions of 2′-hydroxy-1,1′-binaphthyl ester enolates with a variety of carbonyl electrophiles has also been explored;[185] the tendency of the ester enolates, generated by BuLi, to react with aldehydes to give *threo* products preferentially with high diastereoselectivity has been interpreted in terms of an acyclic transition state of chelated lithium enolate involving the aldehyde carbonyl and the 2′-hydroxy group.

Nucleophilic addition of ester-derived enolate to the bicyclo[3.3.0]octan-2-one system of diacetone glucos-3-ulose usually occurs at the convex β-face of the carbonyl (as for other nucleophiles), except for senecioate-derived enolate (from 3-methyl crotonate) for which α-attack in diethylether solvent is in contrast to the β-face attack in THF;[36] the reason for this anomalous behaviour is not clear.

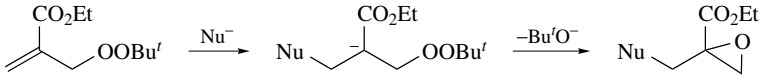
The Baylis–Hillman reaction (Scheme 3) of ethyl vinyl ketone with electron-deficient aromatic aldehydes (e.g. where $R^1 = o\text{-}NO_2C_6H_4$), in MeCN or EtCN solution, has been found to proceed enantioselectively in presence of catalytic base (**32**) derived from proline.[37] The Michael adduct formed between the catalyst and the vinyl



(**32**)

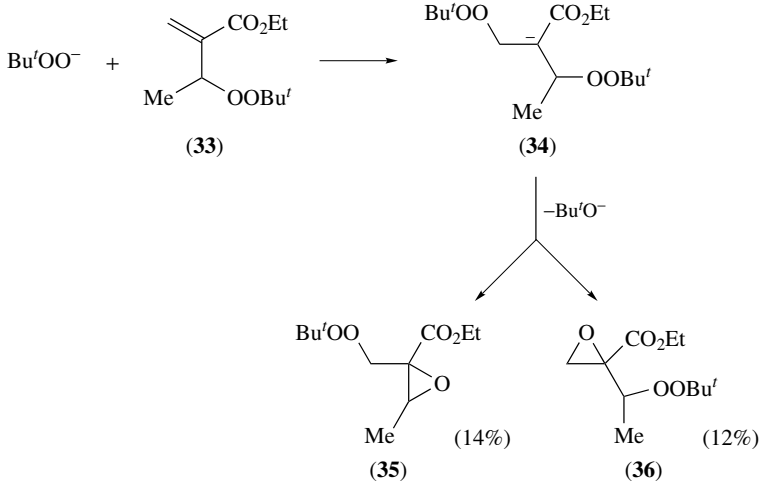


SCHEME 3



[$Nu^- = {}^-CH(CO_2R)_2$]

SCHEME 4

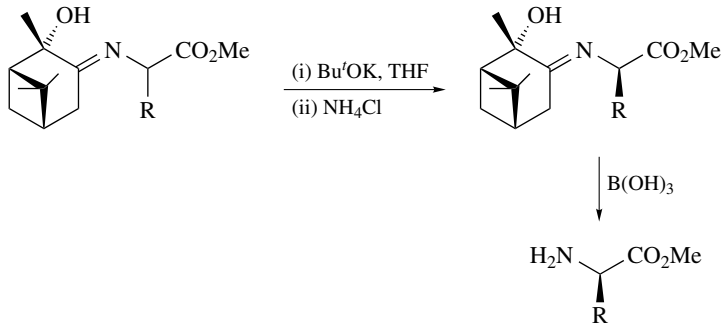


ester is believed to be directed in its nucleophilic attack on the aldehyde as a consequence of metal ion bridging between the aldehyde carbonyl group and the 2′-hydroxyl group of the catalyst.

A study of the anion-induced decomposition of 2-ethoxycarbonyl prop-2-enyl peroxides has established that epoxides so formed arise (Scheme 4) through (i) addition of the nucleophile to the acrylic unsaturated bond and (ii) intramolecular anionic

substitution on the peroxidic bond.[38] The formation of two peroxy epoxides, (**35**) and (**36**), on addition of Bu^{t}OOK to peroxide (**33**) is consistent with competing S_Ni reactions of a carbanion intermediate (**34**) in this two-step process.

Potassium enolates derived from the chiral Schiff bases obtained by reaction of racemic α-amino esters with 2-hydroxypinan-3-one undergo diastereoselective protonation, as evidenced by release of optically active α-amino esters on subsequent cleavage of the imine (Scheme 5).[39]



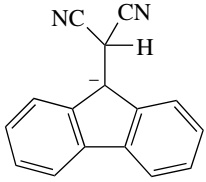
SCHEME 5

Nucleophilic addition of phenolic nucleophiles to 1,1-dicyano-2-arylethenes in the gas phase and in water has been studied theoretically[40] using the semiempirical AM1 method and the Cramer–Truhlar solvation model SM2.1. The difference between the Brønsted coefficients ($\alpha^n = 0.81$ and $\beta^n = 0.65$) determined for the gas-phase reaction is indicative of a small positive transition state imbalance of $I = 0.16$. For reaction in water the estimates ($\alpha^n = 0.61$ and $\beta^n = 0.36$, giving $I = 0.25$) are close to the experimental values ($\alpha^n = 0.55$ and $\beta^n = 0.35$) obtained with amine bases, and the small imbalance is as expected for a reaction involving no hybridization change at the incipient carbanion site.

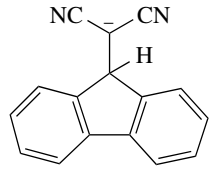
The fluorenide anion (**37**), which is thermodynamically much less stable than its isomer (**38**), 9-fluorenylmalononitrile carbanion, has been generated for the first time by a hydride transfer from 1-benzyl-1,4-dihydronicotinamide to (**39**), in dry acetonitrile; quenching of (**37**) with CH_3CO_2D gave 9-*d*-fluorenylmalononitrile (**40**). [41] Furthermore, salt (**41**) gave (**42**) and (**44**) on prolonged heating at 60 °C.

Benzylideneacetone reacts with lithiated phenylacetonitrile under kinetic control, in THF and media that favour association, to give 1,2- and 1,4-adducts in proportions which are directly related to concentrations of monomeric and dimeric ion pair species, respectively.[42] An attempt has been made to explain the different regioselectivities towards α,β-unsaturated carbonyl compounds, including cyclic α-enones and cinnamaldehyde, in terms of intermediate complex formation.

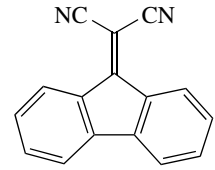
Results of an investigation of the structure of lithiated α-aminonitriles have been used to aid interpretation of the diastereofacial preference found for reaction of their chiral counterparts with Michael acceptors.[18]



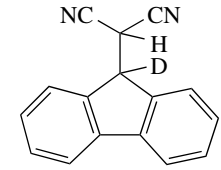
(**37**)



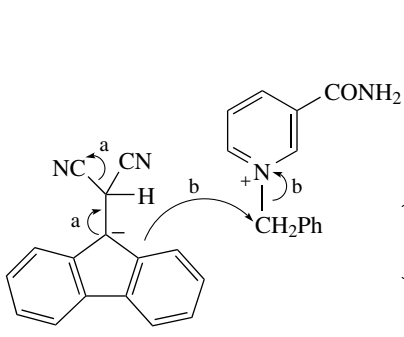
(**38**)



(**39**)



(**40**)



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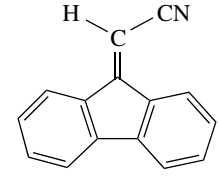
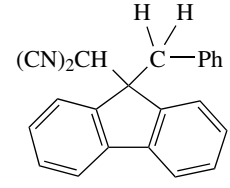
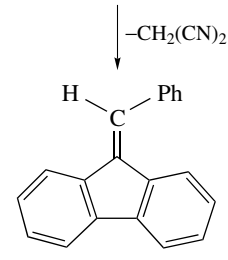


(**42**)

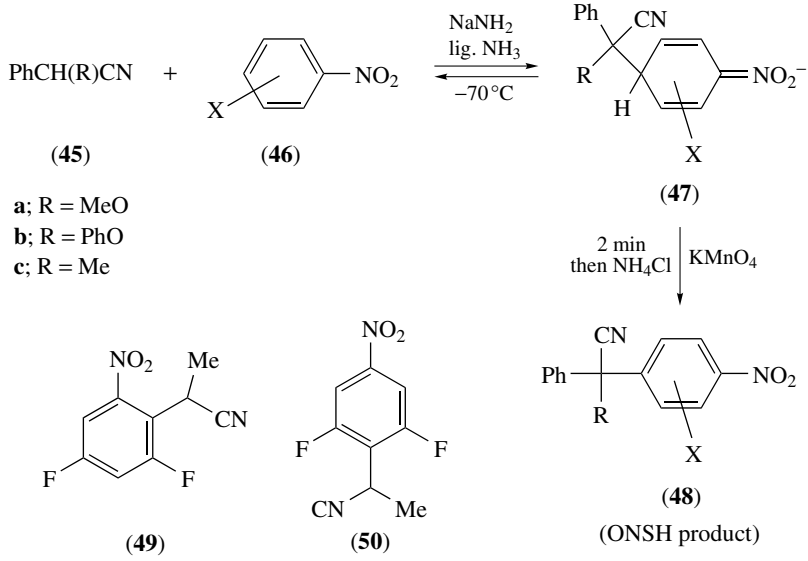


(**43**)



(**44**)

Reactions of nitrobenzenes with tertiary carbanions, generated from α-substituted phenylacetonitriles (**45**) in liquid ammonia, to give competing products of oxidative nucleophilic substitution of hydrogen (ONSH) or vicarious nucleophilic substitution (VNS) have been found to depend strongly on the nature of the leaving group on the carbanion.[43] Carbanions from (**45a**) and (**45b**) react with $PhNO_2$ predominantly to form the ONSH product (**48**); in contrast, 2-chloropropionitrile fails to react with $PhNO_2$, or even the very electrophilic 3,5-difluoronitrobenzene, via an oxidative pathway in absence of $KMnO_4$ but forms a moderate yield of VNS products (**49**) and (**50**).



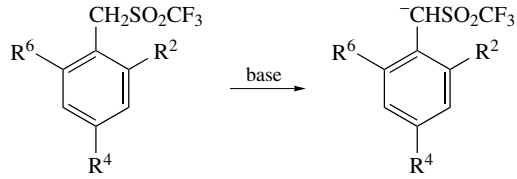
The ONSH reaction of the carbanion of 2-phenylpropionitrile (**45 c**) with nitrobenzene in liquid ammonia at −70 °C involves rate-limiting C_{arom}−H bond breaking, as evidenced by the 9.8 times faster rate than for reaction of the analogous substitution of deuterium in 4-*d*-nitrobenzene and perdeuterionitrobenzene.[44] Reactions of the carbanion derived from (**45c**) with 4-chloro-3-trifluoromethylnitrobenzene and 4-chloronitrobenzene in toluene under phase transfer catalysis has also been studied.[45]

Novel episulfone substitution and ring-opening reactions via α-sulfonyl carbanion intermediates have been reviewed.[46]

Kinetic, thermodynamic and NMR approaches have been applied in a study of the ionization of benzyltriflones in Me_2SO and H_2O–Me_2SO mixtures.[47] The high intrinsic Marcus reactivities for deprotonation of (**51a–e**) and the enhancement of acidity (in contrast to the effect on acidity of arylnitromethanes) on going from hydroxylic solvents to Me_2SO indicate that, in solution, the anionic charge [at least for unsubstituted (**51a**)] resides predominantly on C_α; stabilization by the SO_2CF_3 group is a consequence of polarization effects rather than of conjugative $d-p$ π-bonding or negative hyperconjugation. This is not in agreement with earlier crystal structures or with results of high level *ab initio* gas-phase studies.

Hydrolysis of 2,2,2-trifluoroethanesulfonyl chloride has been found to proceed via intermediate sulfene ($CF_3CH{=}SO_2$) formed by $E1cB$ reaction.[48] At pH 1.8–5.0 the $(E1cB)_{irr}$ mechanism applies, whereby water and hydroxide ion act, respectively, as the carbanion-forming base at low and high pH extremes. The $(E1cB)_{rev}$ reaction applies in dilute acid and is accompanied by the expected H–D exchange of substrate protons when D_2O is used as solvent.

Hammett correlations of effects of substituents (R) on dehydrochlorination of 2-chloroethylsulfones p-$RC_6H_4SO_2CH_2CH_2Cl$ and p-$RC_6H_4SO_2CH_2CHClPh$ with



(**51**) (**52**)

a; $R^2 = R^4 = R^6 = H$

b; $R^2 = R^6 = H$, $R^4 = CN$

c; $R^2 = R^6 = H$, $R^4 = NO_2$

d; $R^2 = R^4 = NO_2$, $R^6 = H$

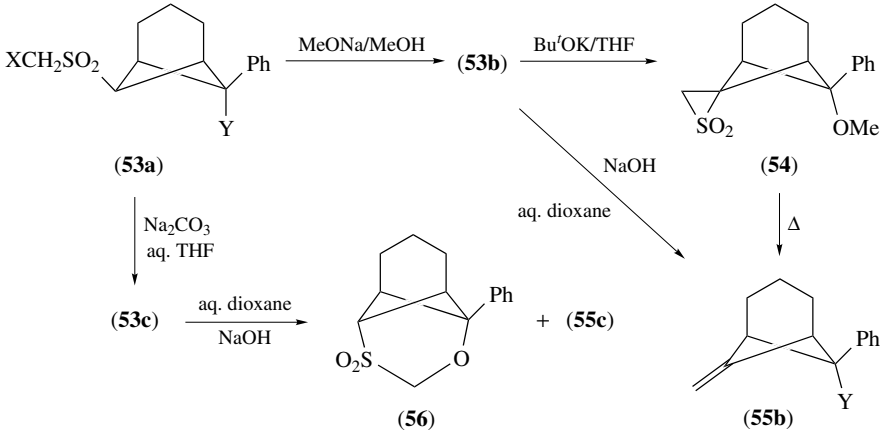
e; $R^2 = R^4 = R^6 = NO_2$

Et_3N suggest that both reactions proceed via carbanion formation, to give the corresponding aryl vinyl and aryl styryl sulfones, respectively.[49]

α-Sulfonyl carbanion intermediates have been proposed to account for the series of transformations of 6-halomethylsulfonyl-substituted bicyclic[3.1.1]heptanes (**53**) depicted in Scheme 6.[50]

Dimethylcarbonate, in presence of K_2CO_3, has been found to react with benzyl aryl and alkyl aryl sulfones RCH_2SO_2Ar at 180–210 °C to form the corresponding mono-*C*-methyl derivative selectively and in high yield.[51] The monomethylation has been attributed to a methoxycarbonylation-methylation-demethoxycarbonylation sequence via $ArSO_2C(Me)(CO_2Me)R$.

Carbanions of chloromethyl aryl sulfone (Ar = Ph or *p*-tolyl) in DMSO–Bu^{t}OK react with 9,10-anthraquinone by vicarious nucleophilic substitution or addition to the



X = Br, **a**; Y = Br, **b**; Y = OMe, **c**; Y = OH

SCHEME 6

carbonyl group; the VNS reaction is favoured by strong electron-donor substituents on the anthraquinone.[52]

The favourable effect of lithium bromide on facial enantioselective protonation of methyl tetralone enolate by α-sulfinyl alcohols has been attributed to coordination of lithium to both enolate and sulfinyl alcohol followed by competition between diastereomeric paths involving intramolecular proton transfer; the proposed transition-state model is supported by results of PM3 semiempirical calculations.[53]

High levels of *syn*-diastereoselectivity have been achieved on reaction of lithiated chiral phosphine oxides [apparently existing as rapidly equilibrating diastereomeric lithiated species such as $RCH(Me)CHLiP{=}O(Ph)_2$] with electrophilic ketones, esters or Me_3SiCl.[54]

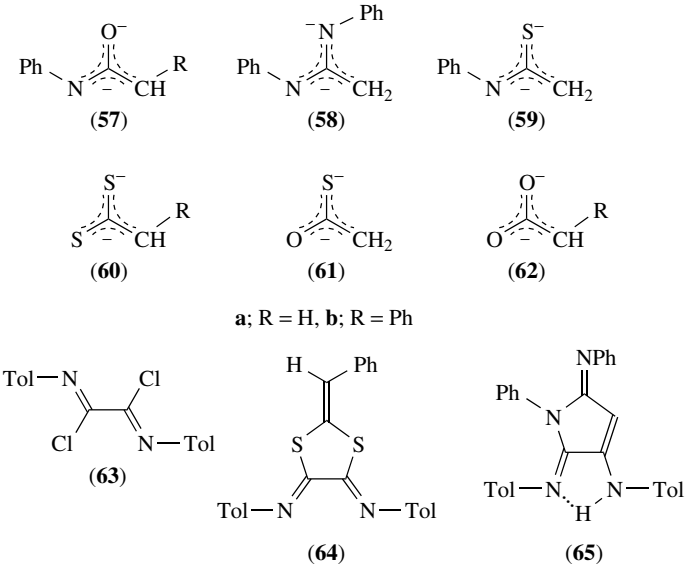
A double S_N2 reaction, which proceeds via a Favorskii-like cyclopropanone intermediate, has been proposed to account for the novel stereoretentive replacement of NO_2 by OH on reaction of α-nitro ketones (which must bear an acidic hydrogen at the α'-position) with aqueous base.[55]

Heteroatom-stabilized Species

The generation and reactions of non-stabilized α-aminocarbanions has been reviewed.[56] and developed further in the case of bis(α-aminocarbanions) which can be trapped by a variety of electrophiles.[57]

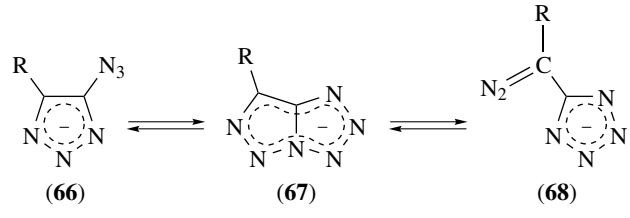
Imidazolines bearing *t*-butoxycarbonyl groups on both nitrogen atoms have been used as acyl anion equivalents; thus, electrophilic trapping of the conjugate base at C(2) can be followed by acid cleavage of the imidazolidine ring to give the deprotected carbonyl product.[58]

The effect of the heteroatoms of the Y-shaped ambident dianions (**57**–**62**) on regiochemistry of their cyclization reactions with oxalic acid dielectrophiles (**63**) has been

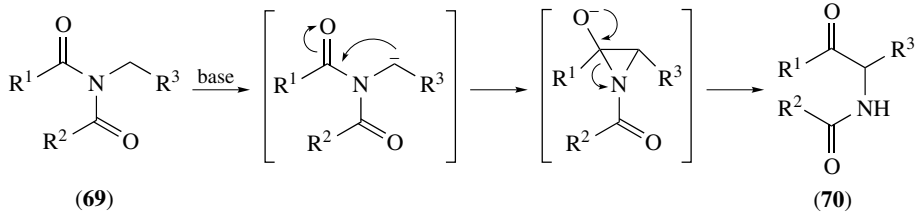


explored.[59] The most nucleophilic centre (the carbon centre which is deprotonated last on carbanion formation) is usually involved in cyclization, although sulfur may compete. The cyclization modes adopted by (**57, 58, 59, 60b, 61**, and **62**) are *C*,*N*, *C*,*N*, (*C*,*N* and *S*,*N*), *S*,*S*, *S*,*O* and *C*,*O*, respectively; thus (**60b**) formed (**64**) whereas (**58**) formed (**65**).

The scope of the rearrangement reaction whereby azido-1,2,3-triazolide ion (**66**) is converted to the (diazomethyl)tetrazolide ion (**68**) has been studied.[60] Where R = H, substituted phenyl, Me, and CO_2Me the reaction proceeds at a rate which is largely independent of substituent; extensive decomposition is observed where R = COMe, COAr, and CN. PM3 calculations used to explore the energy profile of the reaction pathway indicate that the order of anion stability is (**67**) < (**66**) < (**68**) and that the rearrangement is of the type (**66**) $\rightleftarrows$ (**67**) $\rightarrow$ (**68**) for which k_2 and $k_{-1} \gg k_1$.



(**66**) (**67**) (**68**)



(**69**) (**70**)

Crossover experiments have been used to establish that the novel N to C acyl migration reaction of acyclic imides (**69**), to give α-amino ketones (**70**), proceeds by intramolecular reaction of the base-generated carbanion.[61]

Comparison of rates of Brook rearrangement of β-substituted α-silyl allyl alcohols as a means of estimating the α-carbanion stabilizing ability of heteroatom substituents suggests that PhS is much more stabilizing than Me_3Si.[62]

Phosphorus ylides have been reviewed[63] and an intermediate betaine lithium salt adduct (stabilized by complexation with lithium ions and by the chelating effect of pyridyl ligands) has been observed spectroscopically for the first time during the course of a Wittig reaction.[64]

The preferential formation of (*E*)-alkene on Wittig reaction of phenyl 3-pyridyl ketones (bearing an oxazole carboxamide group at the *p*-position of the phenyl ring) with $Ph_3P{=}CH(CH_2)_4CO_2^-K^+$ has been attributed to interaction between the amide (rather than oxazole) moiety and the carboxyl terminus during oxaphosphetane formation.[65]

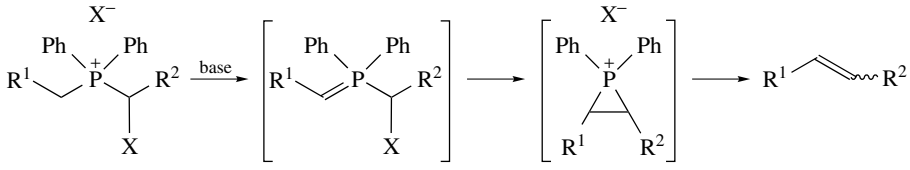
The results of *ab initio* (HF and MP2) and MNDO-PM3 molecular modelling of the Wittig reaction of unstabilized ($Me_3P{=}CHMe$), semistabilized ($Me_3P{=}CHC{\equiv}CH$) and stabilized ($Me_3P{=}CH{-}CN$) ylides with ethanal have been compared with experimental findings.[66]

A high-level quantum chemical exploration of the Horner–Wandsworth–Emmons reaction has indicated that ring closure of the P–O bond (which favors formation of *E*-product) is rate determining in the gas phase and that the C–C bond-forming addition step is rate determining in most solvated systems;[67] several effects that could account for the *E*/*Z* selectivities observed have been identified.

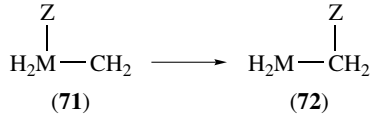
Asymmetric addition of phosphonate [$RCH_2PO(OEt)_2$] to 4-substituted cyclohexanones has been promoted by chiral ligand additives with preferential formation of the *Z*-diastereoisomer in high enantiomeric excess.[68]

Stabilized halogenated phosphoylides (haloylides) $Ph_3P{=}CXCO_2Me$ have been prepared, *in situ*, by reaction of $Ph_3P{=}CHCO_2Me$ with the corresponding *N*-halosuccinimide in $CDCl_3$ at $-40\,^{\circ}C$;[69] their application to synthesis of halogenated compounds is being explored.

A phosphonium analogue of the Ramberg-Bäcklund reaction, which exhibits the same *Z*-stereoselectivity, has been used to form stilbenes by the action of amine bases on (α-bromobenzyl)benzyldiphenylphosphonium bromide.[70] The reaction is believed to proceed via a strained *epi*-phosphonium salt (Scheme 7) but the origin of the stereoselectivity is unknown.



SCHEME 7

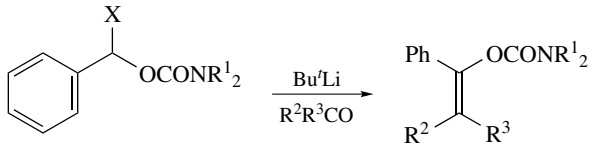


(**71**) (**72**)

M = P, As
Z = H, Me, CH=CH$_2$, SiH_3, GeH_3

A theoretical investigation of the Stephens rearrangement, whereby P and As ylides (**71**) convert to (**72**), has established that the migration mechanism is strongly dependent on the migrating group; concerted migration is predicted for the silyl and germyl groups whereas methyl migration should proceed by radical dissociation–recombination.[71]

The effects of solvent, temperature, and bulk of the silyl and carbamate functionalities on the stereoselectivity of Peterson olefination of silylated benzyl carbamates (Scheme 8) have been described.[72]



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

X = TMS, TBS, TPS

SCHEME 8

1-Silyl homoallylic alcohols are obtained with high γ-regioselection and *E*-stereoselection on reaction of chiral alkoxy- and aminomethyl-substituted α-silylallyl carbanions with aldehydes;[73] factors which influence the diastereomeric excess have been identified.

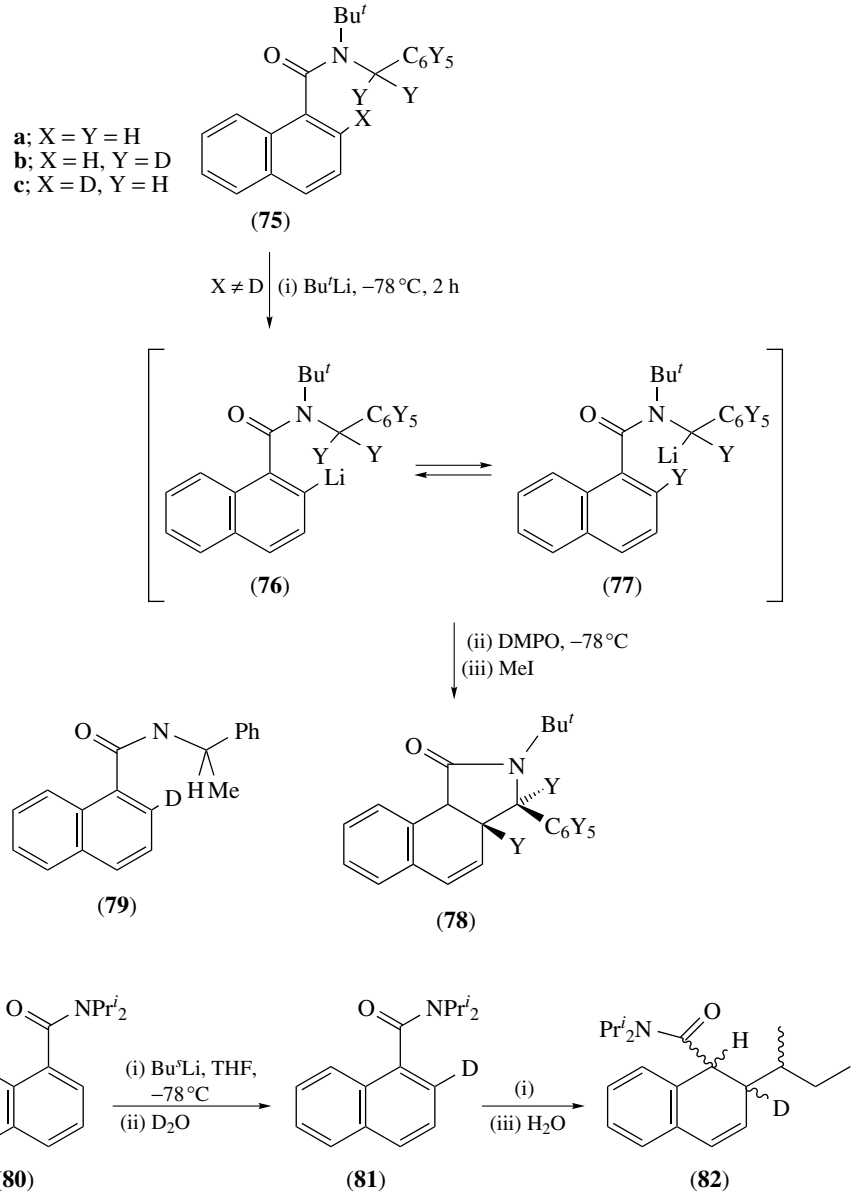
It has been shown that the tetrahedral oxyanion formed on addition of the conjugate base of fluoroform to solvent DMF acts as a masked form of F_3C^- with which to effect trifluoromethylation of aldehydes.[74]

Organometallic Species

Selective lithiation of 1,2,4-tris(trifluoromethyl)benzene, primarily at position 5, by hydrogen/metal exchange reaction with lithium 2,2,6,6-tetramethylpiperidide in diethylether has been reported.[75] Lithiation of 1-(*m*- or *p*-fluorophenyl)pyrroles by BuLi–TMEDA (or BuLi–PMDTA) has been found to occur exclusively *ortho* to the fluorine substituent even though the α-hydrogens of the pyrrole rings are the most acidic in the ground state; theoretical calculations support the view that the regioselectivity is a consequence of the higher kinetic acidity of the hydrogens adjacent to fluorine.[76]

A further investigation of the ortholithiation of anisole has taken advantage of previous spectroscopic evidence of the exclusive formation of disolvated dimers of n-BuLi in TMEDA, combined with rate studies which demonstrate that this combination promotes ortholithiation via $[(\text{n-BuLi})_2((\text{TMEDA})_2(\text{anisole})]^{\neq}$ in pentane.[77] The substantial kinetic isotope effect $[k_{\text{obs(H)}}/k_{\text{obs(D)}} = 20 \pm 3]$ found on comparison of anisole with anisole-d_8 is indicative of rate-determining proton transfer but the unusually high value has not been explained satisfactorily.

The potential synthetic application of anion translocation, whereby an anion (organolithium) formed under kinetic control undergoes an intramolecular proton transfer to form an alternative anion, has been explored.[78] Thus, it has been shown by deuterium labelling that formation of an α-lithiated tertiary naphthamide (**77b**) and thence the product (**78b**) of anion cyclization involves anion translocation following ortholithiation of (**75b**). However, a different result is obtained in the case of (**75c**), for which ortholithiation is disadvantaged by the *ortho*-deuterium isotope effect and (**78**) arises through direct lithiation α- to nitrogen without anion translocation. This interpretation has been confirmed by suppressing cyclization of the intermediate anions (absence of DMPU) and identifying products (**75**; X = Me, Y = D) and (**79**) from alkylation of (**75b**) and (**75c**), respectively, in the presence of MeI.



The regiospecific ortholithiation of 3*H*-naphtho[2,1-*b*]pyrans has also been used to advantage in methylteretifolione B synthesis.[79]

The deuterium kinetic isotope effect has been used to protect the 2-position of (**80**) from deprotonation and thereby force an organolithium to add to the naphthamide ring of (**81**).[80]

The sydnone ring has also been used as an *ortho*-director of lithiation.[81] Thus, on reaction with Bu^{t}Li–TMEDA, 3-phenylsydnone has been found to form a dilithio species which can be regiospecifically acylated at the *ortho*-position by a weak electrophile.

A study of the regioselective lithiation of 1-substituted 1,2,4-triazoles has established that for 1-*n*-alkyl and 1-allyl derivatives monolithiation occurs at ring C(5) whereas 1-propargyl-1*H*-1,2,4-triazole initially undergoes lithiation at the γ-position.[82]

The *ortho*-directing properties of the (aryloxy)tetrazole functionality has been demonstrated for the first time and rapid anionic rearrangement of the resulting lithiated derivative to form 5-(hydroxyaryl)-1-phenyl-1*H*-tetrazoles has been reported.[83]

Enantiocontrol of carbanion reactions of organolithium reagents has been the subject of a short review.[84]

Enantiomeric excesses of up to 76% have been obtained for alkyllithium–aldehyde condensations using 3-aminopyrrolidine lithium amides as chiral auxiliaries.[85] Addition of organolithiums to imines has been achieved with up to 89% *ee*, in the presence of C_2-symmetric bis(aziridine) ligands.[86]

Nucleophilic additions of ethyl-, vinyl-, and ethynyl-lithium and Grignard reagents to a 2-alkyl-substituted cycloheptanone have been found to yield the corresponding *cis*-cycloheptanol preferentially.[87] The selectivity, which increases with size of the nucleophile, has been attributed to a combination of steric repulsions and torsional effects in the transition state. Application of the MM2* force field to analyse nucleophilic attack of hydride and ethynyl lithium on 2-methylcycloheptanone gave results comparable to those obtained experimentally and from *ab initio* calculations.

A reaction scheme involving electron transfer from PhLi to (*E*)-cinnamaldehyde and further reaction of the radical ions formed (and also reaction of dimeric PhLi) has been proposed to account for the four main products of the reaction.[88]

Conjugate addition of RLi to simple alk-2-enoic acids provides a convenient synthesis of branched saturated carboxylic acids.[89]

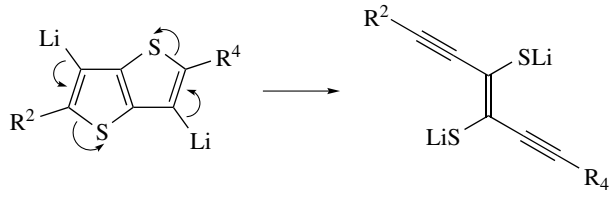
Diastereoselectivities observed for 1,2-additions of carbon nucleophiles, and 1,4-additions of lithium diorganocuprates, to enantiomerically enriched bicyclo[*m*.1.0]alk-3-en-2-ones possessing 8-, 12-, and 15-membered rings have been discussed.[90]

A three-step protocol has been applied to obtain homoallylic carbanions from cyclopropylmethanol derivatives by regioselective opening of intermediate cyclopropyllithiums.[91]

A tandem ring-opening of 3,4- and 3,6-dilithiated thienothiophenes has been used to synthesize polyfunctionalized enediynes (e.g. Scheme 9).[92]

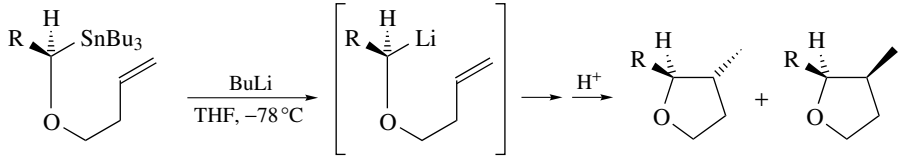
A review entitled 'α-heteroatom-substituted 1-alkenyllithium regents: carbanions and carbenoids for C–C bond formation' has addressed the methods of generation of such species, illustrated the carbenoid reactivity of α-lithiated vinyl halides and vinyl ethers, and emphasized the synthetic potential of the carbanion species in asymmetric synthesis of α-hydroxy- and α-amino-carbonyl compounds.[93]

A domino reaction, whereby up to four equivalents of a nitrile can be added to dilithiated allenes, is believed to proceed via a novel rearrangement.[94]



SCHEME 9

It has been found that enantio-enriched α-(homoallyloxy)alkyllithiums (**84**), formed from the corresponding stannanes (**83**) by stereoretentive transmetallation, cyclize with complete retention of configuration at the lithium-bearing sp^3-carbon to yield enantio-enriched α,β-disubstituted tetrahydrofurans (**85** and **86**).[95] This is consistent with earlier theoretical calculations which suggested that the lithium might coordinate with the olefinic bond in the transition state.



R = $PhCH_2CH_2$

(**83**) (**84**) (**85**) (**86**)

(*R*)–(**83**) (90% *ee*) 88 : 12

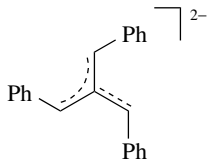
An unexpected elimination of cyclopentadienide anion results on reaction of silacyclohexadienes with an extremely hindered aryllithium.[96]

Mechanisms of the manifold reactions of α-dialkylamino alkyllithium intermediates $R(Me_2N)CLiNu$, formed when tertiary amides ($RCONMe_2$) react with $PhMe_2SiLi$ followed by a second lithium reagent NuLi, have been discussed.[97] The formation of diverse products following 1:1 insertion of an isonitrile RNC into the Li−C bond of $LiCH(SiMe_3)_2$ has been discussed.[98]

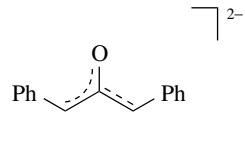
A theoretical study of the reaction of alkyllithium (RLi) with pyridylphosphines ($R'PPy_2$) has been conducted in order to explain the formation of RPy, R′Py, (R)(Py)PLi, and (R′)(Py)PLi and the possible role of an intermediate $(R)(R')(Py)_2P^-Li^+$.[99]

Addition–elimination (for the chloro compound) and elimination–addition (via an intermediate haloalkyne, for the bromo and iodo compounds) mechanisms account for the activation parameters determined for reaction of 2-(β,β-dihalovinyl)-5-nitrothiophenes with MeONa–MeOH.[100]

Y-conjugated derivatives of trimethylene methane (**87**) and α,α'-acetonediyl dianions (**88**) give good yields of expected mono- and di-substitution products on



(**87**)

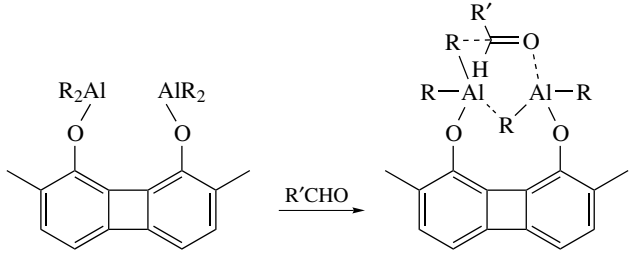


(**88**)

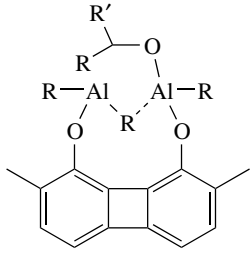
quenching with a variety of electrophiles (other than Me_3SiCl), and of ring closure or stereospecific dimerization products on oxidation.[101]

The high rate of nucleophilic alkylation of aldehydes by the bis(dialkylaluminium) reagent (**89**) has been ascribed to initial formation of a 1:1 coordination complex (**90**) which is easily transformed into product (**91**) via a cyclic six-membered transition state.[102] The amphiphilic alkylation system formed by reaction of (**89**) with MeLi (1 mol) uses both nucleophilic and electrophilic centres to achieve even more effective alkylation at temperatures of -78 to $-40\,^{\circ}C$.

$MgBr_2$-mediated asymmetric nucleophilic addition of Grignard reagents and allyltributyltin to aldehydes bearing sugar-derived β- or γ-tetrahydropyranyloxy chiral auxiliaries designed to complex with $MgBr_2$ has been achieved.[103]



(**89**) (**90**)

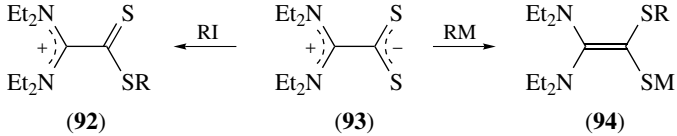


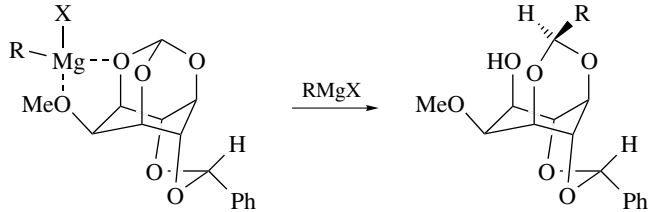
(**91**)

The addition of MeMgCl to chiral α-alkoxy carbonyl compounds has been explored theoretically by PM3 semiempirical procedure and *ab initio* method at HF level of theory.[104] The stereochemistry of the global process is apparently governed by initial exothermic formation of puckered five-membered rings of the *anti* or *syn* chelate complexes; C−C bond formation, via 1,3-migration of the nucleophilic methyl group to the carbonyl carbon, occurs in the second step. Similar conclusions have been drawn from a theoretical study of gas-phase reactions of 2-hydroxypropanal with methylmagnesium reagents.[105]

Nucleophilic additions of Grignard reagents to the *N*-benzylnitrone derived from 1,2-*O*-isopropyl-D-glyceraldehyde have found synthetic application.[106]

The inner salt (**93**) is able to react with both electrophiles (RI) and nucleophiles (RM) to give (**92**) and (**94**), respectively.[107] Radical combination following single electron transfer from the nucleophile is believed to account for the thiophilic addition whereby the negatively charged nucleophile fails to react at the positively charged carbenium carbon.





Chelation complex (**95**) has been proposed to account for the regio- and diastereoselective formation of *myo*-inositol derivatives (**96**) by cleavage of orthoesters with 1–2 equiv. of Grignard reagents in benzene–diethylether.[108]

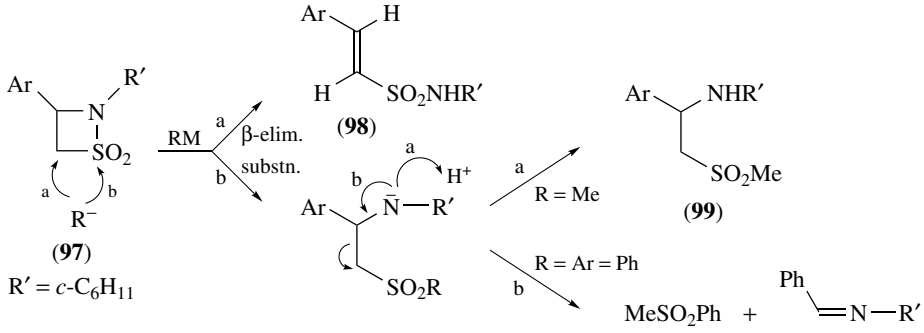
Enantioselective addition of diethylzinc to benzaldehyde has been promoted by indole-containing chiral oxazolidines[109] (which are able to use both O and N atoms to effect metal coordination in the transition state), and by chiral *o*-hydroxyphenyl diazaphospholidine oxide,[110] and by chiral aziridino alcohols.[111] Enantioselective addition of dialkylzinc to prostereogenic ketones has been promoted using chiral camphorsulfonamide derivatives.[112]

Organozinc species $RXZnCH_2I$ generated by reacting $Zn(CH_2I)_2$ with RXH (e.g. ROH or CF_3CO_2H) have been explored as effective agents for cyclopropanation of alkenes at room temperature;[113] chiral alcohols (RXH) induce asymmetric reaction.

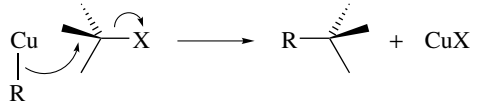
The two stereoisomeric 2-alkyl branched 2-alkenyl potassium species obtained upon deprotonation of (*E*)- and (*Z*)-isocaryophyllene equilibrate to afford an *endo–exo*

mixture of about 95:5; this is consistent with the combined effects of ring strain difference and the '*endo* preference' of open-chain counterparts.[114]

Reactions of 1,2-thiazetidine 1,1-dioxides (β-sultams) with organometallics may occur by competing elimination and substitution reactions.[115] Only (*E*)-vinylsulfonamide (**98**) is obtained on reaction of (**97**) with MeLi whereas MeMgBr also gives 2-aminoethyl sulfone (**99**) as a minor product. 4-Monosubstituted derivatives of (**98**) react with RLi stereoselectively to give the corresponding (*E*)-vinylsulfonamide regardless of the configuration of the 3- and 4-substituents.



A theoretical study of the S_N2 reaction of MeBr with $Me_2CuLi.LiCl$ has addressed two mechanistic possibilities: a simple S_N2 reaction with the carbon nucleophile (eq. 4) and the S_N2 reaction with the copper atom (followed by rapid reductive elimination of a triallylcopper(III) intermediate in a manner which forms only the cross-coupling product RR′) (eq. 5).[116]



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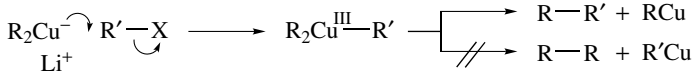

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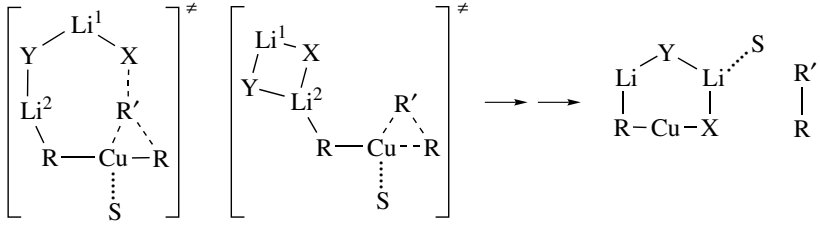
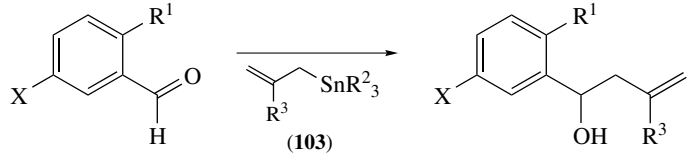


(**100**) (**101**)

Density functional calculations, incorporating clusters with and without solvent coordination to lithium and/or copper, reveal that the S_N2 transition state always features inversion and retention at the electrophilic and nucleophilic centres, respectively. This transition state (**100**) is such that the carbons of the three alkyl groups are in a different electronic and spatial environment; thus, the formation of RR′, rather than RR, is governed by the transition state (**101**) for the reductive elimination reaction of the Cu(II) intermediate.

A study of substituent influences on reaction of carbonyl compound (**102**) with trialkylallyltin (**103**) has established that high yield of allylation product (**104**) is obtained only when $X = NO_2$ and $R^1 = OH$ (where $R^2 = Bu$ or Me and $R^3 = H$ or Me).[117] The role of the intramolecular hydrogen bond in promoting rate enhancement and regioselective allylation (and reduction by $HSnBu_3$) of carbonyl compounds has been discussed.



(**102**) (**103**) (**104**)

Proton-transfer Reactions

Further evidence has been presented in support of the idea that for a chemical transformation where only one thing happens there will be a simple increase or decrease in energy, there being no kinetic barrier (intrinsic barrier in terms of Marcus theory); however, actual reactions involve several things happening simultaneously and the resulting multi-dimensional reaction surface features a kinetic barrier between reactants and products.[118] The ideas have been applied to proton-transfer reactions involving carbon acids. Rate constants have been predicted with an r.m.s. error in log k of 0.99 for 51 reactions of mono- and di-carbonyl compounds with pK_as ranging from 7 to 25.6 and rate constants for water or HO^- ranging from $10^{-9.3}$ to $10^{4.6}$.

A detailed discussion of the effects of sulfenyl, sulfinyl, and sulfonyl groups on acidities and homolytic bond dissociation energies of adjacent C−H and N−H bonds has included interpretation of the following Hammett-type correlations: σ_p^- values versus pK_{HA} values for 4-$GC_6H_4CH_2SO_2Ph$ and for 4-GC_6H_4NHSPh; BDEs of the N−H bonds of 4-$GC_6H_4NHSO_2Ph$ versus σ^+ values.[112] Linear relationships between BDEs and corresponding $E_{ox}(A^-)$ for each of the series 4-GC_6H_4NHSPh, 4-$GC_6H_5NHSO_2Ph$ and 4-$GC_6H_4CH_2SO_2Ph$ have also been explained. In each case the correlation between parameters is ascribed to an underlying molecular connection.

It has been shown, by comparison of ΔG°_{acid} (gas phase) and kinetic acidities measured in MeONa−MeOH, that proton transfer to form a hydrogen-bonded carbanion and the subsequent breaking of that weak bond to form a free carbanion in MeOH may differ greatly even for compounds of comparable acidity, such as 9-phenylfluorene

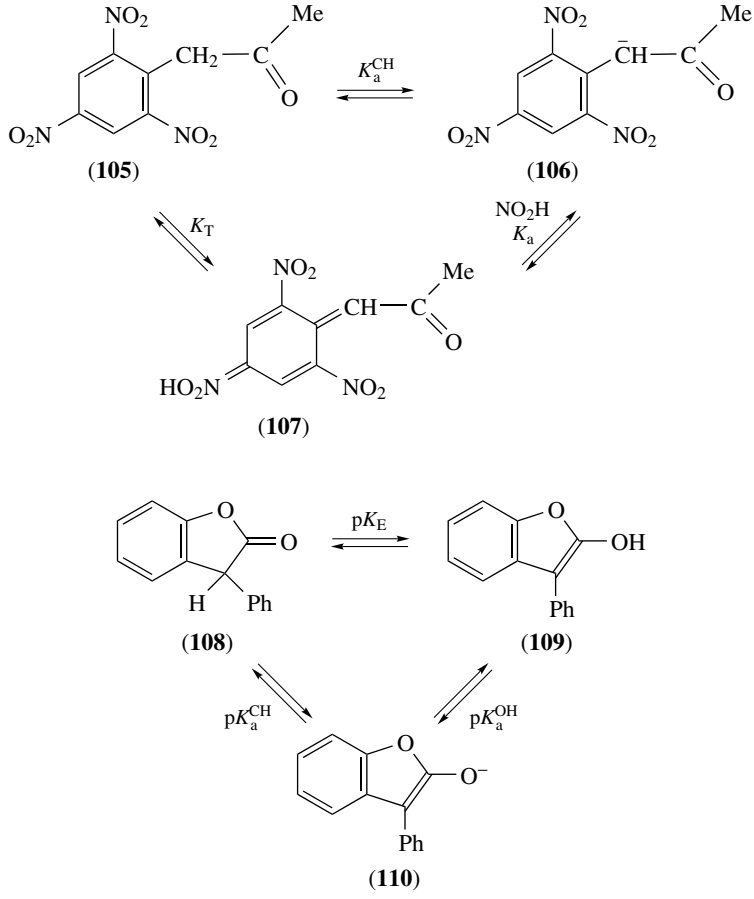
and *p*-$CF_3C_6H_4CTClCF_3$.[120] Several fluorinated benzyl compounds (trifluoromethyl derivatives of $PhCH_2CF_3$ and $PhCHClCF_3$) and pentafluorobenzene were found to behave differently from fluorene and its 9-phenyl derivative, for which internal return is less likely to accompany formation of the free carbanion.

The kinetics of proton transfer from benzoylnitromethane and 1,2-diphenyl-2-nitroethanone to various bases have been compared with those for nitromethane and phenylnitromethane, respectively, in order to determine the influence of the acidifying benzoyl substituent in resonance, inductive, steric, and transition-state hydrogen-bonding effects on the intrinsic rate constants.[121] The acidifying effect of PhCO substitution of CH_3NO_2 is the combined result of electron-withdrawing induction/field effects and increased charge dispersion (resonance) which lessens the hydrogen-bonding solvation by water. The effect of replacement of a methylene hydrogen of $PhCH_2NO_2$ by PhCO is less than for CH_3NO_2 as a consequence of steric crowding which reduces π-overlap and charge dispersion of the anion. The intrinsic rate constants for reaction of $PhCOCH(NO_2)Ph$ with secondary alicyclic amines are reduced by steric effects whereas that for deprotonation by thiolate ion is relatively enhanced since stabilization of the transition state by hydrogen bonding is less important and desolvation of thiolate ion is less energetically demanding than for amines and oxyanions.

The effect of steric hindrance on the rates and kinetic isotope effects for reactions of 1-nitro-1-(4-nitrophenyl)alkanes and their deuterated analogues with two bicyclic guanidines of comparable basicity (1,5,7-triazabicyclo[4.4.0]dec-5-ene, TBD, and its 7-methyl derivative, MTBD) in THF has been studied.[122] The results disagree with the notion that deuterium kinetic isotope effects are enhanced by steric hindrance, since for the reactions of MTBD with various carbon acids the KIEs decrease with steric hindrance in the carbon acid but the converse is true for reactions of TBD.

The kinetics and thermodynamics of the *aci*-nitro equilibrium of picrylacetone (**105**) in 50:50 and 30:70 (v/v) H_2O–Me_2SO mixtures have been reported.[123] Rate of general base-catalysed deprotonation of (**105**) and general acid-catalysed reprotonation of the resulting anion (**106**) have been monitored; at low pH a fast equilibrium protonation of (**106**) to give a directly observable short-lived nitronic acid species (**107**) has been found to precede conversion to (**105**). The constants $pK_a^{NO_2H}$, pK_a^{CH} and pK_T, determined for each solvent mixture, are consistent with preferential stabilization of the large polarizable sp^2-hybridized carbanion (**106**) by Me_2SO; the low intrinsic reactivity of (**105**), as determined from Brønsted plots, also suggests that the negative charge of (**106**) is dispersed through the picryl ring.

The Brønsted coefficient $\beta_B = 0.52$ for deprotonation of 3-phenylcoumaran-2-one (**108**) by a series of bases in 50% (v/v) water–dioxane, and $\alpha_{BH} = 0.48$ for reprotonation by the conjugate acid of the buffer, are indicative of a fairly symmetrical transition state for proton transfer, although the primary KIE, $k_H/k_D = 3.81$, found for proton abstraction by HO^- is lower than expected.[124] The moderate intrinsic rate constant for deprotonation of (**108**) suggests that generation of the charge in the transition state is accompanied by only a small amount of molecular and solvent reorganization. In acidic solution, below pH 5, *O*-protonation of (**110**) occurs initially to form (**109**)



and ketonization occurs subsequently by *C*-protonation of the minor species (**110**); the constants $pK_a^{OH} = 6.0$, $pK_a^{CH} = 8.9$, and $pK_E = 2.9$ have been estimated.

Transition state imbalance in the deprotonation of substituted 2-tetralones by hydroxide ions has been described. A Brønsted plot of log*k* versus substrate pK_a is linear, with slope $(-\alpha)$ of -0.60 ± 0.01 but the negative deviation of the point for the 6-nitro derivative suggests that delocalization of charge lags behind proton transfer.[128]

The loss of optical activity accompanying deprotonation of (*R*)-2,2,6-trimethylcyclohexanone by lithium diisopropylamide (LDA, which exists as a dimer) in THF is governed by the rate equation $v = k[\text{ketone}][\text{LDA}]^{0.5}$, which is consistent with a rate-determining proton transfer involving amine monomer.[126]

An *ab initio* study of the energetics of deprotonation of cyclic vinyl ethers by organolithium reagents has clarified the ring-size-dependent competition between vinylic and allylic deprotonation.[127] The respective transition states involve pre-equilibrium complexation of lithium to the electron-rich vinyl ether oxygen, prior to deprotonation via a multi-centre process; free ions are not formed during the lithiation.

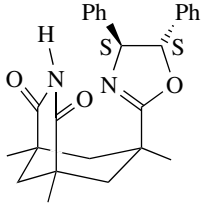
The kinetics and mechanism of proton transfer from diarylcyanomethanes to a proton-sponge, *cis*-1,2-bis(diethylaminomethyl)cyclohexane, in acetonitrile has been studied.[128]

Results of a theoretical study of 1,3-prototropic rearrangement of 1-methylindene, catalysed by ammonia and Me_3N in water and in cyclohexane, have confirmed earlier predictions that the proton moves freely over the indene ring once it has been abstracted by the base.[129] The relative rates of deprotonation, ion-pair collapse and ion-pair rearrangement have been estimated and discussed in each case.

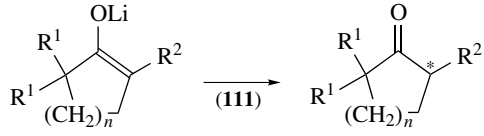
Rate constants for ionization of carbon acids (chloroform-*t* and acetophenone-*t*) in alkaline aqueous sulfolane have been determined and their dependence on solvent composition and temperature has been interpreted for this highly basic medium.[130]

Results of a study of polar, steric and structural influences on the kinetics of proton transfer (ylide formation) from phosphonium ions to electrogenerated bases have been interpreted with caution.[131]

A new chiral proton source (**111**), based on an asymmetric 2-oxazoline ring, has been found to be capable of effecting asymmetric protonation of simple prochiral metal enolates (**112**) to give corresponding ketones (**113**) which need not bear polar groups.[132]



(**111**)



(**112**) (**113**)

Catalytic asymmetric protonation of a prochiral amide enolate by a chiral diamine (10 mol%) has been achieved through careful optimization of the 'proton-shuttle' conditions which must apply.[133]

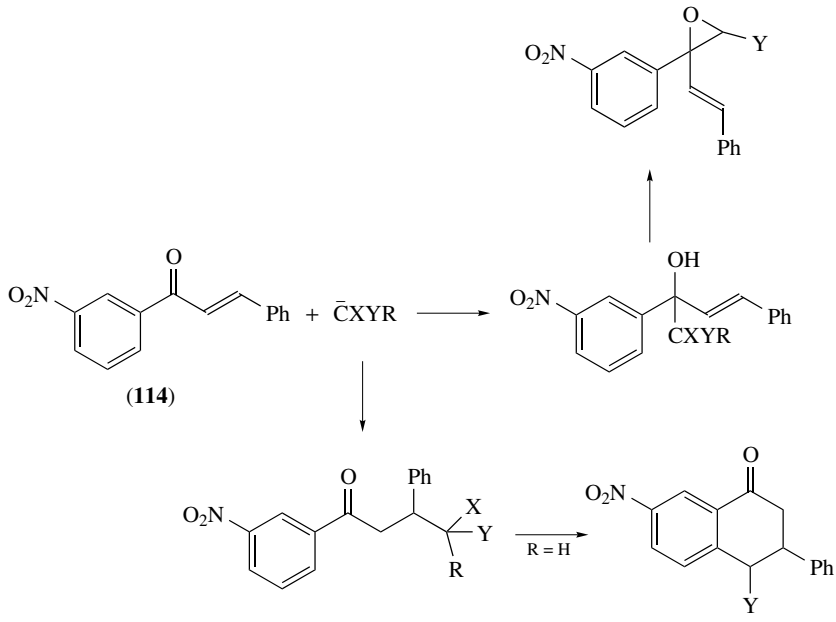
Miscellaneous

Michael additions to benzotriazole-stabilized carbanions have been reviewed.[134] A review of the structural dependence of heterolytic bond dissociation energy of carbon–carbon σ-bonds in hydrocarbons has summarized the synthesis and behaviour of molecules in which highly stable cationic and anionic hydrocarbon moieties have apparently been combined.[135]

Ab initio calculations at the HF/6–31G* level have been used to explore energy changes, structural variation, and electron density shifts during π-face selective addition of substituted acetylide ions to cyclohexanone and cyclohexanethione.[136] Charge polarization of the π-bond on approach of the nucleophile is such that the carbonyl carbon becomes considerably electron deficient for most of the reaction path (and may

benefit from hyperconjugation with vicinal C−H and C−C bonds); the stereoelectronic preference for axial approach is largest in the region of the reaction coordinate where the electron deficiency is greatest and therefore optimum for moderately basic anions rather than those for which very early or very late transition states apply.

3-Nitro-ω-benzylideneacetophenone (**114**) has been found to form only products of addition to the electrophilic side chain (at either the carbonyl group or the double bond) on reaction with carbanions containing leaving groups (Scheme 10).[137] However, in some cases conjugate addition may be followed by intramolecular vicarious nucleophilic substitution of aromatic hydrogen *para* to the nitro group.



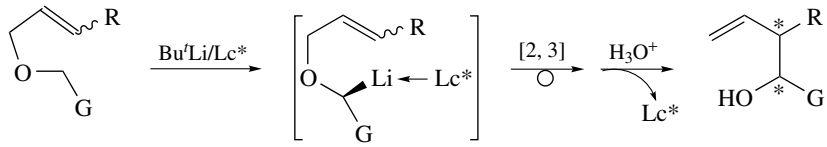
SCHEME 10

Chiral bicyclic 1,2,4-triazolium salts, designed with a hindered heterocyclic ring face, have proved to be more effective cocatalysts of asymmetric benzoin condensation than analogous thiazolium salts.[138]

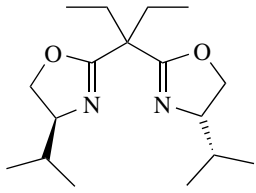
The benzyl anion of 1-benzyloxy-2,2,4,4-tetramethylpentan-3-ones undergoes intramolecular nucleophilic addition to the carbonyl group without competing Wittig rearrangement or decomposition;[139] the stereoselectivity observed is consistent with avoidance of interaction between aryl and *t*-butyl groups.

The bis(oxazoline) (*S*, *S*)-(**115**) has been used as an external chiral ligand to induce asymmetric diastereoselective lithiation by *t*-BuLi during [2,3]-Wittig rearrangement of achiral substrates, (*E*)-crotyl propargylic ethers.[140] It is believed that the enantioselectivity is determined predominantly at the lithiation step.

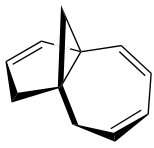
Results of *ab initio* calculations of [1,2]-shifts in acetylide anions indicate that hitherto unknown rearrangements of SiH_3, GeH_3 and AlH_2 groups should be observable



Lc* = (**115**)

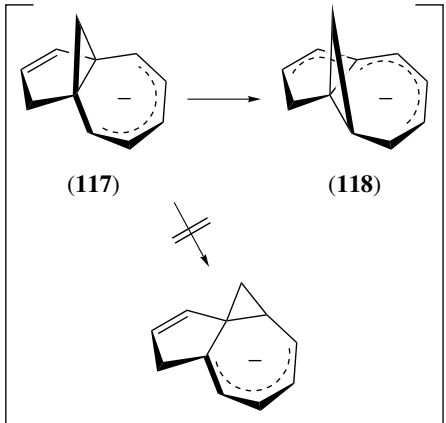


(**115**)



(**116**)

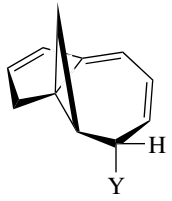
Bu^{n}Li
THF–HMPA
−78 °C



(**117**) (**118**)

(**119**)

−78 °C | $H_2O(D_2O)$



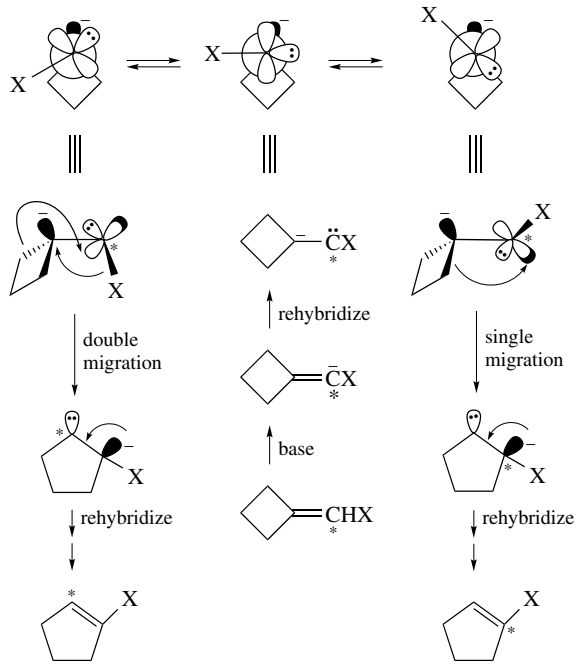
(**120**)

a, Y = H
b, Y = D

experimentally since the barriers to migration ($R{-}C_\alpha{\equiv}C_\beta^- \rightarrow {}^-C_\alpha{\equiv}C_\beta{-}R$) are relatively low.[141] Migratory aptitude depends on ability of the atom or group to attain hypervalent bonding by means of negative hyperconjugation; consequently, the best acceptors have valence-empty *p*-orbitals and low-lying π^*- or σ^*-orbitals. Polarizability of the migrating atom is unimportant and population of extravalence *d*-orbitals is negligible. Study of some [1,2] migrations in the ethenyl ($RCH{=}CH^-$) and ethyl ($RCH_2CH_2^-$) anions revealed that the energy barrier is determined by the orbital orientation of the carbanionic centre with respect to the migrating group rather than directly dependent on hybridization.

Chemical evidence in support of a circumambulatory cyclopropane ring migration on the periphery of a cyclic polyenide has been reported for the first time.[142] The rearrangement of tricyclic undecatrienyl anions, derived from tricyclo[5.3.1.$0^{1,7}$]undeca-2,4,9-triene (**116**), is apparently promoted by the creation of conjugation between the dienide part and the five-membered ring alkene in the product, this is evidenced by the preferential conversion of (**117**) to (**118**), rather than the less conjugated tricyclic anion (**119**), and the reluctance of the anion derived from 9,10-dihydro-(**116**) to rearrange. The anion (**118**) yields (**120b**) by stereoselective deuterium incorporation on quenching with D_2O.

The influence of the halogen on the mechanistic course of carbanionic rearrangement of 3-hexylhalomethylenecyclobutanes (Scheme 11, X = F, Cl, Br, I) to 1-halo-4-hexylcyclopentenes has been explored by studying the fate of ^{13}C-labelled methylene

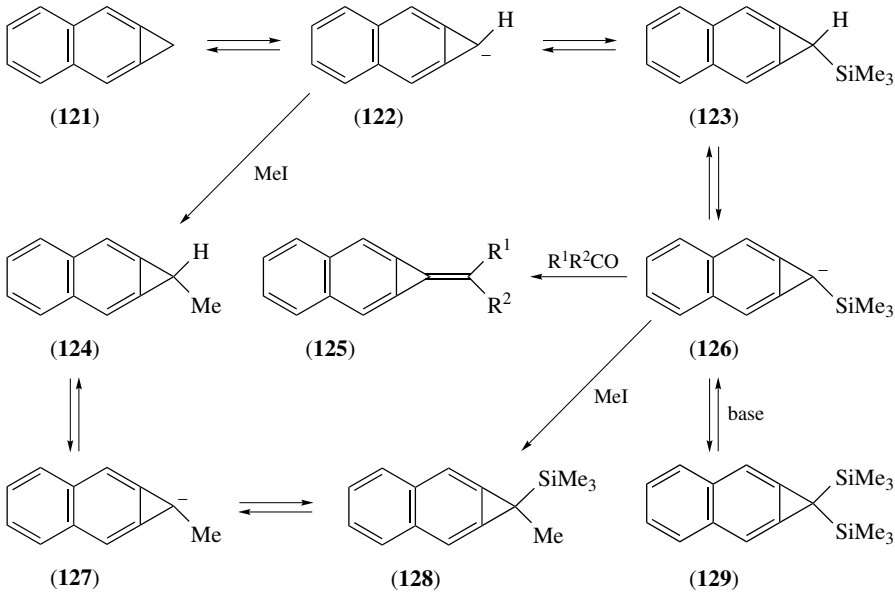


SCHEME 11

carbon.[143] Alternative single migration and double migration mechanisms give rise to product 1-halo-4-hexylcyclopentenes bearing ^{13}C at positions 1 and 2, respectively. In all cases both labelled forms are obtained, in a ratio which is a function of temperature and the nature of the halide; double migration is favoured by increase in temperature and size of the halogen.

Ab initio calculations have been used to investigate the reasons for the unusually rapid formation of cyclopropanes by cyclization of 3-chlorocarbanions [$ClCH_2CH_2CHZ^-$, where Z = C(O)H, CCH or CN].[144] It has been concluded that because the nucleophile is already held close to the electrophilic site ('proximity effect') the energy barrier for S_N reaction is less than for the S_N2 process which is disadvantaged by the energetic price of forcing the nucleophile to approach the electrophile (steric repulsion). The proximity effect, which is purely enthalpic, amounts to 6–9 kcal mol^{-1} barrier reduction (by destabilizing the ground state for the cyclization process) and can therefore outweigh the angular strain of the transition state, especially when augmented by the known entropic advantage. The proximity effect is most significant when bulky delocalized nucleophiles (carbanions) are used and unable to overcome angular strain effects when small localized oxygen or nitrogen nucleophiles are involved.

The chemistry of reaction of the highly reactive 1-trimethylsilylcyclopropan[*b*]naphthalen-1-ide anion (**126**) with electrophiles has been explored.[145] The anion can be trapped as the 1-methyl-1-trimethylsilyl derivative (**128**) [along with some (**121**) and (**124**)] when generated from (**129**) by action of Bu^tO^-–THF in the presence of iodomethane. If (**126**) is formed by action of HO^-–H_2O on (**129**) it is converted quantitatively into cyclopropanaphthalene (**121**) but can be trapped by carbonyl compounds such as benzophenone, fluoren-9-one, or 4-(dimethylamino)benzaldehyde.

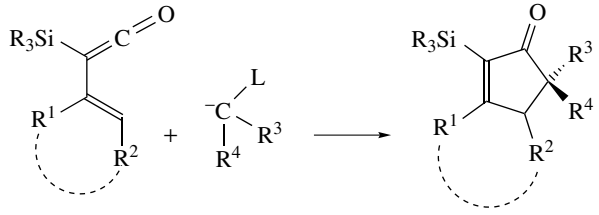


The stereoselectivity of cyclopropanation of chiral acyclic allylic alcohols bearing an aryl group at the remote allylic position has been found to reverse on changing the alkylating agent from $Sm-ICH_2Cl$ to $Et_2Zn-ICH_2Cl$.[146] This has been attributed to direction of the zinc carbenoid to the more crowded face of the alkene by aryl–metal coordination.

The potential energy surface for the reaction between ethylene and $ClCH_2ZnCl$ has been investigated, by a DFT (B3LYP) approach, as a model for the Simmons–Smith cyclopropanation reaction;[147] the addition transition state corresponds to a three-centered structure and is 11 kcal mol^{-1} more favourable than for competing insertion.

Ab initio calculations have been used to explore the mechanism of polymerization of *gem*-disubstituted cyclopropanes, with particular regard to the initiation by H^q, OH^q, and $CH_3{}^q$ ($q = +, 0, -$) and the corresponding transition state.[148] The anionic process is easily attainable through an S_N2-like direct addition of the initiator to a ring methylene, with the CX_2 group acting as the leaving group.

The reaction of (trialkylsilyl)vinylketenes with nucleophilic 'carbenoid' reagents, such as sulfur ylides and diazo compounds, has been used for synthesis of substituted cyclopentenones by stereoselective 4 + 1-annulation (Scheme 12).[149] The strategy relies on the remarkable ability of silyl substituents to stabilize ketenes and suppress their tendency to undergo dimerization and 2 + 2-cycloaddition.



SCHEME 12

Decarboxylation of 1,3-dimethylorotic acid in the presence of benzyl bromide yields 6-benzyl-1,3-dimethyluracil and presumably involves a C(6) centered nucleophilic intermediate which could nonetheless have either a carbene or ylide structure.[150]

Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometry has been used to explore the gas-phase reactions of methyl nitrate with anions from active methylene compounds;[150] anions of aliphatic ketones and nitriles react by the S_N2 mechanism and E_{CO} reactions yielding $NO_2{}^-$ ions are also observed; nitronate ions are formed on reaction with the carbanions derived from toluenes and methylpyridines.

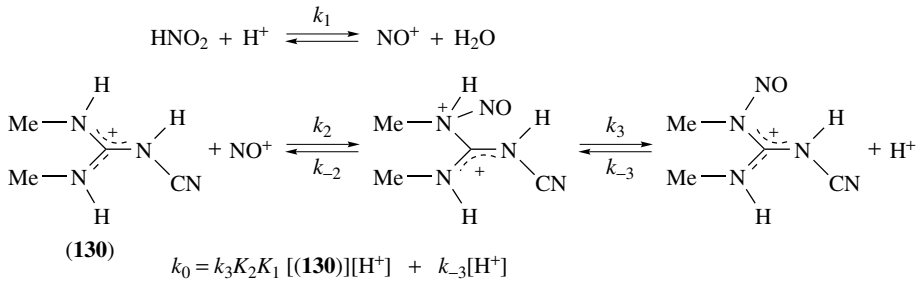
Perhaloalkanes have been found to scramble halogen atoms via consecutive halophilic reactions following carbanion generation by halophilic attack by base.[152]

S_E2' reaction of an allylsilane has been applied in a stereocontrolled synthesis of (±)-dihydronepetalactone,[153] and functionalized aryl and arylmethyl carbanions have been generated by reductive cleavage of aryl and arylmethyl alkyl ethers by electron transfer from alkali metals.[154]

Electrophilic Aliphatic Substitution

The nitrosation of *N*-alkylureas in dioxane–acetic acid mixtures is governed by the expression $v = k[HNO_2][urea]$, at fixed pH, and dependent on rate-determining proton transfer from the protonated *N*-alkyl-*N*-nitrosourea to acetate anion;[155] the order of reactivity, which reflects relative impediment by the alkyl groups, is as for nitrosation in aqueous media (methyl- ≫ ethyl- ≈ propyl- ≈ butyl- > allyl-urea).

A study of the kinetics of nitrosation of *N*,*N*′-dimethyl-*N*″-cyanoguanidine in acid media (Scheme 13) [where the substrate exists as its conjugate acid (**130**)] has established that the mechanism of the reversible reaction is similar to that found for nitrosation of amides and ureas, rather than amines (for which attack of the nitrosating agent on the free base is usually rate limiting).[156] The reaction, which is subject to general-base catalysis but not influenced by halide ion, involves reversible rate-limiting proton transfer in the final step and exhibits solvent deuterium isotope effects of 1.6 and 1.2 for nitrosation and denitrosation, respectively. The composite nitrosation isotope effect is believed to reflect $k_3(H)/k_3(D) = 4.1$ combined with $K_1(D)/K_1(H) = 2.55$ and negligible influence on K_2.



SCHEME 13

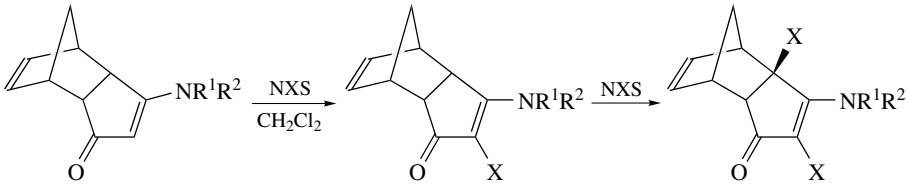
The kinetics and mechanism of *N*-nitration reactions have been reviewed[157] and the nitration of alkanes with nitronium hexafluorophosphate in CH_2Cl_2 or $EtNO_2$ has been shown to involve direct electrophilic insertion of NO_2^+ into C–H and C–C σ-bonds.[158]

Both fluorination and chlorination of methylaziridine-2-carboxylates (using F_2–NaF and Bu^{t}OCl, respectively) involves stereodirected *N*-halogenation *trans* to the carboxylate group. This has been attributed to fixed orientation of the lone pair on nitrogen, as a consequence of intramolecular hydrogen bonding to the carboxylate group. This view is supported by the observation that *N*-fluorination and *N*-chlorination of methyl 2-trifluoromethylaziridine-2-carboxylate also occurs predominantly *trans* to the carboxylate, even though this involves halogenation from the more hindered side.[159]

The formation of *N*-fluorinated aziridine-2-carboxylates can be achieved by fluorinolysis of their *N*-aminomethyl derivatives, apparently via the immonium ion–fluoride ion pair formed by initial electrophilic attack of F_2 on nitrogen.[160]

A catalytic acid hydrolysis, Aac_2 mechanism, has been implicated in bromination of *N*-acetyl-*N′*-arylurea, $MeCONHCONHC_6H_4R$-*p* (R = Me, Cl, NO_2) in the presence of mercuric chloride.[161]

N-Halosuccinimides (NXS) have been found to react with tricyclo[5.2.1.$0^{2,6}$]decenylenaminones (**131**) to give (**132**) by exclusive α-halogenation when one equivalent of NXS is used; subsequent introduction of either γ- or *N*-halogen is caused by an additional equivalent of NXS.[162] The remarkable inertness of the C(8)−C(9) double bond may be a consequence of orbital interaction with the enaminone π-system.



(**131**) (**132**) (**133**)

The influence of substituents on the regioselectivity of fluorination of allylic alcohols with DAST has been studied[163] and halogenation of the nitrogen of carbohydrate *N*-acetyl side-chains by HOCl has been monitored.[164]

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CHAPTER 12

Elimination Reactions

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$E1cB$ Mechanisms

Results of a kinetic study of base-promoted elimination reactions of some 1,1,1-trihalo-2,2-bis(dialkoxyphenyl)ethanes in alcoholic solutions have shown that (for 3,4-dimethoxy) the tribromo derivative reacts faster than the trichloro derivative and the reactions are general-base promoted, with Brønsted β values of ca 0.6 and a kinetic isotope effect $k_H/k_D = 3.5–5.7$ for the trichloro compound.[1] Arrhenius pre-exponential factors for the alkoxy-promoted reactions provide evidence of tunnelling, but difficulty in distinguishing between $E1cB_I$ and $E2$ mechanisms is apparent; thus the leaving group effect ($k_{Br}/k_{Cl} = 22–26$) seems to be explained better by the latter (rather than as a consequence of anionic hyperconjugation) whereas the activation parameters and near identity of β values for the chloro and bromo derivatives are consistent with the former. The results support the view that the $E1cB_I$ mechanism is transformed into the $E2$ mechanism with very little change in transition-state structure.

The difficulty of distinguishing mechanisms at the $E1cB–E2$ borderline has also been discussed for reactions of secondary halides (**1-X** and **2-X**) which feature a β-hydrogen made acidic by incorporation of an α-indenyl substituent (Scheme 1).[2] 1,2-Elimination reactions of (*R*,*S*)-1-(1-X-ethyl)indene (**1-X**, X = Cl, Br, I, OBs) and the corresponding *R*,*R* isomers (**2-X**) promoted by water containing 25 vol.% acetonitrile

H(D)
OH
Me
(D)H
H
(7)
H+
Me
H
OH
H(D)
(6)
k2′
k2
H(D)
X
(D)H
H
Me
(2–X)
kE
H(D)
H
Me
(8)
+
H(D)
H
Me
(5)
kE
H(D)
X
(D)H
Me
H
(1–X)
k1′
k1
Me
H
OH
H(D)
(4)
H+
H(D)
OH
(D)H
Me
H
(3)
kS = k1 + k1′, or
kS = k2 + k2′,

SCHEME 1

occur non-stereospecifically and stereospecifically, respectively, and are in competition with solvolytic substitution via homoallylic cations formed in leaving group rate order $Br^- < I^- < BsO^-$. The kinetic deuterium isotope effects ($k_H/k_D = 4.6–6.8$) found for solvent-promoted elimination reactions of (**1-X**, X = Cl or Br) and (**2-Br**) are too large for the $E1$ mechanism and greatly exceed the values close to unity actually determined for the competing substitution reactions [to form primarily (**3**) and (**7**) from (**1-X**) and (**2-X**), respectively]. The large Brønsted coefficients [$\beta = 0.38$, 0.37, 0.47, and 0.40 for (**1-I**), (**1-Br**), (**2-Br**), and (**2-OBs**), respectively] for reaction with substituted acetate ions indicate that the reactions proceed by either $E2$ or $E1cB_I$ mechanisms; the former is favoured for (**2-Br**) and (**2-OBs**), which exhibit higher stereospecificity (95–99% *anti* elimination) than found for (**1-X**) (80–85% *anti* elimination). The *syn* elimination of (**1-X**) is apparently favoured by the absence of steric interaction of the methyl group with the adjacent phenyl hydrogens; however, the *anti* stereochemistry, which has been ascribed to the $E2$ process, increases with basicity of the added base and is favoured by negative charge on the base.

Isotope effects and element effects associated with hydron-transfer steps during methoxide promoted dehydrohalogenation reactions of p-$CF_3C_6H_4C^iHClCH_2X$ (X=Br, Cl, or F) have also been discussed, with regard to distinction between $E2$ and multi-step pathways.[3] The Arrhenius behaviour of hydrogen isotope effects was used to calculate the amounts of internal hydrogen return associated with the two-step mechanism.

The acidifying influence of the sulfonyl group, combined with its ability to transmit electronic effects is apparent from results of Hammett studies of the dehydrochlorination of p-$RC_6H_4SO_2CH_2CH_2Cl$ and $RC_6H_4SO_2CH_2CHClPh$, on reaction with Et_3N; the nearly identical positive ρ values indicate that for each series reaction proceeds via carbanion formation.[4]

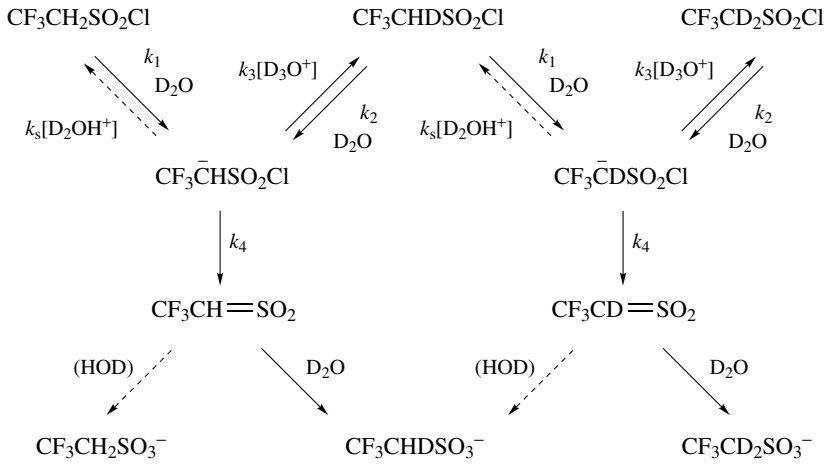
An intermediate sulfene ($CF_3CH{=}SO_2$) is formed by an irreversible $E1cB$ process during hydrolysis of 2,2,2-trifluoroethanesulfonyl chloride in water at pH 1.8–5.[5] Water acts as the carbanion-forming base in the lower pH range and hydroxide anion at higher pH; in dilute acid the hydron transfer becomes reversible and deuterium exchange of the sulfonyl chloride is observed (Scheme 2). This is believed to be the first clear demonstration of reversible and irreversible $E1cB$ reactions induced by water. The change from $E1cB_I$ to $E1cB_R$ with increasing acidity provided a means of distinguishing the $E1cB_I$ and $E2$ processes.

A change in mechanism [at pH $\approx$ pK_a of (**9**)] from $E1cB_I$ to $E1cB_R$ is also believed to account for the biphasic Brønsted plots ($\beta_1 \approx 0.7$, $\beta_2 \approx 0$) and associated entropy changes obtained for aminolysis of 4-nitrophenyl N-benzylsulfamate (**9**), apparently via $ArN{=}SO_2$, in MeCN.[6]

$$\underset{\textbf{(9)}}{ArNHSO_2ONp} + RR'NH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Ar\bar{N}SO_2ONp + RR'NH_2^+$$

$$Ar\bar{N}SO_2ONp \xrightarrow{k_2} ArNHSO_2NRR' + HONp$$

$Np = p\text{-}NO_2C_6H_4^-$



SCHEME 2

Non-linear kinetics have been reported for aminolysis of sulfamate esters $RNHSO_2ONp$ (Np=*p*-$NO_2C_6H_4$) in chloroform.[7] The first-order rate constants k_{obs} for reaction with imidazoles (primarily) under pseudo-first-order conditions display saturation curvature with increasing amine concentration, according to the expression

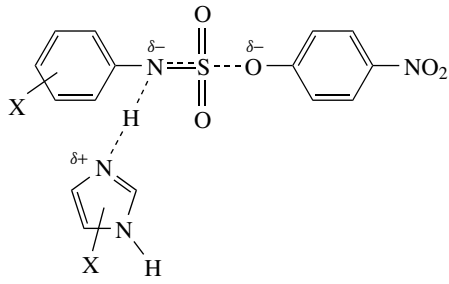
$$k_{obs} = K_m k'[\text{amine}]/(1 + K_m[\text{amine}])$$

where K_m and k' are defined by

$$\text{S} + \text{amine} \underset{}{\overset{K_m}{\rightleftharpoons}} [\text{S.amine}] \xrightarrow[\text{rds}]{k'} \text{products}$$

There was no evidence of a second-order term in amine, nor did amine self-association account for the non-linear behaviour. Hammett ρ values (for variation of $RNHSO_2$) determined for formation of the complex [S.amine] ($\rho = 1.64$) and for expulsion of the anion ($^-$ONp) ($\rho_{acyl} = -1.78$) are consistent with an *E*1*cB* process and uncomplicated by any steric effects of bound amine in the complex. The value of ρ_{acyl} is identical with that reported previously for *E*1*cB* reaction of the same esters in 50% acetonitrile–water and much greater than for their *E*2-type reactions in chloroform. Consequently, an *E*1*cB* mechanism involving extensive S–O bond cleavage with the formation of a *N*-sulfonylamine, $ArN{=}SO_2$, is supported.

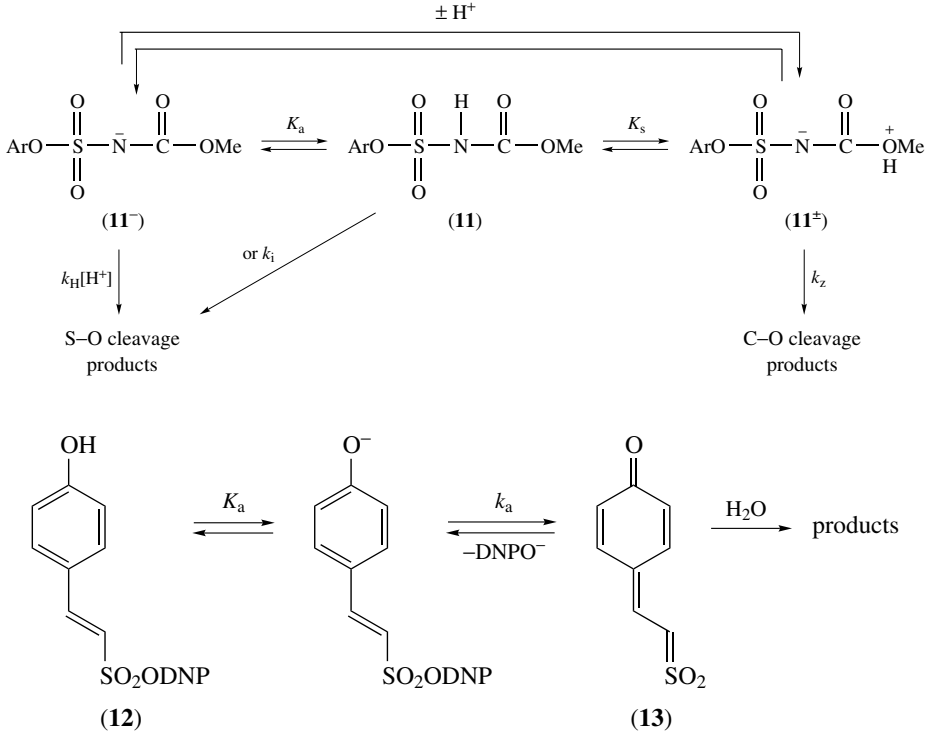
A report of a more extensive Hammett study has included estimates of values of ρ_{acyl} for aminolysis of members of the sulfamate ester series ($XC_6H_4NHSO_2ONp$) in chloroform and acetonitrile using piperidine and a set of five pyridines; variation of the pyridines allowed the determination of ρ_{pyr} values for several esters.[8] The ρ_{acyl} values become less negative with decrease in amine basicity, apparently as a consequence of diminished N_β–H cleavage and a progression from a partial carbanion-like transition state to a more central *E*2 type mechanism (**10**).



(**10**)

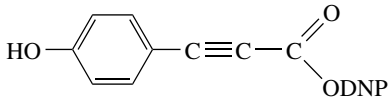
The ρ_{acyl} value for 4-dimethylaminopyridine almost doubles from −0.91 to −1.53 on change from chloroform to acetonitrile, thereby approaching the value $\rho_{acyl} \approx -1.8$ which is believed to be indicative of formation of a sulfonylimine intermediate by the $E1cB$ mechanism. The values of ρ_{pyr} (ca −1.2) suggest that there is only a small amount of positive charge on the pyridine nitrogen in the transition state; corresponding values of β_{nuc} (ca 0.2) confirm this view. General conclusions are that for the $E2$ mechanism $\beta_{nuc} = 0.2–0.6$ whereas for the $E1cB_I$ mechanism $\beta_{nuc} \geqslant 0.7$; biphasic behaviour ($\beta_{nuc} \approx 0.7$ and ca 0) is indicative of transition from $E1cB_I$ to $E1cB_R$ behaviour. This aminolysis of sulfamate esters in $CHCl_3$ and CH_3CN generally occurs by an $E2$ type mechanism which may vary from 'central' to E1cB-like. In certain cases in CH_3CN the biphasic behaviour indicative of a change from $E1cB_I$ ($\beta_{nuc} \approx 0.7$) to $E1cB_R$ ($\beta_{nuc} = 0$) is found. Aminolysis of sulfamoyl chlorides in chloroform and acetonitrile has also been found to occur by an elimination mechanism, via the corresponding N-sulfonylamine, PhN=SO_2; the $E2$ reaction is believed to become more $E1cB$-like in the more polar solvent.[9] The monosubstituted sulfamoyl chlorides react ca 10^6 times more rapidly than disubstituted sulfamoyl chlorides and primary deuterium isotope effects in the range 2.6–5.3 (Y = H) have been determined for reaction of $YC_6H_4NHSO_2Cl$ with $XC_6H_4NH_2$ in $CHCl_3$. The dependence on X is reflected in Hammett ρ values of −4.76 (Y = p-Me), −3.57 (Y = H) and −2.63 (Y = p-Cl) which are comparable to that reported previously for the related phenylmethanesulfonyl chloride system ($\rho = -3.5$).

The $E1cB$ reaction has also been invoked to account for several of the competing processes whereby aryl N-(methoxycarbonyl)sulfamates (**11**) decompose in aqueous media.[10] The pH profiles indicate a rate law that includes three terms; two pH independent terms, k_a in acid and k_p around neutral pH, with $k_a > k_p$, and a hydroxide ion-dependent term, k_{OH}. In acid, both S−O (k_{SO2}) and C−O (k_{CO}) bond cleavage reactions are involved; the former may involve either intra- or inter-molecular general-acid-catalysed decomposition of (**11**) or (**11**$^-$), respectively; the latter involves protonation of the leaving group and its expulsion from the dipolar intermediate (**11**$^\pm$) thus formed, and consequently fails to display the deuterium solvent isotope effect which characterizes a general-acid-catalysed process. The spontaneous reaction of (**11**$^-$) takes place (k_p) with exclusive S−O bond fission (to give O_2S=NCOOMe) whereas k_{OH} governs a process of HO^- attack at the carbonyl centre or at the aromatic ring.

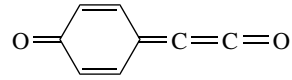


The pH profile for hydrolysis of 2,4-dinitrophenyl 4′-hydroxy-β-styrenesulfonate (**12**) in aqueous buffers (pH 5–13) features an approach to a rate plateau at high pH; this has been ascribed to a dissociative pathway, with the probable formation of a thioquinine dioxide intermediate (**13**) which benefits from the stabilizing influence of external delocalization.[11] The $\Delta S^{\neq}$ values for hydrolysis of (**12**) at various pH values are positive, as expected for a unimolecular process, and in contrast with the large negative entropy of activation for hydrolysis of 2,4-dinitrophenyl β-styrenesulfonate by an associative mechanism. The large negative value of β_{LG} (−1.85) determined through variation of the phenoxide leaving group is indicative of advanced fission of the S−OAr bond in the rate-determining transition state and within the range expected for the $E1cB$ mechanism (−1.5 to −2.4).

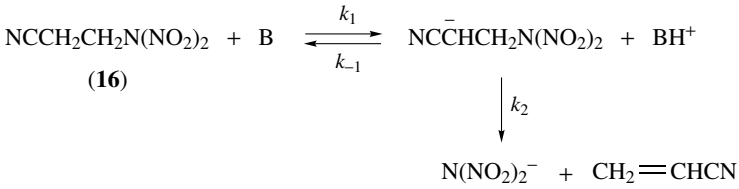
A dissociative elimination–addition pathway has also been proposed to account for the kinetics of alkaline hydrolysis of 2,4-dinitrophenyl 4′-hydroxyphenylpropionitrile in 40% (v/v) dioxane–water, although participation of the associative $B_{AC}2$ mechanism cannot be ruled out since it may be facilitated by the electronic effect of the triple bond.[12] Formation of intermediate (**15**), having a conjugated and cumulated double-bond system, should favour the $E1cB$ mechanism and thereby account for the contrasting entropies of activation found for hydrolysis of (**14**) and the corresponding 4′-methoxyphenylpropionate.



(**14**)



(**15**)



(**16**)

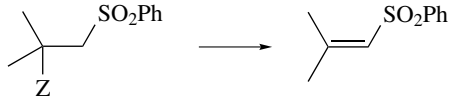
SCHEME 3

The general-base-catalysed formation of dinitramide anion, (NO_2N^-), on reaction of 2-(*N*,*N*-dinitroamino)propionitrile (**16**) in aqueous buffer solutions (pH 9.5–11.5), has been ascribed to the $E1cB_I$ mechanism ($k_2 \gg k_{-1}[BH^+]$), for which $k_{ap} = k_{OH^-}[HO^-] + k_B[B] + k_{H_2O}$. The Brønsted β value is close to unity and the entropy of activation, $\Delta S^{\neq} = 10 \pm 1\,\text{cal mol}^{-1}\text{K}^{-1}$, for reaction with hydroxide ion is consistent with the combined effects of bimolecular collision (ca $-11\,\text{cal mol}^{-1}\,\text{K}^{-1}$) and near-complete desolvation of HO^- (ca $+20\,\text{cal mol}^{-1}\,\text{K}^{-1}$).[13]

The Ad_N-*E* mechanism proposed to account for the kinetics of substitution of 9-(α-bromo-α-arylmethylene)fluorenes by thiolate ions in aqueous acetonitrile also features elimination of the leaving group in a fast step following rate-determining carbanion formation (by nucleophilic addition).[14]

*E*2 Mechanisms

Further study of the effect of strain on 1,2-elimination reactions has revealed that the formation of a carbon–carbon double bond exocyclic to a cyclopropane ring is inhibited by factors which increase from 1.4 to $10^{4.5}$ as the leaving group becomes poorer.[15] Five different leaving groups (Z = Br, Cl, SO_2Ph, SPh, and OMe) featured in the comparison of rate constants for unstrained (eq. 1) and strained (eq. 2) reactions induced by EtO^-–EtOH. It is estimated that the strain energy differences between cyclopropane and methylenecyclopropane is ca $50\,\text{kJ mol}^{-1}$ and that ca 50% of the enthalpy difference between strained and unstrained products can be induced in the elimination transition state.

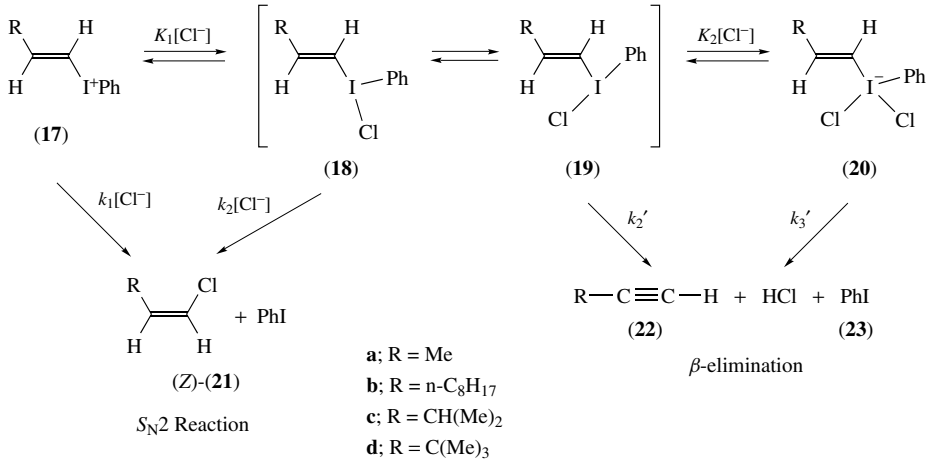


(1)

(2)

Combined use of the HSAB principle and DFT reactivity descriptors has provided a means of interpretation of the effect of basicity of *para*-substituted phenolate ions on the known elimination-substitution ratios for their reactions with *p*-nitrophenethyl bromide in 45.9% alcohol.[16] It has been concluded that *para*-substituted phenolates with higher basicity (harder), less delocalized negative charge into the fragment RC_6H_4, and a more polarizable oxygen atom (softer) have a lower (relative) attraction towards an alkyl carbon atom (soft) than towards a hydrogen atom (softer) of *p*-nitrophenyl bromide. The interactions have been explained from a local–local viewpoint which is in contrast with a global–local interpretation suggested previously.

In order to strengthen evidence in favour of the proposition that concerted in-plane S_N2 displacement reactions can occur at vinylic carbon the kinetics of reactions of some β-alkyl-substituted vinyliodonium salts (**17**) with chloride ion have been studied.[17] Substitution and elimination reactions with formation of (**21**) and (**22**), respectively, compete following initial formation of a chloro-λ^3-iodane reaction intermediate (**18**). Both (**17**) and (**18**) undergo bimolecular substitution by chloride ion while (**18**) also undergoes a unimolecular (intramolecular) β-elimination of iodobenzene and HCl. The [**21**]/[**22**] ratios for reactions of (**18a–b**) increase with halide ion concentration, and there is no evidence for formation of the *E*-isomer of (*Z*)-alkene (**21**); iodonium ion (**17d**) forms only the products of elimination, (**22d**) and (**23**).



Ring opening of an epoxide with a strong non-nucleophilic base is often used for the synthesis of allylic alcohols and incorporation of a silyl group is known to induce regioselective cleavage of the C–O bond α to silicon.[18] In order to broaden understanding of the reason for the regiochemistry of eliminative ring opening of α,β-epoxysilane, the products of reaction of non-nucleophilic bases with epoxides bearing the bulky trimethylsilyl group (unlikely to coordinate with base) have been determined. The observed preference for eliminative α-opening of these epoxysilanes has been correlated with the character of the AM1 LUMO isosurface.

Gas-Phase Base-Promoted Elimination Reactions

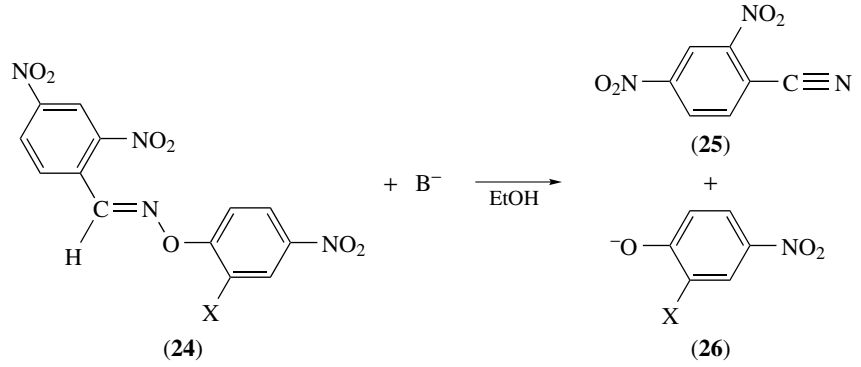
There have been several studies of gas-phase $E2$ reactions.[19–21] Results of *ab initio* calculations, up to the MP2/6–31 + G** level, on gas-phase reactions of fluoride ion with 3-chlorocyclohexene and 3-fluorocyclohexene predict that the lowest energy barrier is for *anti* 1,4-elimination but that the barriers to *syn* 1,4-elimination and *anti* 1,2-elimination are within 2.5 cal mol^{-1} of the preferred path;[19] the barriers for S_N2 and S_N2' reactions are comparable but much higher than for elimination processes. Transition states have also been located for fluoride ion promoted reactions of chlorocyclopropane;[20] the barrier for *syn* elimination is only 3.6 kcal mol^{-1} larger than for *anti* elimination as a consequence of the inherent periplanarity of the transition state for the former and the disadvantage of torsional ring strain in that for the latter. However, the S_N2 pathway dominates ($E_a = 7.3$ kcal mol^{-1}) over the $E2$(anti) pathway ($E_a = 18.6$ kcal mol^{-1}).

Ab initio methods using the 6–31 + G* basis sets have been used in a theoretical study of competing S_N2 and $E2$ reactions of $NCCH_2CH_2Cl$ with HO^- and HS^- in the gas phase.[21] The antiperiplanar elimination transition state, which is favoured over those for S_N2 and $E2$(*gauche*) reactions, is more $E1cB$-like than that for the slower $E2$(*anti*) reaction of ethyl chloride.

Formation of Double and Triple Bonds to a Heteroatom

$E2$ elimination reactions of *O*-substituted oximes have received further attention.[22–25] Thus, reaction of (*E*)-2,4-dinitrobenzaldehyde *O*-pivaloyloxime with $R_2NH/R_2NH_2^+$ buffer in 70% MeCN (aq.) exhibits second-order kinetics and general-base catalysis with Brønsted $\beta = 0.45$; the decrease in Hammett ρ value from 1.6 to 2.3 with change of the base–solvent system to DBU in MeCN is also believed to be consistent with the concerted mechanism.[22] Reactions of (*E*)-2,4-dinitrobenzaldehyde *O*-aryloximes (**24a–c**) promoted by RO^-–ROH buffers in EtOH have been shown to give 2,4-dinitrobenzonitrile (**25**) and aryl oxides (**26**) as the only products.[23] The Brønsted $\beta = 0.55$–0.75 decreases as the leaving group is made more nucleofugic and $|\beta_{lg}| = 0.39$–0.48 increases as the base becomes weaker; the interpretation in terms of a positive interaction coefficient provides further support for the $E2$ mechanism.

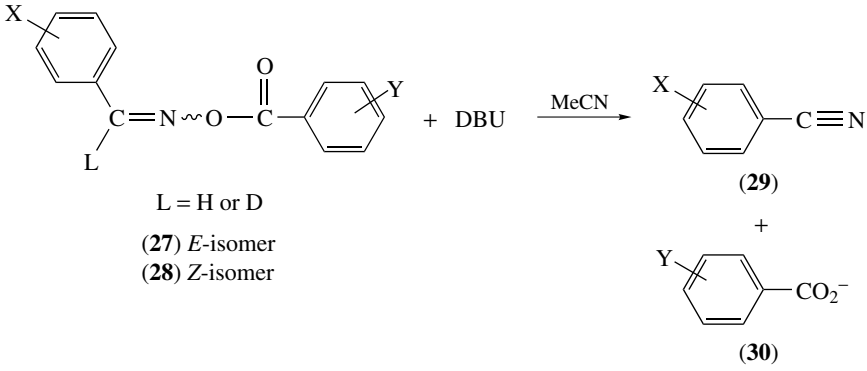
Nitrile-forming eliminations from (**28**), promoted by DBU in MeCN, have been found to occur 36 000-fold faster than for (**27**) via more symmetrical transition states, with less negative charge development at the β-carbon and smaller degrees of proton transfer and N_α–OC(O)Ar bond cleavage.[24] This is evidenced by the following values determined for reaction of (**27**), $k_H/k_D = 3.3 \pm 0.2$, Hammett $\rho = 2.19 \pm 0.05$, $\beta_{lg} = -0.49 \pm 0.2$, $\Delta H = 10.4 \pm 0.6$ kcal mol^{-1} and $\Delta S^{\neq} = -34.3 \pm 2.6$ cal mol^{-1} K^{-1}, when compared with the corresponding values for (**28**), $k_H/k_D = 7.3 \pm 0.2$, $\rho = 1.21 \pm 0.05$, $\beta_{lg} = -0.40 \pm 0.1$, $\Delta H = 6.8 \pm 0.6$ kcal mol^{-1} and $\Delta S^{\neq} = -25.8 \pm 1.9$ cal mol^{-1} K^{-1}, respectively. The extent of proton transfer and negative charge density at the β-carbon decreases with a better leaving group, and the extent of leaving group departure decreases with the electron-withdrawing ability of the β-aryl substituent. The results have been interpreted with reference to a More



(**24**) (**25**) + (**26**)

X = **a**; H, **b**; Cl, **c**; NO_2

B^- = EtO^-, PhC(Me)=NO^-/PhC(Me)=NOH, $CF_3CH_2O^-$/CF_3CH_2OH



L = H or D

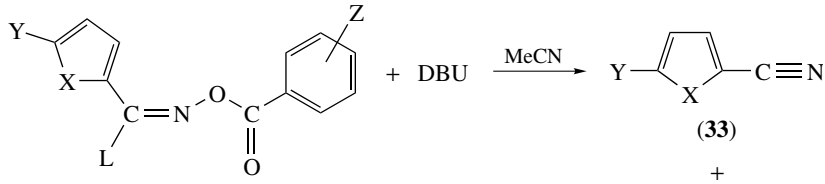
(**27**) *E*-isomer

(**28**) *Z*-isomer

(**29**) + (**30**)

O'Ferrall–Jencks diagram and *ab initio* calculations with the 6–31 G basis set. It is concluded that the transition state is slightly *E*1c*B*-like for (**27**) and more symmetrical for (**28**).

Nitrile-forming *anti* eliminations from the (*Z*)-oximes (**31**) and (**32**) have also been found to proceed by the *E*2 mechanism; the symmetrical transition state is little



(**31**) X = S

(**32**) X = O

L = H, D; Y = various

(**33**) + (**34**)

affected by the aromatic resonance energy of the β-substituent, becomes slightly more product like with a larger degree of proton transfer, more negative charge development at the β-carbon, and a greater extent of leaving group departure as the substituent is changed from phenyl to thienyl to furyl (relative rates 1:1.1:0.6); this trend is evidenced by the corresponding increase in k_H/k_D, ρ and $|\beta_{lg}|$ values.[25] The following respective values were determined for (**31**) and (3**2**): $k_H/k_D = 8.2 \pm 0.1$ and 8.8 ± 0.2, $\rho = 1.22 \pm 0.19$ and 1.87 ± 0.05, $\beta_{lg} = -0.43 \pm .01$ and -0.55 ± 0.1, $\Delta H^{\neq} = 5.9 \pm 0.1$ and 6.5 ± 0.1 kcal mol^{-1}, and $\Delta S^{\neq} = -28.5 \pm 0.3$ cal mol^{-1} K^{-1} and -29.0 ± 1.5 cal mol^{-1} K^{-1}.

An $E2$ mechanism has been proposed to account for the kinetics of formation of 3-azabicyclo[3.3.0]oct-2-ene on dehydrohalogenation of *N*-chloro-3-azabicyclo[3.3.0]octane in alkaline medium.[26]

The vicarious nucleophilic substitution of carbo- and hetero-cyclic nitroarene hydrogen by a hydroxyl group, on reaction with silylhydroperoxide anions, has been shown to proceed via nucleophilic addition of ROO^- followed by base induced elimination of ROH by an $E2$-type mechanism; the required orientation of the hydroxylation can be controlled by the conditions selected.[27]

Although no rates have been determined, the results of semiquantitative experiments involving competition between displacement of hydrogen and halogen have been interpreted in terms of the following equation for the VNS process:

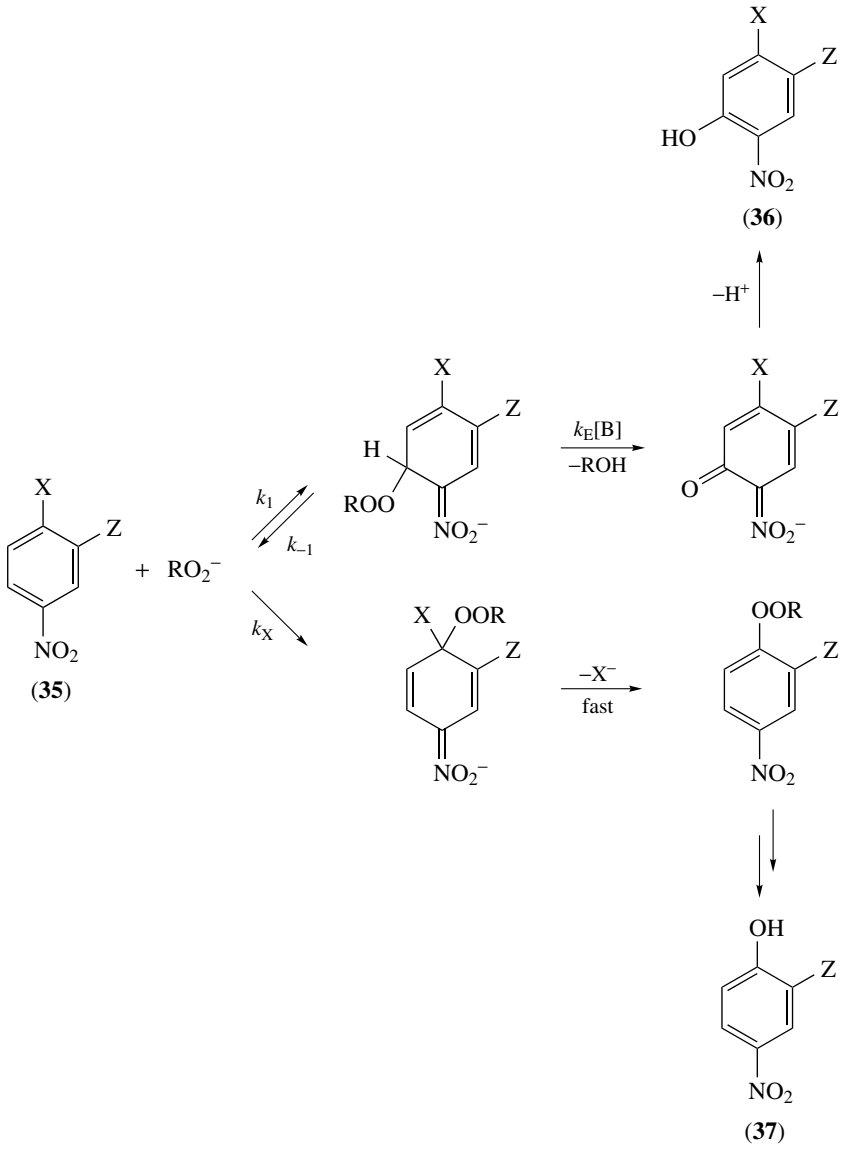
$$HArNO_2 + RO_2^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} RO_2(H)Ar{=}NO_2^- \xrightarrow[-ROH]{k_E[B]} O{=}Ar{=}NO_2^-$$

$$v = k_{obs}\,[HArNO_2][RO_2^-] \qquad \text{where } k_{obs} = k_1k_E[B]/(k_{-1} + k_E[B])$$

The ratio of products (**36**) and (**37**) from VNS of hydrogen (P_H) and substitution of halogen (P_X), respectively (Scheme 4), will depend on the strength and concentration of base, provided that the elimination is a kinetically important step in the VNS reaction, namely $P_H/P_X = k_1k_E[B]/k_{-1}k_X$. The influence of base will decrease until a constant value $P_H/P_X = k_1/k_X$ is reached as $k_E[B] \gg k_{-1}$. This has been demonstrated for 4-chloronitrobenzene, which undergoes exclusive substitution of chlorine unless strong base is present to favour the VNS process. The deuterium isotope effect for VNS hydroxylation by Bu^{t}OOH, determined as the ratio of H versus D substitution of 1-deutero-2,4-dinitrobenzene, varied from 7.0 ± 0.3 to 0.98 ± 0.01 as the base in NH_3 was changed from NaOH to Bu^{t}OK; the former value is consistent with a rate determining $E2$ process.

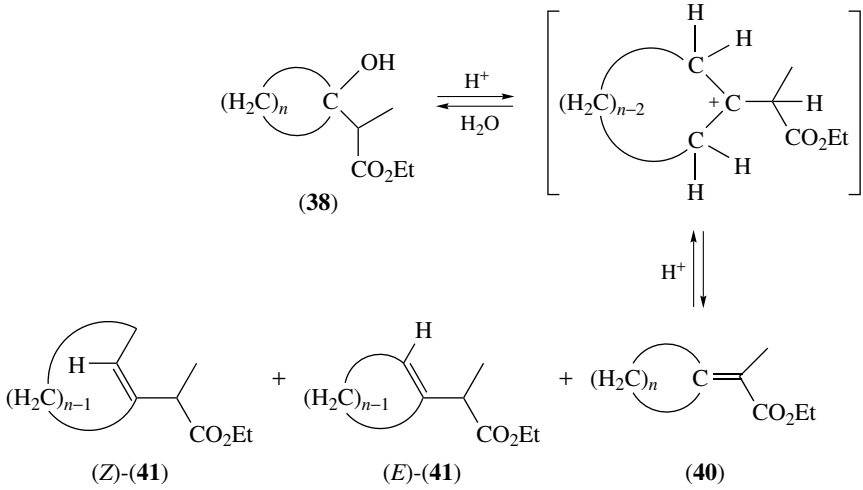
Solvolytic Reactions

Salt effects on monomolecular heterolysis reactions (S_N1, $E1$, $F1$, solvolysis) have been reviewed[28] and the effects of salts on the rate of dehydrobromination of 3-bromocyclohexene have been interpreted.[29] The regiochemistry and stereochemistry



SCHEME 4

of elimination of water from tertiary alcohols (**38**) of ring size $(n + 1) = 5–16$ have been reported (see Table 1).[30] The reaction is presumed to proceed via an intermediate carbenium ion which then deprotonates to give isomeric alkenes (**40**) and (*E*)- or (*Z*)-(**41**). The behaviour of the medium sized rings can be explained in terms of I-strain.



(**38**)

(*Z*)-(**41**) (*E*)-(**41**) (**40**)

TABLE 1. Distribution (%) of alkenes formed from (**38**)

$n+1$	(**40**)	(*E*)-(**41**)	(*Z*)-(**41**)
5	34	66	0
6	0	100	0
7	20	80	0
8	8	92	0
9	2	96	2
10	0	100	0
11	1	89	10
12	1	86	13
13	4	68	28
14[a]	15	60	25
15	28	54	18
16	7	73	20

[a]Results calculated by extrapolation.

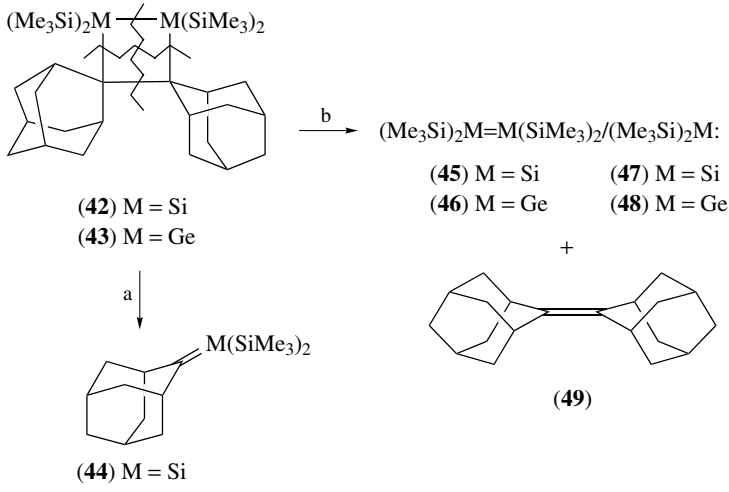
Specific acid-catalysed solvolysis of 1-methoxy-1,4-dihydronaphthalene or 2-methoxy-1,2-dihydronaphthalene in 25% acetonitrile in water has been found to yield mainly the elimination product, naphthalene, along with a small amount of 2-hydroxy-1,2-dihydronaphthalene, there being no trace of either the 1-hydroxy-1,4-dihydronaphthalene or the rearranged ether.[31] The nucleophilic selectivity, $k_{N3}/k_{HOH} = 2.1 \times 10^4$, between added azide ion and solvent water has been estimated for the relatively stable ($k_w = 1 \times 10^7$ s^{-1}) intermediate benzallylic carbocation for which the barrier to dehydronation is unusually low ($k_e = 1.6 \times 10^{10}$ s^{-1}), as evidenced by the large elimination-to-substitution ratio with solvent water as base/nucleophile. The kinetics of acid-catalysed solvolysis of 1-hydroxy-1,4-dihydronaphthalene and 2-hydroxy-1,2-dihydronaphthalene have also been studied.

Pyrolytic Reactions

Cycloreversions

The retro-Diels–Alder reaction has been reviewed.[32] A fully concerted cyclic transition state has been proposed for conrotatory opening of cyclobutenes, in order to account for the low activation entropy and unexpected activation volume of ca -2 to $-3\ cm^3\ mol^{-1}$.[33]

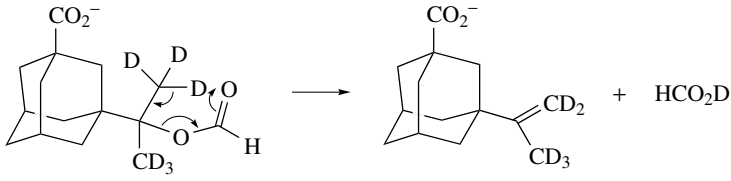
2 + 2-Cycloreversions of a 1,2-disilacyclobutane (**42**) and a 1,2-digermacyclobutane (**43**) have been induced in solution both thermally and photochemically; fragmentation of sterically congested (**42**) follows Scheme 5 paths a and b, respectively; fragmentation of (**43**) yields (**46**) (which photodissociates to **48**) in each case.[34]



SCHEME 5

Acid Derivatives

Further evidence has been reported in favour of the loss of neutrals (even-electron) from even-electron anions by a charge-remote process.[35] Thus, the parent $(M-H)^-$ ion (**50**), in which the 1- and 3-substituents on adamantane can neither interact through bonds nor approach through space, has been found to fragment by exclusive loss of HCO_2D. The corresponding carboxylate cation $(M-H)^+$, generated by charge reversal of anion (**50**), has been shown to behave likewise.

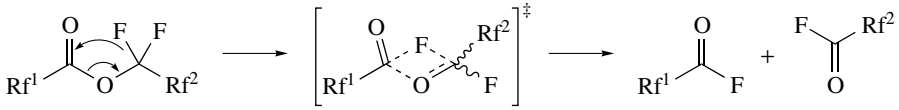


(**50**) (**51**)

Unimolecular pyrolysis of the tautomers of monothioformic acid (two conformers of thiol- and two conformers of thiono-) have been studied by *ab initio* methods with STO-3 G and 6–31 G** basis sets.[36] The barrier heights for dehydrogenation (via a four-centre transition state) and dehydrogensulfidation (via a three-centre transition state) of thiol formic acid are 67.47 and 67.09 kcal mol^{-1}, respectively. Dehydration of *s-cis*-HCSOH occurs via a three-centre transition state with an activation energy of 81.18 kcal mol^{-1}; this is much greater than for dehydration of the *s-trans* form, which occurs via a four-centre transition state with a barrier of only 68.83 kcal mol^{-1}.

Results of HF/3–21 G theoretical studies of gas-phase dehydration of α-hydroxy acids suggest that the reaction is favoured by electron-donating substituents via a three-membered ring intermediate formed via a five-membered ring transition state; a three-membered ring transition state governs formation of product in the second step.[37]

Certain perfluoro esters (**52**) (incapable of the eliminative fragmentation, with β-hydrogen migration, commonly displayed by hydrocarbon esters) have been shown to decompose at elevated temperature (230–250 °C).[38] AM1 semiempirical calculations suggest that a four-membered transition state (**53**) featuring transfer of α-fluorine to the carbonyl carbon is involved; this is consistent with the negative entropy of activation and relatively high activation energy.



(**52**) (**53**)

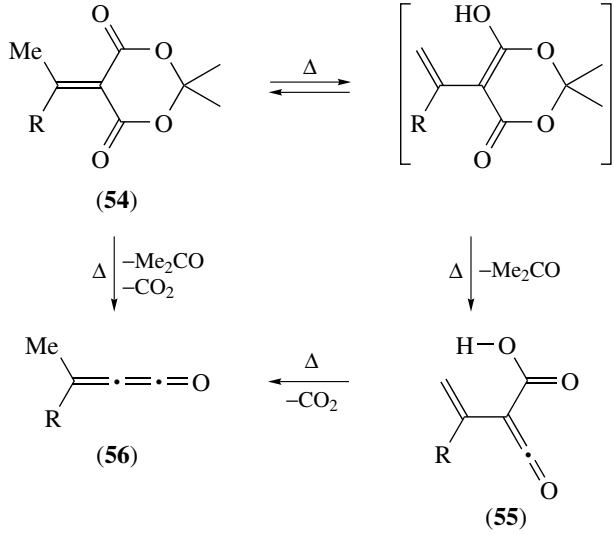
Further theoretical study of the mechanism of decomposition of β-propiolactone and β-butyrolactone, to form CO_2 and ethene or propene, respectively, has concluded that the process can best be described as asynchronous and concerted.[39] Calculations also suggest that concerted processes are preferred for both decarbonylation and decarboxylation of η-thiobutyrolactone.[40]

Direct evidence has been reported for the formation of methoxyvinyl- and methylthiovinyl-(carboxy)ketenes (**55c** and **55d**) upon flash vacuum thermolysis of Meldrum's acid derivatives (**54c**) and (**54d**), respectively;[41] the intermediates decarboxylate readily to give (**56c**) and (**56d**), respectively, and are more transient than those obtained previously from (**54a,b**).

First-order kinetics have been reported for gas-phase thermal decomposition of nitroethyl carboxylates to give nitroethylene and the corresponding aliphatic acid.[42]

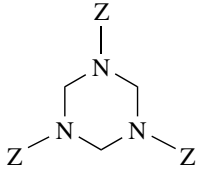
Nitrogen Compounds

Activation parameters have been determined for eliminative thermal decomposition of hexahydro-1,3,5-trinitro-1,3,5-triazine and related compounds, under high pressure in dilute solution.[43] The negative activation volumes, low enthalpies of activation,

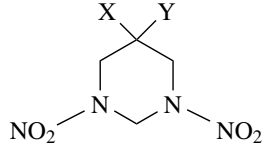


a; R = H, **b**; R = Me, **c**; R = MeO, **d**; R = MeS

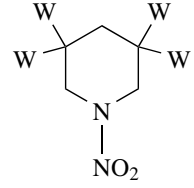
order of thermal stability and detection of aromatic products suggest that these cyclic nitramines and nitrosamines decompose through elimination of HNO_2 or HNO by a non-homolytic pathway which is dependent on reaction conditions and structural features. The order of stability (**58a > 57b > 57a > 58b > 59**) is consistent with the expected decrease in acidities of the methylene hydrogens.



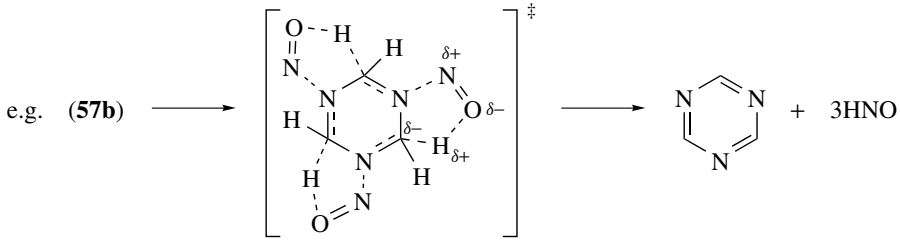
(**57a**) Z = NO_2
(**57b**) Z = NO



(**58a**) X = Me, Y = NO_2
(**58b**) X = NO_2, Y = NO_2

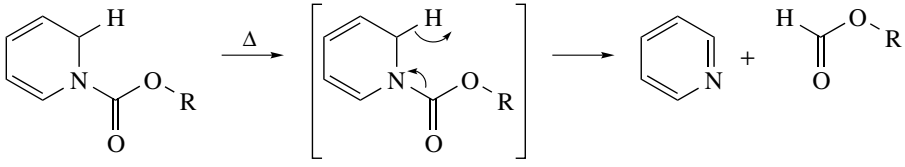


(**59**) W = NO_2



Formation of 2*H*-azirines by thermal decomposition of vinyl azides has been shown to exhibit small entropy of activation and insensitivity to solvent polarity; acyclic vinyl azides decompose more readily than analogous cyclic ones and it is advantageous to have a hydrogen atom *cis* to the azido group (*E*-are more reactive than *Z*-isomers).[44] These results and the linear correlation found for ring-substituent effects on decomposition of α-styryl azides are consistent with a nonconcerted mechanism in which elimination of nitrogen and cyclization into a three-membered ring proceeds synchronously.

It is clear from a study of thermal and radical-induced decompositions of *N*-alkoxycarbonyldihydropyridines that radical processes are of minor importance, and that pyridine formation is probably a consequence of 1,2-elimination of formate (Scheme 6).[45] It has also been concluded that the rate of 1,4-elimination of formate from *N*-alkoxycarbonyl-1,4-dihydropyridines at higher temperatures is too rapid to be explained by a homolytic process.

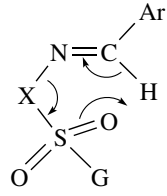


SCHEME 6

The thermodynamics and shock-tube kinetics of pyrolysis of azetidine, in argon at high dilution, have been compared with those for trimethylene oxide, sulfide and imine.[46]

Thermochemical parameters estimated by semiempirical AM1 calculations have been found to support the proposal that isobutene formation on gas-phase thermolysis of *N*-methyl-*N*-phenyl-*tert* -butylsulfenamide and morpholinyl-*tert* -butylsulfenamide occurs by a unimolecular mechanism involving a four-centre cyclic transition state and co-formation of the corresponding thiohydroxylamines.[47]

Kinetics and mechanisms of gas-phase pyrolysis of sulfonyl hydrazones and their oxime analogues have been reported for the first time;[48] it is proposed that cyanoarene formation arises in each case via a six-membered transition state (**60**). The lower limit



(**60**)

e.g. Ar = Ph, G = *p*-Tol, X = O or NH

for rate enhancement on replacing the hydrazone N−NH bond by the oxime N−O bond is $6-9 \times 10^4$ and the Hammett ρ value for the hydrazones is negligible (ca 0.01).

Other Pyrolytic Reactions

Comparison of results of single-pulse shock-tube experiments with those from an earlier study suggest that the existing rate expression for HF elimination from 1,1,1-trifluoroethane may need to be re-evaluated.[49]

The transition state for elimination of HF from hydrofluorocarbons has been probed by determining threshold energies and unimolecular rate constants for such reactions of chemically activated $CF_3CH_2CH_3$ and $CF_3CH_2CF_3$.[50] Chemically activated $CF_3CH_2CH_3$* containing 95 and 101 kcal mol^{-1} internal energy can be produced by combination of $CF_3CH_2^{\bullet}$ with $CH_3^{\bullet}$, or $CF_3^{\bullet}$ with $CH_3CH_2^{\bullet}$, respectively. The unimolecular elimination rate constants calculated from RRKM theory were fitted to the experimental values in order to obtain threshold energies, E_0, of 73 kcal mol^{-1} for $CF_3CH_2CF_3$ and 62 kcal mol^{-1} for $CF_3CH_2CH_3$; these, on comparison with those for CF_3CH_3 and CF_3CH_2Cl, show that replacement of H of $CF_3CH_3$by a methyl substituent lowers E_0 by ca 5 kcal mol^{-1}. The chlorine and fluorine substituents have the same effect on E_0 as a CF_3 group. Approach to the transition state for HF elimination apparently involves a flow of electron density from the departing hydrogen to the β-carbon, and from the β- to the α-carbon and to the α-carbon from its substituents; most of the incoming electron-density is passed from the α-carbon to the departing fluorine. Thus, electron-withdrawing substituents on either carbon raise E_0 because they hinder the flow of electron density.

Results of a PEPICO study of the dissociation dynamics of 2-bromobutane ions have been analysed with tunnelling-corrected RRKM statistical theory using vibrational frequencies obtained from *ab initio* MO calculations.[51] It has been concluded that the slow rate of loss of HBr, to form the but-2-ene ion, occurs via a concerted mechanism in which tunnelling is a feature of the proton transfer.

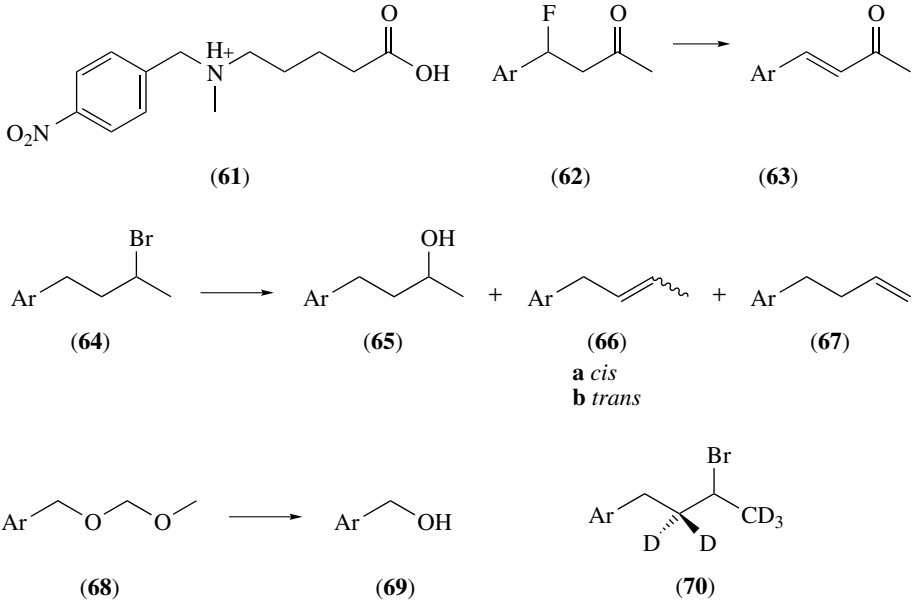
Theoretical predictions, based on AM1 MO theory, for gas-phase elimination reactions of 3-chloropropanoic and 2-chlorobutanoic acids are consistent with experimental results; four-, five-, and six-membered transition states have been discussed.[52]

o-Quinone methide is formed as a common intermediate on very low-pressure pyrolysis (550−1210 K) of *o*-hydroxybenzyl alcohol, 3,4-dihydro-2*H*-1-benzopyran (chroman) and 1,4-benzodioxin.[53] The respective processes involve dehydration, ethene elimination following initial cleavage of the phenoxy−carbon bond, and phenyl−vinoxy bond cleavage leading to formation of a four-ring intermediate which decarbonylates.

Reactions Catalysed by Biomolecules

Hapten design strategy for generation of an active site with a suitable catalytic residue has been further demonstrated. Thus, catalytic antibody 43D4−3D12, which was generated against the tertiary amine (**61**), has been found to catalyse the selective

elimination of HF from β-fluoro ketone (**62**) in aqueous medium and without competing substitution.[54] $Glu^{H}50$ acts as a general base at the active site; likewise, the antibody effects conversion of (**64**) to (**66a**) (18%), (**66b**) (72%), (**67**) (1%), and (**65**) (9%) by selective abstraction of the proton β- to the nitrophenyl ring. Reactions of the pentadeutero substrate (**70**) are subject to kinetic isotope effects of 2.9 and 4.1 for *cis* and *trans* elimination reactions, respectively. In contrast, $Glu^{H}50$ is believed to act as a general acid in catalysing hydrolysis of acetal (**68**) to the alcohol (**69**). The reactions share the nitrophenyl ring as a common recognition element and proton transfer as a mechanistic feature.



π-Stacking interactions and solvation effects within the highly preorganized cleft of a bifunctional C-shaped host are believed to benefit the base-promoted conversion of 5-nitrobenzisoxazole to 2-cyano-5-nitrophenolate relative to the acetate-promoted reaction; structural variation of the host has been explored.[55]

Elimination Reactions in Synthesis

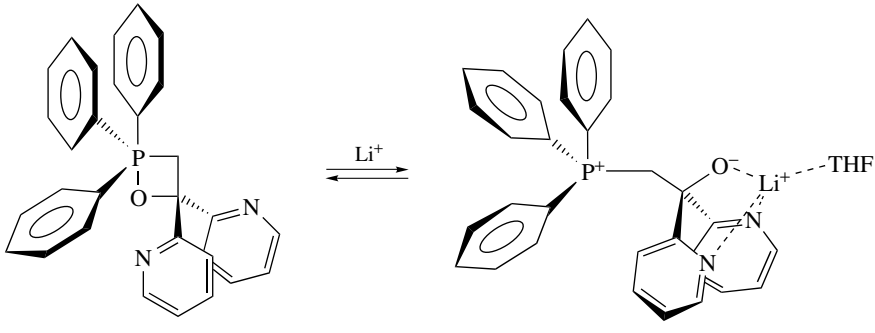
High-level quantum mechanical calculations have been used to explore the Horner–Wandsworth–Emmons reaction in the gas phase and also with a solvation contribution evaluated using the PCM/DIR method.[56] Ring closure of the P–O bond (TS2), to form oxaphosphetane, is rate determining in the absence of solvation; however, the oxyanion becomes a true intermediate, at an energy minimum on the reaction path, only in response to the effects of solvation, whereupon its formation by carbonyl addition (TS1) becomes rate limiting. Formation of *E*-product is always

favoured by TS2, whereas TS1 shifts the preference towards *Z*-selectivity if the phosphorus bears hydrogen-bond-donor ligands. The results emphasize the importance of addressing the relative stabilities of TS1 and TS2 in any interpretation of *E*/*Z* selectivities.

The *ab initio* MO(HF/3–21 G*) method and density functional (B3LPY/6–31 G*) theory have been used in higher level calculations for a range of oxaphosphetane reactions of MeCHO and PhCHO.[57] For both non-stabilized (alkylidene) and semi-stabilized (benzylidene) ylides it has been found that *cis* and *trans* oxaphosphetanes are formed via puckered and nearly planar transition states, respectively. However, in contrast with previous semiempirical calculations and in agreement with known product distributions, the puckered transition state is found to be favoured by the latter, on reaction with benzaldehyde. For reaction between PhCHO and $Ph_3P{=}CHPh$ the computed carbonyl kinetic isotope effect (at HF/3–21 G*) is 1.051 at 0 °C and in agreement with the experimental KIE; in contrast, disagreement between the computed value (1.039) and the experimental value (1.0) for reaction with $Ph_3P{=}CHPr$ suggests that some rate-determining alternative to the puckered transition state may apply for formation of *cis*-oxaphosphetane from this non-stabilized ylide.

Ab initio (HF and MP2) and MNDO-PM3 theoretical studies of the reaction of unstabilized ($Me_3P{=}CHCH_3$), semi-stabilized ($Me_3P{=}CHC{\equiv}CH$), and stabilized ($Me_3P{=}CHCN$) ylides with acetaldehyde have also been reported.[58] It has been concluded that oxaphosphetane formation proceeds by a very asynchronous cycloaddition (borderline two-step mechanism) in which the alignment of P, C, C, and O atoms is almost planar in the transition state; the extent of C–C bond formation ranges from 44% (unstabilized case) to 60% (stabilized case), whereas the degree of P–O bond formation is insignificant. Oxaphosphetane decomposition (retrocycloaddition) is also very asynchronous, with P–C bond breakage running ahead of C–O bond breakage. Unfortunately, the energy barriers calculated for the formation, pseudorotation, and decomposition of oxaphosphetane were very dependent on the level of theory employed.

Spectroscopic evidence for formation of a betaine lithium salt adduct during the course of a Wittig reaction has been reported for the first time.[59] The ylide $Ph_3P{=}CH_2$ formed oxaphosphetane (**71**) on treatment with 2,2′-dipyridyl ketone at −60 °C in

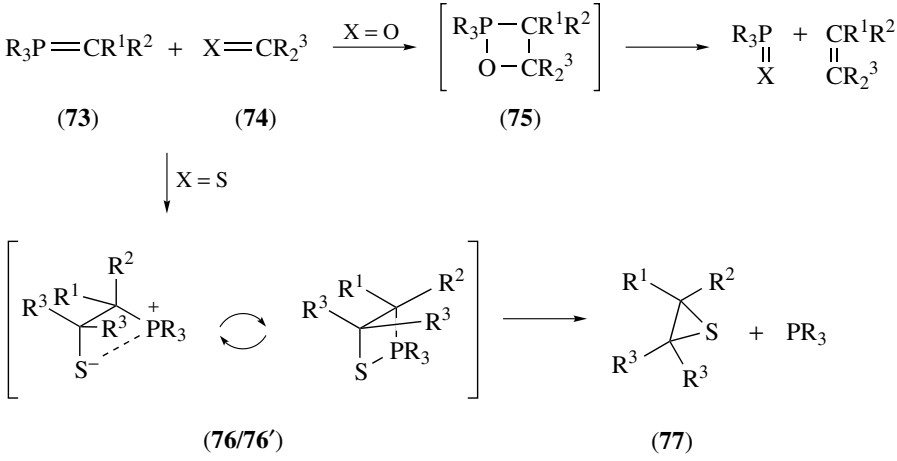


(**71**) (**72**)

THF; the ^{31}P NMR reveals only a singlet at $\delta_P = -63.2$, which, on addition of LiBr, gives way to a weak singlet at $\delta_P = +23.7$ which has been ascribed to the rather insoluble betaine (**72**).

A transition between thiaphosphetane- and *gauche*-betaine-type structures of intermediates in the thio-Wittig reaction of ylides $R_3P{=}CR^1R^2$ with $S{=}CR^3_2$ has been detected by ^{31}P NMR spectroscopy and predicted by computational study.[60] Thus *ab initio* calculations for reaction of (**73b**) with (**74b**) (X = O) reveal the formation of a conventional oxaphosphetane intermediate (**75b**) that features a planar four-membered ring, whereas the intermediate of the corresponding thio-Wittig reaction (X = S) is characterized by a large P−S separation and departure from planarity. The betaine character of the intermediate decreases upon reducing the phosphonium stabilization electronically, by substituting the Me_3P moiety consecutively by H_3P (**76c**) and $(CF_3)_3P$ (**76d**). The intermediate (**76a**) formed on reaction of ylide (**73a**) with thioketone (**74a**) in toluene at 233 K exhibits a ^{31}P NMR signal at −40 ppm in the range expected for a thiaphosphetane structure, whereas the product in dichloromethane features a signal at δ +1.0 ppm (at 243 K); both products decompose at slightly elevated temperatures to produce Ph_3PS and $Ph_2C = CH_2$ via a 2,2-diphenylthiirane intermediate (**77a**) and Ph_3P (Scheme 7). The ^{31}P NMR chemical shift of (**76a/76a′**) in toluene–dichloromethane mixtures varies continuously with solvent composition.

It has been suggested that the preferential formation of (*E*)-alkene on Wittig reaction of amide-substituted phenyl 3-pyridyl ketones with non-stabilized phosphorus ylides which contain a carboxyl terminus is a consequence of either hydrogen bonding or salt



a, $R^1 = R^2 = H$, $R = R^3 = Ph$

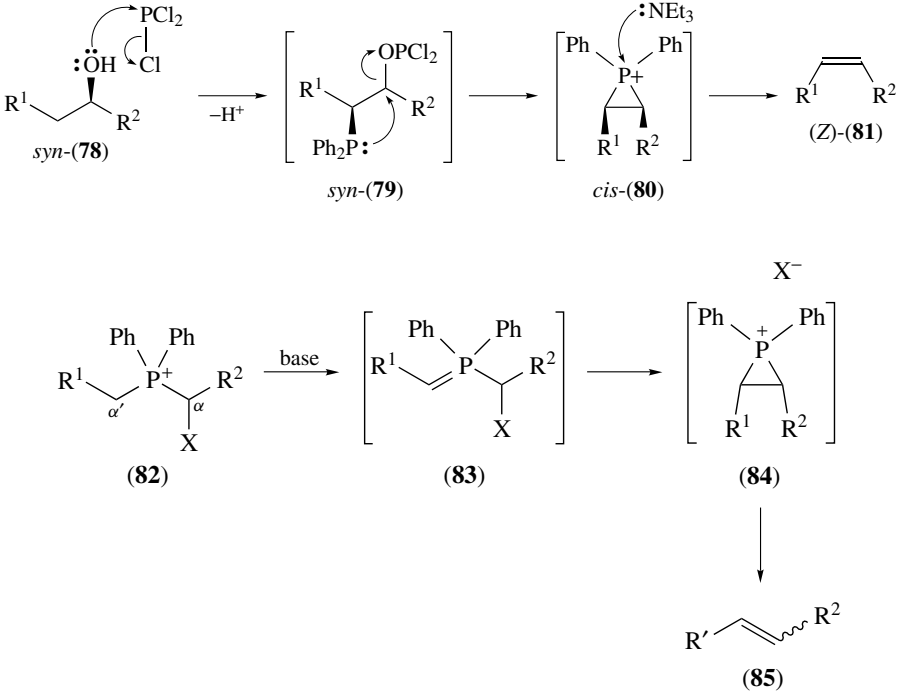
b, R = Me, **c**, R = H, **d**, $R = CF_3$, where $R^1 = R^2 = H$ and $R^3 = Me$

e, $R^3 = p\text{-}C_6H_4NMe_2$, **f**, $R^3 = p\text{-}C_6H_4OMe$, where $R^1 = H$, $R^2 = Me$ and R = Et

SCHEME 7

bridge formation between the amide group and the carboxyl terminus during formation of the oxaphosphetane intermediate.[61]

A means of forming alkenes by *anti* β-elimination of OH and a heteroatom group X on adjacent carbon atoms has been developed.[62] The reaction involves an *anti* Wittig elimination via an *epi*-phosphonium species (**80**); the reaction is induced by reacting *anti*- or *syn*-1,2-phosphinyl alcohols (**78**) with PCl_3 and Et_3N to give (*E*)- and (*Z*)-alkenes, respectively. The *epi*-phosphonium intermediate (**80**) undergoes nucleophile-induced extrusion of the phosphorus atom. Support for this suggestion has been gained by development of a phosphorus Ramberg–Bäcklund-type reaction (Scheme 8).[63] Treatment of (**82**, $R^1 = R^2 = Ph$, $X = Br$) with Et_3N gave stilbene (**85**) with *cis*-selectivity ($Z:E \approx 78:22$) that is comparable to that observed in the conventional Ramberg–Bäcklund reaction; the *E*/*Z* ratios determined for a series (**82**, $R^1 = Ph$, $R^2 = YC_6H_4$, $X = Br$) do not correlate with known effects of substituent Y.



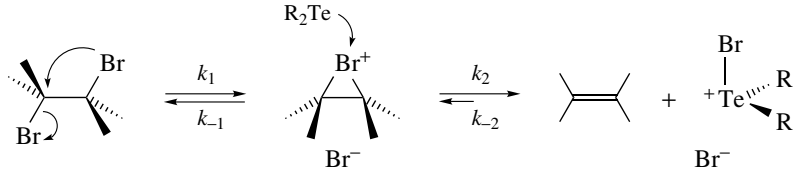
SCHEME 8

A new and convenient method of preparation of trichloro- and trifluoromethyl sulfones has found application in β-elimination of haloform via an unusually facile Ramberg–Bäcklund rearrangement under extremely mild and non-aqueous conditions.[64] Thus, 9-fluorenyl trichloromethyl sulfone in $CHCl_3$ affords

9-dichloromethylenefluorene in quantitative yield at room temperature on treatment with DBU, Et_3N, DABCO, morpholine, or even 2,6-lutidine. The expected β-elimination of $CHCl_3$ and accompanying sulfene formation did not occur, nor could they be achieved by using alternative benzylic or benzhydrylic trichloromethyl sulfones.

The effects of solvent, temperature, and bulk of the silyl and carbamate functionalities on the stereochemistry of Peterson olefinations of silylated benzyl carbamates (to give substituted vinyl carbamates) has been investigated.[65] Steric/electronic bulk of the triphenylsilyl moiety appears to be the overriding factor in promoting *Z*-selectivity.

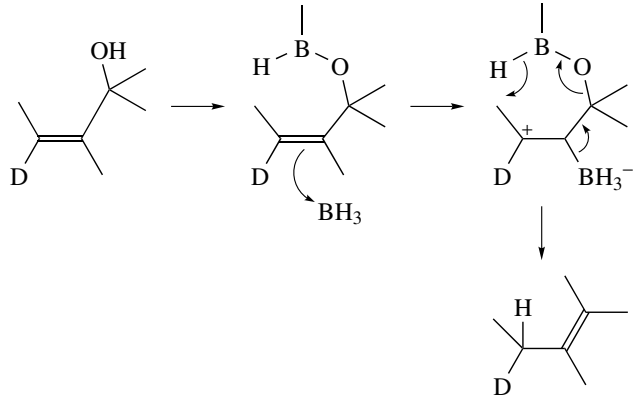
A study of debrominations of *vic*-dibromides promoted by diaryl tellurides and di-*n*-hexyl telluride has established several key features of the elimination process: the highly stereoselective reactions of *erythro*-dibromides are much more rapid than for *threo*-dibromides, to form *trans*- and *cis*-alkenes, respectively; the reaction is accelerated in a more polar solvent, and by electron-donating substituents on the diaryl telluride or carbocation stabilizing substituents on the carbons bearing bromine.[66] Alternative mechanistic interpretations of the reaction, which is of first-order dependence on both telluride and *vic*-dibromide, have been considered. These have included involvement of $TeAr_2$ in nucleophilic attack on carbon (with displacement of Br^- and formation of a telluronium intermediate), nucleophilic attack on bromine (concerted *E*2-like debromination) and abstraction of Br^+ from an intermediate carbocation. These alternatives have been discounted in favour of a bromonium ion model (Scheme 9) in which the role of $TeAr_3$ is to abstract Br^+ in competition with reversal of the preequilibrium bromonium ion formation. The insensitivity of reaction rate to added LiBr suggests that the bromonium ion is tightly paired with Br^-.



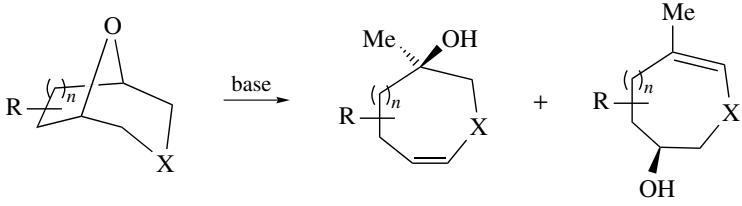
SCHEME 9

A modification of an earlier procedure for debromination of *vic*-dibromides in the presence of catalytic amounts of diorganotellurides has allowed the synthesis of terminal alkenes and *cis*- and *trans*-1,2-disubstituted alkenes from appropriate precursors;[67] the relative substrate reactivities suggest that, as for the stoichiometric reaction, the catalytic reaction involves intermediate bromonium ion formation. The Te(IV) dibromides formed in the debrominative elimination are reduced back to the catalysts by either sodium ascorbate or the thiol glutathione.

Hydroboration of a 5β-hydroxyandrost-3-ene has been found to induce facile elimination of the 5β-hydroxy group; results of a deuterium labelling study of the fate



SCHEME 10



(**86**) (**87**) (**88**)

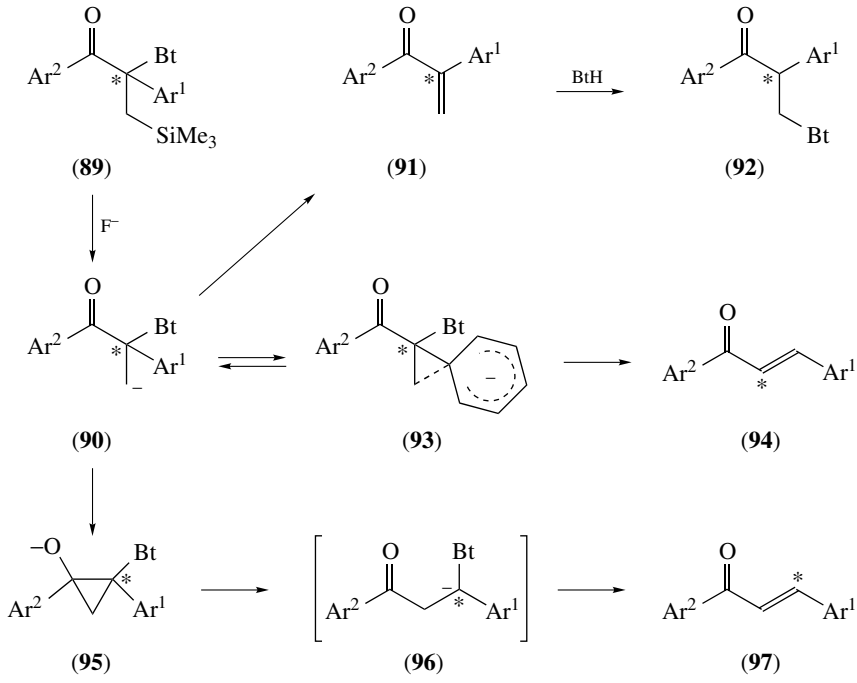
X = S, SO_2, *N*-Boc
n = 1,2

of deuterium at C(3) suggest that this may involve a *trans*-diaxial borane–borinate elimination coupled with a *syn* transfer of hydrogen from the bromide (Scheme 10).[68]

A study of ring opening of hetero-oxabicyclic [3.2.1] and [3.3.1] systems (**86**) has established that for X = SO_2 or *N*-Boc the selectivity is low.[69] Preferential formation of (**87**) rather than (**88**) is dependent on selective removal of the axial versus the equatorial proton.

Other Reactions

A carbon labelling study has elucidated the rearrangement mechanism for formation of chalcone (**97**) which accompanies formation of (**91**) by the expected vicinyl elimination of trimethylsilyl and benzotriazolyl groups from 2-benzotriazolyl-2-aryl-3-ketopropylsilanes, on reaction with fluoride ion in DMF.[70] Thus, it has been possible to distinguish between the two alternative mechanisms depicted in Scheme 11 (via intermediates (**93**) or (**95**), respectively, by determining the fate of the labelled quaternary carbon of substrate (**89**). The results are consistent with the formation of a cyclopropane intermediate (**95**) which subsequently ring opens, with relief of strain, to form delocalized carbanion (**96**), from which the chalcone (**97**) is obtained (labelled



SCHEME 11

β- to the carbonyl group) following protonation and β-elimination of triazole. Formation of (**95**), and hence (**97**), are favoured by aryl (Ar^2) substituent effects which increase the electrophilicity of the adjacent carbonyl group

On acetolysis in the presence of NaOAc, triterpenoid tosylates have been found to form substitution products by bimolecular processes (S_N2 on carbon, S_AN on sulfur) and elimination products often via intermediates formed by hydride and/or methyl shifts.[71]

Rate and equilibrium constants for ring opening of 2-[(4-dimethylamino)phenyl]-1,3-thiazolidine to an imminium ion in aqueous solution at 25 °C have been compared with literature values for *N*-Bu-and *N*-Ph-substituted thiazolidines derived from 4-dimethyaminocinnamaldehyde and discussed with reference to Baldwin's rules.[72] The rate of ring opening (which is greatest for the N−H thiazolidine) varies by 10^8-fold, mainly as a consequence of steric interactions between the substituents at N and C(2) in the ring-opening transition state; the corresponding variations in equilibrium constants are small.

The mechanism of formation of $PhC{\equiv}CCO_2H$ from *trans*-$PhCH{=}CHCO_2H$ by stepwise bromination–dehydrobromination has been explored.[73]

Nucleophilic attack of hydroxide ion on the α-carbon atom, with subsequent cleavage of the $C_\alpha-C_\beta$ bond, has been proposed to account for the kinetics of retro-aldol reaction of substituted benzylidene malononitriles with hydroxide ion in 90%

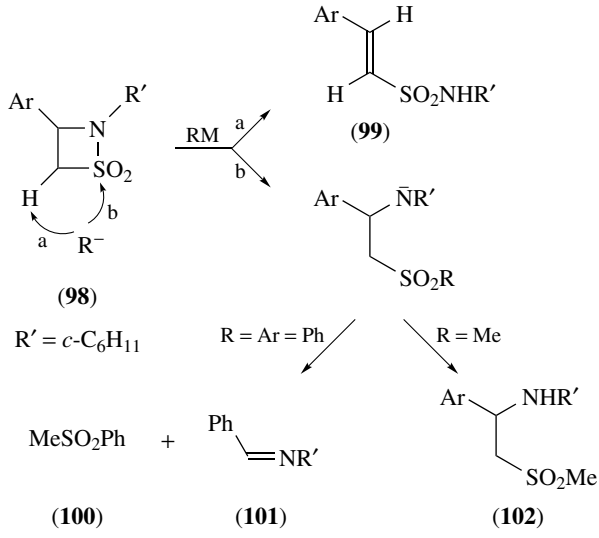
MeOH–10% H_2O.[74] The reaction rates, which are increased by electron-withdrawing aryl substituents, have been correlated using the Hammett equation.

The leaving group dependence of activation parameters found for reaction of 2-(β,β-dihalovinyl)-5-nitrothiophenes with NaOMe in MeOH ($\Delta S^{\neq}$ negative for Cl, zero for Br, and positive for I) suggest that the substitution reaction proceeds via an addition–elimination mechanism, with formation of an intermediate haloalkyne, for the bromide and iodide.[75]

A search for examples of charge-remote reactions of even-electron organic negative ions in the gas phase has featured collision-induced decompositions of 3-substituted adamantanecarboxylate anions.[76] Fragmentations of the 3-substituent (which the CO_2^- group is unable to approach) is likely to occur when there is no suitable lower energy decomposition channel directed by the charged site. Charge-remote radical losses from 3-$CH(Et)_2$ and 3-CO_2Me are observed and elimination of MeOD and HCO_2D from 3-$C(CD_3)_2$(OMe) and 3-$C(CD_3)_2$(OCH=O), respectively, has been studied.

4-Non-substituted β-sultams (**98**) undergo eliminative formation of (*E*)-vinylsulfonamides (**99**) on reaction with MeLi but are subject to competing substitution (with ring opening) to give (**102**) when MeMgBr is used.[77] 4-Monosubstituted β-sultams react with organometallics, MeLi, PhLi, MeMgBr, by stereoselective formation of only (*E*)-vinylsulfonamides regardless of the configuration of the 3- and 4-substituents.

The pH–rate profile for reaction of nitrosobenzene with *N*-methylhydroxylamine (to form only 1-methyl 2-phenyldiazene-2-oxide) has been found to exhibit a negative break between pH 0.5 and 3.0. This has been ascribed to a change in rate-determining step from nucleophilic attack on nitrosobenzene at low pH to dehydration of the *N*,*N*′-dihydroxy intermediate at higher pH;[78] the dehydration is subject to general-acid catalysis ($\alpha = 0.34$) and specific and general-base catalysis ($\beta = 0.20$). The pH–rate profile is similar to that for reaction of *N*-methylhydroxylamine with



p-chlorobenzaldehyde, which is also believed to proceed by an ionic (rather than free radical) mechanism. However, the behaviour of MeNHOH contrasts with that for analogous reaction of nitrosobenzene with phenylhydroxylamine for which dehydration of the addition intermediate is rate determining throughout the pH range. Comparison of the rate constants for the oxonium-ion-catalysed reactions of PhNO with MeOH and PhNHOH provides further indication that special factors apply to the latter (as found previously for reaction with benzaldehyde); a pre-association mechanism has been discussed.

Results of *ab initio* studies lend support to a mechanism, involving initial formation of Me_3C^+, CO_2 and $Me_3COC(O)N{=}N^-$, proposed to account for oxidative fragmentation of di-tert-butyl azodicarboxylate promoted by thianthrenium perchlorate.[79]

Results of a study of acid-catalysed epimerization of indolo [2,3-*a*]quinolizidine derivatives support a mechanism involving nitrogen lone pairs in an eliminative ring opening–ring closure.[80]

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CHAPTER 13

Addition Reactions: Polar Addition

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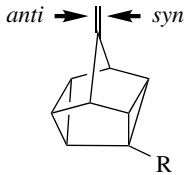
Reviews

During the coverage period of this chapter, reviews have appeared on the following topics: reactions of electrophiles with polyfluorinated alkenes,[1] the mechanisms of intramolecular hydroacylation and hydrosilylation,[2] Prins reaction (reviewed and redefined),[3] synthesis of esters of β-amino acids by Michael addition of amines and metal amides to esters of α,β-unsaturated carboxylic acids,[4] the 1,4-addition of benzotriazole-stabilized carbanions to Michael acceptors,[5] control of asymmetry in Michael additions via the use of nucleophiles bearing chiral centres, α,β-unsaturated systems with the chirality at the γ-position, and the presence of chiral ligands or other chiral mediators,[6] syntheses of carbo- and hetero-cyclic compounds via Michael addition of enolates and activated phenols, respectively, to α,β-unsaturated nitriles,[7] and transition metal catalysis of the Michael addition of 1,3-dicarbonyl compounds.[8]

Electrophilic Additions

Facial selectivity in electrophilic additions (carbene addition, mercuration, epoxidation, and hydroboration) to 4-substituted 9-methylenenorsnoutanes (**1**) as model alkenes has been elucidated and the observed preference for *syn*-attack (Table 1)



(**1**)

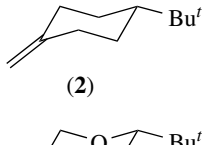
TABLE 1. *Syn/anti* ratio in electrophilic additional to (**1**)

	syn/anti			
R	$:CCl_2$	$(AcO)_2Hg$	MCPBA	$BH_3.THF$
CN	61:39	>90:10	—	—
CO_2Me	60:40	>90:10	66:34	60:40
CH_2OMe	56:44	76:24	57:43	54:46

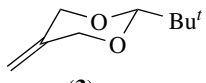
rationalized by theoretical methods. The *ab initio* MESP maps indicate that electrostatic factors and through-space interaction between the double bond and cyclopropane Walsh orbitals are unimportant in determining the face selectivity, whereas AM1 transition-state energetics suggest that the observed preferences are determined primarily by through-bond interactions.[9]

The origin of stereofacial selectivity in electrophilic additions to methylenecyclohexanes (**2**) and 5-methylene-1,3-dioxane (**3**) has been elucidated experimentally (Table 2) and theoretically. *Ab initio* calculations suggest that two electronic factors contribute to the experimentally observed axial stereoselectivity for polarizable electrophiles (in epoxidation and diimide reduction): the spatial anisotropy of the HOMO (common to both molecules) and the anisotropy in the electrostatic potential field (in the case of methylenedioxane). The anisotropy of the HOMO arises from the important topological difference between the contributions made to the HOMO by the periplanar β C−H σ-bonds and opposing β C−O or C−C σ-bonds. In contrast, catalytic reduction proceeds with equatorial face selectivity for both the cyclohexane and the dioxane systems and appears to be governed largely by steric effects.[10]

In a related study, axial attack on the exomethylene double bond of (**2**) and (**4**) was also observed for *N*-bromo- and *N*-iodoacetamide (Scheme 1). However, the regiochemistry differed dramatically, as (**2**) obeyed the Markovnikov rule whereas (**4**) gave anti-Markovnikov products. Here, the direction of initial electrophile attack is in line with the frontier orbital and electrostatic considerations. The regiochemistry of addition is strongly affected by hyperconjugative effects, acting between the intermediate epihalonium ion and the β C−X bonds. Where the β C−X bonds bear a fixed periplanar relation to the epihalonium ion and X [as shown for carbocation (**5**)] is more electronegative than hydrogen, anti-Markovnikov addition is strongly promoted and becomes exclusive when two such β C−X bonds are present [as in (**4**)].



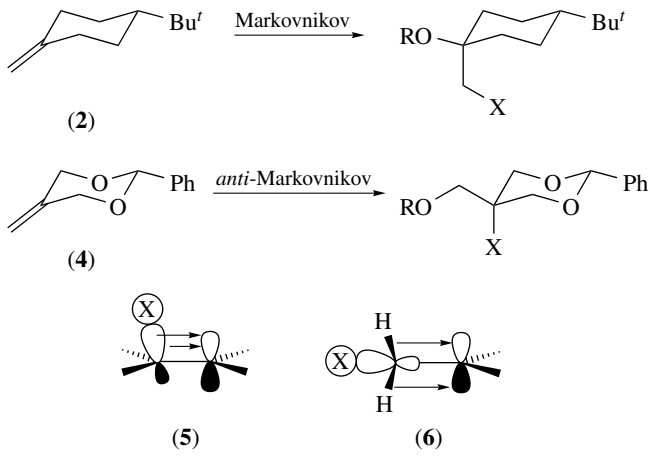
(**2**)



(**3**)

TABLE 2. Axial/equational attack in electrophilic additions to (**2**) and (**3**)

Compound	Reagent	ax:eq
(**2**)	RCO_3H	70:30
(**3**)	RCO_3H	56:44
(**2**)	Diimide	51:49
(**3**)	Diimide	95:5
(**2**)	H_2/Pt	16:84
(**3**)	H_2/Pt	9:91



SCHEME 1

If the β C−X bond is free to rotate away from periplanarity, then β C−H bonds will adopt the geometry required for hyperconjugation [as shown for carbocation (**6**)] and Markovnikov regiochemistry will be favoured. The results are consistent with *ab initio* theoretical calculations and can be rationalized using a simple electrostatic model.[11]

The observed regioselectivity of the addition of asymmetrically substituted olefins $RCH{=}CH_2$ (R = Me, OH, CO_2H, CN, Cl, etc.) was rationalized in terms of the magnitude of the electronic effect, calculated by using the ^{13}C NMR chemical shifts for monosubstituted benzene and polarizability.[12]

Halogenation and Related Reactions

The kinetics of chlorination of ethylene, allyl chloride, 3,4-dichlorobutene, 2,3-dichloropropene, and 1,2-dichloroethylene in 1,2-dichloroethane have been investigated in the presence of Bu_4NCl. The mathematical treatment of the results was performed with due regard to the equilibrium constants of the formation of complexes between Cl_2 and Cl^-. For all the substrates at 256 K, the introduction of Cl^- into the system has been found to result in an increase in the rate of the addition. The reaction turned out to be of first order with respect to both the substrate and the salt and second order with respect to chlorine. As expected, the dependence of the reaction rate on the substituents at the double bond is compatible with the electrophilic addition, initiated by electrophilic chlorine.[13]

Semiempirical and *ab initio* calculations of the potential-energy surface for the addition of Cl_2 to $CH_2{=}CH_2$ in the presence of Cl^- in the gas phase and in polar solvent led to the identification of the reactant [$Cl^-{\bullet}Cl_2{\bullet}CH_2{=}CH_2$] and the product [$CH_2ClCH_2Cl{\bullet}Cl^-$] minima in the gas phase; only the product minimum was found in the solution. Potential barriers in the two systems were compared.[14]

The deuterium kinetic isotope effect (DKIE) for the electrophilic bromination of ethylene-h_4 and ethylene-d_4 in methanol and dichloroethane at 25 °C has been

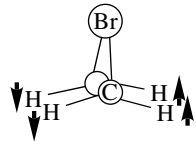
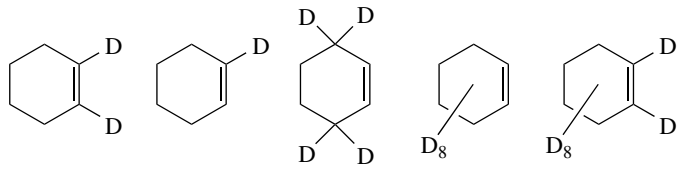


FIGURE 1 Symmetric twist in CH_2.

determined using mass spectrometry. The DKIEs are inverse, that in methanol being $k_H/k_D = 0.664 \pm 0.050$ and that in dichloroethane being $k_H/k_D = 0.572 \pm 0.048$. A product study of the bromination of *trans*-ethylene-d_2 in dichloroethane confirmed the *anti* stereochemistry of the addition. Computations of the expected equilibrium deuterium isotope effect (EIE) for the equilibrium $C_2H_4 + Br^+ \rightarrow C_2H_4Br^+$, using density functional theory (DFT), revealed that the EIE is also inverse at $K_H/K_D = 0.63$. Detailed analyses of the molar partition functions and the zero-point energies for the various vibrational modes in the ground and ion states indicate that the major contributor to the EIE is the creation of a new mode in the ion, termed the CH_2-symmetric twist, arising from the loss of the rotational freedom about the C−C axis in ethylene (Figure 1). In the absence of this new mode, the computed EIE is normal, $K_H/K_D = 1.12$. The computations also indicated that the ion state undergoes very little rehybridization of the carbons.[15]

The electrophilic addition of Br_2 to specifically deuteriated cyclohexenes (**7**)–(**11**) has been studied in MeOH by stopped-flow kinetics in order to determine a DKIE for the various isotopomers. The DKIE was also determined by a mass spectrometric method where the exactly known quantities of two of the cyclohexenes were incompletely brominated in MeOH and where the ratio of the remaining isotopomers was determined. A computational study using DFT was undertaken to examine the EIE for the equilibrium involving the formation of the cyclohexenyl bromonium ion from cyclohexene and Br_2. The agreement between experiment and theory was very good and indicated that, for perdeuteriocyclohexene, the inverse DKIE and EIE of ca 1.5 can be partitioned two-thirds to the two vinyl CHs and one-third to the four homoallylic CHs; the four allylic CHs contribute negligibly to the overall effect. The computational study also revealed an extensive mixing of the C−C and C−H vibrational modes but failed to identify all the individual modes responsible for the large inverse EIE. Analysis of the computational data suggests that the isotopic effects may be divided into two groups; those associated with the deuteriums at the vinyl positions and those associated with the remaining allylic and homoallylic carbons. In the former, the inverse EIE is due to the changes in all bending modes whereas, for the

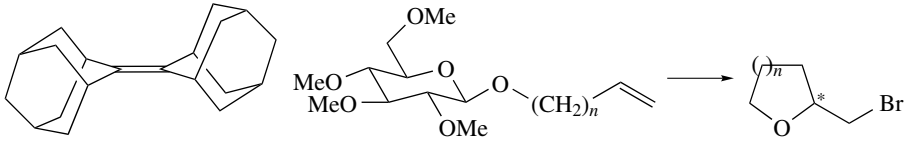


(**7**) (**8**) (**9**) (**10**) (**11**)

latter, the isotopically sensitive modes are those of all 10 C−H stretches with changes in bending frequencies being unimportant. The bending vibrational modes were found to be strongly coupled.[16]

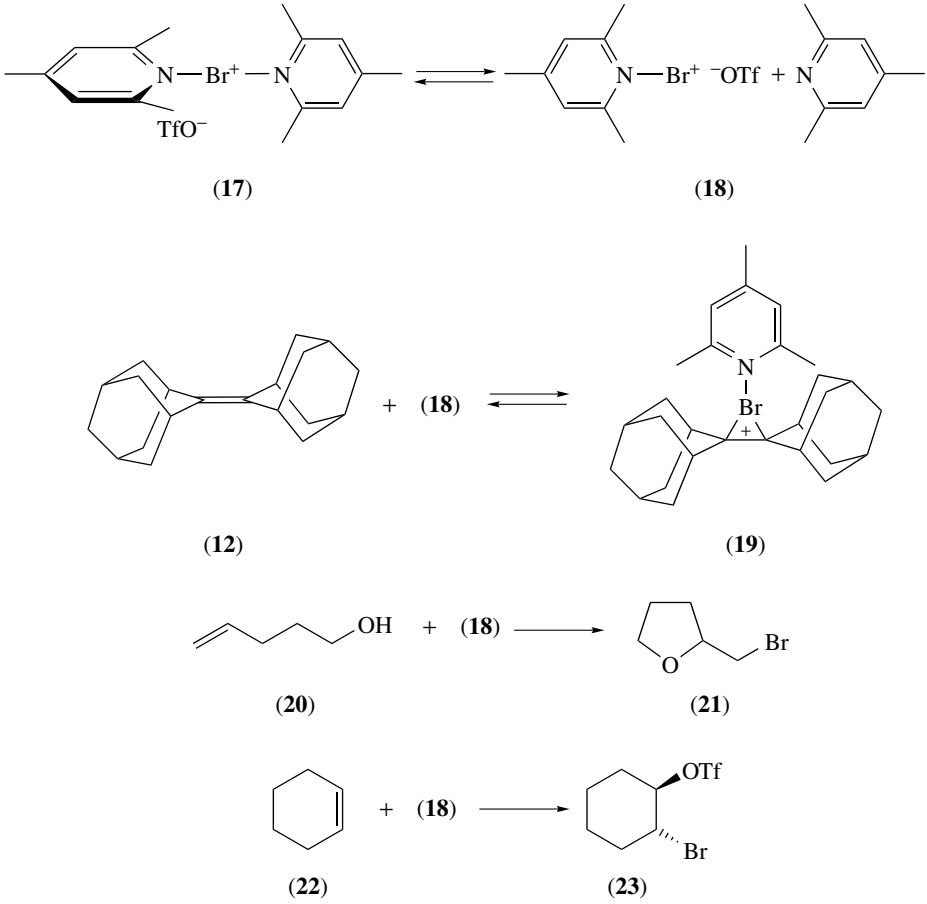
Rates and products of electrophilic bromination of ring-substituted *cis*- and *trans*-stilbenes have been investigated in acetic acid, trifluoroethanol, ethanol, methanol, and water–methanol mixtures. The mY_{Br} relationships (linear for nucleophilic solvents only, with $m = 0.8$), the deviations of the two non-nucleophilic solvents from the mY_{Br} plots (Δ_{AcOH} and Δ_{TFE}) positive, negative, or negligible), the kinetic solvent isotope effects ($k_{MeOH}/k_{MeOD} = 1.1–1.6$), the chemoselectivity (predominant dibromide, or solvent-incorporated adducts), and the high dependence of the stereochemistry on the solvent and the substituents (from stereoconvergency to stereospecificity) were analysed. The results were interpreted in terms of a mechanistic scheme, analogous to the Jencks' scheme for aliphatic nucleophilic substitutions, in which pre-association, free-ion, and ion-pair pathways compete. In particular, the stereochemical outcome of these reactions is consistent with a marked change in the nucleophilic partners of the product-forming ionic intermediate arising from different ionization routes. The observed change in the rate-limiting step from ionization to product formation, has been shown to be related to substituent-dependent (but not solvent-dependent) bromine bridging.[17]

The bromonium ion of adamantylideneadamantane (**12**) has been employed to induce the bromocyclization of a pent-4-enyl- and hex-5-enyl-glycosides (**13**) and (**14**) in CH_2Cl_2. The kinetics of those processes have been studied at 25 °C in varying concentrations of (**12**) and, in the case of (**13**), in the presence of pentanol. The second-order rate constants are $(1.04 \pm 0.06) \times 10^{-1}$ and $(5.34 \pm 0.2) \times 10^{-2}$ M^{-1} s^{-1}, respectively; the added (**12**) or pentanol did not alter the reaction rate. The kinetic behaviour was interpreted in terms of cyclization occurring directly from a 1:1 complex of (**12**)/Br_2 and (**13**) or (**14**). The asymmetric induction for (**13**) was 20% *ee*, (*S*)-(**15**) being the dominant enantiomer.[18]



(**12**) (**13**) $n = 3$ (**14**) $n = 4$ (**15**) $n = 3$ (**16**) $n = 4$

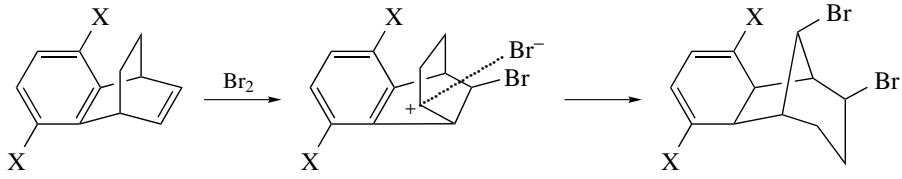
The kinetics of the reaction of bis(*sym*-collidine)bromonium triflate (**17**) with adamantylideneadamantane (**12**), pent-4-en-1-ol (**20**), and cyclohexene (**22**) have been investigated in 1,2-dichlorethane at 25 °C under a variety of conditions (Scheme 2). The rates of all the reactions proved to be depressed by added collidine, indicating that the first step for all is a reversible dissociation of (**17**) into free collidine and a reactive intermediate (**18**), which is then captured by the alkene. The product of the reaction of (**12**) with (**18**) is complex (**19**), while that of reaction of (**20**) is



SCHEME 2

the cyclic ether 2-bromomethyltetrahydrofuran (**21**). The reaction with cyclohexene (**22**) turned out to be more complex: it involves at least two reversibly formed intermediates, one of which is captured by attack of triflate to give *trans*-1-bromo-2-trifluoromethanesulfonylcyclohexane (**23**). Detailed kinetic analysis shows that the reactions of collidine, Ad=Ad, cyclohexene, and pent-4-en-1-ol with the reactive intermediate (**18**) are fast but not very sensitive to the nature of the nucleophile. The second-order rate constants are as follows: 3×10^6, 1.1×10^6, 1.5×10^5, and 4.5×10^4 M^{-1} s^{-1}, respectively. ^1H NMR analysis of the reaction of (**23**), produced *in situ* from cyclohexene and (**17**) in CD_2Cl_2, with $Bu_4N^+Br^-$ or $Bu_4N^+AcO^-$ indicates a very rapid and quantitative production of *trans*-1,2-dibromocyclohexane and *trans*-1-bromo-2-acetoxycyclohexane, respectively.[19]

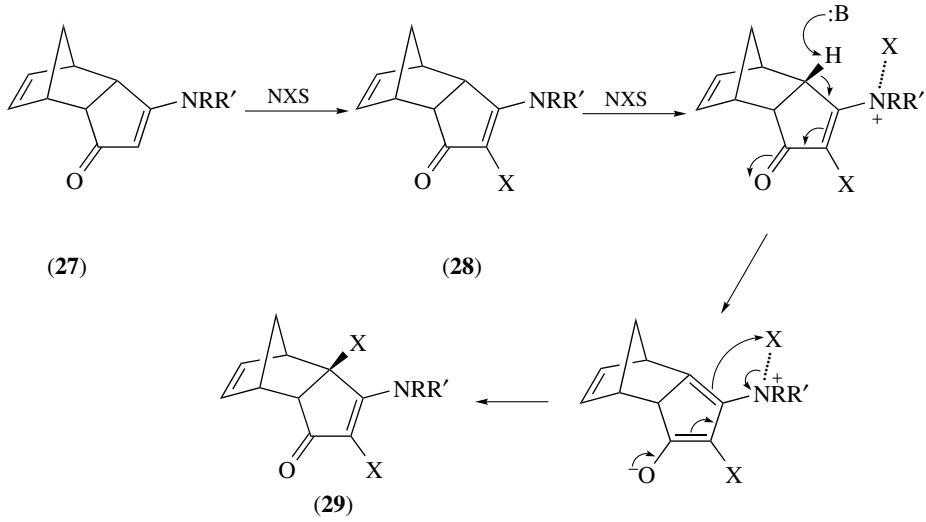
The bromination of 5,8-diacetoxy-1,4-dihydro-1,4-ethanonaphthalene (**24a**) was previously reported[20] to yield a single stereospecifically formed dibromide (**26a**), which was interpreted as indicating a significant interaction between the aryl



(**24a**) X = AcO (**25a**) X = AcO (**26a**) X = AcO
(**24b**) X = H (**25b**) X = H (**26b**) X = H

and alkene π-electron systems. A new *ab initio* study of the mechanism of the bromination of benzobicyclooctadiene (**24b**) now suggests that the stereochemistry is best accomodated by an asynchronous concerted electrophilic addition of bromine across carbons 1 and 3, and that it proceeds via an ion-pair transition structure (**25b**), in which the Wagner–Meerwein portion of the reaction has already occurred. All final results were calculated at the Becke3LYP/6–31 G* level.[21]

5-Amino-*endo*-tricyclo[5.2.1.$0^{2,6}$]deca-4,8-dien-3-ones (**27**) undergo a surprisingly effective regioselective halogenation using *N*-halosuccinimides (NXS) under electrophilic conditions (Scheme 3). Exclusive α-halogenation (**28**) was observed using 1 equiv. of NXS, whereas α,γ-bishalogenation products (**29**) are formed in quantitative yields with two equivalents of NXS. Interestingly, halogenation of the C(8)–C(9) norbornene bond was not observed.[22]

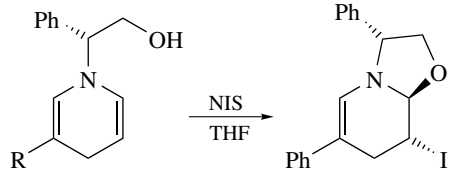


(**27**) (**28**)

(**29**)

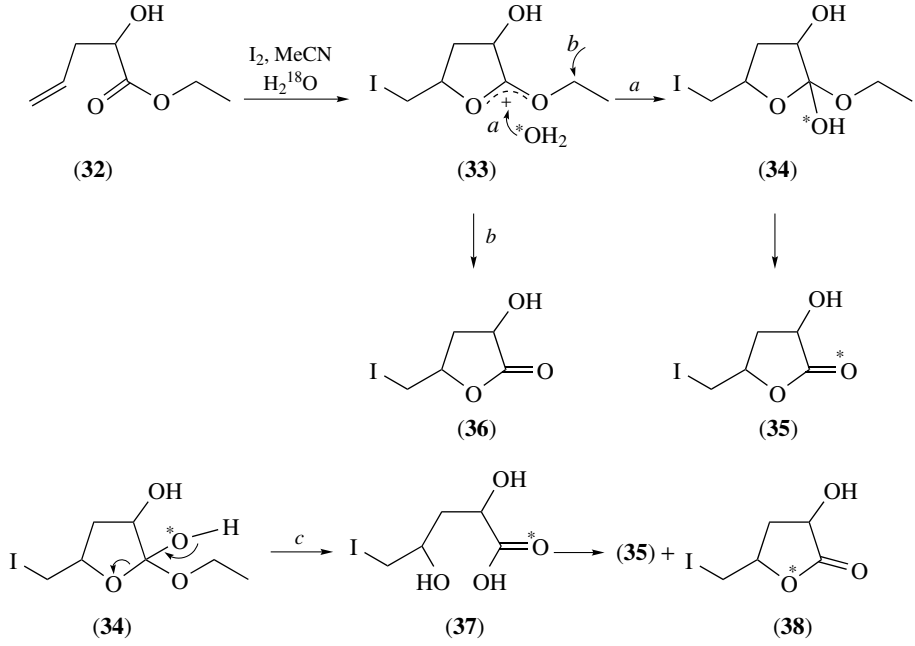
SCHEME 3

Iodine addition to 1,4-dihydropyridines, such as (**30**), with chiral appendix at the nitrogen atom, leads to an enantio-controlled 5(O)^n-*exo-Trig* cyclization to afford (**31**) as a 3:1 mixture of diastereoisomers.[23]



(**30**) (**31**)

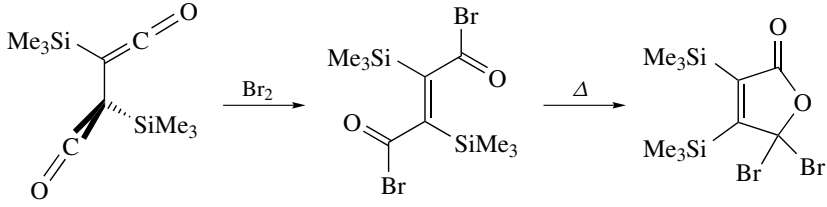
Iodocyclization of ethyl 2-hydroxyhex-5-enoate (**32**) and the homologous hept-6-enoate under thermodynamic or kinetic conditions gave the corresponding lactones (Scheme 4).[24] As an extension of this and earlier work,[25–27] oxygen-18 studies have revealed that the mechanism of iodolactonization of (**32**) is dependent upon the reaction conditions employed. Thus, when the reaction was carried out in MeCN and $H_2{}^{18}O$ in the presence of $NaHCO_3$, pathway *a* was identified as the only one that operates. By contrast, carrying out the reaction in anhydrous MeCN, followed by quenching with $H_2{}^{18}O$, promoted path *b*. Finally, anhydrous MeCN and anhydrous $NaHCO_3$, followed by quenching with $H_2{}^{18}O$, gave primarily the corresponding iodohydrin (**37**) that was then cyclized to the lactone (path *c*).[24]



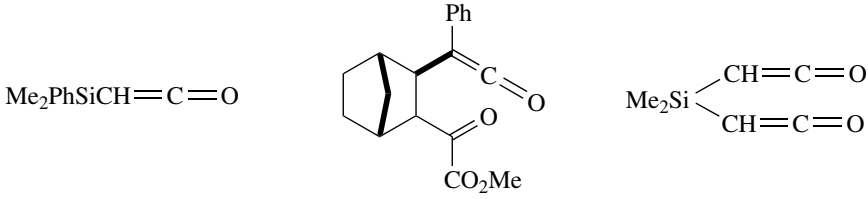
SCHEME 4

Addition of bromine to bisketene ($Me_3SiC{=}C{=}O)_2$ (**39**) has been shown to produce the fumaryl dibromide (*E*)-(**40**), which rearranged upon warming to furanone

(**41**) (Scheme 5). The latter process proved to be faster in the more polar CD_3CN than in $CDCl_3$, which is consistent with an ionization pathway for the rearrangement. The bromination of (**39**) in CH_2ClCH_2Cl followed second-order kinetics with a rate constant $(2.1 \pm 0.1) \times 10^4\ M^{-1}\ s^{-1}$ at 25 °C. The first-order dependence of bromine addition to (**39**) on $[Br_2]$ has been attributed to intramolecular nucleophilic assistance by the second ketenyl moiety in an initial complex of (**39**) and Br_2 to give (*E*)-(**40**). A transition structure for this process has been calculated by *ab initio* methods. By contrast, ketene (**42**) and γ-oxoketene (**43**) underwent bromination by third-order kinetics, second order in $[Br_2]$, indicating the absence of neighbouring group participation in the rate-limiting step. The bisketene (**44**) underwent bromination by mixed kinetics with both first- and second-order terms in $[Br_2]$.[28]



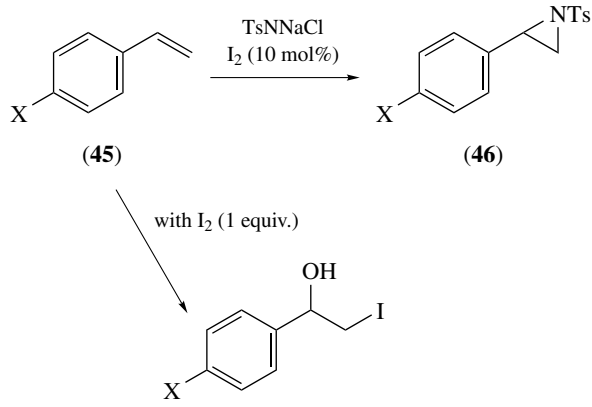
(**39**) (*E*)-(**40**) (**41**)



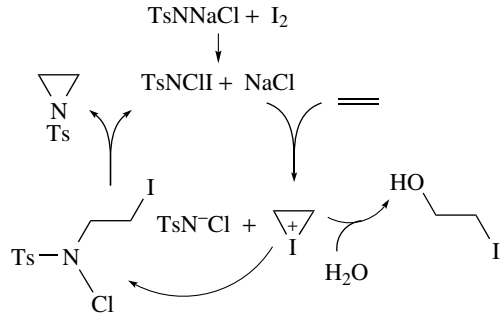
(**42**) (**43**) (**44**)

SCHEME 5

Iodine was found to be an efficient catalyst for the aziridination of alkenes (Scheme 6) utilizing chloramine-T (*N*-chloro-*N*-sodio-*p*-toluenesulfonamide) as the nitrogen source. For example, when 2 equiv. of styrene (**45a**) were added to chloramine-T in the presence of a catalytic amount of iodine (10 mol%) in a 1:1 solvent mixture of acetonitrile and neutral buffer, the corresponding aziridine (**46**) was obtained in 91% yield. The reaction proved to work with other acyclic and cyclic alkenes, such as oct-1-ene and cyclohexene. The aziridination of *para*-substituted styrene derivatives (**45b**–**e**) demonstrated that, as expected for an electrophilic addition, electron-rich alkenes reacted faster than electron-poor alkenes. However, with 1 equiv. of I_2, mainly iodohydrin (**47**) was formed. A catalytic cycle has been proposed to account for the fact that only a catalytic amount of iodine is required (Scheme 7).[29]



SCHEME 6

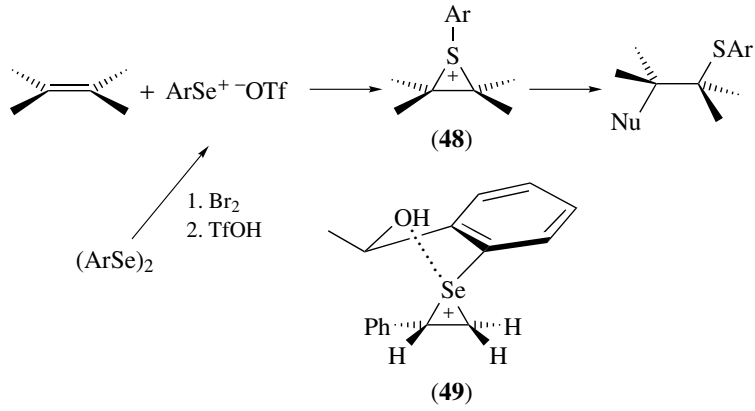


SCHEME 7

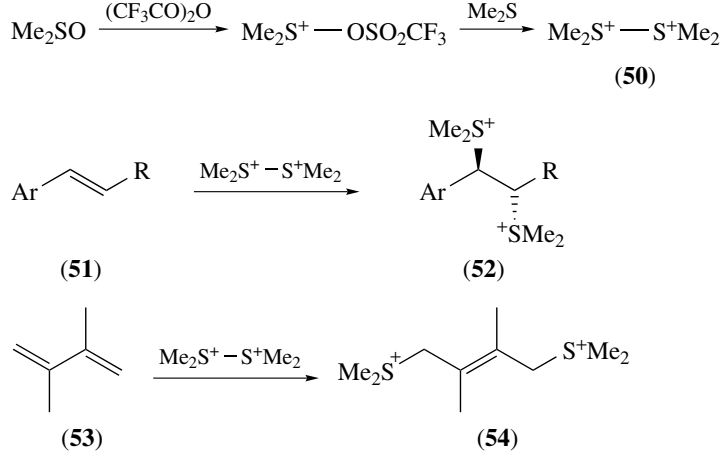
Mechanistic studies on the formation of $PhC{\equiv}CCO_2H$ from *trans*-$PhCH{=}CHCO_2H$ by stepwise bromination–dehydrobromination have been reported.[30,31]

Additions of ArSX, ArSeX, and Related Reactions

The mechanism of the asymmetric methoxyselenenylation of alkenes has been investigated using competition experiments and computational methods (Scheme 8). The experiments have demonstrated that the formation of the intermediate seleniranium ion (**48**) is reversible. Ions of type (**49**), generated in the addition of chiral selenium electrophiles to alkenes, are the key intermediates in the asymmetric methoxyselenenylation; their stability is strongly dependent on the strength of the selenium–heteroatom interaction. Calculations have been carried out to determine the relative stabilities of the diastereoisomeric seleniranium ions (**49**). The results obtained from the calculations support the experimental findings.[32]



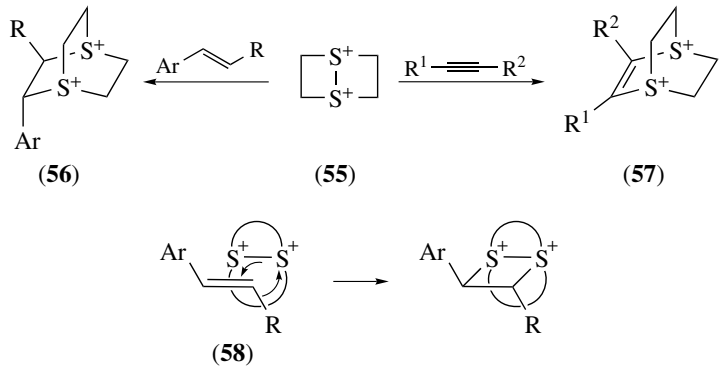
SCHEME 8



SCHEME 9

The first example of an acyclic S−S dication (**50**) has been prepared by acylation of DMSO with trifuoroacetyl anhydride followed by reaction with Me_2S (Scheme 9). The S−S dication (**50**) has been shown to add across a double bond in an *anti* fashion: (**50**) + (**51**) → (**52**). Conjugated dienes undergo 1,4-addition: (**53**) → (**54**).[33]

In a related study, the reactions of a bicyclic dithioether dication (**58**) (generated from 1,4-dithiane 1-oxide) with alkenes and alkynes has been found to proceed as conjugate addition of two sulfonium groups, giving rise to derivatives of dithioniabicyclo[2.2.2]octane (**56**) and (**57**), respectively (Scheme 10). The reaction is sensitive to electronic and steric factors and appears invariably to proceed with retention of the relative arrangement of substituents at the double bond of the original alkene (**58**).[34]



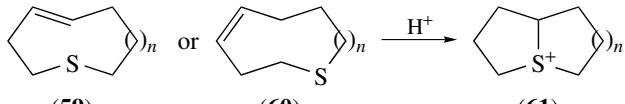
SCHEME 10

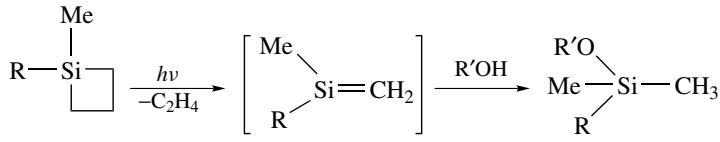
Additions of Hydrogen Halides and Other Acids

Ab initio calculations and density functional theory studies of the gas-phase addition of HF to $CH_2{=}CH_2$ have revealed the possibility of forming trimolecular (two HF and one ethylene) and dimolecular (one HF and one ethylene) complexes and transition-state structures and of the catalytic effect of the second molecule of the reagent. An energetically favourable pathway was selected on the basis of the computed potential-energy surface for these two reactions.[35]

The addition of 0.1 M quaternary ammonium halide to a solution of 20% trifluoroacetic acid in methylene chloride has been reported to cause a large rate increase in the addition of HX to simple alkenes,[36] alkynes,[37] and allenes.[37] The proposed mechanism involves a halide-assisted protonation of the alkene, which produces a carbocation intermediate sandwiched between the attacking halide ion and the trifluoroacetate ion. At higher concentrations of halide ion, the proton-donating ability of the solution decreases, slowing the reaction and increasing the efficiency of cation capture by the halide ion. This leads to a greater proportion of unrearranged halide product. At the highest concentration of the halide ion, cation rearrangement is virtually eliminated.[36,37]

The acid-catalysed transannular cyclization of 8–10-membered γ,δ-unsaturated cyclic sulfides (**59**) or (**60**) yields *cis*-fused bicyclic sulfonium salts (**61**) independently of the geometry of the double bond. The rate varies linearly with the acidity function $-(H_0)_I$ with a slope of 1. The rate variations span a range of about 10^6, the maximum rate difference being observed for the (*E*/*Z*)-thiacyclooct-4-ene pair. The data are consistent with the classical interpretation of the intramolecular reactivity in terms of internal strain of the substrate and/or of the transition state.[38]

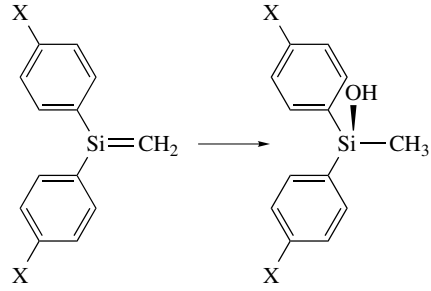




(**62**) (**63**) (**64**)

The reactivities of a series of substituted 1-methylsilenes RMeSi=CH_2 (**63**; R = H, Me, Et, Bu^t, vinyl, ethynyl, Ph, Me_3Si, and Me_3SiCH_2) in hydrocarbon solvents have been investigated by far-UV (193 nm) laser flash photolysis techniques, using the corresponding 1-methylsilacyclobutane derivatives (**62**) as silene precursors. Each of these silacyclobutanes yields ethylene and the corresponding silene (**63**), which can be trapped as the alkoxysilane (**64**) cleanly upon 193 or 214 nm photolysis in solution in the presence of aliphatic alcohols. UV absorption spectra and absolute rate constants for reaction of the silenes with MeOH, EtOH, and Bu^tOH have been determined in hexane solution at 23 °C. The rate constants vary from $3 \times 10^7\ M^{-1}\ s^{-1}$ (for reaction of 1-methyl-1-trimethylsilylsilene with Bu^tOH) to $1 \times 10^{10}\ M^{-1}\ s^{-1}$ (for reaction of 1-ethynyl-1-methylsilene with MeOH). In several cases, rate constants have been determined for addition of the deuteriated alcohols, and for addition of methanol over the range 0–55 °C. Invariably, small primary deuterium kinetic isotope effects and negative Arrhenius activation energies were observed. These characteristics are consistent with a mechanism involving reversible formation of a silene–alcohol complex which collapses to alkoxysilane by unimolecular proton transfer from oxygen to carbon. Silene reactivity proved to increase with increasing resonance electron-donating and inductive electron-withdrawing ability of the substituents at silicon and is significantly affected by steric effects. The authors suggested that this is due to a combination of effects on both the degree of electrophilicity at silicon (affecting the rate constants for the formation and reversion of the complex) and nucleophilicity at carbon (affecting the partitioning of the complex between product and free reactants). Two 1-methyl-1-alkoxysilacyclobutanes were also investigated, but proved to be inert to 193 nm photolysis.[39]

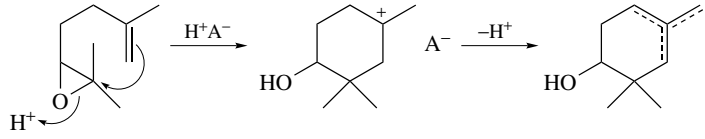
Absolute rate constants for the reactions of a series of 1,1-diarylsilenes (**65a–c**) with MeOH, Bu^tOH, and AcOH in MeCN at 23 °C have been determined using nanosecond laser flash photolysis techniques. The reaction has been found to exhibit small positive Hammett ρ values, consistent with a mechanism involving initial, reversible nucleophilic attack at Si to form a σ-bonded complex that collapses via rate-limiting proton transfer. Deuterium kinetic isotope effects and Arrhenius parameters have been determined for the reaction of (**65b**) and (**65c**) with MeOH and compared with those for the parent compound (**65a**). Proton transfer within the complex is dominated by entropic factor, resulting in negative activation energies. A comparison of the Arrhenius activation energies for the reactions of AcOH with (**65a**) ($E_a = +1.9 \pm 0.3\ kcal\ mol^{-1}$) and the more reactive (**65c**) ($E_a = +3.6 \pm 0.5\ kcal\ mol^{-1}$) suggests that carboxylic acids also add by a stepwise mechanism, but with formation of the complex being rate determining.[40]



(**65a**) X = H
(**65b**) X = Me
(**65c**) X = CF_3

Additions of Electrophilic Carbon

A detailed mechanistic study of acid-catalysed monocyclization of 5,6-unsaturated epoxides, such as (**66**), has now provided compelling evidence for a pathway in which the oxirane C−O cleavage and the C−C bond formation are concerted.[41] These experimental results are now further supported by theoretical evidence for a concerted mechanism of the oxirane cleavage and A-ring formation in epoxysqualene cyclisation, obtained at the RHF/6−31G* and B3LYP/6−31 + G* levels.[42] The chemical pathway thus parallels the mechanism of the enzymatic cyclization[43] that plays a role in the biosynthesis of isoprenoids.

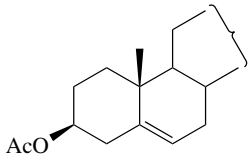


(**66**) (**67**) (**68**)

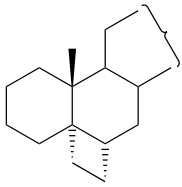
Additions Initiated by Metals and Metal Ions as Electrophiles

In the hydroboration of terminal alkenes, carrying a ketone or aldehyde group, with a variety of borane reagents, dicyclohexylborane has been identified as the most efficient reagent. Analogous hydroboration of alkynyl ketones and alkynyl aldehydes with dicyclohexylborane yields the corresponding olefinic carbonyl compounds after protonation, or dicarbonyl compounds after oxidation.[44]

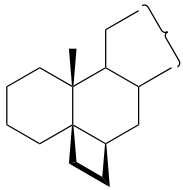
The investigation of factors affecting facial selectivity in the hydroboration of steroidal Δ^5-alkenes revealed the facial (α vs β) stereoselectivities of hydroboration of androst-5-enes (**69**) and B-norandrost-5-enes (**70**) do not parallel the difference between the calculated force-field energies for α- and β-cyclobutane models (**71**)–(**74**). This finding appears to suggest that the facial selectivity is not determined by the four-centre transition state but by the relative ease of formation of the initial π-complex.[45]



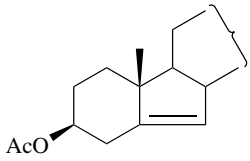
(**69**)



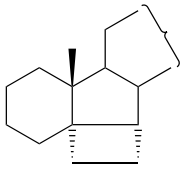
(**71**)



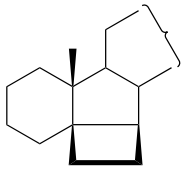
(**72**)



(**70**)



(**73**)

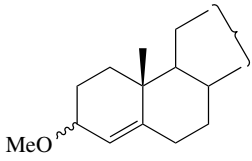


(**74**)

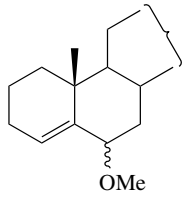
The hydroboration of 3α-, 3β-, 6α-, and 6β-methoxyandrost-4-enes (**75**)–(**78**) has been shown to proceed predominantly *trans* to the MeO group, which parallels the behaviour of the corresponding alcohols. With 6-OMe derivatives (**77**) and (**78**), a small amount of Markovnikov hydration, giving 5-alcohols, has been observed.[46]

Epoxidation, osmylation, and bromination of 5β-androst-3-enes (**79**) have been found to take place from the β-face; in the last reaction, diequatorial dibromide and bromohydrin accompany the axial addition products.[47]

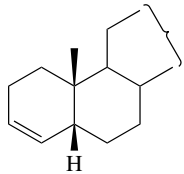
Palladacycles, such as (**80**), derived from tri(1-naphthyl)phosphine, proved to be very active catalysts for Heck reactions to produce (**81**) (ArX = PhI, 4-MeCOC$_6$H$_4$Br,



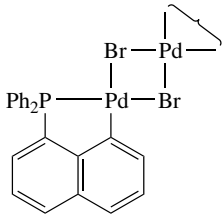
(**75**) α-MeO
(**76**) β-MeOH



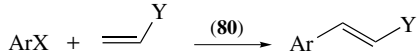
(**77**) α-MeO
(**78**) β-MeOH



(**79**)



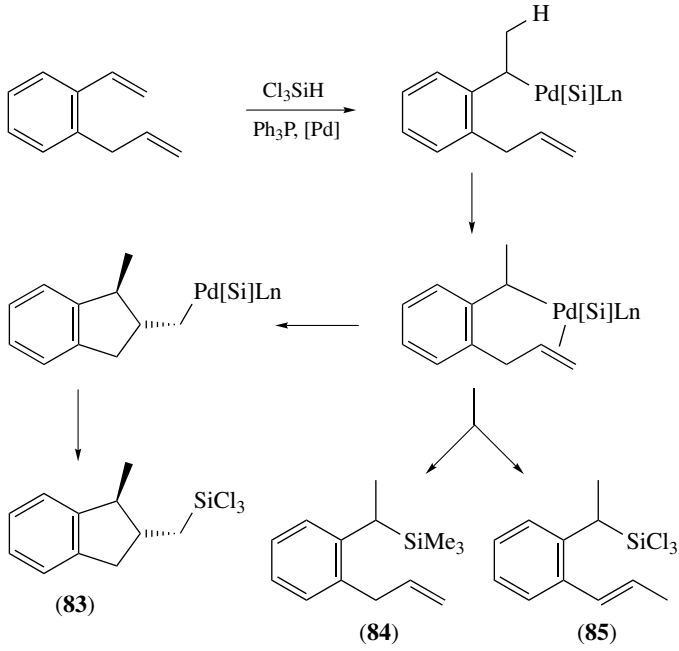
(**80**)



(**81**)

4-NCC_6H_4Br; Y = Ph, CO_2Me). Mechanisms based on a Pd(II)–Pd(IV) cycle were proposed and a new, very efficient method of separating the product from the catalyst has been devised, which involves treatment with cyanide ion.[48]

Hydrosilylation of *o*-allylstyrene (**82**) with trichlorosilane in the presence of 0.3 mol% of a palladium catalyst bearing triphenylphosphine has been found to produce a mixture of indane (**83**) and the open-chain products (**84**) and (**85**) (Scheme 11). The reaction of styrene with trichlorosilane gave a quantitative yield of 1-phenyl-1-(trichlorosilyl)ethane whereas allylbenzene did not give silylation products under the same reaction conditions. These results show that the hydropalladation process is operative in the hydrosilylation of styrene derivatives with trichlorosilane catalysed by palladium–phosphine complexes.[49]

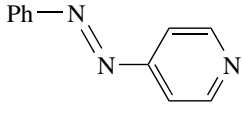


SCHEME 11

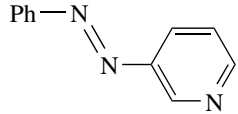
Miscellaneous Electrophilic Additions

Addition of perfluoroalkyl iodides to allyl chloride unexpectedly afforded polyfluorinated alkenes $R_FCH_2CH{=}CH_2$ aside from the expected adduct $R_FCH_2CH(I)CH_2Cl$. The ratio of these two products increased with increasing molar ratio of the reagents and temperature. A mechanistic rationale has been offered.[50]

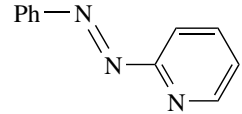
A kinetic and product analysis study of the reactions of the three isomeric phenylazopyridines (**86**)–(**88**) (PAPys) in aqueous sulfuric acid media (30–97 wt% H_2SO_4) has been reported. The γ-isomer (**86**) afforded a mixture of the hydroxylated product 4-(4-hydroxyphenylazo)pyridine, the reduction products 4-aminophenol and



(**86**)



(**87**)



(**88**)

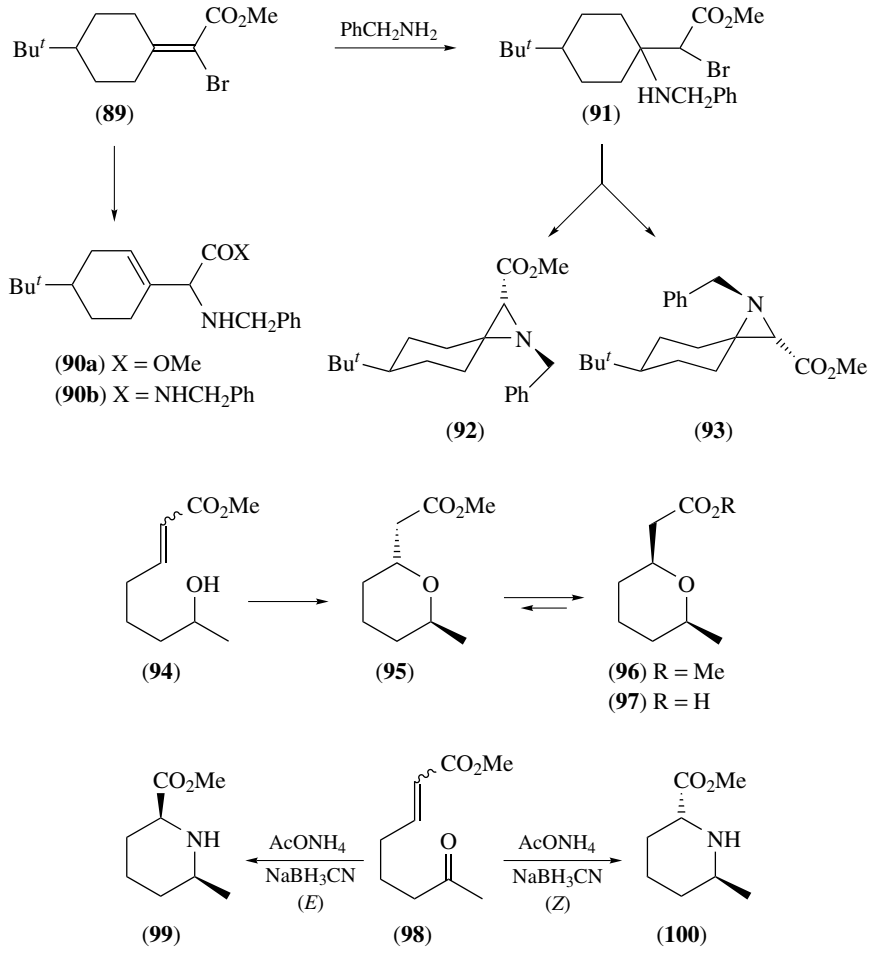
4-aminopyridine, and a small amount of a dimerized product. β-Isomer (**87**) proved to be unreactive, but α-isomer (**88**) gave 2-(4-hydroxyphenylazo)pyridine, 4-aminophenol, and 2-aminopyridine products. This reactivity pattern, resulting in an oxidized azo compound and two reduced amines, is similar to that found in the disproportionation of di-*para*-substituted hydrazinobenzenes observed in benzidine rearrangement studies. Consequently, it has been proposed that the corresponding [N'-(4-hydroxyphenylhydrazino)] pyridines were formed as reaction intermediates in the present system, which was confirmed by showing that [N'-4-(4-hydroxyphenylhydrazino)]pyridine synthesized independently gave the same products as (**86**) under the same conditions. The kinetic study has demonstrated that the γ-isomer (**86**) reacted faster than the α-isomer (**88**) at all the acid concentrations investigated. Rate maxima were observed, at ca 72 wt% H_2SO_4 for (**86**) and ca 86 wt% H_2SO_4 for (**88**). To facilitate the kinetic analysis, values of $pK_{BH_2^{2+}}$ for the protonation of the substrates and the possible hydroxy products at the azo group were determined, using the excess acidity method; the first protonation occurs on the pyridine nitrogen. An excess acidity analysis of the observed pseudo-first-order rate constants as a function of acidity indicate an *A*2 mechanism, with the diprotonated substrate and either one HSO_4^- ion or one H_2O molecule in the activated complex. The proposed mechanism thus involves nucleophilic attack of HSO_4^- or H_2O at an aryl carbon of the diprotonated substrate in the slow step, resulting in an intermediate hydrazo species which gives the observed products in a subsequent fast step (cf. benzidine rearrangement).[51]

Nucleophilic Additions

Additions to Multiple Bonds Conjugated with C=O

High pressure vs thermal activation in the conjugate addition of amines has been examined as part of an effort to develop a new access to spirocyclamines. The reactions of methyl or ethyl 4-*t*-butylcyclohexylidene bromoacetates (**89**) with amines turned out to afford various products depending on the experimental conditions and the nature of the amine. When the starting ester (**89**) was treated with benzylamine in refluxing methanol, ester (**90a**) and the corresponding amide (**90b**) were isolated as the main products. By contrast, the same reaction, carried out at room temperature and under high pressure, led to a diastereoisomeric mixture of the spiroaziridine derivative (**92**) and (**93**) in good yield and high stereoselectivity.[52]

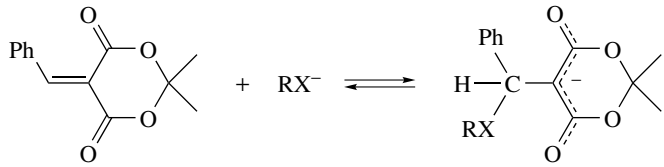
Microwave irradiation has been reported to accelerate the Michael addition of primary and cyclic secondary amines to esters of α,β-unsaturated α-unsubstituted carboxylic acids to produce β-amino acids.[53]



SCHEME 12

Intramolecular Michael addition of *N*- and *O*-centred nucleophiles to tethered acrylates has been elucidated and the role of double-bond geometry in controlling the diastereoselectivity of cyclizations assessed. Thus, the oxyanion derived from hydroxyacrylate (*E*)-(**94**) has been found to undergo readily an intramolecular Michael addition to give the *trans*-2,6-disubstituted tetrahydropyran (**95**) as the major product. By contrast, the oxyanion obtained from (*Z*)-(**94**) cyclizes to afford the *cis*-2,6-disubstituted tetrahydropyran (**96**). This chemistry has been extended to the enantioselective synthesis of (+)-(**96**), an intermediate in the synthesis of acid (+)-(**97**), a constituent of the glandular secretion from the civet cat (*Viverra civetta*). Similarly, the corresponding (*E*)- and (*Z*)-ketones (**98**) undergo a one-pot reductive amination, followed by a diastereoselective Michael-type cyclization to produce *cis*- and *trans*-piperidines (**99**) and (**100**), respectively. Chair-like transition-state structures have been proposed to account for the diastereoselectivities observed in these cyclizations.[54]

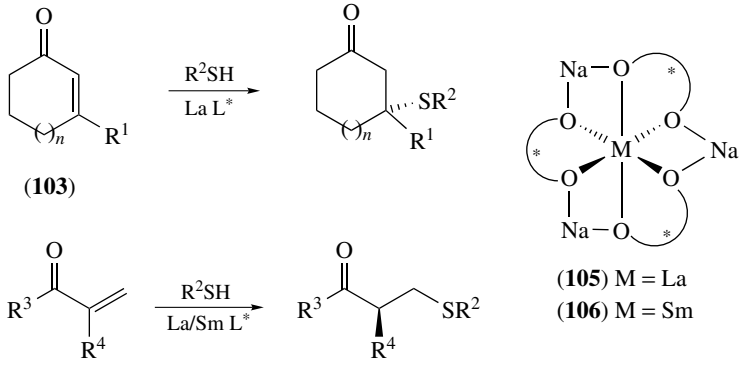
A kinetic study of the reaction of benzylidene Meldrum's acid (**101**) with a series of thiolate and alkoxide ions RX^- (X = S or O) in DMSO–water (1:1, v/v) at 20 °C has been reported. The reactions lead to adducts of the type (**102**), which can be viewed as a model for the intermediate of a nucleophilic vinylic substitution on substrates such as $PhC(LG)=C(CO_2)_2CMe_2$ (LG = leaving group). The kinetic measurements allowed the determination of rate and equilibrium constants for these processes with RS^- = *n*-BuS^-, $HOCH_2CH_2S^-$, $MeO_2CCH_2CH_2S^-$, and $MeO_2CCH_2S^-$ and RO^- = HO^-, MeO^- (only rate constant of breakdown of adduct), $HCCCH_2O^-$, and $CF_3CH_2O^-$. The results show that there are major differences between the alkoxide and thiolate ions with respect to their thermodynamic and kinetic affinities to (**101**). They arise mainly from differences in the polarizability and solvation between the sulfur and the oxygen bases. Similar differences in the reactions of thiolate ions with α-nitrostilbenes have also been discussed.[55]



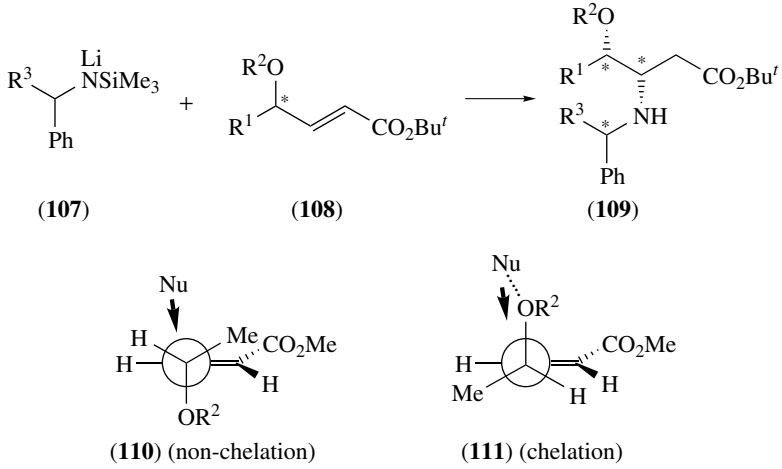
(**101**) (**102**)

An efficient asymmetric Michael addition of thiols to cycloalkenones (**103**) (56–90% *ee*) and an effective asymmetric protonation in Michael additions of thiols to non-cyclic enones (**104**) (75–90% *ee*), catalysed by $LaNa_3$• tris(binaphthoxide) (**105**) and $SmNa_3$• tris(binaphthoxide) (**106**) complexes, respectively, has been reported.[56]

Both diastereoisomers of β-homothreonine derivatives (**109**) and their 2-deuteriated analogues have been synthesized by 1,4-addition of homochiral lithium amides (**107**) as nitrogen nucleophiles to γ-alkoxyenoates (**108**) (Scheme 13). The product distribution of the 1,4-addition depends strongly on the nature of the substrate (**110**) vs



(**111**). The configuration can in one case be controlled by the reagent irrespective of the substrate stereochemistry; in other cases the topicity of the addition is complementary to the published results.[57]

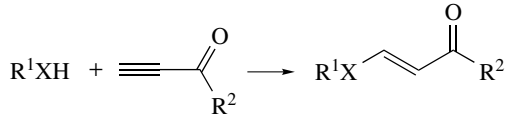


(**107**) (**108**) (**109**)

(**110**) (non-chelation) (**111**) (chelation)

SCHEME 13

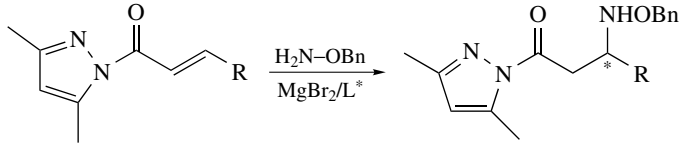
Suitably protected amino acids (**112**) (cysteine, serine, and lysine) have been added via the side-chain heteroatom (S, O, and N, respectively) to conjugated alkynones, alkynoic ester and alkynoic amide (**113**). The expected heterosubstituted vinyl product (**114**) was formed in each case, mainly as the *E*-isomer.[58] In an accompanying paper,[59] this type of addition was applied to the derivatives of fluorescein, 7-hydroxycoumarin, Sudan 1, and dansyl chloride with linker arms containing a conjugated terminal alkyne.



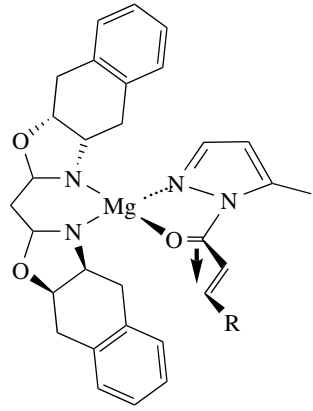
(**112**) (**113**) (**114**)

Chiral, Lewis acidic bisoxazoline complexes of Mg(II) have been employed as catalysts in asymmetric Michael addition of *O*-benzylhydroxylamine to unsaturated amides, (**115**) → (**116**). The enantioselectivity (67–90% *ee*) was rationalized by transition state (**117**). This approach constitutes a promising methodology for the synthesis of β-amino acids.[60]

Regiospecific, uncatalysed hydrophosphination of typical Michael acceptors, such as methyl acrylate, has been reported to proceed readily with alkenyl- an alkynylphosphine oxides, e.g. R(Pr^i)P(H)O. Good stereoselectivity was observed when a chiral electrophile was used. The reaction is believed to proceed owing to the strong



(**115**) (**116**)



(**117**)

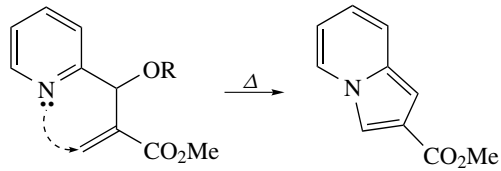
P−H activation by the unsaturated fragments directly bonded to the phosphorus atom.[61]

Kinetics of the formation of indolizines (**119**) via thermal cyclization of 3-acetoxy-2-methylene-3-(2-pyridyl)propanoic esters (**118**) and analogues have been investigated using ^{1}H NMR spectroscopy; the data obtained were as follows: $\Delta H^{\neq} = 97 \pm 6\,\text{kJ mol}^{-1}$, $\Delta S^{\neq} = 413 \pm 11\,\text{J K}^{-1}\,\text{mol}^{-1}$ and $\rho^* = 3.75$. A mechanism involving the 5-*endo-Trig* ring closure was proposed to account for the formation of (**119**).[62] Since this would be a typical disfavoured process according to the Baldwin rules, the present reviewer feels that an alternative mechanism would be more a likely, namely one involving Claisen rearrangement, generating (**120**) as the substrate for an S_N2-type 5-*exo-Tet* process, or a conrotatory cyclization of cation (**121**) arising by departure of AcO^-.

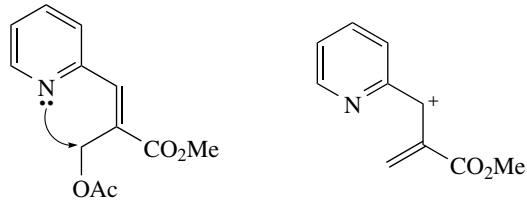
A detailed elucidation of both solid-state and solution structures of a series lithiated α-aminonitriles $[RC(NR'_2)CN]^-Li^+$ has been employed to formulate the transition-state structures that account for the diastereofacial selectivity observed in their 1,4-additions to Michael acceptors.[63]

In the presence of $ZnCl_2$, Michael addition of anthrone (**122**) to α,β-unsaturated ketones has been reported to proceed smoothly, producing mono-adducts (**123**), whereas bis-adducts (**124**) are formed in basic solution.[64]

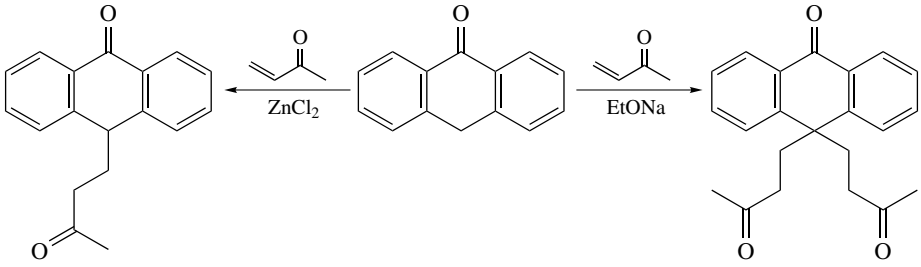
Sodium benzoate has been identified as a mild and efficient catalyst for the tandem Michael–aldol self-condensation of γ,δ-unsaturated-β-keto esters, affording conjugated vinylcyclohexenonedicarboxylates, some of which exhibit biological activity against ectoparasites in cattle.[65]



(**118**) (**119**)



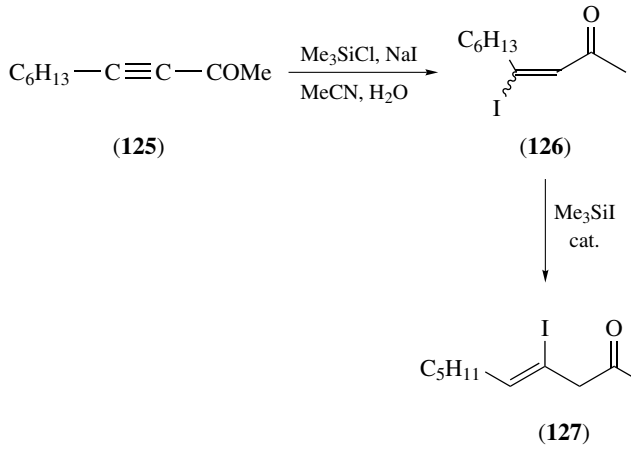
(**120**) (**121**)



(**123**) (**122**) (**124**)

Second-order rate constants have been measured spectrophotometrically for the addition of a series of alicyclic amines to HC≡CCOMe to yield the corresponding enamines at 25 °C. The reactivity of the amines proved to increase with increasing basicity of the amines. However, the Brønsted-type plot exhibits a downward curvature as the basicity of the amines increases, i.e. β_{nuc} decreases from 0.3 for weakly basic amines ($pK_a < 9$) and to 0.1 for highly basic amines ($pK_a > 9$). Such a curvature in the Brønsted-type plot is clearly indicative of a change in the reaction mechanism or transition-state structure. From the corresponding reactions carried out in D_2O, the magnitude of kinetic isotope effect (KIE) has been calculated to be about 1.21 for weakly basic amines and 0.8 for highly basic amines. The difference in the magnitude of KIE has been interpreted as being supportive of a change in the reaction mechanism or transition-state structure upon changing the basicity of the amines. Furthermore, the small KIE clearly suggests that H^+ transfer is not involved in the rate-determining step. Therefore, the addition reaction can be considered to proceed via a stepwise mechanism, in which the attack of the amines to the acetylene is the rate-determining step. The curvature in the Brønsted-type plot has been attributed to a change in the degree of bond formation between the amine and the acetylene.[66]

A mechanistic study of the transformation of dec-3-yn-2-one (**125**) into (*Z*)-4-iododec-4-en-2-one (**127**) on treatment with Me_3SiCl and NaI in wet MeCN has revealed the following (Scheme 14): (1) Me_3SiCl undergoes an exchange reaction with NaI and the resulting Me_3SiI reacts with 0.5 equiv. of H_2O to produce HI and $(Me_3Si)_2O$; (2) the liberated HI is non-stereoselectively added in a Michael fashion across the conjugated C≡C bond to generate vinyl iodide (**126**) as a mixture of *E*- and *Z*-isomers; (3) the latter intermediate is then deconjugated by the remaining Me_3SiI to give the final product (**127**) stereoselectively as the *Z*-isomer.[67]



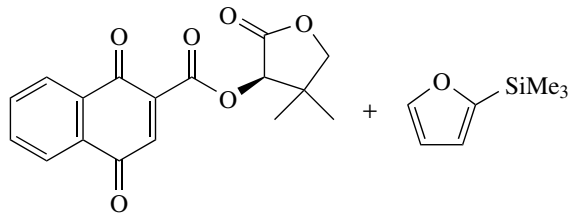
$$Me_3SiCl \xrightarrow[-NaCl]{NaI} Me_3SiI$$

$$2Me_3SiI + H_2O \longrightarrow HI + (Me_3Si)_2O$$

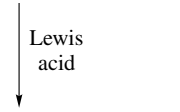
SCHEME 14

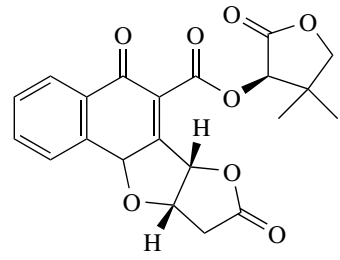
Asymmetric Michael reactions of 1,4-naphthoquinones (**128**) bearing a chiral auxiliary with 2-trimethylsilyloxyfuran (**129**) using various Lewis acids afforded the corresponding furofuran adducts (**130**). Moderate levels of diastereoisomeric excess ($\leqslant$ 60% *de*) were obtained using (*R*)-pantolactone, (*S*)-*N*-methyl-2-hydroxysuccinimide and (*R*)-(+)-4-benzyl-2-oxazolidinone as chiral auxiliaries. Low asymmetric induction was achieved using a camphorsultam auxiliary. Evidence that the addition of (**129**) occurs via a Michael reaction rather than a Diels–Alder cycloaddition has been provided.[68]

The diastereoselectivity in the asymmetric Michael reaction using chiral enamines, derived from β-dicarbonyls and chiral 1-alkylphenylamines, e.g. (**131**), under neutral conditions has been investigated with the aid of AM1 calculations. The energy differences between the two competing transition states involving enamino ketone and methyl acrylate (**132**) are in good agreement with the diastereoselectivities observed for the corresponding chiral imines, derived from 1-phenylethylamine (95% *de*). The calculated transition structures indicate that the π-facial discrimination originates in steric factors.[69]

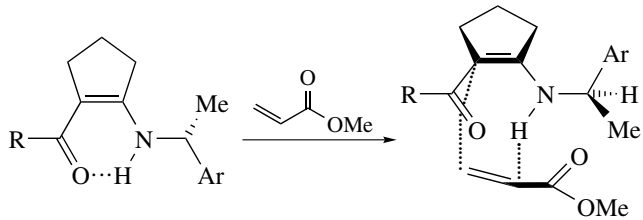


(**128**) (**129**)





(**130**)

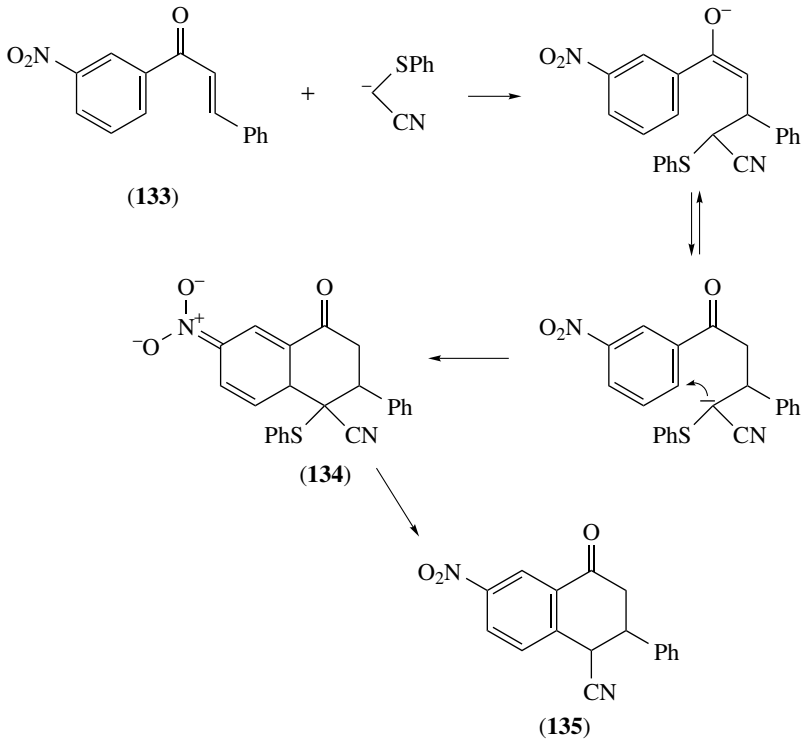


(**131**) (**132**)

A ^{1}H NMR study of reactions of methyl 2-(bromomethyl)-but-2-enoate with the sodium enolate of methyl 2-methyl-3-oxobutanoate has been carried out to rationalize the observed solvent-dependent regioselectivity in terms of addition–elimination sequences.[70]

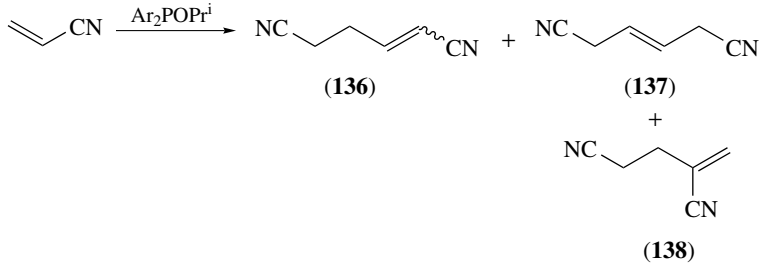
3-Nitro-ω-benzylideneacetophenone (**133**) reacts with carbanions containing leaving groups to give addition products via Michael addition (**134**), followed by intramolecular vicarious nucleophilic substitution of hydrogen in the nitroaromatic ring in the position *para* to the nitro group, to produce (**135**).[71]

Isopropyl diarylphosphinites (Ar_2POPr^i) catalyse the dimerization of acrylonitrile to a mixture of *cis*- and *trans*-1,4-dicyanobut-1-ene (**136**), *trans*-1,4-dicyanobut-2-ene (**137**), and 2,4-dicyanobut-1-ene (**138**). The kinetics and mechanism of the reaction,



SCHEME 15

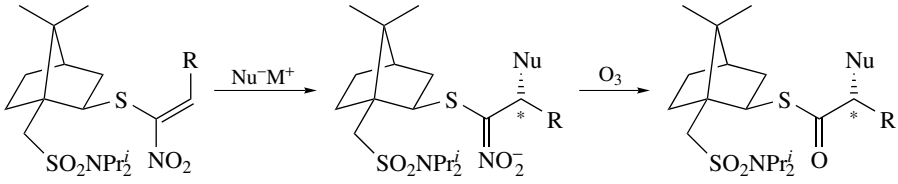
which is a potential source of hexamethylenediamine, were reported in detail and the factors which govern rate and selectivity to form the linear products (**136**) and (**137**) rather than the branched isomer (**138**) were elaborated.[72]



Additions to Multiple Bonds Activated by Other Electron-withdrawing Groups

Diastereoselective tandem conjugate addition of both oxygen- and nitrogen-centred nucleophiles (potassium phthalimide, TsNHK, MeONa, and Me_3SiOK) to the novel (1*S*)-10-camphorsulfonic acid-derived nitroalkenes (**139**; R = Me, Pr^i, and

p-$C_6H_4CO_2Bu^t$), followed by ozonolysis, gave the α-hydroxy and α-amino thiol acid derivatives (**140**). In all cases, the (*R*)-diastereoisomer was formed as the major component albeit with only modest levels of selectivity (33–71% *de*).[73]

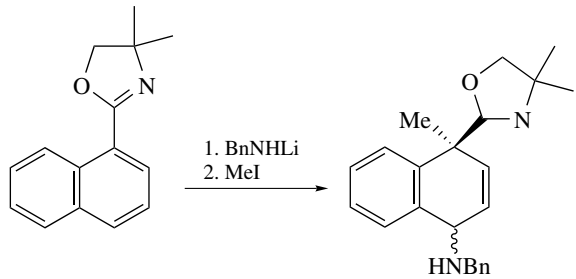


(**139**) (**140**)

SCHEME 16

The addition of substituted anilines to *trans*-β-nitrostyrene has been reported to involve the formation of a zwitterionic intermediate in the rate-determining step, followed by a rapid intramolecular proton transfer.[74]

The 1,6-addition reaction of lithium amides to the naphthalene ring system (**141**) followed by the electrophilic alkylation has been reported (Scheme 17).[75]



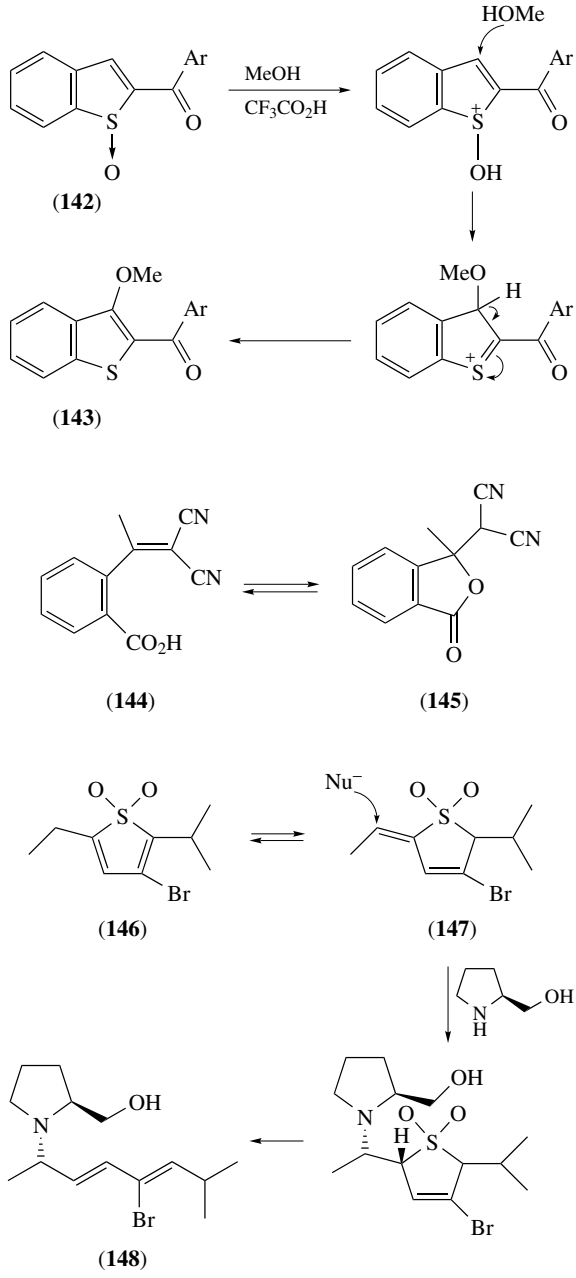
(**141**)

SCHEME 17

The benzo[*b*]thiophene sulfoxides, such as (**142**), generated from the parent benzothiophene on the H_2O_2–TFA-mediated oxidation, undergoes Michael-type nucleophilic addition of oxygen and sulfur nucleophiles in acidic media to produce 3-substituted benzo[*b*]thiophenes (**143**). This method provides an easy two-step functionalization of 2-acylbenzo[*b*]thiophene derivatives.[76]

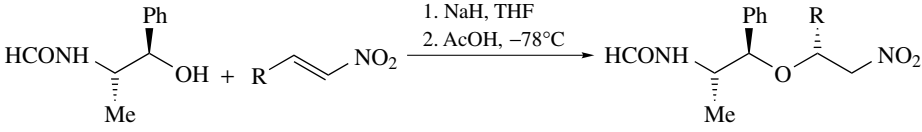
A ring–chain transformation with slow interconversion (compared with the NMR time-scale) has been reported in the solution of (**144**) and related derivatives. On the other hand, no tautomerism was observed when the benzene ring was replaced by a thiophene ring or an aliphatic double bond.[77]

In the Michael addition reaction of (*S*)-phenylethylamine and L-alanine isopropyl ester to ω-nitrostyrene, the diastereoisomer formation has been found to be thermodynamically controlled.[78]



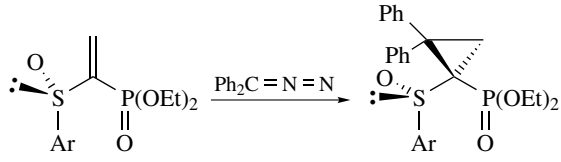
The reaction of prolinol with 3-bromo-5-ethyl-2-isopropylthiophene-1,1-dioxide (**146**) has been reported to occur via an initial Michael-type addition to the tautomer (**147**), followed by cheletropic elimination of SO_2, giving (**148**) as a 65:35 mixture of diastereoisomers.[79]

N-Formylnorephedrine (**149**) has been employed as the first chiral hydroxide equivalent in conjugate additions to aliphatic (*E*)-nitroalkenes (**150**; R = Me, Et, Pr, Pr^i, Bu^t, cyclohexyl, Ph, furyl, ferrocenyl, etc.); good yields (35–87%) and excellent diastereoselectivities (94–98% *de*) have been attained. Transition states, accounting for the overall stereochemical outcome, were presented.[80]

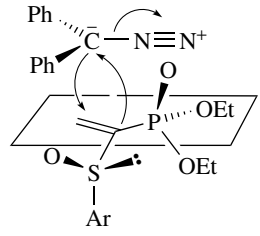


(**149**) (**150**)

Sulfoxide (*S*)-(+)-(**151**) undergoes a highly diastereoselective asymmetric cyclopropanation with diphenyldiazomethane and diphenylsulfonium isopropylide to form the corresponding cyclopropanes (**152**) (Scheme 18). A mechanistic rationale to account for the observed stereoselectivities is illustrated for Ph_2CN_2 (**153**).[81]



(**151**) (**152**)

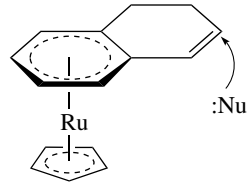


(**153**)

SCHEME 18

An unexpected *endo* selectivity in addition of certain carbon and sulfur nucleophiles to the α,β-unsaturated (arene)ruthenium(II)cyclopentadienyl compound (**154**) has been reported. This stereochemistry has been compared with that of the S_N2' reactions but a detailed theoretical approach is yet to be undertaken.[82]

The substitution of 9-(α-bromo-α-arylmethylene)fluorenes by MeS^- and *p*-$TolS^-$ ions in MeCN–H_2O (4:1) is a second-order reaction and its rate decreases on increasing the water content of the medium. With MeS^-, for the change of the α-aryl group,

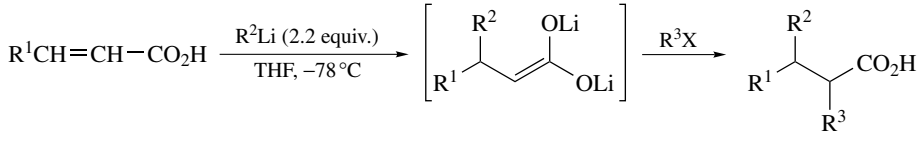


(**154**)

Hammett's $\rho = 1.07$ in MeCN. The Ad_N-E route is the dominant reaction pathway, as revealed by the effects of the changes in the substituent, solvent, nucleophile and nucleofuge; no competitive S_N1 reaction was observed.[83]

Additions of Organometallics to Activated Double Bonds

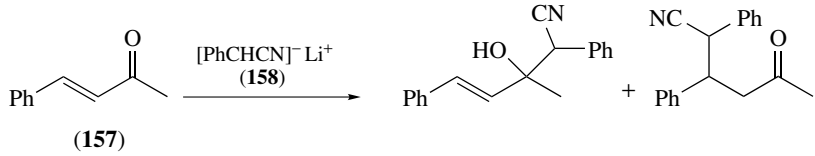
Organolithium reagents R^2Li (R^2 = Me, Bu, Bu^s, Ph) can be added to α,β-unsaturated carboxylic acids (**155**; R^1 = H, Me, Ph) in the Michael fashion in THF at −78 °C, affording substituted alkanoic acids (**156**) after quenching with electrophiles RX (R = H, Me). (*E*)-3-Phenylpropenoic acid also affords significant amounts of isomeric 1,3-addition products.[84] Substitution by methyl groups at the α-carbon of the starting acid (**155**) strongly decreases reactivity, whereas deprotonation of the starting acid occurs almost exclusively with methyl substitution at the β-carbon of the alk-2-enoic acid.[85]



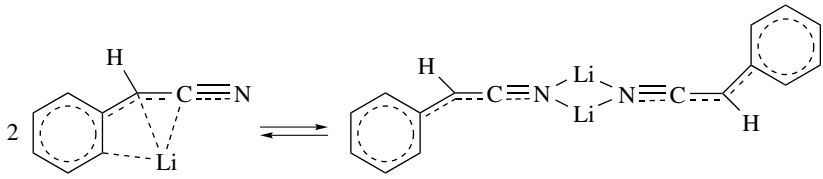
(**155**) (**156**)

The reaction of lithiated phenylacetonitrile (**158**) with benzylideneacetone (**157**) in THF and THF–toluene, at low temperature, led to the same ratio of 1,2- and 1,4-adducts after 5 or 30 min (Scheme 19). The concentrations of the monomeric bridged ion pair (**158a**) (preferentially formed in THF) and of the dimer (**158b**) (predominating in media that favour association, such as THF–toluene), were established from the IR-integrated intensities of the $\nu_{(C\equiv N)}$ bands. The results lend credence to the kinetic control of this reaction. Intermediate complexes that take into account the peculiar geometries of the monomer (**158a**) and the dimer (**158b**) were proposed to interpret the different regioselectivities observed with (**157**). Similar trends hold for cyclic α-enones, whereas cinnamaldehyde prefers 1,2-addition. The formation of intermediate complexes is believed to rationalize the cinnamaldehyde behaviour but appears insufficient to explain the 1,4-addition with cyclic α-enones.[86]

Systematic studies of organocuprate conjugate additions to three pairs of γ-epimeric and geometrically isomeric γ-chiral acyclic enones and enoates (**159a**,**b**) and (**160a**,**b**) have allowed one to generalize diastereofacial selectivity of these reactions (Scheme 20).

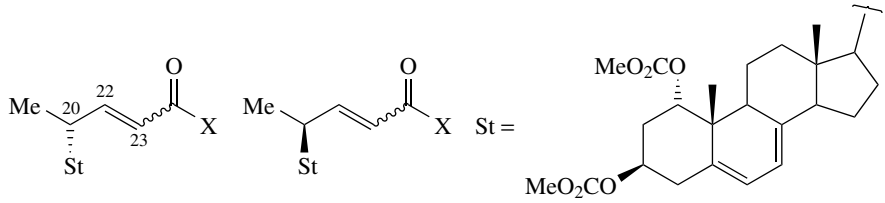


(**157**)



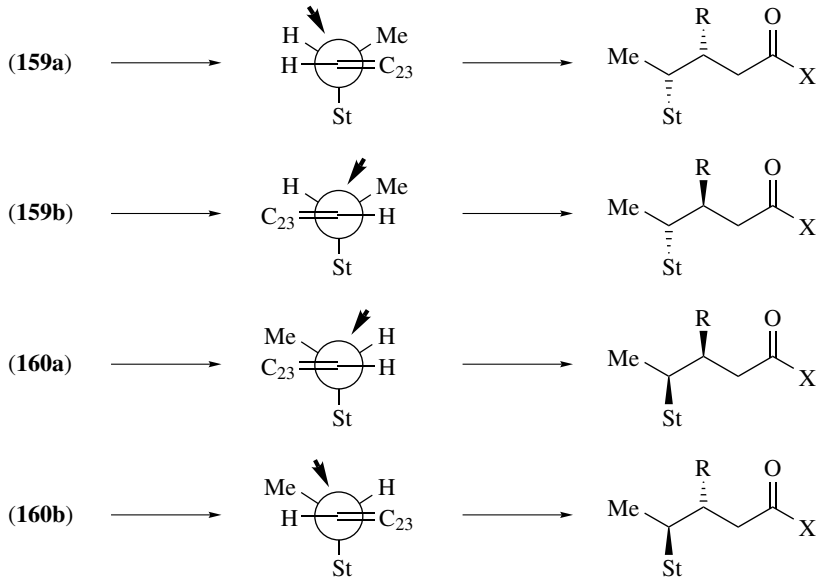
(**158a**) (**158b**)

SCHEME 19



(**159a**) *trans*
(**159b**) *cis*

(**160a**) *trans*
(**160b**) *cis*



SCHEME 20

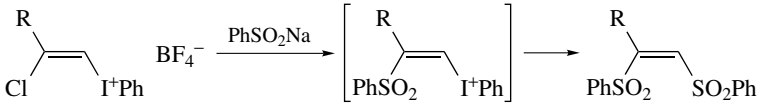
It appears that the diastereoselectivity depends on the double-bond geometry, the configuration at the γ-position [i.e. C(20)], and the reaction conditions. In reactions without activating additives, cuprates add to the *si*-face of the geometrically isomeric pair of (*E*)- and (*Z*)-enones (**159a**,**b**) with high diastereoselectivity (98%), whereas their epimers at the γ-position (**160a**,**b**) yield *re*-facial adduct preferentially (86–97%). Addition of TMSCl and HMPA together not only accelerates the addition reaction but also completely changes the pattern of π-facial selectivity. In reactions containing those additives, cuprates add to isomeric (*E*)- and (*Z*)-enones with reverse facial selectivity; thus, (*E*)-enone (**159a**) gives the *si*-facial adduct exclusively, whereas isomeric (*Z*)-enone (**159b**) yields the *re*-facial adduct (97%). Their γ-epimers give opposite results; (*E*)-isomer (**160a**) reacts with *re*-facial selectivity (97%), whereas the (*Z*)-isomer (**160b**) reacts with *si*-facial selectivity (75%). Under the conditions where both TMSCl and HMPA are present, even the enoates react efficiently with similar reversal and with high facial selectivity. On the basis of these results, the authors postulated a general and clear-cut rule to predict diastereofacial selectivity of cuprate conjugate additions, in which a possibility of $Z-E$ isomerization of starting enones is taken into account as a crucial determinant.[87]

Miscellaneous Nucleophilic Additions

The reaction of HO^- with 1,ω-bis(2-bromopyridinium)alkanes, where the reaction centres are separated by a varying number of methylene groups (with propyl, butyl, pentyl, hexyl, and octyl spacer), has been investigated in aqueous solvents to model the increased velocity of HO^- attack on pre-micellar aggregated *N*-alkylpyridinium compounds. The kinetics with HO^- fitted two consecutive first-order reactions; the intermediate products, i.e. 1-(2-pyridone)-ω-(2-bromopyridinium)alkanes, and also the final products, i.e. 1,ω-bis(2-pyridone)alkanes, were isolated. Deuterium isotope effects, activation parameters, and salt effects on the reaction rates suggest that the HO^- attack is rate limiting and that there is a through-space acceleration of the initial attack due to the proximity of the positive charges. These results place an upper limit of 20-fold for the electrostatic acceleration in HO^- attack in pre-micellar aggregates.[88]

Theoretical interpretation of the relative reactivity of *m*-, *o*- and *p*-chlorophenoxypropargyls towards the enolate generated from 1,2,5-trimethylpiperidin-4-one and KOH afforded satisfactory agreement with the experiment.[89]

Evidence for a Michael addition of a nucleophile to alkenyl(phenyl)iodonium salts at the C_β atom has now been reported for the first time. Nucleophilic vinylic substitutions of (*Z*)-(β-bromoalkenyl)iodonium tetrafluoroborates (**161**) and its (*Z*)-(β-chloroalkenyl) analogue with sodium benzenesulfinate in THF afforded stereoselectively (*Z*)-1,2-bis(benzenesulfonyl)alkene (**163**) with retention of configuration. Intermediate formation of (*Z*)-[β-(benzenesulfonyl)alkenyl]iodonium salt (**162**) in these reactions was established by ^1H NMR experiments in $CDCl_3$. The formation of (*Z*)-(**162**) involves a hitherto unobserved Michael addition of benzenesulfinate anion to the alkenyliodonium salts at the C_β atom, followed by halogen extrusion.[90]



(**161**) (**162**) (**163**)

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CHAPTER 14

Addition Reactions: Cycloaddition

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Density functional theory and MC-SCF calculations have been applied to competing concerted and stepwise mechanisms of cycloaddition reactions.[1]

Diphenylketene undergoes 2 + 2- or 2 + 4-cycloaddition reactions with various 1,3-diazabuta-1,3-dienes.[2] The 2 + 4-, 4 + 2-, 6 + 4- and 8 + 2-cycloaddition reactions of heptafulvenes have been reviewed.[3]

The acceleration effect on 4 + 2-, 3 + 2- and 2 + 2-cycloadditions in the presence of aluminium, gallium and boron halides is due to the increase of π-acceptor properties of the dienophiles.[4]

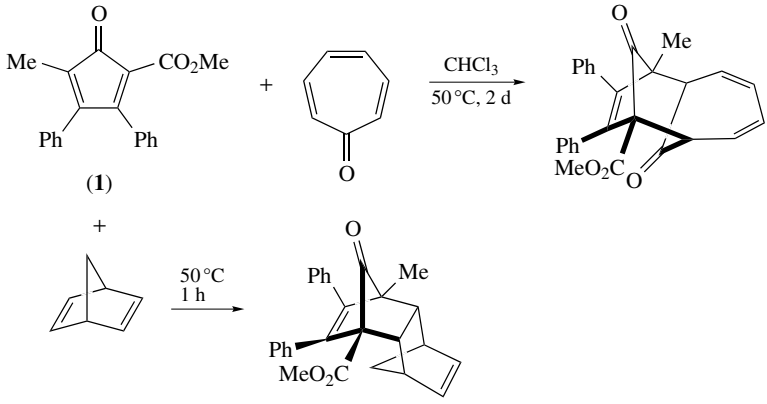
2-Methoxycarbonyl-5-methyl-3,4-diphenylcyclopentadienone (**1**) undergoes 4 + 2- and 4 + 6-cycloadditions with a variety of dienophiles (Scheme 1).[5]

The reaction of 1,4-diphenylbuta-1,3-diene (**2**) with trithiazyl trichloride (**3**) yields a bi(thiadiazole) (**4**), an isothiazoloisothiazole (**5**), a dithiazolothiazine (**6**), and two thiazinodithiatriazepines (**7**) and (**8**) by 1,2-, 1,3-, and 1,4-cycloaddition reactions (Scheme 2).[6]

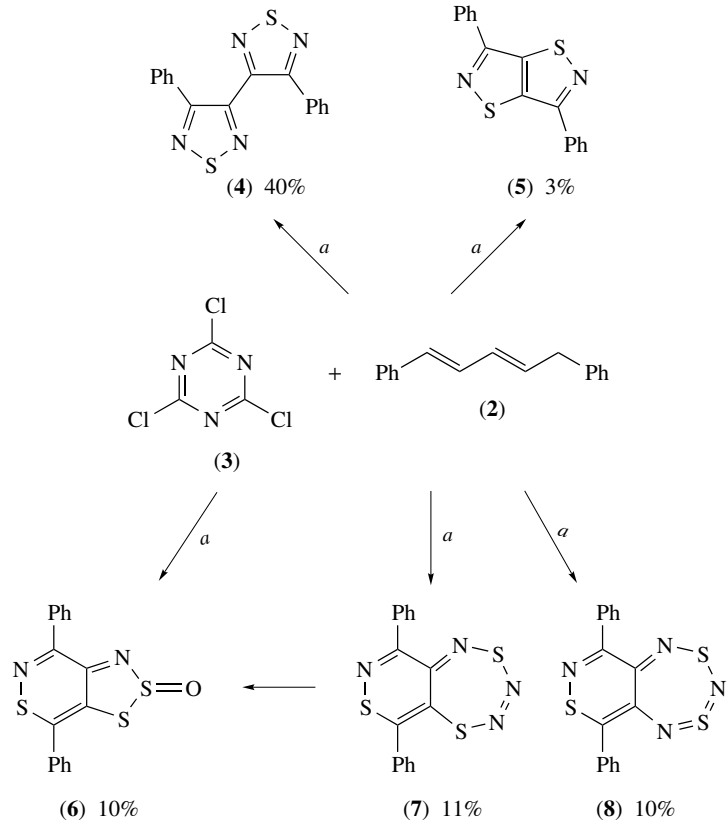
The bridged-mode (β-tether) tandem inter-[4 + 2]/intra-[3 + 2] cycloaddition of (*E*)-2-methyl-2-nitrostyrene (**9**) with 1-butoxypenta-1,4-diene (**10**) produces stable tricyclic nitroso acetals (**11**) which afford, after reduction and protection, highly functionalized aminocyclopentanedimethanol triacetates (**12**) (Scheme 3).[7,8]

2 + 2-Cycloaddition

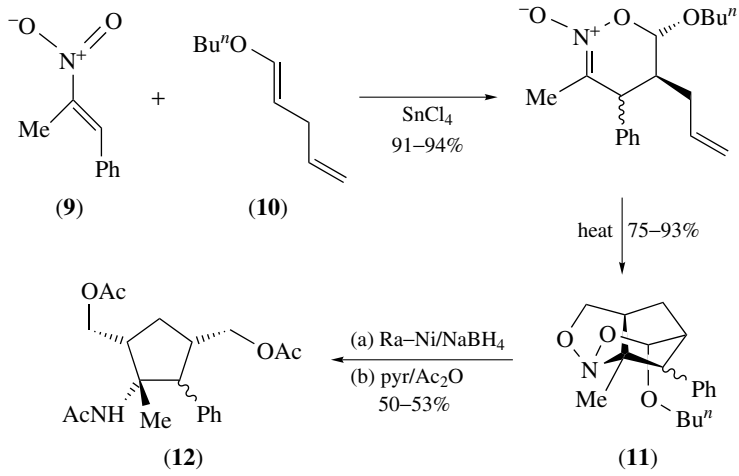
The mechanisms of regioselective and stereoselective 2 + 2-photocycloadditions have been extensively reviewed.[9] The intramolecular 2 + 2-photocycloaddition of 2-allyl-2-(1*H*)-naphthalenone (**13**) on the surface of silica produces all four cycloadducts (**14**)–(**17**) (Scheme 4).[10] Molecular mechanics have been used to study the regio- and stereo-selectivity of the 2 + 2-photocycloadditions in complexes containing crown ether styryl dyes and alkaline earth metal cations.[11]



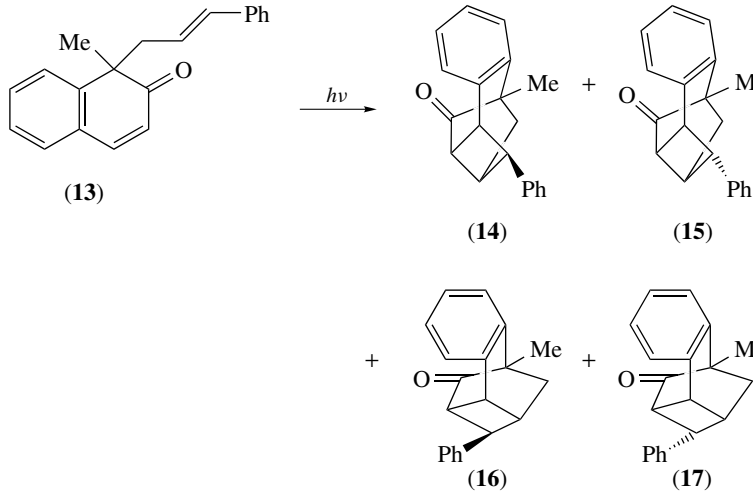
SCHEME 1



SCHEME 2



SCHEME 3

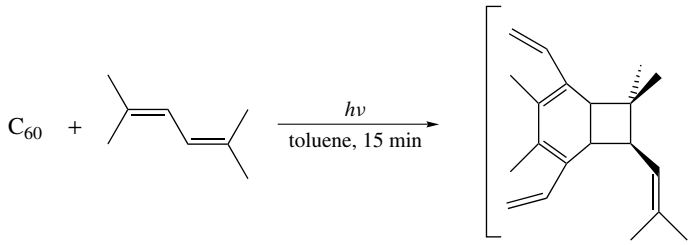


SCHEME 4

A study of the stereochemistry and secondary isotope effects for the 2 + 2-cycloaddition of alkyl-substituted buta-1,3-dienes with C_{60} indicates the formation of an open biradical intermediate in the rate-determining step leading to the cycloadduct (**18**) (Scheme 5).[12] The addition of benzyne to C_{70} produces four isomeric monoadducts. One of these adducts is the first example of an adduct of a 5–6 ring fusion where the ring-fusion bond remains intact.[13]

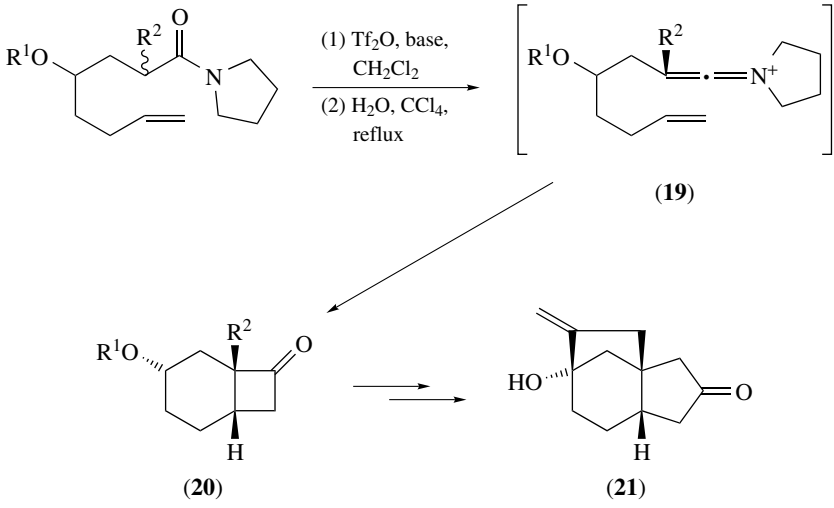
A review of the mechanism of thermal 2 + 2-cycloadditions of activated alkenes to allenes and ketenes has been published.[14] Stereoselective intramolecular 2 + 2-cycloadditions of alkene–keteniminium salts (**19**) derived from L-glutamic salts yield

optically active bicyclo[4.2.0]octan-7-ones (**20**) which can be converted into (+)-gibberellic acid intermediates (**21**) (Scheme 6).[15] *Ab initio* calculations predict that the thermal 2 + 2-cycloaddition reactions between C_{2v}-symmetric ketenes and enantiopure aldehydes proceed with high stereocontrol.[16] The influence of photoinduced electron-transfer steps in the regio- and diastereo-specificity of Paterno–Büchi reaction with 2,3-dihydrofuran in polar solvents has been demonstrated.[17] The reaction of ethoxyacetylene with alkoxyaldehydes (**22**) in the presence of $MgBr_2$–Et_2O yields 4-ethoxy-2*H*-oxetes (**23**), thus providing experimental evidence for a 2 + 2-cycloaddition mechanism (Scheme 7).[18] The asymmetric 2 + 2-cycloaddition of silylketenes and aldehydes, in the presence of Ti–TADDOL catalysts, proceeds with good reactivity and moderate enantioselectivity.[19] *Ab initio* and MNDO-PM3 treatment of the Wittig reaction of ylides with acetaldehyde indicate that the oxaphosphetane formation is a very asynchronous cycloaddition.[20]



(**18**)

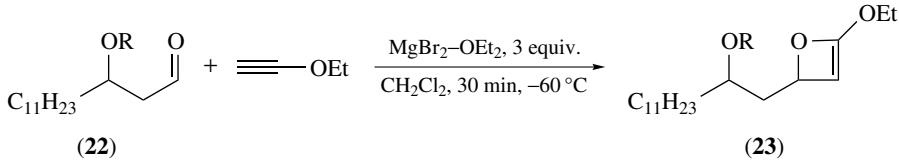
SCHEME 5



(**19**)

(**20**) (**21**)

SCHEME 6



(**22**)

R = Bn, Me

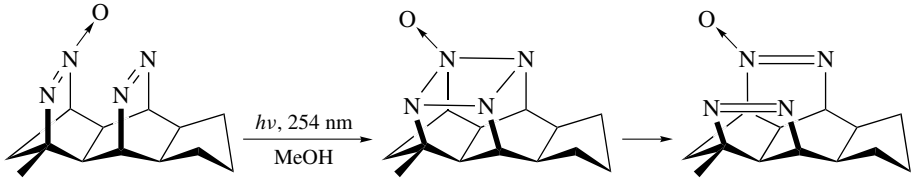
(**23**)

SCHEME 7

A very remote secondary H/D isotope effect has been measured for the 2 + 2-cycloaddition of TCNE to 2,7-dimethylocta-2,*trans*-4,6-triene.[21] The reaction of nitric oxide with *N*-benzylidene-4-methoxyaniline to produce 4-methoxybenzenediazonium nitrate and benzaldehyde is thought to proceed via a 2 + 2-cycloaddition between nitric oxide and the imine double bond.[22] A novel mechanism for the stepwise dimerization of the parent silaethylene to 1,3-disilacyclobutane involves a low-barrier [1,2]-sigmatropic shift.[23] Density functional, correlated *ab initio* calculations, and frontier MO analysis support a concerted 2 + 2-pathway for the addition of SO_3 to alkenes.[24]

The enone cycloaddition reactions of dienones and quinones have been reviewed.[25] The 2 + 2-photocycloadditions of homochiral 2(5*H*)-furanones to vinylene carbonate are highly diastereoisomeric.[26]

Monochromatic π, π^* excitation of the proximate (**24**) yielded the metathesis isomer (**26**) with retention of optical purity thus providing support for the $\pi 2 + \pi 2$-photocycloaddition pathway involving a tetrazetidine oxide intermediate (**25**) (Scheme 8).[27]



(**24**) (**25**) (**26**)

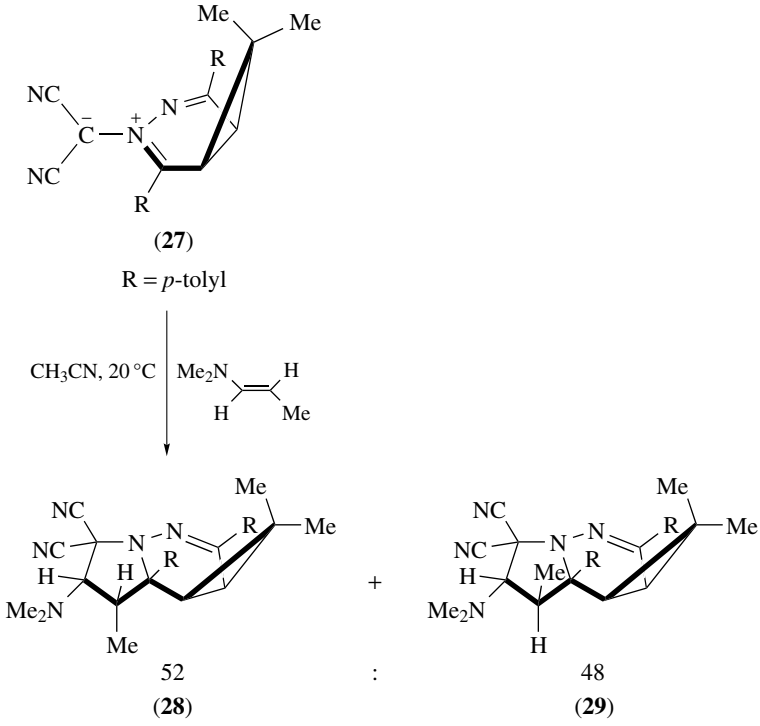
10%

SCHEME 8

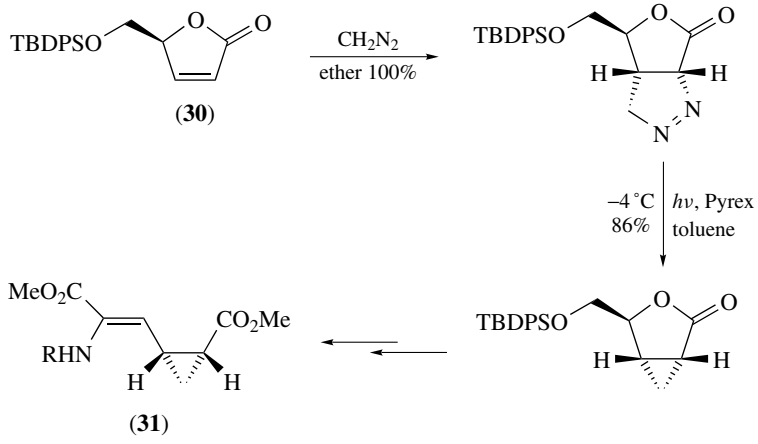
2 + 3-Cycloaddition

The 3 + 2-cycloaddition of 1,2-dithiophthalides with nitrilimines yields benzo[*c*]thiophenespirothiadiazoles regioselectively.[28] The azomethineimines isoquinolinium-*N*-aryllimide and *N*-(2-pyridyl)imide readily undergo 1,3-dipolar cycloaddition with electron-deficient dipolarophiles, dimethyl fumarate and dimethyl maleate, to yield tetrahydropyrazolo[5,1-*a*]isoquinolines in high yield.[29,30] The 1,3-dipolar cycloadditions of electron-poor 1,3-dipoles, bicyclic azomethine ylides (**27**), with (*E*)-1-*N*,*N*-dimethylaminopropene to yield cycloadducts (**28**) and (**29**) are examples of non-stereospecific cycloadductions (Scheme 9).[31] The synthesis of protected

2,3-didehydro-4,5-methano amino acids (**31**) involves the π-diastereoselective 1,3-dipolar cycloaddition of diazomethane with chiral furanones (**30**) derived from D-glyceraldehyde acetonide as the only chiral precursor (Scheme 10).[32]

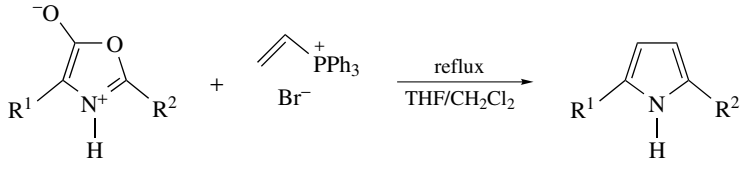


SCHEME 9



SCHEME 10

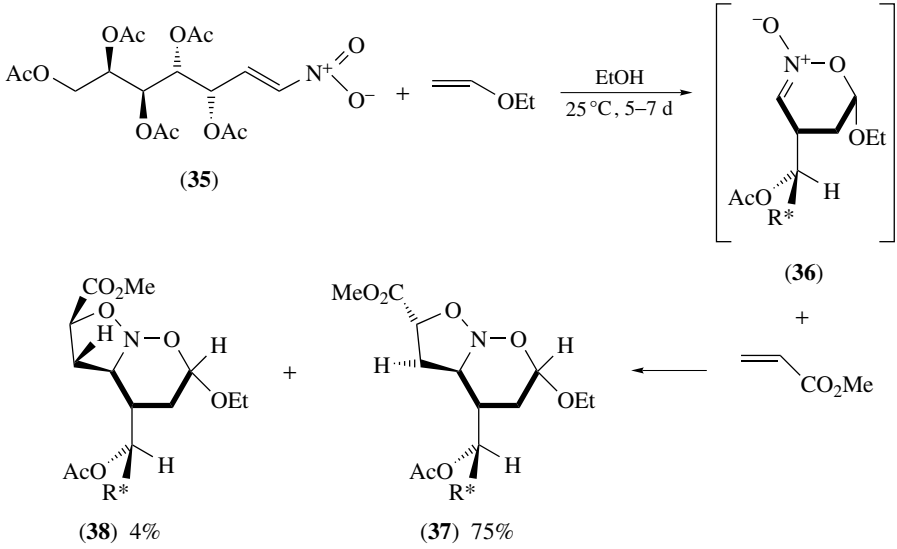
The reaction of 5(4*H*)-oxazolones (**32**) and münchnones with triphenylvinylphosphonium bromide (**33**) provides a mild synthesis of substituted pyrroles (**34**) (Scheme 11).[33] The cycloaddition–elimination reactions of 5-imino-1,2,4-thiadiazolidin-3-ones with enamines and ester enolates produce 2-iminothiazolidines.[34] Chiral isomünchnone dipoles show π-facial diastereoselectivity with *N*-phenyl- or *N*-methyl-maleimide in refluxing benzene.[35]



(**32**) (**33**) (**34**) 40%

R^1	R^2
Ph	Ph
4-ClPh	Ph
Ph	4-ClPh
4-MePh	Ph
Ph	4-MePh
Ph	*i*-Pr
i-Pr	Ph

SCHEME 11



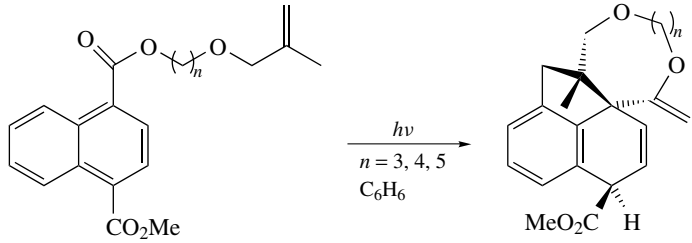
(**35**) (**36**) (**38**) 4% (**37**) 75%

SCHEME 12

The asymmetric tandem cycloaddition of the chiral carbohydrate nitroalkene (**35**) with ethyl vinyl ether involves the initial formation of the nitronate (**36**) which reacts exclusively with electron-withdrawing alkenes by 3 + 2-cycloaddition to yield chiral bicycles (**37**) and (**38**) (Scheme 12).[36]

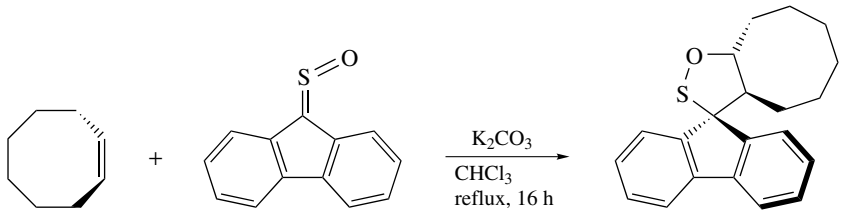
Intramolecular 3 + 2-photocycloadditions of alkenyl methyl 1,4-naphthalenedicarboxylates (**39**) yield 3 + 2-cycloadducts (**40**) having 9–11-membered ring systems in addition to the characteristic five-membered ring structure (Scheme 13).[37]

The 1,3-dipolar cycloaddition of fluorenethione *S*-oxide (**41**) and *trans*-octene yields the corresponding sultine (**42**) which readily converts olefins to episulfides (Scheme 14).[38]



(**39**) (**40**)

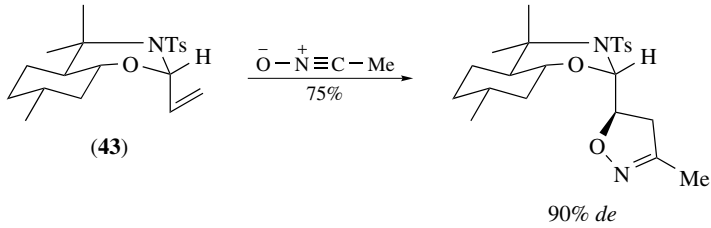
SCHEME 13



(**41**) (**42**)

SCHEME 14

A study of the regioselectivity of the 1,3-dipolar cycloaddition of aliphatic nitrile oxides with cinnamic acid esters has been published.[39] AM1 MO studies on the gas-phase 1,3-dipolar cycloaddition of 1,2,4-triazepine and formonitrile oxide show that the mechanism leading to the most stable adduct is concerted.[40] An *ab initio* study of the regiochemistry of 1,3-dipolar cycloadditions of diazomethane and formonitrile oxide with ethene, propene, and methyl vinyl ether has been presented.[41] The 1,3-dipolar cycloaddition of mesitonitrile oxide with 4,7-phenanthroline yields both mono- and bis-adducts.[42] Alkynyl(phenyl)iodonium triflates undergo 2 + 3-cycloaddition with ethyl diazoacetate, *N*-*t*-butyl-α-phenyl nitrone and *t*-butyl nitrile oxide to produce substituted pyrroles, dihydroisoxazoles, and isoxazoles respectively.[43] 2β-Vinyl-*trans*-octahydro-1,3-benzoxazine (**43**) undergoes 1,3-dipolar cycloaddition with nitrile oxides with high diastereoselectivity (90% *de*) (Scheme 15).[44]



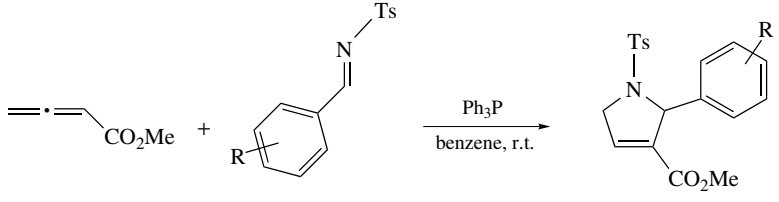
(**43**) 90% *de*

SCHEME 15

The 1,3-dipolar cycloadditions of benzonitrile oxides with tertiary cinnamides yield the 5-phenyl and 4-phenyl regioisomers in a reversal of the expected regioselectivities shown with methyl cinnamate. Calculations have shown that steric factors are responsible for this reversal of regioselectivity.[45] The 1,3-dipolar cycloadditions of benzonitrile oxide with electron-rich and electron-poor dipolarophiles are accelerated by sodium dodecyl sulfate micelles.[46] Phenyl nitrile ylides react with electron-deficient alkenes to produce five-membered *N*-heterocycles where measured rate constants are between 4×10^5 and $7 \times 10^9\,\mathrm{l\,mol^{-1}\,s^{-1}}$.[47]

The reaction of buta-2,3-dienoates (**44**) with electron-deficient imines (**45**) in the presence of triphenylphosphene yields 3 + 2-cycloadducts (**46**) in excellent yields and high chemoselectivity (Scheme 16).[48] The 1,3-diaza-2-azoniaallene salts (**47**) react with alkynes, *N*,*N*′-dialkylcarbodiimides, and *N*,*N*-dialkylcyanamides to produce 1,2,3-triazolium salts, 1,3,4,5-tetrasubstituted 4,5-dihydrotetrazolium salts, and 1,3,5-trisubstituted tetrazolium salts, respectively (Scheme 17).[49]

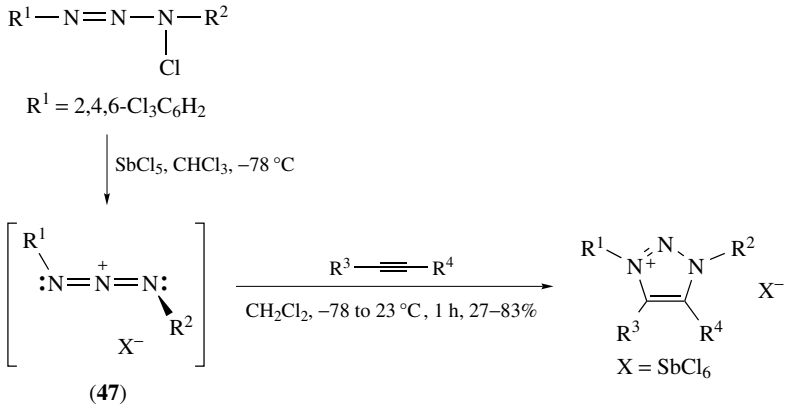
For the first time, DFT theory has been applied to a study of diastereofacial selectivity in 1,3-dipolar cycloadditions of nitrones to *cis*-3,4-dimethylcyclobutene.[50] The stereochemical outcome of the INAC reactions of nitrones (**49**) and (**52**) derived from 3-*O*-allyl-D-hexoses is dependent only on the relative configuration at C(2,3), and thus 3-*O*-allyl-D-glucose (**48**) and -D-altrose (*threo* configuration) afford oxepanes (**50**) selectively whereas 3-*O*-allyl-D-allose (**51**) and -D-mannose (*erythro* configuration) give tetrahydrofurans (**53**) and (**54**) selectively (Scheme 18).[51] *trans*-2-Methylene-1,3-dithiolane-1,3-dioxide (**55**) reacts regiospecifically with acyclic and cyclic nitrones (**56**) to produce 4,4- (**57**) rather than 5,5-disubstituted isoxazolidines (Scheme 19).[52]



(**44**) (**45**) (**46**)

R = H, 2-MeO, 4-MeO, 4-Me, 4-Cl, 4-NO_2

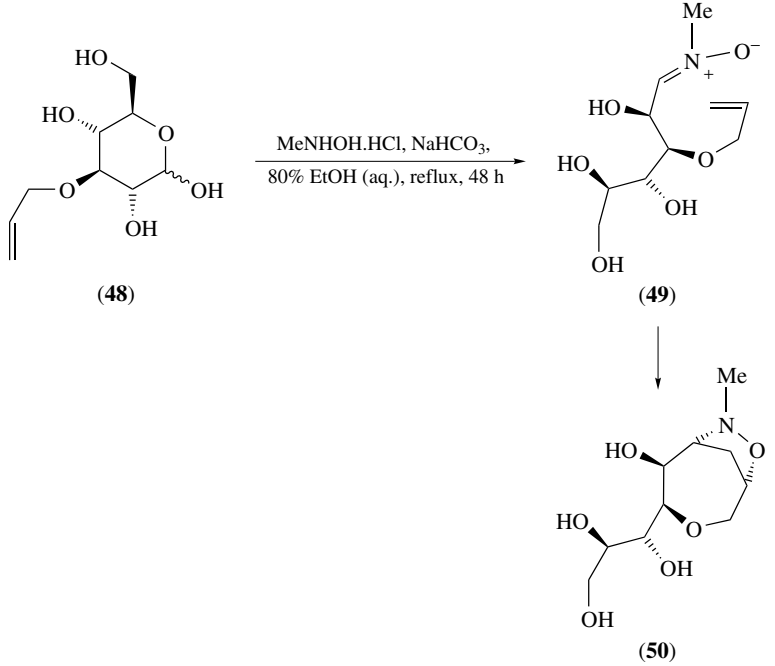
SCHEME 16



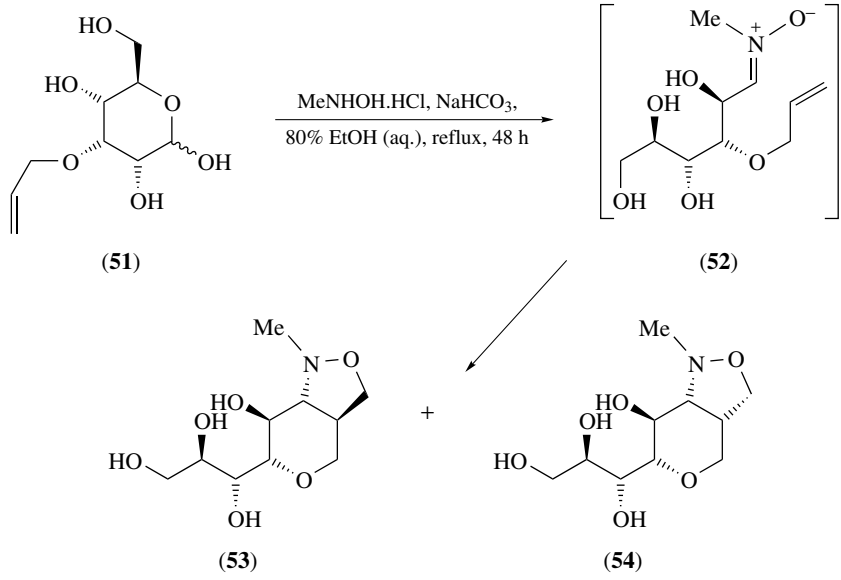
(**47**)

R^3	R^4
H	H
Bu	H
Bu^t	H
CH_2OH	H
Et	Et
CH_2Cl	CH_2Cl
Me	Ph
Ph	Ph
CO_2Me	CO_2Me

SCHEME 17

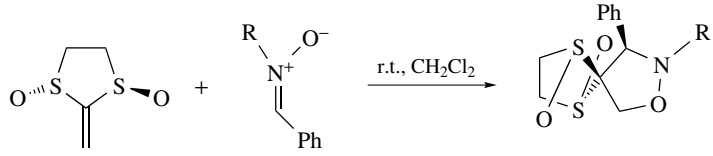


(**48**) (**49**) (**50**)



(**51**) (**52**) (**53**) (**54**)

SCHEME 18



(**55**) (**56**) (**57**)

R = Bu^t, Ph, Me

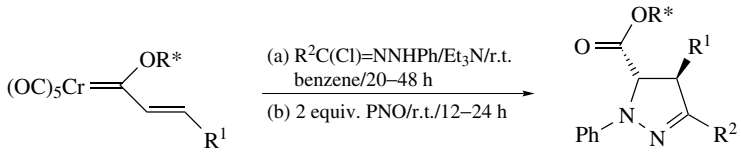
SCHEME 19

α-Phenyl-*N*-butyl nitrone undergoes 1,3-dipolar cycloadditions with dibromo- and dichloro-malononitrile, chlorotricyanomethane, tetracyanomethane, trichloroacetonitrile, and carbamoylchlorodicyanomethane to yield 2-butyl-3-phenyl-5-*R*-2,3-dihydro-1,2,4-oxadiazoles.[53] The stereochemical outcome of the 1,3-dipolar cycloaddition of formaldehyde *N*-benzylnitrone with β'-alkoxy- and γ-alkoxy-α,β-unsaturated esters was explained by application of the 'inside alkoxy' theory emphasizing the electrostatic interactions in the transition state.[54] Cyclic nitrones react with γ-bromo α,β-unsaturated esters and lactones to yield isoxazolines with major isomer showing *endo* regiochemistry.[55] Cyanomethylenecyclopropane is more reactive than ethoxycarbonylmethylenecyclopropane in 2 + 3-cycloaddition reactions with 5,5-dimethylpyrroline *N*-oxide.[56]

A kinetic study of the 1,3-dipolar cycloadditions of alkynyl Fischer carbene complexes with nitrones showed first-order kinetics for both nitrones and the alkynyl carbene complexes.[57] The 1,3-dipolar cycloaddition of chiral non-racemic Fischer

carbene complexes (**58**) with nitrilimines yield Δ^2-pyrazolines (**59**) with high regio- and diastereo-selectivity (Scheme 20).[58]

The 3 + 2-cycloaddition of pyrroline *N*-oxide to 2-chloro-2-cyclopropylidene acetate and its spiropentane analogues (**60**) yields spiro[cyclopropane-1,5′-isoxazolidine]s (**61**) which undergo a novel cascade ring enlargement to yield indolizinones (**62**) in high yield (Scheme 21).[59]



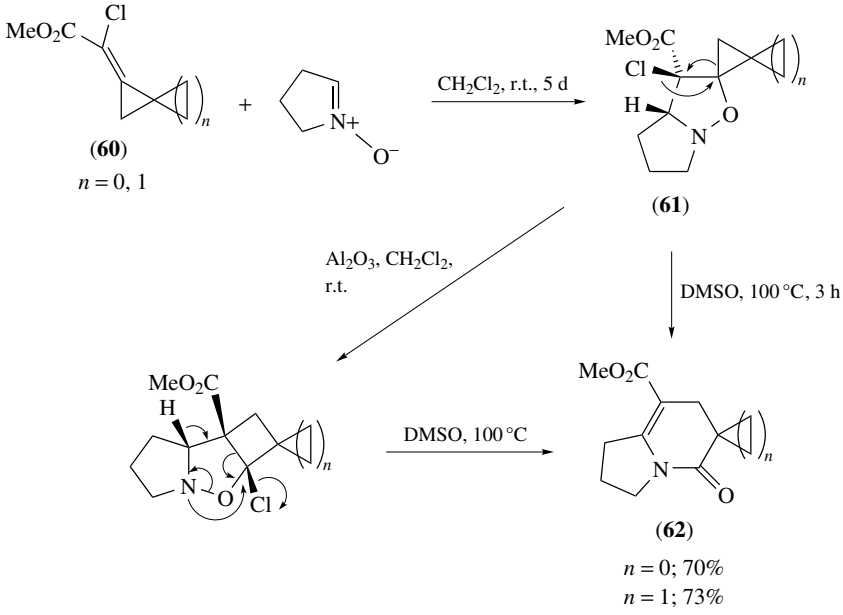
(**58**)

R* = (+/−)-menthol

(**59**)

R^1	R^2
Ph	Ph
2-furyl	Ph
p-anisyl	Ph
Ph	*p*-anisyl
2-furyl	*p*-anisyl
p-anisyl	*p*-anisyl
Ph	CO_2Et

SCHEME 20



(**60**)

n = 0, 1

(**61**)

(**62**)

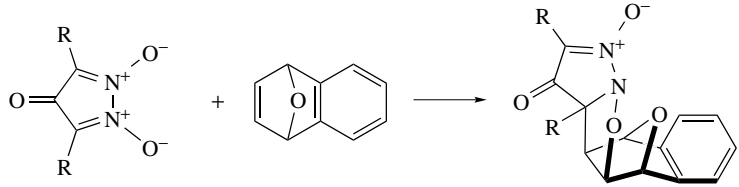
n = 0; 70%

n = 1; 73%

SCHEME 21

Camphor-derived oxazoline *N*-oxides react with α,β-unsaturated esters or nitroalkenes to produce cycloadducts which exhibit high regio- and stereo-selectivities.[60] The 3 + 2-cycloaddition of pyrazolone *N*,*N*-dioxide (**63**) with epoxynaphthalene (**64**) yields only the *endo*-cycloadduct (**65**) as a result of interaction between the epoxide oxygen and the N−O group in the dioxide (Scheme 22).[61] The thermal isomerization of 1,3-dipolar cycloadducts of 3,4-dihydro-β-carboline 2-oxide has been investigated using ^{1}H NMR spectroscopy.[62] The 1,3-dipolar cycloaddition of iminodifluoromethanides with carbonyl compounds produces oxazolidine derivatives.[63]

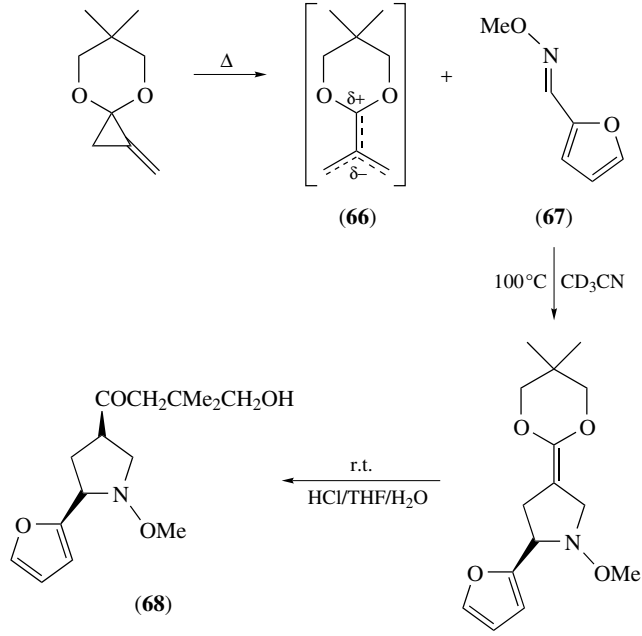
An *ab initio* computational study of the 3 + 2-cycloaddition of allyl-, 2-borylallyl-, and 2-azaallyl-lithium to ethylene favours the two-step pathway over the $4\pi_s + 2\pi_s$



(**63**) (**64**) (**65**)

R = H, Me, Ph, CO_2Me

SCHEME 22



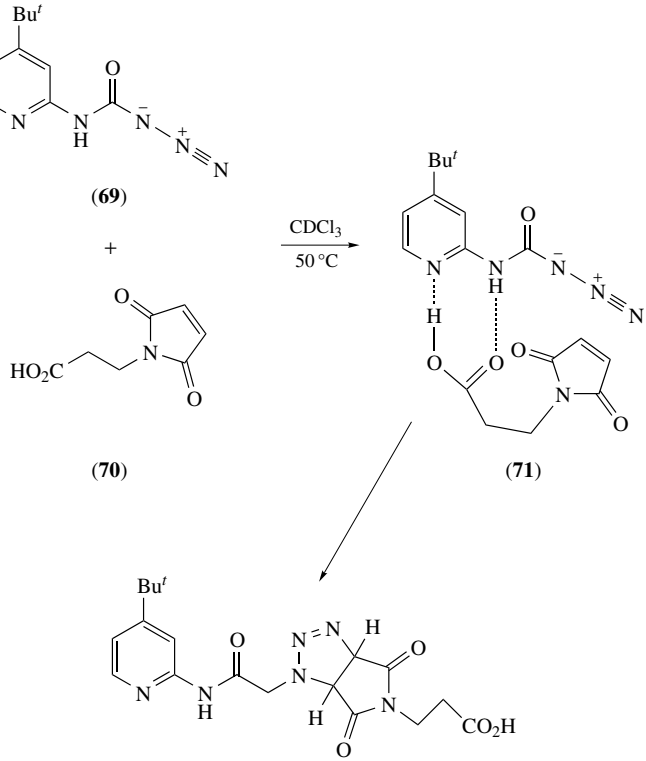
(**66**) (**67**)

(**68**)

SCHEME 23

mechanism.[64] 3-(Alkylthio)-2-siloxyallyl cationic species undergoes regio- and stereoselective 3 + 2-cycloaddition with various alkenes to produce cyclopentanones in good yields.[65] The thermal 3 + 2-cycloaddition of dipolar trimethylenemethane (**66**) to *anti*-*O*-alkyl oximes (**67**) provides a synthetic route to substituted pyrrolidines (**68**) and prolines (Scheme 23).[66]

PM3 calculations of the 2 + 3-cycloaddition of *t*-butylphosphaacetylene with 2,4,6-triazidopyridine are consistent with the dipole-LUMO-controlled reaction type.[67] An FTIR spectroscopic study of the 1,3-dipolar cycloaddition of aryl azides with acetylenes shows that the rate of reaction increases logarithmically with pressure (below 1 GPa).[68] The 3 + 2-cycloaddition between an azide (**69**) and a maleimide (**70**) has been greatly accelerated by utilizing molecular recognition between an amidopyridine and a carboxylic acid [see (**71**)] (Scheme 24).[69,70]



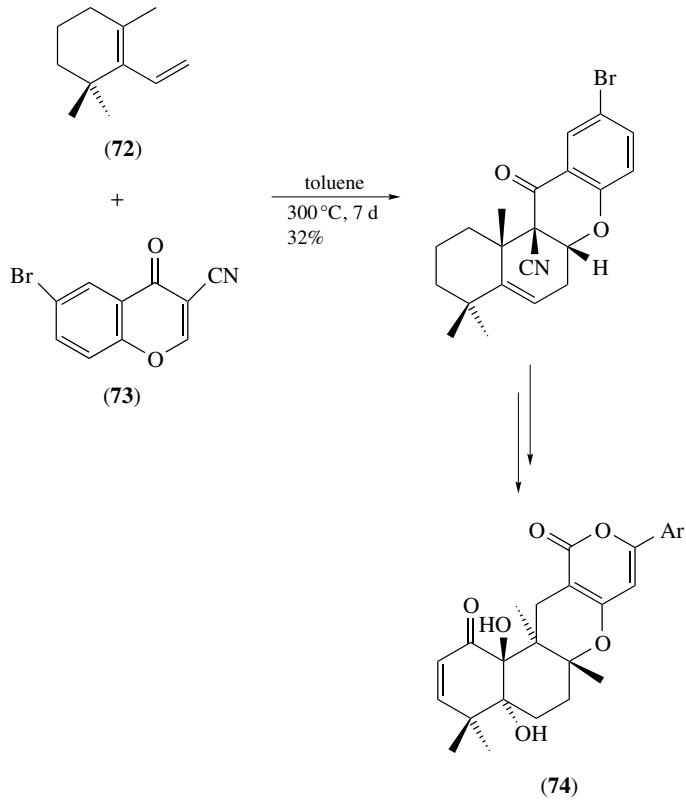
SCHEME 24

2 + 4-Cycloaddition

A modern valence-bond description of the Diels–Alder reaction has been presented.[71] The method of reaction classification by similarity has been expanded to include the effect of steric congestion in the classification of cycloaddition reactions.[72]

The retro-Diels–Alder reaction has been extensively reviewed (1387 references).[73] AM1 MO and density functional theory have been applied to Diels–Alder and retro-Diels–Alder reactions involving heterocyclic compounds as the diene or the dienophile.[74]

The *ab initio* method at the 3–21G level has been used to investigate the Diels–Alder reaction mechanism of cyclohexa-1,3-diene with propenenitrile.[75] The *ab initio* UHF/6–31G* method was used to study the 4 + 2-cycloaddition of cyclohexa-1,3-diene with propylene.[76] Second-order rate constants determined for the Diels–Alder reaction of dienes with *N*-substituted maleimides in different solvents indicate that hydrophobic groups near the reaction centre lose their hydrophobic character completely in the activated complex of the Diels–Alder reaction, whereas more distant groups retain their non-polar character throughout the reaction.[77] The Diels–Alder addition of push-pull alkenes, dicyanovinyl acrylates with cyclic dienes proceeds with significant stereoselectivity.[78] The 4 + 2-cycloaddition of 3-cyanochromone derivatives (**73**) with electron-rich dienes (**72**) is highly stereoselective and shows potential for the construction of the ABC tricyclic frame of arisugacin (**74**), a selective inhibitor of acetylcholinesterase (Scheme 25).[79]



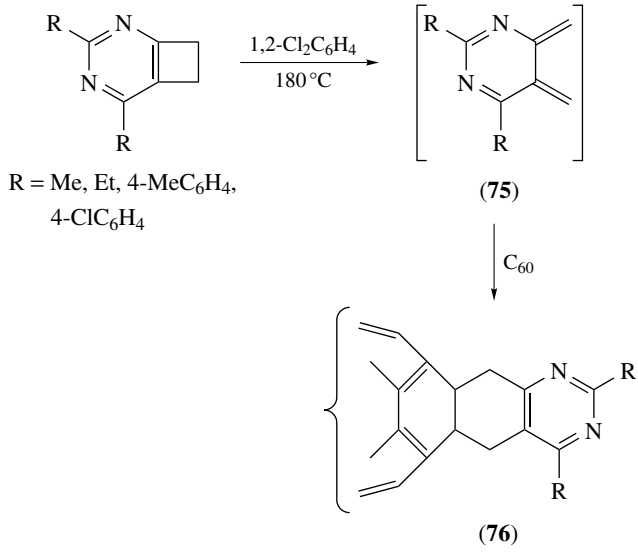
(**74**)

Arisugacin Ar = 3,4-dimethoxyphenyl

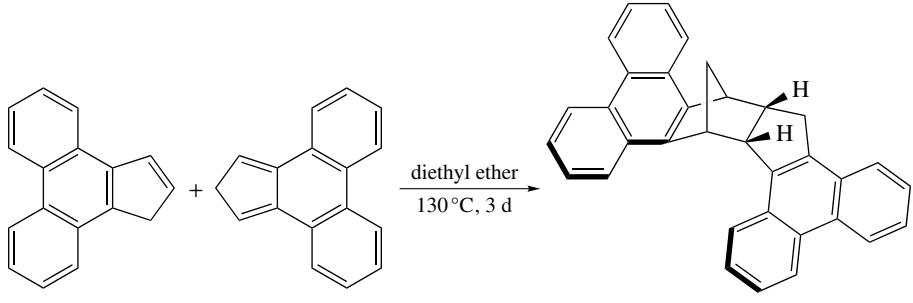
SCHEME 25

A review of Diels–Alder reactions of fullerenes with acyclic and cyclic dienes has been presented.[80] The addition of substituted pyrimidine *o*-quinodimethanes (**75**) to [60]fullerenes yields novel organofullerenes (**76**) bearing a pyrimidine nucleus covalently attached to the C_{60} cage (Scheme 26).[81] The Diels–Alder dimerization of cyclopenta[*l*]phenanthrene (**77**) with isobenzindene (**78**) yields the dimer (**79**) in 85% yield (Scheme 27).[82] Further evidence has been supplied to support an early reorganization of the π-network in the dimerization of 2-methoxycarbonylbuta-1,3-diene.[83]

The Lewis acid-catalysed Diels–Alder reactions of acrylate derivatives of new carbohydrate-based chiral auxiliaries with cyclohexadiene show excellent *endo*:*exo*



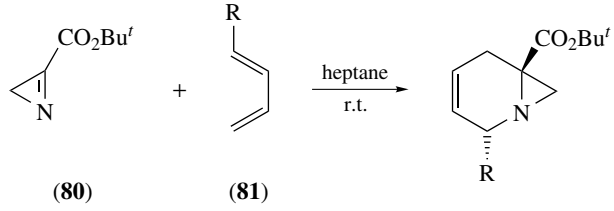
SCHEME 26



SCHEME 27

ratios but only moderate π-facial selectivities.[84] The 4 + 2-cycloaddition of 2-*N*-(acetylamino)-1-thia-1,3-dienes containing chiral auxiliaries react with dipolarophiles to produce thiopyrans of high optical purity.[85] Alkyl 1-*N*-benzoyl-2-oxoimidazolidin-4-carboxylates are powerful chiral auxiliaries in the Diels–Alder reactions of their 3-*N*-enoyl derivatives.[86]

Ab initio calculations on aza-Diels–Alder reactions of electron-deficient imines with buta-1,3-diene show that these reactions are HOMO (diene)–LUMO(dienophile)-controlled and that electron-deficient imines should be more reactive than alkyl- or aryl-imines.[87] The Diels–Alder reaction of *t*-butyl 2*H*-azirine-3-carboxylate (**80**) proceeds with high diastereoselectivity with electron-rich dienes (**81**) (Scheme 28).[88] The hetero-Diels–Alder additions of imines with sterically demanding dienes yield perhydroquinolines bearing an angular methyl group.[89] The asymmetric hetero-Diels–Alder reaction between alkenyloxazolines and isocyanates produces diastereometrically pure oxazolo[3,2-*c*]pyrimidines.[90]



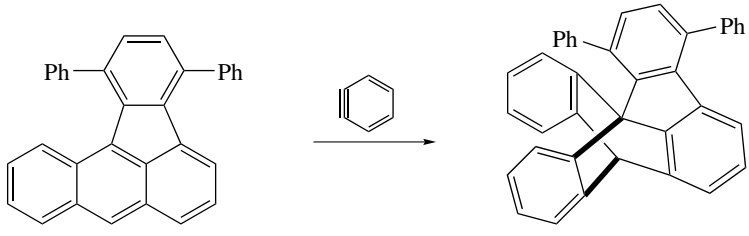
(**80**) (**81**)

R = OMe, Me

SCHEME 28

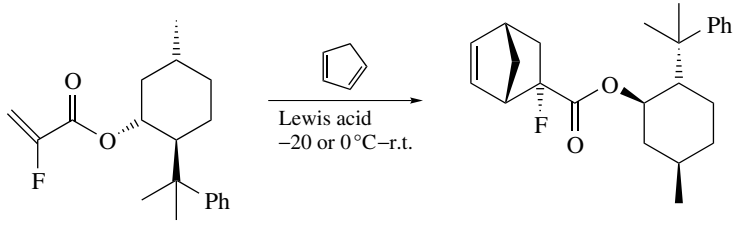
An *ab initio* study of the Diels–Alder reaction between 5-substituted cyclopenta-1,3-dienes and various dienophiles indicates that facial selectivity is primarily due to steric hindrance between the dienophile and the plane non-symmetric groups on the diene.[91] A theoretical study of the role of steric and electronic factors in controlling π-facial selectivities in Diels–Alder reactions of π-facially non-equivalent dienes with MTAD, PTAD, and NMM is described.[92] The Diels–Alder reactions between 1,4-diphenylbenz[*a*]aceanthrylene (**82**) and maleic anhydride, bromomaleic anhydride, *N*-phenylmaleimide, and benzyne show *endo* regiochemical π-facial selectivity (Scheme 29).[93] The Diels–Alder cycloadditions of enantiopure hydroxy-2-sulfinylbutadienes with *N*-phenylmaleimide and phenyltriazolinedione show high π-facial selectivity controlled by the chiral sulfur atom.[94] The Diels–Alder reaction of (*R*)-4-[(*p*-tolylsulfinyl)methyl]quinols with cyclopentadiene and penta-1,3-diene show total π-faced diastereoselectivity from the C−OH side.[95] The high stereoselectivity observed for the Diels–Alder reactions of 1,5,5-trimethylcyclopentadiene with 4-substituted- and 4,4-disubstituted cyclohexadienones arises from the lower steric demand of oxygen relative to methylene groups.[96]

In the Diels–Alder reaction between 2-pyridones and electron-deficient alkenes, 2,4,6-triisopropylbenzenesulphonyl is a better *N*-substituent than 4-methylbenzenesulfonyl.[97]



(**82**)

SCHEME 29



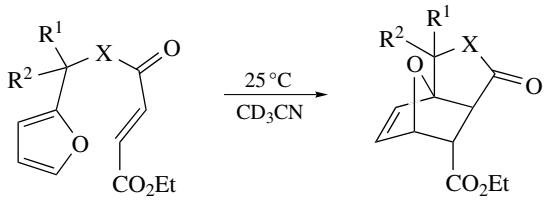
(**83**) 84–95%

SCHEME 30

The Diels–Alder reaction between a 2-fluoroacrylic acid derivative of 8-phenylmenthol (**83**) and cyclopentadiene shows high *exo*- and π-diastereofacial selectivity (Scheme 30).[98] The C(2) of endocyclic 'cross-conjugated' 2-(acylamino)-1,3-dienes exerts excellent diastereofacial control on the Diels–Alder addition with electron-deficient dienophiles to produce octahydroquinolines.[99]

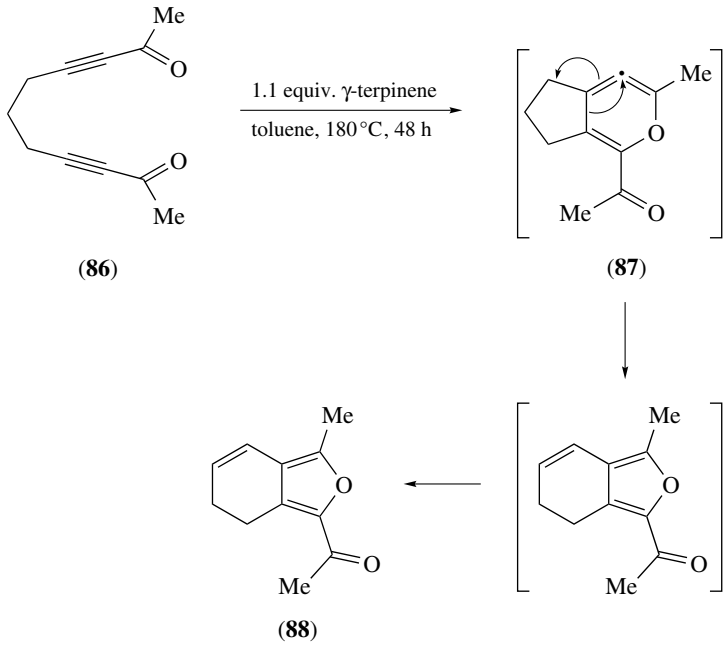
The Diels–Alder reactions of the chiral reagents *N*-allyl-*o*-butylanilide and *N*-(*o*-butylphenyl)-2-methylmaleimide proceed with high *endo* and diastereofacial selectivity.[100]

A study of the rates of intramolecular Diels–Alder cyclization of furfuryl methyl fumarates (**84**) and the corresponding furyl ethyl keto esters (**85**) provides evidence that the presence of the oxygen atom in the tether is the factor responsible for larger than normal rate enhancement (Scheme 31).[101] Bulky protecting groups such as trityl group have been used to stimulate the intramolecular 4 + 2-cycloaddition reactions of *N*-allylfurylamines that normally do not undergo thermal cycloaddition.[102] The activation and reaction volumes of intramolecular Diels–Alder reactions of (*E*)-nona-1,3,8-triene and (*E*)-deca-1,3,9-triene have been shown to be dependant on the ring size.[103] An intramolecular 4 + 2-cycloaddition of bisalkynones (**86**) yields dihydroisobenzofurans (**88**) via the generation and rearrangement of strained heterocyclic allenes (**87**) in high yields (Scheme 32).[104] 2-*H*-Phospholes undergo intramolecular 4 + 2-cycloaddition to coordinated unsaturated phosphines, phospholes and an arsine.[105]



(**84**) X = CH_2
(**85**) X = O
$R^1 = R^2$ = H, Me

SCHEME 31

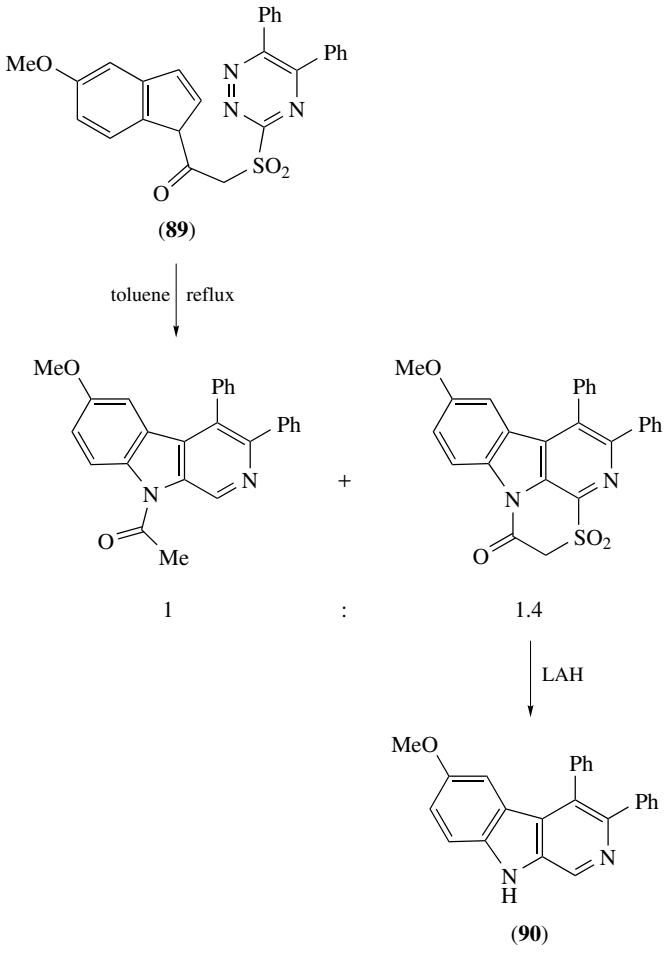


(**86**) (**87**) (**88**)

SCHEME 32

A semiempirical AM1 study of the inverse-electron-demand Diels–Alder reaction of 4-substituted 6-nitrobenzofurans with enol ethers and enamines favours a stepwise mechanism involving short-lived diradical intermediates.[106] The inverse-electron-demand intermolecular Diels–Alder reactions of 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine with acyclic and cyclic dienophiles followed by the elimination of N_2 produce 4,5-dihydropyridazines, which cycloadd further to yield cage compounds.[107] The preparation of β-carbolines (**90**) via an intramolecular inverse-electron-demand Diels–Alder

reaction involves the use of a fully removeable β-sulfonoacetyl tether linking indole with 1,2,4-triazines (**89**) (Scheme 33).[108]



SCHEME 33

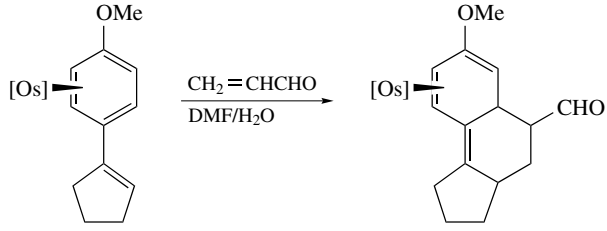
The inverse-electron-demand Diels–Alder reaction of 3,6-dichloro[1,2,4,5]tetrazine with alkenes and alkynes provides the synthesis of highly functionalized pyridazines.[109] Also, the 4 + 2-cycloaddition reactions of the parent [1,2,4,5]tetrazine with donor-substituted alkynes, alkenes, donor-substituted and unsubstituted cycloalkenes, ketene acetals, and aminals have been investigated.[110]

N-Protonated 2-azabuta-1,3-diene undergoes $4^+ + 2$-cycloaddition with alkenes activated by electron-donating and electron-withdrawing substituents.[111] The $2^+ + 4$-cycloadditions of 1,3-dithian-2-ylium ions with buta-1,3-dienes follow second-order kinetics which do not exclude a mechanism involving a concerted pathway.[112] The

cation radical Diels–Alder addition of aryl vinyl sulfide to cyclopenta-1,3-diene in the presence of tris(4-bromophenyl)aminium hexachloroantimonate does not occur via outer-sphere electron transfer but by strong covalent interaction between aminium salt acting as an electrophile and the aryl vinyl sulfide substrate acting as a nucleophile.[113]

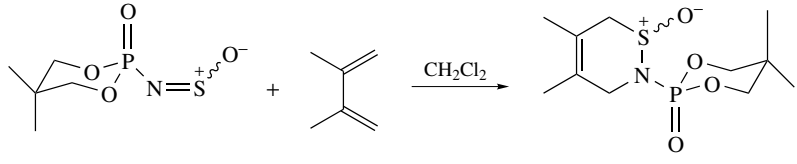
C_2-Symmetric Cu(II)–bis(oxazoline) complexes have been used in stereoselective Diels–Alder reaction between α,β-unsaturated acyl phosphonates and enol ethers to produce cycloadducts in 89% yield and 99% *ee*.[114] The asymmetric Diels–Alder reactions between α-thioacrylates and cyclopentadiene are catalysed by Cu(II)–bis (oxazoline) complexes to produce cycloadducts in up to 92% yield, 88% *de* and > 95% *ee* for the *endo* adduct.[115] Osmium(II) has been used to activate styrene (**91**) towards Diels–Alder reactions with electron-deficient alkenes to yield tetrahydronaphthalene complexes (**92**) (Scheme 34).[116] The use of Cu(II) complexes of simple α-amino acids will increase the enantioselectivity of Lewis acid-catalysed Diels–Alder reaction between 3-phenyl-1-(2-pyridyl)prop-2-en-1-one and cyclopentadiene in water.[117]

The rhodium complexes $[\eta\text{-}C_5Me_5)RhClL]X$ ($X = PF_6, SbF_6$) prepared from bidentate oxazoline-containing ligands are enantioselective catalysts for asymmetric Diels–Alder reaction of methacrolein with cyclopentadiene.[118] The Diels–Alder reaction of *N*-sulfinylphosphoroamidates (**93**) with cyclohexa-1,3-diene are highly diastereoselective in both the presence and absence of Lewis acid catalysts (Scheme 35).[119] The $TiCl_4$-catalysed Diels–Alder addition of trienes [e.g. (**94**)] produce decahydropyrido[2,1-*a*]isoindoles and decahydro-2*H*-pyrido[1,2-*b*]isoquinolines (**95**) and (**96**) stereoselectively in moderate yields (Scheme 36).[120] Mg(II) complexes of crown ylidene malonates have a strong catalytic effect on the Diels–Alder reaction between crown ylidene malonates and cyclopentadiene.[121]



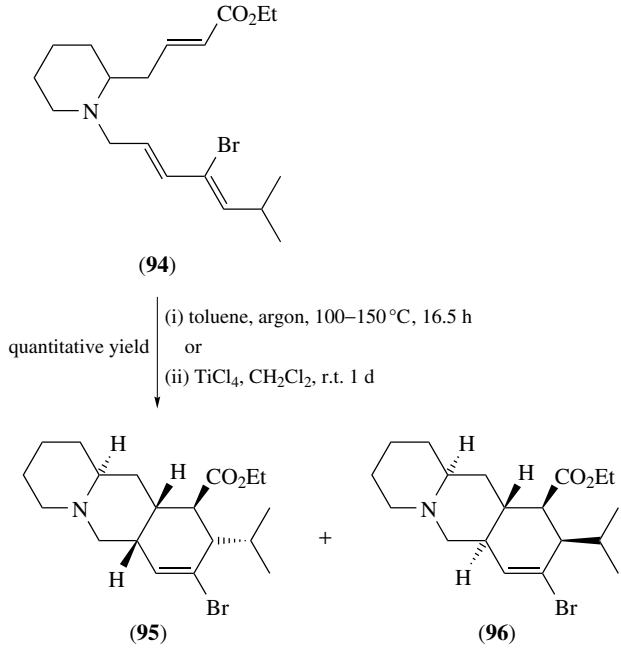
(**91**) (**92**)
80%

SCHEME 34



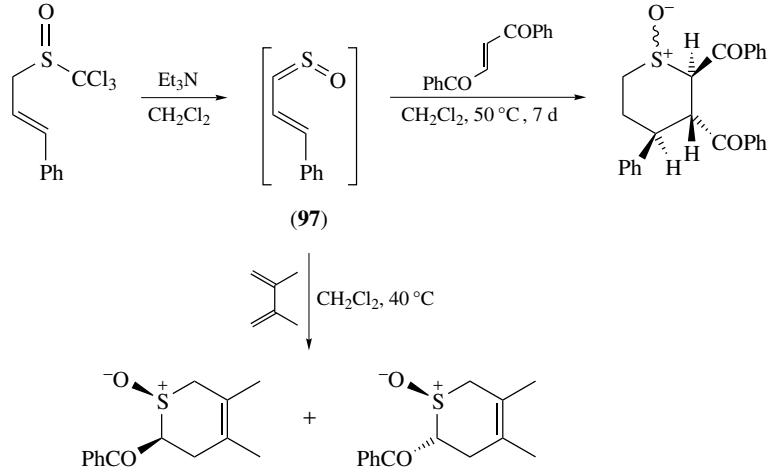
(**93**) 65%

SCHEME 35



SCHEME 36

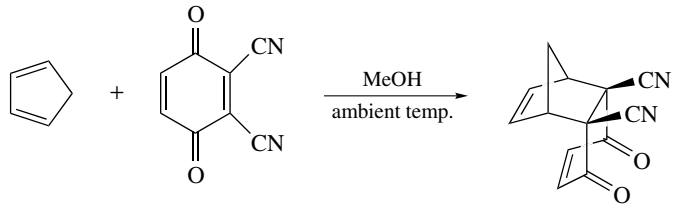
Density functional and semiempirical AM1 molecular orbital calculations have been used to investigate substituent effects on site selectivity in heterocumulene–heterodiene 4 + 2-cycloadditions between ketene imines and acroleins.[122] The new and novel heterocumulenes α,β-unsaturated thioaldehyde *S*-oxides (**97**) behave as both diene



SCHEME 37

and dienophile in Diels–Alder reactions (Scheme 37).[123] AM1 and PM3 calculations show that the Diels–Alder reactions of carbonyl *S*-oxide and thiocarbonyl *S*-oxide with cyclopentadiene form cycloadducts through asynchronous transition states.[124]

The asymmetric Diels–Alder cycloadditions of enantiopure (*S*)-*S*-(*p*-tolylsulfinyl)-1,4-benzoquinones with Dane's diene under thermal and Lewis acid conditions produce tetracyclic quinones after spontaneous elimination of the sulfinyl group.[125] The Diels–Alder reaction of barrelene with *o*-benzoquinone produces tetracyclo[6.2.2.$2^{3,6}$.$0^{2,7}$]tetradeca-9,11,13-triene-4,5-dione.[126] Under kinetic control, the Diels–Alder cycloaddition of 2,3-dicyano-*p*-benzoquinone (**98**) with cyclopentadiene in MeOH produces the single cycloadduct (**99**) (Scheme 38).[127]



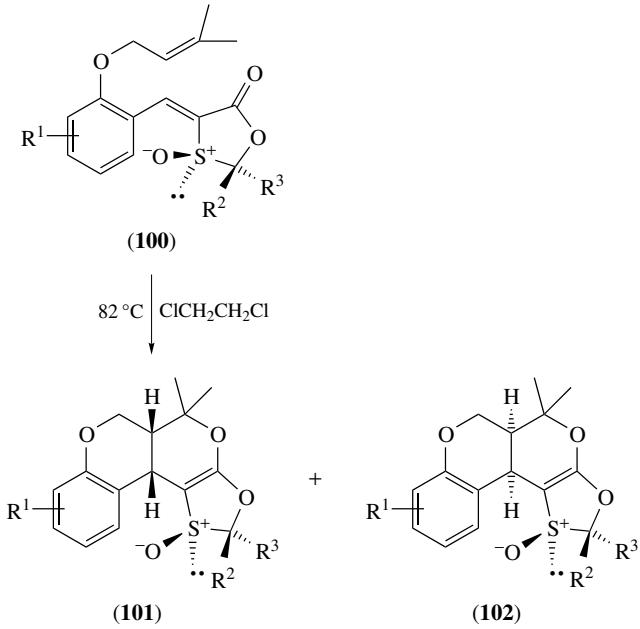
(**98**) (**99**)

SCHEME 38

An extensive review of the use of chiral Lewis acid catalysts in Diels–Alder cycloadditions has been presented.[128] Brønsted acid-assisted chiral Lewis acids have been shown to be highly efficient catalysts for the enantioselective Diels–Alder reactions of α- and β-substituted-α,β-enals with numerous dienes.[129] The chiral Lewis acid-catalysed Diels–Alder reaction between cyclopentadiene and alkenoyloxazolidinones can be catalysed by bis(oxazolone)magnesium catalysts.[130]

An extensive review of the hetero-Diels–Alder reactions of 1-oxabuta-1,3-dienes has been published.[131] *Ab initio* calculations of the Diels–Alder reactions of prop-2-enethial with a number of dienophiles show that the transition states of all the reactions are similar and synchronous.[132] Thio- and seleno-carbonyl compounds behave as 'superdienophiles' in Diels–Alder reactions with cyclic and aryl-, methyl-, or methoxy-substituted open-chain buta-1,3-dienes.[133] The intramolecular hetero-Diels–Alder reactions of 4-benzylidine-3-oxo[1,3]oxathiolan-5-ones (**100**) produce cycloadducts (**101**) and (**102**) in high yield and excellent *endo/exo*-selectivity (Scheme 39).[134] A density functional theoretical study of the hetero-Diels–Alder reaction between butadiene and acrolein indicates that the *endo s-cis* is the most stable transition structure in both catalysed and uncatalysed reactions.[135] The formation and use of amino acid-derived chiral acylnitroso hetero-Diels–Alder reactions in organic synthesis has been reviewed.[136] The 4 + 2-cycloadditions of *N*-acylthioformamides as dienophiles have been reviewed.[137]

High-pressure kinetic studies indicate that the concertedness of [$\pi^4 + \pi^2$] cycloadditions is not altered by the presence of a Lewis catalyst.[138] The intermolecular hetero-Diels–Alder reactions between enantiopure α,β-unsaturated sulfinimines and



R^1 = H, 3-OMe, 4-OMe, 5-OMe, 6-OMe;
R^2 = Me; R^3 = Me, Bu^t; $R^2 - R^3 = CH_2$

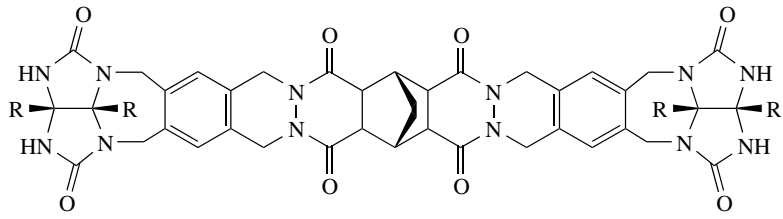
SCHEME 39

enol ethers at 11 kbar produce tetrahydropyridines in high yield and with good *endo/exo* selectivity.[139] At high pressure (3 kbar), the rates of reaction of intramolecular Diels–Alder addition between furan and bicyclopropylidine or methylenecyclopropane are significantly increased, as shown by FTIR spectroscopy.[140]

Density functional theory has been used to investigate the Diels–Alder reactions of triazolinedione with *s-cis*- and *s-trans*-butadiene.[141] Combined quantum mechanics–molecular mechanics calculations have been used to investigate the asymmetric Diels–Alder reaction of cyclopentadiene with the complex dienophiles $AlCl_3$–methyl acrylate and methoxyaluminium dichloride–acrolein.[142] Equilibrium constants have been determined for the molecular complexes formed from 1-alkyl-1-(2-naphthyl)ethenes and 1-vinylnaphthalene with TCNE in $Cl(CH_2)_2Cl$ at 27.1 °C.[143]

Extensive reviews of Diels–Alder reactions and hetero-Diels–Alder reactions in aqueous media have been presented.[144–146] Micelles in the presence of catalytically active transition-metal ions catalyse the Diels–Alder reaction between 3-(*p*-substituted phenyl)-1-(2-pyridyl)prop-2-en-1-ones with cyclopentadiene by a factor of 1.8×10^6 compared with the uncatalysed reaction in MeCN.[147] Diels–Alder reactions have been shown to be accelerated by encapsulation of both reactants by pseudospherical capsules assembled from self-complementary molecules (**103**).[148]

Experimental and computational studies of the effect of solvents on the rate and selectivity of the concerted Diels–Alder reaction between cyclopentadiene and methyl



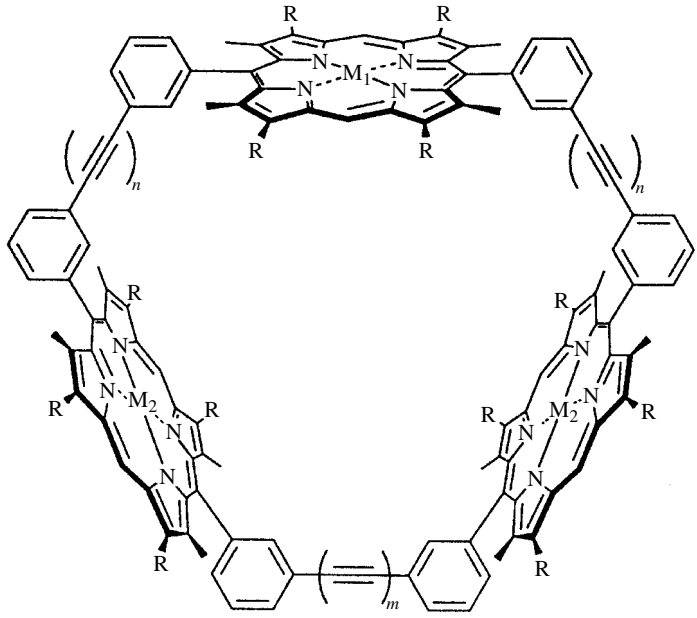
(**103**)

R = C_6H_5, CO_2-*i*-pentyl

acrylate are presented.[149] The stereoselectivity of Diels–Alder reactions of cyclopentadiene and electron-deficient dipolarophiles in structured solvents such as water and formamide is influenced by the internal pressure.[150] Solvent polarity has been shown to affect the rate coefficients and activation parameters of the hetero-Diels–Alder reaction between enamino ketones and isopropenyl methyl ether under high pressure (5 kbar).[151]

AM1 computational theory was used to compare the reactivities of benzo[*c*]furan and benzo[*b*]furan in Diels–Alder reactions using several dienophiles.[152]

Zn–metalloporphyrin oligomers (**104**) have been successfully used to reverse the stereochemistry of a Diels–Alder reaction by stabilizing the thermodynamically disfavoured *exo*-transition state.[153]



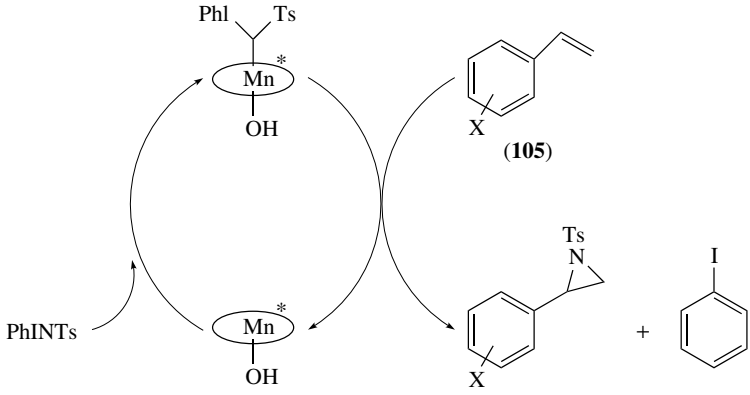
(**104**)

n = 1, *m* = 2, $M_1 = M_2 = Zn$; R = $CH_2CH_2CO_2Me$

The domino cycloaddition–*N*-acyliminium ion cyclization cascade has been extensively reviewed.[154] Tandem reactions combining Diels–Alder reactions and sigmatropic rearrangement reactions in organic synthesis have been extensively reviewed.[155] The tandem Diels–Alder reaction between acetylenedicarboxaldehyde and *N*,*N*′-dipyrrolylmethane has been extensively studied at the RHT/3–21G and RHF/6–31G* levels.[156] The molecular mechanism of the domino Diels–Alder reaction between hexafluorobut-2-yne and *N*,*N*′-dipyrrolylmethane has been studied using density functional theory.[157]

Miscellaneous Cycloadditions

A chiral D_4-manganese(III) porphyrin catalyst, Mn(P*)(MeOH)(OH) [$H_2P^* = 5, 10, 15, 20$-tetrakis(1,2,3,4,5,6,7,8-octahydro-1,4:5,8-dimethanoanthracene-9-yl)porphyrin], has been shown to catalyse the asymmetric aziridination of substituted styrenes (**105**) with enantiomeric excess of 43–68% (Scheme 40).[158]

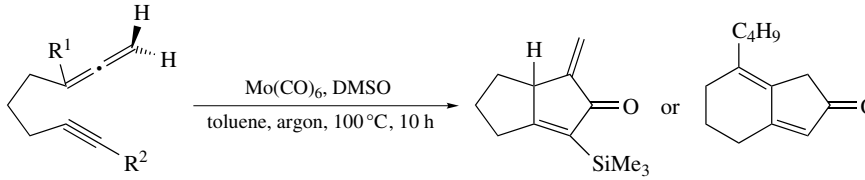


SCHEME 40

The intramolecular 2 + 2 + 1-cycloadditions of allene, alkyne (**106**), and carbon monoxide yield α-methylene-(**107**) or 4-alkylidene-cyclopentenones (**108**) depending on the allene structure or the reaction conditions (Scheme 41).[159,160]

The cobalt-catalysed 4 + 2 + 2-cycloaddition of norbornadienes (**109**) with buta-1,3-dienes readily produces cycloadducts (**110**) when a bimetal system is used (Scheme 42).[161]

An extensive review of 4 + 3-cycloaddition reactions has been presented.[162] The 1,3-difluorooxyallyl intermediate obtained from 1-bromo-1,3-difluoropropan-2-one undergoes 4 + 3-cycloaddition with cyclopentadiene and furan to give difluorobicyclo[3.2.1]octenones.[163] The use of 4 + 3-cycloaddition reactions of cyclic oxyallyls in the synthesis of natural products has been extensively studied.[164] The intramolecular 4 + 3-cycloaddition of allylic sulfones (**111**) possessing a diene in the side-chain in the presence of Lewis acids yield cycloadducts (**112**) in good to excellent yields (Scheme 43).[165]



(**106**)

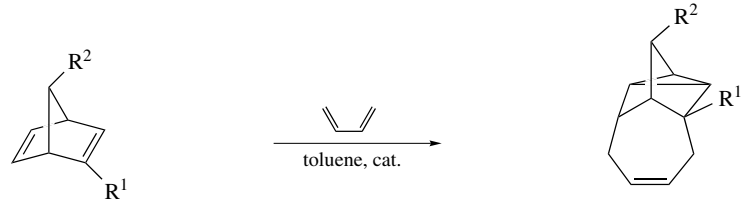
(**107**) 68%

(**108**) 60%

R^1, R^2 = H, $SiMe_3$

R^1, R^2 = C_4H_9, H

SCHEME 41



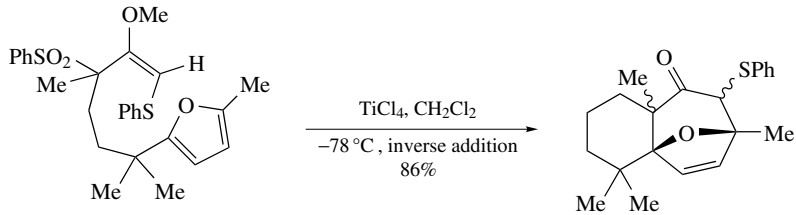
(**109**)

cat. = $Co(acac)_2$–DPPE–Et_2AlCl (1:1.5:10),
1 mol% based on Co relative to (**109**)

(**110**)

R^1	R^2
H	Bu^{t}O
Me	Bu^{t}O
Me	H
CH_2OMe	H

SCHEME 42



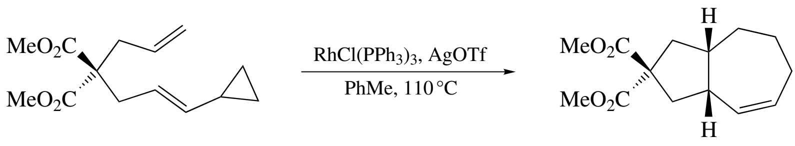
(**111**)

(**112**)

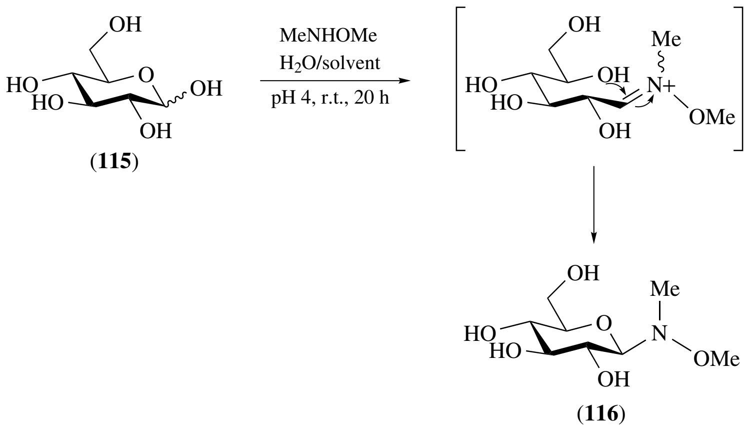
SCHEME 43

Molecular mechanics–valence bond dynamics have been used to study the model 4 + 4-photocycloadditions of butadiene with butadiene.[166] The photoirradiation of *t*-butyl 9-anthroate and furan produces a mixture of 4 + 4-cycloadduct and 4 + 4-cyclodimers.[167]

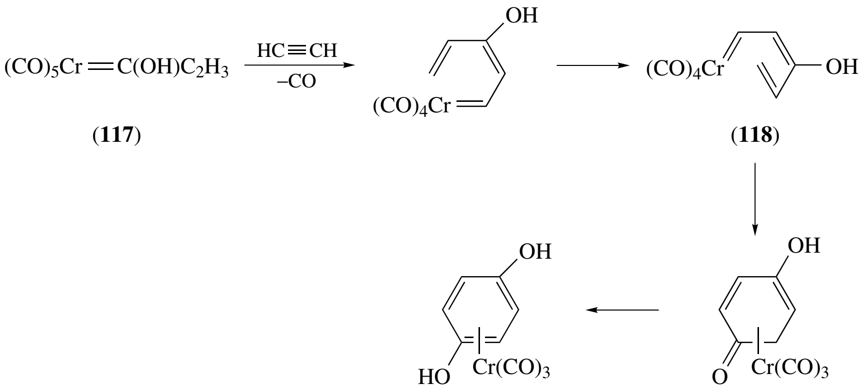
The rhodium(I)-catalysed 5 + 2-cycloadditions between vinylcyclopropanes and alkenes (**113**) yield only *cis*-5,7-fused cycloadducts (**114**) in high yields (Scheme 44).[168,169]



SCHEME 44



SCHEME 45



SCHEME 46

The glycosylation of N,O-disubstituted hydroxylamines with unprotected reducing sugars (**115**) proceeds with high chemo- and stereo-selectivity to yield the cycloadduct (**116**) (Scheme 45).[170]

A new chromahexatriene (**118**) route has been proposed for the mechanism of the Dötz benzannulation reaction between vinylcarbene complexes (**117**) and ethynes (Scheme 46).[171]

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CHAPTER 15

Molecular Rearrangements

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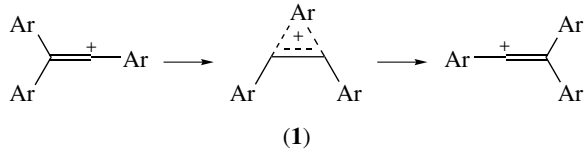
Aromatic Rearrangements

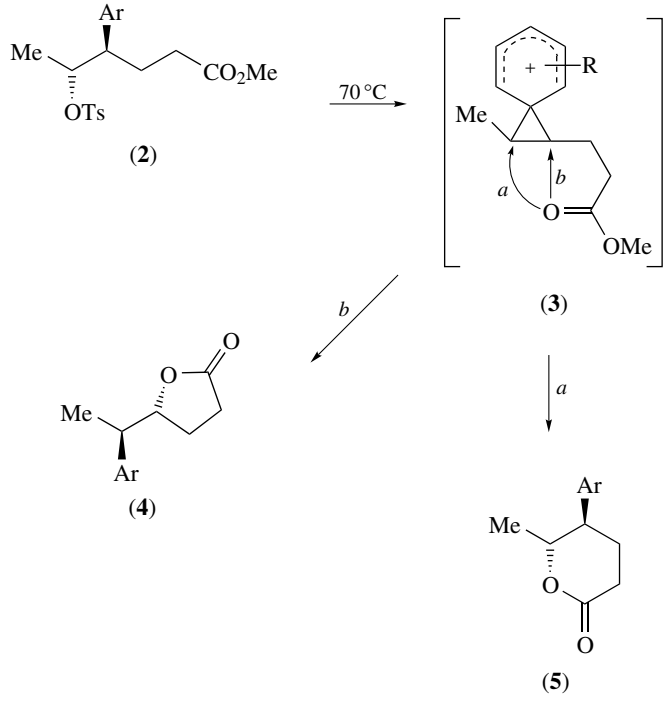
Benzene Derivatives

The thermodynamic stabilities of phenonium ions have been determined[1] based on bromide-transfer equilibria in the gas phase and, depending on the substituents, the bridged species (**1**) has been proposed[2] as an intermediate or transition state on the potential-energy surface for the 1,2-aryl rearrangement of triarylvinyl cations (see Scheme 1). Phenonium ion (**3**) has been presented[3] as an intermediate to account for the fact that lactonization of methyl 4-aryl-5-tosyloxy hexanoate (**2**) produces γ-lactone (**4**) selectively under thermodynamic conditions, but affords δ-lactone (**5**) preferentially under kinetic conditions. It has been shown that anodic oxidation of *trans*-stilbene in alcohols in the presence of KF or Bu_4NBF_4 is accompanied by its electro-oxidative rearrangement into diphenylacetaldehyde acetals. The mechanism outlined in Scheme 2 has been proposed[4] for the transformation.

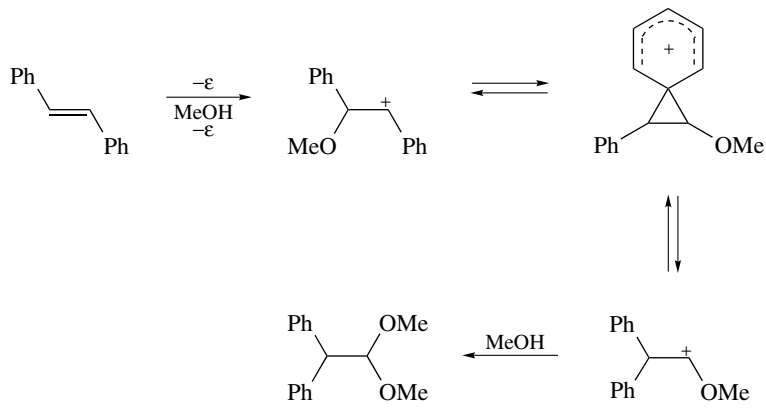


(**1**)

SCHEME 1

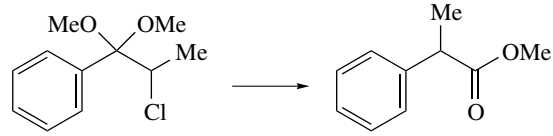


(**2**) (**3**) (**4**) (**5**)

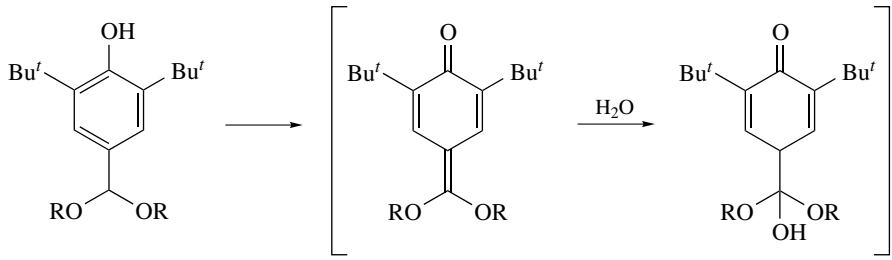


SCHEME 2

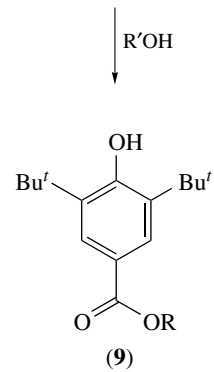
The $AgBF_4$-catalysed phenyl rearrangement of the dimethyl acetal of 2-chloropropiophenone (**6**) has been found[5] to proceed with inversion of stereochemistry at the reaction centre to give 2-phenylpropionic acid (**7**) with high stereoselectivity. This result suggests an Ag^+-aided, phenyl-assisted, intramolecular S_N2 mechanism for the rearrangement. 3,5-Di-*t*-butyl-4-hydroxybenzaldehyde acetals have been observed to rearrange to various esters when oxidized with potassium ferricyanide in alkaline medium. The authors[6] suggested that the initial step in the transformation involves formation of quinone methide (**8**). Addition of water and subsequent elimination of alcohol would lead to the formation of ester (**9**). A free-radical mechanism involving initial homolysis of different bonds in the acetal molecules has been postulated[7] to explain the plethora of products obtained on the thermal rearrangement of aromatic acetal and thioacetal derivatives. On the other hand, a carbocation mechanism (see Scheme 3) has been proposed[8] to account for the fact that aromatic acetals react with iodobenzene dichloride to give esters and aldehydes depending on the solvent.



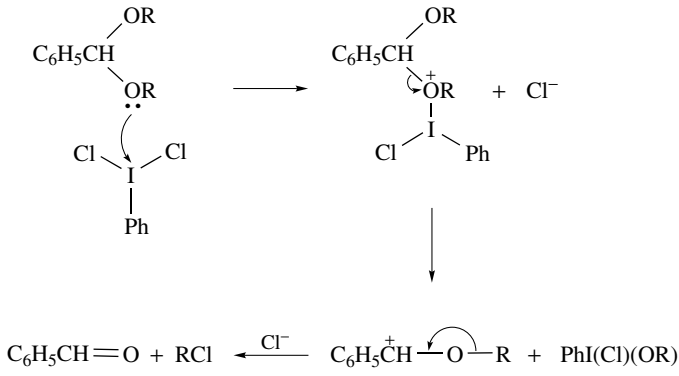
(**6**) (**7**)



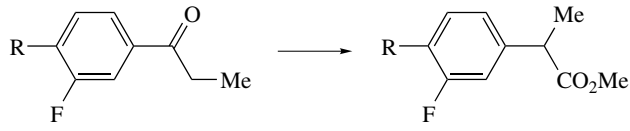
(**8**)



(**9**)



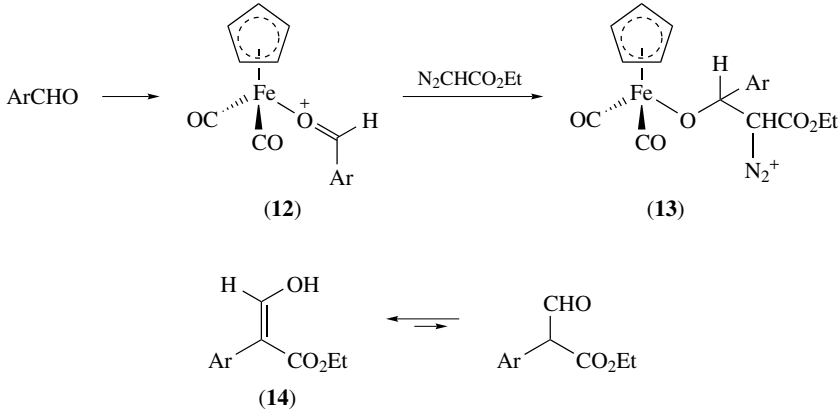
SCHEME 3



(**10**) (**11**)

R = cyclohexyl

It has been shown[9] that the lead tetraacetate-mediated 1,2-aryl shift of various *meta*-substituted *p*-cyclohexyl aryl ketones, e.g. (**10**), results in excellent yields of the corresponding rearranged esters (**11**). A unique reaction, providing 3-hydroxy-2-arylacrylic acid ethyl esters (**14**), has been observed[10] between aryl aldehydes and ethyl diazoacetate in the presence of the iron Lewis acid [$\eta^5 - (C_5H_5)Fe(CO)_2(THF)BF_4$]. It appears that the enol esters are formed by an unusual 1,2-aryl shift from a possible intermediate (**13**), which in turn is formed from the reaction of the iron aldehyde complex (**12**) with ethyl diazoacetate (see Scheme 4).



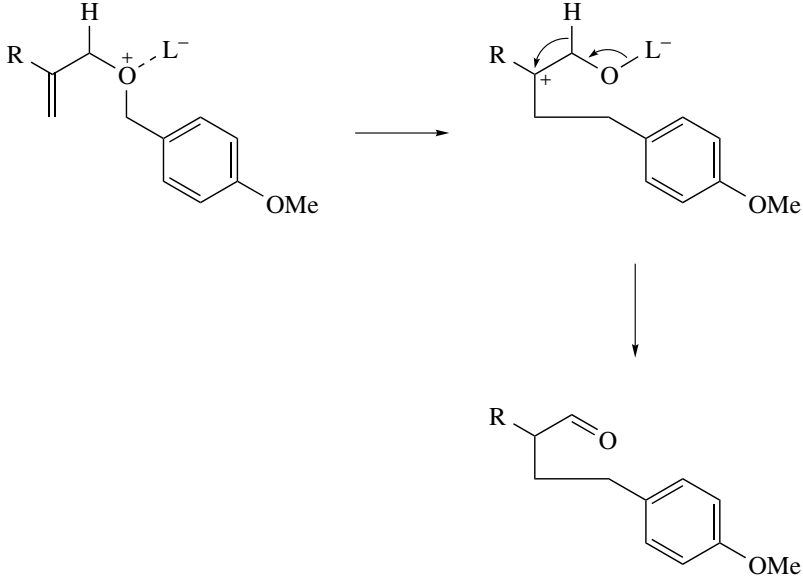
(**12**) (**13**)

(**14**)

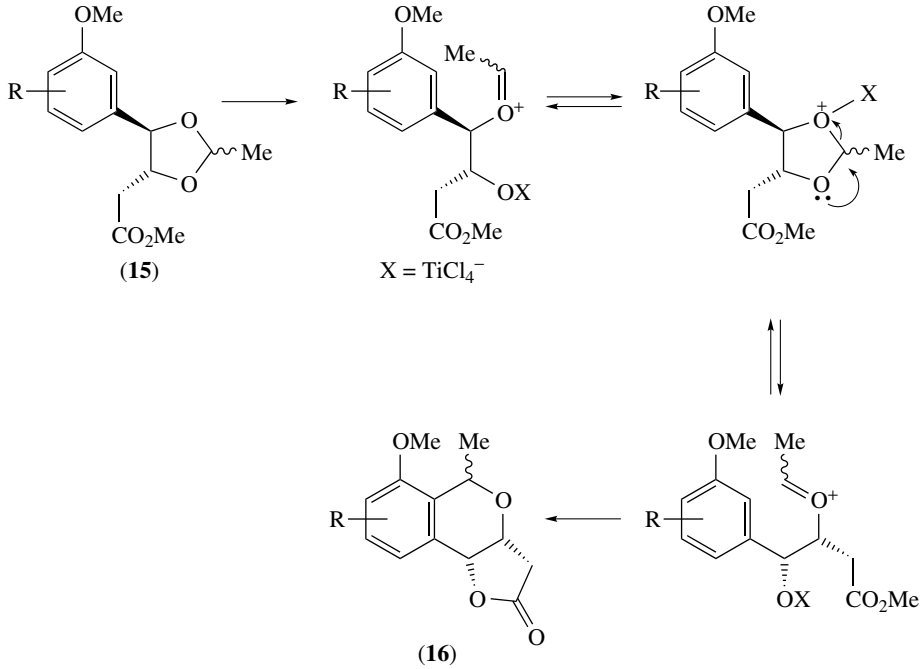
SCHEME 4

The rearrangement reaction of a variety of alkyl phenyl ethers over a dealuminated HY zeolite has been shown to involve both intramolecular and intermolecular processes to afford phenol, (alkoxyalkyl)benzenes and alkylphenols as the main products.[11] *o*-Benzylphenol has been obtained[12] as the exclusive product in the rearrangement of benzyl phenyl ether in the presence of montmorillonite. The mechanism for a novel zeolite β-catalysed rearrangement of alkoxybenzyl allyl ethers to aldehydes and ketones has been investigated by the use of cross-over reactions and deuterium labelling. The reaction was found to be mainly intramolecular and has been described[13] as a nucleophilic attack of the double bond on the electrophilic benzylic carbon of the ether–Lewis acid complex, followed by a 1,2-hydride (or alkyl) migration (see Scheme 5). The best conditions for this rearrangement have been examined,[14] and preliminary results have indicated that there is a dependence between the size of the substrate and the pore size of the zeolite. Several allylic *p*-methoxybenzyl ethers have been rearranged under these conditions to afford a variety of 4-arylbutanals or 5-arylpentan-2-ones, depending on the substituent pattern of the allylic moiety.[15] The Lewis acid-catalysed diastereoselective rearrangement of methyl 4,5-*trans*-4-aryldioxolan-5-yl acetates (**15**) has been used[16] to provide a convenient route to substituted isochromane-γ-lactones (**16**) (see Scheme 6).

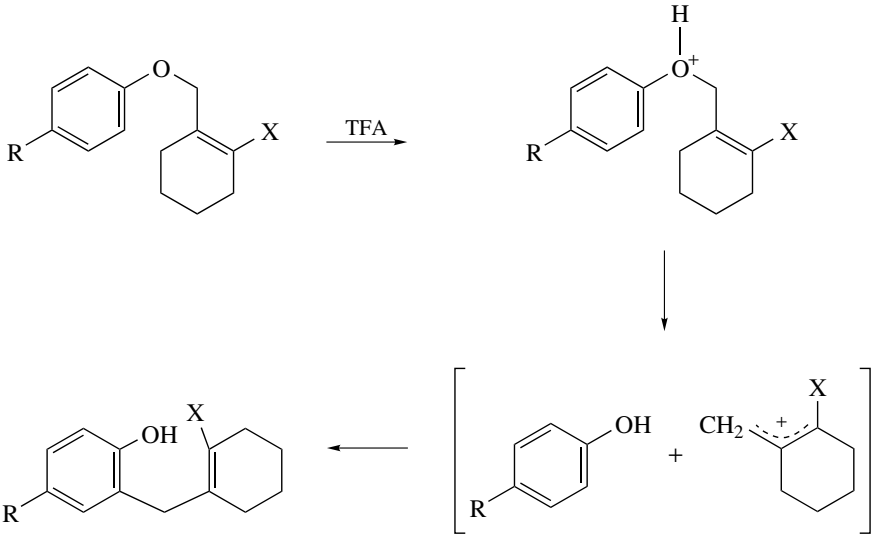
An unusual [1,3]-rearrangement of aryl 2-halocyclohexenylmethyl ethers promoted by trifluoroacetic acid has been observed.[17] Products due to a Claisen rearrangement were not formed and the proposed pathway for the process is outlined in Scheme 7. It has been shown[18] that $AlCl_3$-mediated decomposition of *N*-phenoxybenzamide



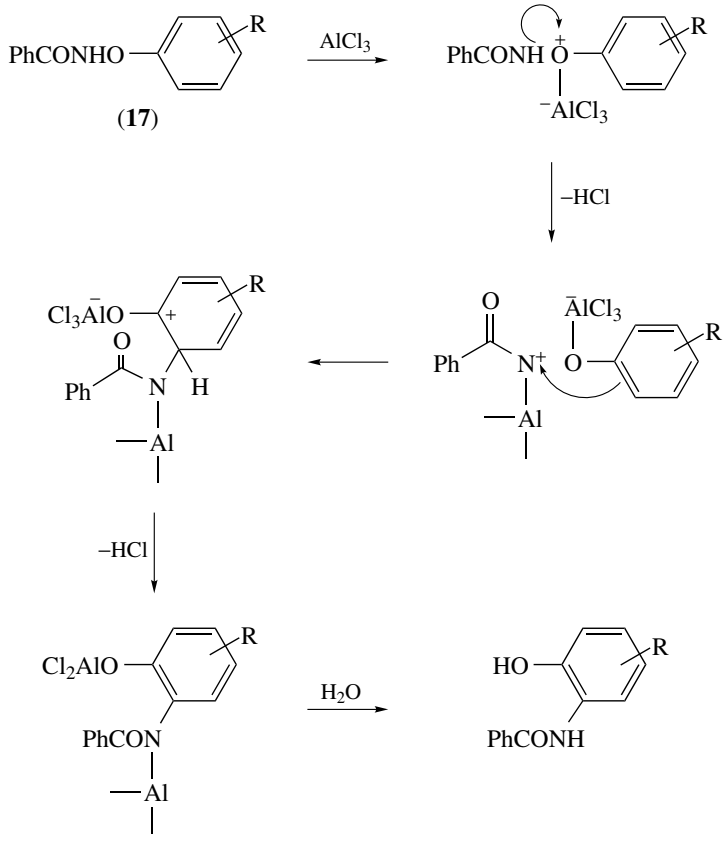
SCHEME 5



SCHEME 6

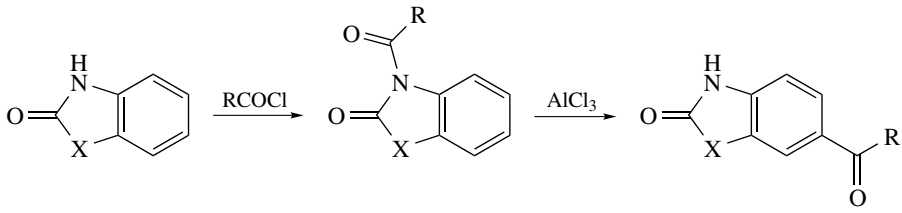


SCHEME 7



SCHEME 8

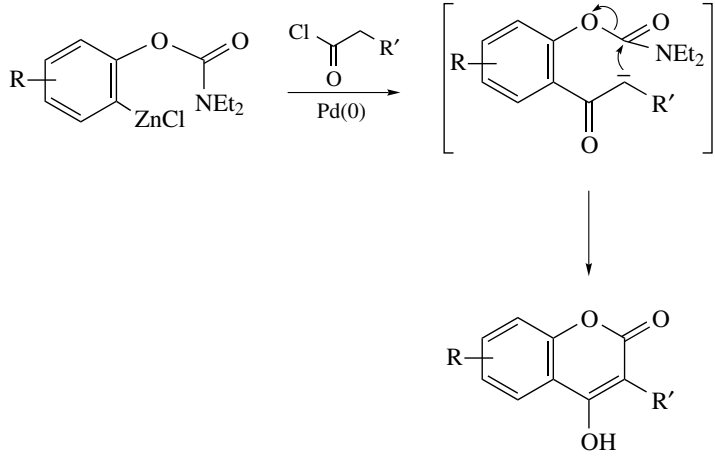
derivatives (**17**) leads mainly to regioselective intramolecular migration of the benzamido group from oxygen to the *ortho* position of the phenyl group as shown in Scheme 8. Zeolite catalysts have been evaluated[19] for the Fries rearrangement of acetanilide to the corresponding aminoacetophenones, and the selectivity of the Fries rearrangement over various silica composite catalysts has been compared.[20] Alumina in methanesulfonic acid has been used as an efficient reagent for the Fries rearrangement of phenolic esters.[21] A novel method of acylating 2(3*H*)-benzoxazolone and 2(3*H*)-benzothiazolone at the 6-position has been described.[22] It consists of a Fries-like transposition of the acyl group from the nitrogen atom to the 6-position (see Scheme 9). The photo-Fries rearrangement of *N*-acetyl- and *N*-benzoyl-carbazoles has been studied.[23] The anions resulting from the treatment of mono- or dicarbamates of 1,1′-bi-2-naphthols with Bu^{t}Li/TMEDA have been found[24] to undergo anionic Fries rearrangements to yield mono- and di-(3-alkyl)- or -(3-amido)-substituted 2, 2′-binaphthols. The Fries migration of various calix(*n*)arene esters ($n = 4, 6, 8$) under the influence of different solvents and Lewis acid catalysts has been examined,[25]



SCHEME 9

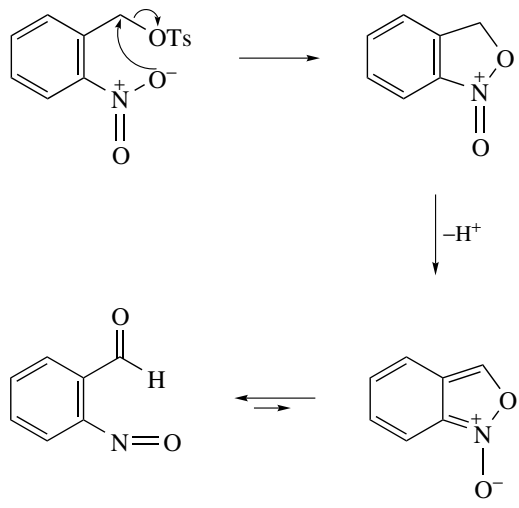
and an unusual benzoyl rearrangement has been observed[26] during the synthesis of asymmetrically substituted calix(4)arenes.

A new synthetic protocol consisting of sequential directed *ortho* metallation, cross-coupling and a carbamoyl Baker–Venkataraman rearrangement has been applied[27,28] to an efficient construction of coumarins (see Scheme 10). The formation of *o*-nitrosobenzaldehyde during the hydrolysis of *o*-nitrobenzyl tosylate in aqueous acetonitrile has been presented[29] as a strong indication that the nitro group participates in the departure of the tosylate group as shown in Scheme 11.

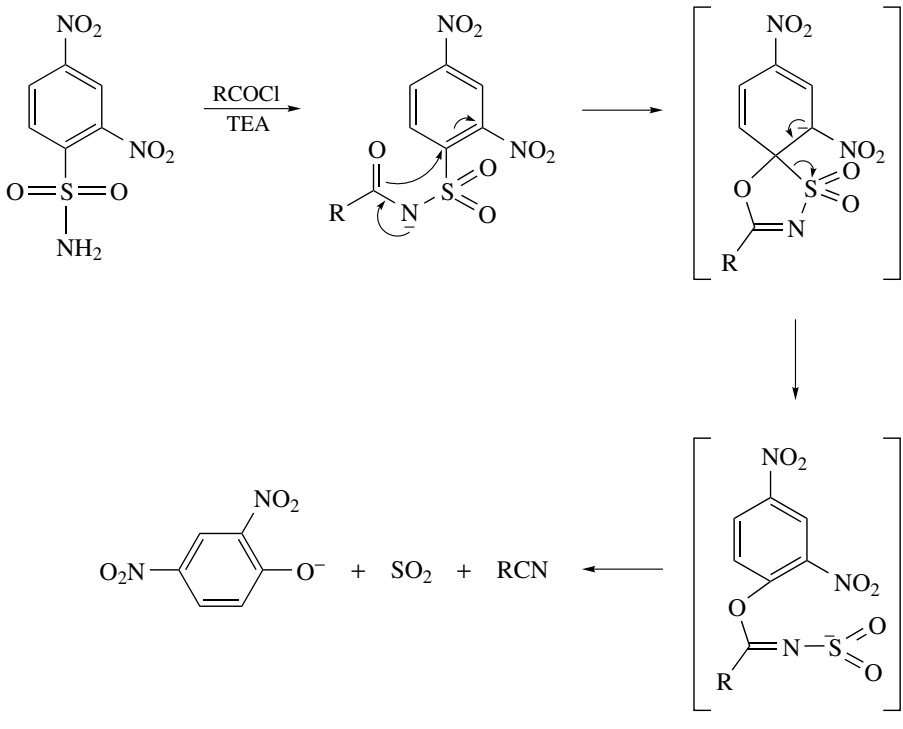


SCHEME 10

The α- and β-cyclodextrins have been found to accelerate the Smiles rearrangement of 4-nitrophenyl salicylate.[30] The reaction of 2,4-dinitrobenzenesulfonamide with acyl chlorides in the presence of excess triethylamine has been found to produce the corresponding nitrile in good yield. Mechanistic studies have indicated[31] that the reaction proceeds via a Smiles rearrangement of the initially formed *N*-(2,4-dinitrobenzenesulfonyl)amide to form the nitrile, 2,4-dinitrophenol, and sulfur dioxide (see Scheme 12). 1-Chloro-3-fluorophenothiazines have been prepared[32] by Smiles rearrangement of 3-chloro-5-fluoro-2-formamido-2′-nitrophenyl sulfides in alcoholic



SCHEME 11

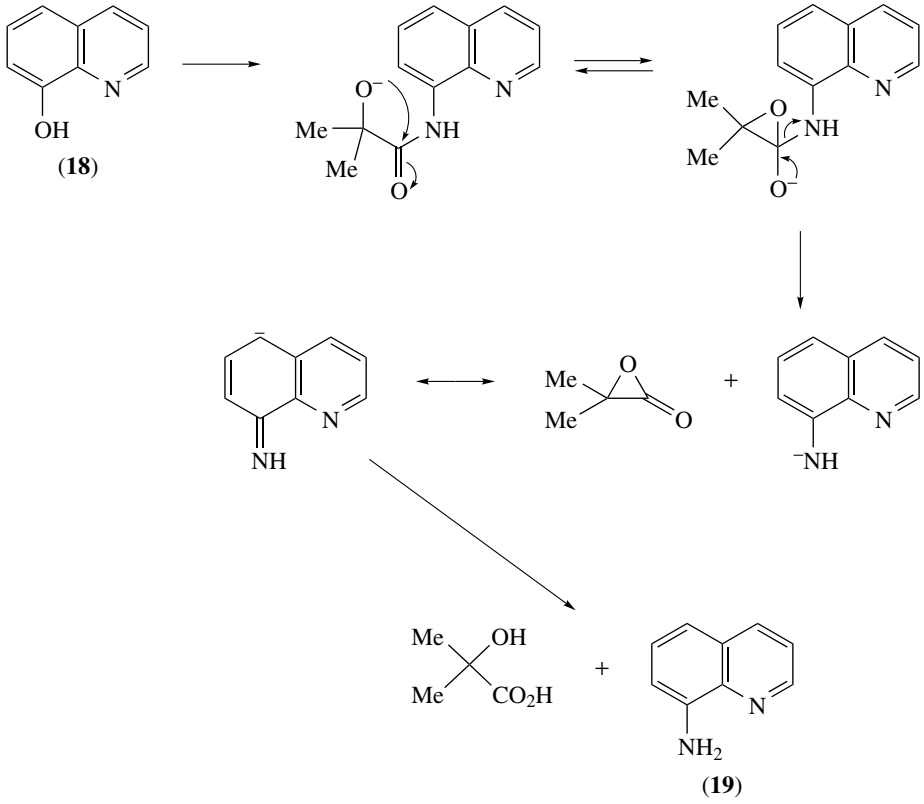


SCHEME 12

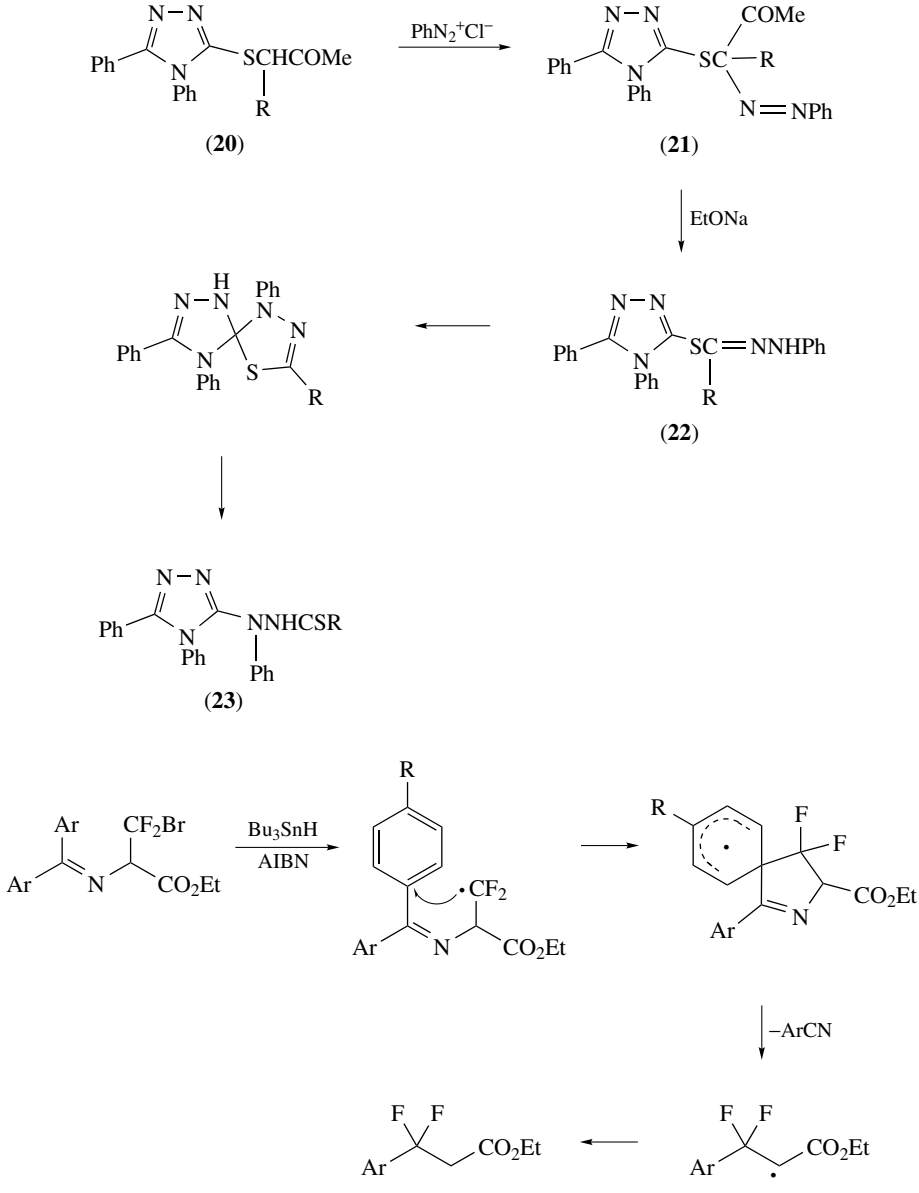
potassium hydroxide solution, and 8-hydroxyquinoline (**18**) has been converted[33] into 8-aminoquinoline (**19**) in a one-pot procedure involving alkylation with 2-bromo-2-methylpropionamide followed by Smiles rearrangement and hydrolysis (see Scheme 13). The reaction of benzenediazonium chloride with 3,4-diphenyl-1,2,4-triazol-5-yl-thiomethylene compounds (**20**) resulted in the formation of azo coupling products (**21**), which upon treatment with sodium ethoxide in ethanol have been found[34] to yield thiohydrazonate esters (**22**) that rearrange *in situ* by a Smiles-type rearrangement to afford thiohydrazides (**23**).

The formation of 3,3-difluoro-3-arylpropanoates in good yields from the radical-induced rearrangement of 3-bromo-3,3-difluoroalanine Schiff bases has been explained[35] by postulating a radical *ipso*-substitution at the aromatic ring as shown in Scheme 14.

Montmorillonite K10 clay and its various cation-exchanged forms have been found to promote the formation of an unexpected product, *p*-nitrosodiphenylamine, from *N*-phenylhydroxylamine, rather than the typical Bamberger products.[36] A Bamberger rearrangement has been shown to occur during the metabolism of 2,4,6-trinitrotoluene



SCHEME 13



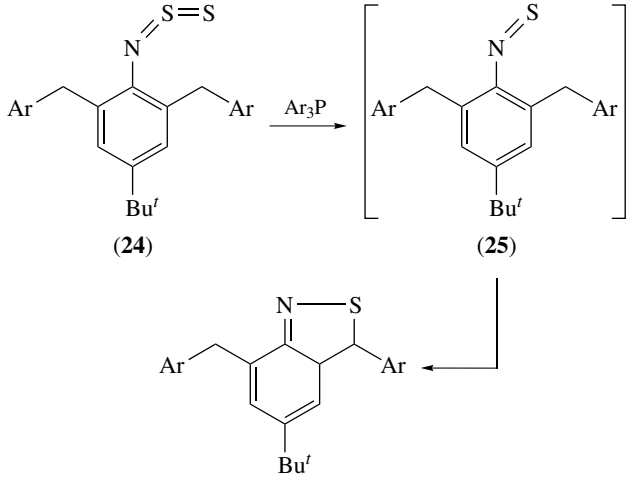
(**20**) (**21**) (**22**) (**23**)

SCHEME 14

by *Clostridium acetobutylicum*.[37] Daszkiewicz *et al*.[38] have discussed the mechanism of the nitramine rearrangement in the light of the fact that the acid-catalysed rearrangement of *N*-methyl-*N*-phenylnitramine was found to be accompanied by side-reactions involving nitrosation and methylation. MO theory employing the semiempirical AM1 method has been used to locate and discuss the energetics of the intermediates and

transition states for the Wallach rearrangement.[39] A study of the acid-catalysed benzidine rearrangement of unsymmetrical hydrazoaromatics has been undertaken, and the results have indicated[40] the importance of disproportionations to understanding benzidine rearrangements.

Products isolated from the thermal fragmentation of *N*-arylbenzamide oximes and *N*-arylbenzamide *O*-phenylsulfonyl oximes have been accounted for by invoking a free-radical mechanism which is initiated by the preferential homolysis of the N—O bond.[41] Time-resolved IR spectroscopy has revealed that photolysis of *N*, *N′*-dipheny1-1,5-dihydroxy-9,10-anthraquinone diimine affords acridine-condensed aromatic products via excited-state intramolecular proton transfer.[42] The absolute and relative rates of thermal rearrangements of substituted benzyl isocyanides have been measured,[43] and it has been found that the relative rates are independent of temperature and exhibit excellent Hammett correlations. Thionitrosoarene (**25**), thought to be generated by desulfurization of the stable *N*-thiosulfinylaniline (**24**), has been established[44] as an intermediate in the formation of 3,3a-dihydro-2,1-benzisothiazole (**26**) from *o*-alkylthionitrosoarene (**24**).



(**24**) (**25**)

(**26**)

The pyrolysates obtained from the flash vacuum pyrolysis of the allyl esters of a number of biphenyl carboxylic acids, biphenyldicarboxylic acids and biphenyldicarboxylic anhydrides have been examined by ^{1}H NMR spectroscopy. In all cases the spectra showed the presence of cyclopent[*a*]indene and acenaphthylene with other products. On the basis of the findings the authors[45] have postulated that high-temperature reactions of polycyclic aromatic hydrocarbons that result in the loss of two hydrogen atoms and formation of polycyclic hydrocarbons containing five-membered rings take place by loss of a sterically constricted hydrogen atom; this is followed by ring contraction of the resulting six-membered aryl radical, radical-induced

ring formation, loss of a second hydrogen atom and further rearrangement by interconversion of five- and six-membered rings. On the other hand, pyrolytic reactions which result in the loss of the elements of acetylene from polycyclic aromatic hydrocarbons are considered to take place by loss of a hydrogen atom followed by ring contraction and radical-induced ring formation, loss of a second hydrogen atom followed by rearrangement of the rings, loss of a C_2 fragment and hydrogen-atom shifts. Electronic structure studies have provided a wealth of information on the 1,2-didehydrogenation of polycyclic aromatic hydrocarbons and the ring contraction of the resulting arynes. The calculations have confirmed[46] the experimentally postulated existence of a cyclopentadienylidene carbene in these processes. More recently, three distinct pyrolytic pathways connecting the thermally induced cyclodehydrogenation of 1-phenylnaphthalene to fluoranthene have been identified.[47] The thermal conversion of 1-phenylbut-1-en-3-yne into its cyclo-isomerization products, viz. naphthalene, azulene, and 1-methylene-1*H*-indene, has been studied[48] at high temperatures, while an investigation of the reactions on the C_6H_6 potential-energy surface has revealed that, although several mechanisms operate simultaneously, benzvalene is one of the key intermediates in the thermal intramolecular topomerization of benzene.[49]

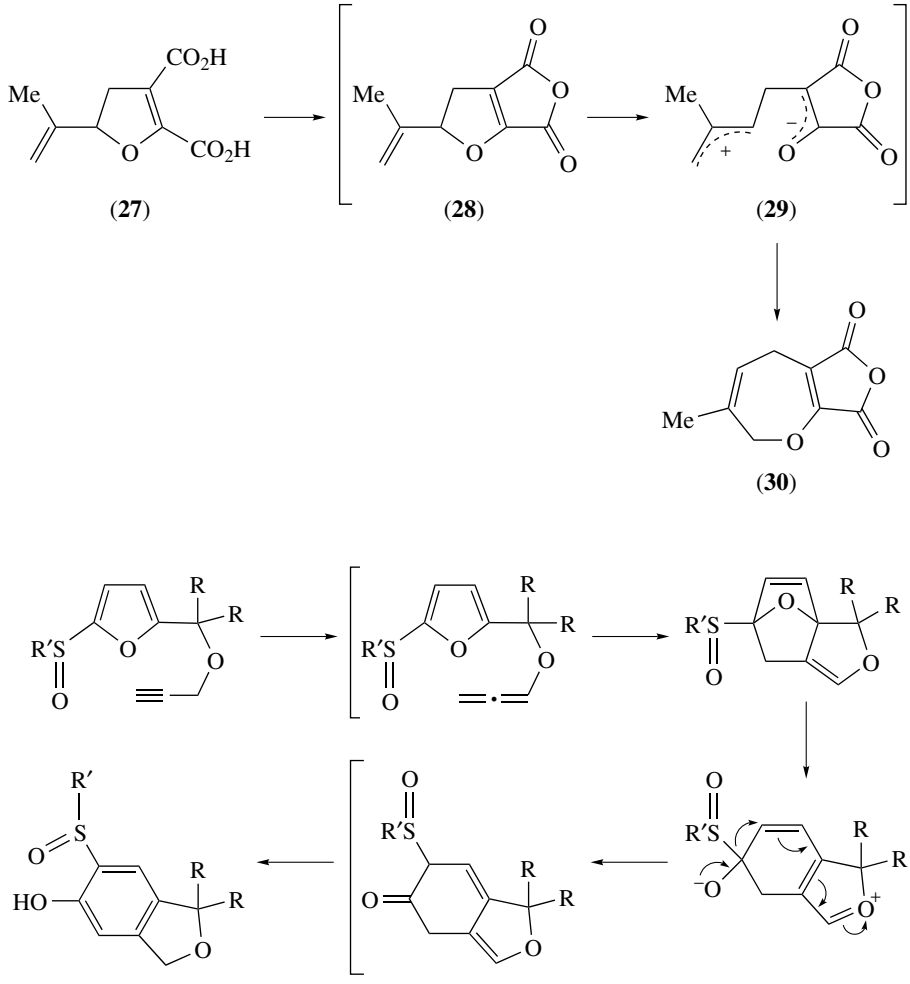
Heterocyclic Derivatives

A novel transformation of *N*-alkoxycarbonylprolines to trifluoroacetyl-2,3-dihydropyrroles has been achieved[50] by utilizing trifluoroacetic anhydride. A mesoinic 1,3-oxazolium-5-olate is thought to be the probable intermediate in this transformation.

The molecular mechanism for the pyrrole ring expansion to yield 3-chloropyridine as a model for the abnormal Reimer–Tiemann rearrangement has been characterized theoretically,[51] while extensive rearrangement reactions, in particular ring expansions, have been observed for differently *N*-substituted 2,5-dimethylpyrroles under electron ionization.[52] The rearrangements of model pyrrolenines carrying one or two pyrrolylmethyl groups at the disubstituted 2-position of the 3,4-disubstituted pyrrolenine ring have been investigated.[53] The results have shown that the rearrangement of pyrrolylmethylpyrrolenines matches exactly that proposed for the porphyrin biosynthesis and occurs readily under both acid-catalysed and thermal conditions. By far the major route for the rearrangement is by a mechanism involving fragmentation–recombination; indeed, it appears highly probable that this is the sole route; no evidence was found to implicate possible [1,5]-sigmatropic shifts in the process. A detailed investigation of the reaction path for the thermal rearrangement of 3,4-dihydro-1 αH-azirine[2,3-*c*]pyrrol-2-one to a cyanoketene–formaldimine complex has been carried out.[54]

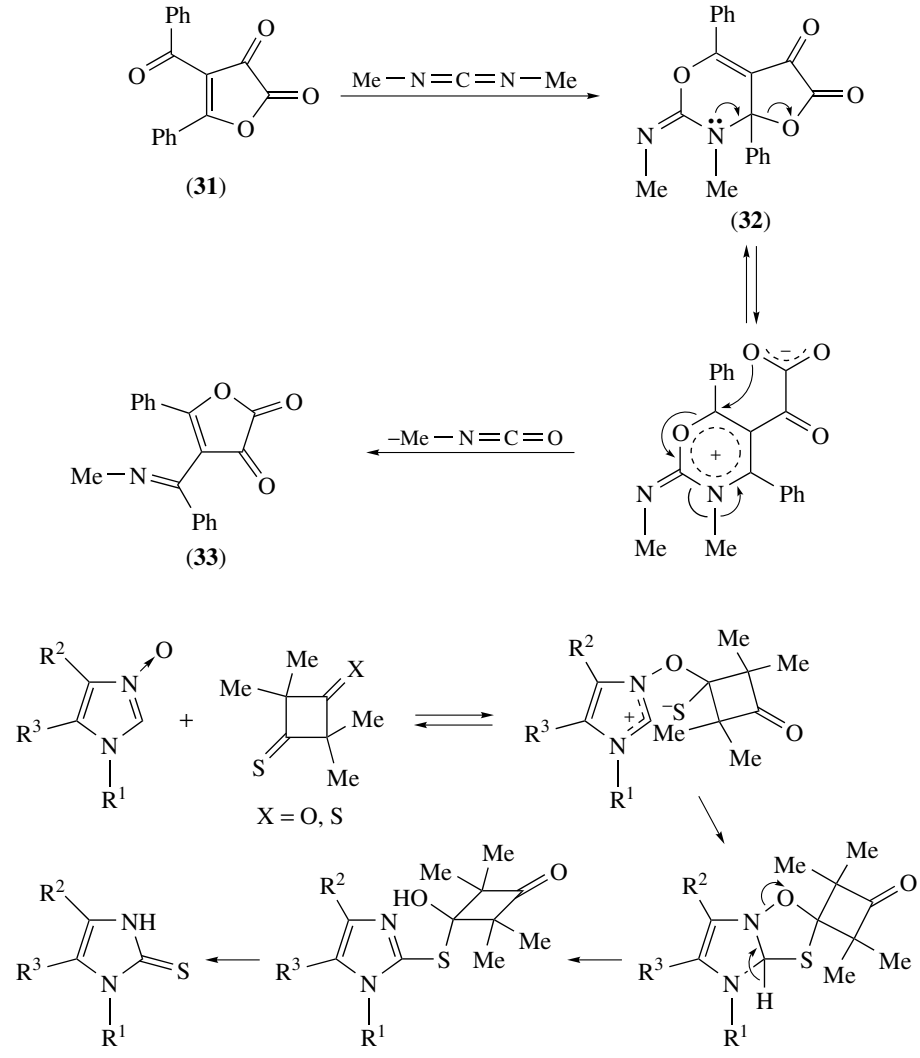
A review of the indoledione–indole rearrangement has appeared.[55] The photoirradiation of 1-ethoxy-2-phenylindole in methanol has been shown to afford 3- and 6-ethoxy-2-phenylindoles.[56]

An unexpected ring expansion of 5-isopropenyl-4,5-dihydrofuran-2,3-dicarboxylic acid (**27**) to 4,7-dihydro-6-methyloxepin-2,3-dicarboxylic anhydride (**30**) has been reported.[57] The transformation is thought to proceed via anhydride (**28**) which is converted into the seven-membered oxepindicarboxylic anhydride (**30**) via (**29**) to



SCHEME 15

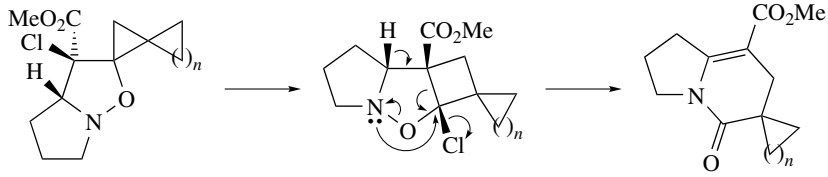
release the ring strain. A series of reactions involving the intramolecular Diels–Alder reaction of a furan diene with an allenyl ether dienophile, followed by alkylsulfinyl group, alkylsulfonyl group, and trimethylsilyl group rearrangements, has been accomplished.[58] A typical example of the methodology is outlined in Scheme 15. The reaction of 4-benzoyl-5-phenylfuran-2,3-diene (**31**) with carbodiimides has been shown to afford novel mono- and/or bi-cyclic heterocyclic systems. The reaction is considered[59] to start with a cycloaddition of the carbodiimide to the oxadiene moiety of (**31**) leading to adduct (**32**). These primary adducts undergo the furandione rearrangement, probably initiated by a 4 + 2-cycloreversion with loss of the corresponding isocyanate, leading to an iminobenzylfurandione system (**33**).



SCHEME 16

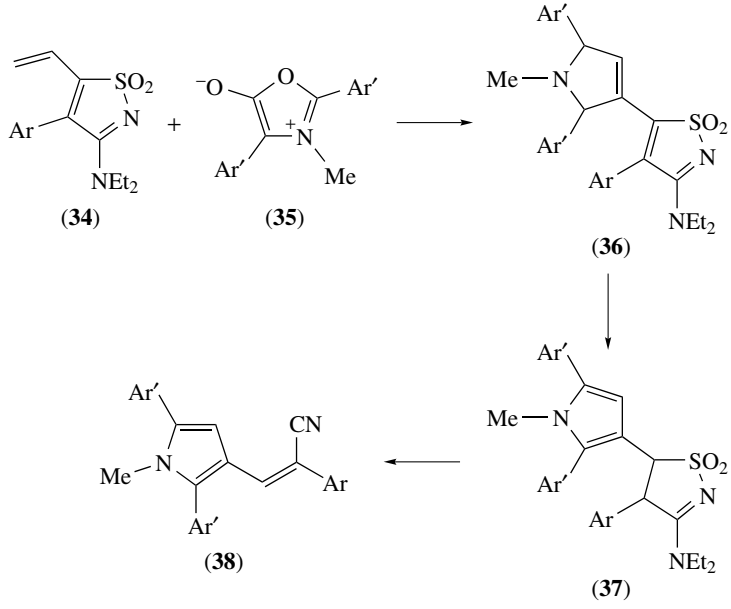
α-Carboline has been obtained[60] on pyrolysis of 1-benzylpyrazole in chloroform at 550 °C. 4-Benzoyl-5-hydroxy-3-trifluoromethylpyrazole derivatives have been synthesized by a new procedure[61] which involves the rearrangement of the benzoyl group in 5-benzoyloxy-4-bromo-3-trifluoromethylpyrazole derivatives via lithium–bromide exchange using *t*-butyllithium.

It has been demonstrated that the reaction of azole *N*-oxides with cycloalkane thiones offers a simple and efficient route to azole-thiones.[62] The described reaction sequence has subsequently been found to constitute a useful synthesis of imidazole-2(3*H*)-thiones (see Scheme 16).



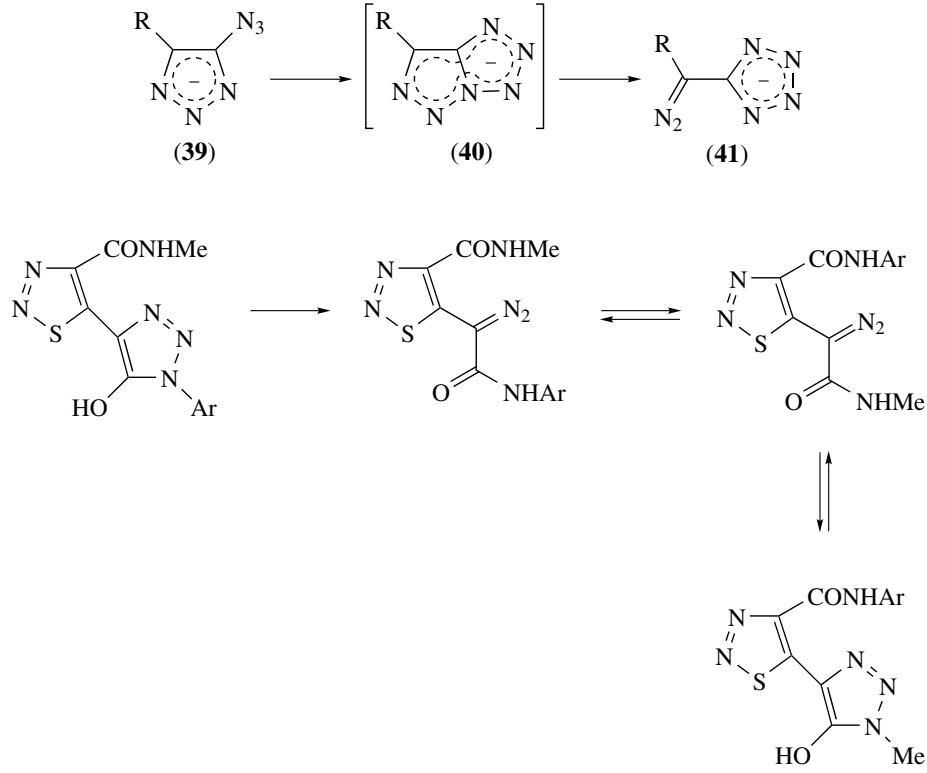
SCHEME 17

A new selective thermal cascade ring-enlargement process of 4-chloro-substituted spiro[cyclopropane-1,5′-isoxazolidines], leading to a new method for the synthesis of the indolizine skeleton, has been reported[63] (see Scheme 17). Apparently, the process is made possible by the presence of a chlorine substituent on the carbon α to the spirocyclopropane ring which facilitates a cyclopropyl-to-cyclobutyl ring enlargement mediated by a polar solvent.



In the presence of various metal ions, 2-(fluoroenone)benzothiazoline has been found to rearrange to *N*-2-mercaptophenylenimine,[64] while a free radical mechanism involving the homolysis of C−S and C−N bonds has been invoked[65] to explain the formation of 3-phenyl-1,2,4-triazole derivatives from the thermal fragmentation and rearrangement of 2-(arylidenehydrazino)-4-(5*H*)-thiazolone derivatives. The cycloadducts (**36**) formed from the reaction of 3-diethylamino-4-(4-methoxyphenyl)-5-vinyl-isothiazole 1,1-dioxide (**34**) with nitric oxides or münchnones (**35**) have been found[66] to undergo pyrolytic transformation into α, β-unsaturated nitriles (**38**) by way of pyrrole–isothiazoline 1,1-dioxide intermediates (**37**).

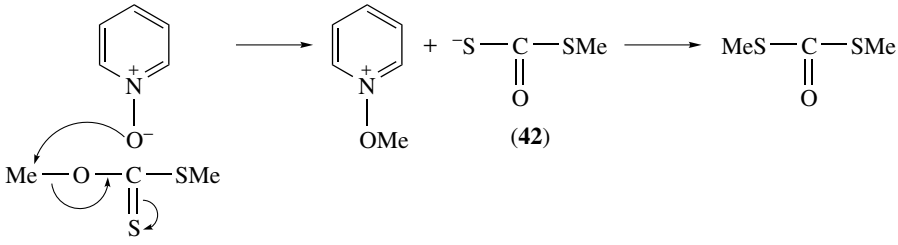
Spiro-fused tricyclic 7,8,9,10-tetrahydro-3*H*,5*H*-benzo[*d*]pyrrolo[1,2-*c*][1,2,3-triazoles] have been found to rearrange on heating to afford high yields of 1-arylamino-2-(4-cyanobutyl)-3,4-bis(alkoxycarbonyl)pyrroles.[67] An interesting base-catalysed rearrangement of α-benzotriazolyl alkoxide anions in the presence of aldehydes has been found to result in the formation of one-carbon homologated α-substituted alkyl ketones.[68] A detailed study of the rearrangement of substituted azido-1,2,3-triazolides (**39**) to (α-diazoalkyl)tetrazolides (**41**) via (**40**) has been undertaken.[69] Anions (**39**), having R = H, substituted Ph, and CO_2Me, were all found to react cleanly. A method for the synthesis of heterocyclic ring conjugates containing 1,2,3-triazole and 1,2,3-thiadiazole nuclei has been elaborated, and their rearrangements studied. A mechanism involving ring opening of the triazole ring to form the diazo compound which rearranges to the isomeric diazo compound followed by cyclization to the final product has been proposed[70] for these transformations (see Scheme 18). The isomerization of 5-(1-aryl-1,2,3-triazol-4-yl)-1,2,3-thiadiazole-4-(*N*-methyl)carboxamide to the corresponding *N*-arylcarboxamides has been studied. The isomerization is considered to proceed by a three-step process, involving ring opening, isomerization of the diazothiadiazole, and ring closure.[71]



SCHEME 18

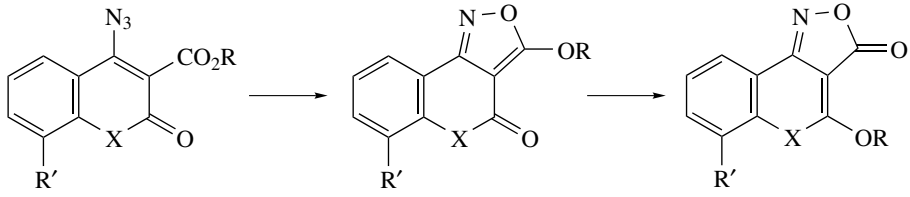
A theoretical study of degenerate Boulton–Katritzky rearrangements concerning the anions of 3-formylamino-1,2,4-oxadiazole and 3-hydroxy-iminomethyl-1,2,5-oxadiazole has been carried out.[72] The treatment has shown the participation of asymmetric transition states and non-concerted processes via symmetrical intermediates. A detailed *ab initio* and density functional study of the Boulton–Katritzky rearrangement of 4-nitrobenzofuroxan has indicated a one-step mechanism for the process.[73]

A study of the mechanism of the rearrangement of the oxide of a tertiary amine to the *O*-substituted hydroxylamine has been carried out by the semiempirical method AM1, using the *N*-oxide of *N*-(2,4-dinitrophenyl)piperidine as a model.[74] It has been proposed[75] that a benzidine rearrangement-type mechanism is the most likely mechanism for the acid-catalysed disproportionation of 4-[*N*′-(4-hydroxyphenylhydrazino)]pyridine and 4-(*N*′-phenylhydrazino)pyridine. A bimolecular mechanism involving an intermolecular transfer of the alkyl group, with inversion of configuration, to the *N*-oxide, followed by a second transfer of one of the alkyl groups of the cationic intermediate to one of the oxygens of the anionic intermediate, also with inversion of configuration, has been confirmed[76] to account for the thermal rearrangement of 2-alkoxypyridine-1-oxides to 1-alkoxy-2-pyridones. The pyridine *N*-oxide-catalysed thione-to-thiol rearrangement of *O,S*-dialkyl xanthates has been analysed[77] by semiempirical and *ab initio* molecular-orbital methods. The transition-structure analyses have indicated that the attack of pyridine *N*-oxide toward xanthates proceeds through an S_N2 mechanism to give the dithiolcarbonate anion (**42**), which acts as actual catalyst (see Scheme 19).



SCHEME 19

1-Alkyl-1,4-dihydro-4-imino-3-quinolinecarboxylates have been found to undergo basic hydrolysis to afford the corresponding 1-alkyl-4-oxo-3-quinolinecarboxylic acids together with a variety of other rearranged products.[78] Acridine has been obtained from the acid-catalysed rearrangement of *N*-aryl-2-vinyltetrahydro-4-oxoquinoline. A mechanism involving a retro-Michael process followed by the attack of the electron-rich aromatic ring on to the keto group has been proposed[79] for the transformation. Upon thermolysis, 4-azido-2-oxoquinoline 3-carboxylates (**43**; X = NH) and 4-azidocoumarin-3-carboxylates (**43**; X = O) have been found



(**43**) (**44**) (**45**)

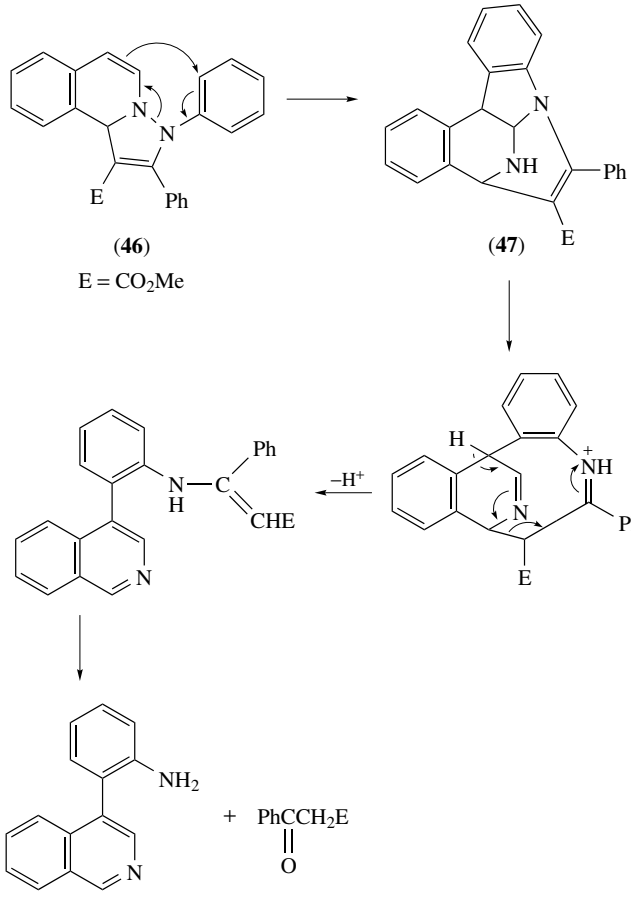
to cyclize to 3-alkoxyisoxazolo[4,3-*c*]quinolin-4(5*H*)-ones (**44**; X = NH) or the corresponding coumarins (**44**; X = O), whereas at slightly higher temperatures a 3-*O*, 4-*O* rearrangement was found to occur, yielding the 4-alkoxyisoxazolo[4,3-*c*]quinolin-3-ones (**45**; X = NH) and the corresponding coumarins (**45**; X = O). The mechanism for the formation of (**45**) from (**44**) is assumed to involve a thermally allowed suprafacial [1,5]-sigmatropic rearrangement.[80] 1,2,3,5,6,10b-Hexahydro-8,9-dimethoxypyrrolo[2,1-*a*]isoquinolin-2-ones have been obtained from the reaction of 5,6-dimethoxy-3,4-dihydroisoquinoline *N*-oxide with diketene. The formation of these novel hexahydropyrrolo[2,1-*a*]isoquinolines has been proposed[81] to arise via an initial cycloaddition reaction of the nitrone to the exocyclic double bond of diketene followed by a novel consecutive rearrangement involving NO bond cleavage rather than elimination of carbon dioxide. The cycloadducts (**46**) formed from isoquinolinium *N*-arylamides and acetylenic dipolarophiles have been found[82] to undergo a [3,3]-sigmatropic rearrangement to yield a pentacyclic product (**47**), which on treatment with strong base furnishes 4-(*o*-aminophenyl)isoquinoline and methyl benzoylacetate (see Scheme 20).

1,7b-Disubstituted cyclopropa[*c*]isoquinolines (**48**) have been found to undergo the usual thermal rearrangement to yield 5-substituted 2-benzazepines (**49**). However, when R^2 and $R^3 \neq H$ and either was an alkyl group, the reaction was found to divert into a new reaction pathway leading to the formation of 1,4-dihydro-4-alkenylisoquinolines (**50**) in high yield. It seems likely that these latter products are formed via a homo-[1,5]-sigmatropic hydrogen shift, a new mode of rearrangement for this system.[83]

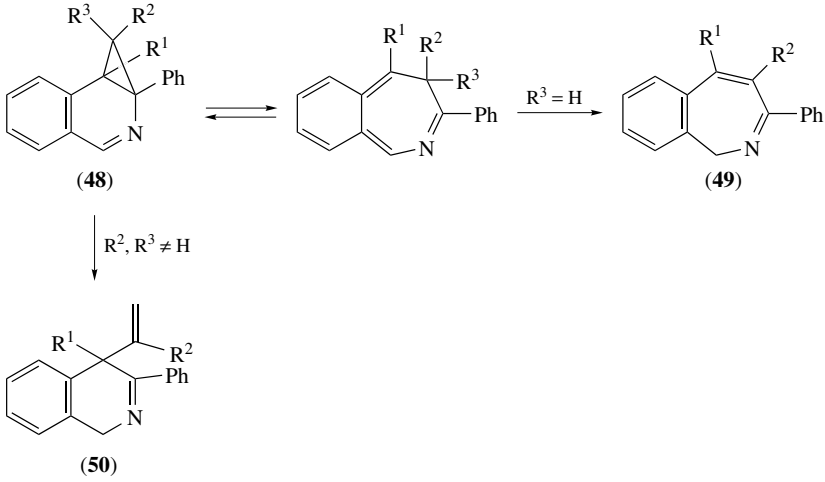
New rearrangements of 2-imino-2*H*-1-benzopyran-3-carboxamides under the action of anthranilic acid as an *N*-nucleophile have been revealed.[84] Depending on the conditions 2-(2-oxo-2*H*-1-benzopyran-2-yl)-3*H*-quinazolin-4-ones or 2-oxo-2*H*-1-benzopyran-3-(*N*-2-carboxyphenyl)carboxamides were found to be the products.

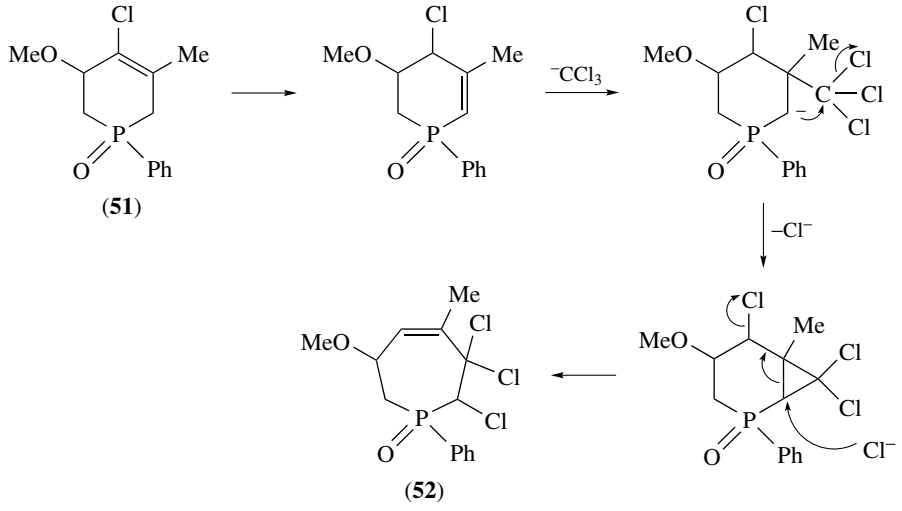
Reaction of the regioisomers of tetrahydrophosphinine oxide (**51**) with $NaOH–H_2O–CHCl_3$ under phase-transfer conditions was found to afford tetrahydrophosphepine oxides (**52**) through an unexpected path[85] involving isomerization of (**51**) and cyclopropanation via Michael addition of $^{-}CCl_3$. (Scheme 21).

Advances in the Dimroth rearrangement in the adenine series have been reviewed.[86] *N*-1-Methoxy derivatives of adenosine and 2′-deoxyadenosine have been found to

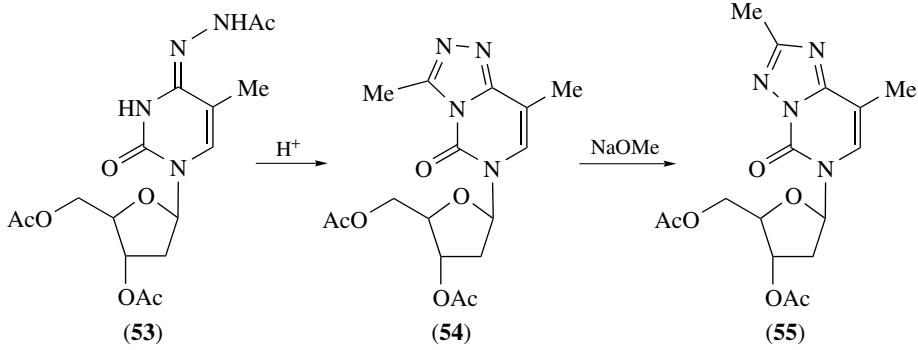

N
N
E
Ph
(46)
E = CO2Me
N
NH
Ph
E
(47)
H
+
NH
N
Ph
E
–H+
Ph
N
H
C
CHE
N
NH2
N
+ PhCCH2E
O

SCHEME 20


R3
R2
R1
Ph
N
(48)
R1
R2
R3
Ph
N
R3 = H
R1
R2
Ph
N
(49)
R2, R3 ≠ H
R1
R2
Ph
N
(50)

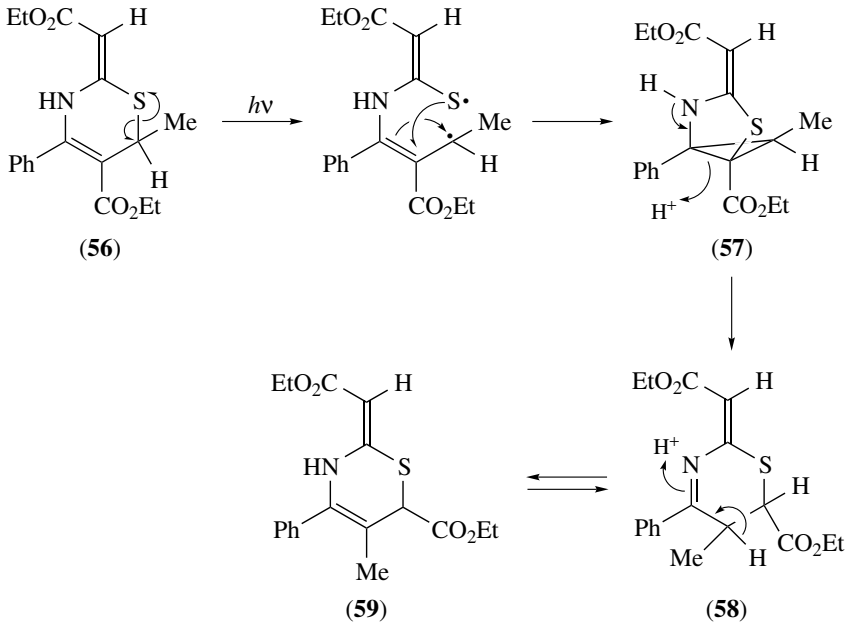


SCHEME 21



undergo a Dimroth rearrangement in which the intermediate *N,N*-dimethylamino adducts turn out to be stable compounds.[87] It has been shown[88] that, in reactions between styrene oxide and the ring nitrogen at the 1-position of deoxyadenosine, the epoxide is opened at both the α-(benzylic) and β-carbons. The 1-substituted nucleosides formed in the reaction are unstable and have been found to undergo either Dimroth rearrangement to give *N*-6-substituted deoxyadenosines or deamination to give 1-substituted deoxyinosines. The 1,2,4-triazolo[4,3-*c*]pyrimidinone (**54**) formed by acid-promoted cyclization of *N*-4-acetylamino-2′-deoxycytidine (**53**) has been observed[89] to isomerize under basic conditions via a Dimroth-type rearrangement to yield the 1,2,4-triazolo[1,5-*c*]pyrimidinone (**55**). The Dimroth rearrangement of a new class of tetracyclic condensed quinolines, viz. pyrimido[4′, 5′:4,5]selenolo[2,3-*b*]quinolines, has been studied.[90]

A possible mechanism for the observed[91] photochemical rearrangement of dihydrothiazine (**56**) to dihydrothiazine (**59**) is shown in Scheme 22. It involves a

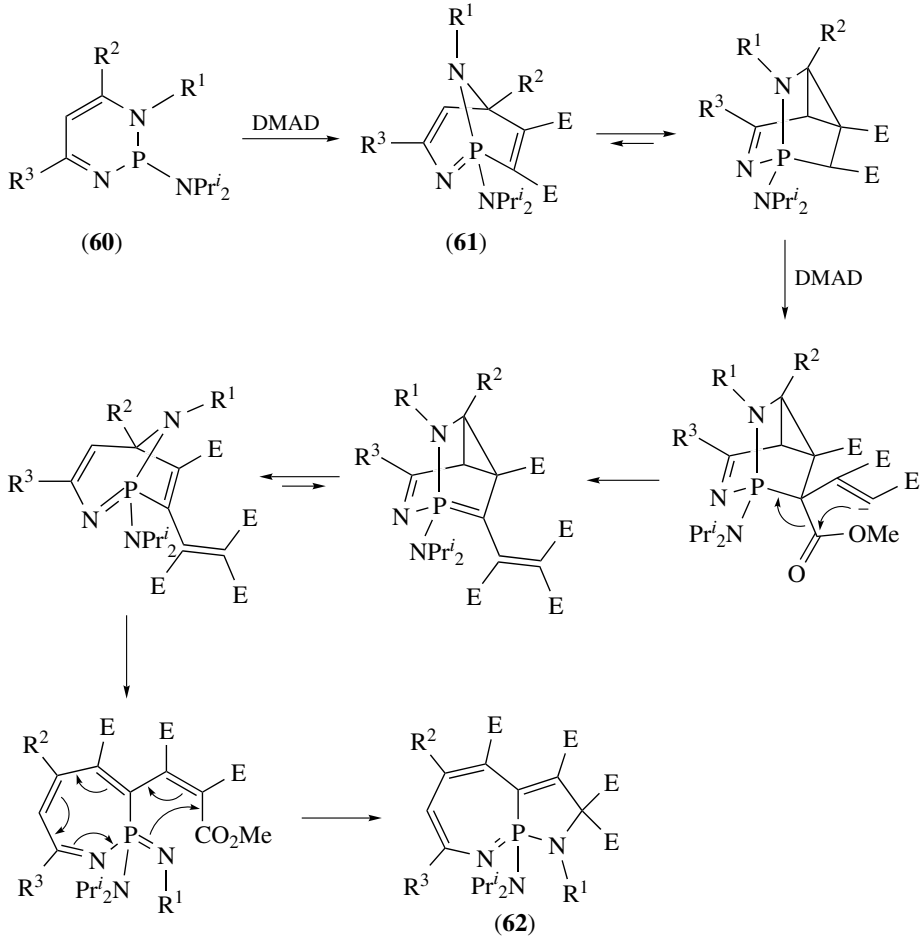


SCHEME 22

sulfur–carbon homolysis followed by ring closure to the cyclopropathiazolidine (**57**) which could ring open to the photo-product (**58**). A subsequent hydrogen shift would give the dihydrothiazine (**59**).

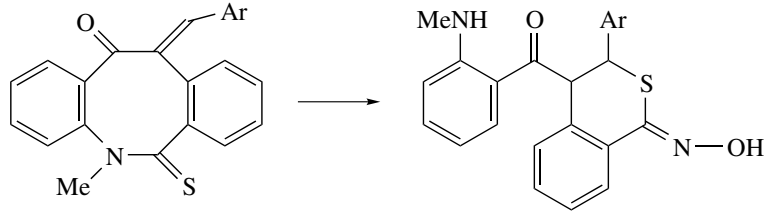
It has been shown[92] that readily available 1,2-dihydro-1,3,2-diazaphosphinines (**60**) are excellent precursors for the efficient synthesis of novel phosphorus heterocycles. Thus reaction with acetylenic diesters yields the monoadduct (**61**) which is readily converted into the λ^5-diazaphosphaazulene skeleton (**62**), probably by the pathway outlined in Scheme 23.

The reaction of the benzylidene derivative of 5-methyl-6-thioxo-5,6,11,12-tetrahydrodibenzo[*b*,*f*]azocin-12-one (**63**) with hydroxylamine has been found[93] to initiate a novel rearrangement to yield the hydroximinoisothiochromene (**64**), while the mechanism shown in Scheme 24 has been invoked[94] to explain the formation of 2,3,4,4a-tetrahydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one-1-carboxylic acids from the treatment of 1,10,11,11a-tetrahydropyrrolo[2,1-*c*][1,4]benzodiazepin-5,11-diones (**65**) with concentrated hydrochloric acid. De Lucca[95] has discovered that hexahydro-5,6-dihydroxy-1,3-diazepin-2-ones can undergo a stereospecific, stereoselective rearrangement, ring contraction reaction to give the corresponding tetrahydro-5-hydroxypyrimidin-2-ones. He proposed that the rearrangement proceeds through the formation of the aziridinium cationic intermediate (**66**) which is subsequently opened by nucleophilic attack at the less hindered carbon to give the rearranged product (see

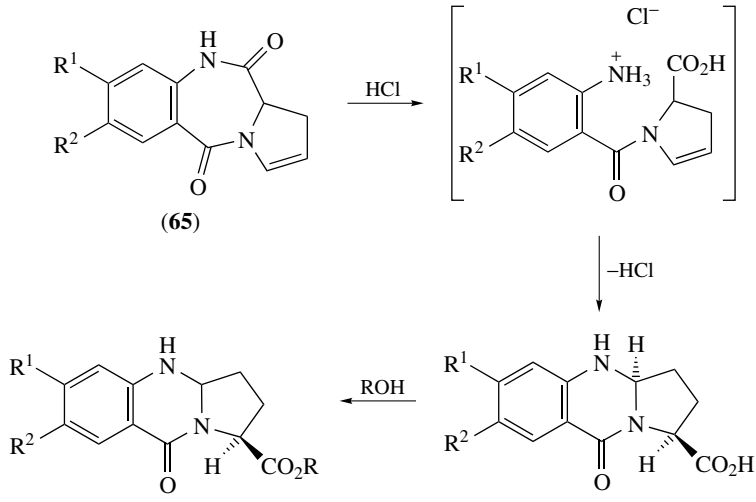


(**60**) (**61**) (**62**)

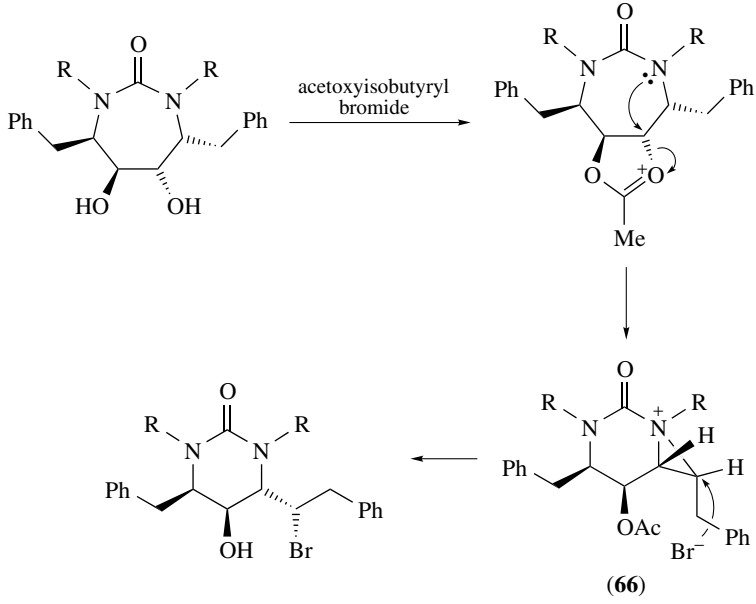
SCHEME 23



(**63**) (**64**)



SCHEME 24

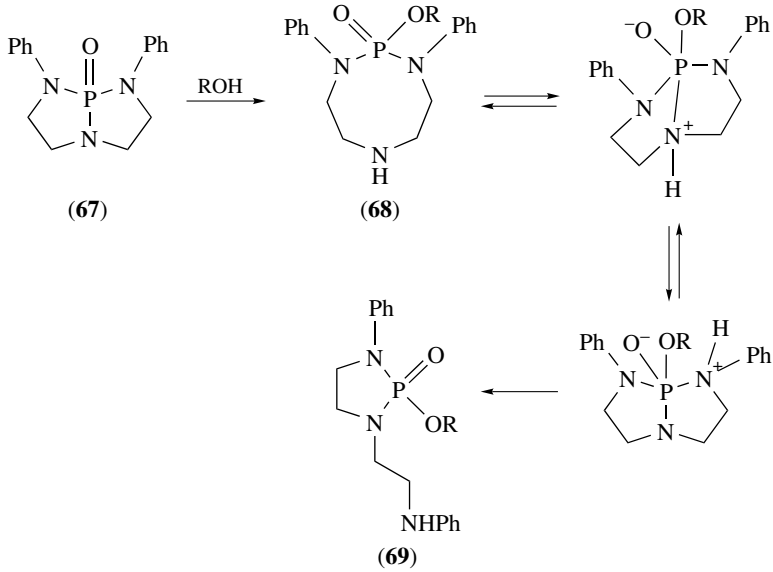


SCHEME 25

Scheme 25). 1-Oxo-2,8-diphenyl-2,5,8 triaza-1 λ^5-phosphabicyclo[3.3.0]octane (**68**) formed by acid catalysis of the bicyclic phosphoric triamide (**67**) has been found to isomerize via a new type of rearrangement to yield the ring contracted 3-[2-(phenylamino)ethyl]-2-oxo-2-ethoxy-1-pheny1-1,3,2 λ^5-diazaphospholidine (**69**). The rearrangement has been explained[96] in terms of intramolecular 1,5-nucleophilic attack

of the amine nitrogen at the phosphoryl centre, followed by proton transfer and P−N bond cleavage (see Scheme 26).

The origin of equilibria (see Scheme 27) involving 16-membered diimine, 24-membered triimine, and 32-membered tetraimine oligomers of 3,4-dihydro-2*H*-1,5-benzooxazocines and -benzothiazocines and 1,2,3,4-tetrahydro-1,5-benzodiazocines has been ascribed to facile acid-catalysed rearrangements between the macrocyclic imines. A stepwise mechanism involving 1,3-diazetidine intermediates has been suggested.[97]



SCHEME 26

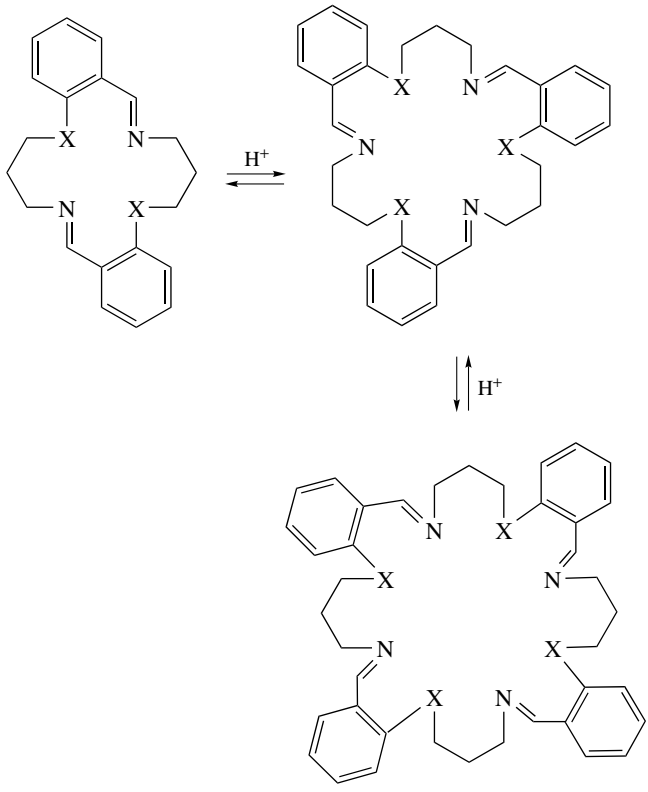
Sigmatropic Rearrangements

[3,3]-Migrations

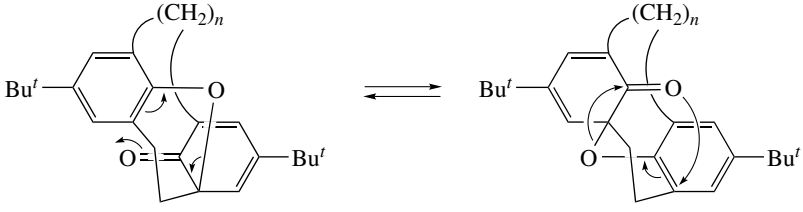
Claisen and related rearrangements

A review of Claisen rearrangements in aqueous solution has appeared.[98] The synthesis of natural products utilizing tandem Diels–Alder additions with sigmatropic rearrangement processes has been reviewed,[99] and a brief review of the regioselective synthesis of coumarins, quinolones and thiocoumarins with 3,4-fused pyran or furan ring systems by the Claisen rearrangement has been presented.[100]

A quantum-chemical study has been undertaken[101] on the isomerization of *cis*-1-vinyl-, -1-formyl-, -1-thioformyl-, and -1-iminomethyl-2-vinylcyclopropane to cyclohepta-1,4-diene, 2,5-dihydrooxepine, 2,5-dihydrothiepine, and 2,5-dihydroazepine, respectively. Reaction pathways for circumambulatory rearrangements of main group migrants (NO, PO, NCS, SCN, NCO, OCN, SR, Cl, Br, and XX where X



SCHEME 27

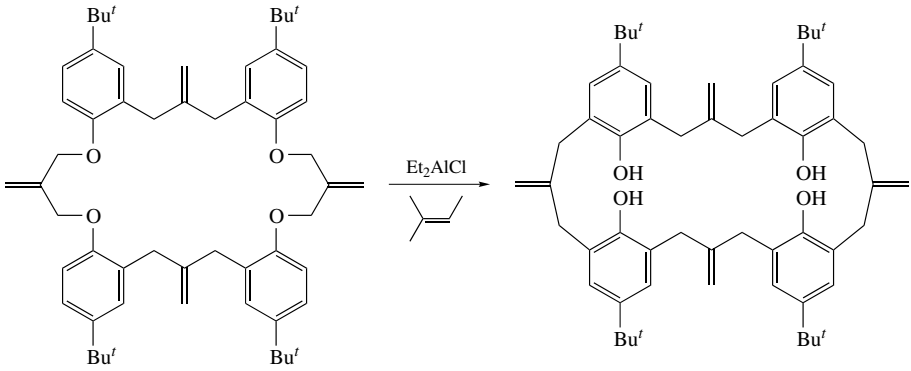


(**70**) (**71**)

is CH_2, NH, O, S) around the periphery of a cyclopropene ring have been studied computationally by the use of semiempirical methods.[102]

Zeolites[103] and silica gels and mesoporous molecular sieves[104] have been used to initiate Claisen rearrangements. A synthetic route has been devised[105] to the neurotrophic illicinones using sequential aromatic Claisen rearrangements, and it has been systematically demonstrated[106] for the first time that the strain of a medium ring lowers not only the rearrangement barriers but also the conformational fixation of a [3,3]-sigmatropic rearrangement by means of the bridge; see (**70**) ⇄ (**71**).

A new method has been developed for the preparation of calixarene analogues[107] from macrocyclic polyethers via intramolecular successive carbon–carbon bond formation in a tandem Claisen rearrangement, and a similar tandem Claisen rearrangement promoted by Et_2AlCl and 2-methylbut-2-ene, has been used[108] to synthesize macrocycles containing phenolic moieties from the corresponding macrocyclic polyether compounds (see Scheme 28). A number of furo[3,2-*c*:5,4-*f*]bis[1]benzopyran-3-ones have been synthesized regioselectively by the sequential [3,3]-sigmatropic rearrangements of 6-(4-aryloxybut-2-yn-1-yloxy) [1]benzopyran-2-ones.[109]

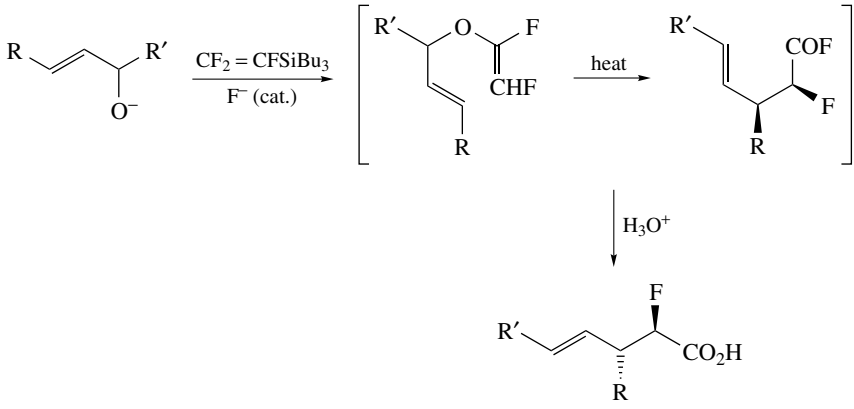


SCHEME 28

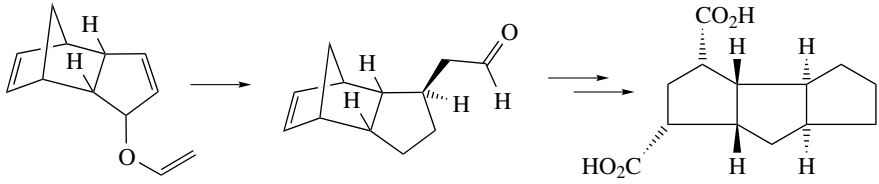
The ratios of nucleophilic substitution versus [3,3]-sigmatropic rearrangement for the collapse of allenyl(aryl)iodine(III), generated from the reaction of aryliodanes with propargylsilanes in the presence of $BF_3.OEt_2$ in alcohols, have been determined. The mechanism proposed by the authors[110] involves the generation of propargyl cations from the allenyliodine (III) via a unimolecular pathway.

The $SnCl_4$-catalysed Claisen and Cope rearrangements of *N*-allylanilines and *N*-allylenamines,[111] and the effect of *meta*-substituents in the aromatic ring on the Claisen aromatic amino rearrangement of a series of fluorinated anilines,[112] have been investigated.

A short and novel synthesis of hitherto unknown 3-allylbenzofurans using a Wittig olefination of protected 2-hydroxybenzaldehydes followed by a Claisen rearrangement, has been described.[113] The enantioselective Claisen rearrangement of difluorovinyl allyl ethers has been achieved[114] for the first time in moderate-to-good enantioselectivity using a chiral boron reagent as the Lewis acid, and a one-pot synthesis of α-fluoro-β-substituted-γ-unsaturated acids via a diastereoselective Claisen rearrangement of allylfluorovinyl ethers has been described[115] (see Scheme 29). The one-pot combination of a Claisen rearrangement of allyl vinyl ethers followed by a rhodium-catalysed intramolecular hydroacylation has been used as a key step in the synthesis of spiro[4.5]decan-2-ones,[116] and in the synthesis of erythrodiene and spirojatamol,[117] and a short, versatile synthesis of pseudo-sugars from sugars utilizing



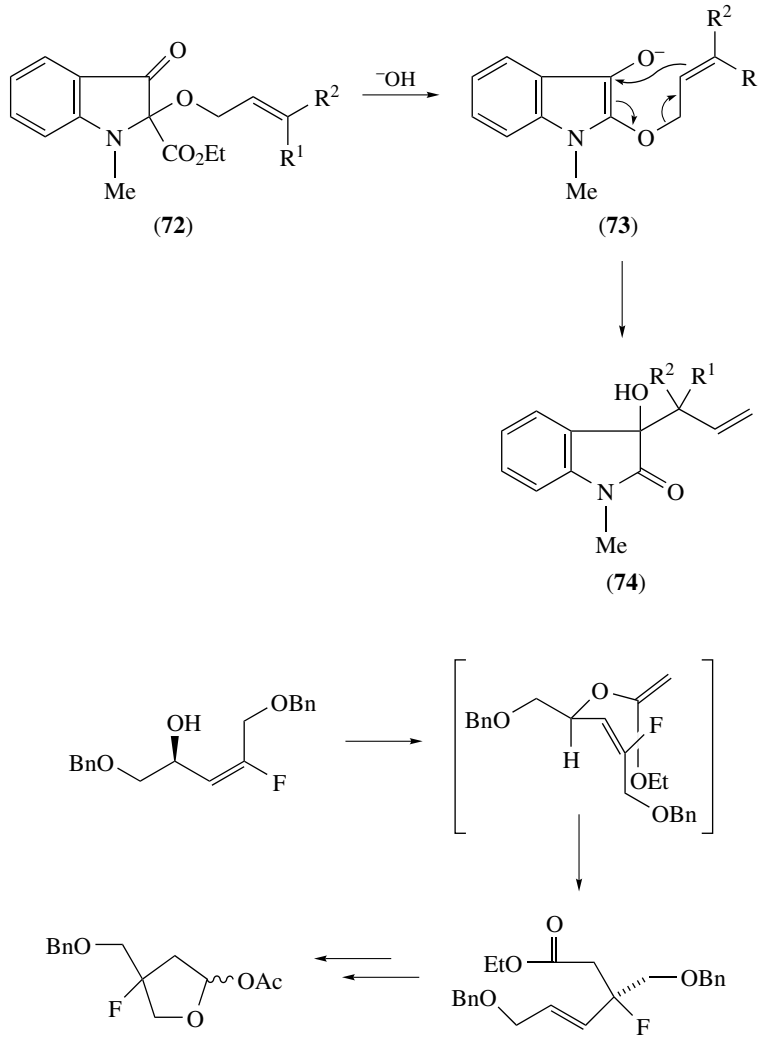
SCHEME 29



SCHEME 30

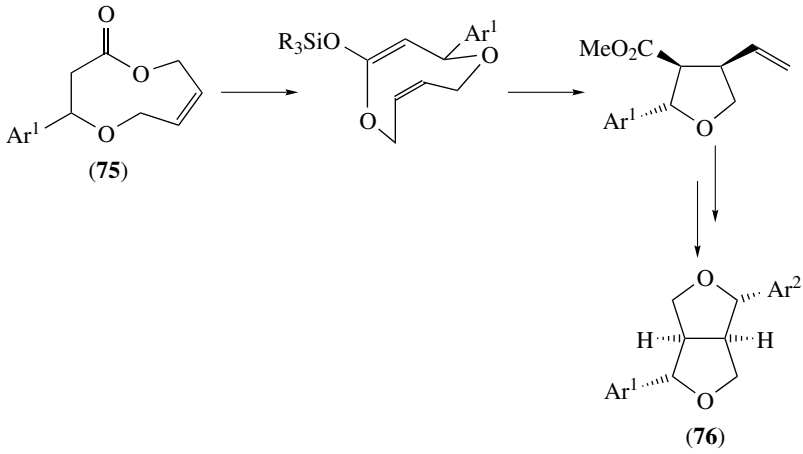
the Claisen rearrangement as the key step has been reported.[118] A Claisen rearrangement methodology using lithium perchlorate–diethyl ether-mediated rearrangement of α- and β-endo-dicyclopentadienyl vinyl ethers has been exploited[119] for the stereospecific generation of new chiral centres in the synthesis of linear triquinanes (see Scheme 30). The conversion of 1,2-di- and 1,2,4-trichloro-6,9-dioxaspiro[4.4]non-1-en-3-ones into 5-allyl(allenyl)-5-chloro-2-(2-hydroxyethyloxy)cyclopent-2-ene-1,4-diones has been reported.[120]

A two-step synthesis of functionalized dienoic esters has been devised starting from γ-hydroxyvinyl sulfones.[121] Johnson–Claisen and Eschenmoser–Claisen rearrangements of chiral γ-trifluoromethylated allylic alcohols have been shown to be important methods for the preparation of highly functionalized chiral trifluoromethylated compounds.[122] Diastereoselective γ-alkylation of unsaturated carboxylic acids has been attained by esterification of the acid with allylic alcohols and consecutive Ireland–Claisen and Cope rearrangements.[123] The formation of 3-allyl-3-hydroxy-1-methylindol-2(3*H*)-one (**74**) from 2-allyloxyindole keto ester (**72**) has been explained[124] by invoking a Claisen rearrangement of transient 2-allyloxy-3-hydroxymethylindole (**73**) generated by decarboxylation of (**72**). The Ireland–Claisen rearrangement has been employed to provide an efficient route for the stereoselective synthesis of 2,3-disubstituted succinates,[125] and matrix metalloproteinase inhibitors have been synthesized by a route involving an Ireland–Claisen rearrangement which has allowed systematic modification of the substituent α to the hydroxamic function.[126]

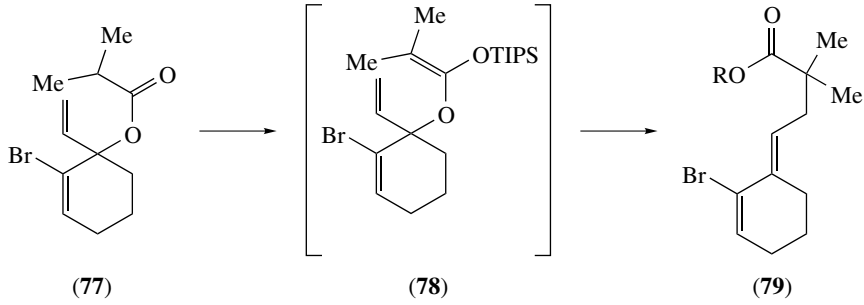


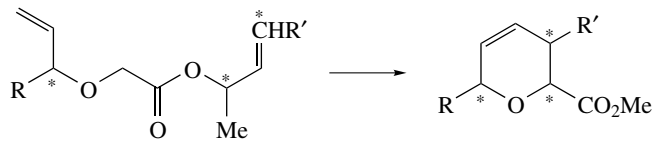
SCHEME 31

A novel synthetic method which can provide enantiomeric apionucleosides with high enantioselectivity has been developed[127] using a [3,3]-sigmatropic Claisen rearrangement (see Scheme 31), and a new diasterospecific approach based on the Ireland–Claisen rearrangement of unsaturated oxamacrolides (**75**) has been used[128] to synthesize furanofuran lignans (**76**) (see Scheme 32). Unsymmetrical bis-allyl silyl-ketene acetals (**78**), derived from cyclohexenones (**77**), have been found to undergo regio- and stereo-selective Ireland–Claisen rearrangements[129] to afford alkylidenecyclohexenes (**79**) in good yield. From a mechanistic point of view an *exo*-Claisen pathway is preferred for the process. A stereochemically general



SCHEME 32

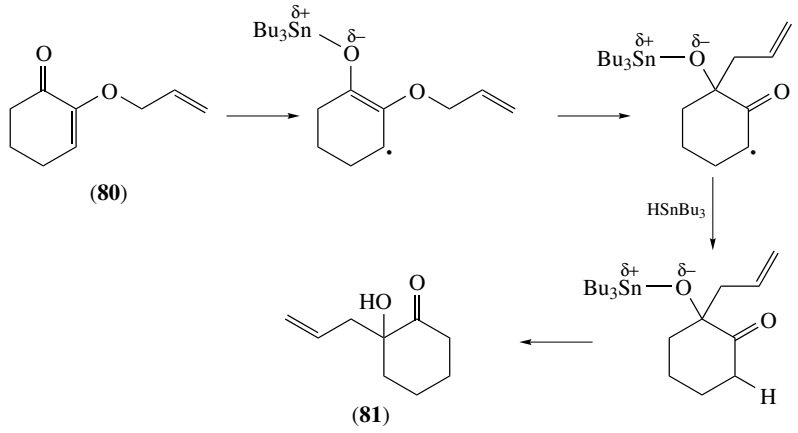




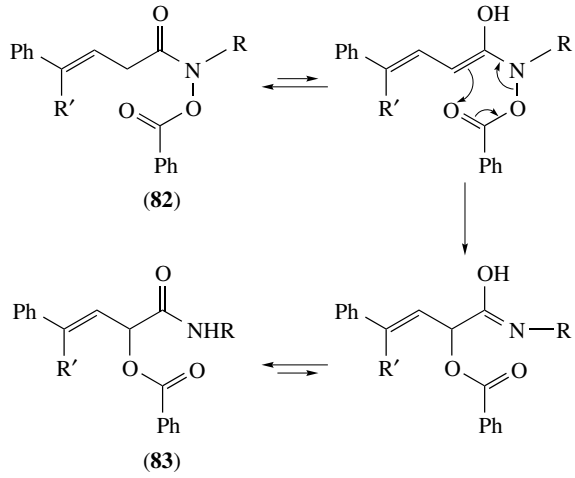
SCHEME 33

synthesis of substituted dihydropyran-2-carboxylates involving a tandem glycolate Claisen rearrangement/ring-closing metathesis has been described[130] (see Scheme 33). It has been demonstrated[131] that Claisen rearrangements can be 'triggered' by a tin-associated ketyl radical anion. Thus treatment of (**80**) with tin hydride and 2,2′-azobisisobutyronitrile afforded the rearranged α-hydroxy ketone (**81**) (see Scheme 34).

It has been shown that the Claisen rearrangement of lithium enolates of amino acid enynol esters allows the synthesis of very sensitive γ, δ-unsaturated amino acids with conjugated enyne side chains.[132] The chelate–enolate Claisen rearrangement has also been applied to the synthesis of unsaturated polyhydroxylated amino acids,[133] polyhydroxylated piperidines,[134,135] and unsaturated peptides.[136]



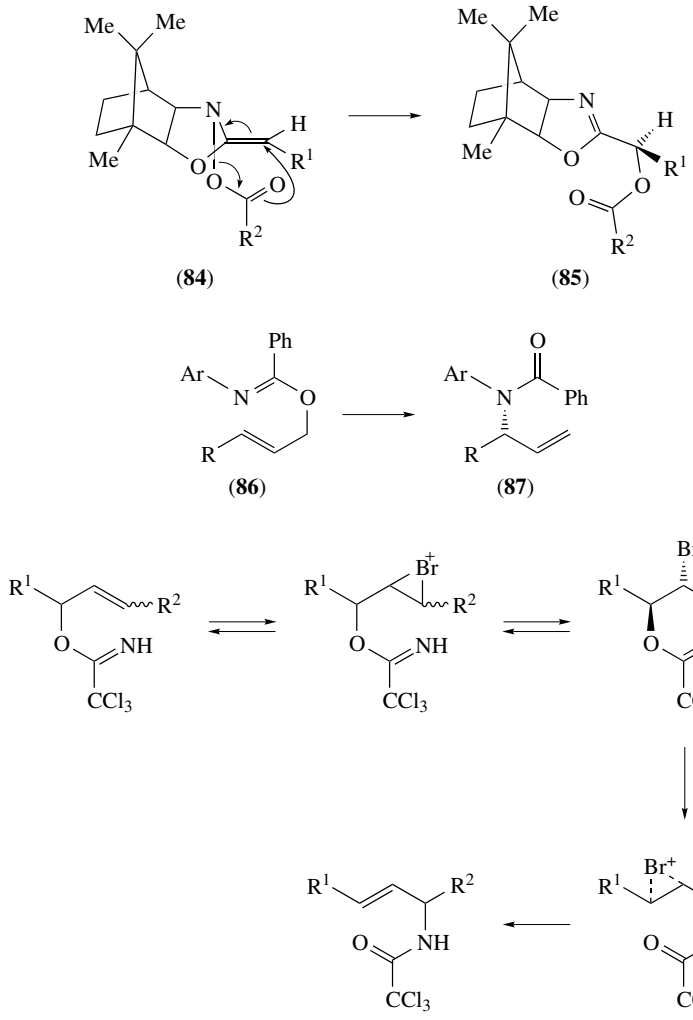
SCHEME 34



SCHEME 35

4-(2-Aminoethyl)indoles have been prepared[137] from 3-hydroxy-2-methoxyindolines by way of a Claisen *o*-amide rearrangement. *O*-Acylhydroxamic acid derivatives (**82**) have been found to undergo a base-catalysed rearrangement to give secondary 2-acyloxyamides (**83**). The authors[138] have suggested that the mechanism proceeds via an anionic hetero[3,3]-sigmatropic rearrangement of the corresponding enol or enolate (see Scheme 35). In the presence of various acylating agents, camphor-derived oxazoline *N*-oxides (**84**) have been found to afford α-acyloxyoxazolines (**85**) resulting from a diastereoselective [3,3]-rearrangement.[139]

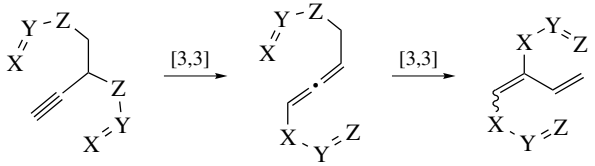
The asymmetric aza-Claisen rearrangement of allyl imidates, (**86**) $\rightarrow$ (**87**), has been shown to be catalysed by homochiral cationic palladium(II) complexes,[140] and a series of enantiopure cyclopalladated ferrocenyl amines and imines have been



SCHEME 36

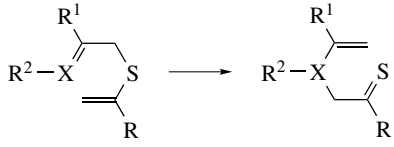
established[141] as efficient catalysts for the [3,3]-sigmatropic rearrangement of allylic imidates to allylic amides. Improved conditions have been developed[142] for the [3,3]-sigmatropic rearrangement of trichloroacetamides, and a novel, efficient and stereospecific method for the [3,3]-sigmatropic rearrangement of (*E*)-allylic trichloroacetimidates bearing electron-withdrawing groups has been reported[143] (see Scheme 36). A sequence of [3,3]-sigmatropic isomerizations of the type (**88**) → (**89**) → (**90**) has been utilized to provide a convenient approach to 1,2-difunctionalized buta-1,3-dienes.[144]

A theoretical study of substituent effects in the thio-Claisen rearrangement (**91**) → (**92**) has been carried out. The study[145] has shown that 2,5-disubstitution leads to tighter transition states and to a substantial lowering of the enthalpy of



(**88**) (**89**) (**90**)

e.g. XYZ = C−CO_2R, C−C=C



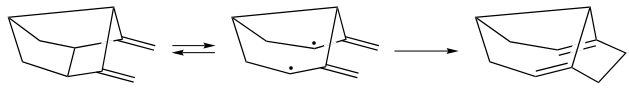
(**91**) (**92**)

X = CH, N

activation. Quantum-chemical calculations of the [3,3]-sigmatropic rearrangement of *S*-allyl *O*-methyl *N*-(2- and 4-substituted acridin-9-yl)thiocarbonimidates have pointed to a chair configuration in the transition state of the reaction,[146] and a new synthetic route to *N*-allyl-*N*-(9-acridinyl)thiocarbamic acid *O*-methyl and *S*-methyl esters via the [3,3]-sigmatropic rearrangement of *O*(*S*)-methyl-*S*(*O*)-allyl-*N*-(9-acridinyl)iminothiocarbonates has been elaborated.[147] The thio-Claisen rearrangement has proved to be a powerful synthetic tool in the preparation of a (−)-trichodiene intermediate bearing vicinal stereogenic quaternary centres.[148] A recent analysis has shown that the concerted [3,3]-sigmatropic rearrangement of allylic xanthates in protic solvents, and the ionic rearrangement in hydroxylic solvents, are extremes in a continuous spectrum of mechanism for the thione-to-thiol rearrangement. The solvation mode for the rearrangement via an ionic intermediate was found to be different from that of the concerted mechanism.[149]

Cope and related rearrangements

Characteristics and energetics of the photo-induced electron-transfer degenerate Cope rearrangement of 2,5-diarylhexa-1,5-dienes have been reported in detail.[150] Oxygen-trapping experiments have established[151] the two-step nature of the rearrangement of (**93**) to (**94**) (see Scheme 37), while it has been shown that both [2.2.2]propellane and the Cope rearrangement of hexa-1,5-diene follow reaction paths that pass through singlet diradicaloid portions of the potential-energy surface.[152] A theoretical analysis of the Cope rearrangements of hexa-1,5-diyne, hexa-1,2-dien-5-yne, hexa-1,2,5-triene,

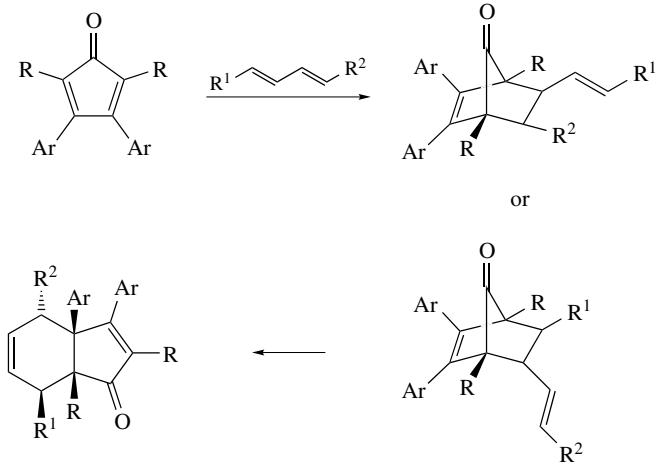


(**93**) (**94**)

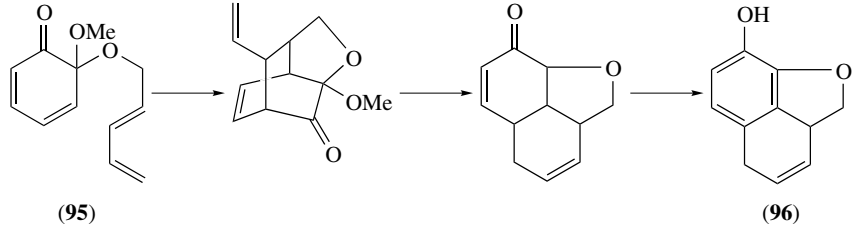
SCHEME 37

hexa-1,2,4,5-tetraene, and hexa-1-en-5-yne, has been undertaken.[153] In each case the mechanism was predicted to be concerted through an aromatic transition state. The effect of deuterium substitution on the positional equilibrium and rate of the Cope rearrangement of barbaralone-*d*(1) has been investigated[154] by ^{1}H and ^{13}C dynamic NMR spectroscopy. It has been proposed that every transition state should be accompanied by a bond-excited state with a similar structure, the properties of which should in principle be measurable by spectroscopic methods and can thus constitute a source of information about the transition state. This idea has been demonstrated computationally through the example of the degenerate Cope rearrangement of semibullvalene.[155] The effects of substituents on the degenerate Cope rearrangement of semibullvalenes and barbaralones have been reviewed,[156] and the mechanism of the Cope rearrangement in halobullvalenes in solution and in the solid state has been investigated by NMR techniques.[157]

It has been established[158] that the course of the sequential pericyclic reaction of cyclopentadienones with acyclic conjugated alkadienes depends on the reaction temperature, thermal treatment at low temperatures affording 3a,4,7,7a-tetrahydroinden-1-one derivatives by way of a Cope rearrangement (see Scheme 38). Roman *et al.*[159] have developed an efficient stereoselective synthesis of enantiomerically pure 1-nitrotricyclo[5.2.2.0^{2,6}]undeca-3,8-dienes via a tandem consecutive asymmetric Diels–Alder–Cope rearrangement (see Scheme 39). Adducts



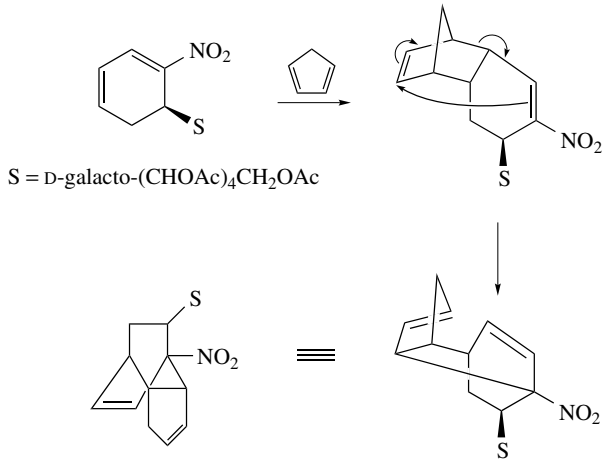
SCHEME 38



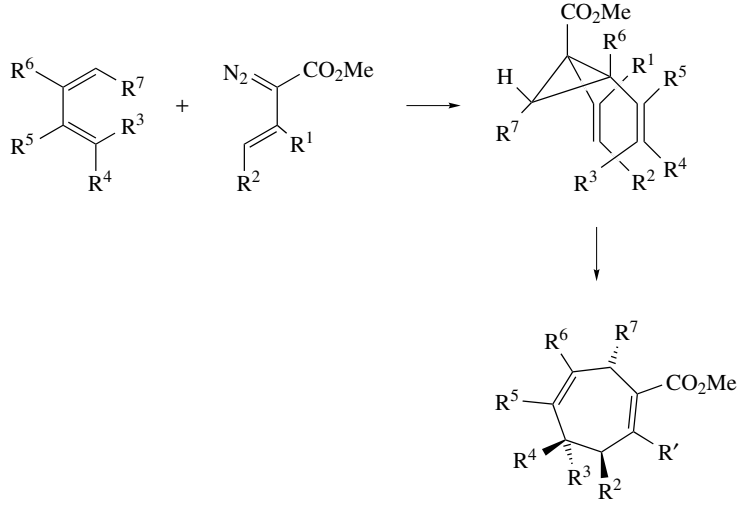
(**95**) (**96**)

of the intramolecular Diels–Alder reaction of *o*-benzoquinone monoketals, viz. (**95**), have been rapidly converted via Cope rearrangements to naphthofurans (**96**) and phenanthrofurans related to (−)-morphine.[160] Catalytic amounts of bis(benzonitrile)palladium(II) chloride have been found[161] to enhance the Cope rearrangement of germacranolides to elemanolides.

Rhodium(II) (*N*-dodecylbenzenesulfonyl)prolinate has been found to act as an effective catalyst for the enantioselective decomposition of vinyldiazoacetates to *cis*-divinylcyclopropanes. Combination of this process with a subsequent Cope rearrangement has resulted[162] in a highly enantioselective synthesis of a variety of cycloheptadienes containing multiple stereogenic centres (see Scheme 40). The tandem



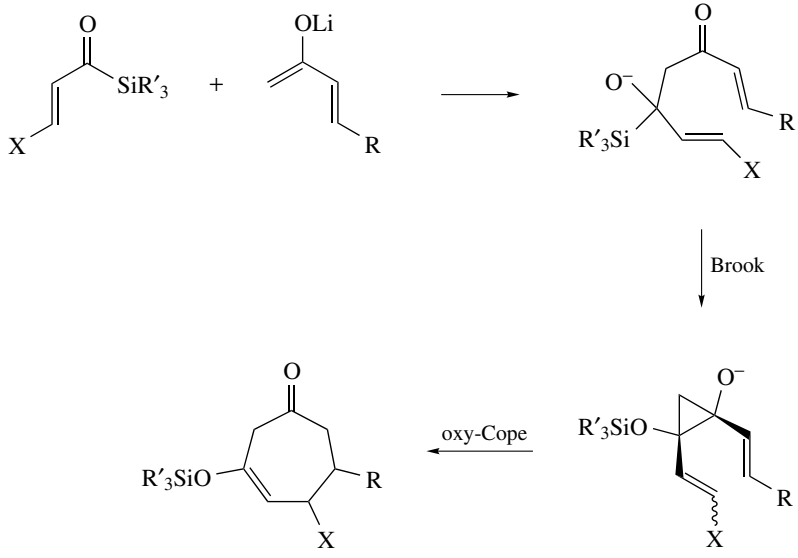
SCHEME 39



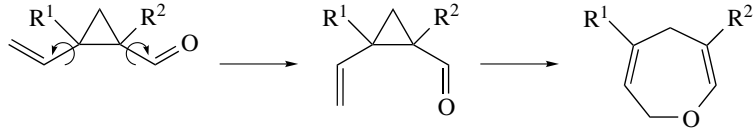
SCHEME 40

cyclopropanation–Cope rearrangement sequence has been used to synthesise members of the tremulane sesquiterpenes.[163] A useful and mechanistically interesting 3 + 4-annulation methodology has been reported for the stereo-controlled construction of highly functionalized cycloheptenone derivatives. The reaction has been presented[164] as an anionic oxy-Cope reaction of a 1,2-divinylcyclopropanediol intermediate generated via a Brook rearrangement of the 1,2-adduct of a lithium enolate (see Scheme 41). The prototypical 1,2-*cis*-vinylcyclopropanecarbaldehyde to 2,5-dihydrooxepin hetero-Cope type rearrangement (see Scheme 42) has been studied[165] by density functional theory. Divinylcarbinols of the type (**97**) have been found to undergo oxy-Cope rearrangement very rapidly at low temperatures although the rearrangement was found to proceed in a reversible manner. It appears[166] that the return to alkoxide can materialize only as long as the enolate anion has its oxygen atom oriented up towards the methano bridge as in (**98**). However, such a structure is thermodynamically unstable relative to its oxygen-down form (**99**).

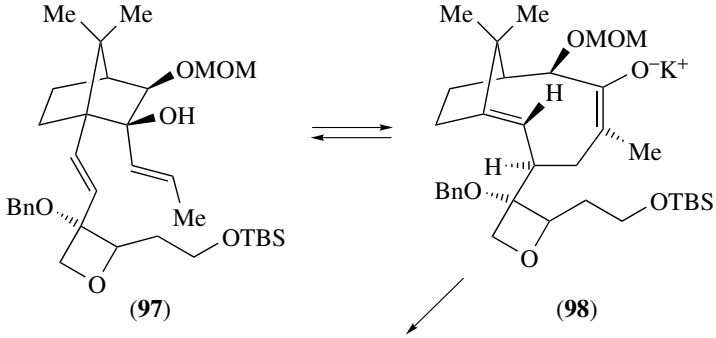
NMR and kinetic studies have been carried out[167] on the antibody-catalysed oxy-Cope rearrangement of hexadiene (**100**) to aldehyde (**101**). An aromatic oxy-Cope rearrangement involving a benzene ring [see (**102**) → (**103**)] has been observed to



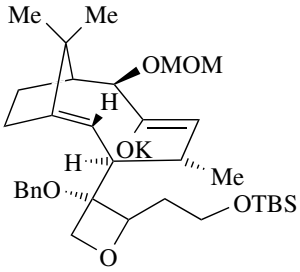
SCHEME 41



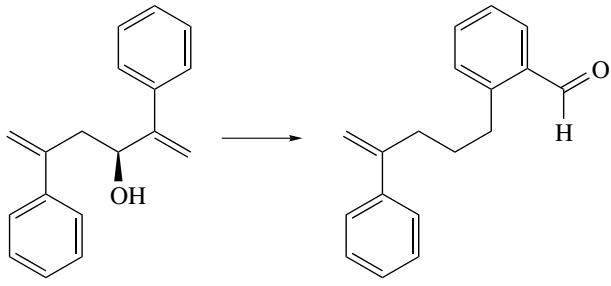
SCHEME 42



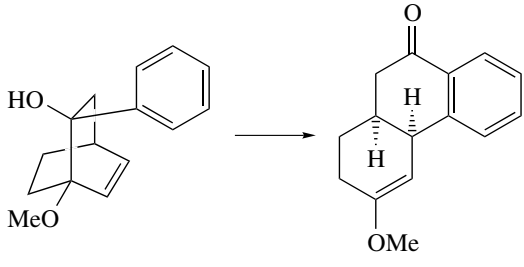
(**97**) (**98**)



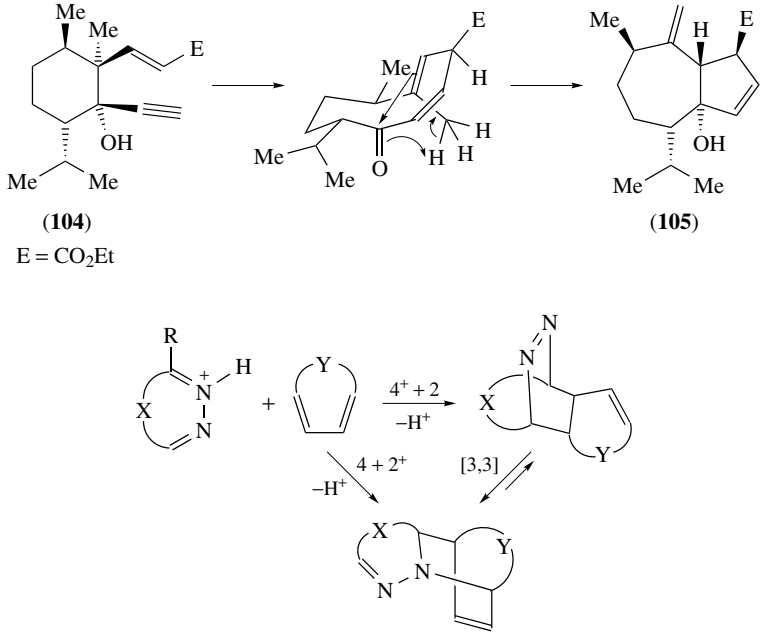
(**99**)



(**100**) (**101**)



(**102**) (**103**)

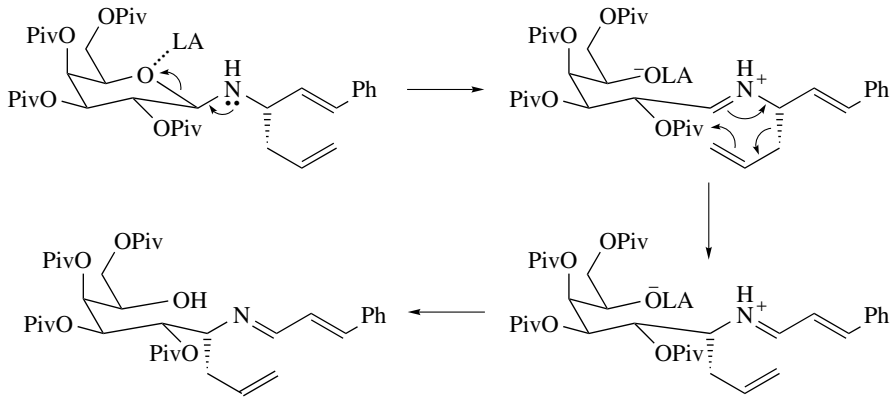


SCHEME 43

take place[168] when 1-methoxy-2-arylbicyclo[2.2.2]oct-5-en-2-*exo*-ols are treated with potassium hydride in THF. The thermally allowed oxy-Cope rearrangement of the optically active ethynyl alcohol (**104**) has been used[169] to construct the functionalized hydrazulenoid skeleton (**105**). A short, stereoselective synthesis of the C(1)−C(10) polyol fragment of nystatin A has been achieved[170] using a highly selective and efficient oxy-Cope rearrangement of a chiral unprotected aldol product as the key step, and a stereoselective synthesis of the natural product (+)-lasiol has been carried out in a similar manner using a silyloxy-Cope rearrangement of a chiral aldol product.[171] It has been demonstrated for the first time[172] that an anion-accelerated oxy-Cope rearrangement can produce strained medium-ring compounds from larger, less strained carbocycles.

The first unambiguous glimpse of the heteroatomic modulation of oxyanionic Cope rearrangement rates has been described[173] in the context of paclitaxel synthesis. Recent calculations have indicated[174] that anionic oxy-Cope substrates react via a concerted pathway, whereas anionic amino-Cope substrates react via a stepwise, heterolytic cleavage pathway. It has been demonstrated[175] that, in the acid-catalysed 4 + 2-cycloaddition between cyclic azines and 1,3-dienes, both partners may play the role of the diene or the dienophile, depending on particular structural features. Moreover, it has been shown that the thermal or acid-catalysed interconversion of isomeric 4 + 2-cycloadducts definitely occurs by a Cope rearrangement and not by a 4 + 2-cycloreversion (see Scheme 43). 3-Alkylideneindolin-2-ones have been prepared from propargylbenzotriazoles via

a selective nucleophilic reaction of an allene dianion followed by a 3-aza-Cope rearrangement,[176] and the reaction of 1-methyl-1-cyanohydrazones with methyl trifluoromethanesulfonate was found to afford 2-(methylamino)-1-methylimidazoles as their triflic acid salts. The authors[177] have proposed that this transformation involves the formation of the 1-cyano-1,2-dimethyl ene-hydrazine derivative which undergoes a 1,3,4-triaza-Cope rearrangement *in situ*. Chain-extended amino sugar derivatives have been synthesized[178] via the stereo-controlled Lewis acid-catalysed aza-Cope rearrangement of *N*-glycosylhomoallylamines (see Scheme 44). The anionic amino-Cope rearrangement of a series of 3-amino-1,5-diene substrates has been achieved[179] at low temperatures by using butyllithium to generate the lithium anion. The absolute stereochemistry of the major product has been predicted from simple transition-state models, the major enantiomer being produced from a chair-like conformation of the substrate with the amine component occupying a pseudo-equatorial orientation. High asymmetric induction has also been achieved in the anionic amino-Cope rearrangement of 3-amino-1,5-dienes by using β-amino alcohol auxiliaries.[180]



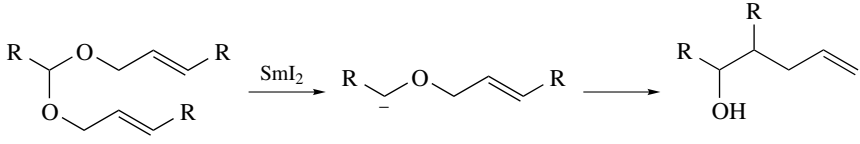
SCHEME 44

[2,3]-Migrations

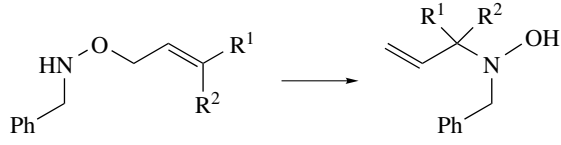
The tactical combination of Diels–Alder reactions with [2,3]-sigmatropic rearrangements, as well as the one-pot version of these tandem processes, have been used to create unusual structures with high efficiency.[181] The influence of the relative stereochemistry of the epoxide and benzyloxy functionalities present in *cis*- and *trans*-1-benzyloxy-3,4-epoxycyclopentanes on the tandem epoxide–allylic alcohol [1,2]/[2,3]-Wittig rearrangement has been studied,[182] together with the Wittig rearrangement of the intermediate alcohols. The study has shown that the reaction involving the *cis*-epoxybenzyl ether has a strong preference for [1,2]-rearrangement with retention whereas, in contrast, the rearrangement of the intermediate alcohol leads to a 9:1 mixture of [2,3]-products. A chiral non-racemic base-promoted [2,3]-Wittig rearrangement of a series of (allyloxymethylbenzene)tricarbonylchromium(0)

complexes has been reported to proceed with remarkably high enantioselectivity.[183] The *N,N*-diethylcarbamoyl group has been shown to act as an efficient director in the (−)-sparteine-mediated enantioselective [2,3]-Wittig rearrangement of *o*-substituted benzyl allyl ethers,[184] and the [2,3]-sigmatropic rearrangement of α-propargyloxyacetic acids has been achieved[185] by the use of a BuLi–(−)-sparteine complex. Tomooka *et al.*[186] have demonstrated that a chiral bis(oxazoline) system is effective as an external ligand for the enantioselective [2,3]-Wittig rearrangement of (*E*)-crotyl propargylic ethers. An asymmetric synthesis of the chiral β-lactone precursor of the HMG–CoA synthase inhibitor L-659,699 has been described.[187] It involves, as the key step, an asymmetric [2,3]-Wittig rearrangement to control the stereogenic centres at the ring carbons. It has been reported[188] that diallyl acetals (**106**) undergo reductive cleavage of an allyloxy group by SmI_2 to generate α-allyloxy carbanions (**107**), which can be transformed by a [2,3]-Wittig rearrangement into homoallylic alcohols (**108**). A novel [2,3]-sigmatropic rearrangement whereby *N*-benzyl-*O*-allylhydroxylamines (**109**) are transformed into the corresponding *N*-allylhydroxylamines (**110**) has been described, and evidence for the intramolecular nature of the process has been presented.[189] The diastereoselective formation of a 2,8-dioxabicyclo[3.2.1]octane skeleton has been accomplished[190] from methyl acetoacetate through the generation and [2,3]-rearrangement of a bicyclic oxonium ylide (see Scheme 45). Apparently, this is the first example of an exocyclic [2,3]-shift from an acetal-derived oxonium ylide.

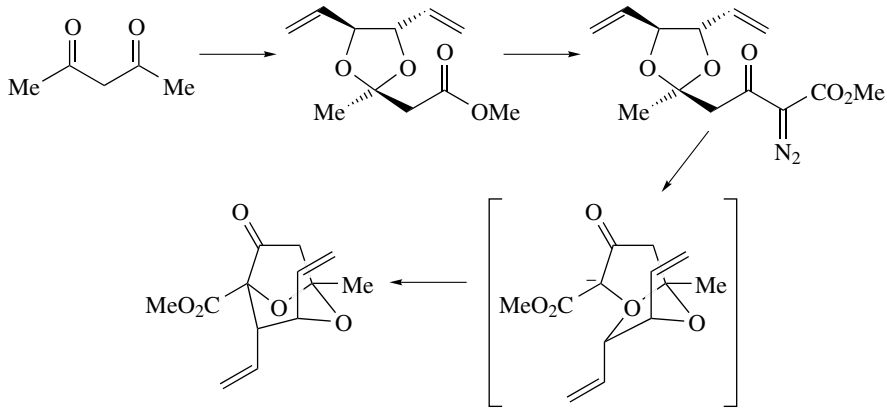
A study of the mechanism of the rearrangement of a tertiary amine oxide to the *O*-substituted hydroxylamine has been carried out by the semiempirical AM1 method.[191] The use of prolinol as a chiral auxiliary has allowed the formation of single diastereomeric amine *N*-oxides from *N*-allyl prolinol derivatives. However, on warming, these amine oxides were found to undergo the [2,3]-Meisenheimer rearrangement with only low stereoselectivity.[192] The Meisenheimer rearrangement of allyl *N*-oxides has been used[193] as a route to initiators for nitroxide-mediated free-radical polymerizations. A detailed study of the [2,3]-Meisenheimer rearrangement of 2-vinylazetidine *N*-oxides has been undertaken.[194] A competitive study of the Meisenheimer rearrangement in a substrate tertiary amine with allylic and propargylic



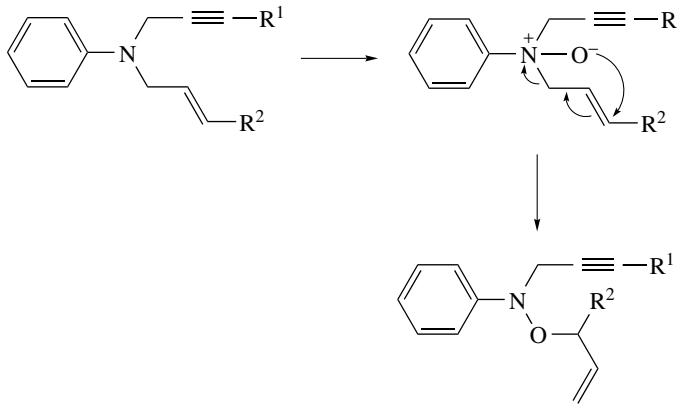
(**106**) (**107**) (**108**)



(**109**) (**110**)



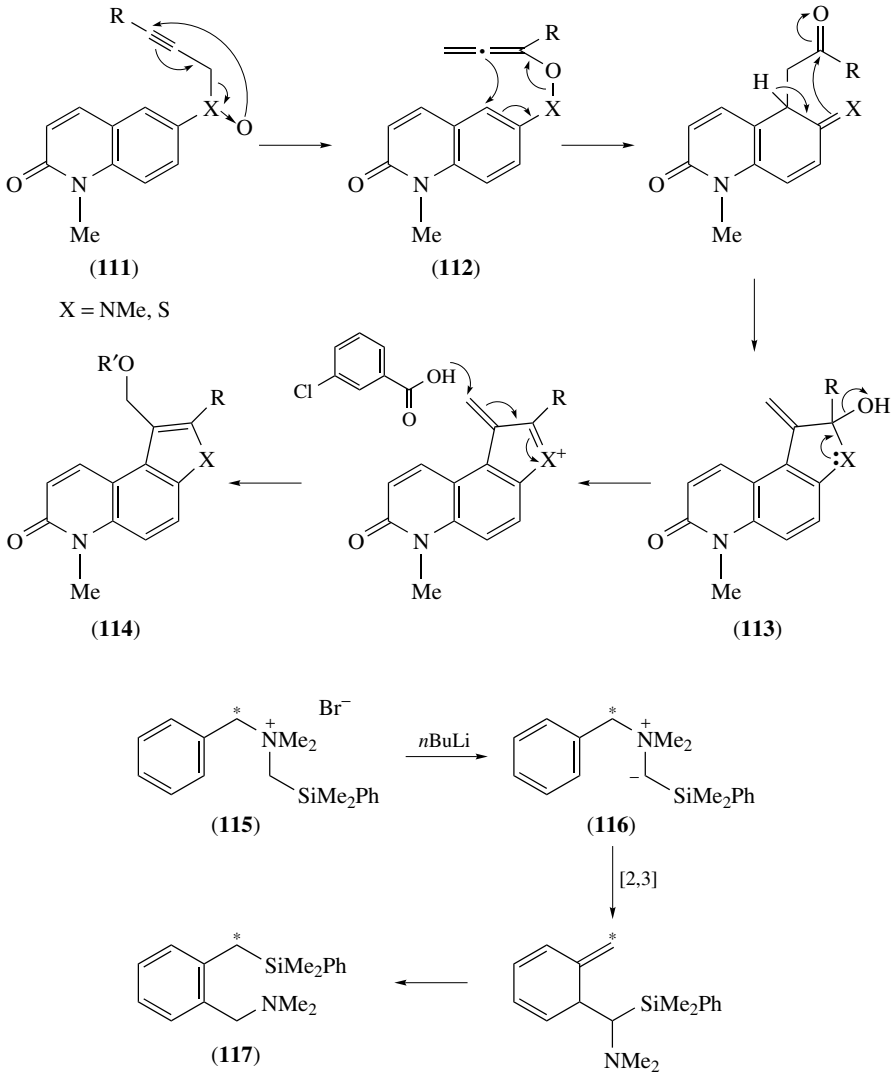
SCHEME 45



SCHEME 46

moieties has shown[195] that the rearrangement of the allyl aryl amine moiety is preferred over the rearrangement of the allyl propargyl amine oxide moiety (see Scheme 46). Several derivatives of pyrrolo-[196] and thieno-[3,2-*f*]quinolin-7-ones[197] have been synthesized. Formation of the products has been explained by invoking a [2,3]-sigmatropic rearrangement of the *N*-oxide or sulfoxide (**111**) in a manner similar to a Meisenheimer rearrangement to give an intermediate (**112**) which undergoes a [3,3]-sigmatropic rearrangement followed by ketol formation to give (**113**). Acid-catalysed allylic rearrangement of (**113**) gives the final product (**114**). A similar methodology has been used[198] to prepare a number of pyrrolo[3,2-*d*]pyrimidine derivatives from the corresponding 5-[*N*-[4-(aryloxy)but-2-ynyl]-*N*-ethylamino]-1,3-dimethyluracils.

It has been shown that the tri-*n*-butyltin group can control the diastereoselection of an aza-[2,3]-Wittig rearrangement,[199] and the silicon-assisted aza-[2,3]-Wittig rearrangement of crotyl-type amines has been used to furnish each diastereoisomer of the

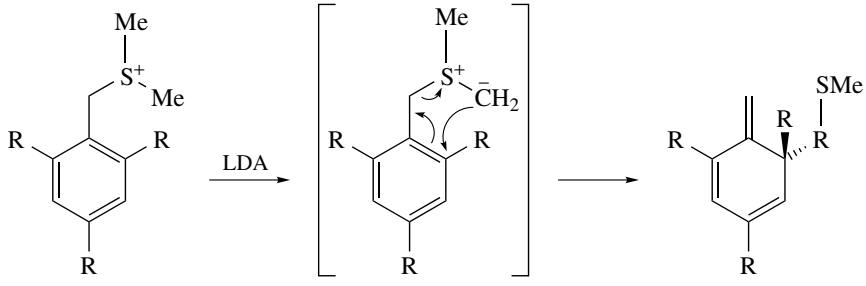


SCHEME 47

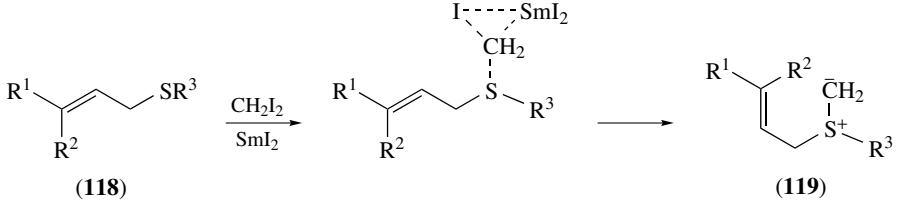
product homoallylic amines in good yield.[200] A number of ketene dithioacetals have been found to react readily with aziridine to afford the corresponding *N*-vinylaziridines which undergo an iodine ion-assisted ring expansion to produce pyrrolines.[201] Investigations into the aza-[2,3]-Wittig rearrangement of *N*-alkyl-*N*-allyl-α-amino esters have demonstrated[202] that the rearrangement of tertiary amines with Lewis acids is less effective than the [2,3]-Stevens rearrangement using ylides generated from quaternary ammonium salts. Both approaches, however, have been shown to have potential for the formation of novel, substituted allylglycine esters. The application of ^{13}C NMR spectroscopy and ^{13}C-labelled benzylammonium salts to the study of the rearrangements of

ammonium benzylates has revealed[203] that the ylide (**116**) generated from *N*-benzyl-N,*N*-dimethyl-*N*-[(dimethylphenylsilyl)methyl]ammonium bromide (**115**) and BuLi affords N,*N*-dimethyl-2-[(dimethylphenylsilyl)methyl]benzylamine (**117**) via a [2,3]-shift in the silylmethylide followed by subsequent [1,4]-silicon and [1,2]-hydrogen shifts (see Scheme 47).

It has been established[204] that the thia-Sommelet dearomatization leading to the formation of hexatrienes containing quaternary stereogenic centres can be achieved in excellent yield by deprotonation with LDA (see Scheme 48). Allylic sulfides (**118**) have been transformed into homoallylic sulfides (**120**) with complete allylic inversion by treatment with SmI_2 and CH_2I_2. The reaction is considered[205] to involve addition of a samarium carbenoid to a divalent sulfur leading to the formation of a sulfonium ylide (**119**) which rearranges to the homoallylic sulfide. A rearrangement of *O,O*-silylketene acetals (**121**) leading to the γ-thiomethylation of butenoic acid derivatives has been reported. The process has been explained[206] by invoking the [2,3]-sigmatropic rearrangement of the intermediate ylide (**122**) to give

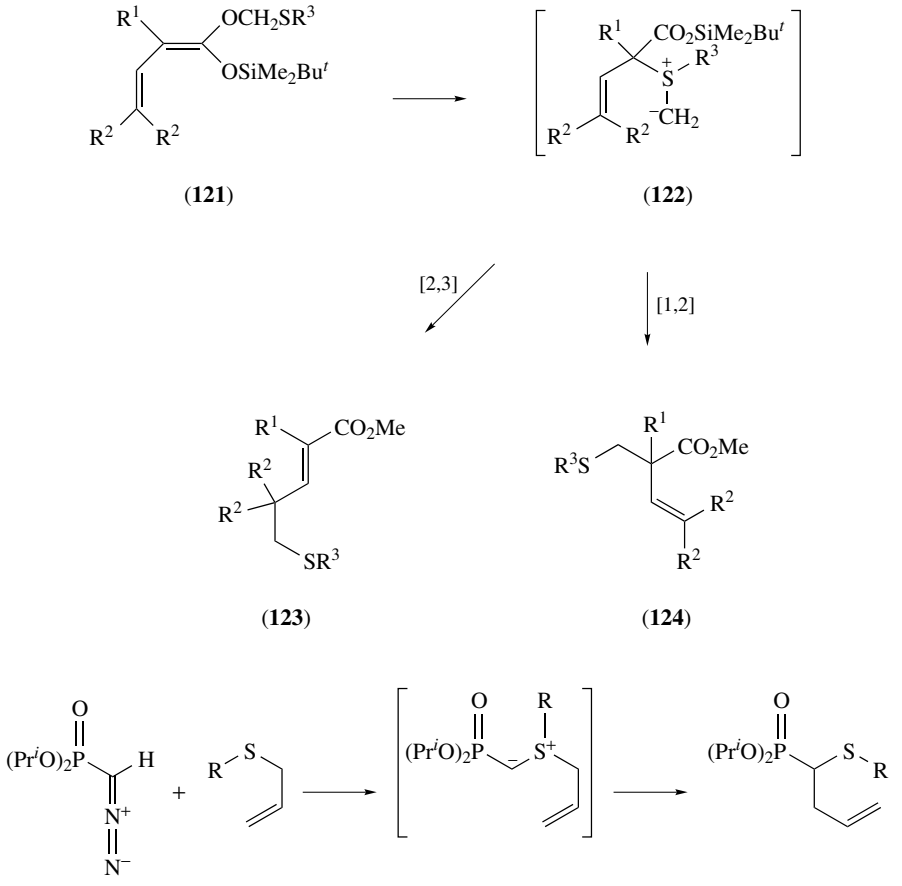


SCHEME 48



(**118**) (**119**)

(**120**)



SCHEME 49

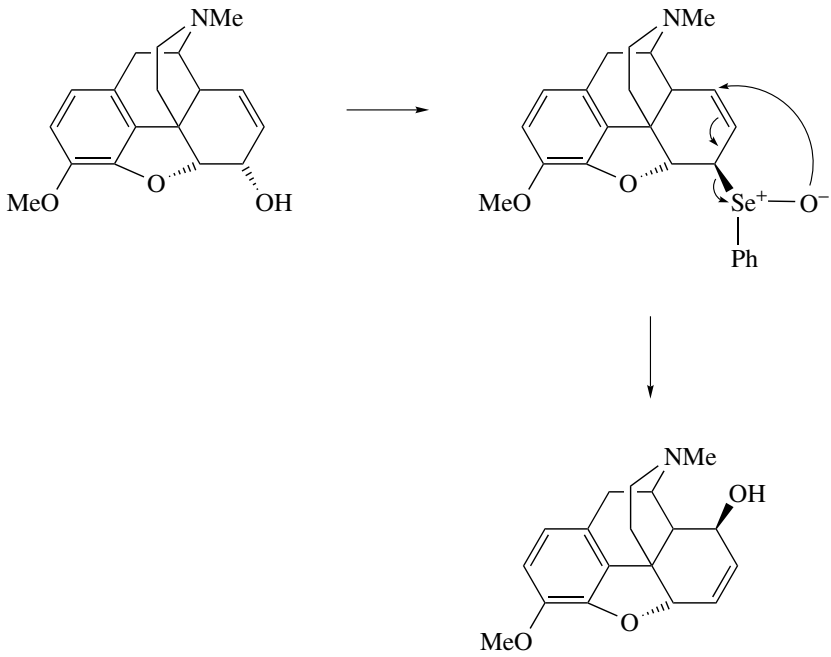
the γ-alkylated product (**123**). Alternatively, a [1,2]-shift analogous to the Stevens rearrangement leads to the α-substituted product (**124**), the major product in the case of phenylthiomethyl esters. New nine-membered heterocyclic compounds, 6,7,9,10-tetrahydro-4*H*-thieno[3,2-*f*][1,4]oxathionine and 4,7,8,10-tetrahydro-5*H*-thieno[2,3-*f*][1,4]oxathionine, have been synthesized[207] by [2,3]-sigmatropic rearrangements of the *S*-methylides generated by the fluoride ion-induced desilylation of 3-(2-thienyl)-4-[(trimethylsilyl)methyl]-1,4-oxathianium triflate and the (3-thienyl)-analogue, and 1,3,4,5,6,11a-hexahydro-(7*E*)-2-benzothionine has been obtained[208] in a similar manner by the fluoride ion-induced desilylation of *trans*-2-phenyl-1-[(trimethylsilyl)methyl]tetrahydrothiopyranium perchlorate. The reaction of diisopropyl diazomethylphosphonate with allylic sulfides in the presence of a catalytic amount of copper(II) acetylacetonate or rhodium acetate dimer, has been shown to afford[209] the corresponding α-phosphorylated γ,δ-unsaturated sulfides, presumably by way of a [2,3]-sigmatropic rearrangement of the intermediate sulfonium ylide (see Scheme 49). This reaction has been successfully extended to

α-vinyltetrahydrothiophene and dipropargyl sulfide. A theoretical study of the sulfenate–sulfoxide rearrangement has indicated[210] that a biradical mechanism is the lowest energy pathway and therefore the most likely mechanism for this rearrangement.

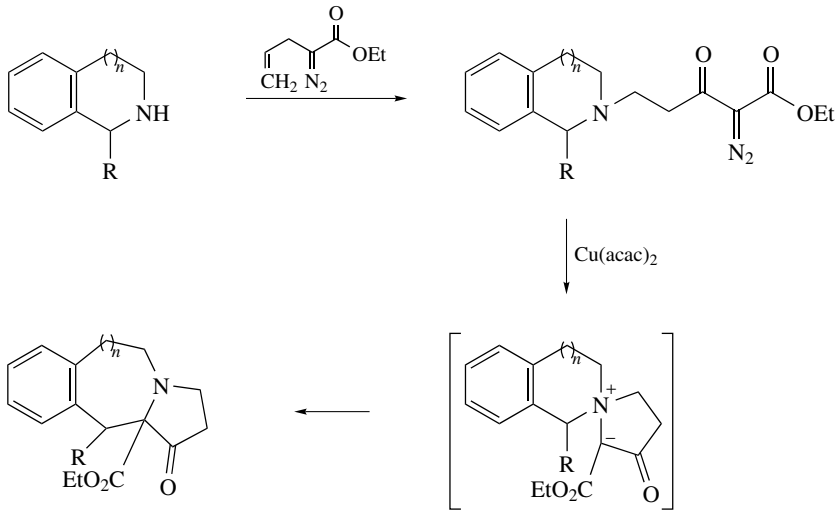
A [2,3]-sigmatropic rearrangement using selenium intermediates has been used[211] in a recent stereospecific synthesis of pseudocodeine (see Scheme 50).

Miscellaneous

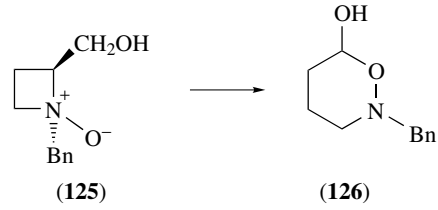
Theoretical calculations have been performed[212] for the Stevens rearrangement of phosphorus and arsenic ylides ($ZH_2MCH_2 \rightarrow H_2MCH_2Z$; Z = H, CH_3, $CH{=}CH_2$, SiH_3 and GeH_3; M = P or As), and ammonium ylides derived from the Cu(II)-catalysed decomposition of α-diazocarbonyl compounds tethered to tertiary amines have been found[213] to undergo a benzylic Stevens [1,2]-rearrangement to afford tetrahydroisoquinolines and benzazepines containing fused five-membered rings (see Scheme 51). The rearrangement of *N*-benzyl-2-hydroxymethylazetidine *N*-oxide (**125**) to the novel tetrahydrooxazine (**126**) in warm CH_2Cl_2 has been rationalized either as a Cope-type elimination followed by tautomerism of the enol to an aldehyde and lactol formation, or as a [1,2]-rearrangement.[214] The first phosphorothiolate to mercaptophosphonate [1,2]-sigmatropic rearrangement has been described[215] and used to prepare a new (mercaptomethylene)diphosphonate (see Scheme 52).



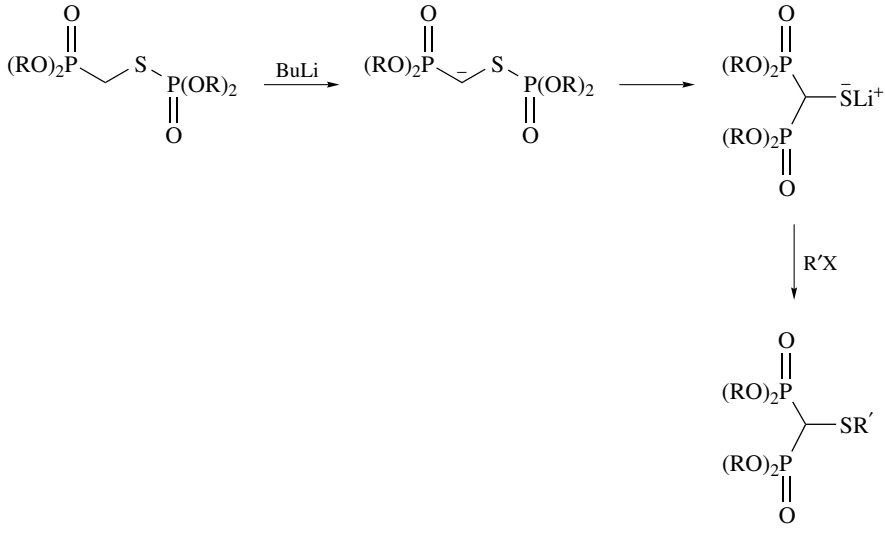
SCHEME 50



SCHEME 51



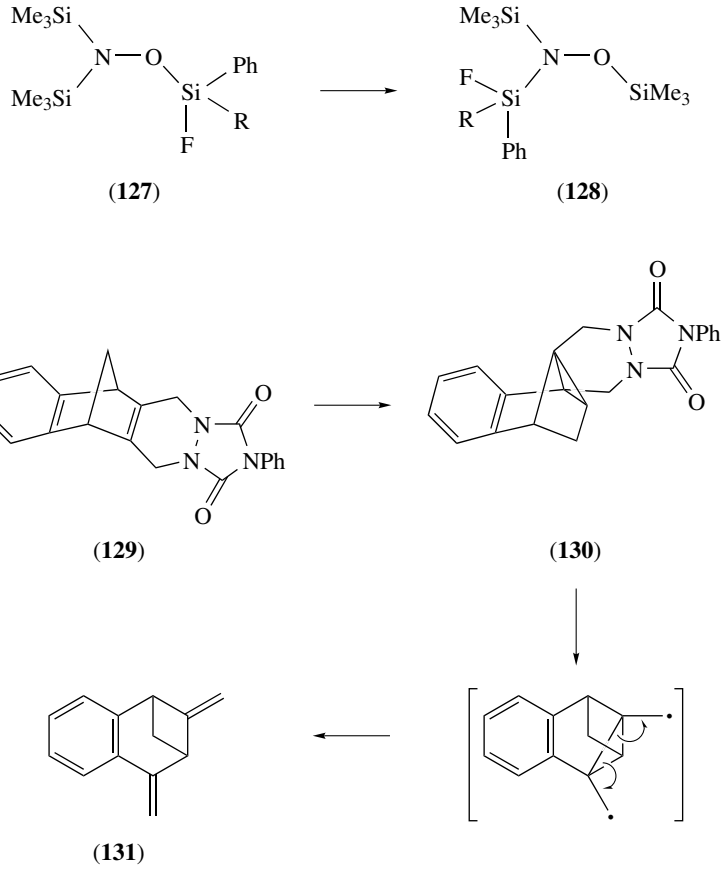
(**125**) (**126**)



SCHEME 52

An irreversible dyotropic rearrangement of fluoro-substituted tris(silyl)hydroxylamines (**127**) → (**128**) has been reported[216] and *ab initio* and density functional calculations for model compounds have confirmed the dyotropic course of this rearrangement.[217]

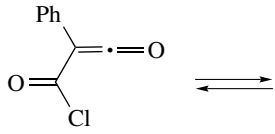
The photochemical di-π-methane rearrangement of quinoxalinobarrelenes has been studied,[218] and the novel hydrocarbon 8,10-dimethylidenetricyclo[7.1.1.$0^{2,7}$]undeca-2,4,6-triene (**131**) has been synthesized[219] by triplet-sensitized di-π-methane rearrangement of the norbornadiene derivative (**129**) and hydrolysis of the resulting urazol (**130**) (see Scheme 53). A method involving an oxa-di-π-methane rearrangement has been developed[220] to introduce appropriate substituents at both bridgehead positions of a bicyclo[2.2.2]oct-5-en-2-one leading to a formal total synthesis of modhephene, a propellane-type triquinane sesquiterpene. The oxa-di-π-methane rearrangement of bicyclo[2.2.2]oct-5-en-2-one and bicyclo[2.2.1]hept-5-en-2-one has also been induced by the external heavy-atom cation effect within a zeolite.[221]



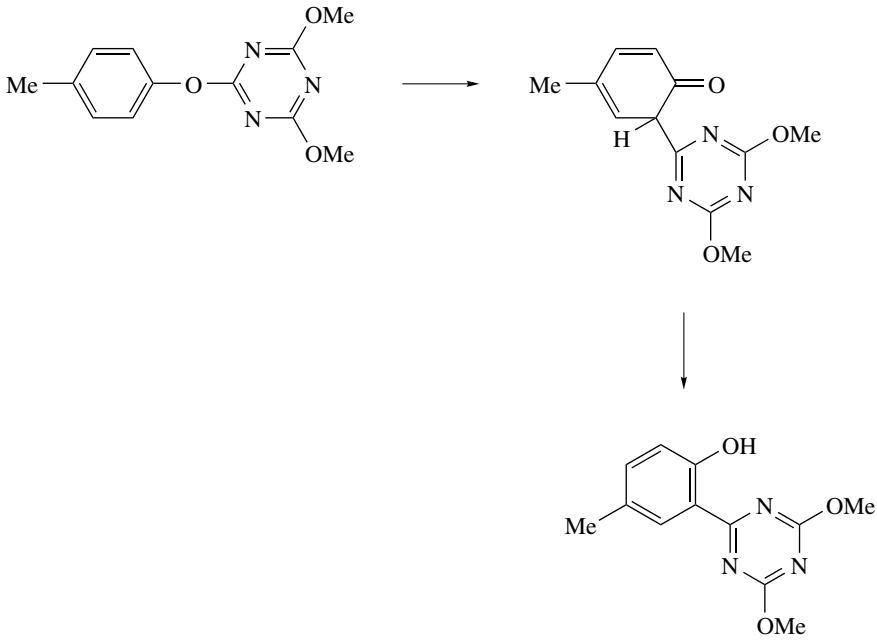
SCHEME 53

It has been shown[222] that [1,3]-dialkylboryl shifts in cyclononatetraenyl systems are facile and are slightly favoured over [1,2]-shifts. Apparently, neither Woodward–Hoffmann rules nor the 'least motion principle' alone can be used for the prediction or rationalization of large-ring sigmatropic migrations. Adequate analyses require a combination of dynamic NMR techniques and high-level *ab initio* calculations. α-Oxo ketenes have been found to undergo a degenerate thermal rearrangement by a [1,3]-shift of the acyl substituent.[223] Imidoyl-ketenes have been converted into α-oxo ketenimines by a similar rearrangement, while ^{13}C NMR spectroscopy has shown[224] that chlorocarbonyl(phenyl)ketene undergoes a degenerate [1,3]-shift of chlorine [see (**132**) $\rightleftarrows$ (**133**)].

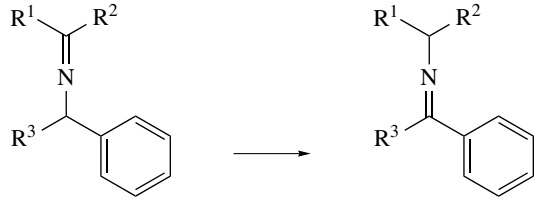
Theoretical considerations based on the tunnel-effect theory have shown[225] that in the intramolecular [1,3]-sigmatropic hydrogen shift in the photo-Fries rearranged intermediate of 2,4-dimethoxy-6-(*p*-tolyloxy)-*s*-triazine, the hydrogen atom migrates directly to the carbonyl oxygen without being enhanced by the basic catalytic action of the adjacent triazine ring (see Scheme 54). The ruthenium (II)-catalysed



(**132**) (**133**)



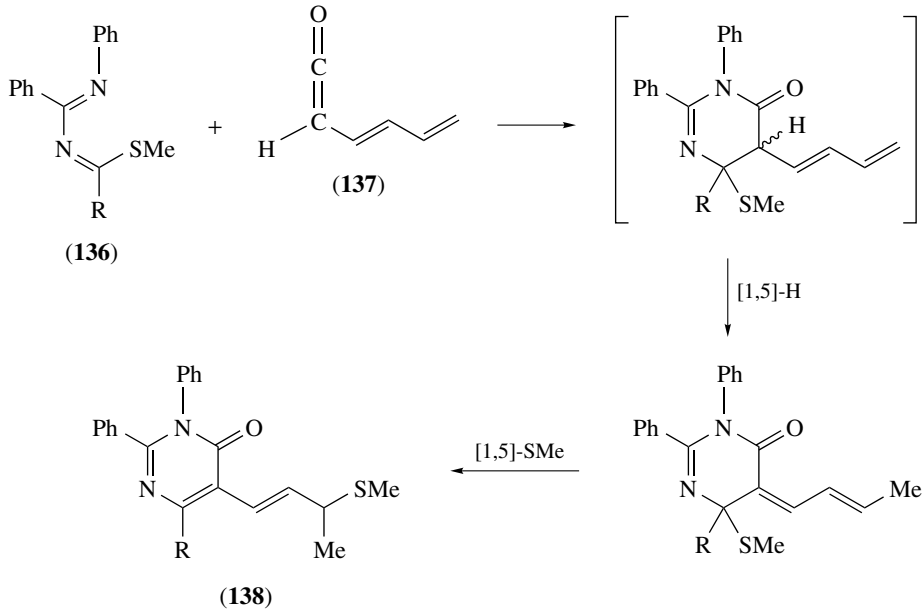
SCHEME 54



(**134**) (**135**)

isomerization of imines via a [1,3]-hydrogen shift [see (**134**) → (**135**)] has been described.[226] A convenient asymmetric synthesis of both (*R*)-(−)- and (*S*)-(+)-2-benzyl-2-hydroxycyclohexanones starting from racemic 2-benzyloxycyclohexanone and the chiral auxiliary 1-phenylethylamine has been reported.[227] The route involves a [1,3]-sigmatropic shift and a new diastereoselective α-iminoamine rearrangement of a 2-benzyl-2-iminocyclohexanamine substrate. The photochemical [1,3]-stannyl rearrangement of allylic stannanes has been investigated[228] in some detail, and a pentacoordinate *t*-alkoxy-1,2-oxastannetanide, considered to be formed by a novel tin [1,3]-migration from carbon to oxygen involving the formation of an oxetane ring and subsequent tin–carbon bond cleavage, has been obtained[229] from the treatment of a bis (β-hydroxyalkyl)stannane with potassium hydride in THF in the presence of 18-crown-6. Under the influence of potassium hydride, bicyclo[3.2.1]oct-6-en-2-ols have been found to undergo a [1,3]-sigmatropic shift to afford 8-*endo*-hydroxybicyclo[3.3.0]oct-2-en-4-ones.[230] It has been observed[231] that hydride reduction of the 2(*Z*)- and 2(*E*)-isomers of methyl and *t*-butyl 3-methyl-4-phenylthioheptenoates is accompanied by [1,3]-migration of the phenylthio group in both cases. The rhodium(I)-catalysed regioselective ring expansion of allenylcyclopropanes into methylenecyclopentenes has been achieved.[232] A stereochemical investigation of the thermal isomerization of 1-ethenyl-7-*exo*-phenylbicyclo[4.1.0]heptane to 7-phenylbicyclo[4.3.0]non-1(9)-ene has indicated[233] that vinylcyclopropane to cyclopentene rearrangements occur through diradical structures that allow for some conformational flexibility before a transition-state region of the potential-energy surface is reached.

A density functional theory computational approach has been used[234] to investigate the [1,5]-hydrogen shift in (*z*)-penta-1,3-diene. *Ab initio* calculations of the activation barriers to proton transfer in nitrogen derivatives have been computed and these values used to show that the proton transfer in pyrazole is formally a [1,5]-hydrogen shift.[235] The novel photochemical rearrangement of 1,3-diaryl-1,2-dihydropentalenes to the 1,5-dihydropentalenes has been viewed[236] as a photo-induced [1,5]-hydrogen shift. Tandem [1,5]-hydrogen and [1,5]-thiomethyl shifts have been invoked[237] to explain the formation of 5-butenylpyrimidones (**138**) from the reaction of 1,3-diazabuta-1,3-dienes (**136**) with butadienylketene (**137**) (see Scheme 55). *trans*-1,2,3,3a,4a,5,6,7-Octaphenyl-3a*H*, 4a*H*-dicyclopenta[*b,e*] [1,4] dithiin has been prepared by thionation of 2,3,4,5-tetraphenylcyclopenta-2,4-dien-1-one. A pathway involving dimerization and subsequent [1,5]-phenyl migration has been proposed[238] for the transformation.



SCHEME 55

The mechanism of the degenerate [5,5]-sigmatropic rearrangements of 5,5a,10,10a-tetrahydroheptalene and (*z, z*)-decatetraene-1,3,7,9 has been explained. A stepwise diradical mechanism has been predicted for both reactions.[239]

Electrocyclic Reactions

Density functional theory and MC-SCF calculations have been applied to a number of pericyclic reactions including cycloadditions and electrocyclizations.[240] It has been established[241] that the transition states of thermally allowed electrocyclic reactions are aromatic. Apparently they not only have highly delocalized structures and large resonance stabilizations, but also strongly enhanced magnetic susceptibilities and show appreciable nucleus-independent chemical-shift values.

The molecular mechanisms for the ring openings of various cyclopropanone systems in the gas phase have been studied[242] at the PM3 semiempirical level and shown to be disrotatory processes, while an experimental study of the stereomutation of 1,1-difluoro-2-ethyl-3-methylcyclopropane has confirmed[243] the predicted preference for disrotatory ring opening and ring closure for this system.

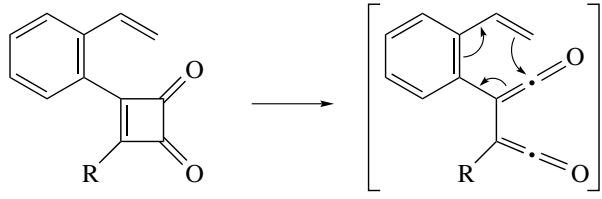
Spin-coupled theory has been used to study the changes that occur in the electronic wavefunction as a system moves along the intrinsic reaction coordinate for the case of the conrotatory and disrotatory pathways in the electrocyclization of cyclobutene to *cis*-butadiene.[244] Against intuitive expectations, conrotatory opening of cyclobutenes was found to be promoted by pressure.[245] *Ab initio* MO and density functional calculations have indicated[246] that the ring opening of the cyclobutene

radical cation follows two competitive pathways. The reported double 1,2-addition of alkenyl, cycloalkenyl and alkynyllithium reagents to squarate esters and subsequent 4π conrotatory ring openings and 8π conrotatory cyclizations has constituted an expedient method for producing polycyclic products of considerable structural complexity.[247] An unprecedented intramolecular cyclization of an intermediate bioketene (**140**) has been invoked[248] to account for the thermal rearrangement of substituted cyclobutanediones (**139**) to substituted naphthofuranones (**141**).

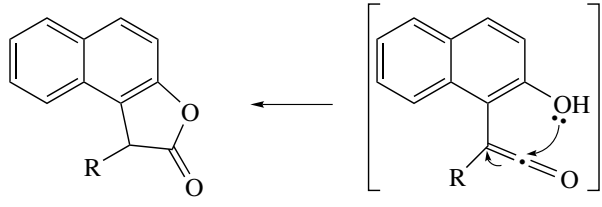
Upon exposure to UV light, α-tropolone methyl ether (**142**), included within chirally modified Y zeolite, has been found to undergo 4π-electron disrotatory electrocyclic ring closure to afford[249] the bicyclic photo-isomer (**143**).

Several 4-aminocyclopent-1-enes have been prepared[250] in two steps from conjugated dienes via the corresponding 2-alkenylcyclopropylamines and their thermal rearrangement.

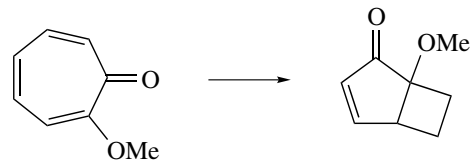
Ketenimines (**144**), generated from α-substituted benzophenone 1-acetamidoethylidenehydrazones with a mixture of triphenylphosphine, carbon tetrachloride and triethylamine in dichloromethane (Appel's conditions), have been used[251] to synthesize a variety of 1,2,4-triazole-fused heterocycles (see Scheme 56). Mechanistically, the



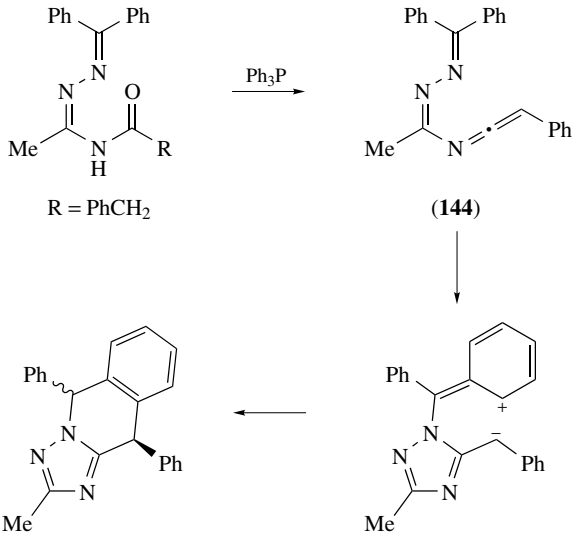
(**139**) (**140**)



(**141**)

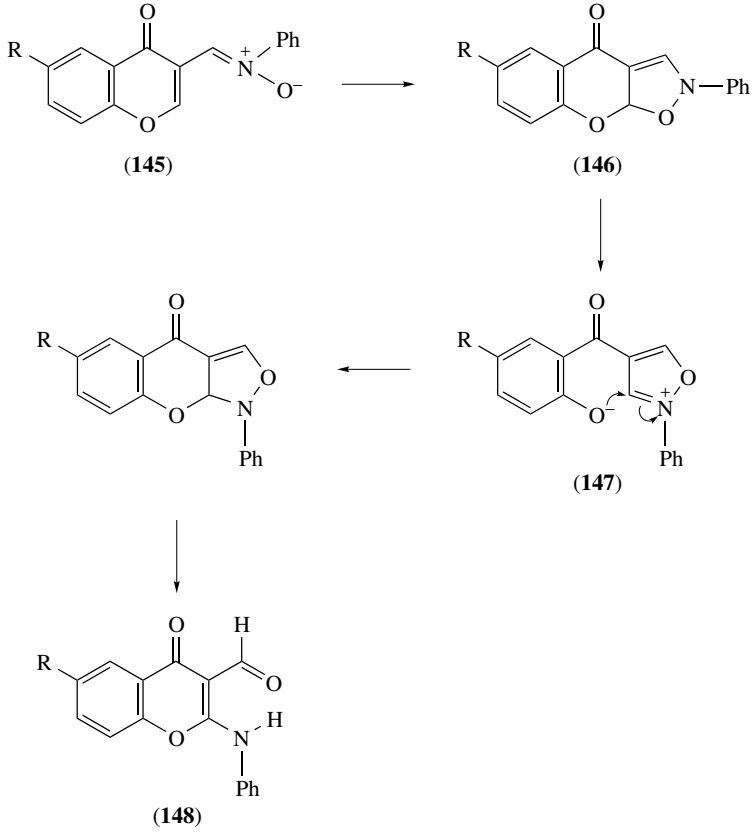


(**142**) (**143**)



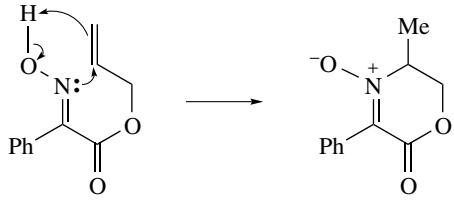
R = $PhCH_2$ (**144**)

SCHEME 56



formation of 2-(*N*-phenylamino)-4-oxo-4*H*[1]benzopyran-3-carboxaldehydes (**148**) as major products from *C*-(4-oxo-4*H*[1]-benzopyran-3-yl)-*N*-phenyl nitrones (**145**) on heating the latter in benzene, has been rationalized[252] in terms of an initial 1,5-electrocyclization to give intermediate (**146**) which is converted into the chromone ring-opened intermediate (**147**) which, after recyclization followed by a [1,5]-hydrogen shift, affords (**148**).

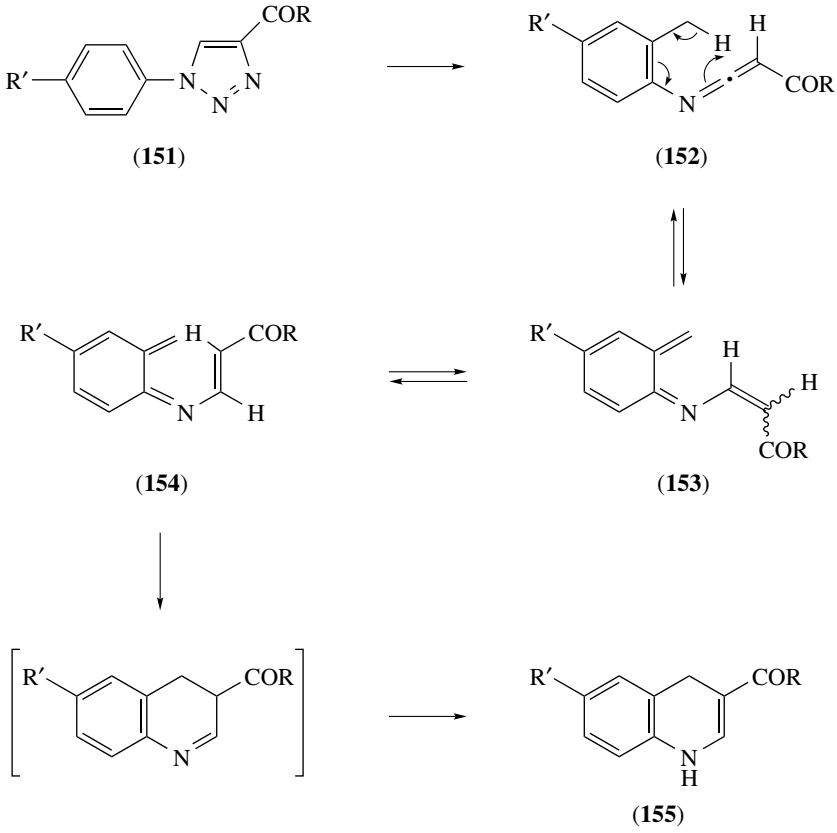
The formation of cyclic nitrones (**150**) from ω-alkenyl oximes (**149**) has been shown to proceed via a concerted pericyclic mechanism.[253] Kinetic and computational studies have provided evidence for the involvement of a novel pseudo-pericyclic electrocyclization in the conversion of *o*-vinylphenyl isocyanates into quinolin-2-ones.[254] Such reactions have also provided evidence of torquoselectivity in a 6π system. Flash vacuum thermolysis of triazoles (**151**) has been found to afford dihydroquinolines (**155**), presumably by generation of α-oxoketenimines (**152**) which can undergo a [1,5]-hydrogen shift to the *o*-quinoid imines (**153**)/(**154**) and subsequent electrocyclization[255] (see Scheme 57).



(**149**) (**150**)

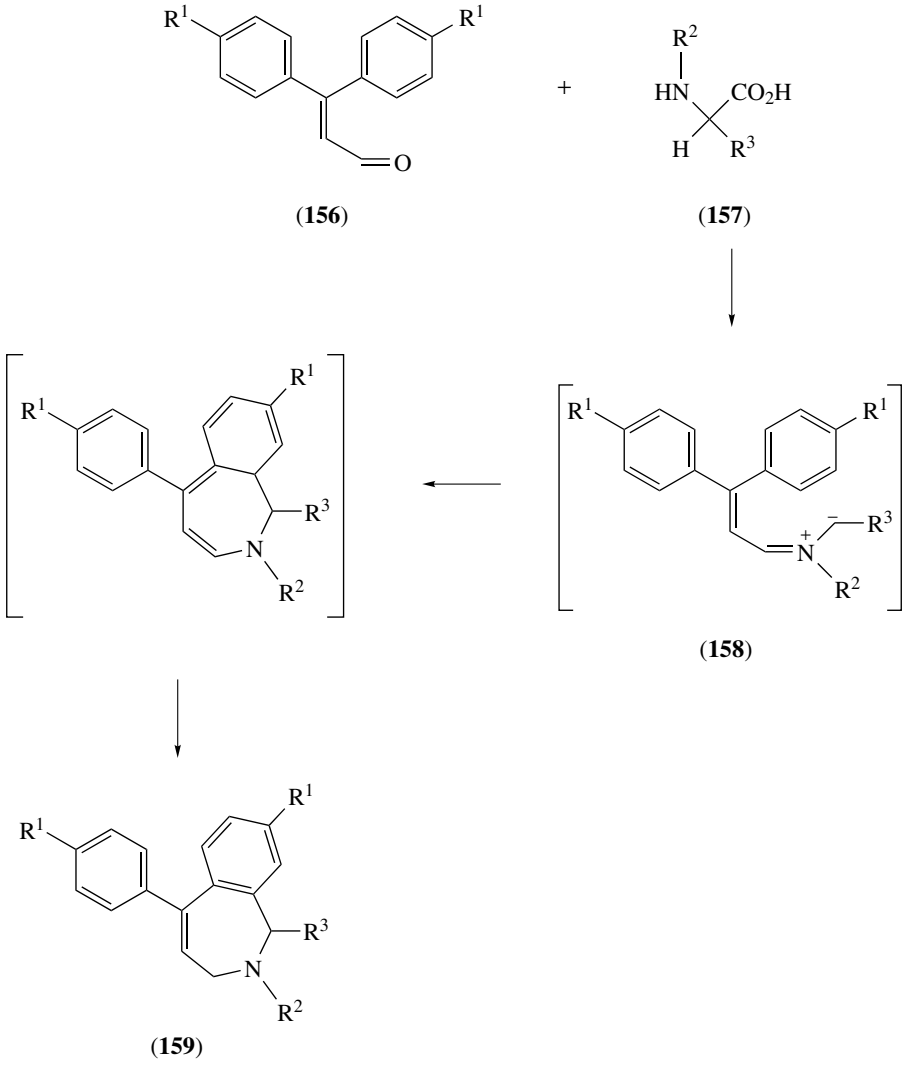
Non-stabilized $\alpha,\beta:\gamma,\delta$-unsaturated azomethine ylides (**158**), generated by the decarboxylation method from 3,3-diarylpropenals (**156**) and secondary amino acids (**157**), have been found[256] to undergo [1,7]-electrocyclization followed by a [1,5]-hydrogen shift, to yield 2,3-dihydro-1*H*-2-benzazepines (**159**).

The intramolecular 4 + 2-cycloaddition of conjugated ynones, e.g. (**160**), has been shown[257] to produce, initially, highly strained heterocyclic allenes (**161**) which undergo an unusual rearrangement leading to polycyclic furans (**162**) (see Scheme 58). The dimeric derivatives of 1,1,2,2-tetraethynylethene, viz. (**163**), have been found to undergo an unexpected rearrangement to a permethylenated cycloocta-1,5-diyne (**164**) in the presence of acid. Formation of (**164**) has been rationalized[258] by assuming a cascade mechanism consisting of electrocyclic or radical reactions. In the first step, thermal cleavage of the carbon–carbon bonds in both dioxolane rings occurs by a conrotatory 12π-electrocyclic ring opening. A formal intramolecular $4\pi + 4\pi$-cycloaddition between the central butatriene units of the intermediate would finally result in the formation of the strained cycloocta-1,5-diyne system. The photochemical reaction of a series of enediynes to yield a cyclization product identical to that which would be expected from a thermal Bergman rearrangement has been reported.[259] Reaction coordinates have been computed[260] for the Bergman cyclization of hex-3-en-1,5-diyne and neutral and protonated 3-azahex-3-en-1,5-diyne.



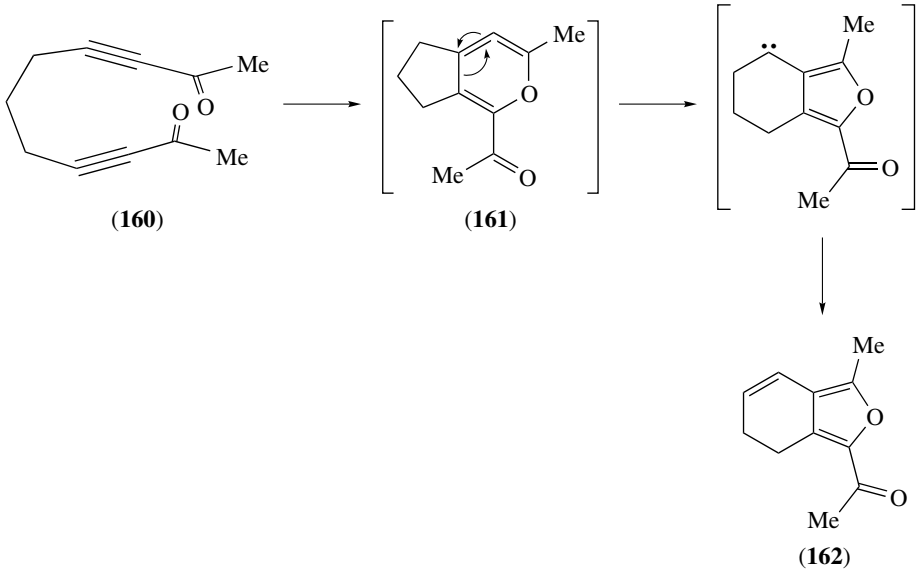
SCHEME 57

The ruthenium-catalyzed Alder ene addition of alkenes and alkynes has provided a powerful new method for the construction of complex organic molecules.[261] The ene reaction between propene and various enophiles has been examined[262] by *ab initio* methods. The transition structures were all found to be cyclic and the reactions found to be concerted. The complex *trans*-[Ru(salen)(NO)(H_2O)]$^+$ has been found to catalyse the ene reaction between activated enophiles and alkenes to yield homoallylic alcohols by a stepwise process.[263] High enantioselectivity has been achieved[264] in the ene reactions of *n*-butylglyoxylate to α-methylstyrene using multi-component titanium catalysts, while bidentate bis(oxazolinyl)Cu(II) complexes have been established[265] as highly selective catalysts for the glyoxylate–ene reaction. Scandium trifluoromethanesulfonate has been found to act as an efficient catalyst for both intra- and intermolecular carbonyl-ene reactions.[266] Not surprisingly, different cyclization products have been obtained in the ene cyclization of 5-methyl-2-(1-methylethyl)-hex-5-enal when different Lewis acids are used.[267] A facile and diastereoselective route to various chiral β-amino acids has been developed[268] using the carbonyl–ene reaction of



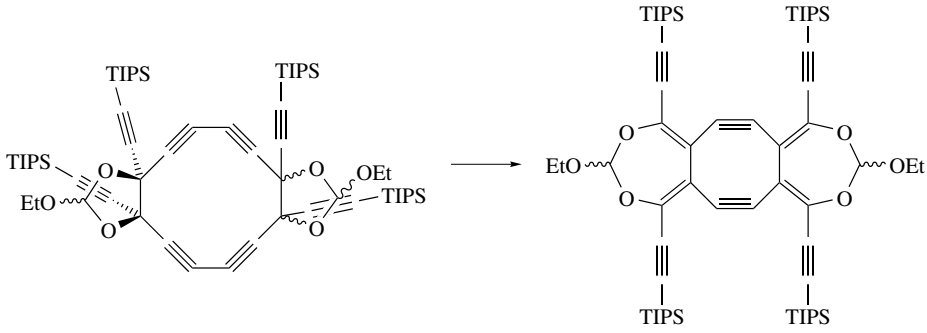
N-tritylaziridine-2-(*S*)-carboxaldehyde. The application of a novel, sequential, trans-acetalation oxonium ene cyclization has delivered[269] a stereoselective synthesis of the *C*-aromatic taxane skeleton, and a combinatorial sequence of the regioselective propiolate–ene, catalytic enantioselective epoxidation and carbonyl–ene cyclization reactions has been used[270] to complete the synthesis of the A-ring of a vitamin D hybrid analogue.

Allenic esters (**165**) have been found[271] to undergo a retro-ene reaction on flash vacuum thermolysis above 800 °C to give unsubstituted vinylketene together with formaldehyde or acetaldehyde (see Scheme 59).

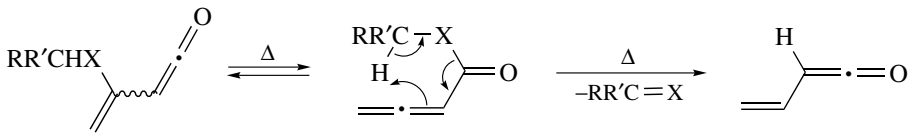


(**160**) (**161**) (**162**)

SCHEME 58



(**163**) (**164**)



(**165**)

X = O or NMe

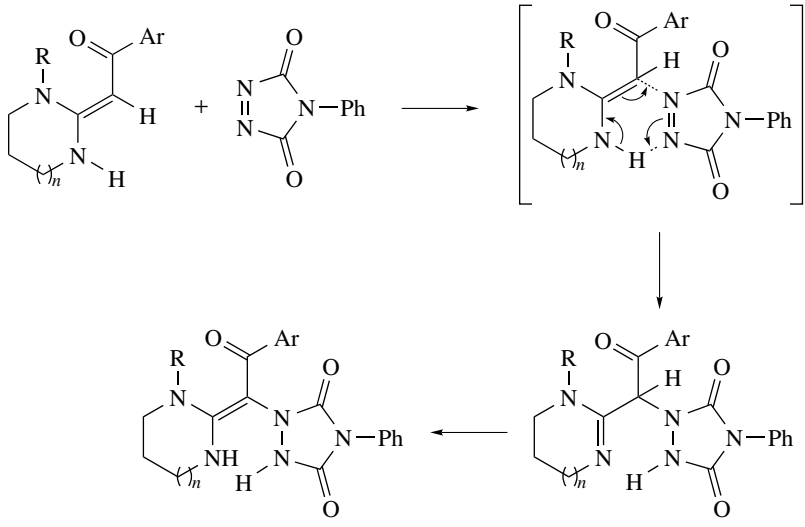
SCHEME 59

A novel stereoelectronic effect rather than intramolecular hydrogen bonding or steric congestion has been shown to determine the *threo*-diastereoselectivity in the ene reaction of singlet oxygen with an electron-poor allylic alcohol and its ethers.[272] The effect of solvent polarity on the photo-oxygenation of 2,4-dimethylpenta-1,3-diene has been studied. The differences observed in the ene and 4 + 2-cycloaddition reactions in different solvents have been explained[273] by competition between a concerted and a perepoxide mechanism. Dramatic diastereoselectivity differences have been observed in the asymmetric ene reactions of triazolinediones and singlet oxygen with chiral 2,2-dimethyloxazolidine derivatives of tiglic acid. These differences have been rationalized[274] in terms of the differences in steric demand of the singlet oxygen and triazolinedione enophiles rather than electronic factors. It has been shown for the first time that the phenyl ring of styrene substrates can dictate the *syn/anti* stereochemistry in their ene reactions with singlet oxygen and triazolinediones. The authors[275] have proposed that a favourable interaction of the enophiles with the phenyl ring directs the orientation of perepoxide or aziridinium imide. Recent studies[276,277] have shown that the ene reactions of triazolinediones with chiral allylic alcohols exhibit high *threo*-diastereoselectivity in non-polar solvents, whereas in polar solvents the diastereoselectivity was shown to decrease substantially. These results support a favourable interaction occurring between the hydroxyl group of allylic alcohols and triazolinediones in the transition state of aziridinium imide formation. This steering effect occurs either between the negatively charged nitrogen during the formation of the aziridinium imide where the triazolinedione is placed *syn* to the hydroxyl, or between the carbonyl group of the triazolinedione and the hydroxyl, in the transition state where the enophile is placed *anti* to OH. These studies have further substantiated the mechanistic equivalence between triazolinedione and singlet oxygen enophiles. Convenient syntheses of 1-deoxy-*neo*-inositol and 1-deoxy-*myo*-inositol have been achieved[278] using ene reactions of singlet oxygen. Heterocyclic ketene aminals bearing a secondary enamine moiety have been found to undergo an efficient aza–ene reaction with 4-phenyl-1,2,4-triazolin-3,5-dione[279] (see Scheme 60).

The diastereofacial selective imine–ene reactions with α-imino esters prepared from (−)-8-phenylmenthyl glyoxylate have provided[280] an efficient entry to the asymmetric synthesis of α-amino acids, and a Lewis acid-mediated intramolecular imine–ene reaction has been used for the key spirocyclization step in a recent synthesis of (−)-perhydrohistrionicotoxin.[281] Asymmetric azo–ene reactions have been effected using the chiral azo–enophile, di-(−)-(1R,2S)-2-phenyl-1-cyclohexyldiazenedicarboxylate.[282]

Ene reactions of Pummerer-type reaction intermediates have been used as key steps in the synthesis of both pellitorine[283] and trichonine.[284]

The effect of ring substituents on the rate constants, deuterium kinetic isotope effects and Arrhenius parameters for ene-additions of acetone to 1,1-diphenylsilane have been explained[285] in terms of a mechanism involving fast, reversible formation of a zwitterionic silene–ketone complex, followed by a rate-limiting proton transfer between the α-carbonyl and silenic carbon. A study[286] of the thermal and Lewis acid-catalysed intramolecular ene reactions of allenylsilanes with a variety of

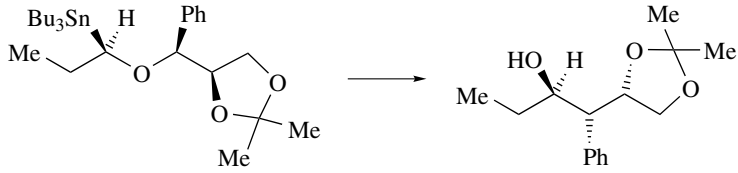


SCHEME 60

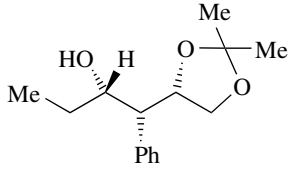
enophiles has shown that, in all cases studied, the cycloaddition reactions were stereoselective. The results of the Lewis acid-catalysed ene reactions of allylic silenes and stannanes with methyl propiolate have been described.[287] They indicated clearly that the chemoselectivity of these reactions was extremely dependent on the identity of the metallic group and the nature of the ene and enophile. Diels–Alder and ene reactions of ethenes $Me_2M{=}C(SiMe_3)_2$ [M = Si, Sn, Ge] have been shown to take place both regio- and stereo-selectively and the results have been explained[288] by the $\pi-\pi^*$ energy differences, the double-bond polarities and the M–C bond energies. A highly diastereoselective synthesis of (−)-erythrodiene has been achieved using an intramolecular Pd-catalysed zinc–ene reaction as the key step.[289] Applications of the phospha–ene reaction to the synthesis of different classes of organophosphorus compounds have been reviewed.[290]

Anionic Rearrangements

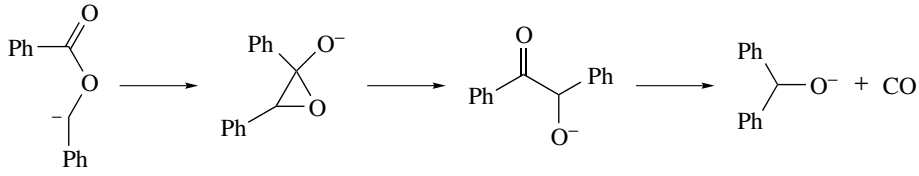
The mechanism of [1,2]-methyl Wittig migration in the free and lithiated anionic methoxymethide model system has been discussed.[291] The study has provided, on the one hand, a picture of the free anion processes taking place in the gas phase and, on the other hand, two extreme descriptions of ionic association relevant to the condensed phase. It has been reported[292] that in the [1,2]-Wittig rearrangement of enantio-defined stannanes such as (**166**), the normal tendency for the α-oxylithium species to undergo an inversion of configuration [see (**166**) → (**167**)] can be suppressed and even overturned by the chelation effect [see (**166**) → (**168**)]. Experimental evidence has been provided[293] to suggest that a cyclization–Wittig-type [1,2]-migration best accounts for the rearrangement of deprotonated benzyl benzoate to the diphenylmethoxide anion and carbon monoxide. Thus cyclization of $PhCO_2^-CHPh$ yields deprotonated



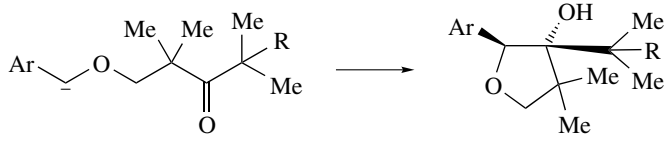
(**166**) (**167**)



(**168**)



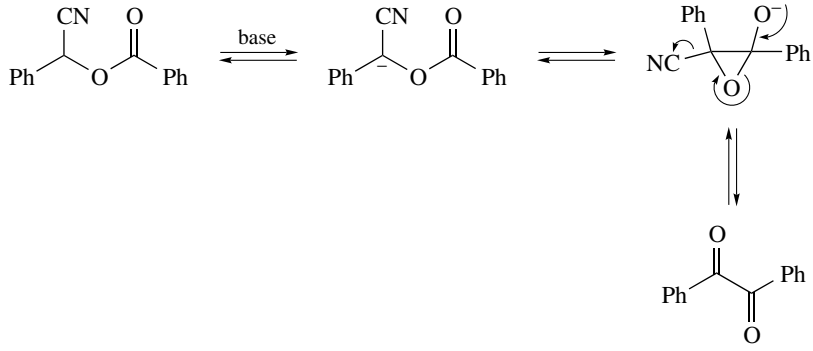
SCHEME 61



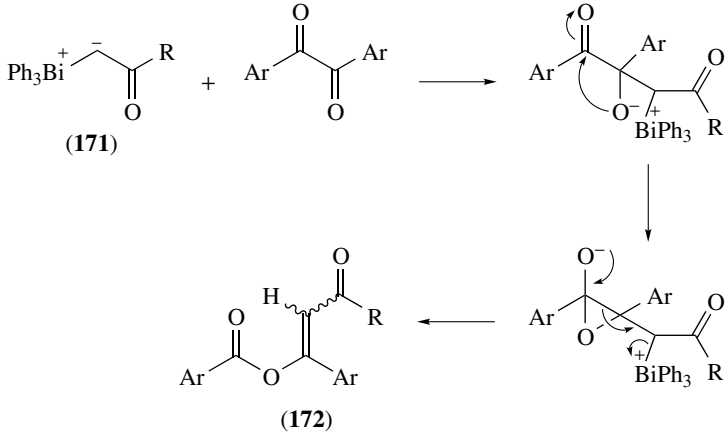
(**169**) (**170**)

diphenylhydroxyoxirane which undergoes ring opening to afford deprotonated deoxybenzoin which then dissociates via an anionic [1,2]-Wittig-type rearrangement (see Scheme 61).

It has been shown[294] that the α-carbanion of an alkyl benzyl ether such as (**169**) undergoes nucleophilic addition to a carbonyl moiety existing in the same molecule [see (**170**)] without Wittig rearrangement or protophilic decomposition. The mechanism shown in Scheme 62 has been postulated[295] to account for the formation of benzil from *O*-benzoylbenzaldehyde cyanohydrin in a reversible base-catalysed reaction. Triphenylbismuthonium 2-oxoalkylide (**171**), generated *in situ* from the corresponding oxonium salt and base, has been shown to react with 1,2-diketones to yield *O*-aroyl enolates of unsymmetrical 1,3-diketones (**172**) via a carbon to oxygen migration of



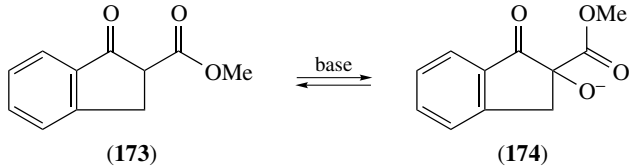
SCHEME 62



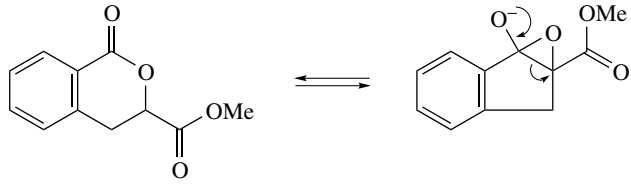
SCHEME 63

the aroyl moiety[296] (see Scheme 63). This type of carbon–carbon bond construction based on 1,2-carbonyl migration is unprecedented in ylide chemistry. It has been proposed[297] that the formation of products such as (**176**) from the oxidation of 1,3-dicarbonyl compounds of the type (**173**) with (camphorylsulfonyl)oxaziridines involves initial generation of the α-alkoxy-β-keto ester anion (**174**) which rearranges via the alkoxy epoxide (**175**). Wasabidienone A (**178**) has been synthesized[298] via a novel rearrangement reaction of an acyl group from carbon to the β-hydroxy oxygen on a cyclohexadienone ring (**177**).

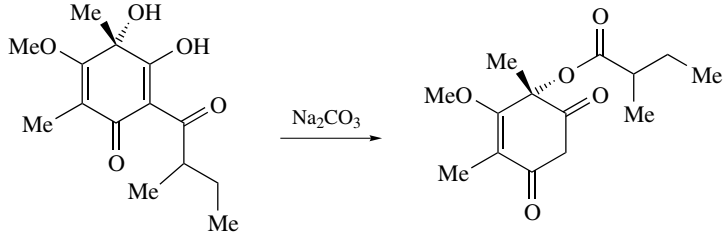
The formation of fluorinated α-hydroxy-β-imino esters (**180**) by treatment of fluorinated imino ethers (**179**) with lithium 2,2,6,6-tetramethylpiperidide has been reported.[299] A possible explanation for this interesting intramolecular rearrangement is proposed in Scheme 64. Acyclic imides derived from primary benzylic amines and amino acid esters have been found to undergo a novel nitrogen to carbon acyl migration via a base-generated carbanion to yield the corresponding α-amino



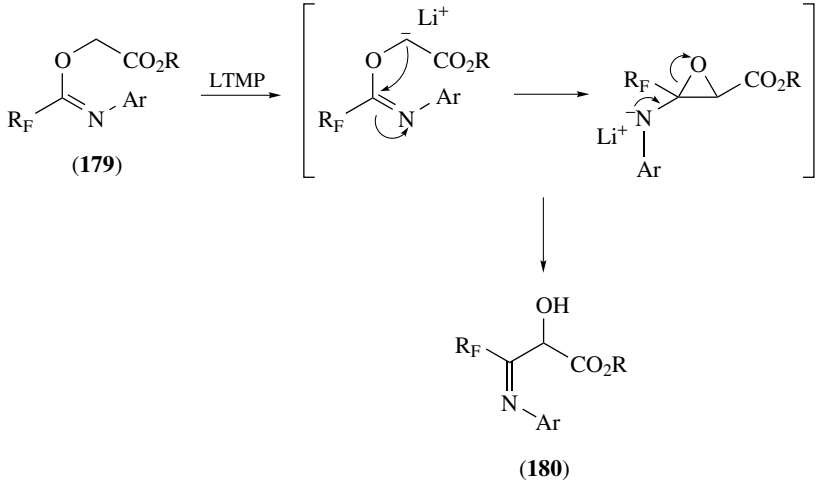
(**173**) (**174**)



(**176**) (**175**)

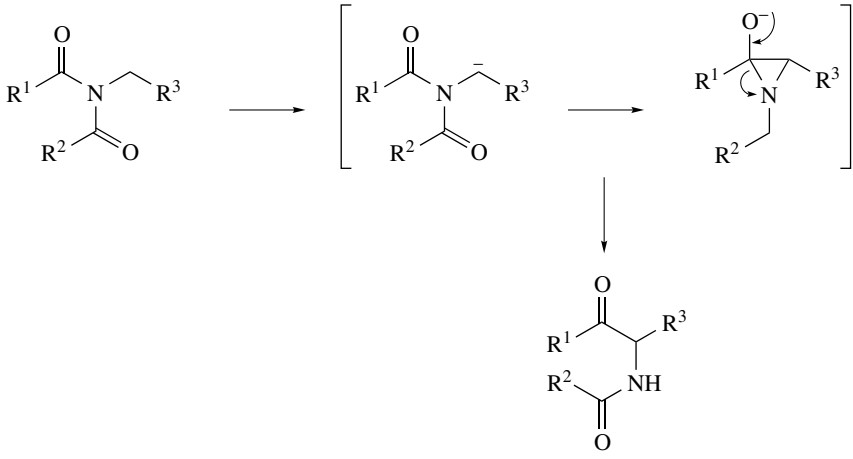


(**177**) (**178**)

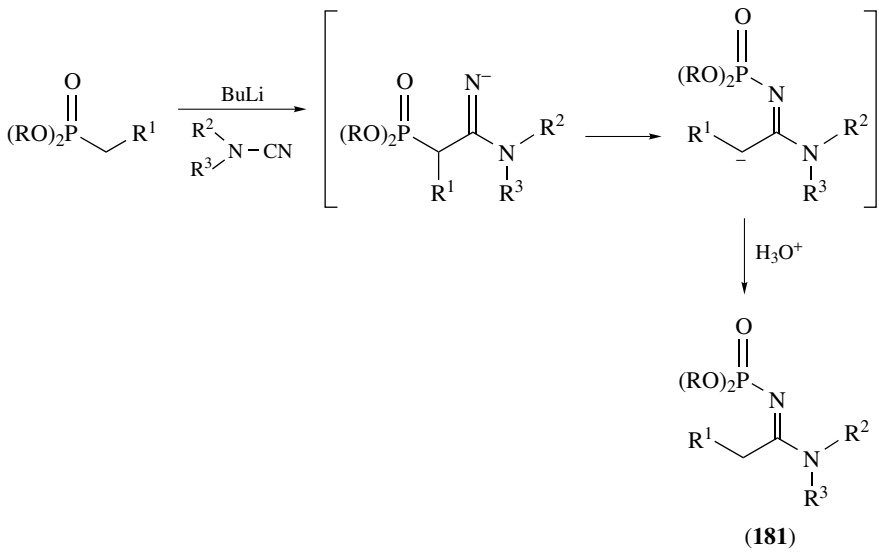


(**179**) (**180**)

SCHEME 64



SCHEME 65



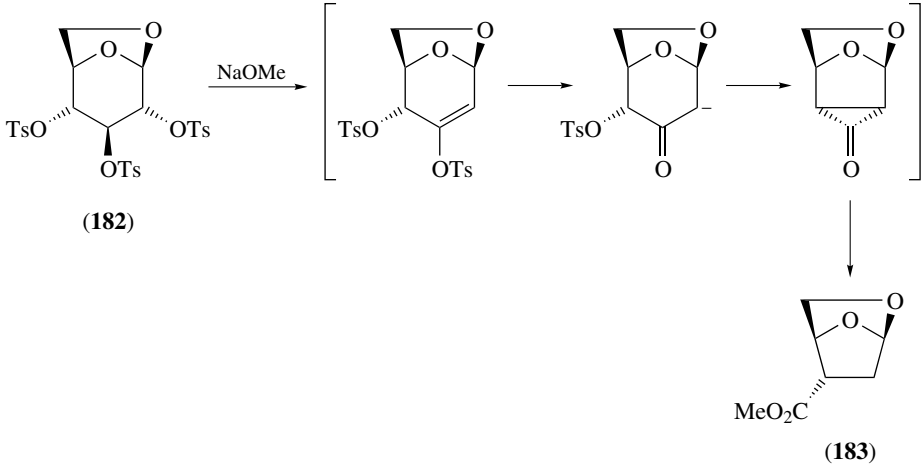
(**181**)

SCHEME 66

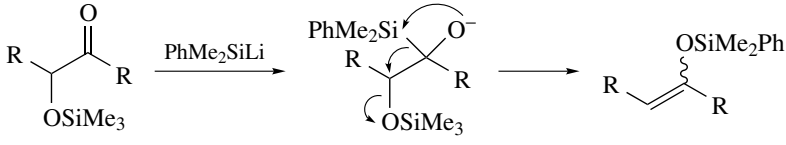
ketones.[300] A possible mechanism for the transformation is outlined in Scheme 65. A new type of [1,2]-rearrangement of a toluenesulfonyl group from nitrogen in azoles to the neighbouring carbon has been initiated[301] by treatment with *n*-butyllithium. *N′*-Phosphorylated amidines (**181**) have been synthesized[302] by the reaction of lithiated alkyl phosphonates with *N,N*-dialkylcyanamide via an unprecedented carbon-to-nitrogen migration of the phosphoryl group (see Scheme 66). A novel electrophilic rearrangement involving the migration of an alkoxycarbonyl group from carbon to a nitrogen anionic centre has been reported.[303]

Recent applications of the Favorskii rearrangement have been reviewed.[304] A PM3 semiempirical study has been undertaken of the molecular mechanism for the Favorskii rearrangement of α-chlorocyclobutanone. The results indicated that, although two competitive reaction mechanisms can exist, viz. the semibenzilic acid and the cyclopropanone rearrangement, the former appears to be the energetically favorable pathway *in vacuo* and in solution.[305] Electrochemically reduced polyhalo ketones have been found to react with amines and phenols to afford the corresponding α,β-unsaturated amides and esters in an electrochemically induced Favorskii rearrangement.[306] A variety of iridolactones have been synthesized using a stereoselective Favorskii rearrangement as the key step.[307] α-Hydroxy ketones have been prepared from the corresponding α-nitro ketones under aqueous basic conditions by a novel transformation which has been explained[308] by a double S_N2 reaction which proceeds via a Favorskii-like cyclopropanone intermediate. 3-Methoxycarbonyl-1,5-anhydro-β-D-*erythro*-pentafuranose (**183**) has been obtained[309] by a tandem elimination–Favorskii rearrangement by treating 2,3,4-tri-*o*-tosyl-1,6-anhydro-β-D-glucopyranose (**182**) with sodium methoxide (see Scheme 67).

Silyl enol ethers have been prepared[310] via a Brook rearrangement from the reaction of phenyldimethylsilyllithium with α-silyloxy ketones (see Scheme 68). The comparison of the rate of the base-catalysed Brook rearrangement in β-substituted



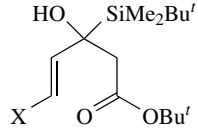
SCHEME 67



SCHEME 68

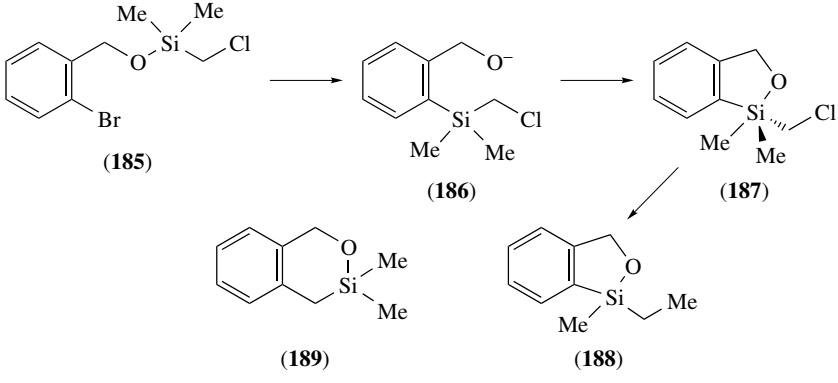
α-silylallyl alcohols (**184**) has been used[311] as a tool for the assessment of the α-carbanion-stabilizing ability of the β-substituent. 3-Trimethylsilylprop-2-yn-1-ol has been prepared[312] from 1-trimethylsiloxy-3-bromomagnesiumprop-2-yne by an unusual 1,4-migration of the trimethylsilyl group from oxygen to carbon, and a recent approach to the C(33)–C(38) fragment of amphotericin B and nystatin has involved a retro-(1,4)-Brook rearrangement and the stereoselective manipulation of the resulting allylsilane.[313] Treatment of 3-[(silyloxy)methyl]furans and thiophenes with *n*-butyllithium has provided[314] 2-silylated-3-(hydroxymethyl)furans and thiophenes via an intramolecular 1,4-oxygen to carbon silyl migration, and a new method which involves the regioselective lithiation of various 2-silylated-3-(hydroxymethyl)furans has been described[315] for the preparation of 2,4- and 3,4-disubstituted furan rings. Treatment of chloromethylsilane (**185**) with *t*-butyllithium has been shown to yield oxasilacyclopentane (**188**), believed to arise via rearrangement of γ-oxidosilane (**186**), followed by methyl migration.[316] Aryl migration would have given oxasilacyclohexane (**189**). The preference for methyl migration in (**185**) suggests that migration is favoured by an apical position of the migrating group in a trigonal bipyramid intermediate (**187**).

Recent applications of the Ramberg–Bäcklund rearrangement to the synthesis of bioactive target molecules have been reviewed.[317] Under Ramberg–Bäcklund conditions, *exo*-6-bromo-*syn*-7-bromo(chloro)methylsulfonyl-*endo*-6-phenylbicyclo[3.1.1]-heptane has been shown to yield *anti*-6-hydroxy-7-methylene-*syn*-6-phenylbicyclo-[3.1.1]heptane along with 3-oxa-2-phenyl-5-thiatricyclo[4.4.0.0^{2,7}]decane S,S-dioxide, the product of an unusual heterocyclization.[318] In contrast to trichloromethyl sulfoxides which undergo base-induced β-elimination of chloroform to produce sulfines, the corresponding sulfones have been found to undergo an unusually

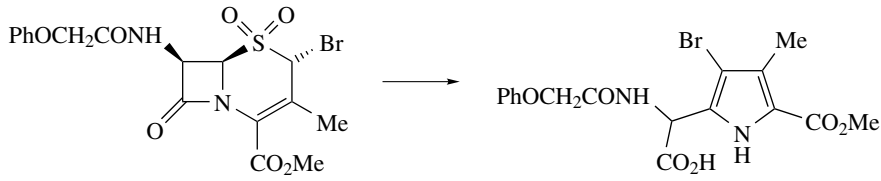


(**184**)

X = SPh, $SiMe_3$



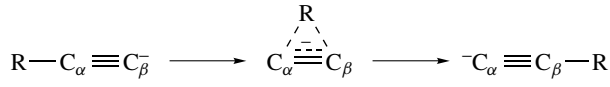
(**185**) (**186**) (**187**) (**189**) (**188**)



(**190**) (**191**)

facile Ramberg–Bäcklund rearrangement with the formation of dichloromethylene products.[319] A new route to *exo*-glycals, which starts from *S*-glycoside dioxides and utilizes a variant of the Ramberg–Bäcklund rearrangement has been described.[320] An unusual Ramberg–Bäcklund-like rearrangement followed by bromination has been invoked[321] to explain the formation of a bromopyrrole derivative (**191**) from α-bromocephem sulfone (**190**) in acetonitrile solution.

Density functional theory has been used to study the rearrangement of the fulminate anion to the cyanate anion. The study has shown that the transformation proceeds via an oxazirinyl anion intermediate.[322] The activation barriers of the 1,2-migrations of various groups (R) in acetylide anions [(**192**) → (**193**)] have been calculated[323] with *ab initio* methods. The barrier for the rearrangement was found to depend on the capability of R to form a hypervalent-type bonding for which its ability to accomplish negative hyperconjugation as well as its polarizability are important. The carbanionic ring enlargement of (halomethylene)cyclobutanes to 1-halocyclopentenes has been extended to the fluoro analogues. Experiments with labelled substrates have shown that, in general, the larger the halide and the higher the reaction temperature, the greater the preference for double migration over single migration as a mechanistic pathway.[324] Chemical evidence has been obtained[325] for the first time to support a cyclopropane ring migration on the periphery of a cyclic polyenide, during the butyllithium-mediated rearrangement of tricyclo[5.3.1.$0^{1,7}$]undeca-2,4,9-triene to tricyclo[6.3.0.$0^{1,3}$]undeca-5,7,9-triene, the sole product of the reaction.



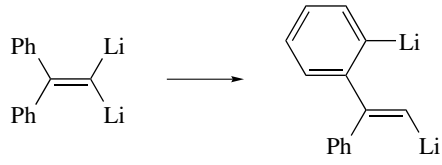
(**192**) (**193**)

A recent study has indicated[326] that the skeletal rearrangement step in the B_{12}-catalysed isomerization of methylmalonyl-CoA to succinyl-CoA occurs not by a radical pathway but by an anionic or organocobalt pathway. A computational study of the isomerization of allyl alcohol into homoallyl alcohol by lithium amide has pointed to[327] a process proceeding via a transition state in which the proton is half transferred between carbon and nitrogen in a hetero-dimer. 1,1-Dilithio-2,2-diphenylethene (**194**), accessible from 1,1-dibromo-2,2-diphenylethene by double bromine–lithium exchange, has been found[328] to undergo an intramolecular rearrangement to (*E*)-1-lithio-2-(2-lithiophenyl)-2-phenylethene (**195**), while the intermolecularity of

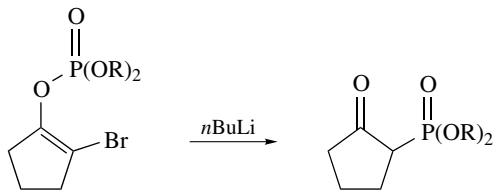
the rearrangement of 3,4-dilithio-2,5-dimethylhexa-2,4-diene to the cross-conjugated 2,5-dimethylhexadienediyl anion has been established.[329]

A new strategy has been developed[330] for the preparation of β-keto-phosphonates (**197**) via a halogen metal exchange-induced 1,3-phosphorus migration of 2-bromovinyl phosphates (**196**). The *ortho*-directing properties of the (aryloxy)tetrazole functionality, and the subsequent anionic 1,3-migration of *ortho*-lithiated (aryloxy)tetrazoles (**198**) to provide 5-(hydroxyaryl)-1-phenyl-1*H*-tetrazoles (**199**) have been demonstrated for the first time.[331] It has been proposed[332] that the base-catalysed rearrangement of 3-halocoumarins to benzofuran-2-carboxylic acids proceeds by rate-determining fission of the carbon–halogen bond following formation of a relatively unstable carbanion intermediate formed by intramolecular nucleophilic attack on the vinyl group by the phenoxide anion (see Scheme 69).

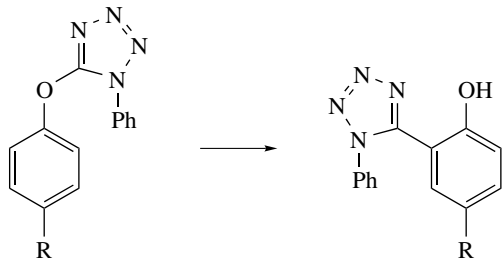
An ^{18}O-labelling investigation of the oxygen to sulfur transposition in the base-catalysed rearrangement of *o*-benzoyl-*N*-(diphenylphosphinothioyl)hydroxylamine (**200**) to (**201**) has been undertaken.[333] The labelling results are outlined in Scheme 70 although further evidence is required to substantiate the mechanism



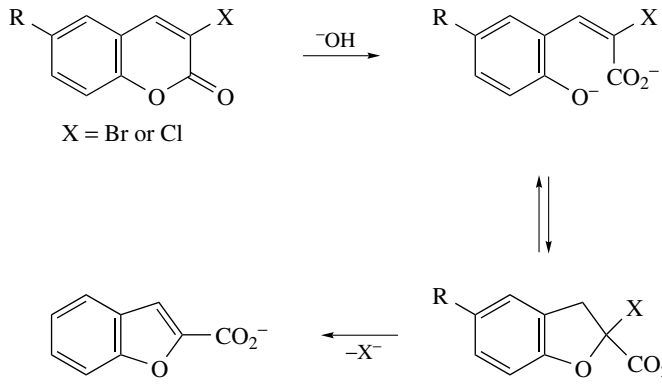
(**194**) (**195**)



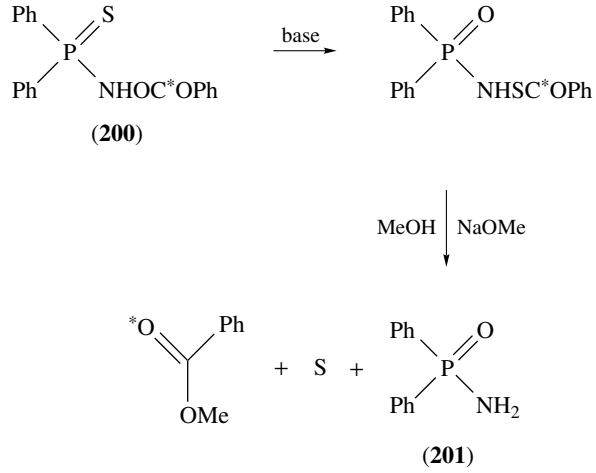
(**196**) (**197**)



(**198**) (**199**)



SCHEME 69

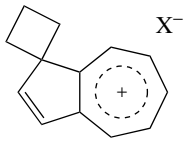


SCHEME 70

of this unusual rearrangement. The *o*-mesyloxime derivatives of ring- and side-chain-substituted 3-phosphonomethylcyclohexenones have been found to undergo a basic aluminium oxide-promoted Neber rearrangement to yield the corresponding vinyl aminocyclohexenonealkylphosphonates, regioselectively.[334] A synthetic route involving a key Neber rearrangement has been described[335] for the preparation of both [1-^{13}C]- and [1-^{15}N]-2-amino-4-phenylbutanoic acids.

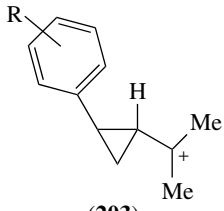
Cationic and Related Rearrangements

A theoretical *ab initio* study of the interconversion of isobutonium ions has been carried out.[336] The 1,1-trimethylene-1*H*-azulenium ion (**202**) has been prepared and its chemical behaviour has been shown[337] to be different from that of its three-membered ring homologue. The solvolysis of 1-[*trans*-2-(*m*- or *p*-substituted phenyl)

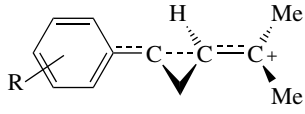


(**202**)

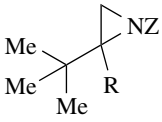
X = BF_4, PF_6



(**203**)

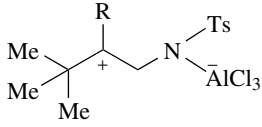


(**204**)

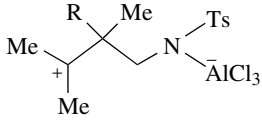


(**205**)

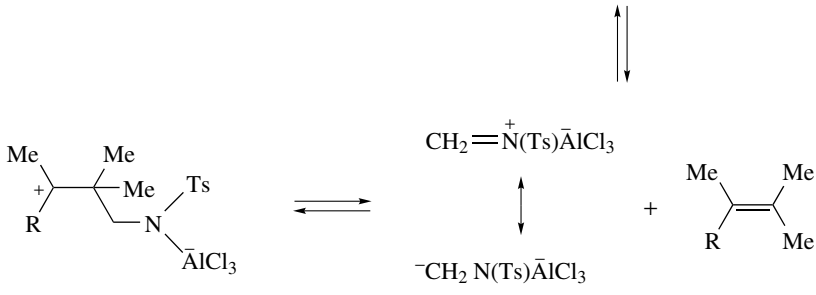
R = Bn, Ph
Z = Ts



(**206**)

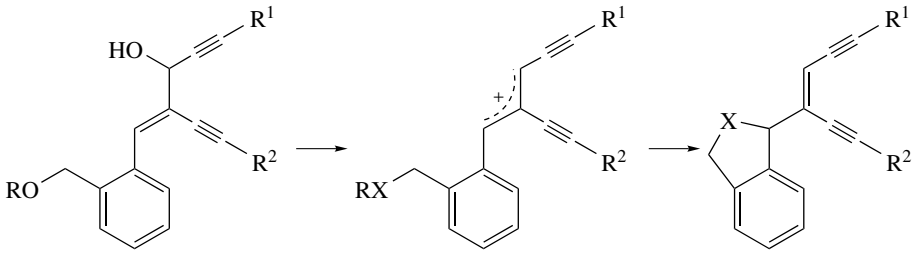


(**207**)

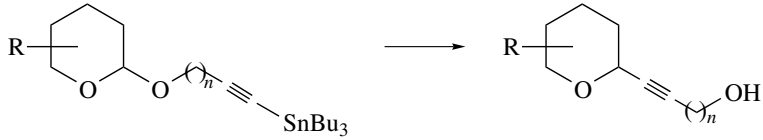


(**209**) (**208**)

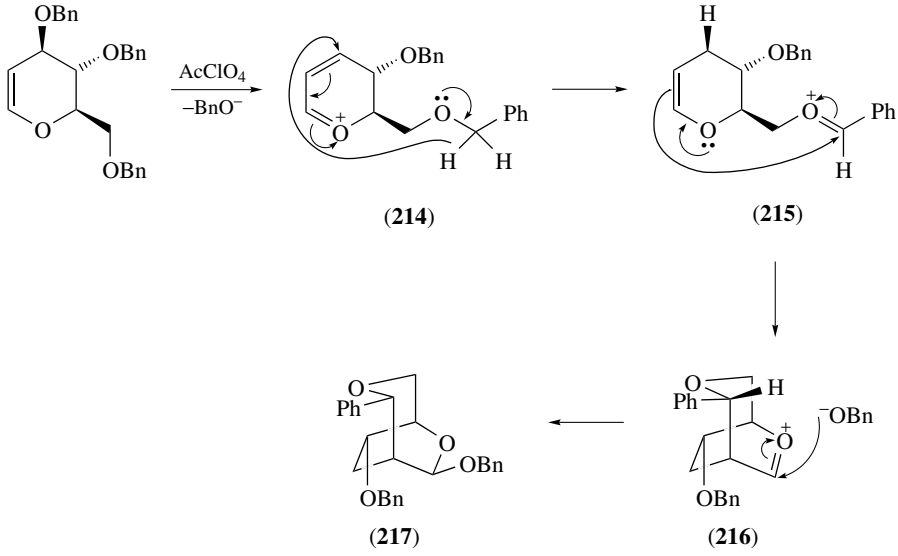
cyclopropyl]-1-methylethyl *p*-nitrobenzoates in 80% aqueous acetone has been shown to proceed via two independent reaction pathways.[338] One intermediate is the correspondent cyclopropylmethyl cation (**203**) and the other is the homoallylic cation (**204**). Aluminium-induced ring cleavage of 2-*t*-butyl-1-tosylaziridines (**205**) has been shown to yield a number of products which can be explained by invoking[339] the generation of carbocations (**206**), which on neopentyl rearrangement afford (**207**) whose β-cleavage generates (**208**) and an alkene. The intermediate then recombines with the alkene at either double-bond carbon, resulting in reversal of the cleavage, or in a formal 1,2-shift to give (**209**). The mechanism of the acid-induced racemization and regioisomerization of *o*-methylated (*S*)-*trans*-hex-4-en-3-ol and (*R*)-*trans*-hex-3-en-2-ol has been investigated in the gas phase at pressures high enough to allow complete thermalization of the reaction intermediates. The study[340] has provided a first comparative analysis of the intrinsic factors governing acid-catalysed racemization of optically active alcohols, and suggests the involvement of intramolecular



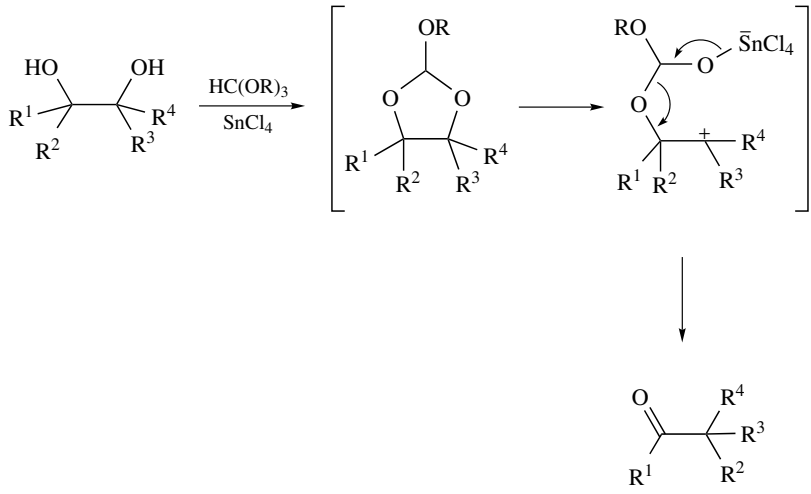
SCHEME 71



processes and the intermediacy of two distinct hydrogen-bonded complexes, wherein the CH_3OH molecule is coplanarly coordinated to the in-plane hydrogens of the 1-methyl-3-ethylallyl moiety. A good example of the control of regiochemistry associated with nucleophilic addition to allylic cations has been demonstrated.[341] Thus the regio-controlled allylic rearrangement of substrates such as (**210**) has proved successful in the synthesis of a number of 2,5-dihydro-2-benzofuryl-*cis*-enediynes (**211**; X = O) and their sulfur analogues (**211**; X = S) (see Scheme 71). Stereo-controlled routes to 2,3-dihydro-4*H*-pyran-4-ones by the Hg(II)-catalysed rearrangement of 1-alkynyl-2,3-epoxy alcohols in acidic media have been reported.[342] A general method for the introduction of carbon-linked substituents adjacent to the heteroatom in pyran ring systems via the Lewis acid-mediated oxygen to carbon rearrangement of a variety of different anomerically linked carbon-centred nucleophiles has been described. Thus treatment of alkynyl tributylstannane tetrahydropyranyl (and tetrahydrofuranyl) ether derivatives such as (**212**) has been found to effect an efficient anomeric oxygen to carbon rearrangement[343] leading to carbon-linked alkynol products (**213**). A further extension of this methodology, encompassing silyl enol ethers as the anomerically linked carbon nucleophile has also been reported,[344] and the strategy has been used to achieve a total synthesis of (+)-goniodiol.[345] An unprecedented 1,6-hydride shift has been observed[346] during acetyl perchlorate treatment of tri-*O*-benzyl-D-glucal (see Scheme 72). Formation of the observed product (**217**) has been rationalized via initial generation of the conjugated oxacarbenium ion (**214**). An intramolecular 1,6-hydride shift then regenerates the glycal producing a benzylic oxacarbenium ion (**215**). Cyclization through attack of the vinyl ether affords, after trapping of the oxacarbenium ion (**216**) with benzyl alcohol, the observed acetal (**217**). The acid-catalysed rearrangement of 1-hydroxy-2,3,4,4a-tetrahydro-9*H*-xanthen-9-ones has been shown



SCHEME 72

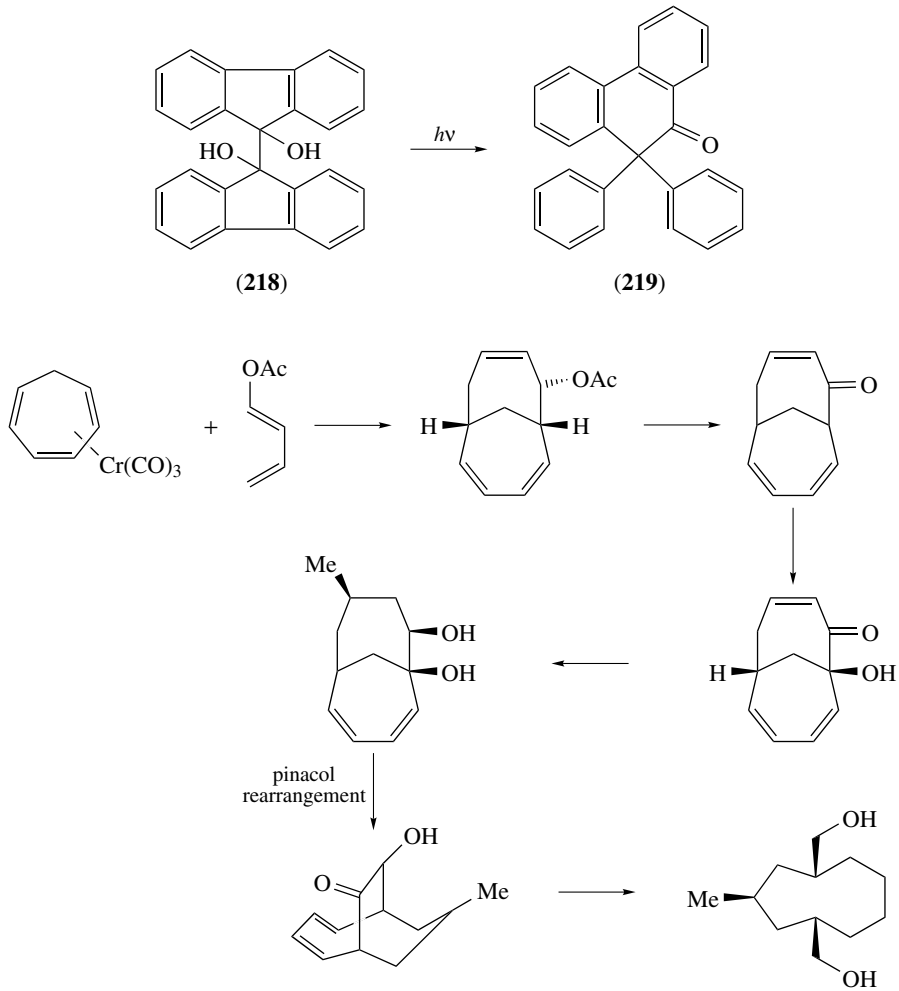


SCHEME 73

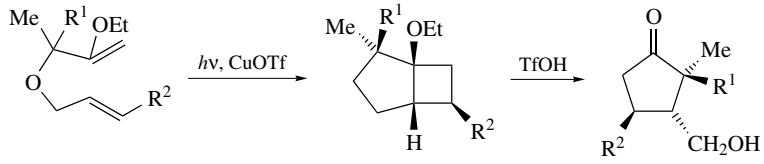
to yield 1-alkoxy- or 1-alkylidene-1,2,3,4-tetrahydro-9*H*-xanthen-9-ones and/or 3,4-dihydro-9*H*-xanthen-9-ones, depending on the conditions employed.[347]

The MNDO method has been employed[348] to study the acid-catalysed rearrangement of propylene 1,2-glycol. Propanaldehyde was found to be the major product with a small amount of acetone also being produced. The solid-state pinacol rearrangement of 1,1,2-triphenylethane-1,2-diol has been performed over various solid

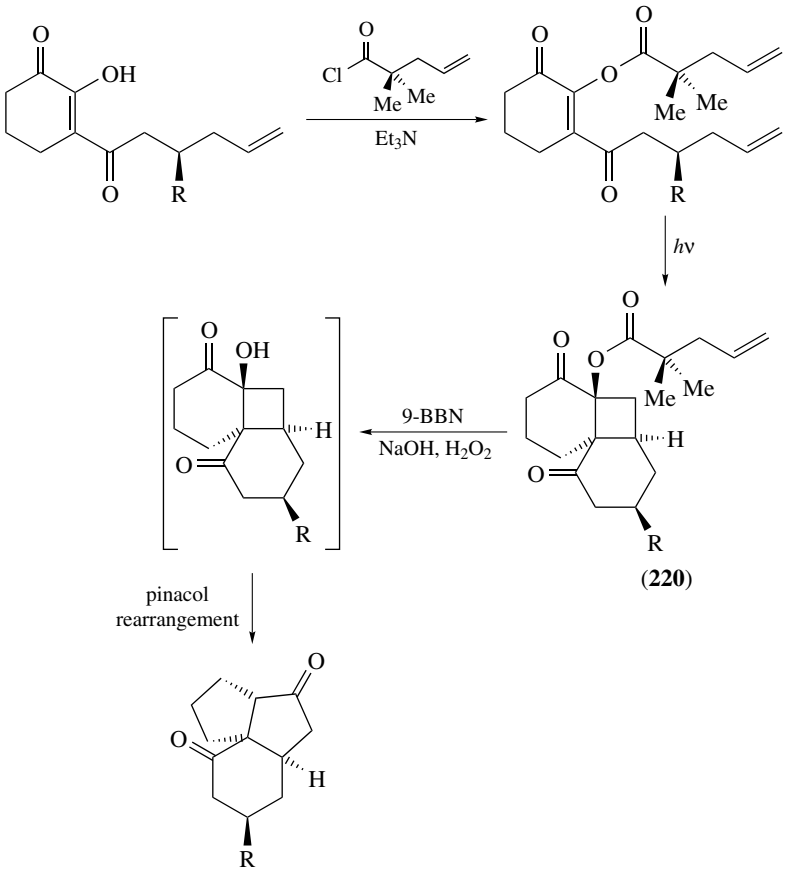
acids,[349,350] and pinacol has been converted into pinacolone and 2,3-dimethylbuta-1,4-diene at relatively mild temperatures over metal-substituted aluminophosphate molecular sieves.[351] An efficient pinacol rearrangement, mediated by trialkyl orthoformate, has been developed[352] (see Scheme 73). It has been shown[353] that a pinacol rearrangement occurs during photo-excitation of 9, 9′-bifluorene-9, 9′-diol (**218**). The reaction proceeds via initial C−O bond heterolysis to give a substituted 9-fluorenyl cation, which undergoes rearrangement and deprotonation to yield spiro[9*H*-fluorene-9, 9′(10′-OH)phenanthren]-10′-one (**219**). A novel chromium(0)-promoted $6\pi-4\pi$-cycloaddition–pinacol rearrangement strategy that delivers substituted nine-membered carbocycles with complete control of substituent stereochemistry has been described,[354] as shown in Scheme 74. An interesting stereo-controlled approach to highly substituted



SCHEME 74

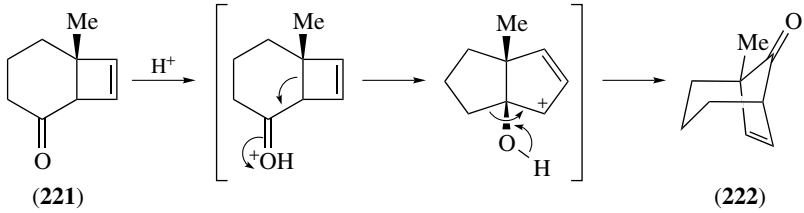


SCHEME 75

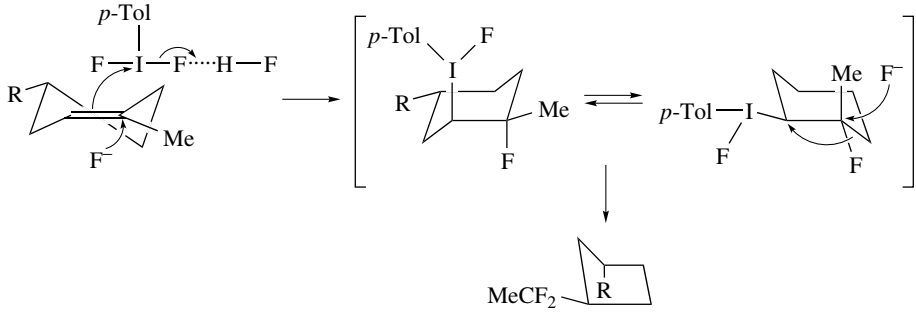


SCHEME 76

cyclopentanones[355] has involved as a key step the stereoselective copper(I)-catalysed photo-cycloaddition of dienes followed by a stereospecific pinacol–pinacolone rearrangement of the resulting cyclobutane derivative (see Scheme 75). A novel vinyl pivalate protecting group, which can be removed either oxidatively or reductively as dictated by the sensitivity of the molecule in question, has been developed. It has been exploited[356] to effect a novel pinacol-type rearrangement of intramolecular photo-cycloadducts such as (**220**) in high yield (see Scheme 76).



SCHEME 77

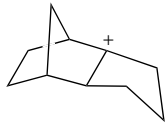


SCHEME 78

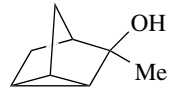
Mono- and bi-cyclic cyclopentanes, known precursors of variety of sesquiterpenes, have been prepared[357] by the acid-catalysed rearrangement of 1-methylcyclobutylmethanols. An acid-catalysed rearrangement (see Scheme 77) has been found to afford a practical method for converting a bicyclo[4.2.0]octene system (**221**) into a bicyclo[3.2.1]octene framework (**222**) in a recent synthesis of verrucarol.[358]

The thallium trinitrate-mediated ring contraction of *trans*-decal-2-ones has opened up a new route to the hydrindane system,[359] and fluorinative ring contraction of cyclic alkenes to afford difluorocycloalkanes has been induced by iodotoluene difluoride and Et_3N–HF. A possible mechanism[360] is shown in Scheme 78. The double bond of the cyclohexene ring is attacked by iodotoluene difluoride activated by HF from the axial direction, followed by the addition of a fluoride ion from the *trans* direction. Reductive elimination of iodotoluene from the resulting adduct, ring contraction and the addition of the fluoride ion to the carbocation stabilized by fluorine then take place to give the ring-contracted difluorinated product.

The reaction of different substituted 2-norbornanones with triflic anhydride in the presence of nitriles has been carried out in order to study the factors that influence the different reaction possibilities of 2-norbornyl carbocations.[361] The chemistry of 2-norbornyl cations with spiro-annellated cyclobutane rings has been found to deviate strongly from that of the cyclopropane analogues.[362] A cyclobutane ring spiro-annellated to the 6-position does not undergo ring expansion, whereas a cyclopropane ring does. On the other hand, a cyclobutane ring spiro-annellated to the



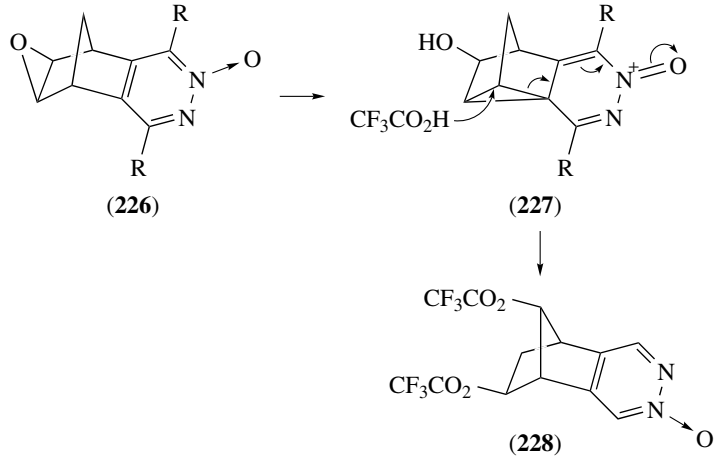
(**223**)



(**224**)

(**225**)

3-position expands readily giving rise to a uniquely *endo*-selective tertiary cation (**223**), whereas an analogously positioned cyclopropane ring remains intact. The main product of the acid-catalysed hydrolysis of 3-methyl-3-nortricyclanol (**224**) has been identified[363] as *endo*-2-methyl-exo,exo-norbornane-2,5-diol (**225**). Acid hydrolyses of 2-*exo*-arylfenchyl alcohols have been found to afford the corresponding cyclofenchones as the kinetic products. These on prolonged treatment with acid are converted into Wagner–Meerwein products via equilibration with the stabilized fenchyl carbocations. These stabilized, sterically unhindered carbocations are proposed to react with water to give 2-*endo*-arylfenchyl alcohols that are stereoelectronically set up for a Wagner–Meerwein rearrangement. The presence of *ortho* substituents on the aryl ring hinders the Wagner–Meerwein rearrangement through decreased resonance stabilization of the carbocation and steric encumbrance to attack by external nucleophiles. However, when the *ortho* substituent itself is a nucleophile, the barrier to Wagner–Meerwein rearrangement is overcome and the authors[364] have suggested that this is due to internal trapping of the carbocation from the *exo*-side to give a reactive intermediate that is stereoelectronically predisposed to concerted bond migration. Epoxide (**226**), on treatment with trifluoroacetic acid, has been found to undergo a regioselective ring opening, followed by a Wagner–Meerwein-type rearrangement, to give the 6,9-bis(trifluoroacetoxy) derivative (**228**). The intermediacy of the 2*H*-pyridazinium ion (**227**) has been invoked[365] for the transformation. The possibility of the intervention of a 2*H*-pyrazinium ion to account for the formation of the skeletally



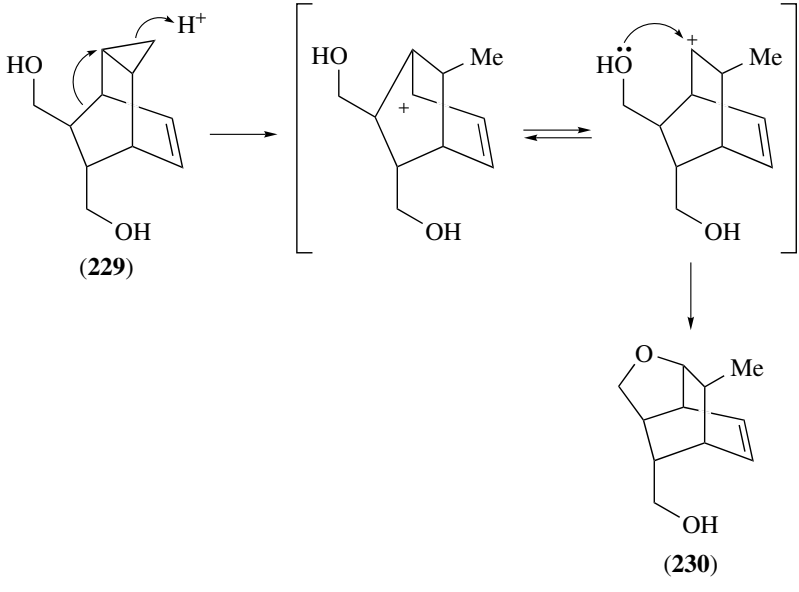
(**226**)

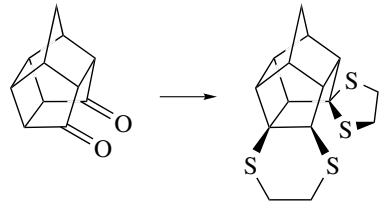
(**227**)

(**228**)

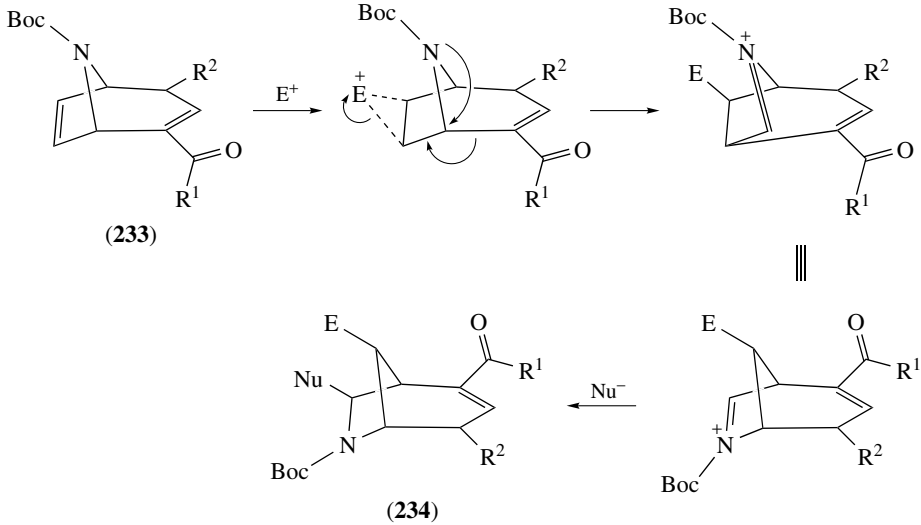
rearranged products, observed during the reaction of norbornadiene-fused pyrazines and their benzo derivatives with bromine, has also been discussed.[366] A recent study[367] has shown that oxabicyclo[2.2.1]norbornadienes, when reacted with Lewis acids, are rearranged to 6-hydroxyfulvenes or 4-phenylphenols. The course of the reaction, which is highly selective, was found to depend exclusively on the nature of the Lewis acid used.

A new cationic rearrangement of a dibenzobicyclo[2.2.2]octadiene alcohol into a fused anthracene has been described.[368] An *ab initio* study of the mechanism of the bromination of benzobicyclooctadiene has been reported.[369] The study proposes that the stereoselectivity of the reaction is best accommodated by an asynchronous concerted electrophilic addition of bromine across carbon atoms 1 and 3 and that it proceeds via an ion-pair transition structure in which the Wagner–Meerwein portion of the reaction has already occurred. The electrophilic-induced opening of a cyclopropyl ring with concerted intramolecular addition of a hydroxymethyl group in a number of tricyclo[3.2.2.0^{2,4}]nonene alcohol derivatives [see (**229**) → (**230**)] has been studied[370] with a view to establishing a procedure for the formation of the tetrahydrofuran ring in the diterpenoid harringtonolide. Acid-catalysed transformations of homodrin and its epoxide have been reported,[371] and several novel products have been obtained from the thermolysis of [4.3.1]propellanes.[372] A novel tetrathio cage compound (**232**) has been obtained[373] in good yield from the Lewis acid promoted reaction of pentacyclo[5.4.0.^{2,6}0.^{3,10}0^{5,9}]undecane (**231**) with excess ethanedithiol. A direct and flexible entry to 6-azabicyclo[3.2.1]octanes (**234**) has been achieved[374] by a facile cation-induced rearrangement of 8-azabicyclo[3.2.1]octa-2,6-dienes (**233**) (see Scheme 79). The unusual isomerization reaction of the sterically congested adamanylideneadamantanes (**235**) has been shown[375] to proceed via a two-step mechanism in





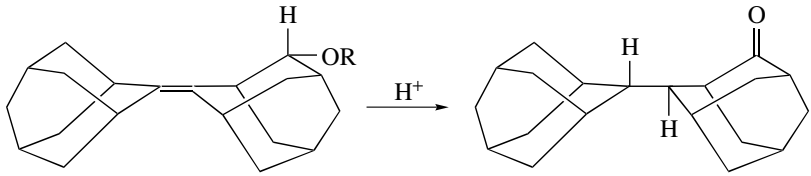
(**231**) (**232**)



(**233**)

(**234**)

SCHEME 79

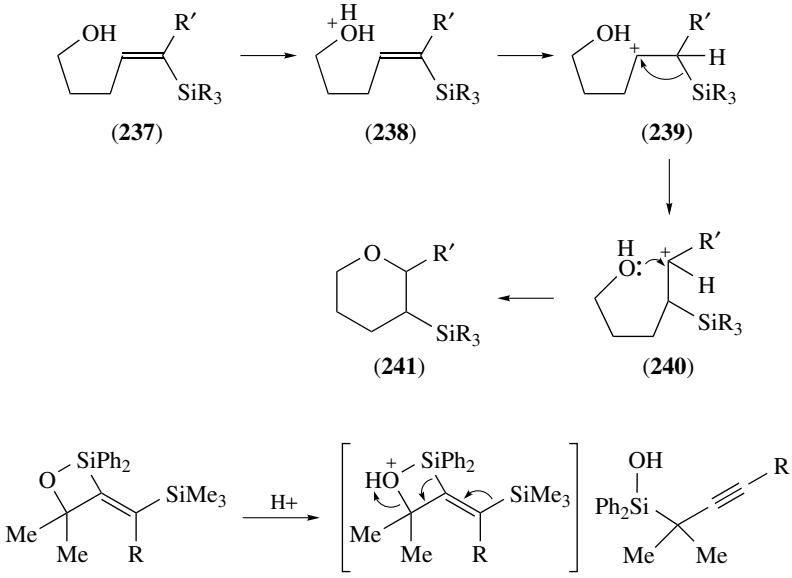


(**235**) (**236**)

R = H or OAc

which protonation of the double bond by an external acid is followed by a rate-determining intramolecular 1,4-hydride transfer to give (**236**). A detailed study of the mechanism of the solvolysis of 2-adamantyl azoxytosylate has been undertaken.[376]

Equilibrium geometries of the nine low-energy isomers in the $SiC_3H_9^+$ system and the transition states for their interconversion have been studied[377] by MO methods. It has been reported[378] that the acid-catalysed cyclization of vinylsilanes (**237**) gives

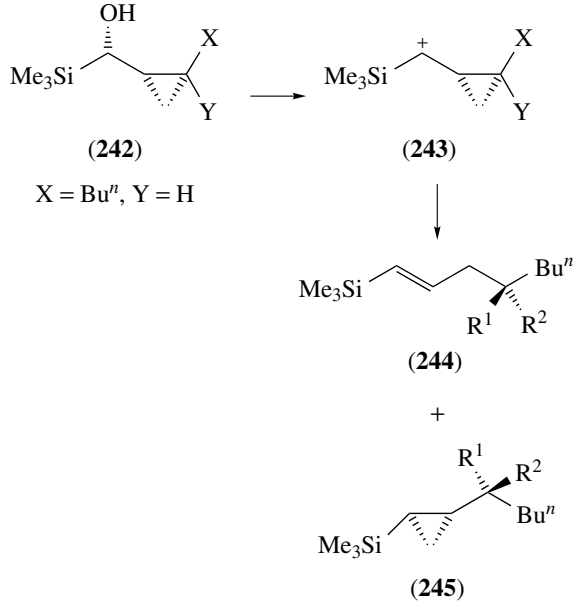


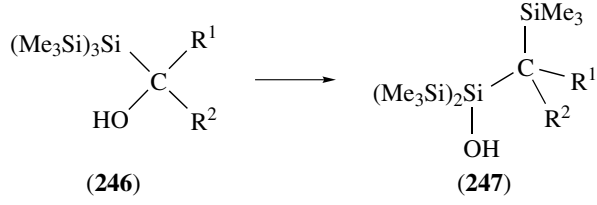
SCHEME 80

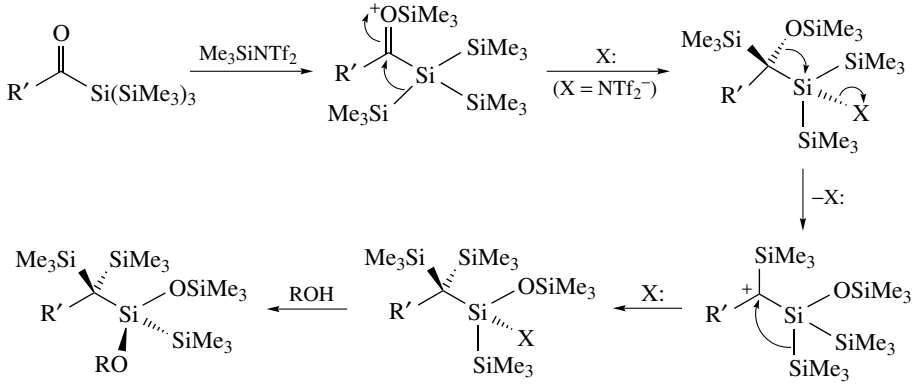
the tetrahydropyrans (**241**) with high *trans*-selectivity. A plausible mechanism for the formation of (**241**) involves attachment of a proton to the hydroxyl group of (**237**) to form the oxonium ion (**238**), shift of the proton from the oxygen atom to the α-carbon, and a 1,2-silyl migration of the β-silyl carbocation (**239**) to yield another β-silyl carbocation (**240**). Intramolecular attack of the oxygen from the side opposite to the silyl group will then give *trans*-(**241**). A highly stereospecific skeletal rearrangement involving a *syn*-1,2-silyl shift and the elimination of a trimethylsilyl group has been invoked[379] to account for the formation of enantiomerically enriched propargylsilanes (and allylsilanes) from the reaction of oxasilacycloalkanes with acid (see Scheme 80). Acidic treatment of the (1S,1′S,2′R)-α-hydroxycyclopropylsilane (**242**) has been found to yield, via the unprecedented α-silyl cation (**243**), a mixture of rearranged products which are composed of the ring-opened (*S*)-vinylsilane (**244**), the tandem (1,2)-carbon–carbon bond migration product, (1S,2R,1′S)-silylcyclopropane (**245:** $R^3 = H$, $R^4 = OH$) and its 1′R isomer (**245;** $R^3 = OH$, $R^4 = H$), respectively.[380]

In the presence of strong acids, 1-hydroxyalkyltris (trimethylsilyl) silanes (**246**) have been found[381] to isomerize by a 1,2-trimethylsilylhydroxy exchange to afford trimethylsilylmethylsilanols (**247**). The reaction of acylpolysilanes with silylbistriflimides has been found[382] to lead to novel silanols via a pathway involving two 1,2-migrations of trimethylsilyl groups from silicon to carbon and one migration of a R_3SiO unit from carbon to silicon (see Scheme 81).

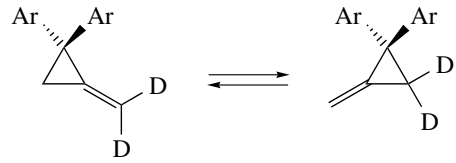
A detailed comparison of the rearrangement of 1,3-radical cations and carbocations derived from tricyclo [3.3.0.$0^{2,4}$] octanes has shown (by electron-transfer oxidation and protonation, respectively) that electronic substituent effects on the diyl sites profoundly influence the regioselectivities of the Wagner–Meerwein 1,2-shifts. The


OH
X
Y
Me3Si
(242)
X = Bu^n, Y = H
(243)
Bu^n
R1
R2
(244)
+
(245)

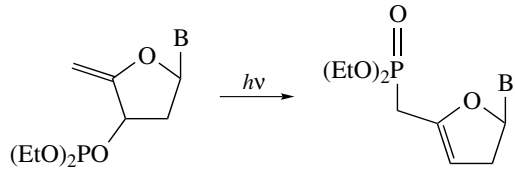

(Me3Si)3Si
R1
C
HO
R2
(246)
SiMe3
(Me3Si)2Si
OH
(247)


O
R′
Si(SiMe3)3
Me3SiNTf2
+OSiMe3
SiMe3
Si
Me3Si
X:
(X = NTf2−)
OSiMe3
–X:
ROH
RO
X

SCHEME 81



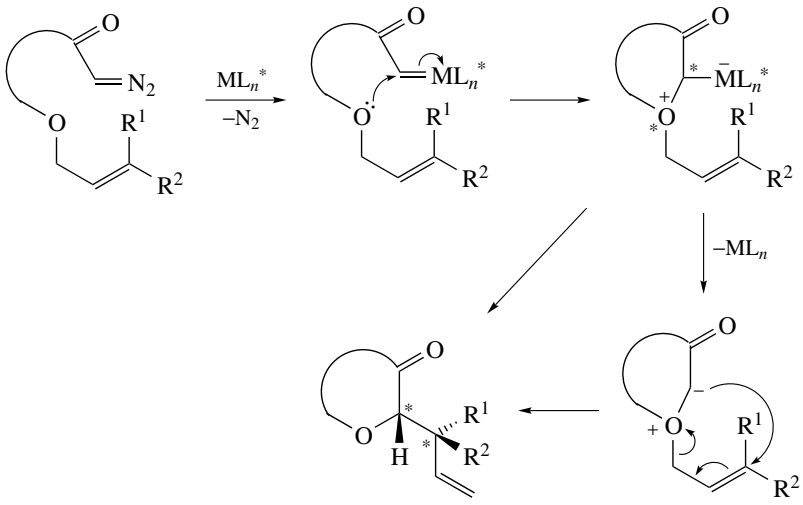
(**248**) (**249**)



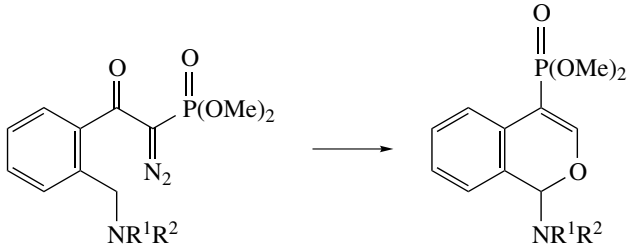
(**250**) (**251**)

regioselectivity of the electron-transfer oxidation has been rationalized[383] in terms of a qualitative MO interaction diagram, whereas that of the protonation is considered to follow the relative stability of the initially formed carbocation. *Ab initio* computational studies of methanethiol and dimethyl sulfide radical cations have demonstrated[384] that both of these groups of compounds have similar decomposition paths that involve rearrangement and fragmentation of initially formed radical cations. Two different types of intermediates, a bisected trimethylenemethane cation radical and a diradical have been directly observed[385] during the photochemical electron-transfer degenerate methylenecyclopropene rearrangement, (**248**) → (**249**). The recently discovered photochemical single electron-transfer-induced rearrangement of allyl phosphites (**250**) has been applied[386] to the preparation of allyl phosphonates (**251**). A number of persistent dihydrobenzofuranyl cations have been investigated by ^{1}H NMR and UV–visible spectroscopy and by cyclic voltammetry, and for the first time a selective and high-yield rearrangement proceeding via radical dications has been unambiguously established.[387]

A density functional study has been made of the competition between the Wolff rearrangement and 1,2-hydrogen shift in β-oxy-α-diazocarbonyl compounds.[388] A report has appeared[389] which shows that five- and six-membered acyclic ethers can be prepared enantioselectively from achiral diazo ketones, using chiral copper complexes as catalysts (see Scheme 82). A highly efficient protocol for the chain elongation of fluorenylmethoxycarbonyl-protected α-amino acids by a Ag^+-catalysed ultrasound-promoted Wolff rearrangement of the corresponding α-diazo ketones has been described.[390] The Wolff rearrangement of diazo ketones derived from *N*-*p*-tolylsulfonyl-protected α- and β-amino acids has been investigated.[391] Several different reaction pathways, including direct carbene N–H insertion, appear to be possible, depending on the nature of the *N*-protecting group, the substrate structure and the solvent. The thermolysis of α-diazo-β-keto-phosphonates (**252**) has been shown to afford 1-(disubstituted)-amino-1*H*-2-benzopyrans (**253**) which can be transformed into 1*H*-2-benzopyran derivatives by the action of various nucleophilic reagents. The extension of this reaction to pyridine and thiophene α-diazo-β-ketophosphonate



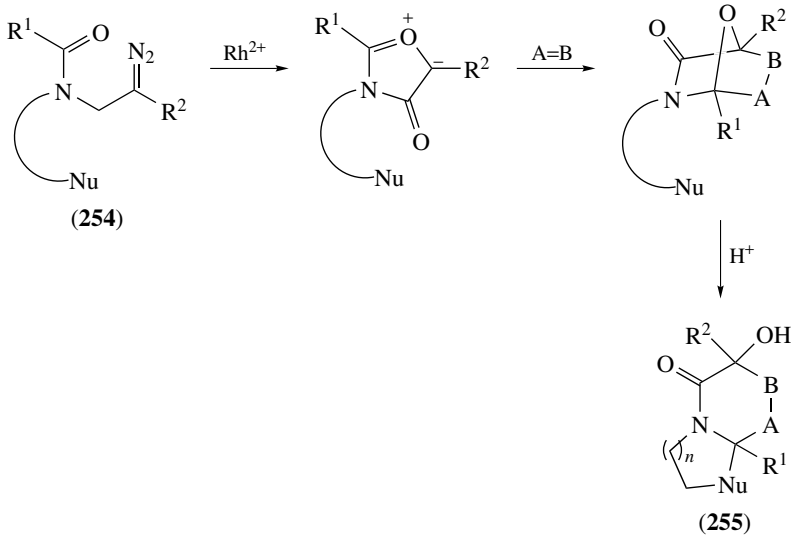
SCHEME 82



(**252**) (**253**)

analogues has also been described.[392] Starting from simple acyclic diazo imides (**254**) a domino carbenoid cyclization–4 + 2-cycloaddition–cationic π-cyclization protocol has been developed[393] for the construction of complex nitrogen poly-heterocycles of the type (**255**) (see Scheme 83).

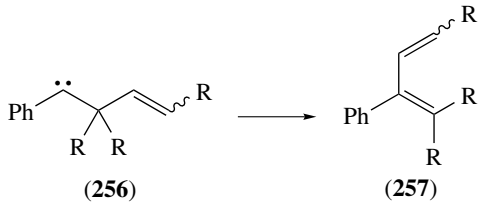
The rearrangement of dimethylcarbene to propene has been studied[394] by laser flash photolysis and *ab initio* MO theory, and substituent effects at the migration origin on the rate of rearrangement of several alkylchlorocarbenes have been studied.[395] It has been shown that the Arrhenius curvature observed for the rate constants of the 1,2-hydrogen rearrangement of benzylchlorocarbene in hydrocarbon solvents is due mainly to competitive intermolecular chemistry.[396] Absolute rate constants and activation parameters have been presented[397] for the 1,2-hydrogen and 1,2-acetyl migrations of a family of alkylacetoxycarbenes, while absolute rate constants detected for 1,2-carbon and 1,2-hydrogen migrations of cyclobutyl-, cyclopentyl-, benzocyclobutenyl-,

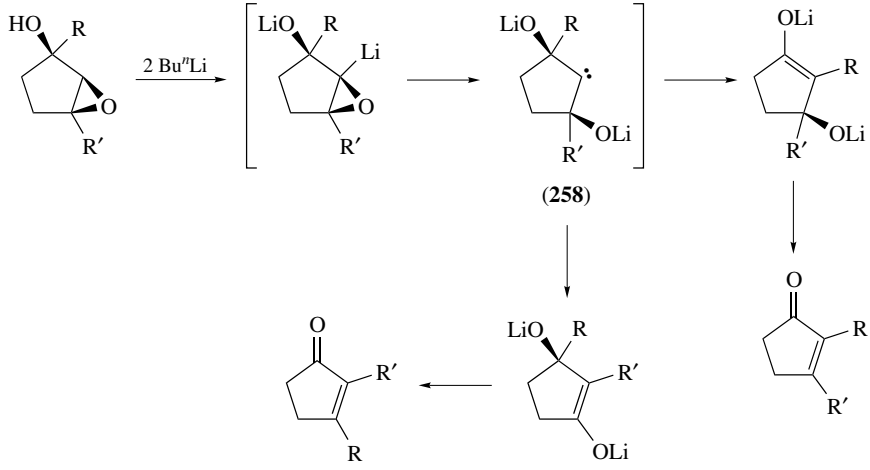


SCHEME 83

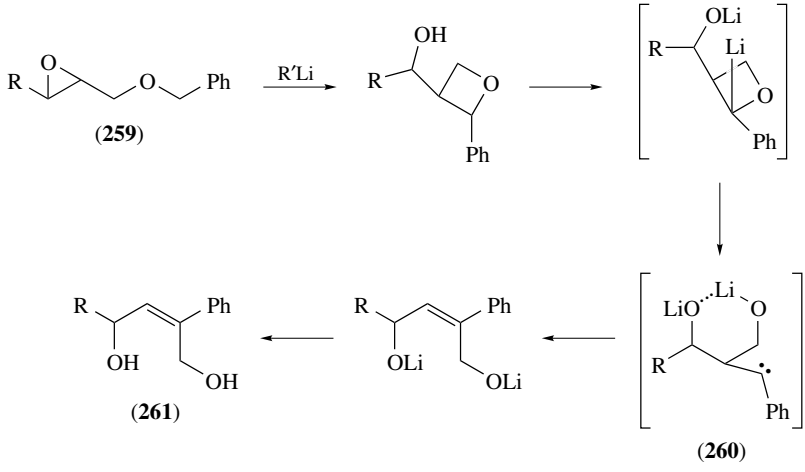
and various benzocyclopentenyl-carbenes have revealed[398] that phenyl carbon migrations are preferred to alternative 1,2-carbon shifts. It has been observed[399] that 1,2-vinyl shifts of 1-phenylbut-3-arylidenes [(**256**) to (**257**)] proceed with retention of configuration. A theoretical study of the adamantene and protoadamantene systems has been undertaken,[400] and adamantylchlorocarbene and its ring-expanded product chlorohomoadamant-3-ene have been characterized[401] by matrix isolation spectroscopy combined with DFT calculations. The latest results on the metal-induced 1,2-alkyl shifts in cyclic *syn* α-hydroxy epoxide systems have been reported.[402] They have shown that the reaction proceeds via a carbenoid intermediate (**258**) which can rearrange along two distinct intramolecular carbenoid insertion routes to yield two regioisomeric α,β-unsaturated ketones (see Scheme 84). A carbene-type intermediate (**260**) has been invoked[403] to account for the unusual base-promoted rearrangement of (*E*)-1-benzyloxy-2,3-epoxyalkanes (**259**) to allylic alcohols (**261**) (see Scheme 85).

A bis(dithia-dication) dimer has been proposed[404] as an intermediate in the remote oxygen migration reactions of 1,4-bis(methylthio)benzene and its derivatives (see

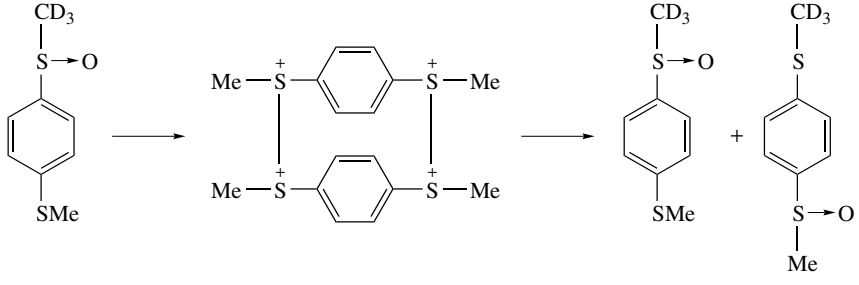




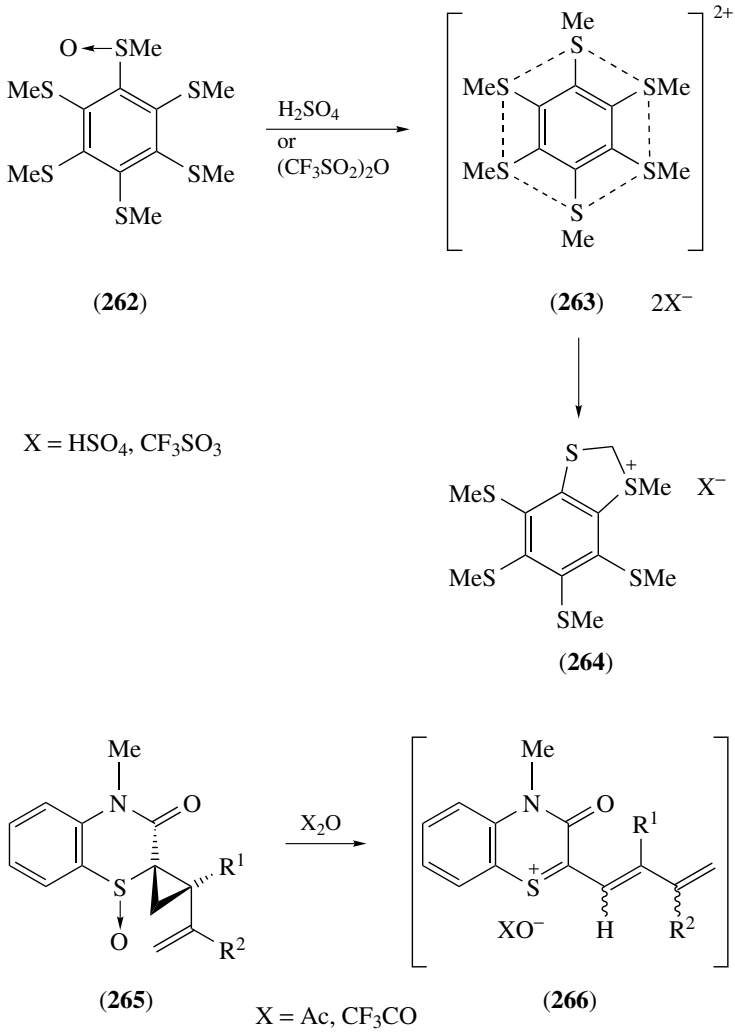
SCHEME 84



SCHEME 85

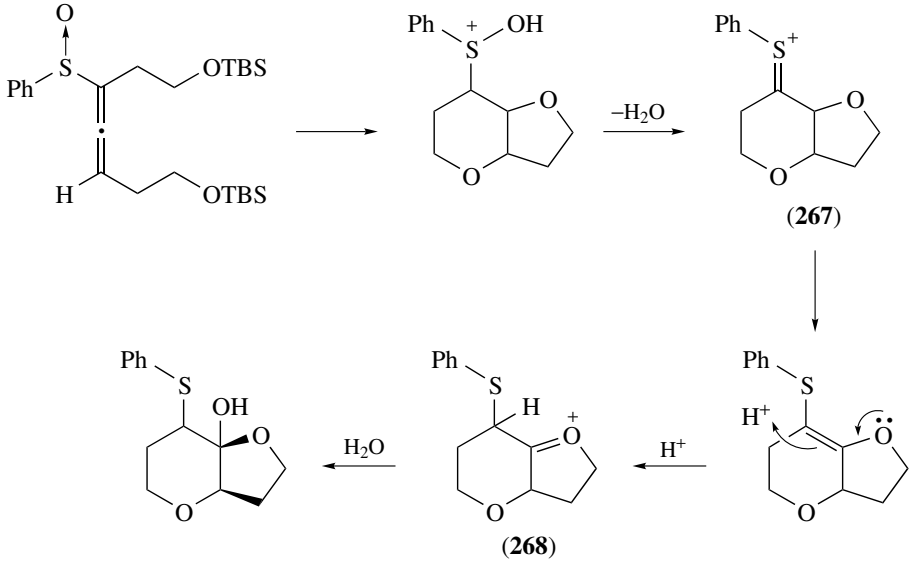


SCHEME 86



Scheme 86), and a σ-delocalized hexathia dication (**263**) is considered[405] to be the most stable intermediate for the Pummerer-type rearrangement of (**262**) into (**264**). The Pummerer reaction of 2-vinylcyclopropyl sulfoxides (**265**) has been shown to proceed via butadienyl thionium ions (**266**) by the proton abstraction from the 2′-methyl group or the cyclopropane ring, to yield cyclic dienes or acyclic dienols.[406] Benzyl 2-(hydroxymethyl)phenyl sulfoxides on treatment with *p*-toluenesulfonic acid monohydrate have been found to undergo a Pummerer-type rearrangement to afford benzaldehydes. The reaction was found to proceed via an oxosulfonium salt as an intermediate.[407] The potential of both additive and vinylogous Pummerer reactions of amido sulfoxides for the preparation of nitrogen-containing heterocycles has

been demonstrated.[408] A new synthesis of the 1,4-dioxahydrindane ring system has been reported[409] using a novel double deprotective-double cyclization rearrangement sequence mediated by aqueous HF. The process is considered to involve fluoride-induced desilylation of both silyl ethers followed by an acid-catalysed double cyclization and finally a Pummerer-type rearrangement, in which the sulfoxide moiety becomes protonated and undergoes subsequent dehydration to give thionium ion (**267**). A deprotonation and subsequent protonation then produces oxonium ion (**268**) which is trapped with water (see Scheme 87).



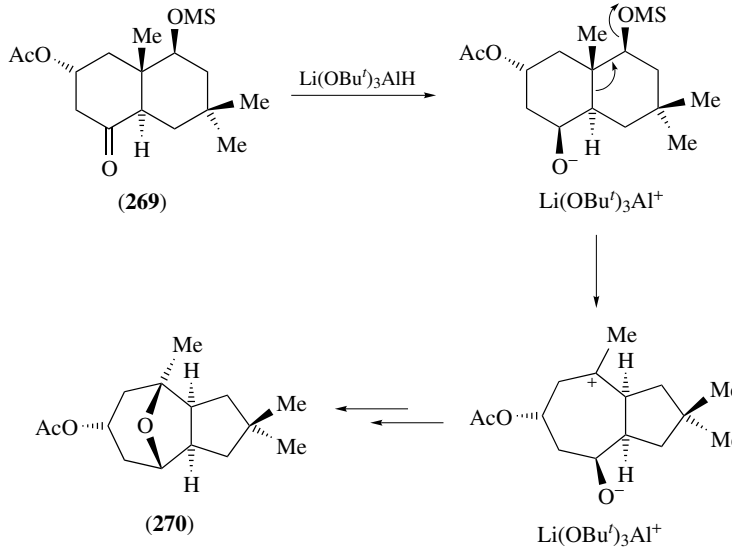
SCHEME 87

The mechanism of phenylseleno-etherification of unsaturated alcohols, which involves seleniranium cationic intermediates, has been studied[410] by the semiempirical molecular orbital MNDO–PM3 method.

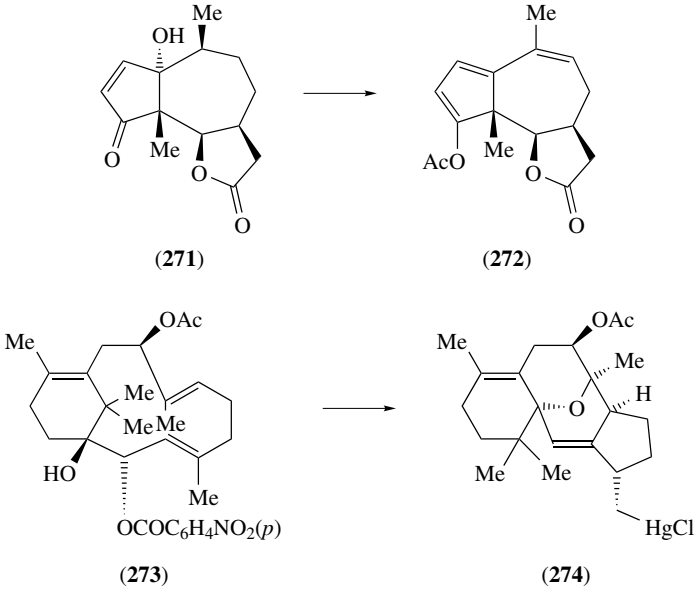
Rearrangements in Natural-product Systems

A comparison has been made[411] of various monoterpenoid rearrangements catalysed by either zirconium phosphates or by zirconium organo-substituted phosphonates, and acid-catalysed rearrangements of α-trans- and β-cis-3,4-epoxycaranes have been described.[412] It has been observed[413] that on exposure to Li $(OBu^t)_3AlH$, perhydronaphthalene-1,4-diol monosulfonate ester (**269**) rearranges to the 11-oxatricyclo-[5.3.1.0.2,6]undecane derivative (**270**) (see Scheme 88).

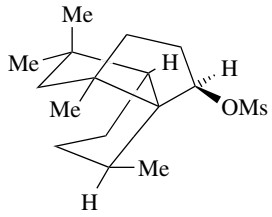
Parthenin (**271**) has been found to undergo a skeletal rearrangement with the introduction of acetate functionality[414] [see (**272**)] upon treatment with $Ac_2O–H_2SO_4$. An



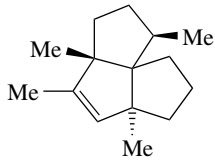
SCHEME 88



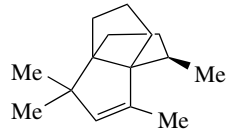
unexpected rearrangement–transannular cyclization product (**274**) has been obtained[415] on treatment of bicyclo[9.3.1]pentadecatriene (**273**), a precursor of taxol, with mercuric triflate. A Wagner–Meerwein rearrangement of rings B and C of the clovane skeleton has been explored[416] by deuterium labelling of 9 α-bromo-2β-methoxyclovane. The formation of isocomene (**276**) and modhephene (**277**) in the solvolytic rearrangements



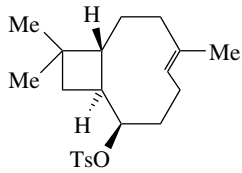
(**275**)



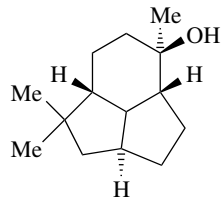
(**276**)



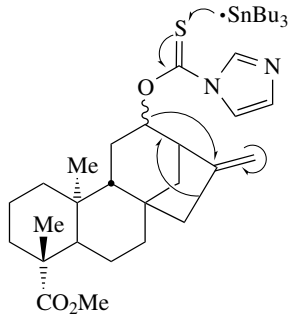
(**277**)



(**278**)



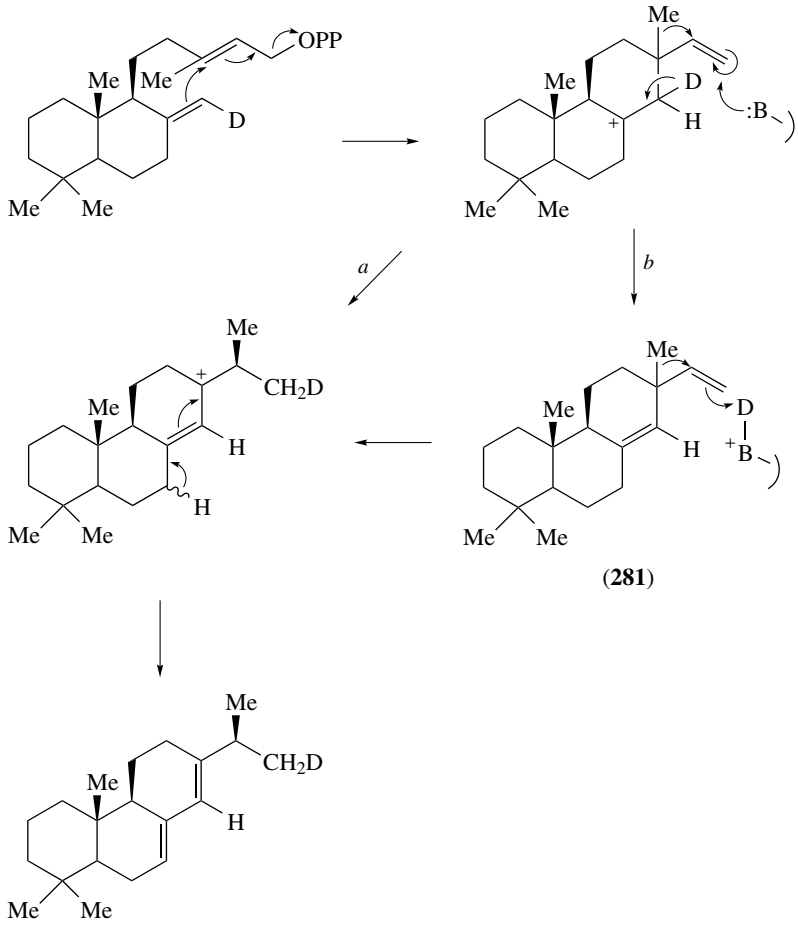
(**279**)



(**280**)

of silphinyl mesylates (**275**) and from the acid-catalysed conversion of silphinene, has provided[417] experimental precedent for the biogenetic linkage of these triquinane sesquiterpenes. 15-Norcaryophyllen-8-β-yl tosylate (**278**) has been found to undergo a stereospecific rearrangement–cyclization to 12-nor-8α-presilphiperfolan-9-β-ol (**279**) upon solvolysis in aqueous acetone. Although the ring bond that participates in the cyclobutylcarbinyl–cyclopentyl rearrangement is unknown, the reaction has provided a chemical precedent for a biogenetic connection between caryophyllene and the presilphiperfolanols.[418]

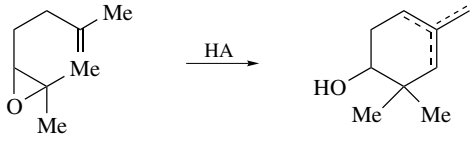
It has been shown[419] that isomerization of the exocyclic allylic system of the five-membered ring D of kaurenols depends on the orientation of the C(15) hydroxyl group. The total synthesis of methyl atis-16-en-19-oate, a tetracyclic diterpenoid possessing a bicyclo[2.2.2]octane skeleton, has been accomplished[420] using a homoallyl-homoallyl radical rearrangement process of methyl 12-hydroxykaur-16-en-19-oate monothioimidazolide (**280**) as the pivotal step. Two plausible mechanisms have been presented[421]



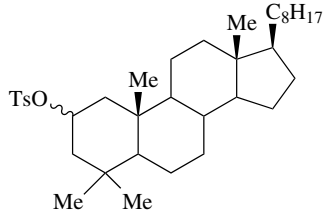
SCHEME 89

(see Scheme 89) for the novel cyclization-rearrangement of (+)-copalyl diphosphate to (−)-abietadiene which is catalysed by recombinant cyclase from *Abies grandio*. However, further research is required to elucidate whether the mechanism involves an intramolecular C(14) to C(16) hydrogen-transfer pathway (path *a*), or an enzyme-mediated proton elimination to form a pimara-8(14),15-diene intermediate (**281**) that incorporates the proton at C(16) (path *b*). The structure of a naphthalene derivative obtained by rearrangement of 13-methoxytotara-5,8,11,13-tetraen-7α-ol has been revised[422] to 5-(5′-isopropyl-6′-methoxy-2′-methyl-1′-naphthyl)-2-methylpent-2-ene.

The involvement of a common concerted mechanistic pathway for the acid-catalysed cyclization of 5,6-unsaturated oxiranes, viz. (**282**) to (**283**), in chemical and enzymatic systems has been demonstrated,[423] and indeed, theoretical evidence has been produced[424] to show the participation of a concerted mechanism for oxirane cleavage and A-ring formation in oxidosqualene cyclization. Further



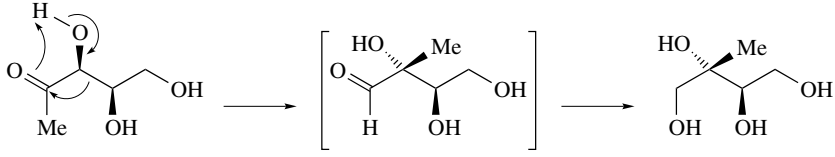
(**282**) (**283**)



(**284**)

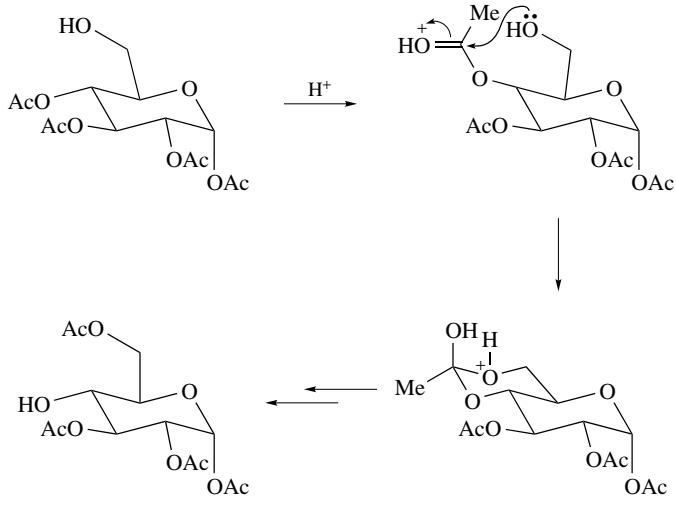
evidence has been obtained[425] to suggest that the polycyclization reaction by oxidosqualene–lanosterol cyclase proceeds via the expansion of a five- to a six-membered ring for C-ring formation of lanosterol. 6-Methyl-3-isopropyl-A,19-dinorcholesta-6,8,10(5)-triene has been identified as a new by-product from the acid-catalysed reaction of 4,4-dimethylcholest-5-en-3-one. A novel enone-benzene rearrangement has been invoked[426] to account for the formation of this product. A number of 4-hydroxyestrogens have been prepared by the thermal rearrangement of steroidal 4,5-epoxides.[427] Sigmatropic and/or contact-ion-pair processes have been invoked[428] to explain the observed rearrangement products obtained on the acetolysis of the epimeric tosylates (**284**). Pinacol rearrangements of 2α,3β,19α-trihydroxyurs-12-triterpenoids have been studied,[429] the peracid-induced oxidative rearrangement of bauerenyl acetate has been investigated,[430] and a novel oxidative skeletal rearrangement of ring A of lupenone has been described.[431] The rearrangement of steroidal α, β-unsaturated pyridine *N*-oxides with acetic anhydride has been shown to afford diastereoisomeric 20-acetoxy-17-picolyl-16-androstene derivatives.[432]

It has been established[433] that the leaves of *Liriodendron tulipifera* convert 1-deoxy-D-xylulose (**285**) into 2-*C*-methyl-D-erythritol (**286**) via a skeletal rearrangement (see Scheme 90) reminiscent of the formation of terpene precursors from 1-deoxy-D-xylulose 4-phosphate. An esterase-catalysed regioselective 6-deacylation of

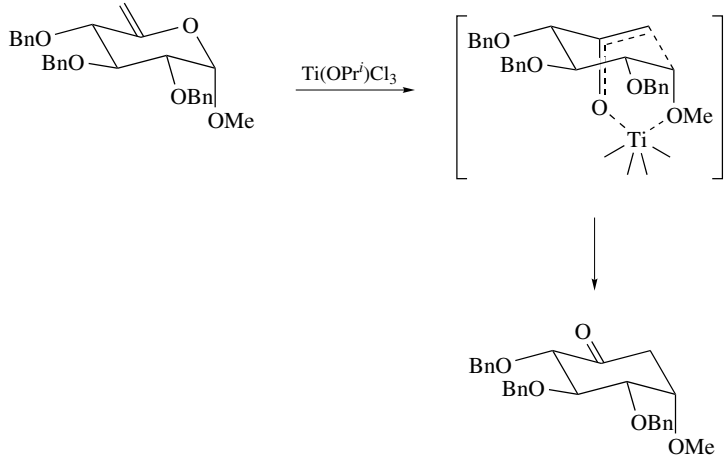


(**285**) (**286**)

SCHEME 90

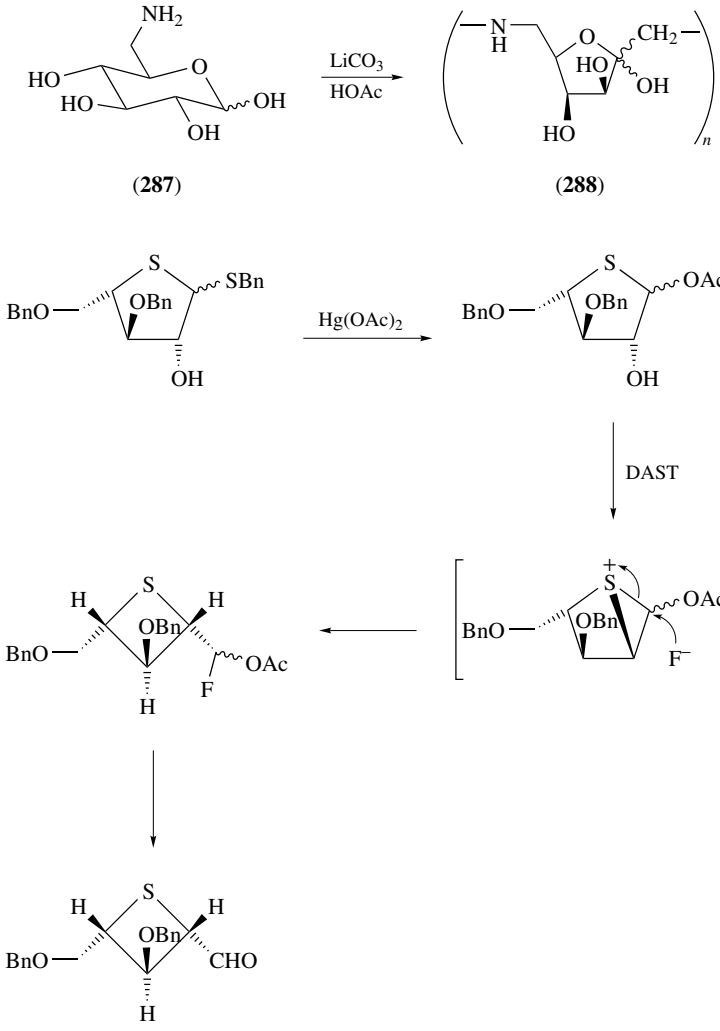


SCHEME 91



SCHEME 92

hexopyranose peracetates has been reported. Moreover, utilization of the propensity of acyl groups to migrate under acidic conditions (see Scheme 91) has ultimately made possible the conversion of C(6) partially acylated monosaccharides into the corresponding C(4) deprotected species, thus providing a simple method for the regiospecific deprotection of the C(4) position of hexopyranosides.[434] A novel stereoselective approach to polyhydroxylated cyclohexanones has been described,[435] starting from benzylated 6-deoxy-hex-5-enopyranosides and promoted by titanium(IV) (see Scheme 92). 2,3-Unsaturated mono- and di-saccharide glycosylglycerol derivatives have been obtained in good yields by the Lewis acid-catalysed allylic

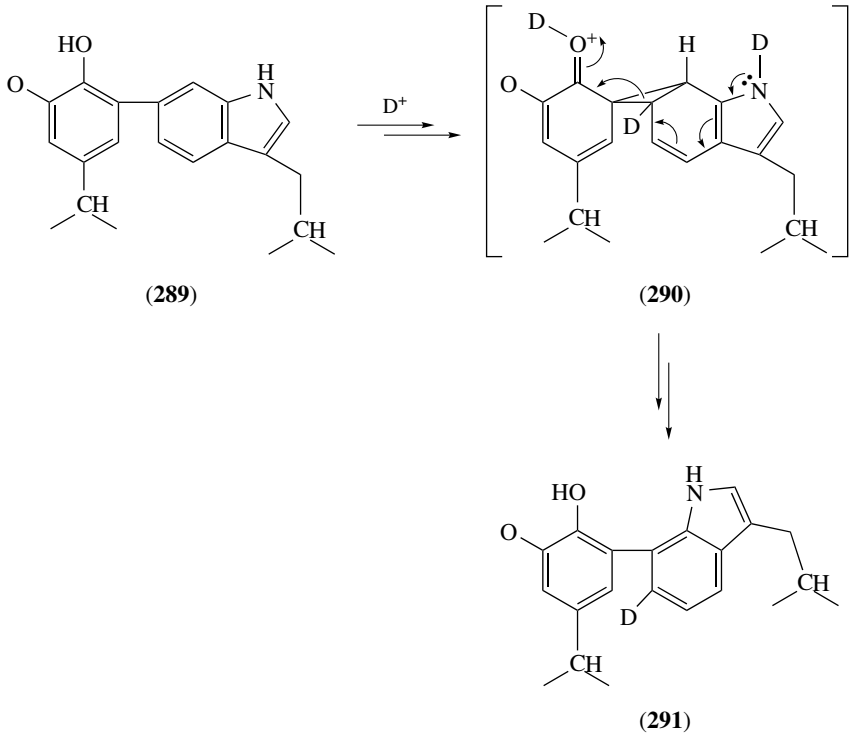


SCHEME 93

rearrangement reaction of various glycals with glycerol derivatives[436] and other *O*-nucleophiles.[437] The synthesis of a new aminopolysaccharide (**288**) having an amino-ketose structure, has been achieved[438] utilizing the thermal polymerization of 6-amino-6-deoxy-D-glucose (**287**) in the presence of acetic acid. The novel Lewis acid-catalysed rearrangement of a sugar-base hybrid to afford an anhydronucleoside has been reported,[439] and the attempted intermolecular addition of malonyl radicals to 1′, 2′-unsaturated nucleosides has been found to lead to furanones.[440] An unusual ring contraction–rearrangement has been observed[441] during the attempted fluorination of thiofuranose derivatives with diethylaminosulfur trifluoride (DAST). Scheme 93

outlines the proposed mechanism for this transformation which is considered to proceed by the regioselective opening of a transient episulfonium ion.

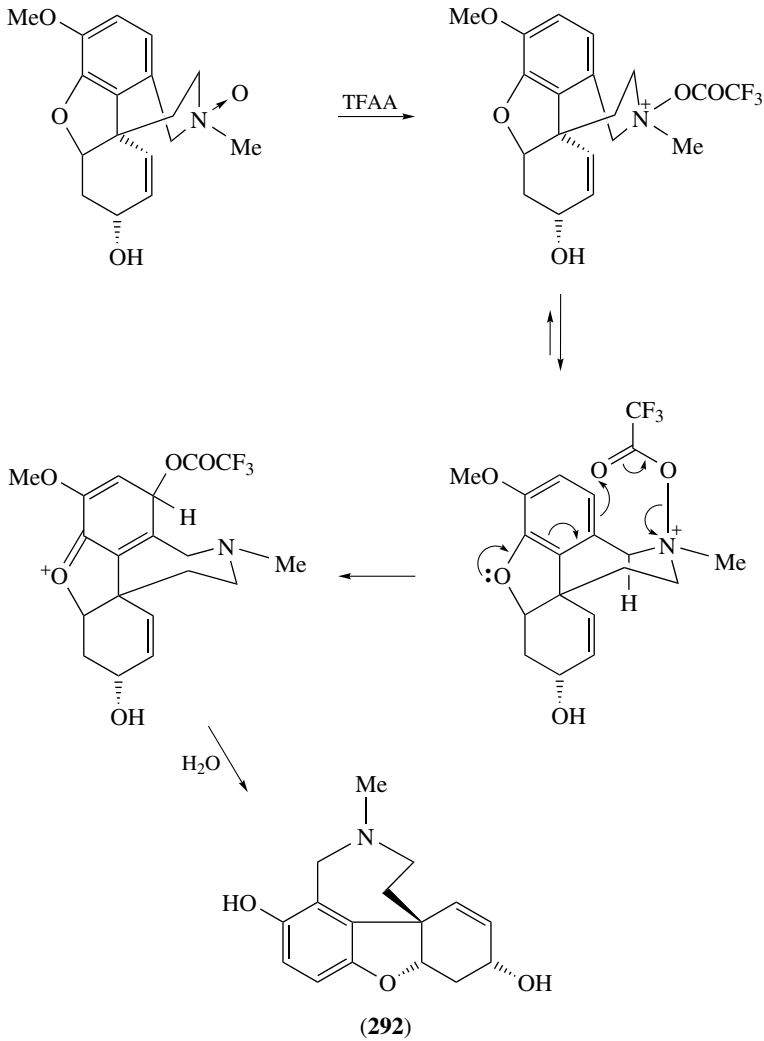
The observed acid-catalysed conversion of complestatin (**289**) into chloropeptin L (**291**) has been envisioned[442] as proceeding through a cyclopropyl intermediate (**290**) (see Scheme 94). An intramolecular oxygen-transfer reaction illustrated in Scheme 95 has been proposed[443] to explain hydroxylation of the aromatic nucleus, viz. formation of (**292**), during the course of a modified Polonovski reaction on galanthamine.



SCHEME 94

Rearrangements Involving Electron-deficient Heteroatoms

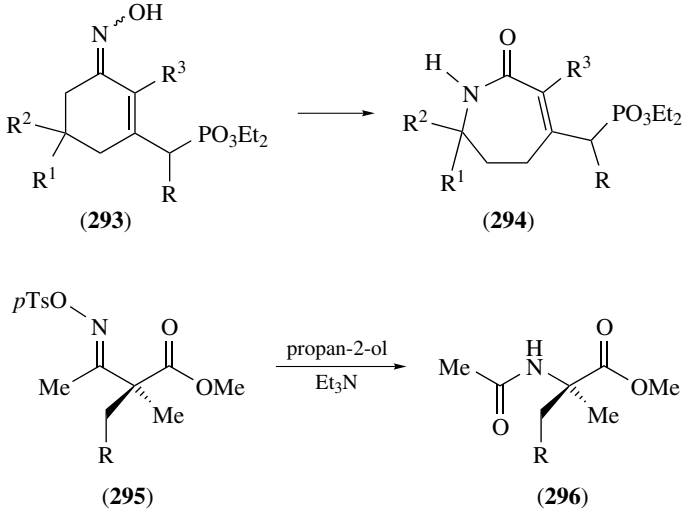
An *ab initio* study of the effects of both substituents and solvents on the Beckmann rearrangement has been undertaken[444] and the potential-energy surfaces corresponding to the Beckmann rearrangement of a series of aliphatic and cyclic alkanone oximes have been explored[445] using density functional theory. The vapour-phase Beckmann rearrangement of cyclohexanone oxime to ϵ-caprolactam, catalysed by mesoporous molecular sieves, has been studied,[446] and a weakly acidic borosilicate has also been utilized[447] as a catalyst in the above reaction. The non-catalytic Beckmann rearrangement of cyclohexanone oxime to ϵ-caprolactam in supercritical water has been reported,[448] and a comparison has been made of the Beckmann rearrangement of



(**292**)

SCHEME 95

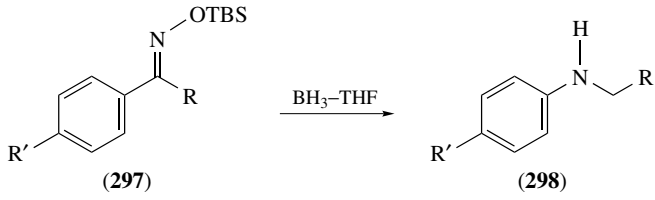
oximes with different molecular sizes over a series of β-zeolites containing different Brønsted acid sites.[449] A facile and efficient synthetic procedure for the Beckmann rearrangement of oximes using aluminium chloride in the absence of solvent has been developed,[450] and the Beckmann rearrangement of 1-indanone oxime using aluminium chloride has been reported.[451] Lactams (**294**), resulting from the regioselective migration of the C(6)-methylene ring-carbon atom, have been obtained[452] from the Beckmann rearrangement of the oximes of 3-phosphonoalkylcyclohexenones (**293**). A convenient method for the preparation of a bicyclo[3.3.3]undecane derivative via the Beckmann rearrangement of bicyclo[3.3.2]decan-9-one has been described,[453] and a novel method for the synthesis of fully protected chiral α,α-disubstituted α-amino



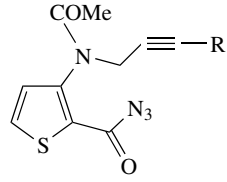
acids via a Beckmann rearrangement has been developed[454] [see (**295**) to (**296**)]. The syntheses of 6-*O*-methylazithromycin and its aza-ketolide analogue have been achieved[455] by carrying out the Beckmann rearrangement of the readily available 9(*E*)-6-*O*-methylerythromycin oxime. The reduction of aromatic and cyclic *O*-(*t*-butyldimethylsilyl) aldoximes and ketoximes with various reducing agents has been investigated and an attempt has been made to explain the effect of substituents on the novel rearrangement [(**297**) to (**298**)] that occurs with a borane–tetrahydrofuran complex.[456]

A re-evaluation of the Hofmann rearrangement in electron-deficient systems has been undertaken.[457] A detailed study of the discrete intermediates, and the sensitivity of the intermediates and products to reagents and to each other in the Hofmann rearrangement of *N*-α-tosylasparagine, has led to a process that produces 2-(*S*)-(tosylamino)-β-alanine on a large scale.[458]

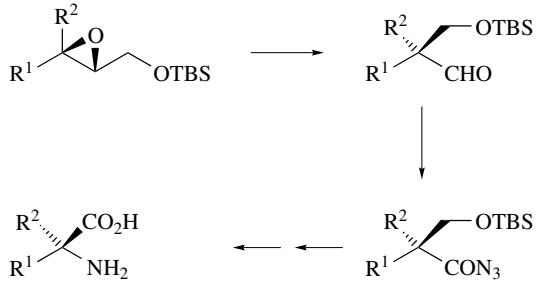
It has been demonstrated that the thermal reaction of a series of alkynyl- or alkenoyl-containing acyl azides such as (**299**) involves competition between intramolecular azide cycloaddition and a Curtius rearrangement. Apparently the substituent R plays a key role in determining the competition between the two possible routes.[459] It has been shown[460] that a silicon group situated at the β-position with respect to an acyl azide group enhances the rate of the Curtius rearrangement by a factor of three, whereas a γ-silyl substituent has a marginal influence. These observations have lent support to the proposition that, during the concerted intramolecular rearrangement of an acyl azide to an isocyanate, an electron-deficient centre at the migration origin is created. An efficient route for the asymmetric synthesis of α,α-disubstituted α-amino acid derivatives, starting from readily available epoxy silyl ethers, has been developed[461] using the Curtius rearrangement as a key step (see Scheme 96).



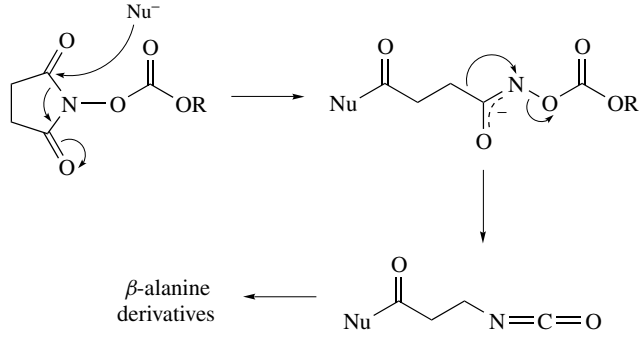
(**297**) (**298**)



(**299**)



SCHEME 96

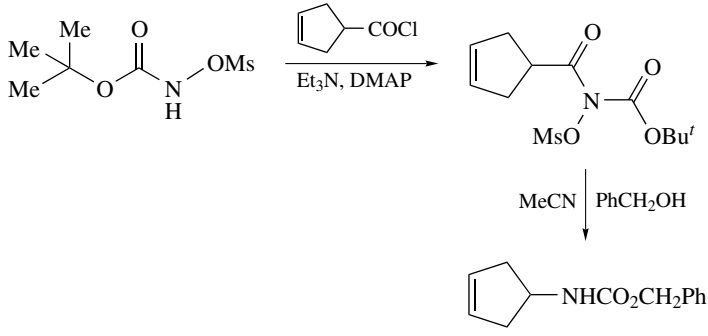


SCHEME 97

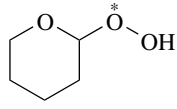
The neutral alkali metal salts of benzohydroxamic acids have been found to undergo an unprecedented rearrangement to *N*,*N*′-diarylureas.[462] A side reaction, producing β-alanine derivatives by way of a Lossen rearrangement, has been observed to accompany the hydrolysis of alkyl succinimidyl carbonates[463] in basic aqueous buffers (see Scheme 97). The development of a modified Lossen rearrangement, whereby

N-(*t*-butyloxycarbonyl)-*O*-methanesulfonylhydroxamic acids have been converted into protected amines in good yield, has been described[464] (see Scheme 98).

A successful synthesis of the tetrahydropyran-protected hydroperoxide (**300;** 1-^{18}O) using the Baeyer–Villiger strategy has been reported.[465] Experimental evidence has been obtained[466] to support the fact that, in the Baeyer–Villiger oxidation and Criegee rearrangement, a stereoelectronic effect directs the migratory aptitude, and it is the bond antiperiplanar to the dissociating peroxide bond that always migrates, even when it is electronically disfavoured from doing so.



SCHEME 98

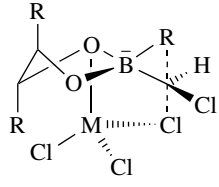


(**300**)

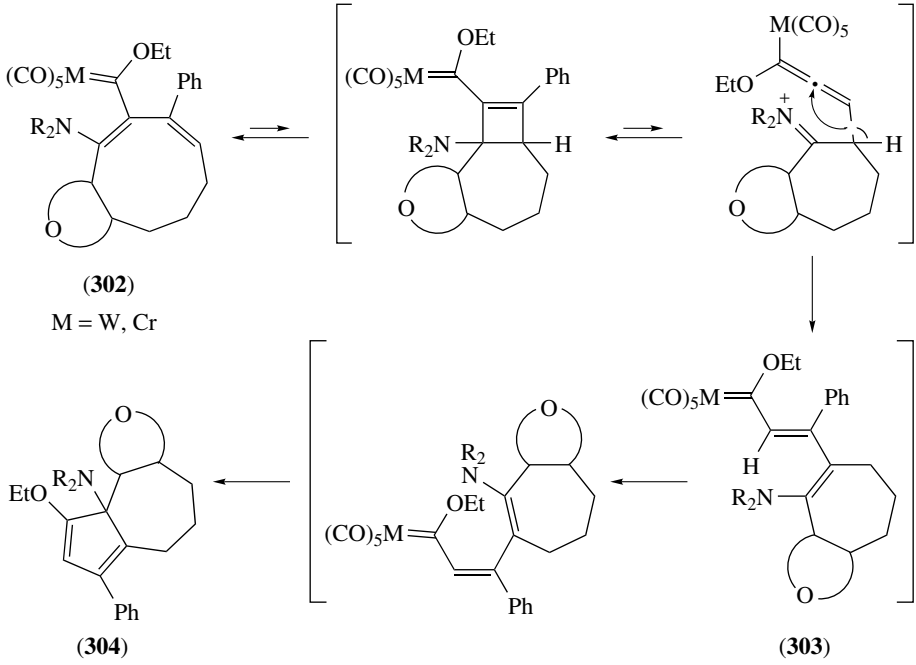
$^{*}O = {}^{18}O$

Rearrangements Involving Organometallic Compounds

An *ab initio* investigation of the transition state for the Lewis acid-associated migration of an alkyl group from boron to an α-dichloro-carbon in a non-racemic boronic ester has been carried out.[467] The calculated transition state has shown that it is important to have the non-participating chlorine atom *anti* to the metal, e.g. as in (**301**). The



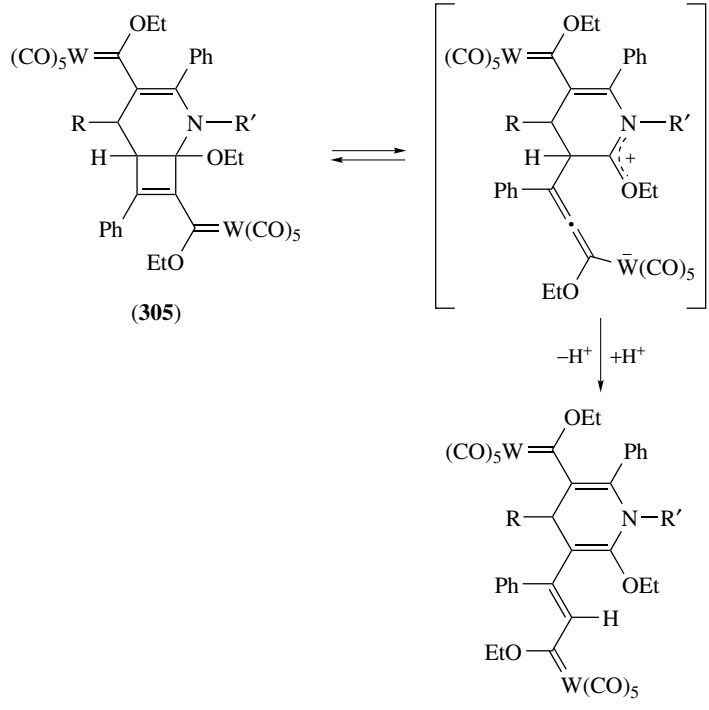
(**301**)

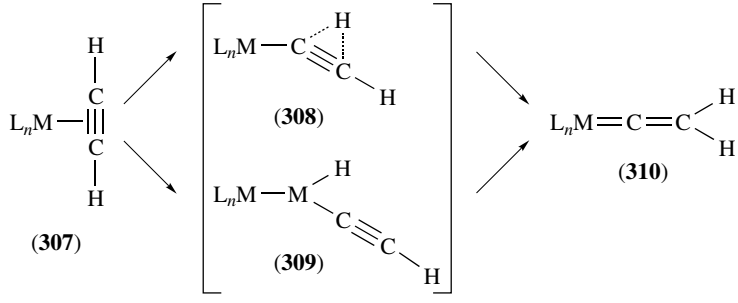


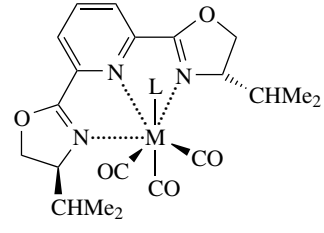
SCHEME 99

stereoselectivity is then dictated by placing the metal on the least-hindered side of the oxygen, *trans* to the R group of the ester. This combination places the Lewis acid in the sterically least hindered position.

2-Aminocyclonona-1,8-dienyl carbene complexes (**302**) in solution have been found to undergo ring contraction of the nine-membered ring to give (2-amino-cycloheptenyl)alkenyl carbene complexes (**303**) which are subsequently transformed into tetrahydroazulenes (**304**) by elimination of the metal unit[468] (see Scheme 99), and (cyclobutenyl)carbene tungsten complexes (**305**) have been shown to rearrange to 1-tungstahexa-1,3,5-trienes (**306**) by ring opening of the cyclobutene ring and subsequent [1,3]-hydrogen migration.[469] It has been reported[470] that the d^2[{*p*-Bu^t-calix[4]-(O_4)}W] fragment assists a variety of ethylene rearrangements which are very similar to those often supposed to occur on metal oxides. Such rearrangements are driven by light, acids, and bases, or occur under reducing conditions. Quantum-mechanical calculations have shown that[471] that two energetically nearly degenerate pathways are possible for the rearrangement of tungsten–acetylene complexes (**307**) to the energetically higher lying vinylidene complexes (**310**). The direct [1,2]-hydrogen migration was found to proceed via a transition state (**308**) which has a non-planar C_2H_2 moiety. The alternative pathway involves the alkynyl(hydrido)metal complex (**309**). Complexes of the chiral bis(oxazoline) 2,6-bis[(4*S*)-isopropyloxazoline-2-yl]pyridine (**311;** M = Mo or W), in which the ligand is restricted to a bidentate bonding mode, have been found to be

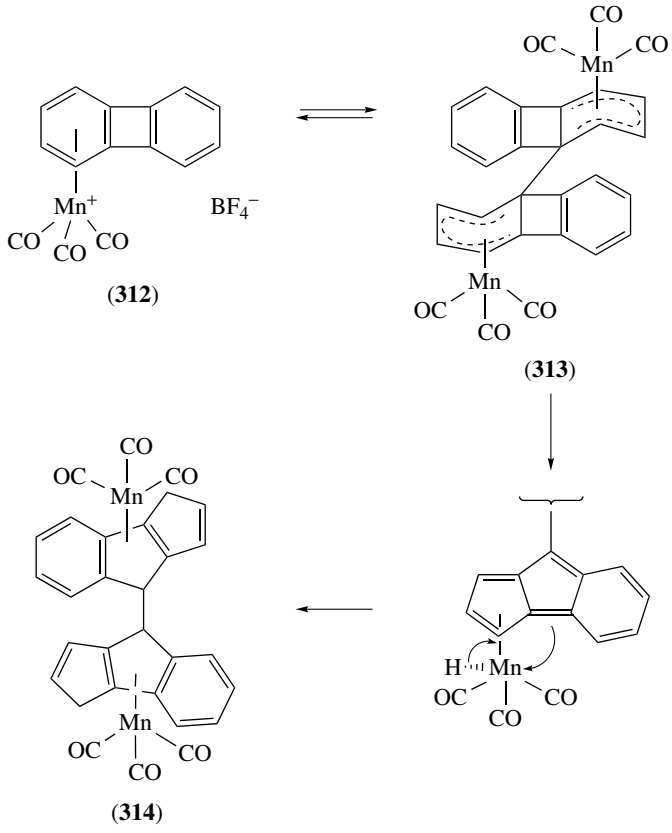

OEt
(CO)5W
Ph
R
N
R′
H
OEt
Ph
W(CO)5
EtO
(305)
OEt
(CO)5W
Ph
R
N
R′
H
Ph
OEt
W(CO)5
EtO
−H+
+H+
OEt
(CO)5W
Ph
R
N
R′
Ph
OEt
H
EtO
W(CO)5
(306)


H
LnM
C
C
H
(307)
LnM
C
H
C
H
(308)
LnM
M
H
C
C
H
(309)
LnM
C
C
H
H
(310)

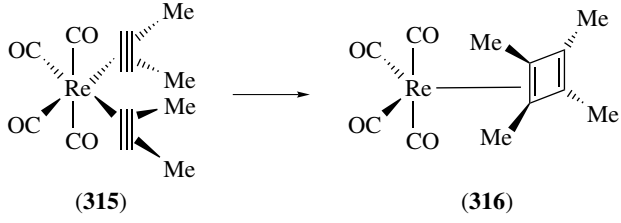

O
N
N
L
CHMe2
O
N
M
OC
CO
CO
CHMe2
(311)

fluxional, with exchange occurring between the pendant and coordinated oxazoline rings. The energetics and mechanism of the rearrangement have been studied in detail[472] by one- and two-dimensional NMR techniques.

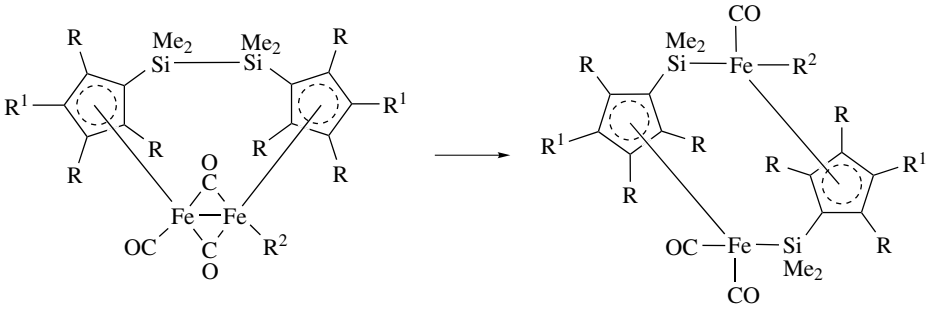
Reduction of (**312**) has been found to afford the dimer (**313**) which upon heating rearranged to yield the unprecedented di(benzopentalene) complex (**314**). The regio- and stereo-specificity of the conversion (**313**) into (**314**) implies a metal-mediated pathway for the process[473] (see Scheme 100). The first observable *cis*-bis(alkyne)cyclobutadiene rearrangement [see (**315**) to (**316**)] has been reported.[474]



SCHEME 100



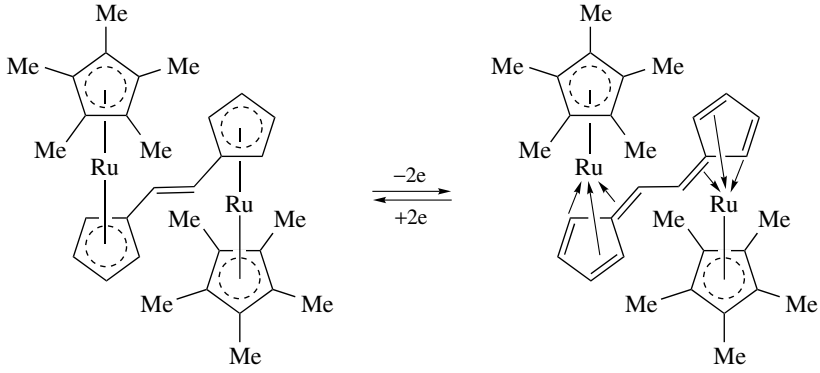
The binuclear iron complexes (**317**) have been found to undergo a thermal rearrangement[475,476] to afford the complexes (**318**), which were evidently formed via a metathesis between Si−Si and Fe−Fe bonds in (**317**). A similar rearrangement has been observed[477] in a disilyl-bridged bis(cyclopentadienyl)tetracarbonyldiruthenium complex. Unprecedented and stable ($\eta - \eta^6 : \eta^6$-pentafulvadiene)diruthenium complexes (**320**) have been prepared[478] from a two-electron oxidation of *trans*-1,2-bis(ruthenocenyl)ethylenes (**319**), and dimethyl analogues have been similarly obtained from *trans*- and *cis*-1,2-dimethyl-1,2-bis(ruthenocenyl)ethylenes.



(**317**) (**318**)

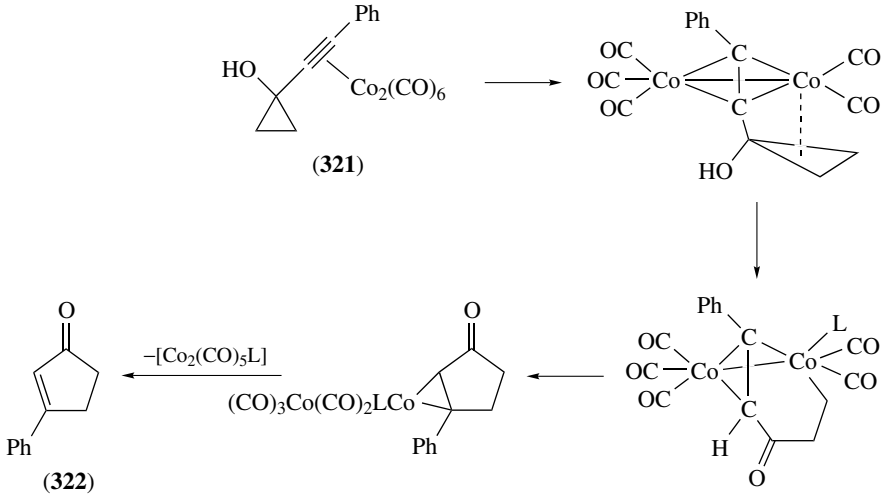
R, R^1 = Me; R^2 = CO

R = H; R^1 = Bu^t; R^2 = $P(OPh)_3$

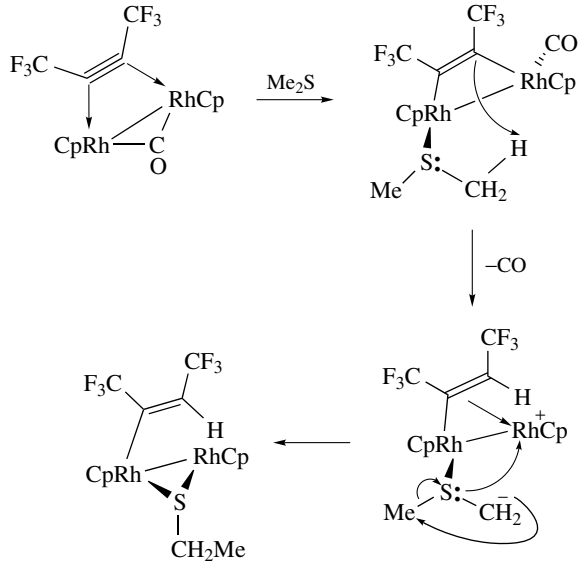


(**319**) (**320**)

A hitherto unknown type of rearrangement of 1-(1-alkynyl)cyclopropanols (**321**) to cyclopent-2-en-1-ones (**322**) mediated by octacarbonyldicobalt[479] and hexacarbonyldicobalt[480] complexes has been described. A possible pathway for the transformation is outlined in Scheme 101. A β-proton transfer accompanied by a metal-mediated Stevens rearrangement, which converts a coordinated dimethylsulfane

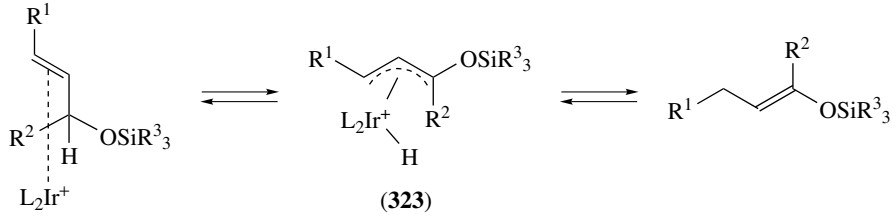


SCHEME 101



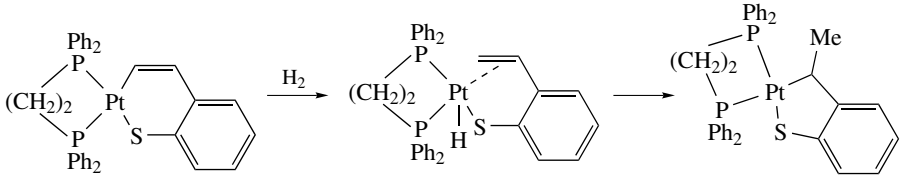
SCHEME 102

to a bridging ethanethiolate group (see Scheme 102), has been invoked[481] to account for the observed rearrangement of organic chalcogenides on a rhodium–rhodium bond. The iridium-catalysed isomerization of allyl silyl ethers has been rationalized[482] as proceeding through the oxidative addition of an allylic C–H bond to the iridium(I) metal centre, giving a *syn*-π-allyliridium complex (**323**) which selectively leads to the *E*-isomer (see Scheme 103).

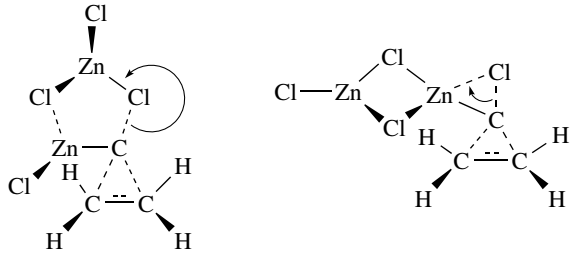


(**323**)

SCHEME 103



(**324**) (**325**) (**326**)



(**327**) (**328**)

A σ-*S*-bonded π-alkene (η^3) intermediate (**325**) has been invoked to account for the hydrogenation of the thiaplatinacycle (**324**) to the complex (**326**) in which two hydrogens have been added and a hydrogen shift has occurred.[483] When coordinated to neutral and cationic palladium(II) and platinum(II) centres, the diphosphine 2,3-bis(diphenylphosphino)propene, on treatment with benzylamine, was found to undergo isomerization to coordinated *cis*-1,2-bis(diphenylphosphino)propene[484] rather than the expected nucleophilic addition to the double bond.

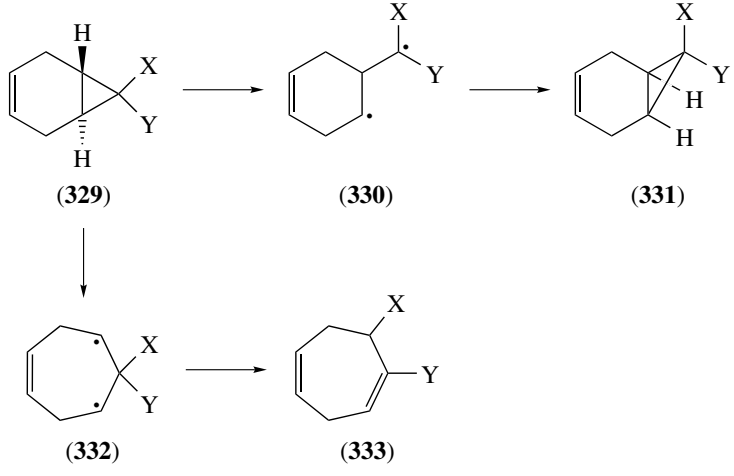
Metallation–demetallation of new multi-porphyrinic [2]rotaxanes in which a gold(III)-porphyrin is part of the ring, has been found to induce a complete changeover of the molecule.[485]

With the aid of density functional theory, the $ZnCl_2$ acceleration of the Simmons–Smith reaction of ethylene and allyl alcohol has been investigated.[486] A pathway involving direct Lewis acid acceleration of the leaving halogen atom (**327**) was found to be a more facile process than the more popular pathway involving 1,2-chlorine migration (**328**).

It has been established[487] that dimers of monofunctional tetrabutyldistannoxanes of the general formulae $[R_4Sn_2X_2O]_2$ rearrange rapidly in solution by an intradimeric dynamic process.

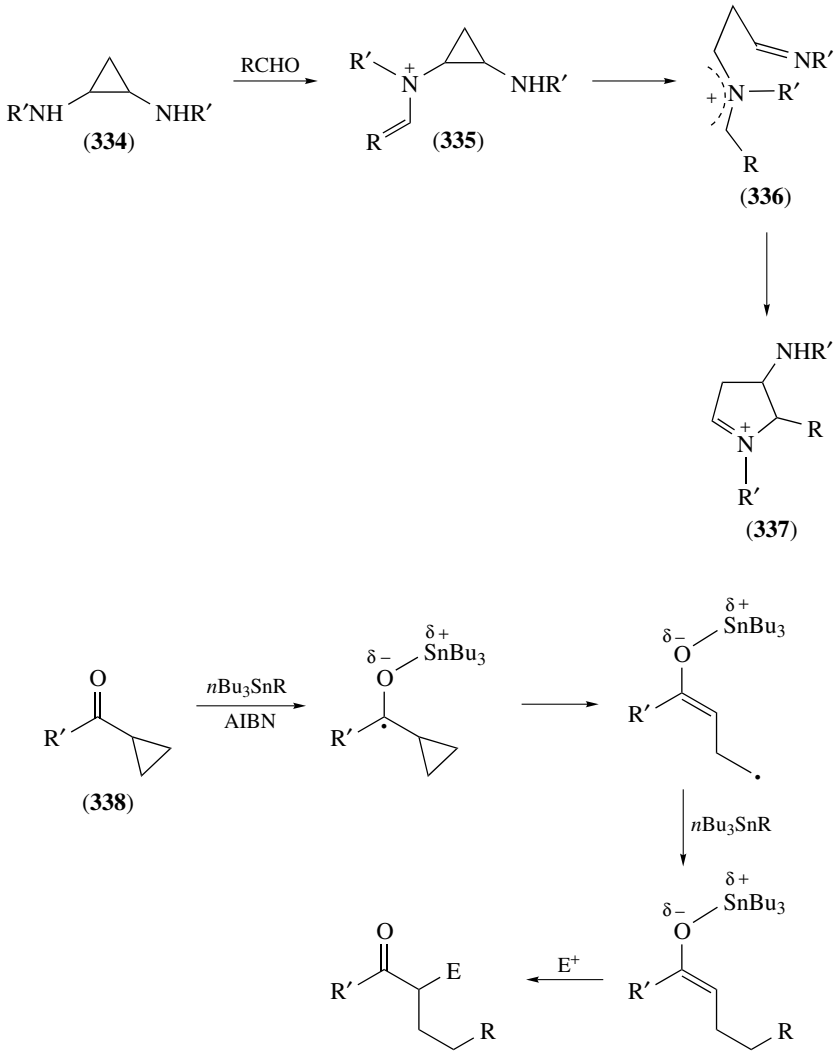
Rearrangements Involving Ring Opening

A study has been made[488] of the ring opening of methyl- and phenyl-substituted 1,1,2-trihalocyclopropanes to acetylenic acetals under a variety of reaction conditions. The thermal rearrangements of *trans*-bicyclo[4.1.0]hept-3-ene with halogen substituents at the 7-position have been examined.[489] Thermolysis of the dichloride (**329;** X, Y = Cl) led to the formation of the *cis*-fused isomer (**331;** X, Y = Cl) by a mechanism which appeared to involve initial cleavage of either the bridgehead or peripheral bond of the three-membered ring and ring closure of the corresponding biradical (**330;** X, Y = Cl). On the other hand, heating the dibromide (**329;** X, Y = Br) resulted in a cycloheptadiene product (**333;** X, Y = Br) which presumably arose via a [1,3]-shift of a bromine atom in the intermediate (**332;** X, Y = Br) generated by cleavage of the bridgehead bond. The formation of pyrroles from the reaction of 1,2-cyclopropanediamines (**334**) with aldehydes has been explained[490] by ring expansion of an intermediate monoiminium ion of the type (**335**) via the azomethine ylides (**336**), to yield the dihydropyrrolinium ion (**337**). It has been shown[491] that the reaction of a cyclopropyl ketone (**338**) with tributyltin radical produces a tin(IV) enolate separated from a carbon-centred radical by a methylene unit, entities which allow for reactions with both electrophiles and radicophiles (see Scheme 104). A theoretical study of the thermal isomerization of buta-1,3-diene to but-2-yne has indicated[492] that a pathway via 1-methylcyclopropene is more energetically favourable than that via a two-step hydrogen-shift process, and a theoretical study of the thermally induced ring opening of substituted cyclopropenes has supported the proposal that alkyl-substituted singlet vinylidenes are intermediates in the process.[493]



(**329**) (**330**) (**331**)

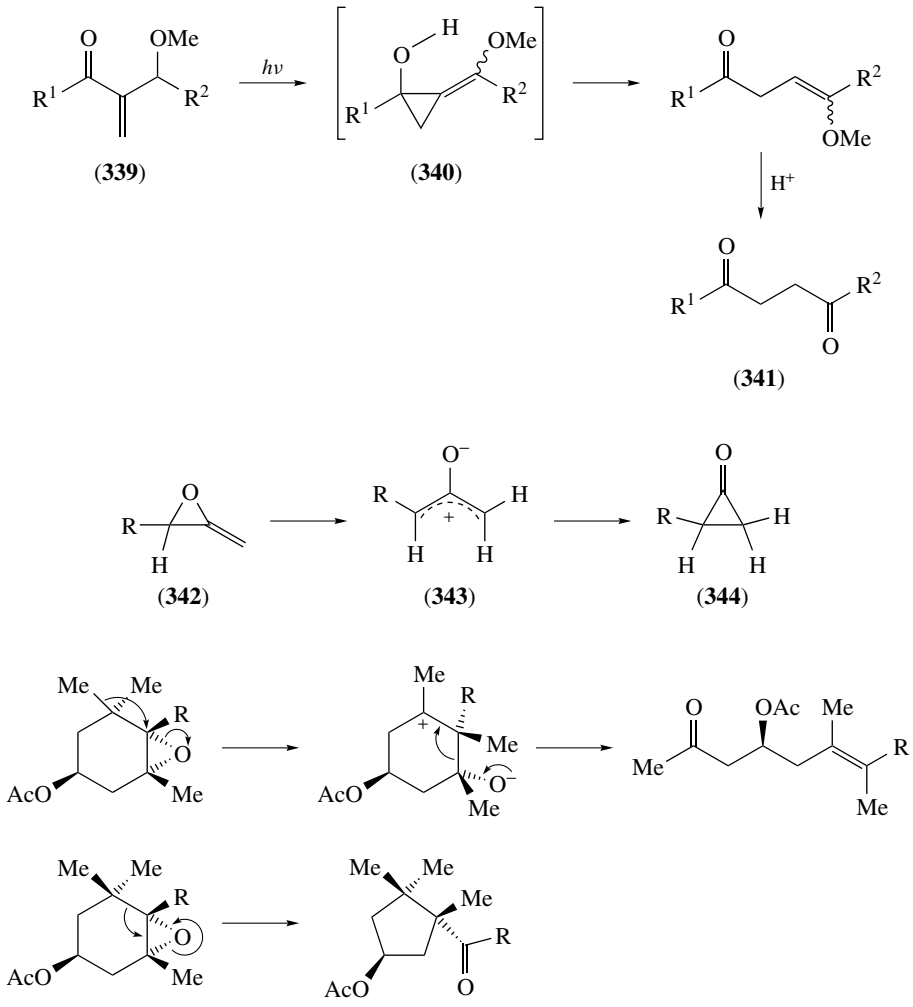
(**332**) (**333**)



SCHEME 104

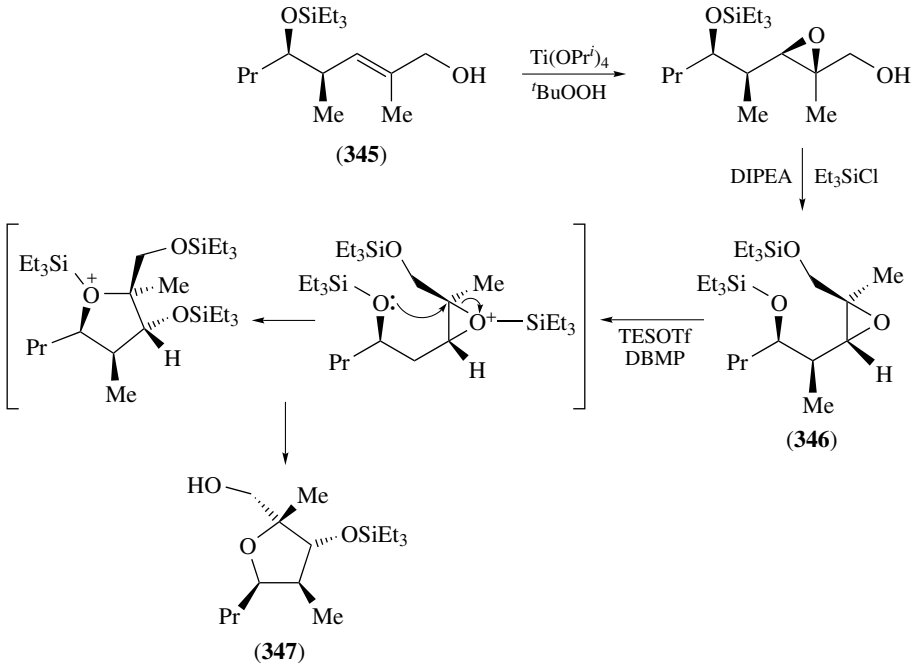
Hydroxymethylenecyclopropanols (**340**) have been shown[494] to be intermediates in the photochemical rearrangement of α,β-unsaturated carbonyl compounds (**339**) to 1,4-dicarbonyl compounds (**341**). The products are eventually obtained by double tautomerization of the enol and cyclopropanol portions of (**340**).

The rearrangements of 3-methylbut-1-ene oxides[495] and 1,2-epoxybut-3-ene[496] on lithium phosphate have been studied, and a detailed theoretical study of the rearrangement of allene oxide (**342**) to cyclopropanone (**344**), which shows that the transformation proceeds via an intermediate oxyallyl (**343**), has been presented.[497] It has been shown that aldehydes, ketones, and cyclic ethers are all produced

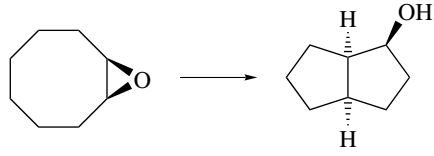


SCHEME 105

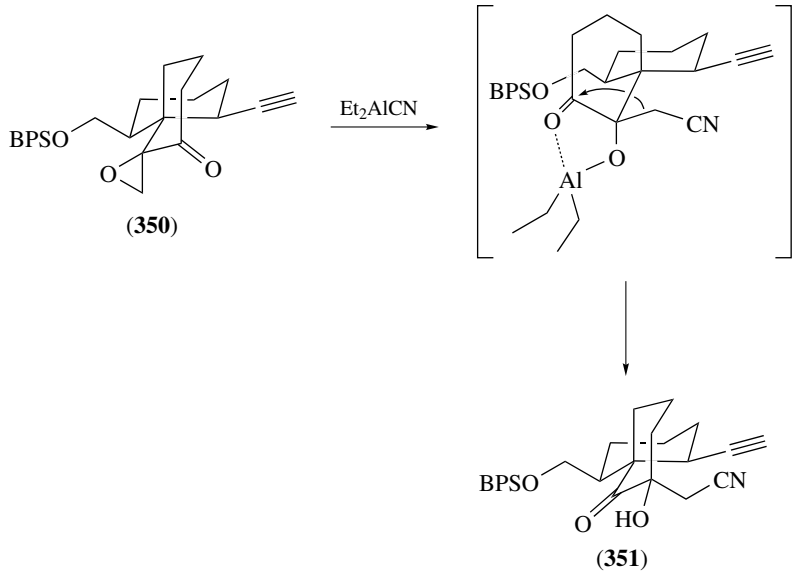
when phenyloxiranes are treated with a clay,[498] while novel acyclic tetrasubstituted olefinic and cyclopentyl end-groups of carotenoids have been obtained[499] by the Lewis acid-promoted stereoselective rearrangement of the epoxide end-group of 5,6-epoxycarotenoids (see Scheme 105). A joint *ab initio* and experimental study of the gas-phase Payne rearrangement has been undertaken.[500] A novel preparative route to a series of tetrahydrofuran-2-methanols (**347**), bearing substituents at all four carbon atoms of the ring, has been described.[501] These compounds have been prepared by the diastereoselective epoxidation of the (*E*)- and (*Z*)-allylic alcohols, e.g. (**345**), silylation of the alcohol to afford the epoxy silyl ether (**346**) and Lewis acid-catalysed rearrangement of (**346**) (see Scheme 106). The isomerization of cycloalkene- and bicycloalkene-derived achiral epoxides [e.g.



SCHEME 106



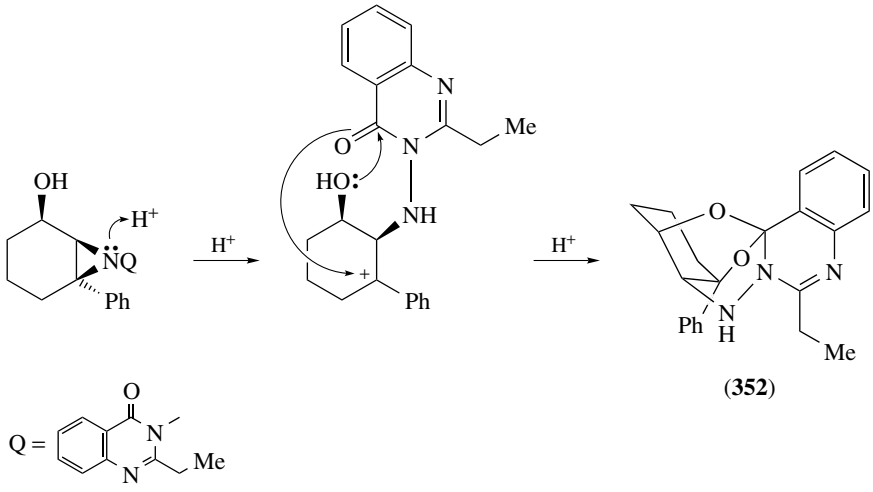
(**348**) to (**349**)] has been achieved[502] by enantioselective α-deprotonation, while a new enantioselective synthesis of *cis*-protected 4,5-dihydroxycyclohex-2-enones from cyclohexa-1,4-diene, via a chiral base-mediated reaction of *meso*-cyclohexene oxides to allylic alcohols followed by oxidation, has been described.[503] Photolysis of *exo*-3,6,7-trioxotricyclo[3.2.2.0^{2,4}]nonane has been found to produce a number of rearrangement products. The authors[504] have proposed that most of these products are the result of initial homolytic cleavage of the C−O bond of the epoxide ring, which does not occur on thermolysis. A new reductive rearrangement of allylic epoxy alcohols to 1,3-diols has been reported,[505] and a tandem epoxide cleavage−1,2-alkyl migration resulting from the hydrocyanation of an α-epoxy ketone has been described.[506] Thus hydrocyanation of (**350**) resulted in regioselective ring opening of the epoxide and subsequent 1,2-cyanomethyl migration to yield the transposed α-hydroxy-ketone (**351**) (see Scheme 107).



(**350**)

(**351**)

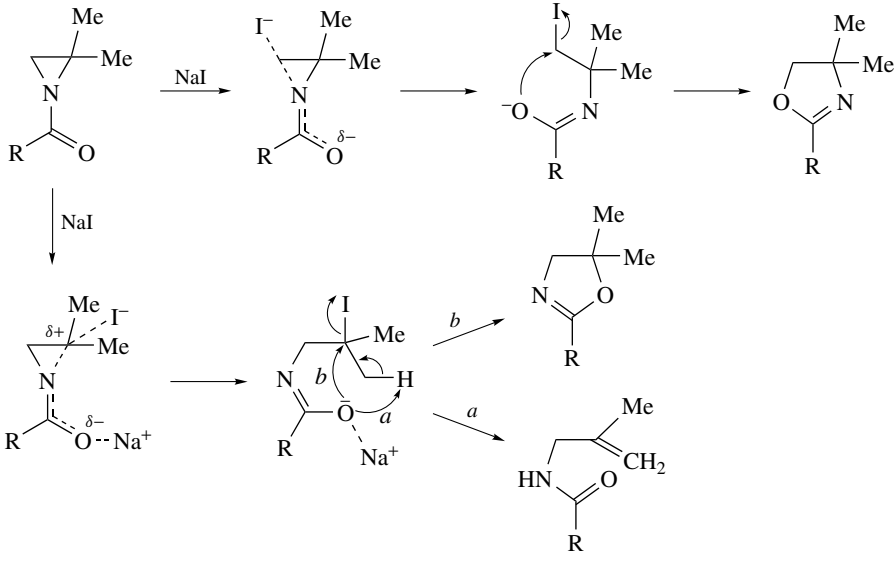
SCHEME 107



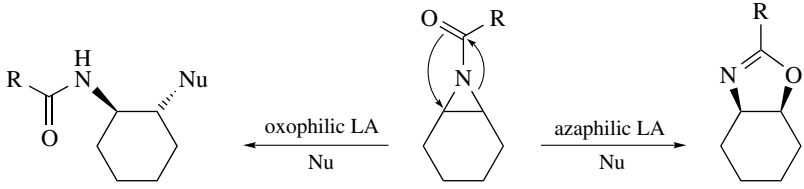
(**352**)

SCHEME 108

The aza-Payne rearrangement and its use as a synthetically valuable equilibration process has been reviewed.[507] Unusual diazadioxabicyclo[2.2.2]octanes (**352**) have been obtained by the acid-catalysed rearrangement of *N*-quinazolinonyl- and *N*-phthalimido-aziridines derived from 3-phenylcyclohex-2-enol.[508] A probable mechanism is outlined in Scheme 108. *N*-Acyl-2,2-dimethylaziridines have been isomerized by sodium iodide into three isomers whose yields appear to depend



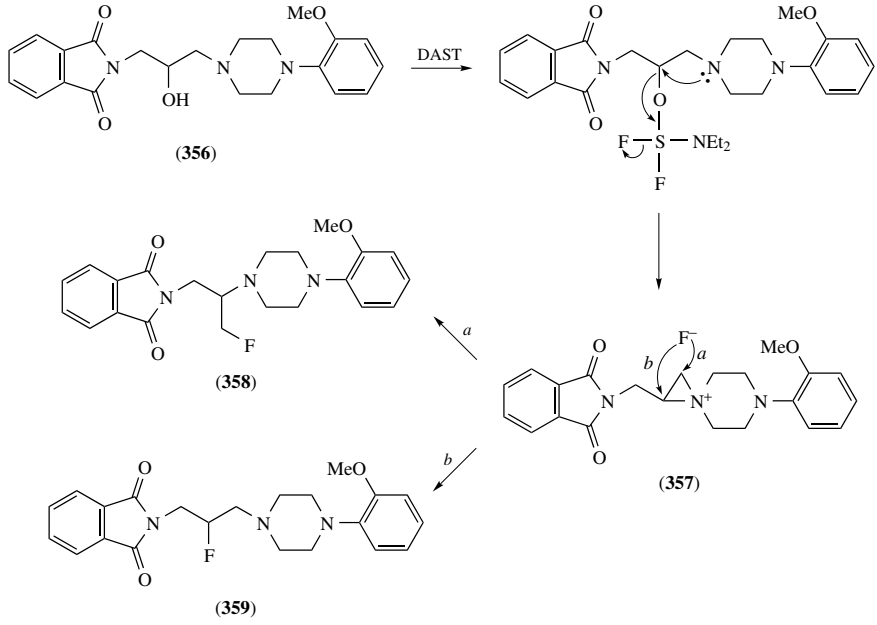
SCHEME 109



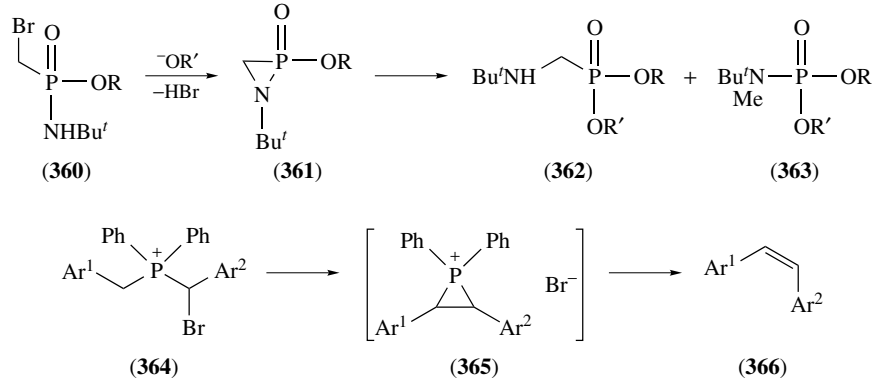
(**354**) (**353**) (**355**)

upon the electronic effect of the acyl group[509] (see Scheme 109), while it has been shown[510] that under certain conditions catalytic quantities of relatively oxophilic metals activate acylaziridines (**353**) predominantly toward external nucleophilic attack, yielding (**354**), whereas more azaphilic Lewis acids catalyse the oxazoline rearrangement to (**355**). Treatment of 1-phthaloylamino-3-[4-(2-methoxyphenyl)piperazin-1-yl]propanol (**356**) with DAST has been found to induce a 1,2-migration via a postulated[511] spiro-aziridinium intermediate (**357**) to yield *N*-[2-fluoromethyl-2-[4-(2-methoxyphenyl)piperazin-1-yl]ethylphthalimide (**358**) and *N*-[2-fluoro-3-[4-(2-methoxyphenyl)piperazin-1-yl]propylphthalimide (**359**) (see Scheme 110).

Methyl *P*-bromomethyl-*N*-*t*-butylphosphonamidate (**360**) has been found to rearrange upon treatment with methoxide to give dimethyl *t*-butylaminomethylphosphonate (**362**) and dimethyl *N*-*t*-butyl-*N*-methylphosphoramidate (**363**). The authors have proposed that the products are derived from an azaphosphiridine oxide intermediate (**361**) by nucleophilic attack at phosphorus and cleavage of the P−N or P−C bond, respectively.[512]



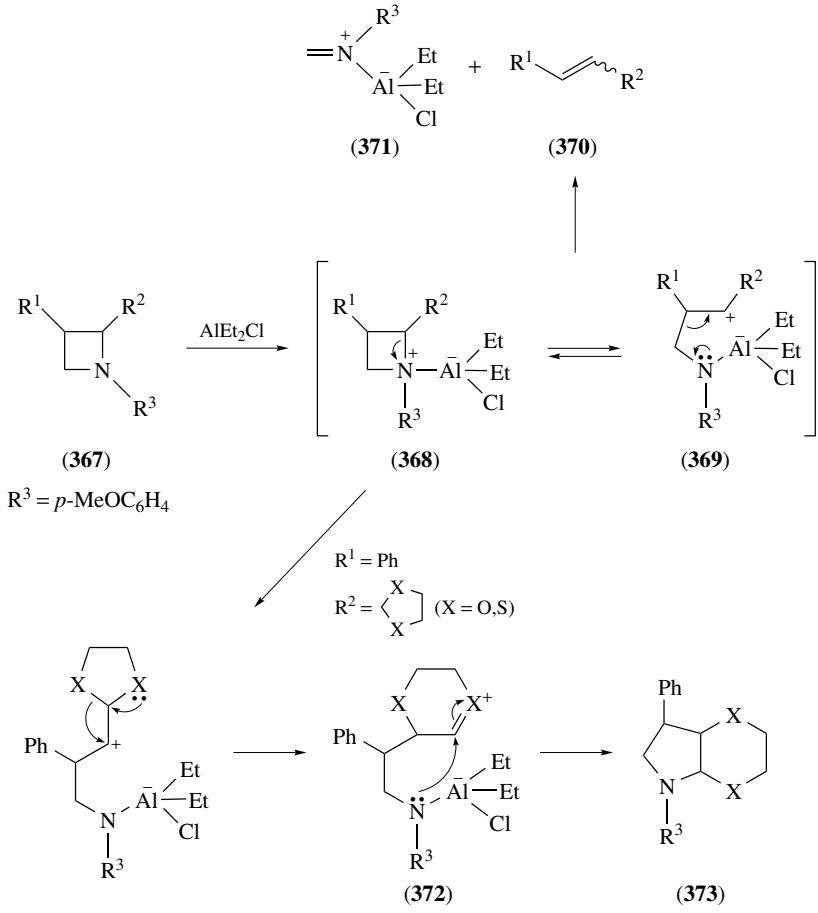
SCHEME 110



Treatment of (α-bromobenzyl)benzyldiphenylphosphonium salts (**364**) with amine bases has been shown to afford alkenes (**366**) with *Z*-selectivity. The reaction is believed to proceed[513] via an *epi*-phosphonium species (**365**) by a mechanism similar to that of the Ramberg–Bäcklund transformation.

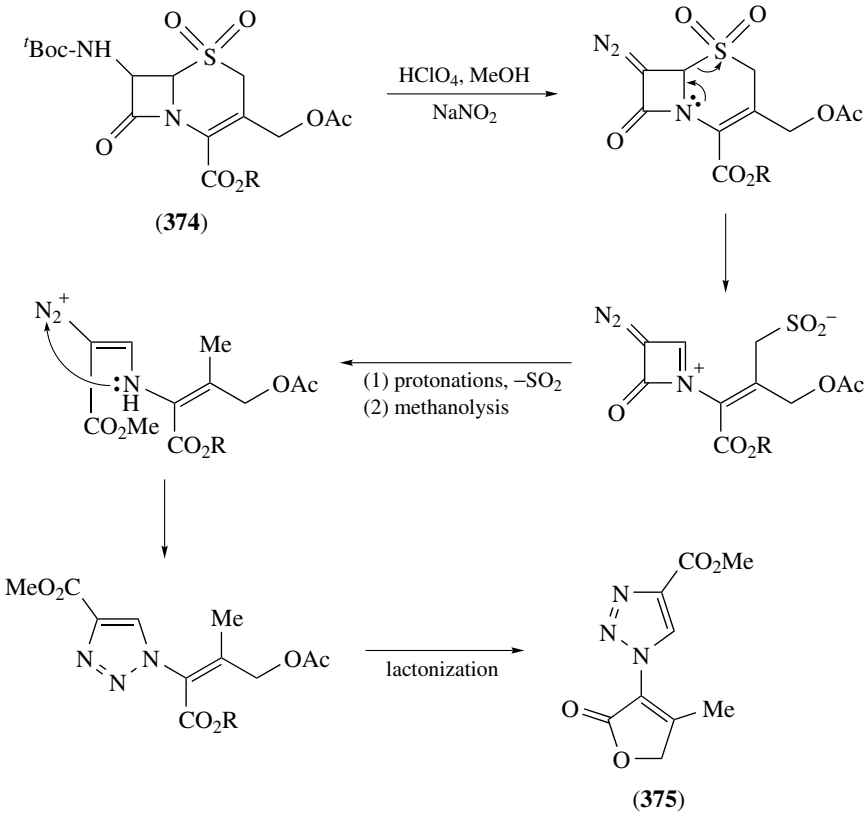
A novel ring-contraction reaction which proceeds via an *epi*-sulfonium ion intermediate has been reported[514] for the simple and regiospecific synthesis of mono- and symmetrically di-functionalized tetrathiamacrocycles, starting with the mono- or dichloro-substituted macrocycles that have one or two more ring atoms.

The formation of a highly strained transient cyclobutane which undergoes cleavage has been invoked[515] to account for the formation of three novel



SCHEME 111

tetracyclic structures formed on acid-catalysed treatment of 5-bromo-3-[1-allyl-2-(3,5-dimethoxyphenyl)ethyl]-2-cyanopyridine. New highly stereoselective fragmentation and rearrangement processes of the azetidine ring (**367**) have been discovered.[516] Plausible pathways for these processes are outlined in Scheme 111 where, as shown, the formation of alkenes (**370**) and fused pyrrolidines (**373**) is considered to occur by the initial coordination of the azetidine nucleus to $AlEt_2Cl$ to give intermediate (**368**). This coordination promotes C(2)−N(1) bond breakage to form zwitterion (**369**) which reacts through two different pathways depending on the nature of the group attached to C(2). For electron-donor aryl groups, the C(3)−C(4) bond breaks to yield the observed olefin (**370**) together with the iminium salt (**371**). The presence of an acetal or thioacetal group on C(2), however, promotes the conversion of intermediate (**368**) into a new carbocation (**372**) which is, in turn, trapped intramolecularly by the nitrogen atom to yield the double-rearranged product (**373**).

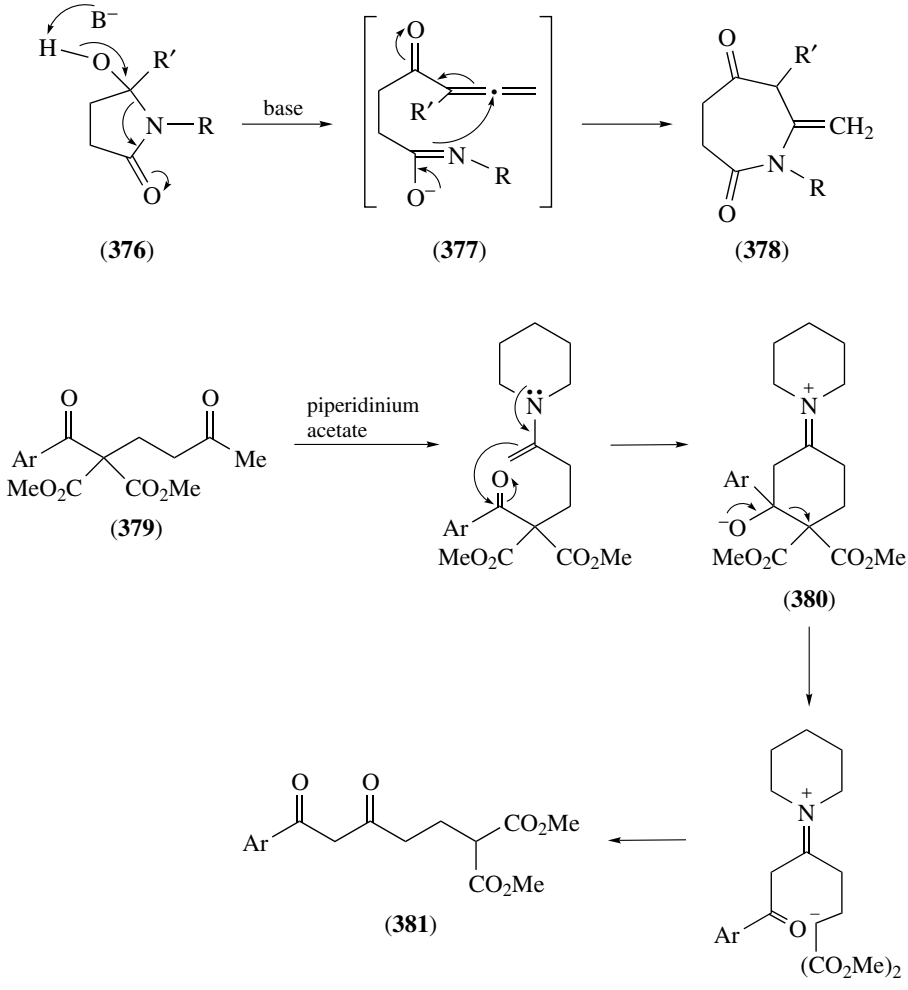


SCHEME 112

7-β-Amino-cephalosporin sulphones, generated *in situ* from the appropriate 7-β-*t*Boc-amino derivatives (**374**) and diazotized in a one-pot reaction in aqueous $HClO_4$–MeOH–$NaNO_2$, have been shown to rearrange exclusively to triazoles (**375**). The multi-step process postulated[517] for this transformation is shown in Scheme 112.

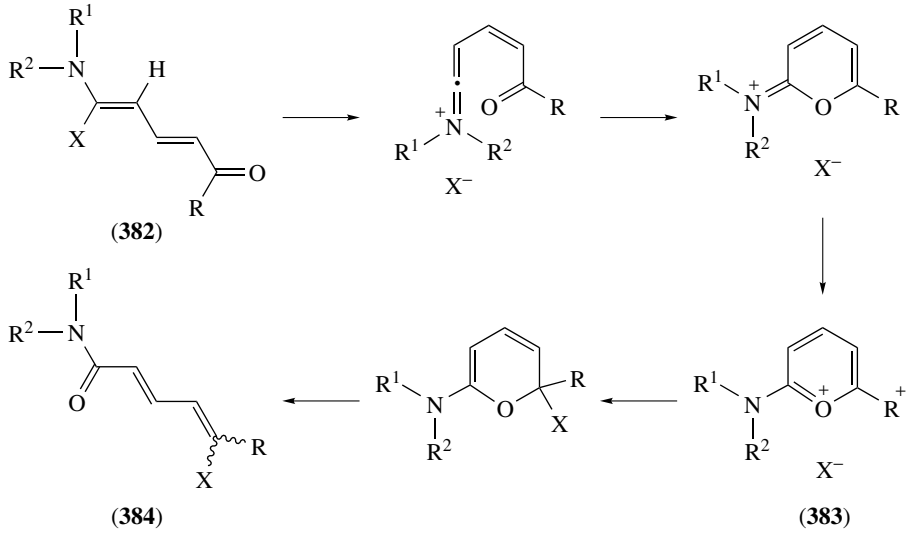
Dihydroxylation of carbapenems bearing an exocyclic vinyl sulfone at C(2) has been found to provide access to the corresponding 2-keto-3-hydroxycarbacephams.[518] In the presence of base, allenylic hydroxy-γ-lactams of the type (**376**) have been found to undergo ring expansion via generation of the conjugated allenyl ketone (**377**), followed by an intramolecular Michael-type addition of the resulting imidate anion to form a two-carbon atom ring-expanded lactam (**378**).[519]

The formation of 1-aryl-1,3-diketones (**381**) from the reaction of the corresponding 1-aryl-1,5-diketones (**379**) with piperidinium acetate has been explained[520] as outlined in Scheme 113 and involves a retroaldol-type reaction in intermediate



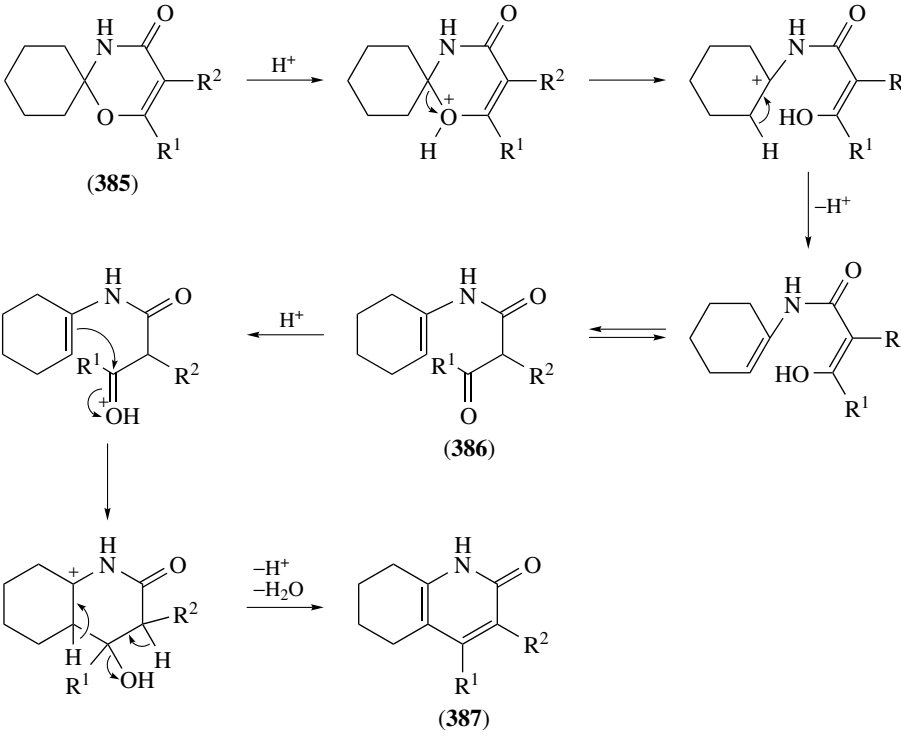
SCHEME 113

(**380**). Undoubtedly, formation of the delocalized malonate anion is the driving force for the carbon–carbon bond cleavage. 2-Aminopyrylium salts (**383**) have been proposed[521–523] as key intermediates in the postulated rearrangement of 5-amino-5-halopentadienals (**382**) to 5-halopenta-2,4-dienamides (**384**) (Scheme 114). 1-Oxa-5-azabicyclo[5.5]undec-2-en-4-ones (**385**) have been readily converted into tetrahydroquinolin-2-ones (**387**) in a one-step reaction involving anhydrous strong acid conditions. A plausible mechanism (see Scheme 115) involves initial ring opening promoted by acid catalysis to afford an enamide intermediate (**386**), which cyclizes to the tetrahydroquinolone ring system.[524]



(**382**) (**383**) (**384**)

SCHEME 114



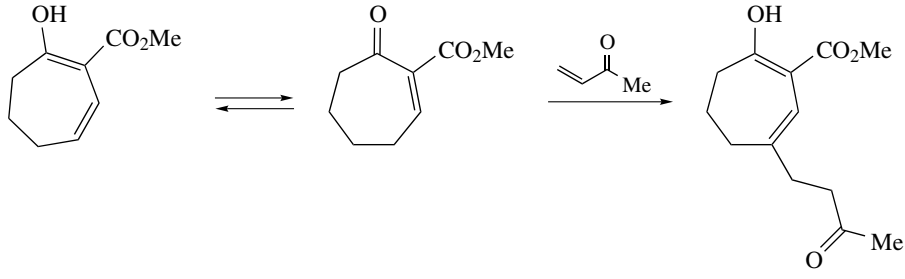
(**385**) (**386**) (**387**)

SCHEME 115

Isomerizations

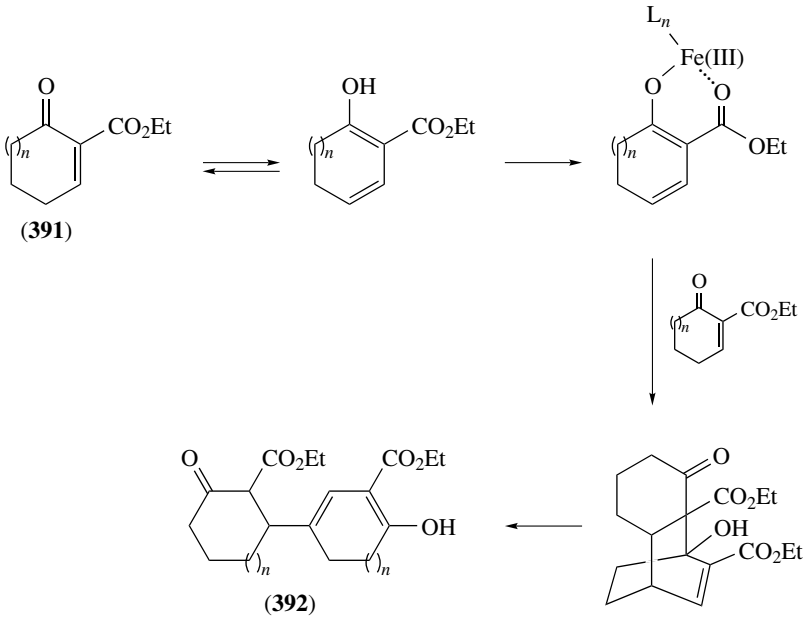
Tautomerism

A mechanistic study of acetophenone keto–enol tautomerism has been reported,[525] and intramolecular and external factors determining the enol-enol equilibria in the *cis*-enol forms of 1,3-dicarbonyl compounds have been analysed.[526] The effects of substituents, solvents, concentration, and temperature on the tautomerization of ethyl 3-oxobutyrate and its 2-alkyl derivatives have been studied,[527] and the keto–enol tautomerism of mono-substituted phenylpyruvic acids has been investigated.[528] Equilibrium constants have been measured[529] for the keto–enol tautomers of 2-, 3- and 4-phenylacetylpyridines in aqueous solution. A procedure has been developed for the acylation of phosphoryl- and thiophosphoryl-acetonitriles under phase-transfer catalysis conditions, and the keto–enol tautomerism of the resulting phosphoryl(thiophosphoryl)-substituted acylacetonitriles has been studied.[530,531] The equilibrium (**388**) $\rightleftarrows$ (**389**) has been catalysed by acid, base and by iron(III). Whereas base-catalysed conversion of (**388**) with methyl vinyl ketone yielded a Michael reaction product in the classical sense, iron(III) catalysis was found[532] to drive the Michael donor (**388**) to react in a vinylogous fashion to yield (**390**). A similar, formally vinylogous Michael reaction product (**392**), generated by a sequence of enone–dienol tautomerization, Diels–Alder, and retro-aldol reactions as outlined in Scheme 116, has been observed[533] during the iron(III)-catalysed dimerization of cycloalkenone-2-carboxylates (**391**).

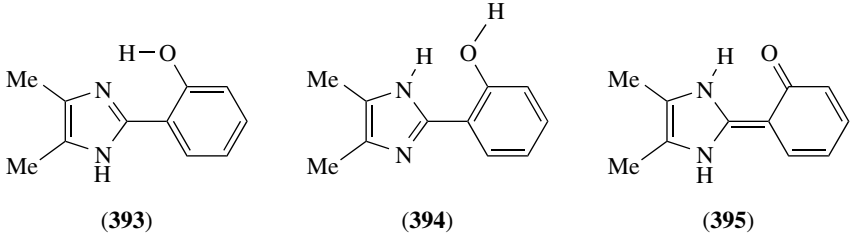


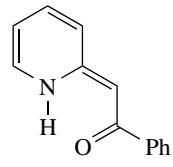
(**388**) (**389**) (**390**)

The various tautomers and rotamers of alloxan have been examined in detail by the MNDO method and it is predicted[534] that the keto form is most important in the gas phase, although in solution the monohydroxy forms are also thought to contribute. A mass spectral study has been used to investigate the enol–keto tautomeric equilibria of a series of substituted salicylaldehyde and 2-hydroxynaphthaldehyde Schiff bases.[535] In neutral, ethanolic solutions, the *cis*- and *trans*-enol forms of 4,5-dimethyl-2-(2′-hydroxyphenyl)imidazoles (**393**) and (**394**) have been found to exist in equilibrium in the ground state. However, in neutral aqueous solutions, the *trans*-enol and keto forms (**394**) and (**395**) were the only species detected.[536] Deuterium isotope effects on



SCHEME 116

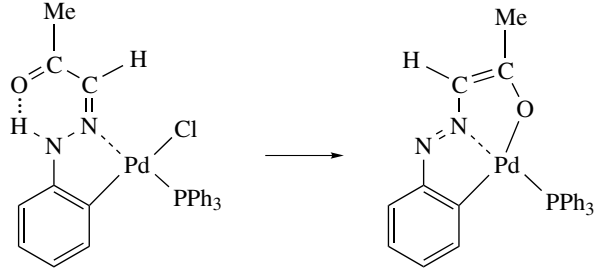




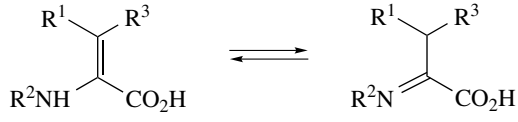
^{13}C chemical shifts have provided independent evidence to show that the enaminone structure (**396**) is the dominant tautomeric form in the enol–enaminone equilibrium of a series of α-heteroaromatic ketones.[537] Semiempirical and *ab initio* calculations on the relative stabilities of the different tautomers of 2,3-dihydroxypyrazine have shown[538] that the species exists predominantly as a dioxo tautomer in both the

solution and gas phase, while a comprehensive theoretical study of the tautomerism of the four isomeric hydroxypyridazine *N*-oxides as well as pyridazine-1,2-dioxide has been presented.[539] The tautomerism of the N(1)-methylated derivatives of uracil, thymine, and 5-bromouracil has been studied in order to analyse its implications in the mutagenicity of 5-bromouridine. The results of the study[540] have provided a basis for ruling out the involvement of non-canonical enol tautomers as the origin of the mutagenic properties. Studies have been reported on the tautomerism of 1-(2-pyrimidinyl)-3-methylpyrazolin-5-one derivatives[541] and 3(5)-ethoxycarbonyl-5(3)-hydroxypyrazole.[542] The significant influence of selenium on the structural properties of the nucleic acid base guanine has been demonstrated.[543]

The azo–hydrazo tautomerism of 1-phenylazo-4-naphthol and its isomers has been investigated by quantum chemical AMI and *ab initio* methods.[544] The syntheses of new palladacycles containing phenylhydrazones derived from 2-oxopropionaldehyde, benzoylformaldehyde, or butane-2,3-dione, in which the organic fragment acts as a bidentate monoanionic ligand in the hydrazo-keto form (**397**), have been described. Deprotonation of the NH group of these complexes has been shown to afford new palladacycles (**398**) in which the organic fragment acts as a terdentate bianionic ligand in the azo-enol form.[545]

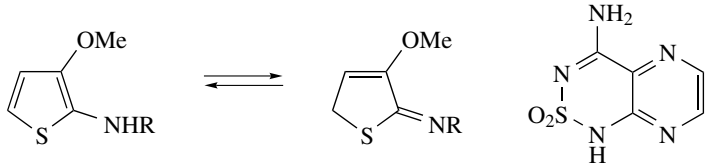


(**397**) (**398**)



(**399**) (**400**)

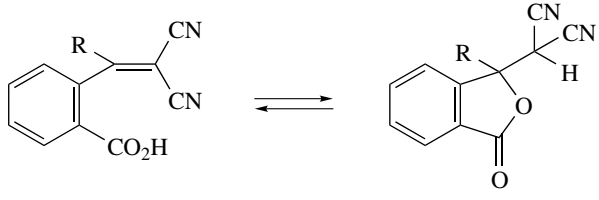
The prototropic tautomerism of 8-azaadenine has been studied[546] theoretically in both the gas phase and aqueous solution by means of *ab initio* methods. It has been shown[547] that dehydrovaline (**399**; R^1 = Me, R^2 = H, R^3 = Me), dehydrophenylalanine (**399**; R^1 = Ph, R^2, R^3 = H), and dehydropipecolinic acid [**399**; $R^1R^2 = (CH_2)_3$, R^3 = H] hydrolyse rapidly via the imine tautomer (**400**) even when the corresponding esters and sodium salts exist as the enamine tautomers. The 3-methoxy-substituted deriva-



(**401**) (**402**)

tives of (**401**; R = Me, Ph) have been reported as the first examples of amino–imino tautomerism in *N*-monosubstituted aminothiophenes.[548] A quantum chemical investigation of the tautomerism of 1,2,3- and 1,2,4-triazoles has been undertaken,[549] the tautomerism of nitrotriazoles has been investigated[550] by combined ^{1}H, ^{13}C and ^{15}N NMR spectroscopy, and the tautomerism of 3-amino-5-nitro-1,2,4-triazole has been studied[551] by *ab initio* MO calculations. A dynamic NMR study of the tautomerism of 2,2′-bisbenzimidazolyl in DMSO-d_6, and a mechanistic interpretation of the process based on a stepwise, single-proton transfer and formation of a zwitterionic intermediate, has been presented.[552] Semiempirical, density functional theory and *ab initio* methods have indicated[553] that, in the gas phase, the most stable tautomer of 4-aminopyrazino[2,3-*c*][1,2,6]thiadiazine 2,2-dioxide is (**402**). A detailed density functional study of the tautomerism of porphyrin and its seven isomers with an N(4)–metal coordination core has been carried out,[554] and the relative energies of different tautomers of inverted porphyrin, carbaporphyrin and certain related ring systems have been determined using geometry optimizations with non-local density functional theory.[555]

Ring–chain tautomerism in 2-acylbenzamides, 8-acyl-1-naphthamides, and 5-acyl-4-phenanthramides has been investigated[556] by IR and ^{1}H NMR spectroscopy. In all cases studied, the hydroxylactam or aminolactone was found to be the predominant species. Ring–chain tautomerism with slow interconversion has been observed[557] in solutions of 2-(2,2-dicyano-1-methylethenyl)benzoic acid and related compounds; see (**403**) ⇄ (**404**). The first examples of ring–chain tautomerism in 2-aryl-substituted imidazolidines have been observed,[558] and instances of ring–chain tautomerism in angularly substituted cycloalkane-fused tetrahydro-1,3-oxazines[559] and in the adducts of 6-nitroazolo[1,5-*a*]pyrimidine with methyl heterocycles[560] have been reported. The ring–chain tautomerism of some Schiff bases of 1-*p*-nitrophenylserinol has been quantitatively described.[561]



(**403**) (**404**)

The valence tautomerism of cobalt–quinone complexes in non-aqueous solvents has been investigated[562] by spectroscopic, electrochemical, and spectroelectrochemical methods, and it has been shown[563] that the cobalt (III) complex of a Schiff base diquinone ligand undergoes an entropy-driven valence tautomeric equilibrium in solution. A new interpretation of the valence tautomerism of 1,6-methano[10]annulenes and its application to fullerene derivatives has appeared.[564]

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