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)

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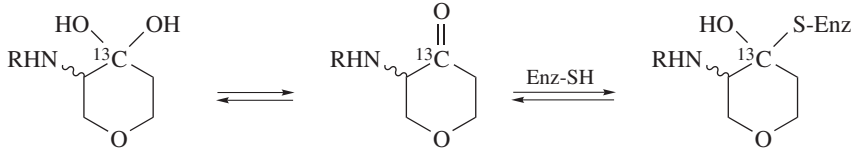
than the simple ethers. Thus the anomeric effect plays an important role in the charged species.

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.

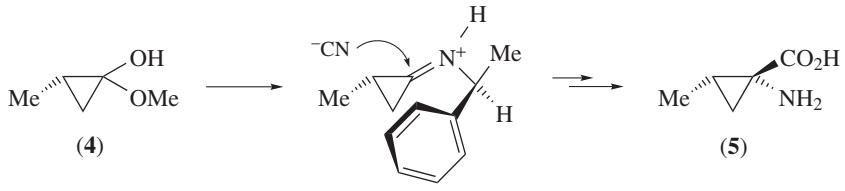
Two stereochemically defined isomeric benzaldehyde acetals, (*R*)- and (*S*)-$ArCH(OMe)(OPr^i)$, undergo methyl-for-methoxy nucleophilic substitution to give the corresponding isopropyl ethers, $ArCH(Me)(OPr^i)$, using $Me_2CuLi{-}BF_3.OEt_2$.[3] The degree of racemization observed indicated that the 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.



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

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.



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

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.

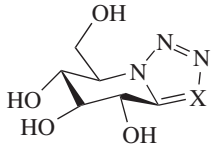
(**7**) (**8**)

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

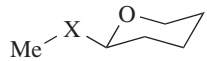
Two azolopyridines (**9a, 9b**; X = N, CH) have been employed as transition-state analogue inhibitors of retaining β-glycosidases, and of glycogen phosphorylase.[10] The roles of catalytic carboxylic acid and carboxylate groups in the β-glycosidases have been calculated; (**9a**) strongly inhibits such 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**)

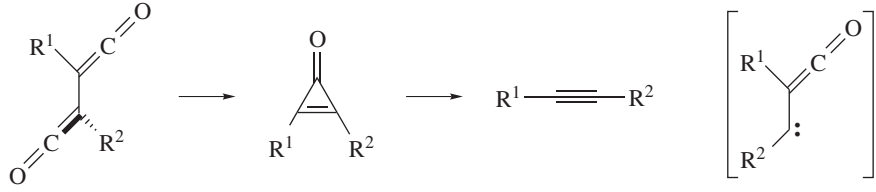
a; X = O
b; X = S

(**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 concerted, 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.

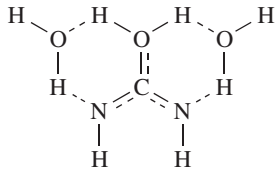
Formation and Reactions of Nitrogen Derivatives

Imines

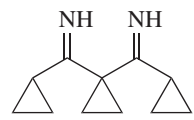
Two theoretical investigations of the condensation of formaldehyde and methylamine to form *N*-methylmethanimine ($H_2C{=}NMe$) have examined the reaction in the gas phase, and also considered the addition of discrete numbers of water molecules.[15,16] Various methods have been employed to quantify solvation-free 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]

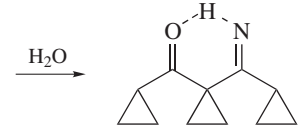
The catalysis of the addition of a water molecule to carbodiimide (HN=C=NH) has been investigated by computational methods, with the number of water molecules being varied.[18] The activation barrier is lowered by 11.6 kcal mol^{-1} with a second water molecule (similar to many such hydrations, e.g. 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.

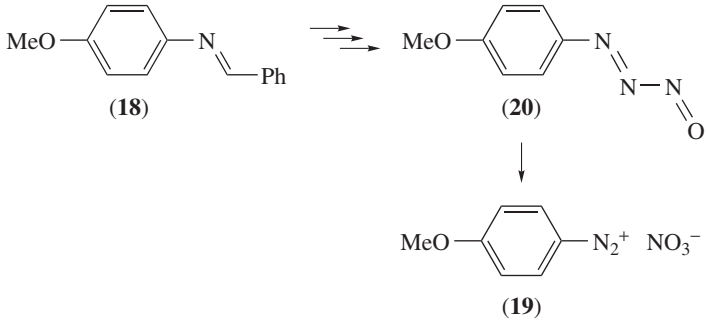
Alkaline hydrolysis of the hypnotic/anxiolytic drug diazepam yields 2-methylamino-5-chlorobenzophenone and its imine, via a dioxide intermediate.[26]

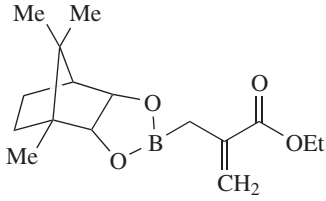
Several reports feature asymmetric synthesis using imines, particularly with organometallics. A chiral sulfoxide lithium salt, *p*-tolyl$-S^*(O)-CH_2Li$, has been added diastereoselectively to a series of *trans*-aldimines, $R^F-CH{=}N-C_6H_4-p$-OMe ($R^F = CF_3$, C_2F_5, CF_2CHF_2).[27a] The sulfoxide 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.





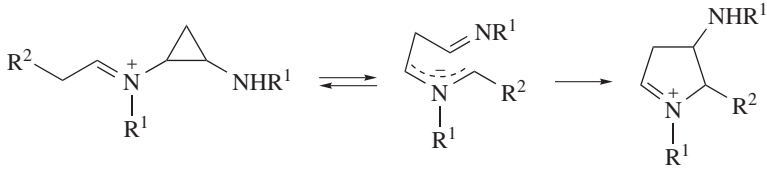
An allylboronate (**21**) reacts with imines in good yield to give homoallylic amines and α-methylene-γ-lactams with high *ee*.[32]

(*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]

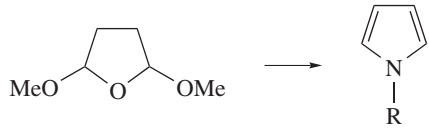
For a stereoselective dialkylzinc reaction with a phosphinoylimine, see *Addition to Organometallics* below; a resolution via a Schiff base is described under *Enolates*.

Iminium Ions and Related Species

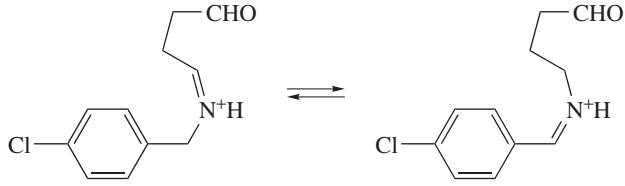
Cis- and *trans*-cyclopropane-1,2-diamines (both primary and secondary) react with a range of aldehydes, R^2CHO, to give pyrroles under very mild conditions.[37] ^1H NMR has been used to identify the intermediates. The key steps involve ring expansion of the monoiminium ion (**22**), via an azomethine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

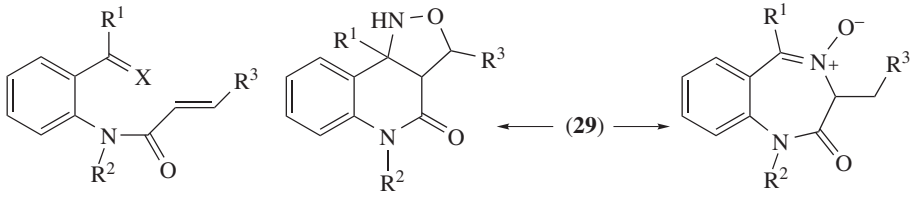
Oximes, Hydrazones, and Related Species

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.



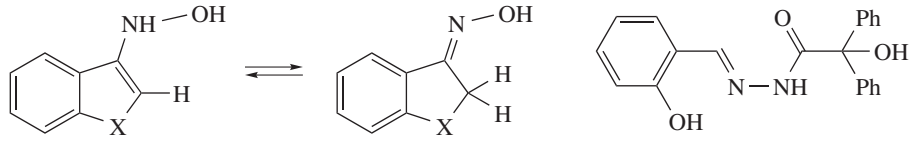
(**28**) X = O
(**29**) X = NOH

(**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**)

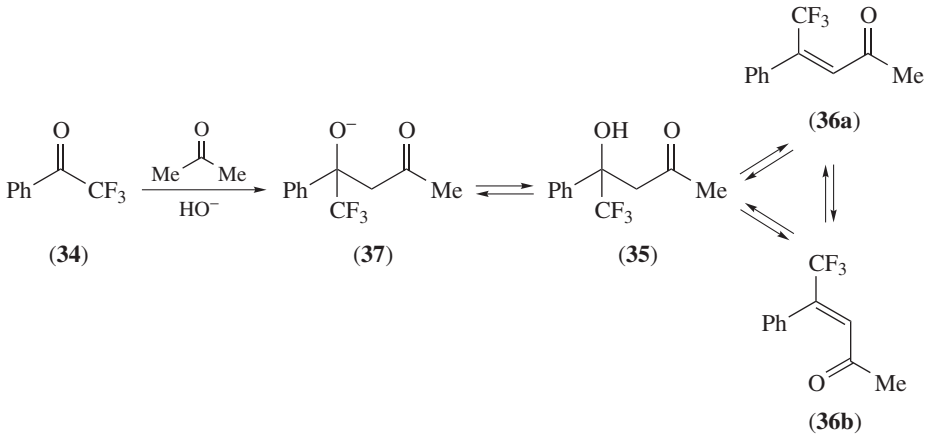
Aminolysis of *O*-aryloximes shows a third-order term for both pyrrolidine and piperidine bases; temperature effects on different routes are reported and explained.[43]

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

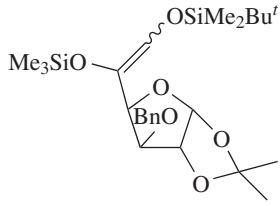
Rate and equilibrium constants have been determined for the aldol condensation of α,α,α-trifluoroacetophenone (**34**) and acetone, and the subsequent dehydration of the ketol (**35**) to the *cis*- and *trans*-isomeric enones (**36a**) and (**36b**).[45a] Hydration of the acetophenone, and the hydrate 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.



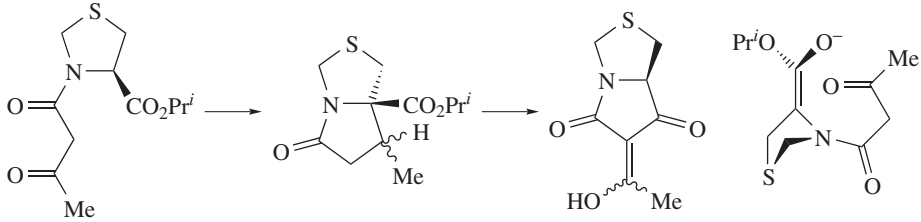
A Hammett correlation has been reported for the retroaldol reaction of a series of *para*-substituted benzylidenemalonitriles, $XC_6H_4CH{=}C(CN)_2$, catalysed by hydroxide in aqueous methanol.[46]

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]

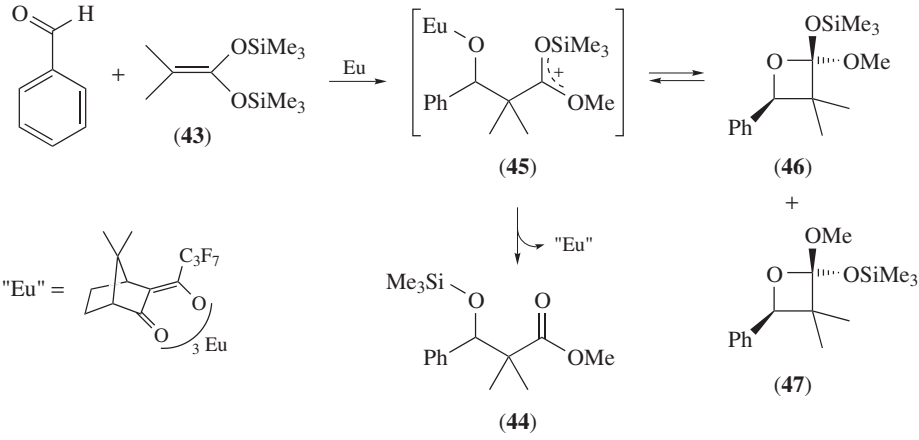
Asymmetric aldol additions of trichlorosilyl enolates of cyclic ketones to aldehydes have been studied, with a particular focus on the electronic effect of the aldehyde on the selectivity achieved.[52]

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

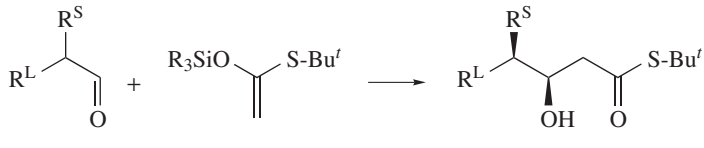
In the Mukaiyama cross-aldol reaction, an aldehyde and a ketene silyl acetal [e.g. (**43**)] react via Lewis acid catalysis to give a β-silyloxy ester (**44**). The reaction

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.



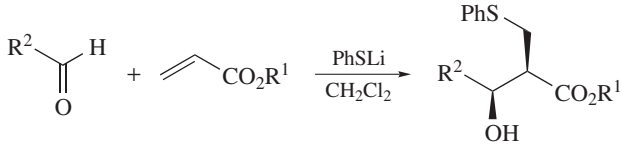
A Mukaiyama-type aldol reaction of silyl ketene thioacetal (**48**) with an aldehyde with large and small α-substituents (e.g. Ph and Me), catalysed by boron trifluoride etherate, gives mainly the *syn*-isomer[56] (**49**), i.e. Cram selectivity. For the example given, changing R from $SiBu^tMe_2$ to $Si(Pr^i)_3$ 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.

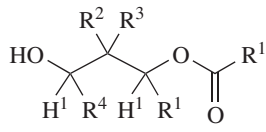


A bulky methylaluminium diphenoxide has been used as a co-catalyst with trimethylsilyl triflate to effect diastereoselective Mukaiyama aldols, including cases with less reactive aldehydes, and with ketones.[58]

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.



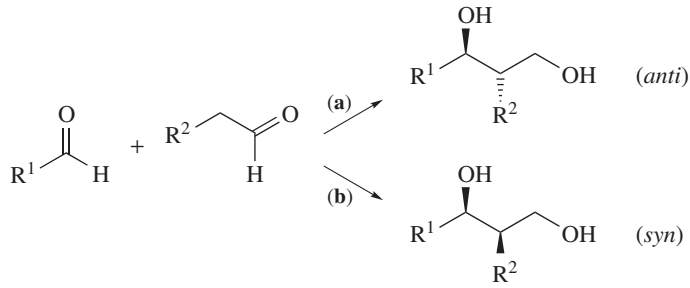
(**50**)



(**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.

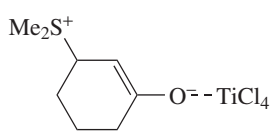


SCHEME 1

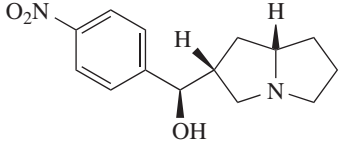
As part of a search for environmentally friendly solid acid–base catalysts, a modified Mg–Al hydrotalcite has been used as a base catalyst for aldol and Knoevenagel condensations.[62] Yields are often quantitative, reaction times are about 1h, the catalyst can be recovered by filtration, and only moderate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

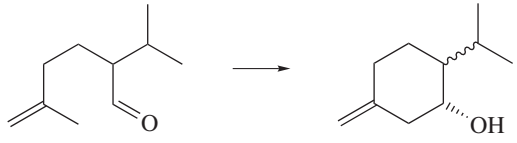
The Baylis–Hillman coupling of activated alkenes with aldehydes or ketones is a useful synthetic route, but can be very slow, even with catalysts from Group 15 (amines, phosphines), or, more recently, lanthanides. A chalcogen variant has now been reported,[65] in which 0.1 equiv. of catalyst gives high 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.

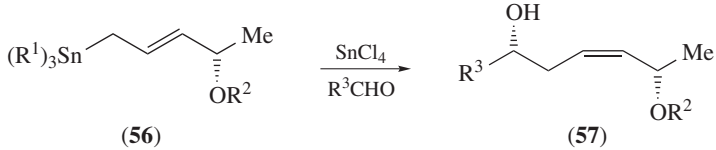
An asymmetric Horner–Wadsworth–Emmons reaction has been developed which uses an external chiral ligand to avoid the need to prepare chiral phosphonate derivatives.[70]

Allylations

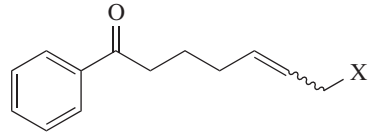
A theoretical study of allylboration of aldehydes shows that (i) an initial complex may form, but if so, it is weak, and predicted reactivity trends are unchanged whether it is taken into account or not, and (ii) electron delocalization from the aldehyde oxygen to the boron *p* atomic orbital governs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

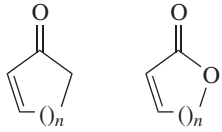
The intrinsic basicities of cyclopentenone and cyclohexenone (**59**), and their lactone analogues (**60**), have been accessed via measurement of their gas-phase proton affinities, and compared with the saturated carbonyl compounds in both cases.[77] The results indicate that:

(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**)

$n = 1, 2$

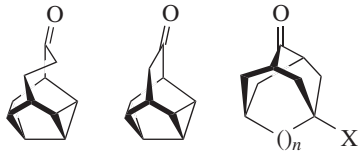
infrared stretching frequency and bond length.[79] However, a correlation of this energy with the atomic charge on the carbonyl oxygen in the isolated molecules failed, but the molecular electrostatic potential at the oxygen *does* show a linear relationship over the whole series studied.

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.

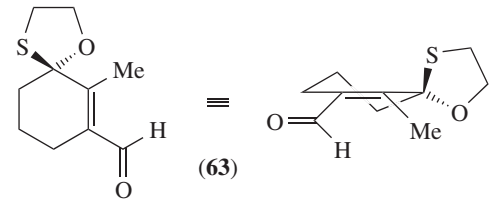
4-Substituted snoutan-9-ones **(61a)** undergo nucleophilic additions with the same facial selectivity as the corresponding norsnoutanones **(61b)**.[82a] However, the selectivity is markedly reduced, apparently owing to electrostatic effects in **(61a)**, and hyperconjugative interactions in **(61b)**.[82b]

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: $n = 2$



(**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]

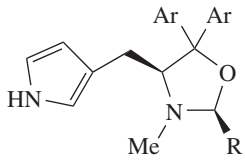
The energy barrier for the gas-phase addition of ammonia to formaldehyde has been calculated,[87] and a molecular dynamics study of its hydration in aqueous sulphuric acid is reported.[88]

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

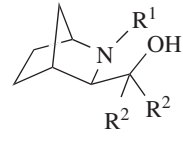
Addition of Organometallics

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).

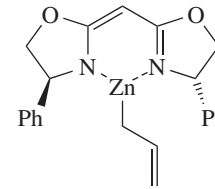
Chiral amines, $ArC^{*}H(R)NH_2$, can be prepared by addition of a dialkylzinc to *N*-(diphenylphosphinoyl)imines, $ArCH{=}N{-}P(=O)Ph_2$, using a suitable auxiliary, followed by acid hydrolysis to cleave the phosphorus moiety.[90] A series of 2-azanorbornylmethanols **(65)** give *ee*s up to 92%, and 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**)

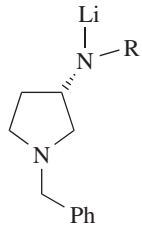


(**66**)

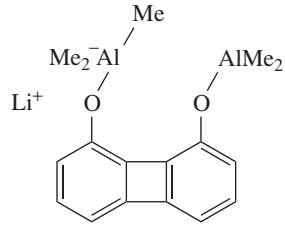
Other diethylzinc studies include enantioselective additions to benzaldehyde using aziridine alcohols as catalysts,[91] to ketones using a camphorsulfonamide–titanium alkoxide catalyst,[92] to aromatic aldehydes using (*S*)-valine-derived *N,S*-chelate ligands possessing a stereogenic nitrogen donor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

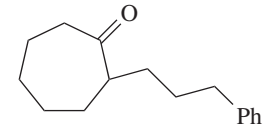
Among other enantioselective alkylations, a series of 3-aminopyrrolidine lithium amides (**67**; derived from 4-hydroxy-L-proline) have been used to induce high *ee*s in the addition of alkyllithiums to various aldehydes.[96] Structure–activity relationships are identified, and the role of a second chiral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

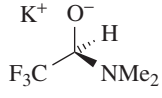
As part of a strategy of employing monosaccharides as a convenient source of chirality, organometallic additions to protected L-erythrulose derivatives have been carried out.[100] Employing silyl, benzyl, trityl, and acetonide protecting groups, the diastereoselectivities obtained are discussed in terms 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]

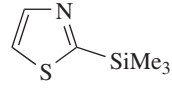
The mechanisms of addition of organomagnesium reagents to 2-hydroxypropanal (a model chiral α-alkoxycarbonyl compound) have been predicted for the gas phase by calculation.[102] Thermodynamics, barrier heights, stereochemistry, intra- versus inter-molecular routes, and stoichiometry ('assisted' intermolecular, 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**)

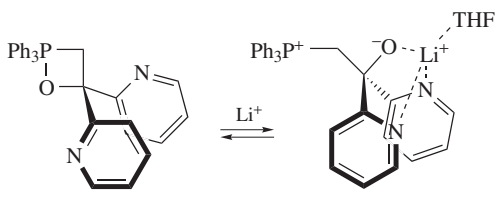
Dondoni pioneered the use of 2-(trimethylsilyl)thiazole (**71**) as a formyl anion equivalent for the homologation of aldehydes.[106a] Extension of this reaction to ketones would be very useful, but has thus far been restricted to trifluoromethyl cases.[106b] However, it has now been widened to include 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.

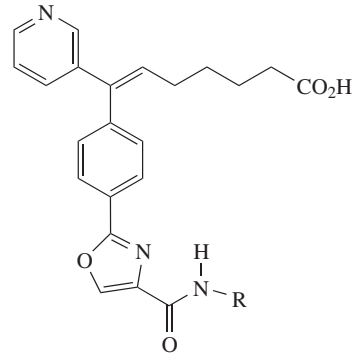
Several studies of the Wittig reaction, and newer variants, are reported.

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**).



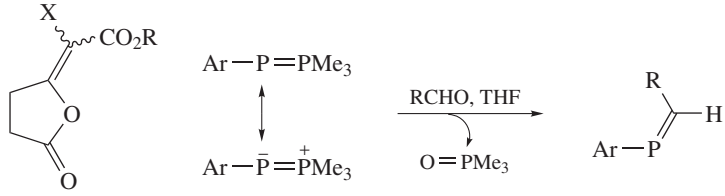
(**72**) (**73**)



(**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]

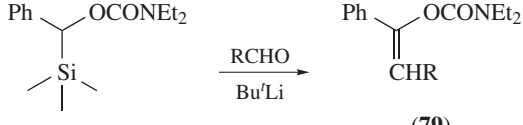
Halo-lactonization of ketophosphoranes has been achieved via reaction with cyclic anhydrides and subsequent halogenation.[111] The products, halo enol lactones (**75**), are synthetically useful compounds, and an alternative synthesis via incorporation of the halogen at the ylid stage is also described. 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*)

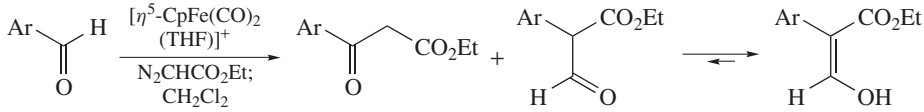
Peterson olefination, a silicon variant of the Wittig reaction, has been used to convert α-silyl benzyl carbamates (**78**) into trisubstituted vinyl carbamates (**79**) in moderate-to-good yields and with some *E*/*Z*-selectivity.[114]

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.

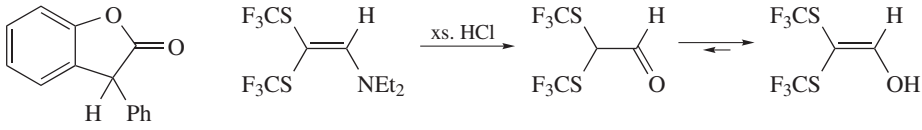
Enantioselective trimethylsilylcyanation of benzaldehydes has been achieved using a lanthanum alkoxide of a chiral binaphthol as catalyst.[120]

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

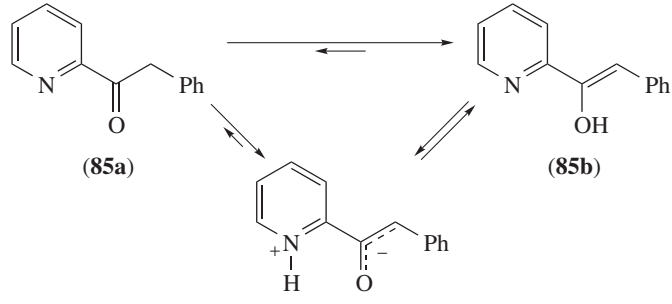
Rate and equilibrium constant measurements for the enolization of 3-phenylcoumaran-2-one (**82**) in aqueous dioxane indicate an enol content of ca 0.1%, a pK_a of 8.9 (6.0 for the enol tautomer), and a fairly symmetrical transition state for enolate anion formation: the Brønsted $\beta_B = 0.52$.[123]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

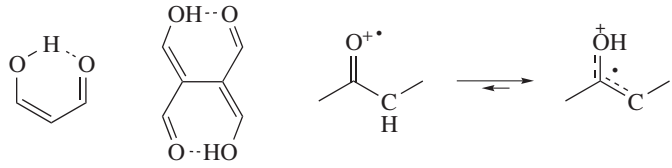


(**85a**) (**85b**) (**85c**)

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]

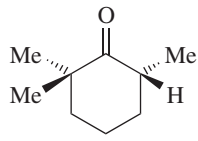
IR spectra of substituted acetophenones, *p*-XC_6H_4COMe, in chloroform suggest the presence of hydrogen-bonded dimers for X = H and NO_2, but not OMe;[130] such association may play a role in keto−enol tautomerization.

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

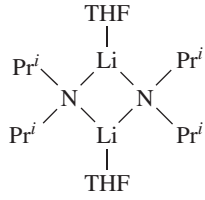
Kinetic and thermodynamic parameters have been measured for the chlorination of simple aliphatic and aryl alkyl ketones in strong acid media by chloramine-B (sodium *N*-chlorobenzenesulfonamide).[132] Catalysis of the monochlorination of acetaldehyde in anhydrous carbon tetrachloride by trichloroacetic 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

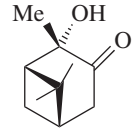
Rates of deprotonation of a simple ketone (**89**) by lithium diisopropylamide (LDA) in THF at −78 °C show a first-order dependence on ketone, and an order of 0.58 (±0.06) in base.[135] Alternative pathways involving the LDA monomer and its solvent-complexed dimer (**90**) are considered.



(**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

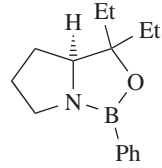
The enantioselective reduction of ketones has been reviewed (317 references).[141]

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.

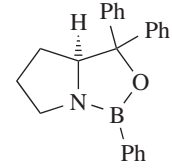
Enantioselective borane reduction of prochiral ketones catalysed by chiral oxaborolidines is of considerable synthetic utility, but the catalytic cycle has to compete with direct borane reduction of the ketone. Accordingly, precise kinetic data on the latter would help optimize conditions for the former.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

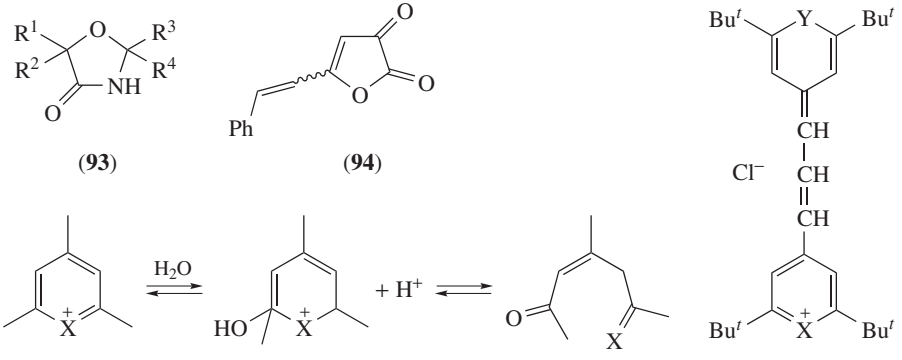
Other Reactions

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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