# ORGANIC REACTION MECHANISMS · 2001

*An annual survey covering the literature dated January to December 2001*

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*Edited by*

**A. C. Knipe**
University of Ulster
Northern Ireland

*An Interscience® Publication*

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# Preface

The present volume, the thirty-seventh in the series, surveys research on organic reaction mechanisms described in the available literature dated January to December 2001. In order to limit the size of the volume, it is necessary to 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 editor conducts a survey of all relevant literature and allocates publications to appropriate chapters. While a particular reference may be allocated to more than one chapter, it is assumed that readers will be aware of the alternative chapters to which a borderline topic of interest may have been preferentially assigned.

In view of the considerable interest in application of stereoselective reactions to organic synthesis, we now provide indication, in the margin, of reactions which occur with significant diastereomeric or enantiomeric excess (*de* or *ee*).

There have been two changes of authorship since last year. We are particularly indebted to Professor K. K. Banerji who, at a late stage, undertook the 'Oxidation and Reduction' chapter in place of Dr C. Braddock. Dr S. K. Armstrong is now contributing the demanding review of 'Molecular Rearrangements', in place of Dr A. W. Murray (who nonetheless provided some welcome bridging assistance). Alistair Murray's formidable contribution to the series over a period of 26 years deserves special mention. During that period he produced ca. 3000 pages of commentary on over 18,000 references. His manuscripts were always notable for their strict adherence to the house style and prompt submission, even though he undertook the longest chapter by far. We thank him for making the editorial task so straightforward and hope that he is now enjoying some light relief in retirement.

Unfortunately authors are not always able to meet even extended deadlines. This may primarily reflect conflicting academic pressures within the U.K. university system but the significant impact on ORM production is evident in our delay in going to press and in the omission of any mechanistic review of radical reactions for 2001.

I wish to thank the production staff of John Wiley and Sons and the team of experienced contributors for their efforts to ensure that the review standards of this series are sustained.

A.C.K.

# CONTENTS

CHAPTER 1

# Reactions of Aldehydes and Ketones and their Derivatives

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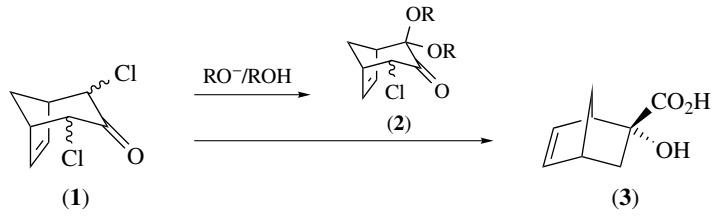
## Formation and Reactions of Acetals and Related Species

The $\alpha,\alpha'$-dihaloketone 2,4-dichlorobicyclo[3.2.1]oct-6-en-3-one (**1**, a mixture of *ax–ax*, *ax–eq*, and *eq–eq* isomers) undergoes a 1,3-transposition in alkoxide–alcohol media to give $\alpha$-ketoacetals (**2**, R = $CH_3$, $CH_2CF_3$, $-CH_2CH_2-$), all of which are readily hydrolysable to the corresponding $\alpha$-diones.[1] The acetal is favoured by an *O,O*-geminal stabilization relative to the $\alpha,\alpha'$-dialkoxy ketone: none of the latter

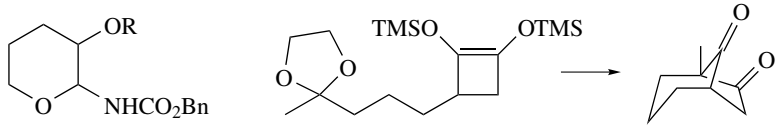
*Organic Reaction Mechanisms 2001*. Edited by A. C. Knipe

was observed. An enolization–ionization mechanism is proposed. In an attempt to produce the $\alpha$-dione directly, (**1**) was treated with aqueous NaOH–THF at 0 °C, but this reaction yielded the ring-contracted product (**3**), via a 1,2-anionotropic shift.

Trimethylsilyl triflate catalyses diastereoselective ring-opening reactions of semi-cyclic *N*,*O*-acetals (**4**) with nucleophiles such as silyl enol ethers.[2] (*de*)




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

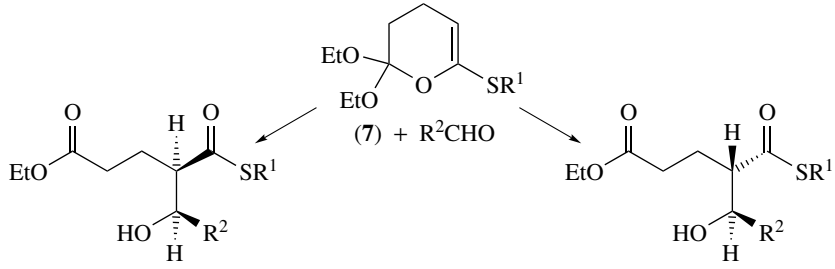



(**4**) (**5**) (**6**)

Acetal (**5**), with a tethered acyloin, undergoes an intramolecular geminal acylation, catalysed by boron trifluoride etherate, to give 1,3-diketone (**6**).[3] The mechanism necessarily differs from the intermolecular version.

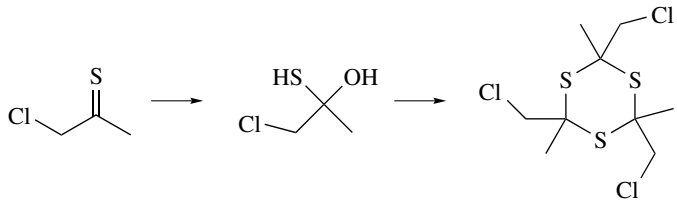
Cyclic ketones can be acetalysed under mild conditions using methanol, with titanium tetrachloride catalyst, whereas cyclic $\beta$-diketones form $\beta$-keto enol ethers under the same conditions.[4] In the case of $\beta$-keto aldehydes, either type of protection can be achieved, depending on the conditions chosen.

*Threo*- and *erythro*-alcohols, (**8t**) and (**8e**), have been prepared by ring opening of a cyclic ketene ortho-ester (**7**) with a range of aldehydes.[5] Enantioselectivities range from 45 to 99%, with *de* values of up to 96%. (*de*)




(**8t**) (**8e**)

A new thioacetal, 1-chloro-2-mercapto-propan-2-ol (**10**), has been isolated from the treatment of 1-chloro-2-propanethione (**9**) with hydrochloric acid; in the presence of water it cyclizes to 2,4,6-tris(chloromethyl)-2,4,6-trimethyl-1,3,5-trithiane (**11**).[6]



(**9**) (**10**) (**11**)

A stereoelectronic correlation of the relative rates of hydrolysis of ketone-derived acetals with their proton affinities considers both cyclic and acyclic cases.[7]

Terminal isopropylidene acetals have been chemoselectively hydrolysed to the corresponding 1,2-diols using $Yb(OTf)_3 \cdot H_2O$.[8] Similar functional groups, even isopropylidene acetals elsewhere in the substrate, are left untouched.

Synthesis and reactions of sugar acetals have been reviewed (21 references).[9]

A stereoselective Prins-pinacol synthesis of acyltetrahydrofurans from cyclic acetals has been reported.[10] Five- and six-membered cyclic acetals have been oxidatively ring opened to give $\omega$-hydroxy esters using hypervalent *t*-butylperoxy-$\lambda^3$-iodanes.[11]

1,3-Dioxan-4-ones, a useful class of cyclic acetals, are described later under *The Baylis–Hillman Reaction*.

## Reactions of Glucosides and Nucleosides

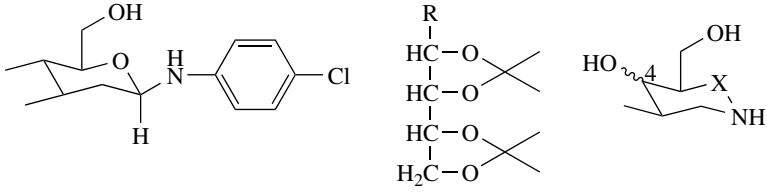
Synthesis and conformational characterization of six new *N*-(pentopyranosyl)imidazoles and their conjugate acids led to a claim that apparent reverse anomeric effects in these systems and, by implication, in many related ones are more accurately described as normal anomeric effects subject to unusual dipolar interactions.[12]

Dynamic density functional theory has been used to identify the conformational origin of the barrier to producing neighbouring group assistance in glycosylations.[13] The authors stress the role of conformation in the kinetic stability of oxocarbenium ions in determining the ultimate outcome of such reactions.

HCl-catalysed mutarotation of *N*-(*p*-chlorophenyl)-$\beta$-D-glucopyranosylamine (**12**) in methanol proceeds via a low-energy acyclic immonium ion formed by protonation of the in-ring oxygen atom; activation parameters are reported.[14]

Rates and equilibria have been calculated for the mutarotation of glucose.[15]

When 2,3 : 4,5-di-*O*-isopropylidene-D-ribose diethyl dithioacetal [**13**, R = CH(SEt)$_2$] is treated under 'standard' hydrolytic deprotection conditions of mercuric



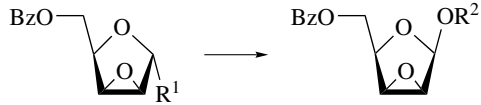
(**12**) (**13**) (**14**)

chloride and oxide in aqueous acetone, a reductive dimeric coupling product is obtained in addition to the expected aldehyde (**13**, R = CHO).[16]

Isofagomines (e.g. **14**; X = $CH_2$) are aza-analogues of monosaccharides, and the p$K_a$s of their conjugate acids are lowered by 0.4 units if the 4-hydroxyl is switched from axial to equatorial, a finding also seen in azafagomines (**14**; X = NH). Looking at other aza-sugars and less highly substituted hydroxyazacyclohexanes, a pattern of 0.4 p$K_a$ units difference emerges when the hydroxyl is in the $\gamma$- and 0.8 when it is in the $\beta$-position. Although modest, the base-strengthening effect of 2.5 or 6.3 for a $\gamma$- or $\beta$-hydroxyl conformational switch is significant, and is not readily explained except as a substituent effect. Such effects should also be evident in ring carbocation stability, and a free energy relationship between rates of acidic hydrolysis of glycosides and p$K_a$s of isofagomines has now been reported.[17]

Kinetic isotope effects have been measured for the hydrolyses of methyl $\alpha$- and $\beta$-xylopyranosides in aqueous perchloric acid[18a] and compared with data for the corresponding glucopyranosides.[18b] The degree of coupling of resonance stabilization of the developing carbenium ion (by the ring oxygen) with exocyclic C−O cleavage is compared for the four systems and extended to the corresponding 5-thio-xylo analogues, which undergo hydrolysis 13.6 ($\alpha$-) and 18.5 ($\beta$-) times faster, respectively.

2,3-Anhydro-$\beta$-D-lyxofuranosylglycosides (**16**) have been prepared in a stereocontrolled synthesis from either the thioglycoside or glycosyl sulfoxide [**15**, $R^1$ = S-Tol or S(O)-Tol].[19] (*de*)

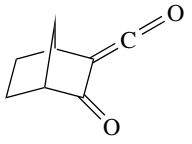



(**15**) (**16**)

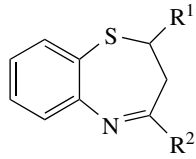
The 'natural' electrophilic reactivity of the anomeric centre in sugars dominated much of their chemistry well into the 1980s. Driven by the increasing recognition of oligosaccharide interactions with proteins or lipids in the cell, synthetic sugar chemistry increasingly involves *nucleophilic* reactivity. Such umpolung methodology using anomeric carbanionoid intermediates has been reviewed (370 references).[20] The coverage systematically works through a wide range of stabilizing groups, such as $NO_2$, $^+PPh_3$, C=O, $CO_2R$, $CONH_2$, CN, $SO_2R$, SPh, and Cl, the elaboration of which allows more control and milder conditions. 'Unstabilized' strategies using glycals are also examined, including their metallations.

## Reactions of Ketenes

Camphorketene (**17**), an early example of an $\alpha$-oxoketene first prepared in 1920, has been reinvestigated.[21] The stereochemistry of its dimers has been determined. It fails to react with benzaldehyde, and camphoric acid derivatives in general show




(**17**)




(**18**)

no enol tautomers, both phenomena apparently arising from ring strain. Evidence for pseudopericyclic mechanisms in some of the reactions of (**17**) is presented.

The products and mechanisms of a series of reactions of 2,4-disubstituted-2,3-dihydro-1,5-benzothiazepines (**18**) with *in situ*-generated chloro- and dichloro-ketene have been investigated for a range of alkyl and aryl substituents $R^1$ and $R^2$.[22]

$N_+$ parameters have been reported for a wide range of amines reacting with cyclic ketenes,[23] covering rate constants (in acetonitrile) of $10^4-10^9$ $mol^{-1}$ $dm^3$ $s^{-1}$.

A new route to fluorine-containing aziridines and $\alpha$-amino esters exploits the reaction of silyl ketene acetals with fluoroalkanesulfonyl azides.[24]

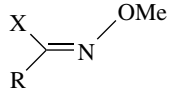
## Formation and Reactions of Nitrogen Derivatives

### *Imines*

The mechanisms of acid-catalysed $Z-E$ isomerization of imine derivatives (**19**; X = Cl, O-alkyl; R = H, Ph, substituted phenyl, CH=$CH_2$, CH=CH−Ph) have been investigated.[25] Two mechanisms have been identified:

(i) iminium ion rotation, the dominant mechanism for the $\alpha,\beta$-unsaturated hydroximate (**19**; X = OMe; R = CH=CH−Ph); and
(ii) nucleophilic catalysis, i.e. nucleophilic attack on the protonated imine to form a tetrahedral intermediate, which undergoes stereomutation and subsequent loss of nucleophile.

Hydroximoyl chlorides (**19**; X = Cl; R = Ph, CH=CH−Ph) proceed via the latter mechanism. In general, the rate of iminium ion rotation is increased by increased conjugation in the protonated imine.




(**19**)

$Z$- to $E$-isomerization has also been studied for azobenzenes and $N$-benzylideneanilines, as a probe reaction for the scope and limitations of transition state theory in viscous solvents.[26] The effects on the rates of slow, diffusive thermal fluctuations

of solvent molecules is discussed, as are the implications for conformational fluctuations in proteins.

*Ab initio* computations suggest that conversion of methane imide azide, HN=CH−$N_3$, to diimide, HN=C=NH, is more exothermic than converting it to tetrazole.[27]

*Ab initio* density functional theory calculations have been used to estimate the geometries and energies of monosubstituted carbodiimides, RN=C=NH, and imines, RN=$CH_2$.[28] Electronegative substituents destabilize carbodiimides whereas electropositive substituents stabilize them. Strongly electropositive groups give a linear geometry, owing to charge repulsion and a preference for *sp*-hybridization at nitrogen. Nitro groups are an exception, stabilizing via a $\pi$-acceptor effect. Comparing other cumulenes, carbodiimides are less sensitive to substituents than isocyanates, but more sensitive than ketenes or ketenimines.

Several papers deal with the formation of imines. New fluorogenic 1,2-indanedione derivatives show potential for use in the identification of fingerprints. The mechanisms of their reactions with amino acids have been probed, and possible intermediates in the form of C−N−C 1,3-dipoles have been trapped with dipolarophiles.[29]

Solvent effects on the rate of condensation of phenylhydrazine with benzaldehyde are reported for pH 11.5 at 25 °C, using aqueous alcoholic solvent mixtures.[30]

The kinetics of interconversion of secondary amines in the condensation of aniline and formaldehyde, and the implications for the manufacture of polymethylene polyphenyl polyamines, have been studied in acidic solution.[31]

Rate and equilibrium constants have been determined for the formation of Schiff bases from pyridoxal 5′-phosphate and a range of hydrazinic pharmaceuticals; hydrolysis of the imines was also measured.[32]

Stereoselective reactions include an *N*-protected $\alpha$-imino ester, EtO−CO−CH=N−P, undergoing an enantioselective nitro-Mannich reaction with nitroalkanes ($O_2$N−$CH_2$−R), to give optically active $\beta$-nitro-$\alpha$-amino esters, EtO−CO−CH(NH−P)−CH(R)−$NO_2$, in up to 94% *de* and 97% *ee*, using a chiral bisoxazoline catalyst.[33] (*de*) In a similar approach, an *N*-tosyl-$\alpha$-imino ester (*trans*-Ts−N=CH−$CO_2$Et) reacts with $\alpha$-carbonyl esters to give highly functionalized 4-oxoglutamic acid esters with comparable *de* and 97% *ee*.[34] (*ee*)

A Mannich-type reaction, in which a lithium enolate of an acetate is added diastereoselectively to aniline-derived aldimines with catalysis by a chiral phenol, depends on the aldimine having an *o*-alkoxy or *o*-fluoro substituent (on the nitrogen side).[35] (*de*) In addition, the aldimine, which is readily isomerizable, is held in an appropriate conformation by the Lewis acid employed.

A Mannich reaction with imines has been used to prepare virtually enantiopure $\beta$-substituted $\alpha$-methyl-$\beta$-amino esters [*trans*-$R^1$−CH*($NHR^2$)−*CHMe−$CO_2$Me].[36]

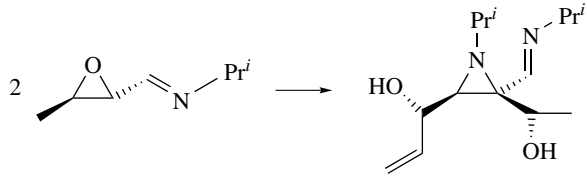
Chiral $\alpha$-amino phosphonates have been prepared by diastereoselective hydrophosphonylation of heterocyclic imines, mediated by Lewis acid catalysts.[37] (*de*)

*N*-Sulfinylimines undergo stereoselective nucleophilic trifluoromethylation with trimethylsilyltrifluoromethane ($Me_3SiCF_3$).[38] This reagent also trifluoromethylates alicyclic perfluoroimines.[39]

Catalytic asymmetric aziridination of imines has been achieved, mediated by sulfur ylids derived from sulfides, and either phenyldiazomethane, a diazo ester, or a diazoacetamide.[40] (de) (ee)

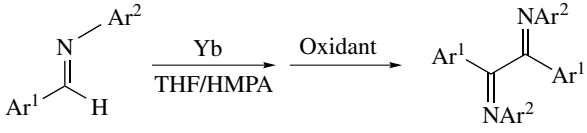
Crossover experiments have been used to assess whether such aziridination of *N*-tosylimines by sulfur ylids is under kinetic or thermodynamic control.[41] Whereas benzyl-stabilized ('semi-stabilized') ylids react irreversibly with imines so that their stereoselectivity is based on the *syn-/anti*-betaine ratio, stabilized cases (e.g. ester- or amide-ylids) react reversibly. Accordingly, stereocontrol will require different strategies, depending on the degree of stabilization selected. (de)

Base treatment of racemic oxiranyl carbaldimine (**20**) gives polyfunctionalized aziridine (**21**), in a new type of highly diastereoselective aza-Darzens reaction.[42] The diastereoselection arises from one enantiomer of (**20**) being deprotonated to form an oxiranyl anion (i.e. a 1-aza allyl anion bearing a $\beta$-oxirane moiety), with the resultant anion attacking the imine carbon *of the other enantiomer*, i.e. a mutual kinetic resolution by double diastereofacial selection. Enantiopure (**20**) does *not* give (**21**). (de)




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

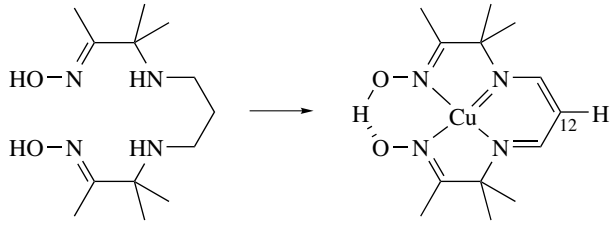
A novel reductive dimerization–oxidative dehydrogenation sequence has been reported for aromatic aldimines (**22**), yielding vicinal diimines (**23**), using 0.5 mol of ytterbium metal and 1-naphthaldehyde (as oxidant).[43]




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

A tetra-aza ligand containing two *N*-hydroxyimine functions (**24**) reacts with copper(II) in alkaline permanganate to give the quasi-aromatic metal complex, 'AH' (**25**),[44] a structure equivalent to [Cu(**24**) − 6H]$^0$. This complex is fairly acidic at the C(12) position, and reacts with aromatic aldehydes to give benzyl alcohols, A–CH(Ar)–OH, and further reaction gives the bis-product, A–CH(Ar)–A.

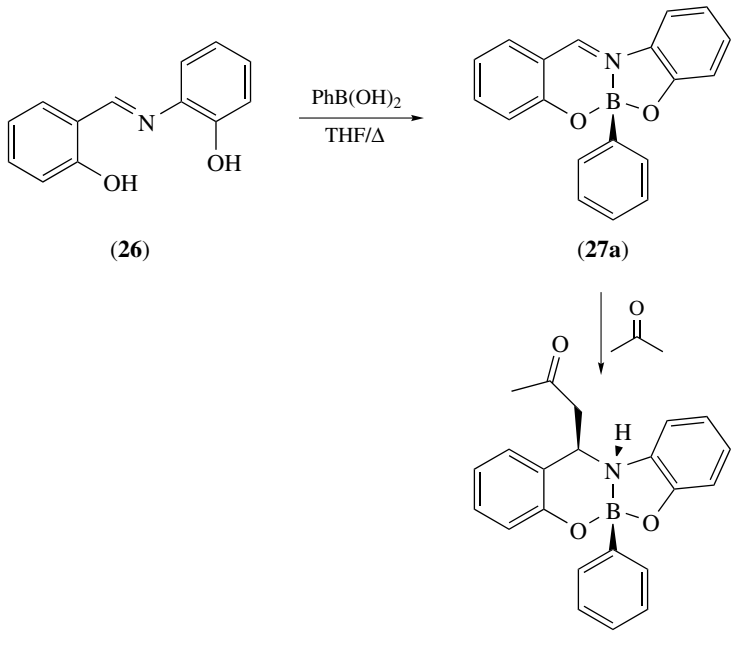
*N*-Salicylidene-2-aminophenolate (**26**), and variants substituted in the aminophenol ring, react with phenylboronic acid to give a [4.3.0]boron heterocycle (**27a**).[45]



(**24**) (**25**; 'AH')

The imine function is now activated by boron, and (**27a**) reacts with acetone to give the all-*cis*-product (**27b**). *de*

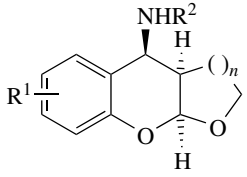
In other stereoselective reactions of imines, a Lewis acid–Lewis base chiral bifunctional catalyst promotes an enantioselective Strecker-type reaction of TMS cyanide with fluorenylimines, including *n*-aldimines and $\alpha,\beta$-unsaturated imines, the latter ultimately giving aminonitriles.[46]



(**26**) (**27a**) (**27b**)

Asymmetric protected 1,2-amino alcohols have been prepared from *t*-butanesulfinyl aldimines and ketimines bearing an $\alpha$-benzyloxy or $\alpha$-silyloxy substituent.[47] *de*

*cis*-Fused furano- and pyrano-benzopyrans (**28**, $n = 1, 2$) can be prepared in high diastereoselectivity from *o*-hydroxybenzaldimines and 2,3-dihydrofuran or 3,4-dihydropyran respectively, using $LiBF_4$ catalysis.[48]



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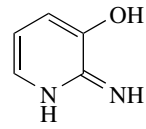

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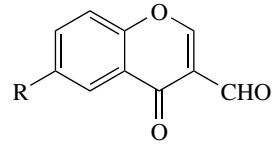


(**30**)

A study of the mechanism and diastereoselectivity of the reaction of naphthols with imines has been undertaken.[49]

In other transformations, a simple iridium(I) complex catalyses direct addition of trimethylsilylacetylene to aldimines, to give $\beta,\gamma$-alkynylamines,[50] and a zirconium catalyst $Cp_2ZrCl_2$, facilitates the addition of Grignard reagents to both aldimines and ketimines.[51] Indeed, the latter substrates are unreactive in the absence of the zirconocene, so this method now opens up a route to amines with a quaternary $\alpha$-carbon. An azazirconapentacycle intermediate is proposed, and initial kinetic and isotope experiments suggest good prospects for an enantioselective version of the reaction. A library screening protocol has been used to synthesize arylamines in up to 98% *ee* and yield, via zirconium-catalysed addition of dialkylzincs to benzaldimines.[52]

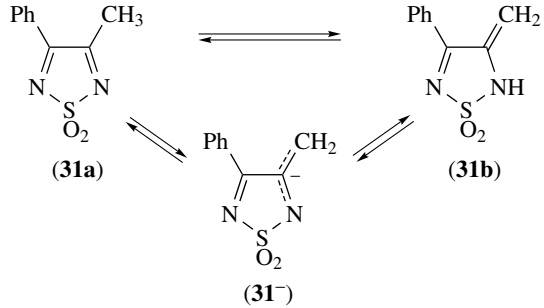
(*ee*)

Several reports describe the tautomerism of C=N systems. The mechanism of tautomerization of 3-hydroxy-2(1*H*)-pyridinimine (**29**), from exo- to endo-cyclic imine, has been probed computationally.[53]

Condensation of aromatic amino acids with 3-formylchromones (**30**) yields an enaminone product in dry aprotic solvent, whereas alcoholic reflux can give an imine-enone tautomer.[54] Structural, hydrogen-bonding, and substituent effects on the tautomeric ratio and on the effective synthetic conditions for maximizing the yield of each structure are reported. Kinetic studies tend to confirm the first tautomer as kinetic product and the second as thermodynamic.

3-Methyl-4-phenyl-1,2,5-thiadiazole 1,1-dioxide (**31a**) undergoes tautomerization to the ene structure (**31b**), via an imine $\alpha$-anion (**31**$^-$);[55] (**31a**) can also react with the anion to form a dimer.

Aliphatic amines react with $\beta$-alkoxyvinyl methyl ketones, $R^1O{-}CR^2{=}CH{-}CO{-}CX_3$ (X = H, F, Cl) to form enaminones; kinetics of the reaction have been measured

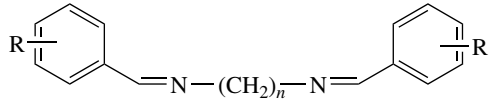


(**31a**) (**31b**) (**31**$^-$)

in a range of solvents.[56] Addition to give a zwitterion is followed by rate-limiting elimination.

Rates of chlorination of substituted benzaldehyde anils by chloramines have been investigated: pH–rate profiles and a Hammett plot have been constructed for the action of dichloramine-B in aqueous methanol,[57] while the use of chloramine-T in aqueous acetic–perchloric acid mixtures exhibits complex acid-catalysed kinetics, with three phases of $H^+$ catalysis.[58]

Studies of imine hydrolysis include a series (**32**, $n = 0, 2, 4, 6$) with cetyloxy groups in either the *ortho*- or *para*-positions of the benzene rings being subjected to acidic conditions in microemulsion systems containing either an anionic (dodecyl sulfate) or cationic (cetyltrimethylammonium) surfactant.[59] The kinetic results have been interpreted as sensors that map the polarity pockets of the microemulsion droplets.




(**32**; R = *o-/p-O*-$C_{16}$)

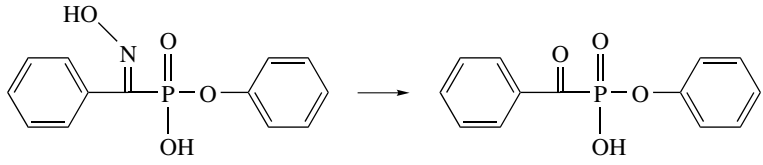
Other papers include measurements of rates and pH profiles for hydrolysis of difunctional Schiff bases derived from *p*-phenylenediamine and aromatic aldehydes,[60,61] and also an examination of the hydrolysis of (benzalamino)quinazolin-4(3*H*)-ones.[62]

The synthetic utility of the addition of alkyl radicals to imines has been investigated, using Lewis acids to control the reaction and to accelerate it.[63] Cases of both activating and deactivating substituents on nitrogen are covered, and modest enantioselectivity can be achieved using a BINAP catalyst. The topic has also been reviewed.[64] (*ee*)

### *Oximes, Hydrazones, and Related Species*

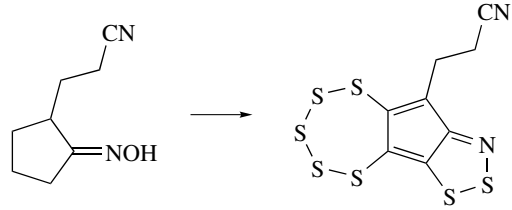
Rate and equilibrium effects have been studied in an investigation of steric and electronic contributions to the reaction of hydroxylamine with a variety of mono-, di-, and tri-cycloketones,[65] and a polarographic method has been used to study the kinetics of the hydrolysis of the 1,3-dioxime of cyclohexane-1,2,3-trione.[66]

(*E*)-Phenyl hydrogen $\alpha$-hydroxyiminobenzylphosphonate (**33**) undergoes two competing reactions in aqueous acid: (i) fragmentation to phenyl phosphate and benzonitrile and (ii) hydrolytic cleavage of the oxime to give the ketone (**34**), which further hydrolyses to phenol and benzoylphosphonic acid, $PhCOP(=O)(OH)_2$.[67] The rate of direct hydrolysis of the ester moiety of (**33**) is estimated as 100 times slower than that of the ketone (**34**), owing to initial protonation of the oxime nitrogen, i.e. the acid-catalysed hydrolysis of the ester in (**33**) is itself retarded by acid, in a type of 'siren effect' in which the 'wrong' site is protonated.




(**33**) (**34**)

Pentathiepin (**36**) has been prepared from a cyclopentanone oxime (**35**), using disulfur dichloride ($S_2Cl_2$), with catalysis by lithium sulfide.[68] A novel cascade sequence, including a vinylogous Beckmann fragmentation assisted by sulfur, is proposed. Structures such as (**36**) are related to natural products such as benzopentathiepins; the latter class include potent antifungals characterized by remarkable stability and a high resistance to inversion of the chair-like pentathiepin ring.




(**35**) (**36**)

Lewis acid catalysts such as aluminium chloride help to optimize Beckmann rearrangements of 1-indanone oximes.[69]

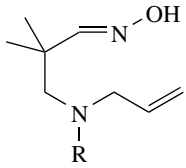
Oximes with $\gamma$- and $\delta$-alkenyl substituents have been cyclized to nitrones, using halogen reagents.[70] In an examination of intramolecular cycloadditions of 3-(*N*-substituted allylamino)propionaldehyde oximes (**37**), the extent and influence of oxime–nitrone isomerizations, to both acyclic and cyclic nitrones, have been considered.[71]

Carbon–nitrogen double-bonded compounds (**38**: oximes, oxime ethers and esters, and hydrazones; $R^4 = H$) bearing an allenic 'tether' undergo a variety of cyclization and isomerization reactions in the presence of tributyltin radical, the product mainly depending on the nature of the Z and $R^3$ substituents;[72] the corresponding dithiosemicarbazides [**38**, $Z = N(Me)CS_2Me$, $R^4 = Me$] typically cyclize under similar conditions to give a range of pyrrole, pyrroline, and pyrrolidine ring systems.[73]

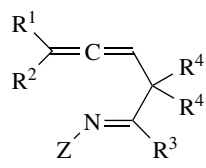
The use of imine derivatives, especially oxime ethers, as radical acceptors in C–C bond construction has been reviewed (25 references).[74]

The reactivities of a series of $\alpha$-acylenamino ketones (**39**) with hydrazine nucleophiles, to form pyrazoles, have been rationalized by a combination of principal component analysis and frontier orbital considerations.[75,76]

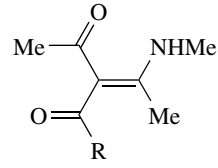
Kinetics of pyrazole formation from the reaction of *E*-4-(*para*-substituted-phenyl)-3-phenylbut-3-en-2-ones with hydrazines have been reported.[77]




(**37**)




(**38**)




(**39**)

The lithio derivative of methoxyallene ($H_2C{=}C{=}CH{-}OMe$) reacts with aldehyde hydrazones to give $\alpha$-allenyl hydrazines, useful precursors to a range of ring systems, especially enantiopure 3-pyrrolines, when SAMP-hydrazones are used;[78] the mechanistic factors determining the balance between the various outcomes have been investigated.[79] (*de*)

Formaldehyde *N*,*N*-dialkylhydrazones, $H_2C{=}N{-}NR^1R^2$, undergo 1,2-addition to carbohydrate-derived $\alpha$-alkoxyaldehydes under neutral conditions, with high *anti*-diastereoselectivity.[80] The hydrazono group can then be manipulated to give an aldehyde (i.e. achieving homologation of the carbohydrate), or converted to a cyanohydrin, and ultimately a nitrile. (*de*)

Homoallylic amines have been prepared rapidly in high yield in DMF at 0 °C without a catalyst, by addition of allyl- and crotyl-trichlorosilanes to benzoylhydrazones.[81] The reactions tolerate considerable steric hindrance in both reactants, and the crotylations display excellent diastereoselectivity.

Benzophenone *N*-(diphenylacetyl)hydrazone reacts with diphenylketene to give a 1,3,4-diazol-2-ene.[82]

Synthetic and mechanistic aspects of heterocyclization of carbohydrate thiosemicarbazones have been examined.[83,84]

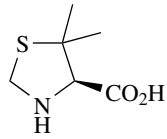
For several examples of oxidative deoximation, see *Other Oxidations*, below.

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

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

L-Proline has moved centre stage not merely as a readily available source of chirality, but also as a catalyst whose sophistication belies its modest structure. Its catalysis of the aldol reaction shows many of the characteristics of an enzymatic system such as aldolase, including high *de* and *ee*.[85] Recent progress in the exploitation of such small molecule 'enzyme mimics' has been reviewed. Other reviews deal more generally with the discovery and development of the asymmetric aldol[86] and with recent advances[87] (47 and 23 references, respectively). (*ee*) (*de*)

Following screening of commercially available chiral secondary amines, L-proline and 5,5-dimethyl thiazolidinium-4-carboxylate (**40**), have emerged as powerful catalysts for the direct asymmetric aldol additions of acyclic and cyclic ketones to aromatic and aliphatic aldehydes with high regio-, diastereo-, and enantio-selectivity.[88] Apparently proceeding via enamine intermediates, these reactions do not require inert conditions, they tolerate water, and they work at room temperature in various solvents. The catalyst can be recovered or immobilized. Extension to imines (*ee*)



(**40**)

(i.e. Mannich-type reactions) and to Michael versions (nitroalkenes, $\alpha,\beta$-unsaturated diesters) are also reported. $\alpha$-Unsubstituted aldehydes have also been employed (in the case of proline).[89]

The origin of the enantioselectivity observed in the proline-catalysed intramolecular aldol reaction has also been elucidated:[90] both selective hydrogen-bonding and the geometry of the proton transfer in the transition state play important roles. (*ee*)

A highly diastereoselective aldol reaction between a $\beta,\gamma$-dialkoxyaldehyde and a silyl enol ether depends on catalysis by magnesium bromide diethyl etherate, which apparently activates both species: the silyl enol ether transmetallates to a magnesium enolate and the magnesium also chelates the alkoxy substituents of the aldehyde.[91] (*de*)

In other bifunctional catalyses, a lanthanide Lewis acid–Brønsted base species accelerates a direct asymmetric aldol reaction,[92] and two binaphthoxide-derived catalysts, one an La–Li bimetallic combination and the other with dinuclear zinc, catalyse direct asymmetric aldol reactions to give *anti*- or *syn*-$\alpha,\beta$-dihydroxy ketones respectively, with modest *de* and good *ee*.[93] (*de*) (*ee*)

Zinc is also used in a phenolate complex with flanking chiral *o*,*o*-bis(amino alcohol) substituents to produce an efficient catalyst: using as little as a 10% excess of an $\alpha$-hydroxyacetophenone and an alkylaldehyde as second reactant, $\alpha,\beta$-dihydroxy ketones [Ar–CO–*CH(OH)–*CH(OH)–R] have been prepared in high *ee* and good to excellent *de*, using a low catalyst loading.[94] (*ee*) (*de*)

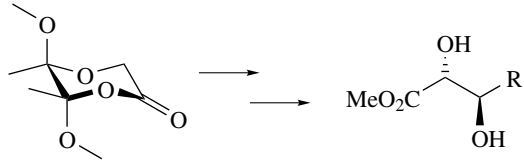
Titanium enolates continue to produce diastereoselective aldols: chlorotitanium enolates of *N*-acyloxazolidinone, oxazolidinethione, and thiazolidinethione propionate substrates, using (−)-sparteine as base, can have their facial selectivity switched by altering the Lewis acid/amine base ratio, apparently bringing about a change from a chelated to a non-chelated transition state.[95] Similarly, titanium enolates of $\alpha$-seleno esters give predominantly *syn*-$\alpha$-seleno-$\beta$-hydroxy esters, with elimination then yielding (*Z*)-$\alpha,\beta$-unsaturated esters[96] (and $\alpha$-selenocyclopentanones react in like manner). Iodide-induced ring opening of cyclopropyl ketones yields enolates that undergo stereoselective aldols, and the $\alpha$-iodoethyl-$\beta$-hydroxy ketone products can be produced in complementary stereochemistries: $TiCl_4$–*n*-$Bu_4NI$ catalyst gives the *syn*-product, whereas $Et_2AlI$ gives the *anti*-product.[97] (*de*) (*de*)

Temperature studies of diastereoselectivities in the aldol condensation of the lithium enolate of *t*-butyl acetate and 2-phenylpropanal in THF and *n*-hexane solvents have allowed separation of enthalpic and entropic contributions.[98] (*de*)

Long-range structural effects on the stereochemistry of the aldol condensation play an important role in a new, efficient synthesis of epothilones (microtubule modulators with anti-cancer potential).[99]

The first catalytic, diastereo- and enantio-selective crossed-aldol reaction of aldehydes has been claimed; using chiral dimeric phosphoramides based on binaphthyl-2,2′-diamine as catalysts, *de*s of up to 98% and a wide range of *ee* performances are reported for the reaction of geometrically defined trichlorosilyl enolates of alkyl aldehydes with a variety of aldehyde acceptors, both aryl and alkyl.[100] (*ee*) (*de*)

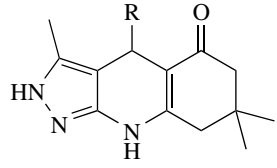
In other diastereoselective aldol reactions, a butane-2,3-diacetal (**41**), acting as a desymmetrized glycolic acid building block, undergoes reaction with aromatic and aliphatic aldehydes to yield enantiopure 2,3-dihydroxy esters (**42**)[101] (following an acidic methanolysis deprotection step). A tandem chain extension–aldol reaction converts $\beta$-keto esters to $\alpha$-substituted-$\gamma$-keto esters,[102] and an aldol reaction of a chiral $\alpha$-silyloxy ethyl ketone is also described.[103] (*de*) (*ee*)




(**41**) (**42**)

Several nitro-aldol-type transformations are also reported, including a proline-catalysed Michael addition of an unmodified ketone to nitroalkenes, to give $\gamma$-nitro ketones in high yield, excellent diastereoselectivity, and moderate enantioselectivity.[104] A similar Michael addition of unmodified aldehydes to nitroalkenes, to produce diastereomeric $\gamma$-formylnitroalkanes, has been achieved in high yield, good *ee*, and excellent *de*, via a morpholinomethylpyrrolidine catalyst.[105] A catalytic enantioselective Henry reaction of nitromethane with $\alpha$-keto esters uses a chiral bisoxazoline–copper(II) catalyst: the product $\alpha$-hydroxy-$\beta$-nitro esters are useful in themselves, but particularly so as a step towards the corresponding $\beta$-amino compounds.[106] (*de*) (*ee*)

3,7,7-Trimethyl-4,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*b*]quinolin-5(6*H*)-ones (**43**), linear tricyclic enaminones, can be prepared in one pot from 5-amino-3-methylpyrazole, dimedone, and an aldehyde (RCHO). When R = H, the product dehydrogenates to the corresponding pyrazolpyridine. No non-linear tricyclic was isolated, and tests using varying order of addition indicate that (i) Knoevenagel condensation of dimedone with aldehyde is the most likely route and (ii) the




(**43**)

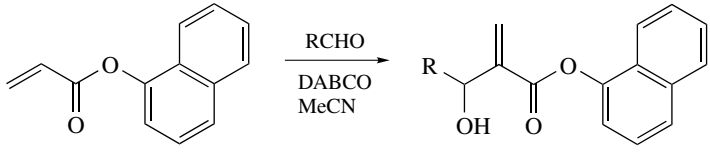
alternative of the pyrazolamine condensing with dimedone *does* give an enaminone, but this does *not* then react with aldehyde. NOESY experiments confirm the 2*H*-structure for (**43**) shown, and not its 1*H*-tautomer.[107]

Knoevenagel condensation of 2-hydroxybenzaldehydes with active methylene derivatives, to produce 2-oxo-2*H*-1-benzopyrans (coumarins), is catalysed by samarium(III) iodide.[108]

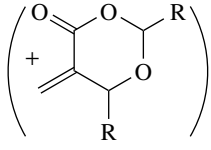
Examples of stereoselective Mukaiyama aldols include the use of chiral BINAP-zirconate enantioselective catalysts[109] (also employed for Mannich reactions of imines), in addition to two vinologous variants of the reaction.[110,111] *ee* *de*

*The Baylis–Hillman Reaction*

This reaction has really come into its own in the last few years, its utilization being driven by marked advances in catalysis, leading to much more convenient reaction times and conditions. An example of the earlier problems is seen in a series of acrylates reacted with aldehydes, using DABCO as a catalyst. Using alkyl, fluoroalkyl, and benzyl acrylates in an attempt to stabilize the enolate intermediate, reasonable yields took days, or even weeks.[112] Phenyl and $\beta$-naphthyl acrylates were somewhat faster, but $\alpha$-naphthyl (**44**) gave (**45**, R = Ph) in 88% yield in 20 min. Further exploration of (**44**) with other aldehydes showed a significant by-product (**46**) for R = Me, Et, and $C_6H_4$-4-$NO_2$. Such 1,3-dioxan-4-ones are a very useful class of cyclic acetals, and excess aldehyde plus 'long' reaction times (i.e. 1–4 h, rather than 20 min) gave (**46**) as major product in 75–91% yield. It is presumed that (**46**) forms from (**45**), followed by elimination of $\alpha$-naphthoxide.

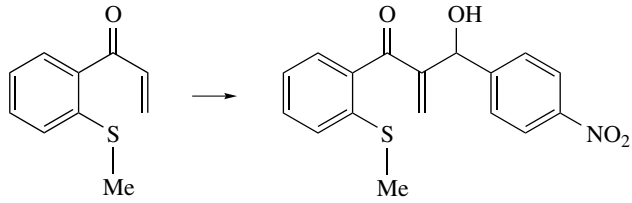



(**44**) (**45**)



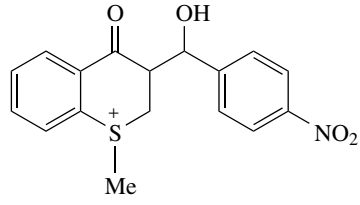

(**46**)

Using a Lewis acid such as boron trifluoride etherate, (methylsulfanyl)phenylpropenone (**47**) undergoes a tandem Michael–aldol reaction to give Baylis–Hillman



(**47**) (**48a**)

+



(**48b**)

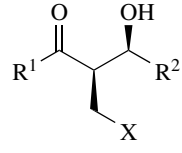
adduct (**48a**) and onium salt (**48b**). Analogous products are obtained from the corresponding seleno reactants, plus some selenochromanone.[113]

Tetramethylguanidine [$Me_2N-C(=NH)-NMe_2$] effectively catalyses the reaction, including examples with simple aliphatic aldehydes. An unsuccessful attempt to use derivatized or supported analogues suggest that the NH is critical to the catalysis.[114]

Titanium(IV) chloride-catalysed Baylis–Hillman reactions are promoted to some extent by oxy compounds, including common oxy solvents such as acetone or alcohols. Aryl aldehydes with electron-withdrawing groups tend to give chlorinated products.[115]

In a modified Baylis–Hillman protocol, a chlorinated aldol adduct has been obtained using quaternary ammonium salts, $R_4NX$, in the presence of titanium(IV) chloride at $-78\,^{\circ}C$. The bromide and iodide salts are more active than the chloride, whereas the fluoride fails.[116]

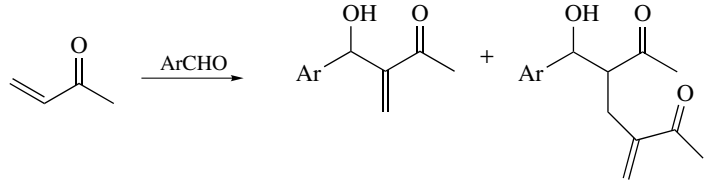
*syn*-$\alpha$-Halomethyl-$\beta$-hydroxy ketones (**49**) have been formed by coupling vinyl ketones and aldehydes using $TiCl_4$–*n*-$Bu_4NX$, with $>99:1$ *syn*-selectivity.[117] (*de*)



(**49**)

Baylis–Hillman reaction of *p*-nitrobenzaldehyde with methyl vinyl ketone (**50**) gives the expected product (**51a**), but also the diadduct (**51b**). Using DABCO as

Lewis base in DMF, high yields are obtained at room temperature in a few days, with the proportion of the dione reaching over 60% when excess MVK (**50**) is employed. A conjugate (Michael) addition is proposed for the second reaction, and substituent and steric effects have been explored.[118]




(**50**) (**51a**) (**51b**)

The reactions of *N*-benzylidene-4-methylbenzenesulfonamide (Ph−CH=N−Ts) with cyclohex- or cyclopent-2-en-1-one give a range of 'normal' and 'abnormal' products, depending on the Lewis base employed.[119]

A catalytic asymmetric aldol reaction of allenoates with aldehydes using *N*-fluoroacyloxazaborolidine as catalyst has been reported.[120] (*ee*)

*Miscellaneous Aldol-type Reactions*

Coupling the enolate of a ketone with the enolate of a carboxylic acid derivative has been reviewed (35 references), focusing in particular on achieving stereoselectivity, especially in the preparation of 1,4-dicarbonyl compounds.[121] (*de*) (*ee*)

The mechanism, reactivity, and stereoselectivity of amine-catalysed aldol reactions involving enamine intermediates have been studied using density functional theory.[122] When primary amines are employed, the reactions involve half-chair transition states with proton transfer set up via hydrogen bonding. This substantially stabilizes charges and lowers the activation energy: without such H-transfer in the transition state (i.e. with secondary amines), oxetane intermediates become important. Stereoselectivities have also been modelled, and intramolecular aldol reactions as well.

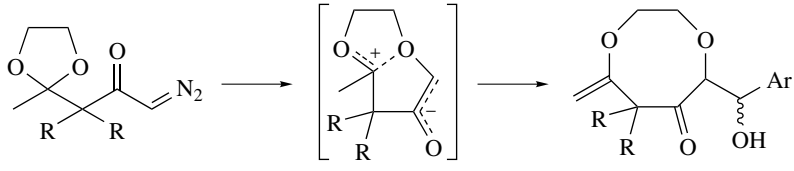
Intramolecular aldol condensations and crotonizations of a wide range of 1,5-diketones and their oxo derivatives have been reviewed (137 references).[123]

The role of tetrachlorosilane in mediating self-condensation of 3,5-dibromoacetophenone in absolute alcohol has been investigated.[124] As well as producing 1,3-bis(3,5-dibromophenyl)but-2-en-1-one, an even larger fraction of the yield turned out to be 1,3,5-tris(3,5-dibromophenyl)benzene.

In a supramolecular exploitation of Curtin–Hammett kinetics, a formylbenzo-15-crown-5 undergoes a potassium-accelerated aldol reaction with an acetylbenzo-15-crown-5, through the fast reversible formation of a 1 : 1 : 1 sandwich complex between the crown ethers and the potassium cation.[125]

Aldol-type C−C bond formation has been reported in the rhodium(II)-catalysed reaction of aromatic aldehydes with diazooxopropyldioxolanes (**52**; R = H, Me) to

give ring expansion products (**54**).[126] This is the first report of such bond formation from ethereal oxonium ylids such as (**53**) via enol silyl ether intermediates. It is suggested that previously such reactions had been unsuccessful since the short lifetime of such zwitterions precluded (kinetic) electrophilic attack of carbon nucleophiles. TMS chloride traps the intermediate, preventing [1,2]-rearrangement, and promotes the $\beta$-elimination (i.e. ring expansion).



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

In a series of papers, the two-step, one-pot synthesis of porphyrins from pyrrole and aromatic aldehydes has been probed by a wide range of spectroscopic and chromatographic methods. The growth, interconversion, and closure of linear oligomers have been studied with a view to optimizing porphyrin yield and purity, including an examination of the synthesis of *trans*-$A_2B_2$-tetraarylporphyrins, from two different benzaldehydes.[127–130]

The kinetics of the isomerization and monomerization reactions of glycolaldehyde dimer have been studied in $D_2O$ (pD = 4.3) at 25 °C.[131] Using $^1$H NMR spectroscopy, seven dimeric and two monomeric forms have been identified and their interconversions characterized.

A kinetic study of the benzoin condensation catalysed by a range of thiazolium ions shows that, with benzaldehyde concentrations typical of synthetic conditions, the three steps of the mechanism are each partially rate determining. This is similar to cyanide catalysis, and may also be relevant to nature's selection of thiamine diphosphate as a coenzyme: many enzymatic processes evolved through the lowering of (high) energy barriers in such a way as to make all barriers in a sequence approximately equal in size under prevailing conditions.[132]

Catalysis of glyoxalate–ene reactions by chiral phosphine–Pt(II) complexes is subject to anion-dependent additive effects, even when the *ee* is little affected. (*ee*) Addition of acidic phenols apparently speeds up the reaction by disrupting contact ion pairs and/or sequestering trace water.[133]

A ligand-controlled addition of acetylene to aldehydes (with *in situ* generation of a zinc acetylide) features a 98% *ee*.[134] (*ee*)

A titanocene(III) complex, $Cp_2TiPh$, promotes inter- and intra-molecular (*ee*) pinacol couplings of aliphatic and aromatic aldehydes to give 1,2-diols diastereoselectively.[135] Air-stable titanium(IV) complexes derived from chiral (*de*) Schiff bases catalyse enantioselective pinacol coupling of benzaldehydes.[136] Stereoselection in pinacol coupling reactions of C=O and C=N double bonds has been reviewed (99 references).[137]

Boron enolates of norephedrine-based glycolate esters react with various aldehydes to produce *syn*-aldol products in high yield.[138] Remote 1,5-stereoinduction has been reported in boron aldol reactions of methyl ketones.[139] (de)

$\alpha$-Stannyl esters have been reacted with $\alpha$-alkoxy and $\alpha$-hydroxy ketones in high yield and >98% *de*.[140] Achieved at room temperature in a few hours, the efficiency of the stereoselection depends on chelation control via a stannous chloride catalyst. (de)

*Allylations*

Indium-mediated allylations of $\alpha$-ketoimides derived from Oppolzer's sultam can be carried out in aqueous ethanol in high yield and *de*, providing a route to enantiopure *t*-$\alpha$-hydroxy acids.[141] (de)

Pyranoside allyltins react with aldehydes, with $BF_3{\cdot}OEt_2$ mediation, in a diastereoselective coupling to give higher carbon sugars, but the corresponding furanosides rearrange and eliminate tin before reacting with aldehyde.[142] (de)

A chiral Lewis base (a binaphthylphosphoramide) has been combined with a weak Lewis acid ($SiCl_4$) to produce a strong chiral Lewis acid. This acts as an enantioselective catalyst for allyation and allenylation of aldehydes in high yield and *ee*.[143] (ee)

Other examples include a highly $\alpha$-regioselective allylation of aldehydes mediated by indium in water[144] (which apparently involves $\gamma$-allylation, followed by rearrangement[145]), and a diastereoselective allylation of aldehydes employing 2-sulfinylallyl building blocks.[146] (de)

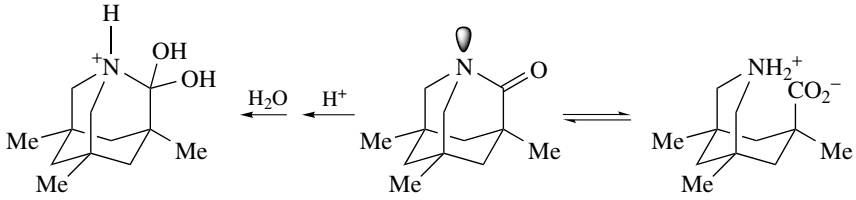
Homoallyl alcohols have been cyclized with aldehydes, mediated by indium trichloride, to yield polysubstituted tetrahydropyrans. The reactions show high yields and excellent diastereoselectivities, with simultaneous control of up to five stereogenic centres. Using the corresponding thiols to synthesize thiacyclohexanes, while giving the same major diastereomers, was somewhat complicated by cyclization–decyclization equilibria.[147] (de)

## Other Addition Reactions

*General and Theoretical*

Synthesis, properties, and reactions of 3,5,7-trimethyl-1-azatricyclo[3.3.1.$1^{3,7}$]decan-2-one (**55**), 'the most twisted amide', have been reported. With an 'amide twist' of 90°, (**55**) behaves as an amino ketone rather than an amide. Its p$K_a$ is 5.2 (for *N*-protonation), and the carbonyl reacts like a normal ketone. Not being stabilized by resonance, it is hydrolysed rapidly to give zwitterionic amino acid (**56**) but, under mildly acidic conditions, this is *reversible*, with the ring closure exhibiting an effective molarity of $\sim 10^{12}$ mol dm$^{-3}$ for the amine nucleophile. (**57**), the hydrate of the conjugate acid (which would be a high-energy intermediate in a 'normal' amide hydrolysis), is stable both in acidic solution and as a crystalline hydrochloride.[148]

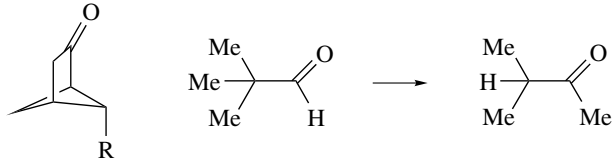
More electrophilic aldehydes and ketones typically react with nucleophiles much faster than less electrophilic analogues. However, this chemoselectivity can be




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

reversed by mediating the reaction with a Lewis acid catalyst. Examples of the exploitation of such reversal are reported.[149]

5-*exo*-Substituted bicyclo[2.1.1]hexan-2-ones (**58**) have been investigated as a new probe of long-range electronic effects on $\pi$-facial selectivity during hydride reduction. Rapid calculation with a simple hydride model setup reproduces the observed selectivities.[150]




(**58**) (**59a**) (**59b**)

*Ab initio* gas-phase calculations on $\alpha$-silyl aldehydes and ketones suggest that hydride attack is stereochemically controlled only by the bulk of the silyl substituent and not by its electropositive nature. Thus hydride approaches *syn* to a silyl group, but *anti* (i.e. in the Felkin–Ahn sense) to a trimethylsilyl group.[151] The finding has implications for the use of H-for-alkyl computational shortcuts in silyl systems.

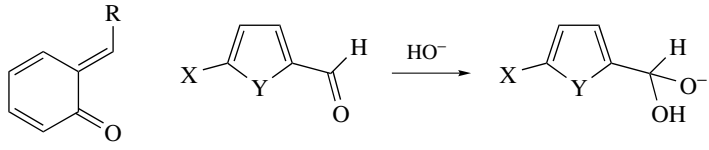
Quantitative rearrangement of pivalaldehyde (**59a**) to methyl isopropyl ketone (**59b**) has been reported in highly acidic media, such as triflic acid, anhydrous HF, and $BF_3 \cdot 2CF_3CH_2OH$. The reaction, which involves formal H-for-methyl exchange on adjacent carbons, apparently involves the *O*-diprotonated aldehyde. Analogies with addition of CO to isobutane in HF–$BF_3$, to give (**59b**), are discussed.[152]

Low-pressure FT-ICR mass spectrometry has been used to probe methyl cation transfer between methanol and protonated methanol, protonated acetonitrile, and protonated acetaldehyde: the enthalpies of activation (16.9, 16.5, and 18.4 kJ mol$^{-1}$, respectively) are strikingly similar, indicating similar transition-state structures.[153]

The factors determining various outcomes in the base-catalysed reaction of cyclic and non-cyclic $\alpha$-dicarbonyls, viz. (i) benzil–benzilic acid-type rearrangement, (ii) bond fission 'outside' the carbonyl system, and (iii) fission between the carbonyls, have been reviewed (23 references). The fate of cyclic substrates largely depends on the extent of ring strain.[154]

*Hydrates and Hydrate Anions*

Several quinone methides (**60**, R = H, Ph, *p*-$MeOC_6H_4$) have been generated by flash photolysis from the corresponding *o*-hydroxybenzyl alcohols. pH–rate profiles for their hydration (back to the precursors) are reported, and also their reaction with nucleophiles such as bromide and thiocyanate. All additions are acid-catalysed, and inverse isotope effects indicate that they involve pre-equilibrium protonation to produce benzyl carbocations.[155]




(**60**) (**61a**) (**61b**)

In a computational study of substituent effects on five-membered heteroaromatic rings, the (X-to-carbonyl) transmission efficiency in the heterocyclic aldehyde (**61a**) increases in the order Y = NH > O > S > PH, but this is reversed for the hydroxide adducts (**61b**).[156]

A polarographic method has been developed for measuring the rate of dehydration of ethane-1,1-diol, the hydrate of acetaldehyde. Due allowance for diffusional effects between depolarizer and bulk solution allow the results to be compared with those obtained by other methods.[157]

For a hydrate of a '1-ammonium ketone', see the 'the most twisted amide' (**55**), above.

*Addition of Organozincs*

The current state of catalytic asymmetric organozinc additions to carbonyl compounds has been reviewed (233 references). The authors emphasize that although enormous efforts with dialkylzinc additions have brought it to a state of maturity, much remains to be done in the cases of aryl-, vinyl-, and alkynyl-zinc additions. The scope for practical technologies exploiting macrocyclic and polymeric chiral catalysts is examined, focusing on the advantages of ease of product isolation and catalyst recovery inherent in such methods and their scope for continuous production.[158] All reports below deal with enantioselection, mainly with diethylzinc. (*de*) (*ee*)

Transition states for addition of dialkylzincs to aldehydes, promoted by chiral amino alcohols, have been characterized using two complementary computational methods: one (Q2MM) allows a rapid survey of conformational space, whereas a slower but more searching follow-up more thoroughly checks the results of the first.[159]

Amino acid-derived $\beta$-amino alcohols catalyse the enantioselective addition of diethylzinc to aldehydes. One case exhibits a strong non-linear effect (i.e. asymmetric amplification), in which a mere 20% *ee* (at 10% catalyst loading) gave 93% *ee* for addition.[160] (*ee*)

$Et_2Zn$ addition to *N*-diphenylphosphinoylimines, Ar−CH=N−P(=O)$Ph_2$, is catalysed by diastereomeric 2-aminoethanols, and yields chiral amines, Ar−CH*(Et)−$NH_2$, after acidic hydrolysis of the initial diphenylphosphinoylamide products.[161] (*ee*)

A fluorous $\beta$-amino alcohol derived from ephedrine acts as an enantioselective catalyst for addition to aldehydes; filtration through a fluorous reversed-phase silica gel allows for its recovery and re-use.[162] (*ee*)

Other papers report catalysis by a new chiral, $C_2$-symmetric titanium diol complex,[163] an azetidine derivative,[164] a menthone-derived amino alcohol,[165] $\beta$- and $\gamma$-amino alcohols derived from (+)-camphor and (−)-fenchone,[166] and a chiral diamine the selectivity of which is reversed on methylation of the nitrogens.[167] (*ee*)

A pyrimidyl aldehyde has been reduced enantioselectively by addition of diisopropylzinc, using a chiral paracyclophane as the initiator of an autocatalytic sequence,[168,169] and an enantioselective addition of an alkenylzinc to an aliphatic aldehyde has been reported.[170] (*ee*)

See *Imines* above for another addition of an organozinc.

### *Addition of Other Organometallics*

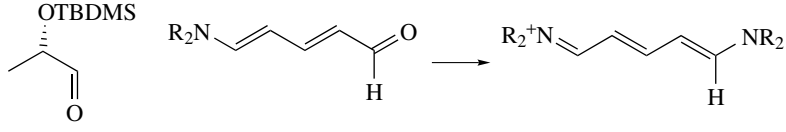
Much of the focus was on diastereoselection: addition of organometallics to five- and six-membered cyclic ketones was achieved via prior incorporation of a (*Z*)-$\beta$-stannylvinyl group;[171] methylmetal reagents were added to 2-methylaldehydes;[172] and methyllithium was added to chiral (*E*)-aryl aldehyde oxime ethers to give *O*-alkylhydroxylamines, which, after reductive N−O bond cleavage, gave (*R*)-1-(aryl)ethylamines.[173] (*de*)

A chiral acetal derivative of tributylstannylmethanol, derived from L-valine, undergoes diastereoselective 1,2-addition to aldehydes, using butyllithium to transmetallate; subsequent acid hydrolysis yields a chiral diol [$HOCH_2$*CH(OH)R] derived from the aldehyde and recovered chiral auxiliary.[174] (*de*)

(2*S*)-*O*-(*t*-Butyldimethylsilyl)lactal (**62**) undergoes diastereoselective addition of ethylmagnesium bromide; the *anti: syn* ratio of the products shows a marked dependence on the nature of the ethereal solvent employed, with an accompanying temperature dependence.[175] (*de*)

1,4-Addition of bulky aryl groups (*o*,*o*,*p*-trisubstituted) to cyclic enones has been achieved using $BF_3$-promoted reaction of aryl cuprates to the $\alpha$-iodoenone; subsequent Grignard formation allows regular enolate chemistry to be pursued.[176]

All-*trans*-5-aminopenta-2,4-dienals (**63**) have been converted to pentamethine cyanine dyes (**64**). Addition of organometallics allows these to be chain extended and elimination then yields a hexatriene.[177]




(**62**) (**63**) (**64**)

*t*-Butanesulfinyl ketimines derived from diaryl and aryl heteroaryl ketones undergo organometallic addition to yield $\alpha,\alpha$-diaryl- and $\alpha$-aryl-$\alpha$-heteroaryl-alkylamines diastereoselectively. The facial selection is counterion dependent in some cases.[178] (de)

The reactions of phenylthiomethyllithium ($PhSCH_2Li$) and cyanomethyllithium ($NCCH_2Li$) with benzaldehyde and benzophenone have been investigated using carbonyl-carbon kinetic isotope effects. Comparison with results for other lithium reagents in the literature suggest electron transfer as the dominant mechanism.[179]

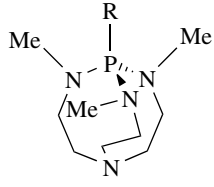
The high diastereoselectivity of the condensation of lithiated (*S*)-(−)-*N*,*N*-dimethyl-1-phenylethylamine with a range of dimethyl- and trimethyl-benzophenones has been investigated.[180] (de)

*The Wittig Reaction and Variants*

A Wittig reaction of 2,2-disubstituted cyclopentane-1,3-dione has produced an alcoholic rather than an olefinic product; a mechanism for this Grignard-like result has been proposed.[181]

(*R*)-Piperidin-3-ol has been used as a new chiral auxiliary for stereoselective synthesis of $\alpha$-hydroxyaldehydes.[182] (de)

A semi-stabilized ylid (**65**, R = Ph−CH=), readily prepared from the commercially available amine (**65**, R = H), gives quantitative *E*-selectivity in Wittig reactions with aldehydes.[183] (de)



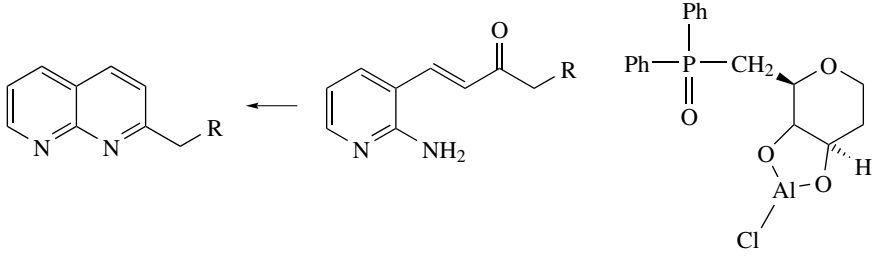

(**65**)

Pursuit of such stereoselectivity is also evident in papers on the Horner–Wadsworth–Emmons (HWE) modification of the Wittig reaction,[184] including a review and computational study[185] which looks at two transition states in the application of the reaction to stereoselective synthesis of $\alpha,\beta$-unsaturated esters. The first involves the addition of the lithium enolate of a (model) trimethylphosphonoacetate to acetaldehyde, followed by oxaphosphetane formation. The second transition state is rate determining in the gas phase and in diethyl ether solvent. On switching to methyl diphenylphosphonoacetate, the first step becomes rate determining; this is synthetically important, as it favours the *trans* product. (de) More generally, the calculations suggest that the *trans*-alkene will be favoured by non-polar solvents and high temperatures, and vice versa for the *cis*-alkene.

A similar study of several mixed phosphonoacetates reacting with aromatic aldehydes points to a switch from *Z*- to *E*-selectivity linked to the electron-withdrawing (de)

ability of the phosphonoacetate substituents, and this in turn has been related to $^{31}P$ NMR shifts.[186]

2-Substituted [1,8]naphthyridines (**66**) can be prepared from 2-aminopyridine-3-carboxaldehyde and an unsymmetrical ketone, $MeCOCH_2R$. This transformation, the Friedlander reaction, is typically not regioselective, also giving the 2-methyl-3-alkyl product. However, presenting the ketone with a phosphonate group on one side [i.e. $(MeO)_2P(=O)CH_2COCH_2R$] makes the reaction up to 100% regioselective, while maintaining high yields.[187] Essentially acting as an activating group, the phosphonate leaves in an HWE-type enone intermediate: apparently this species is *trans*-(**67**), with its isomerization to the ring-closable *cis*-isomer being achieved via addition of methanol (the reaction solvent) to the double bond, followed by its elimination.



(**66**) (**67**) (**68**)

*Addition of Other Carbon Nucleophiles*

Chiral aminoaldehydes have been cyanosilylated diastereoselectively, using a bifunctional catalyst (**68**) based on a sugar unit.[188] A new series of bifunctional Lewis catalysts has been reported. Using a 2,2′-binaphthol (BINOL) or carbohydrate scaffold, a Lewis-acidic metal site (Al or Ti) is juxtaposed with a Lewis base such as a phosphine oxide. Several enantioselective cyanosilylations are reported, and also Strecker- and Reissert-type transformations. Kinetic studies, together with catalyst controls, show that the reaction involves dual activation of substrate and trimethylsilyl cyanide.[189] (*de*) (*ee*)

For another enantioselective Strecker-type reaction of TMSCN, see *Imines* above. (*ee*)

Enantioselective cyanations have been carried out (i) on prochiral ketones, using chiral Lewis bases derived from alkaloids as catalysts,[190] and (ii) on ketones and aldehydes with TMSCN, using titanium(IV)–and vanadium(IV)–salen complexes, respectively, as catalysts.[191] (*ee*)

A fast and diastereoselective cyanation of constrained ketones such as camphor adds TMSCN across the carbonyl; reductive desilylation then yields useful $\beta$-amino alcohols. Catalysed by various lithium cation species, the reaction has also been extended to $\alpha$- and $\beta$-methylcyclohexanones.[192] Another diastereoselective cyanation, this time of chiral $\alpha$-amino aldehydes, uses Nagata's reagent ($Et_2AlCN$) to yield nitriles, which, on hydrolysis, give enantiopure $\beta$-amino-$\alpha$-hydroxy acids.[193] (*de*)

Counterion effects have been reported in the rhodium(I)-catalysed addition of arylboronic acids to aldehydes.[194] Stereocontrol of aryl transfer reactions by means of chiral metal complexes has been reviewed (158 references).[195] (*ee*)

Arylaldehydes can be chloroalkylated by alkylboron dichlorides in the presence of oxygen, apparently via an alkyl peroxide intermediate, followed by migration of chloride.[196]

1,3-Dihalo-1,3-diarylpropanes, $Ar^1-CHX-CH_2-CHX-Ar^2$, have been prepared using the appropriate boron trihalide (X = Cl or Br) to promote addition of an arylaldehyde to a styrene.[197]

The mechanism of nucleophilic addition of unsaturated methyl lactones to pyridine aldehydes has been reinterpreted in the light of a quantum chemical study.[198]

Stannylated oxazolines add regiospecifically to 2-bromo-1,2-naphthoquinones.[199]

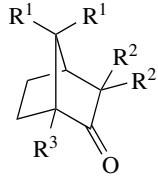
*Miscellaneous Additions*

$\gamma,\delta$-Acetylenic ketones can be hydrosilylated stereoselectively by exploiting $\sigma-\pi$-chelation control: subsequent reduction of the alkyne yields the anti-Felkin–Anh products, not readily obtainable by other reductive methods.[200] Copper(I)-catalysed asymmetric hydrosilylation of aryl ketones has been reported.[201] (*de*) (*ee*)

Ketones with an azido-containing alpha branch [$CH_2(CH_2)_nCH(N_3)Ph$, $n = 1-3$] can undergo two principal intramolecular reactions promoted by Lewis acids: (i) azido-Schmidt, involving azide addition to the ketone followed by rearrangement and ring expansion; and (ii) prior rearrangement to iminium ions, leading to a Mannich pathway. For the four-carbon linker ($n = 1$), Schmidt reaction dominated, giving bicyclic lactams; longer tethers ($n = 2$, 3) favoured Mannich products.[202]

Danishefsky's diene [*trans*-MeO–CH=CH–C(OTMS)=$CH_2$] undergoes a hetero-Diels–Alder reaction with benzaldehydes, and with $\alpha,\beta$-unsaturated aldehydes, giving high *ee*s using cationic metallosalen complexes as catalysts.[203] (*ee*)

Appropriately substituted 2-norbornanones (**69**) undergo a stereoselective Leuckart reaction to yield enantiopure 2-norbornylformamides when the bridgehead substituent, $R^3$, is H or Me. However, *O*- or *N*-acyl groups divert the reaction into a pinacol-type skeletal arrangement, which is nevertheless still stereoselective.[204] (*de*)



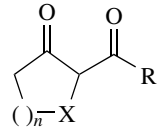

(**69**)

The possibility that hydrogen-bond interactions play an important role in Paterno–Buchi reactions (carbonyl–ene photocycloadditions) has been explored by

comparing the reaction of aldehydes with allylic alcohols and with the corresponding *O*-protected acetate esters. Both excited singlet and triplet states are considered.[205]

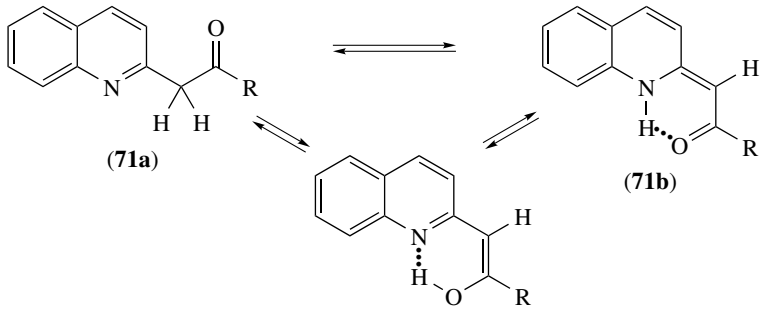
## Enolization and Related Reactions

The kinetics and equilibria of tautomerization of 2-acetylcycloalkanones (**70**, R = Me; X = $CH_2$), the corresponding triones (X = C=O), and cyclic $\beta$-keto esters (R = OMe; X = $CH_2$, C=O), have been measured by a variety of methods for five- and six-membered rings (i.e. $n = 1, 2$) with a particular emphasis on solvent effects.[206]



(**70**)

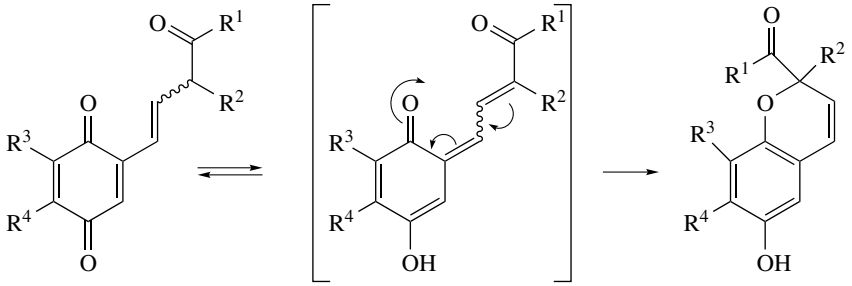
2-(Acylmethyl)quinolines (**71a**) can tautomerize to enaminone (**71b**) and enolimine (**71c**) forms. The equilibria have been studied by $^1H$, $^{13}C$, and $^{15}N$ NMR spectroscopy for a range of phenacyl and cinnamoyl compounds, with or without *p*-pyrrolidinyl substituents [i.e. R = $(CH{=}CH)_n$ $C_6H_4X$-*p*; $n = 0, 1$; X = H, $N(CH_2)_4$].[207] Long-range effects include the cinnamoyl and pyrrolidinyl moieties favouring enolimine tautomers. Enaminone structures are favoured by low temperatures.



(**71a**) (**71b**) (**71c**)

Thermolysis of vinylquinones (**72-k**) yields 2*H*-chromenes (**73**) via enolization to a quinone methide (**72-e**), followed by $6\pi$-electrocyclization.[208]

Computations on the acetaldehyde keto–enol system and on its radical cation analogue (for which the enol is the stable tautomer) have elaborated the role of solvent molecules in the isomerizations of both systems.[209]



(**72-k**) (**72-e**) (**73**)

Keto–enol tautomerization of acetylacetone has been computed by *ab initio* methods.[210]

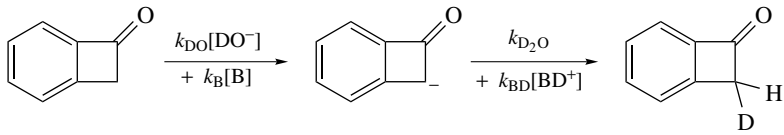
The kinetics of bromination of substituted acetophenones by phenyltrimethylammonium tribromide have been measured in glacial acetic acid alone,[211] and with catalysis by sulfuric acid.[212] Regioselective monohalogenation of bornane-2-thiones proceeds via thione–dihalogen complexes.[213]

*Enolates*

Brønsted acidities of a wide range of neutral C–H acids have been measured in the gas phase and in DMSO solution, and compared with related literature data.[214] Covering a large variety of aromatic structures and also nitriles, nitrile esters, and some ketones, marked attenuations are observed in substituent effects on transfer from the gas phase to solution, except for aromatics in which the conjugate base exhibits very extensive delocalization, e.g. fluorenes, indenes, and aryl-substituted cyclopentadienes.

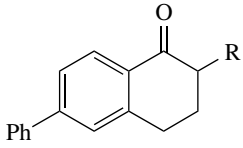
Although benzocyclobutenone (**74-KH**) has been presumed to react in the presence of bases via its enolate (**74-E**$^-$), its low reactivity and unstable products have hampered confirmation. $^1$H NMR observations on extracts from quinuclidene-catalysed reaction in $D_2O$ at 25 °C and pD = 12.5 clearly show the formation of the monodeuterated ketone (**74-KD**).[215] Buffer plots confirm the reaction as buffer-base-catalysed, and the very low reactivity is confirmed: correcting for the isotope, $k_{OH} \approx 7.1 \times 10^{-5}$ mol$^{-1}$ dm$^3$ s$^{-1}$. This is comparable to ethyl acetate ($1.2 \times 10^{-4}$ mol$^{-1}$ dm$^3$ s$^{-1}$; p$K_a$ = 25.6), and much lower than the structurally related 2-indanone (220; 12.2) or even acetone (0.11; 19.3). Ring strain and anti-aromaticity are likely factors destabilizing the enolate (**74-E**$^-$).

House *et al.*'s conjecture[216a] that polyalkylation of alkali metal enolates is due to greater aggregation of the less substituted enolate (with aggregation

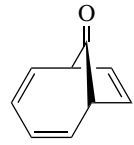


(**74-KH**) (**74-E**$^-$) (**74-KD**)

lowering reactivity) has been confirmed[216b] in the case of 6-phenyl-$\alpha$-tetralone (**75**, R = H). Its lithium enolate forms a tetramer ($K_{1,4} = 4.7 \times 10^{10}$ mol$^{-3}$ dm$^9$), whereas its monobenzyl product (**75**, R = Bn) forms a weaker dimer ($K_{1,2} = 3.8 \times 10^3$ mol$^{-1}$ dm$^3$). In both cases, kinetic studies show that reaction with benzyl bromide is predominantly with the monomer. In one sample of synthetic conditions considered, the second alkylation was already proceeding over 20 times faster than the first at the point when only 10% alkylation had been achieved.




(**75**)




(**76**)

A chiral lithium amide base has been employed to generate bridgehead enolates from bicyclo[4.2.1]nona-2,4,7-trien-9-one (**76**); subsequent silylation gives the $\alpha$-silyl ketone in 76% yield and >96% *ee*.[217]

Kinetic *C*-protonation of enolates by carbonyl-containing weak acids has been reviewed.[218] Oxazolinyloxiranes have been synthesized enantio- and diastereo-selectively via azaenolates.[219] A smooth, rapid cleavage of cyclic silyl enol ethers by potassium ethoxide yields enolates which can react kinetically with electrophiles and oxidants.[220]

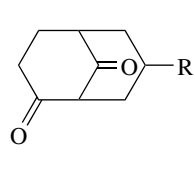
(*ee*) (*de*)

## Oxidation and Reduction of Carbonyl Compounds

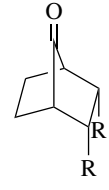
*Regio-, Stereo-, Enantio-, and Diastereo-selective Reductions*

Several reports are concerned with stereoselective reduction in constrained, cyclic ketones, including model compounds selected to probe aspects of facial selectivity at the carbonyl group. The exterior frontier orbital extension (EFOE) model has been used to interpret $\pi$-facial stereoselection in reduction of one and both carbonyl groups of bicyclo[3.3.1]nona-2,9-dione (**77**, R = H) and its *exo*-methyl derivative.[221]

(*de*) (*ee*)




(**77**)




(**78**)

Computations suggest that *anti*-selectivities in the lithium aluminium hydride (LAH) reduction of some 2,3-*endo*,*endo*-dialkylbicyclo[2.2.1]heptan-7-ones (**78**,