

Reactions of Aldehydes and Ketones and their Derivatives

B. A. MURRAY

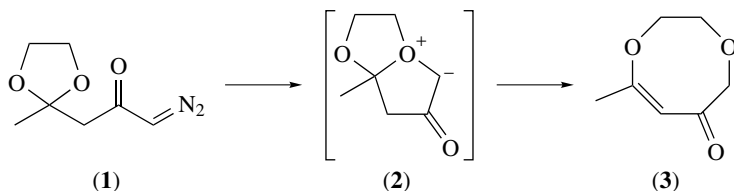
Department of Applied Sciences, Institute of Technology Tallaght, Dublin, Ireland

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Formation and Reactions of Acetals and Related Species

Hammett plots have been constructed for the acid- and base-catalysed decomposition of methyl hemiacetals of benzaldehydes in aqueous solution.¹ The data are analysed in terms of three-dimensional More O’Ferrall–Jencks diagrams and of Cordes interaction effects.

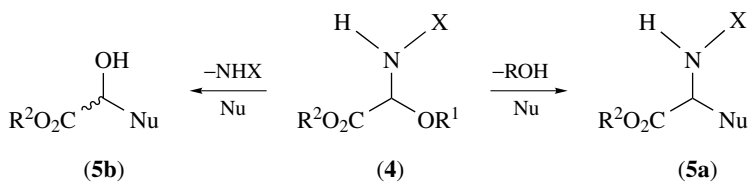
Diazidooxopropyl acetal (**1**) undergoes rhodium(II)-catalysed ring expansion to (**3**) in the presence of TMS chloride;² the latter reagent acts as a Lewis acid–base catalyst for ring expansion of the oxonium ylid intermediate (**2**).



t-Butyl chloromethyl ketone forms a cyclic acetal with sucrose: the 2-hydroxy group of the sugar reacts with the carbonyl, with ring closure via the 3-position, yielding a *t*-butyl hydroxymethyl acetal.³ The results are part of a study of the relative reactivities of the hydroxy groups of (unprotected) sucrose.

An unusual case of cyclopropanol formation from a hemiacetal of a β -silyl aldehyde is ascribed to an enhanced reactivity of the silicon, due to an appropriately placed oxyanion generated from the hemiacetal.⁴

Activated *N,O*-acetals (**4**) can undergo a nucleophilic alkylation which replaces the oxygen (via an imine intermediate) to yield an amine (**5a**), or by replacement of the nitrogen (via an aldehyde) to yield an alcohol (**5b**).⁵ Such amine or alcohol products are valuable, especially if obtainable as single isomers. A catalytic, enantioselective alkylation has been reported to yield the amines (**5a**), using a copper–BINAP catalyst, and a variety of alkene sources for the alkylating group (enol silanes or allylsilanes, ketene silyl acetals). ¹H NMR spectroscopy was used to elucidate mechanistic details concerning the transsilylations involved. For example, a simple *N,O*-acetal (**4**; X = *p*-Ts, R¹ = H, R² = Et) does *not* give amine (**5a**) with 1 equiv. of the enol silane of acetophenone; rather, *O*-silylation occurs. A second equivalent of enol silane is required to form (**5a**), and the catalyst. The paper also reports similar transformations of *N,N*-acetals.



Catalytic, enantioselective alkylations of *N,O*-acetals have been reported.⁶

Reactions of Glucosides and Nucleosides

A theoretical study of the mutarotation of glucose has evaluated the energies of the two transition states (i.e. α -anomer to aldehyde and aldehyde to β -anomer), placing

$n = 0-3$ water molecules as part of a specific proton-transfer network.⁷ The transition states are lowered by ca 28 kcal mol^{-1} with even one water, but significant further stabilizations are observed for $n = 2$ and 3 , both of which exhibit very strong hydrogen-bonded networks. A variant with secondary hydrogen bonding ($n = 2$, with two 'outer' waters) is also evaluated.

A *m*-xylylene moiety has been used as a rigid spacer to align an intramolecular glycosylation at room temperature.⁸ The systems used, involving 15- or 14-membered ring formation, exhibit good face selectivity (i.e. towards formation of α - or β -anomer). They also show promise for oligosaccharide synthesis, with a simple protocol for post-synthesis cleavage of the spacer.

Alkaline hydrolyses of *p*-nitrophenyl α -D-glucoside and the corresponding galactosides are accelerated by a factor of up to 110 on addition of boric, boronic, or borinic acids, relative to their β -anomers.⁹ The selectivity is reversed in the case of the mannosides, indicating that a *cis*-relationship between the 2-hydroxy and the *p*-nitrophenoxy groups is central to the stereoselection. An acceleration of the hydrolysis of *p*-nitrophenyl-D-glucosides in the presence of α -cyclodextrins depends on this same stereochemical relationship.¹⁰ With α -cyclodextrin (20 mmol dm^{-3}), hydrolysis of the α -D-mannoside is accelerated 7.6-fold, whereas the β -anomer is unaffected. For the D-glucoside, -galactoside, and -xyloside, complexation by cyclodextrins favours hydrolysis of the β -sugars, by similar factors. These selectivities are achieved without particularly strong binding ($110 < K/\text{mol}^{-1}\text{dm}^3 < 260$), and are *not* due to binding selectivity: K_α never differs from K_β by more than 60%.

The Maillard reaction involves condensation of an aldose with an amino function (e.g. of a protein), yielding an imine that can undergo rearrangement to an amino form (the Amadori rearrangement), followed by subsequent reactions involving both volatile and polymeric products. In the light of the increasing use of high pressure in food processing, the effect of such pressures on the formation of volatiles has been studied for a model Maillard reaction.¹¹

TMS triflate catalysis of transglycosylations between permethylated methyl D-glucopyranosides and simple alcohols has been reported.¹²

Reactions of Ketenes and Related Species

Mechanistic investigations of additions to ketenes continue to focus on which double bond reacts first, and on the role of the solvent: many theoretical studies probe the latter by systematic incremental inclusion of a series of solvent molecules in the calculation. Experimentally, similar effects for the catalyst are often seen in its kinetic order.

Gas-phase and solution-phase calculations on the hydration of ketene to produce acetic acid, using water clusters of two, three, and four molecules to attack the ketene, show a two-step addition via the 1,1-enediol intermediate, i.e. initial addition to $\text{C}=\text{O}$, rather than to $\text{C}=\text{C}$. The preference is slight, but consistent.¹³

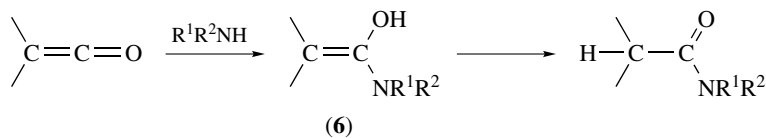
Solvent isotope effects, $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$, have been measured for the hydration of five ketenes, $\text{R}^1\text{R}^2\text{C}=\text{C}=\text{O}$, catalysed by hydroxide ion.¹⁴

Rate constants for hydration of ketene, and of carbon dioxide, have been calculated using No Barrier Theory, Marcus Theory, and a multi-dimensional Marcus treatment.¹⁵

The methods agree except in the case of the *uncatalysed* hydration of ketene, where the multi-dimensional method predicts ΔG^{act} to be lower for addition to C=O, whereas the No Barrier results favour C=C addition. A calculation of k_{HO} for ketene hydration agrees with preliminary experimental results.

Addition of amines to the silylketene $\text{PhMe}_2\text{SiCH}=\text{C}=\text{O}$ to form amides exhibits kinetics in acetonitrile in which the order in amine lies between second and third,^{16a} as found in recent theoretical studies of the parent ketene, $\text{H}_2\text{C}=\text{C}=\text{O}$, and ammonia.^{16b} The result contrasts sharply with a straightforward first-order dependence found for more reactive substrates, such as diphenylketene. The influence of amine basicity is discussed for the silylketene and compared with results for hindered compounds. The reasons for the failure to observe higher order terms for the more reactive substrates are also discussed.

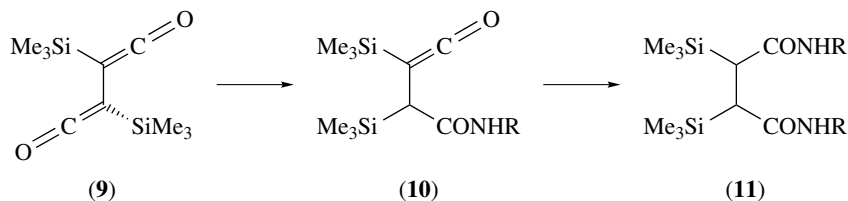
The amination of ketenes to produce amides (see Scheme 1) has been subjected to a variety of computational methods, including several treatments of the solvent, with explicit roles for actively participating amine and water molecules.¹⁷ All the results favour a two-step process with initial addition to the C=O bond, rather than a concerted reaction involving the C=C bond. The former involves a 1-amino-1-hydroxy ene intermediate (**6**), formally the enol of the amide. Inclusion of a second amine molecule lowers the barrier to the two-step reaction. Replacing the second amine with a water molecule lowers it even further, an effect which should be even greater when water is the bulk solvent. Some experimental evidence is presented for the highly hindered substrates, bis(mesityl)ketene and bis(pentamethylphenyl)ketene. Addition of primary or secondary amines clearly shows, from IR and UV spectra, the build-up and subsequent tautomerization of the intermediate enols. The kinetics of these more hindered substrates are first order in amine; this is not inconsistent with the theoretical results, as such hindered ketenes may only react rather slowly with amine dimer, which is also in low concentration under the conditions used.



SCHEME 1

Calculations and low-temperature NMR experiments have been used to investigate the course of reactions of diphenylketene with dienes.¹⁸ While the reaction of cyclic (*s-cis*) 1,3-dienes such as cyclopenta- and cyclohexa-1,3-diene yield 2 + 2 (Staudinger) products, the low-temperature experiments indicate initial formation of 4 + 2 (Diels–Alder) intermediates. For the open-chain reactants, 2,3-dimethyl- and 1-methoxy-1,3-butadiene, both product types are formed initially, with conversion of the Staudinger to the Diels–Alder over time, via a retro-Claisen rearrangement.

Methyleneketene, $\text{H}_2\text{C}=\text{C}=\text{C}=\text{O}$, could undergo cycloaddition at any of its double bonds. Theoretical calculations on its reaction with pyrroline-1-oxide predict



give polymeric products, unless an excess of the bisketene is employed, to give an α,ω -bisketenyl diamide. Kinetic studies of each of the steps in the formation of the succinamide are reported. It is noted that reaction of methanol with ketenylcarboxamide (**10**) to give the ester amide is much faster than the formation of a diester from a ketenyl ester. This and other lines of evidence point to a coordination between the carboxamide group of (**10**) and incoming nucleophiles in the formation of the ‘homo-’ and ‘hetero-’ succinic acid derivatives.

Bromofluoroketene ethyl trimethylsilyl acetal [$\text{Br}(\text{F})\text{C}=\text{COEt}(\text{OSiMe}_3)$, *E/Z*-mixture] undergoes enantioselective aldol reactions with aldehydes in the presence of Masamune’s catalyst.²⁴ The enantioselectivity is markedly temperature dependent, with examples of high *ee* at -78 and -20°C , but of opposite rotation sign.

Lewis acid-mediated addition of silyl ketene acetals to a chiral sulfimine gives precursors of β -amino acids in fair to excellent *de*.²⁵

Mixed diesters of both symmetrical and unsymmetrical diols have been prepared by reaction of carboxylic acids with cyclic ketene acetals of the diols, with the less substituted carbon of the cyclic dioxonium ion intermediate being attacked in most cases.²⁶

Hydration of trifluoroacetylketene is discussed later under *Enolization*.

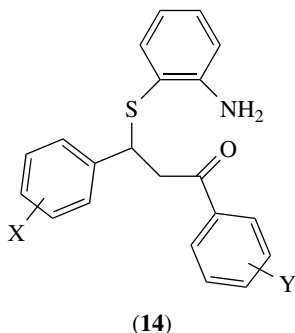
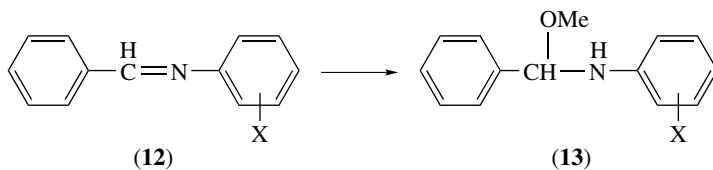
Formation and Reactions of Nitrogen Derivatives

Imines

Proton affinities of imines and heats of formation of immonium ions have been calculated for the gas phase by *ab initio* methods.²⁷ *cis*-Imines are more basic than their *trans*-isomers, reflecting the unusually high ($15\text{--}17\text{ kJ mol}^{-1}$) energy difference between the *cis*- and *trans*-isomers, which decreases significantly in the immonium ions. An additivity scheme for group contributions in immonium ions is proposed.

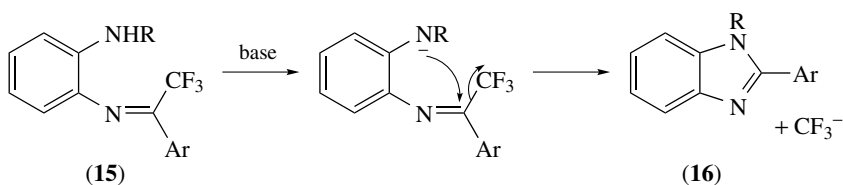
Equilibrium addition of methanol to benzylideneanilines (**12**; X = H, 3-Cl, 3- and 4- NO_2) to give α -amino ethers (**13**) has been studied in methanol solvent, using carboxylate buffers.²⁸ The reaction is general acid-catalysed, with fast iminium ion formation as the initial step. Brønsted α exponents range from 0.67 to 0.88, with electron-withdrawing X giving larger α , an observation also true of the equilibrium constant, which follows σ^- .

The kinetics and mechanisms of acid catalysis of intramolecular cyclization of 1,3-diaryl-3-(2-aminophenylsulfenyl)propan-1-ones (**14**) to yield cyclic imines in mixtures of methanol and various acids have been described. The X substituent significantly affects the rate.²⁹



Oxazolinylaziridines have been prepared by addition of (chloromethyl)oxazolines to imines.³⁰

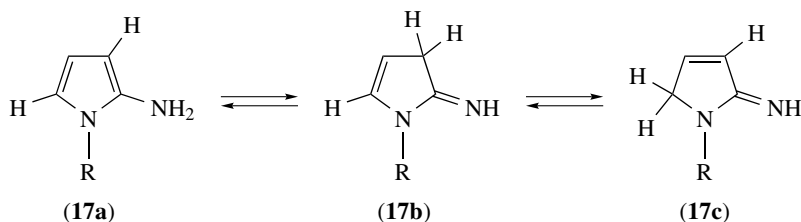
A range of imines derived from trifluoromethyl aryl ketones have been converted into heterocyclic products via intramolecular cyclization with loss of the CF_3 group.³¹ For example, *o*-aminoimine (15), when treated with strong base, cyclizes to benzimidazole (16), with loss of trifluoromethyl anion. The corresponding *o*-phenols yield benzoxazoles, and examples using an external amine lead to aziridines.



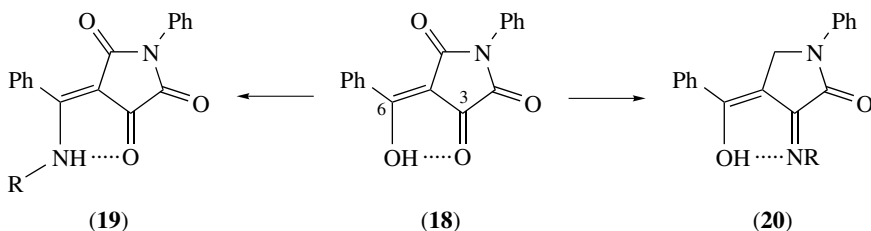
Furfural and nitromethane, in the presence of isobutylamine, form 1-(fur-2-yl)-2-nitroethane, a bioactive material; an aldimine intermediate, *N*-(fur-2-ylmethylene)isobutylamine, has been characterized.³²

A simple disulfonamide catalyses reaction of aldehydes and amines to give imines, via hydrogen bonding to the transition state for nucleophilic attack of the amine.³³

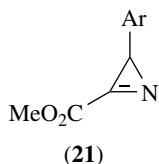
Amino-imino tautomerism in simple 1-substituted-2-aminopyrroles (17a) \rightleftharpoons (17b) \rightleftharpoons (17c) has been studied by NMR spectroscopy and by *ab initio* calculations for R = H, Me, Et, Bu^t, and Ph.³⁴ 1-Methyl-2-aminopyrrole (17a; R = H) is predicted to show observable imino tautomers in water.



1-Phenyl-4-(phenylhydroxymethylidene)pyrrolidine-2,3,5-trione (**18**) can exist as *endo*-(shown) or *exo*-enol, depending on the solvent.³⁵ This equilibrium appears to affect its site reactivity with amines. Ethanolic condensation with glycine (R = CH₂CO₂H) or β-alanine (R = CH₂CH₂CO₂H) gives C(6) products (**19**) which exist in two tautomeric forms: a keto–enamino or enamino (shown), and an enol–imine. In contrast, reaction of the hydrochloride of glycine ethyl ester (R = CH₂CO₂Et) in the same solvent at reflux gave condensation at C(3), i.e. structure (**20**) (enol–imine shown), which again exhibited a similar equilibrium with an enamino tautomer. This compound was also found to undergo transamination with benzylamine (i.e. R = CH₂Ph), as did several others.

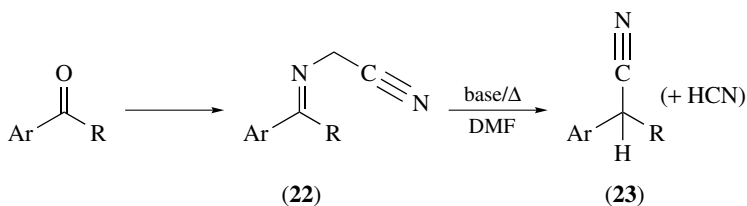


The products of reactions of two methyl 2-aryl-2*H*-azirine-3-carboxylates (**21**; aryl = 2,6-Cl₂C₆H₃ or 4-MeC₆H₄) with a range of nucleophiles are reported.³⁶ Although a wide range of compounds have been added (thiols, propargyl alcohol, amines, enamines, enones and β-diketones), all appear to involve initial addition to the C=N bond.



Aryl alkyl ketones undergo a two-step homologation to give α-aryl-α-alkylnitriles (**23**), via an imine [an *N*-(1-arylalkylidene)cyanomethyl amine (**22**)].³⁷ A mechanism is proposed, and several are ruled out. For example, a series of *para*-substituted

imines (**22**) give reaction rates with a Hammett ρ value of 1.86, suggesting electron-withdrawing substituents enhance the rate by favouring an initial deprotonation. However, alkylation of (**22**) α to the nitrile prevents reaction, indicating that both methylene hydrogens are required. Imine–imine tautomerism was also ruled out, as was photochemical activation. Isotope-labelling experiments ($-^{13}\text{CN}$ and $=^{15}\text{N}-$) suggest an intramolecular nucleophilic substitution, as the cyano group of (**23**) is derived from the $=\text{N}-\text{CH}_2-$ fragment of (**22**). On this basis, an intermediate three-membered nitrogen heterocycle is proposed.



The mechanism of the Gibbs reaction, an assay for phenols using, e.g., 2,6-dichlorobenzoquinone *N*-chloroimine, has been probed for a wide range of imines and phenols.³⁸ The first step of single-electron transfer to produce the *N*-chloroimine radical anion is followed by a mechanistic divergence into three routes, depending on the reactivity of the pair of reactants.

The kinetics of the nucleophilic addition of potassium cyanide to α,N -diphenylnitrone have been reported.³⁹

Stereoselective Imine Reactions

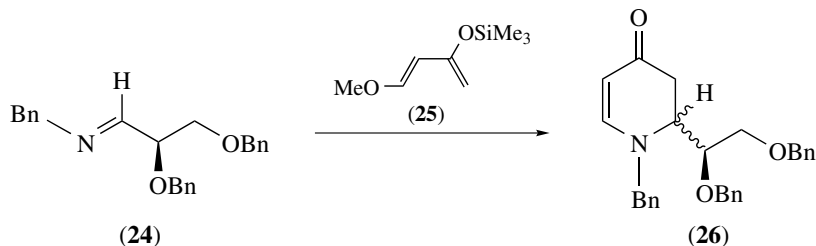
Enthalpic and entropic contributions to diastereofacial selectivity have been explored in the addition of *n*-butyllithium to the C=N bond of $\text{R}^1\text{CH}(\text{OR}^2)\text{CH}=\text{NSiMe}_3$.⁴⁰ Using THF or *n*-hexane as solvent, temperature ranges of up to 150°C can be covered, over which a change in the *anti:syn* ratio of the products from 3 : 1 to 1 : 3 can be achieved. The results are discussed in terms of stereospecific solvation effects on the reacting π -system, an area in need of an appropriate computational approach.

The Exterior Frontier Orbital Extension (EFOE) model has been applied to predict π -facial selectivity in nucleophilic additions to imines and iminium ions of the cyclohexanone, tropinone, and adamantan-2-one systems.⁴¹ A review of the EFOE model,⁴² and other references to its use, are described later under *Regio-, Enantio-, and Diastereo-selective Aldol Reactions*.

Stereoselective aldol reactions, allylations, and aziridinations of imines, including activated imines, have been reported.⁴³ The Sakurai–Hosomi reaction of allylsilane with imine in the presence of tetrabutylammonium fluoride is found not to be strictly catalysed by fluoride; rather, a fluoride-triggered autocatalytic route is suggested.

N-Benzylimine [(**24**); derived from (*R*)-glyceraldehyde], undergoes a tandem Mannich–Michael reaction with Danishefsky's diene (**25**) to give cyclic enamines (**26**).⁴⁴ The diastereoselectivity of the reaction, and the effects of temperature, solvent,

and Lewis acid catalyst, have all been studied. Replacing the *N*-benzyl group of (24) with an (*S*)- α -methylbenzyl residue leads to double stereodifferentiation.



A related reaction of *N*-benzylmethanimine, $\text{MeCH}=\text{NCH}_2\text{Ph}$, has been investigated by NMR and computational methods.⁴⁵ Distinct differences in chemical behaviour are observed when the di- or tri-fluoromethyl analogues are studied.

Aldimines, $\text{R}^1\text{CH}=\text{NR}^2$, react with allyltrimethylsilane in the presence of *n*-butylammonium fluoride to give homoallylamines, $\text{R}^1\text{CH}(\text{NHR}^2)\text{CH}_2\text{CH}=\text{CH}_2$; fluoride-triggered autocatalysis⁴³ is again proposed.⁴⁶ Allylation of imines has been achieved via *in situ* formation of an *N*-tosyliminium species from aldehydes or ketones.⁴⁷

As part of an asymmetric route to α -arylglycinols, a chiral lithium methyl *p*-tolyl sulfoxide has been added to *N*-arylidine-*p*-anisidines ($\text{ArCH}=\text{NC}_6\text{H}_4\text{-}p\text{-OMe}$).⁴⁸ Under thermodynamically controlled conditions (0°C), *de* $\approx 0\%$, regardless of the nature of the *C*-aryl substituent. However, kinetic control at -70°C allows high diastereoselectivity to be achieved, and its direction can be controlled by the electronic nature of the aryl group.

A new enantioselective Strecker synthesis of α -aminonitriles and α -amino-acids reacts *N*-benzhydrylimines with hydrogen cyanide in the presence of a chiral guanidine catalyst; the mechanistic basis of the enantioselectivity is analysed.⁴⁹

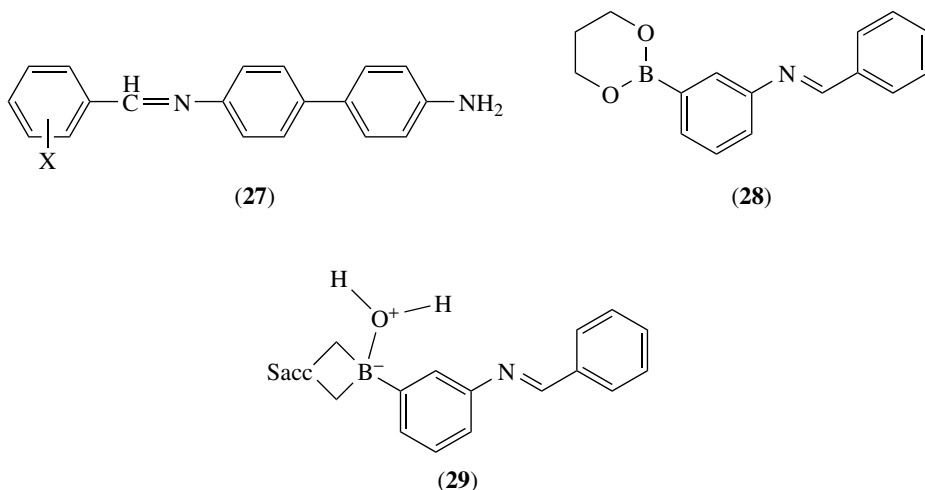
N-*t*-Butanesulfinylimines derived from aldehydes and ketones undergo highly diastereoselective 1,2-addition of organometallic reagents.⁵⁰ The product sulfinamides are readily hydrolysed in acidic methanol, providing enantio-enriched α -branched and α,α -dibranched amines. Steric, electronic, and solvent effects are explored.

Enamines of cyclohexylamine have been enantioselectively cyclized to bicyclo[3.3.1]nonanedione systems, using acryloyl chloride and chiral pyrrolidine catalysis.⁵¹ Enantiopure *N*-sulfinylimines have been used in asymmetric synthesis of isoquinolone alkaloids,⁵² and a stereocontrolled synthesis of 3,4,5,6-tetrahydropyrimidine-based amino acids from imino ethers has been reported.⁵³ Diastereoselective additions of chiral acetals of (2-lithiophenyl)acetaldehyde to arylimines have been used in an asymmetric synthesis of 1-aryltetrahydroisoquinolines.⁵⁴ Organolithiums react with chiral imines, in the presence of Lewis acids or bases, to give amines in up to 100% *de*.⁵⁵ Diastereoselective additions of copper reagents to imines derived from (*S*)-1-phenylethylamine have been reported.⁵⁶

Catalytic enantioselective addition to imines has been reviewed.⁵⁷

Hydrolysis of Imines

pH-rate profiles and transition metal ion catalysis are reported for hydrolysis of *o*- and *p*-hydroxybenzylidene-4-benzidines (**27**) in aqueous dioxane at 20 °C.⁵⁸

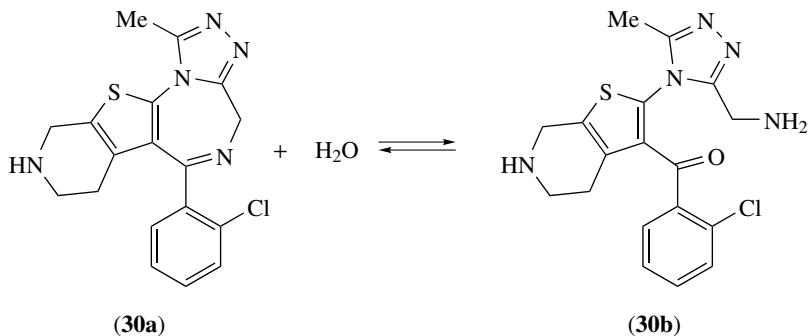


Acidic hydrolysis of a bis(salicylidenamino)diimine, $\text{CH}_2[4\text{-C}_6\text{H}_4\text{N}=\text{CHC}_6\text{H}_4\text{-2-OH}]_2$, has been studied from 30 to 45 °C.⁵⁹ Ni(II) accelerates the hydrolysis, as does Zn(II) to a lesser extent, while Cu(II) has a more complex effect. Activation parameters are reported.

The well-known affinity of saccharides for boronic acids has been exploited to activate imine hydrolysis. Imine (**28**) is hydrolysed much faster in the presence of saccharides, and the acceleration follows the same order as the stability constants of a range of saccharide complexes.⁶⁰ The phenomenon is not merely a substituent effect because (i) it is not observed at all in the absence of the boronate substituent, and (ii) its magnitude is not significantly altered if the substituent is placed on the other side of the imine instead. Using pH-rate profiles and kinetic isotope effects, the mechanism is proposed to involve covalent attachment of saccharide, followed by binding of water to boron, producing an intermediate (**29**) with a very acidic 'bound water,' which sets up protonation of nitrogen through a solvent chain.

Forward and reverse rate constants have been reported for the reversible ring opening of a triazolo-1,4-thienodiazepine (**30a**) over a range of pH values in water, using a combination of UV spectrophotometry and polarography.⁶¹ The results have been analysed in terms of several protonated forms of the reactant (**30a**) and product (**30b**), and similar forms of potential carbinolamine intermediates.

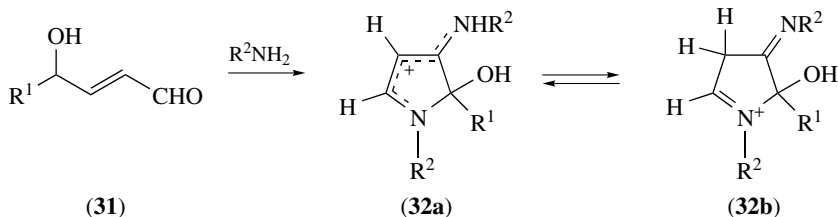
Rate constants for the formation and hydrolysis of Schiff bases derived from pyridoxal 5'-phosphate and co-polypeptides have been determined in the pH range 4–11 at 25 °C.⁶² The co-polypeptides contain L-lysine, and aromatic L-amino acids, and



the interaction of such aromatic moieties with pyridoxal (and, by extension, such interactions in enzymes) are discussed.

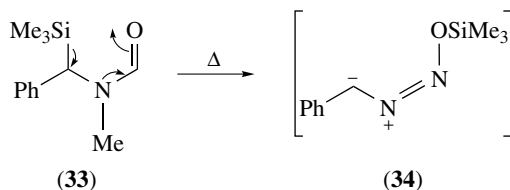
Iminium Ions and Related Species

One of the mechanisms operating in ageing and degenerative disease is lipid peroxidation: this can produce 4-hydroxyalk-2-enals (**31**), giving rise to both cross-linking and fluorophore generation.^{63a} A major fluorophore appears to be derived from (*E*)-4-hydroxy-2-non- (or -hex)-enal [i.e. (**31**; R¹ = C₅H₁₁ or C₂H₅)]. These aldehydes cross-link with lysine residues in protein, and model compounds have been prepared using simple amines. The model fluorophores are 2-alkyl-2-hydroxy-1,2-dihydropyrrrol-3-one iminium cations (**32a**; R² = Pr, Bu, CH₂CH₂OMe). The structure and chemistry of these ions have been studied by ¹⁵N labelling, ¹H and ¹³C NMR spectroscopy, and fluorescence spectroscopy.^{63b} Typical of vinylogous amidinium cations, H(4) is exchanged by a tautomeric equilibrium (**32a**) \rightleftharpoons (**32b**). A mechanism for the formation of the fluorophores, involving initial Schiff base formation and subsequent oxidation, is proposed.



α -Silylnitrosamine (**33**) easily generates azomethine imine (**34**), via a 1,4-silotropic shift.⁶⁴ Subsequent reaction with dipolarophilic alkynes yields pyrazole derivatives.

The iminium ion chemistry of activated indoles has been reviewed (47 references).⁶⁵ Focusing particularly on the Vilsmeier formylation, this reaction has been generalized over time to include a greater variety of amide types. The traditional Vilsmeier protocol



of activating amides by reaction with phosphoryl chloride has also been broadened by the use of triflic anhydride as an alternative.

Oximes

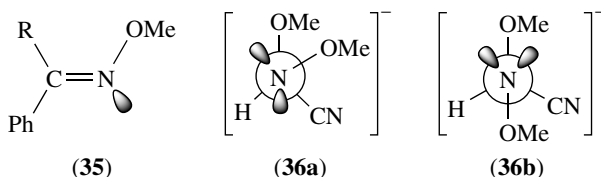
Rate constants have been measured for oxime formation in water for several substituted benzaldehydes and hydroxylamine, over a range of pH from 7 down to 2.⁶⁶ Hammett plots have been constructed for carbinolamine formation and its dehydration.

The use of reversible transformations to set up dynamic combinatorial libraries has received considerable attention recently.^{67a} In such systems, molecular diversity can be generated and screened by allowing a target compound to ‘identify’ a species from the pool in dynamic equilibrium, based on a strong interaction. A kinetic and mechanistic study of imine exchange in *O*-aryl and *O*-alkyl oximes has been undertaken in aqueous solution, to assess the reaction’s suitability for a water-based dynamic library.^{67b} Of particular importance for such an application is the stability of the system, i.e. the rate of exchange must be substantially greater than the rate of hydrolysis. For the example of the *O*-alkyl case, a typical equilibrium that was studied is shown in Scheme 3. In this case, the kinetic behaviour was consistent with fast *N*-protonation, followed by attack of alkoxyamine to give a tetrahedral adduct, which can then back- or exchange-eliminate. In contrast, the *O*-aryl exchange involves slow hydration of the C=N bond to give a tetrahedral intermediate, which can then go on to exchange, or to hydrolyse.

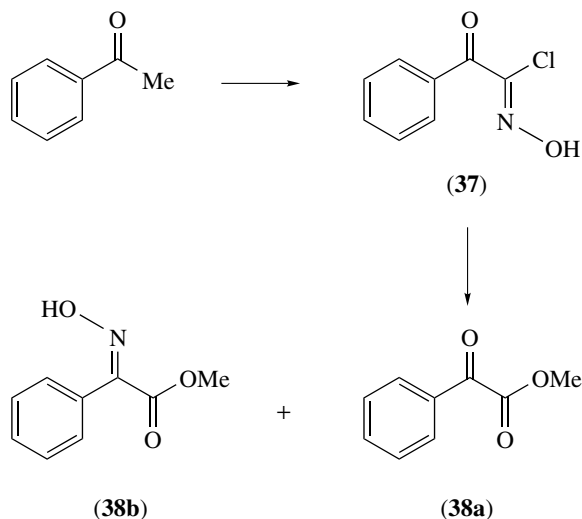


SCHEME 3

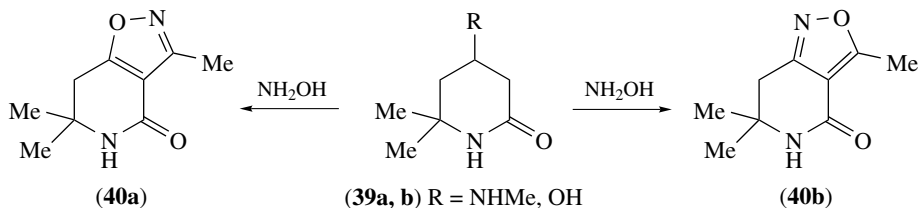
(*Z*)-*O*-Methylbenzohydroximoyl cyanide (**35**; R = CN) reacts with methoxide ion in DMSO–methanol to give the corresponding substitution product (**35**; R = OMe), even though this is thermodynamically the less stable product, and, under the conditions, all the staggered conformations of the tetrahedral intermediate should have been accessible.^{68a} The *E*-reactant isomer was also found to isomerize to the *Z*-isomer faster than it underwent nucleophilic substitution. Theoretical calculations have now been carried out on the tetrahedral intermediate,^{68b} with phenyl replaced by hydrogen for computational expediency. Conformation (**36b**), which would lead to *E*-product, is found to be 7 kcal mol⁻¹ less stable than (**36a**), and the transition states also differ by ca 5 kcal mol⁻¹ in the same sense.



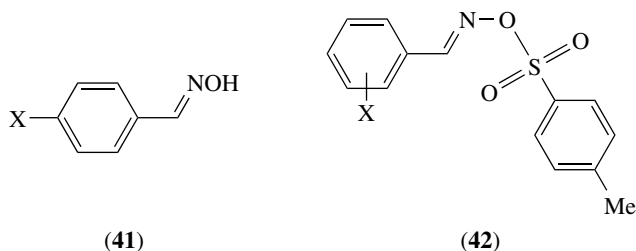
α -Oxooximes [or α -(hydroxyimino) ketones] are potentially useful synthons. *N*-Hydroxy- α -oxobenzeneethanimidoyl chloride (**37**) is a chloro derivative of such a compound, and can be prepared in one step from acetophenone.⁶⁹ Acid-catalysed methanolysis yields methyl α -oxobenzeneacetate (**38a**) and methyl α -(hydroxyimino)benzeneacetate (**38b**). Mechanistic investigation of the solvolysis, using ¹³C labelling, rules out 1,2-arene migration in the formation of (**38b**). Treatment of pure (**38a**) under the same conditions as solvolysis yielded some (**38b**), indicating that it forms via an intermolecular pathway, but also tending to rule out hopes of boosting the yield of (**38b**) from the solvolysis. Compound (**37**) has the configuration and conformation shown i.e. benzoyl and OH are *trans*-, and the oxo- and imino-double bonds are in an *s-trans* relationship; there is no *intramolecular* hydrogen bonding. These structural factors, found also for several related compounds in the literature, are in sharp contrast to the isostructural enols of β -diketones.



4-Aminopyridinone (**39a**) reacts with hydroxylamine to give isoxazolo[4,3-*c*]pyridinone (**40a**), while the 4-hydroxy reactant (**39b**) yields the isomeric [4,5-*c*] structure (**40b**). Semiempirical calculations have been used to tease out four different mechanisms for the reactions, as well as the effects of tautomeric equilibria in the reactants.⁷⁰



Formation of oxime (**41**) from 4-dimethylaminobenzaldehyde ($X = NMe_2$) and 4-trimethylammoniumbenzaldehyde ($X = ^+NMe_3I^-$) has been interpreted in terms of a standard two-step mechanism: initial carbinolamine formation, followed by dehydration.⁷¹ pH–rate profiles have been constructed for both compounds: the amine shows evidence of a change in rate-determining step at low pH (and of the intervention of the reaction of the protonated amine), while the ammonium salt shows a change from acid-catalysed to uncatalysed carbinolamine formation. Equilibrium constants for oxime formation are also reported and discussed.



Arrhenius parameters are reported for pyrolysis of six *p*-toluenesulfonyl arenecarboxaloximes (**42**) in the range ca 334–401 K, giving the sulfonic acid and benzonitrile as products.⁷² The reaction is a thermal electrocyclic elimination, and has been established as being clearly unimolecular and polar in mechanism. The variation of the Arrhenius parameters and relative rates suggest that the polarity of the N–O bond is the major determinant of their high reactivity: the corresponding sulfinyl hydrazones undergo a similar reaction, but ca 10^4 times more slowly (at 500 K).

The reaction kinetics of acetamide and benzamide *o*-(phenoxy-carbonyl)oximes have been studied in aqueous buffers over a wide pH range, with cyclization dominant at high pH, and hydrolysis at lower values.⁷³ A Hammett plot for the benzamide series suggests that *N*-deprotonation occurs, followed by a rate-limiting step involving concerted N–C bond formation and C–O bond breaking.

Ketoximes have been reacted with aliphatic aldehydes and diphenylborinic acid.⁷⁴ α -Hydroxyalkylation at the oxime oxygen is favoured by a bulky substituent in the aldehyde (leading subsequently to a ‘BOCON’ diphenylboron chelate), while formaldehyde reacts by *N*-alkylation (giving a ‘COBON’ chelate).

The kinetics of the oxidation of oximes of substituted acetophenones by vanadium(V) have been measured in aqueous acetic acid, using NaVO_3 .⁷⁵ A two-electron oxidation to the carbocation is proposed, ultimately yielding the ketone.

The kinetics and mechanism of the reaction of sodium methoxide with *para*-substituted *O*-benzoylbenzamidoximes, $p\text{-XC}_6\text{H}_4\text{C}(\text{NH}_2)=\text{NO}_2\text{CC}_6\text{H}_4\text{-}p\text{-Y}$, in methanol have been described.⁷⁶

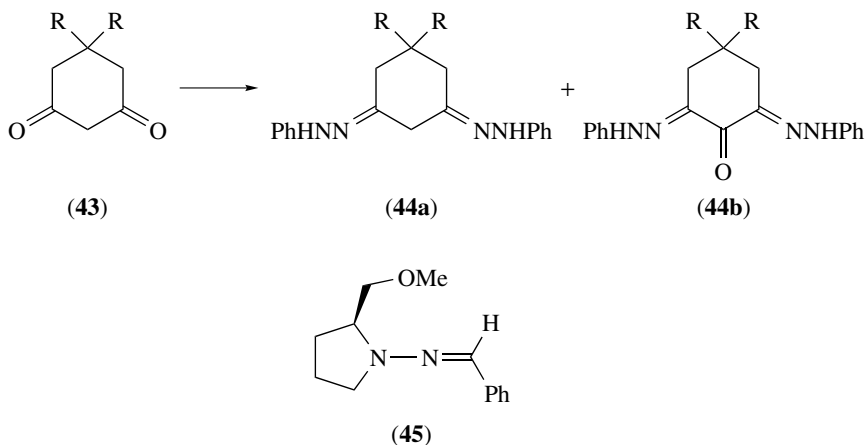
Oximoytris(dimethylamino)phosphonium salts, derived from oximes of ketones, undergo the Beckmann rearrangement.⁷⁷

A review of synthetic methods for arylpyrroles focuses particularly on the Trofimov reaction of oximes of alkyl aryl ketones with acetylene (192 references).⁷⁸

Hydrazones, Semicarbazones, and Related Species

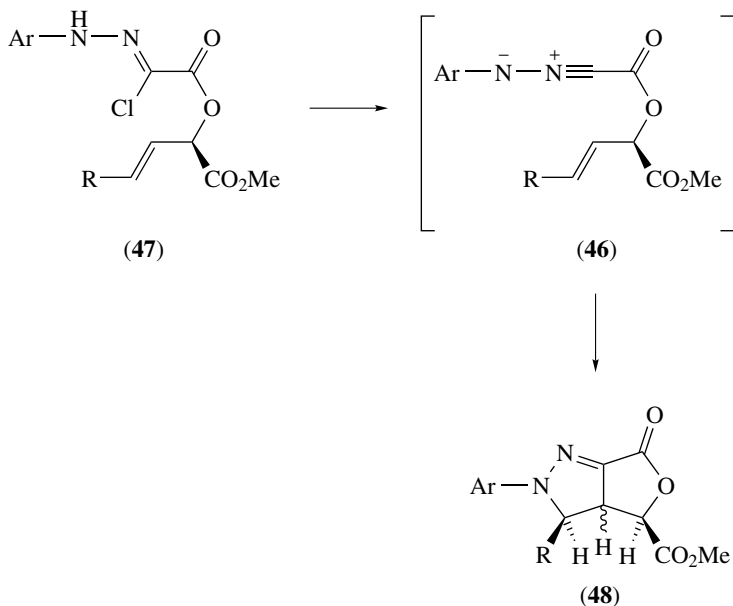
Tosylhydrazones of benzaldehyde have been reacted with a benzotriazole-stabilized benzyl anion, formed from an (arylmethyl)benzotriazole and butyl lithium, to provide a stereoselective, one-step synthesis of stilbenes, with lithium chelation probably setting up the geometric preference for *E*-product.⁷⁹

An attempted Fischer-type bis-indolization of cyclohexane-1,3-dione (**43**; R = H), and (separately) of dimedone (**43**; R = Me) involved treatment with 2 equiv. each of phenylhydrazine and phosphorus trichloride, in anhydrous benzene.⁸⁰ In addition to the expected bis(phenylhydrazones) (**44a**), an oxidation product (**44b**) was also formed. A mechanism is proposed.

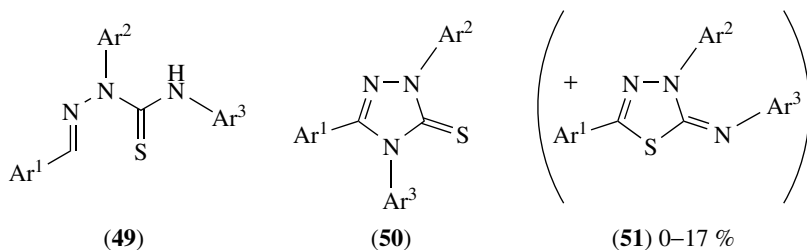


Aromatic SAMP-hydrazones [**45**; SAMP = (*S*)-aminomethoxymethylpyrrolidine] react with the lithio derivative of methoxyallene to yield enantiopure 3-pyrrolines.⁸¹

Homochiral nitrile imines (**46**) can be generated *in situ* by base treatment of hydrazonyl chlorides (**47**);⁸² (**46**) undergoes diastereoselective formation of furo[3,4-*c*]pyrazole derivatives [**48**], easily separable isomers], via intramolecular cycloaddition.



Oxidative cyclization of (thio)semicarbazones is a common route to five-membered rings with three heteroatoms. A quantitative study of the reaction of 2,4-diaryl-substituted aldehyde thiosemicarbazones (**49**) reports rate constants for formation of 1,2,4-triazole (**50**),⁸³ together with the isomeric thiadiazole (**51**), the latter only being formed when the Ar¹ moiety has a strongly electron-withdrawing substituent (CF₃, NO₂) in the *para*-position. The products are not interconvertible under the reaction conditions (FeCl₃ · 6H₂O in refluxing ethanol), indicating that intramolecular attack by nitrogen predominates over sulfur in all cases. The aldehyde-derived ring (i.e. Ar¹) has the most effect on the rate of cyclization: a ρ value of -3.0 ± 0.2 is reported.



Kinetics of the aminolysis of phenyl and methyl 4-nitrophenyl thionocarbonates [Ph- and Me-OC(=S)OC₆H₄-4-NO₂] by secondary cyclic amines, to give the corresponding thionocarbamates, have been measured in aqueous solution at 25 °C.⁸⁴

Using an excess of amine, pseudo-first-order rate coefficients were recorded, but not all plots against amine concentration were linear. The observed behaviours are interpreted in terms of a tetrahedral zwitterionic intermediate, the formation of which is rate-determining for the phenyl substrate. The relative rates of the steps of the mechanism are more finely balanced for the methyl case. The effect of changing from C=S to C=O in the reactant is also examined.

para-Substituted methyl phenylcarbamates have been chloromethylated, using formaldehyde and hydrogen chloride.⁸⁵

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

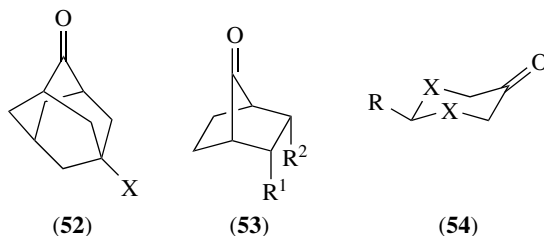
Regio-, Enantio-, and Diastereo-selective Aldol Reactions

Chemical Reviews (1999), Volume 99, issue 5, was devoted to the theme of diastereoselection, with the majority of articles dealing predominantly with ketones, aldehydes, and their derivatives. The titles (*and principal authors*) indicate how comprehensively the field is reviewed. Topics covered include ‘Catalytic Enantioselective Addition to Imines’ (*Kobayashi*)⁵⁷ and ‘Synthesis and Diastereoselective Reactions of *N,N*-Dibenzylamino Aldehydes and Related Compounds’ (*Reetz*).⁸⁶ The range of electronic and steric influences, and the need for tightly controlled model systems to test theories, are exemplified in ‘Around and Beyond Cram’s Rule’ (*Reiser*),⁸⁷ ‘Using Perturbation and Frontier Molecular Orbital Theory to Predict Diastereofacial Selectivity’ (*Dannenberg*),⁸⁸ ‘Inductive and Resonance Effects of Substituents on π -Face Selection’ (*Cieplak*),⁸⁹ ‘Orbital-controlled Stereoselections in Sterically Unbiased Cyclic Systems’ (*Ohwada*),⁹⁰ ‘Structure Distortions in Heteroatom-substituted Cyclohexanones, Adamantanones, and Adamantanes: Origin of Diastereofacial Selectivity’ (*Gung*),⁹¹ ‘Face Selection in Addition and Elimination in Sterically Unbiased Systems’ (*Le Noble*),⁹² ‘Nature of the Electronic Factor Governing Diastereofacial Selectivity in Some Reactions of Rigid Saturated Model Substrates’ (*Adcock*),⁹³ ‘Electronic Control of Facial Selection in Additions to Sterically Unbiased Ketones and Olefins’ (*Mehta*),⁹⁴ and ‘Nucleophilic Additions to 4,4-Disubstituted 2,5-Cyclohexadienones: Can Dipole Effects Control Facial Selectivity?’ (*Wipf*).⁹⁵

A computational approach is applied in ‘The Exterior Frontier Orbital Extension Model’ (*Tomoda*).⁴² Indeed, Tomoda has used the EFOE model in several other papers that are mentioned together here for convenience.

The method involves calculating the accessible space outside the van der Waals radii above and below the carbonyl- (or other π -) plane. The stereoselectivity is then predicted from the difference between the π -plane-divided accessible space on each side. Several hydride reductions of cyclohex- and cyclohept-anones and of adamantan-2-ones have been used to exemplify the method, which does not require consideration of transition-state effects.⁹⁶ For 5-substituted adamantan-2-ones (**52**), π -facial stereoselection is found to arise mainly from steric effects in most cases, except for aryl substituents, where orbital control appears dominant.⁹⁷ In assessing the steric, electronic, and orbital contributions to π -facial stereoselectivity in nucleophilic addition to bicyclo[2.2.1]heptan-7-ones (**53**),⁹⁸ the results are compared with Mehta’s experimental data for the system.^{99a,b} In the case of nucleophilic additions to

2-substituted-1,3-dioxanones and their dithiane analogues (**54**; X = O, S), the reversal of π -facial stereoselection between these systems may be due to ground-state conformational effects.¹⁰⁰ The model has also been used earlier in the section 'Imines'.



A direct catalytic asymmetric aldol reaction using aldehydes and unmodified ketones is promoted by an anhydrous lanthanide, LnLi_3 -tris-(*R*)-binaphthoxide.¹⁰¹ Combination of this catalyst with potassium hydroxide and water yields a more active heteropolymetallic catalyst. The scope and limitations of this reaction have been explored, and ketone deprotonation is the rate-determining step.

Diastereomeric phosphoramides¹⁰² have been employed to catalyse the asymmetric aldol addition of trichlorosilyl enolates to benzaldehyde.¹⁰³ Good *anti/syn* product ratios were achieved, but these were reversed on employing a more hindered catalyst, and the ratios were also affected by the catalyst concentration. A mechanistic switchover is proposed: one transition-state geometry involves a 1:1 complex (catalyst:enolate) favoured by a hindered catalyst in low concentration, while the other route involves a 2:1 stoichiometry.

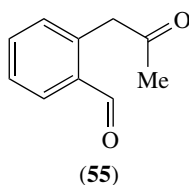
An unusual face selectivity in an aldol condensation has been explained by invoking an interaction between the formyl group and a 4,5-positioned unsaturation.¹⁰⁴

Lithium enolates of α -hydroxy ketones, derived from camphor, undergo aldol reactions with typically 90% *de*;¹⁰⁵ onward reaction to a variety of carbonyl products can be achieved with recycling of the camphor auxiliary.

Diastereoselectivities observed in the addition of titanium enolates to chiral α -silyloxyaldehydes have been rationalized in terms of competing steric and stereoelectronic effects,¹⁰⁶ and put to use in syntheses of polyketide metabolites.¹⁰⁷

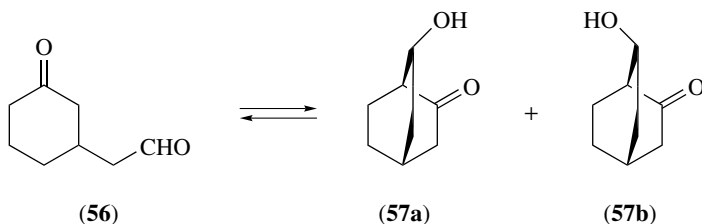
β -Hydroxy- α -amino acids have been synthesized enantioselectively via an aldol reaction.¹⁰⁸

Ketoaldehyde (**55**) undergoes a hydroxide-catalysed intramolecular aldol reaction.¹⁰⁹ Initial deprotonation gives an enolate. This step has been shown to be effectively irreversible by determination of the rate constant ratio for the two possible fates of the



enolate: reprotonation by solvent (k_{HOH}) versus intramolecular addition to the aldehyde carbonyl (k_{C}). The rate ratio value of 35 for water compares with values from 7 up to 450 for the corresponding buffer acid ratio ($k_{\text{BH}}/k_{\text{C}}$) for a series of quinuclidine buffers of $\text{p}K_{\text{BH}} = 11.5$ down to 7.5. The intramolecular reaction displays a rather small Marcus intrinsic barrier.

The acid-catalysed intramolecular aldolization of 3-oxocyclohexanecarbaldehydes (**56**) yields an 85 : 15 mixture of 6-*endo*- and 6-*exo*-hydroxybicyclo[2.2.2]octan-2-ones (**57a**, **57b**), under thermodynamic control.¹¹⁰ The origin of the diastereoselectivity is not, apparently, due to intramolecular hydrogen-bonding in (**57a**), but rather to an unfavourable steric interaction in (**57b**).



Mukaiyama Aldol Reactions

Two themes were prominent in recent developments of the Mukaiyama aldol reaction: a pronounced move towards performing the reaction in water, and a number of examinations as to the precise role of water and, in particular, whether it converts many triflate 'catalysts' into (catalytic) trimethylsilyl triflate, either inadvertently or by design.

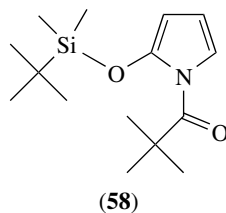
An aldol reaction of a silyl enol ether with an aldehyde has been carried out in water, with a chiral copper(II) bis(oxazoline) catalyst, with moderate to good *ee* and *syn/anti* ratios.¹¹¹ Conveniently performable in aqueous ethanolic solution for typical reactants, the reaction does not merely tolerate water, but its course and selectivities are dependent on it.

Lanthanide Lewis acids are increasingly being utilized in aldol reactions, and some of them have the advantage of being stable in water. The reaction of benzaldehyde and a silyl enol ether takes place in high yield in water at ambient temperature.¹¹² Using a scandium(III) surfactant Lewis acid [$\text{Sc}(\text{O}_3\text{SOC}_{12})_3$ or $\text{Sc}(\text{O}_3\text{SC}_{12})_3$] and HCl, the product is formed without significant hydrolysis of the silyl enol ether. Although the mechanism is still unknown, the Lewis acid-Brønsted acid combination is essential.

Bismuth(III) triflate appears to act as an efficient catalyst, although transmetalation with the silyl enol ether may mean that trimethylsilyl triflate (Me_3SiOTf) is the real catalyst.¹¹³ The system is more catalytic than rare earth triflates and, as the bismuth reagent is water-soluble, it is easily recovered.

A number of Lewis acids such as Ph_3COTf and $\text{TiCp}_2(\text{OTf})_2$ which apparently catalyse Mukaiyama cross-aldols actually proceed via catalysis by trimethyl triflate, due to exchange with the silyl enol ether under the influence of adventitious moisture. The range of mechanisms operating in this reaction is also reviewed (23 references).¹¹⁴

A 2-siloxypyrrole derivative (**58**) shows significant stereoselection in its reactions with aldehydes.¹¹⁵ With boron trifluoride etherate as Lewis acid, aromatic aldehydes (except those with donating groups) gave *erythro* products, whereas aliphatic aldehydes (except an α,β -unsaturated one) gave predominantly *threo* products. Most selectivities were reversed (except for the exceptions!) when tin(IV) chloride was used. Such switching of selectivity is also reported for other Lewis acids and, in some cases, just with a solvent switch. Transition-state structures are proposed to explain the high sensitivity of stereoselection to the nature of the Lewis acid.

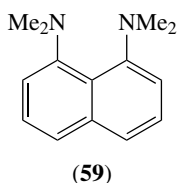


An optically active polymer has been prepared by repetitive Mukaiyama aldol reaction, using a bis(silyl ketene acetal) and a dialdehyde, plus a chiral oxazaborolidinone catalyst,¹¹⁶ and the role of Lewis basicity of aldehydes in oxazaborolidinone-catalysed Mukaiyama aldols has been examined.¹¹⁷

Miscellaneous Aldol-type Reactions

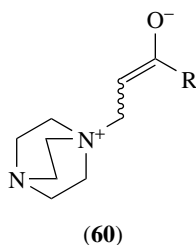
In Knoevenagel condensation of aliphatic aldehydes with β -keto esters (or 1,3-diketones), it can be difficult to isolate the first condensation product, which is often sufficiently reactive to combine with a second mole of ketone. A new strategy for achieving the equivalent of mono-condensation involves the use of an aldehyde in masked form, via the use of indium metal, in water.¹¹⁸

Proton sponge [1,8-bisdimethylaminonaphthalene (**59**), $pK_a = 12.1$] has been investigated as a catalyst for Knoevenagel condensation of benzaldehyde with activated methylenic compounds such as ethyl acetoacetate ($pK_a = 10.3$).¹¹⁹ While the base readily deprotonates the methylene group, in some solvents its protonated form is so well stabilized that the 'desorption step' (i.e. return of the proton to the condensed product) becomes the controlling step, with the catalyst effectively poisoned. Solvents such as DMSO, however, facilitate catalysis by stabilizing the open form of the protonated amine via hydrogen bonding. Such solvent effects are studied in more depth for the case of ethyl cyanoacetate ($pK_a < 9$) in systems covering a wide range of polarity.



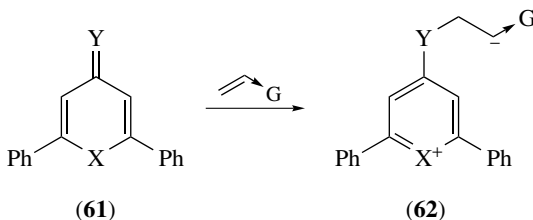
The mechanism of the Horner–Wadsworth–Emmons reaction of the lithium enolate derived from trimethyl phosphonoacetate with acetaldehyde has been investigated by *ab initio* calculations.¹²⁰ Oxaphosphetane formation is rate determining, both in the gas phase and with one ether molecule solvating. The transition state leading to *trans*-alkene is more stable than that giving the *cis* form.

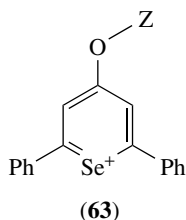
Baylis–Hillman reaction of an aldehyde with an α,β -unsaturated carbonyl compound is catalysed by 1,4-diazabicyclo[2.2.2]octane (DABCO); a zwitterionic intermediate (**60**) is proposed.¹²¹ Lithium perchlorate is found to accelerate the reaction further (in diethyl ether solvent), presumably through further stabilization of such a species. The effect is *not* seen with most other metal salts, presumably because they cannot act as efficient, independent co-catalysts in the presence of a tertiary amine.



Diazabicycloundecene (DBU) is shown to be a superior catalyst to DABCO in a typical Baylis–Hillman reaction.¹²² The finding downplays the importance of the nucleophilicity of the base, as DBU is generally considered to be both non-nucleophilic and hindered. Rather, it appears to stabilize better the β -ammonium enolate intermediate of the reaction.

Chalcogen-based catalysts for the Baylis–Hillman reaction have been further developed.¹²³ 2,6-Diphenyl-4*H*-chalcogenopyran-4-(thi)ones (**61**; X = S, Se; Y = O, S) catalyse the addition of an appropriate alkene to an aldehyde in the presence of titanium tetrachloride in dichloromethane. The first step is proposed to involve Y-(rather than X-)alkylation, driven by aromatization. The resultant zwitterion (**62**) then attacks the aldehyde. Although (**62**) has not been directly observed, the reaction of methyl vinyl ketone with the selenopyranone catalyst (**61**; X = Se, Y = O) shows NMR evidence of an *O*-alkylation product and of a titanium alkoxide (**63**; Z = CH₂CH₂COME and TiCl₃, respectively).





An asymmetric Baylis–Hillman reaction has been reported to give >90% *ee* using an activated acrylate [H₂C=CHCO₂CH(CF₃)₂] and a chiral phenolamine;¹²⁴ another approach uses a chiral pyrrolizidine base with a pendant alcohol.¹²⁵

Diastereoselective pinacol coupling of aldehydes has been achieved using a complex of titanium(IV) and a chiral Schiff base.¹²⁶

Samarium iodide promotes the pinacol homo-coupling of aldehydes to give 1,2-diols, but typically with little difference in the yields of the *syn*- and *anti*-isomers. Addition of Lewis acids, however, improves the selectivity, apparently by complexing both reactants in the transition state.¹²⁷ Chiral aldehydes such as 2-phenylpropanal can give *syn/anti* ratios >50, even without additives, and in some cases they give exclusively one product with appropriate choice of conditions.

The 1 : 1 complexes of samarium(II) iodide and tetraglyme derivatives promote intermolecular pinacol coupling to give vicinal diols.^{128a} When two such glyme chelates are attached (top and bottom) to ferrocene, high yields and diastereoselectivities are obtained; the glyme chelation can hold two samarium ions apart by a distance appropriate for inclusion of two reactant aldehyde molecules in between.^{128b}

The McMurry alkene synthesis has been reviewed, considering the mechanistic alternatives of carbene or pinacolate intermediates.¹²⁹

A phase-transfer-catalysed asymmetric Darzens reaction of cyclic α -chloro ketones has been reported.¹³⁰

1-Benzothiophen-3(2*H*)-one undergoes aldol-type condensations with ketones, promoted by boron trifluoride.¹³¹

A bis(amido)magnesium reagent, Mg[N(SiMe₃)₂]₂, mediates aldol additions; an amidomagnesium aldolate intermediate has been isolated and characterized by X-ray crystallography.¹³²

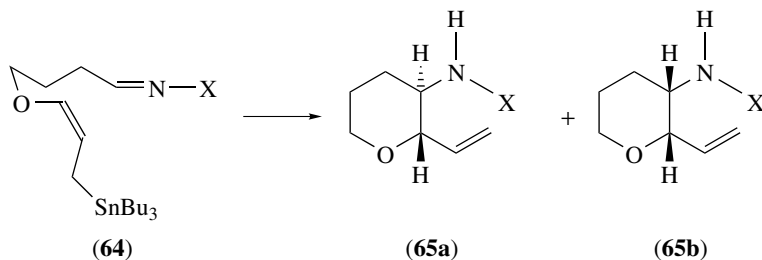
Ketene silyl acetals react readily with ketones in the presence of a Lewis acid such as (F₅C₆)₂SnBr₂, or trimethylsilyl or scandium(III) triflates.^{133a} The reactivity is sufficient to allow ketones to react preferentially over aldehydes or acetals, thus broadening the scope of this type of aldol reaction. Although the nature of the proposed ternary complex of ketene silyl acetal–Lewis acid–ketone is still unclear, ¹³C NMR complexation studies provide a pointer. The ketones complex more strongly than similar aldehydes, but not *too* strongly. Thus it appears that the Lewis acids that are critical to the selectivity are strong enough to catalyse the reaction, but not so strong such that they would fail to discriminate the slightly greater basicity of ketones over aldehydes. However, the structure of a ketene silyl acetal is also essential, as the enol silyl ether of acetophenone reacts with aldehydes, but not ketones.^{133b}

Semiempirical calculations have modelled the addition of dimetal enolate salts of carboxylic enolates to aldehydes, and have been extended to predict the kinetic stereoselectivities of such reactions.¹³⁴

Other reports deal with a pyrrolidine-catalysed homo-aldol condensation of aliphatic aldehydes (further accelerated by benzoic acid),¹³⁵ a diastereoselective aldol-type addition of chiral boron azaenolates to ketones,¹³⁶ the use of TMS chloride as a catalyst for TiCl₄-mediated aldol and Claisen condensations,¹³⁷ a boron-mediated double aldol reaction of carboxylic esters,¹³⁸ gas-phase condensation of acetone and formaldehyde to give methyl vinyl ketone,¹³⁹ and *ab initio* calculations on the borane-catalysed reaction between formaldehyde and silyl ketene acetal [H₂C=C(OH)OSiH₃].¹⁴⁰

Allylations

Diastereoselective syntheses of oxacyclohexanes exploit the coupling of an α -alkoxyallylstannane to a C=N functionality at the end of the chain. Three strategies have been investigated. In a *non-chiral approach*, the use of an ω -hydrazone group (**64**; X = NHTs or NPh₂) gives exclusively the *trans*- β -amino cyclic ether (**65a**). A *chiral auxiliary approach* using an imine derived from (*R*)-(+)-1-phenethylamine [i.e. (**64**) with X = *CHMePh] gives predominantly the *trans*-product (**65a**) in high *de*.¹⁴¹ In a *reagent-controlled approach*, a simple imine function [(**64**) with X = CHPh₂], together with a chiral (external) catalyst, gives mainly the *cis*- β -amino ether (**65b**). All reactions were catalysed by Lewis acids, and the roles of the acids, and of steric effects, in determining the stereochemical outcome are discussed.

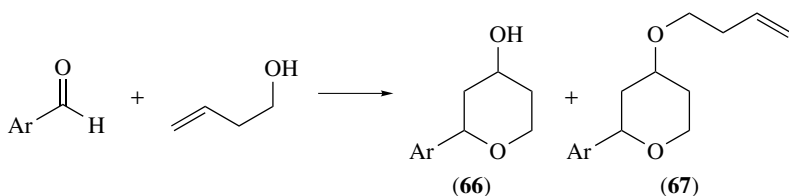


Potassium allyltrifluoroborate (H₂C=CHCH₂BF₃⁻K⁺) and its crotyl analogue are both stable towards oxygen and water, and react rapidly with aldehydes in the presence of boron trifluoride etherate, with high *de*, apparently via an allylboron difluoride intermediate.¹⁴² Allyl- and crotyl-trifluorosilane react stereoselectively with β -hydroxyaldehydes.¹⁴³

Chelation control has been achieved in the aldol and allylation reactions of β -alkoxyaldehydes, using Me₂AlCl or MeAlCl₂; the results are compared with the analogous use of tin and titanium tetrachlorides.¹⁴⁴ A stannylacetylene addition shows similar chelation control with the same reactants.¹⁴⁵

Aromatic aldehydes react with homoallyl alcohols to give tetrahydropyrans (**66**) and the corresponding ethers (**67**).¹⁴⁶ The conditions employed, scandium(III) triflate

catalysis under chloroform reflux, are much milder than those of the classic Prins formation of tetrahydropyrans.



Electronic and steric effects in the reaction of allylstannanes with aldehydes have been explored, using density functional theory (DFT) calculations, to discern the substituent effects that maximize stereoselection in this synthetically useful class of addition.¹⁴⁷

1,2-Addition of six allylindium reagents to 2- and 3-pyridinecarboxaldehyde, and to glyoxylic acid (OHCCO₂H), has been studied in water.¹⁴⁸ The stereoselectivity crosses over between the pyridine aldehyde isomers, which provides evidence for intramolecular complexation of indium by the pyridine nitrogen in the 2-position. The chelation ability of the 2-aldehyde is also compared to that of glyoxalic acid.

Aldehydes, acetals, and acid chlorides have been cyclopropylmethylated stereoselectively with homoallylstannanes, exploiting the γ -effect of tin;¹⁴⁹ a Lewis acid-promoted allylation of aldehydes with allyltin shows stereospecificity,¹⁵⁰ as does an addition of highly substituted cyclic allylzinc reagents.¹⁵¹

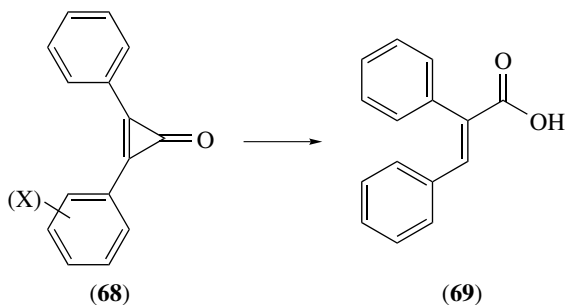
Other Addition Reactions

General and Theoretical

The nature of the interactions between the carbonyl moiety and substituents in a range of functional groups has been reviewed, drawing on computational results in addition to spectroscopic and other data.¹⁵² The σ - and π -interactions of groups such as carbonyl and amino in amides are discussed in terms of group-transfer energies, or bond dissociation energies, with appropriate allowance for the energy changes associated with rotation of the two moieties relative to each other. The effect of carbonyl groups on acidity, their interaction with alkenes, their hydration equilibria and their complexation behaviour with Lewis acids are discussed.

Ab initio calculations have been employed to characterize the nature and energy of addition of water, and of HF, to formaldehyde in the gas phase, and of both species to the 1 : 1 formaldehyde–formic acid complex.¹⁵³ Basicities of over 40 kcal mol⁻¹ are typical in the first cases, but the presence of associated formic acid more than halves the barriers to addition.

2-Phenyl-3-(substituted)phenylcycloprop-2-enones (**68**) undergo base-catalysed ring fission to give (*E*)-2,3-diphenylacrylic acids (**69**).¹⁵⁴ Kinetic studies in water include rates from 30 to 60 °C, a Hammett plot ($\rho = 1.2$ at 30 °C), and a kinetic solvent isotope effect. Hydroxide attack on the ketone is proposed to be rate determining, leading to a carbanion as final intermediate before ring cleavage.



Protonation equilibria of 5-substituted di(2-thienyl) ketones, measured in aqueous sulfuric acid, have been compared with those of the corresponding methyl and phenyl 2-thienyl ketones.¹⁵⁵

Density functional theory calculations have been used to estimate the mechanistic course of hydration and hydrolysis reactions of α -oxocarboxylic acid derivatives (esters and amides), with solvent effects allowed for.¹⁵⁶ For the uncatalysed reactions, stepwise and concerted routes are comparable in energy, whereas catalysis via water assistance significantly favours the stepwise process.

The reactivity descriptors, local softness and local hardness have been calculated using density functional theory for the reactivity of acetaldehyde and aromatic aldehydes towards acid-catalysed oxygen-18 exchange with H_2^{18}O .¹⁵⁷ These descriptors can be used to predict selectivity between reactive sites within a molecule, and experimental intermolecular reactivity, respectively. A new concept, intrinsic global hardness, is defined: for the aromatic compounds studied, it correlates well with the degree of aromaticity.

Addition of Organometallics

The mechanistic spectrum of irreversible additions of hydride and of a range of organometallics to aldehydes has been investigated using isotope effects.¹⁵⁸ Competitive kinetics have been studied for addition to benzaldehyde-H and -D, and to cyclohexanecarboxaldehyde, at -78°C . Hydrides gave inverse secondary deuterium isotope effects, the magnitude of the effect varying with the reactivity of the reagent. The result is consistent with direct polar addition (i.e. two-electron transfer). Many lithium bases and Grignards gave similar effects, except the alkyls: these gave normal effects, indicating rate-determining single-electron transfer. The use of electrochemically determined redox potentials as a guide to which mechanism is operating is discussed for several organometallic reagent types. The results have implications for the design of face-selective addition reactions.

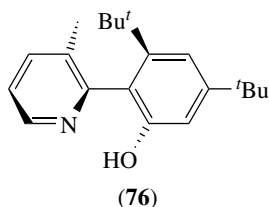
Benzylloxymethane, when treated with Bu^tLi in the presence of a chiral bis(oxazoline), forms two epimeric α -methoxybenzyl lithium complexes.¹⁵⁹ Although these have been shown to epimerize, enantioselective addition of aldehydes is still achieved, in up to 98% *ee*. The variation of the yields and selectivities with aldehyde stoichiometry suggests a 'dynamic thermal resolution,' in which

Enantiopure γ -butenolides (**75**) have been prepared via addition of a chiral lithiated sulfoxide to aldehydes.¹⁶³

The regioselectivity of the addition of α -lithiated arylmethyl phosphonates to cyclohex-2-enones has been investigated for a series of benzyl compounds, $\text{XC}_6\text{H}_4\text{CHLiPO}_3\text{Et}_2$, and for a 1-naphthyl case, $\text{C}_{10}\text{H}_7\text{CHLiPO}_3\text{Et}_2$.¹⁶⁴ Addition is at the carbonyl group for the parent ketone, but regioselectivity is decreased for the 2-methyl derivative, while addition of the naphthyl salt is predominantly 1,4. Conformational analyses by solution ^1H NMR, X-ray crystallography, and molecular modelling are reported.

Addition of Grignards to the carbonyl group of β -keto phosphonates gives β -hydroxyphosphonates with an extended carbon skeleton.¹⁶⁵ Allylmagnesiums add especially with BF_3 catalysis, while allylzincs often give higher yields, even without a Lewis acid. Allylic transpositions follow reactions with crotyl and prenyl organometallics.

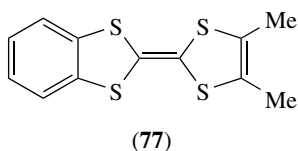
Readily available chiral amines related to the Betti base [phenyl(2-hydroxy-1-naphthyl)methanamine] catalyse enantioselective addition of diethylzinc to aldehydes in moderate to excellent *ee*.¹⁶⁶ Observed enantioselectivities in addition of diethylzinc to aldehydes catalysed by a series of (*S*)-proline-derived pyrrolidines have been explained in terms of steric effects.¹⁶⁷ New 2,5-diazabicyclo[2.2.1]heptanes have been applied to enantioselective addition of diethylzinc to benzaldehyde.¹⁶⁸ (*S*)-2-(3-Methyl-2-pyridyl)-3,5-di-*t*-butylphenol (**76**) has been used as an enantioselective catalyst of diethylzinc addition to benzaldehydes. Reaction in toluene shows a significant variation in % *ee* with temperature, including observation of an 'inversion temperature' with maximum *ee*.¹⁶⁹ This value varies with the nature of the *para*-substituent in the aldehyde, and the overall behaviour may be due to a shift in the rate-determining step of the reaction. Other reports of zinc reagents include: enantioselective addition of diethylzinc to aldehydes,¹⁷⁰ addition of diphenylzinc to aldehydes using a chiral ferrocene-based hydroxyoxazoline catalyst in up to 96% *ee*;¹⁷¹ and 3-*exo*-morpholinoisoborneol has been proposed as a more convenient and efficient enantioselective catalyst of alkylzincs^{172a} than Noyori's original 3-*exo*-dimethylamino catalyst.^{172b}



Indenols, and ultimately indanones, can be prepared via a nucleophilic vinyl palladation of *o*-bromobenzaldehyde.¹⁷³ Stereoselective addition of α -amino-organometallics to aldehydes have been reviewed (62 references).¹⁷⁴ Diastereoselective additions of MeMgX and MeLi to an oxo-sugar have been reported.¹⁷⁵

The Wittig Reaction, and Variants

The application of a Wittig–Horner-type condensation to synthesis of unsymmetrical tetrathiafulvenes [e.g. (77)] has been extended, and the mechanism has also been investigated.¹⁷⁶



A variety of computational methods suitable for organic reactions in solution are reviewed, using the Wittig and several other reaction types as examples, with a particular focus on the handling of solvent effects.¹⁷⁷

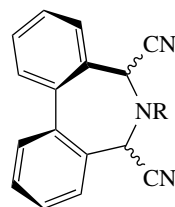
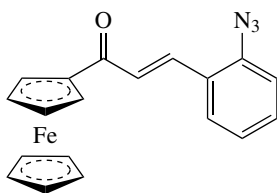
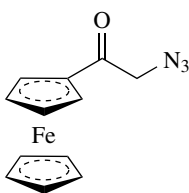
Electro-generated bases have been employed to carry out the phosphonium salt deprotonation step of the Wittig reaction,¹⁷⁸ a method that shows promise as a stereoselective electrosynthesis.

Acetylferrocene has been used as a starting point for the generation of a wide range of functionality. α -Azidoacetylferrocene (78) reacts with isocyanates or acid chlorides (in the presence of triphenylphosphine), to give ferrocenyloxazoles, while the iminophosphorane derived from 3-(*o*-azidophenyl)-1-ferrocenylpropenone (79) undergoes aza-Wittig reactions.¹⁷⁹

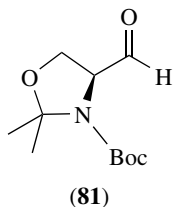
A bis(iminophosphorane) derived from 2,2'-diazidobiphenyl [or a 2,2'-bis(isothiocyanato)biphenyl reacted with aryliminophosphoranes] serves as the entry point for bis(carbodiimides) and their intramolecular cyclizations to 1,3-diazetidines-2,4-diimines.¹⁸⁰ A mechanistic scheme for the aza-Wittig reactions is proposed.

Miscellaneous Additions

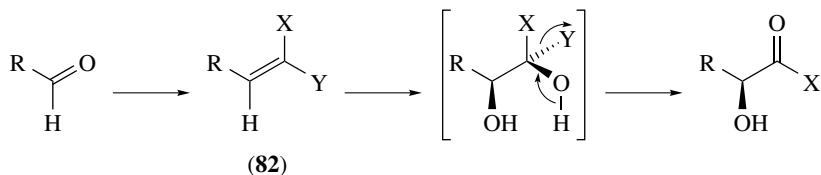
The Strecker reaction of a dial with an amine and hydrogen cyanide, to produce a cyclic α,α' -dicyanoamine, involves HCN addition to a cyclic imino nitrile intermediate as the final step. A highly diastereoselective synthesis of dihydro-5*H*-dibenz[*c,e*]azepines (80) from the biphenyldicarboxaldehyde exploits the chiral twist of the biaryl axis to achieve stereoselection.¹⁸¹



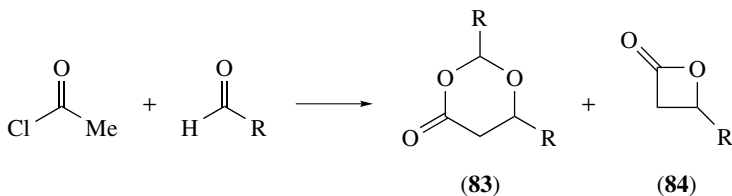
Garner's aldehyde (**81**) has been diastereoselectively hydrocyanated;¹⁸² solvent and temperature effects and the use of Lewis acid or enzyme catalysts are described.



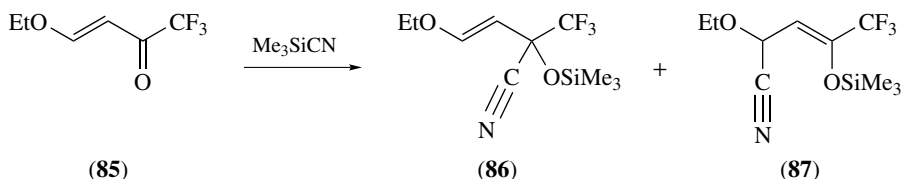
Asymmetric nucleophilic acylation of aldehydes can be achieved by (i) a homologation step to a 1,1-heterodisubstituted alkene (**82**), followed by (ii) asymmetric dihydroxylation. Variants via ketene *O,S*-acetals (**82**; X = O, Y = S) and *O,O*-acetals (**82**; X = Y = O) have been reviewed,¹⁸³ and a wide range of aldehyde types are shown to be suitable.



Lewis acids catalyse the cyclocondensation of acid chlorides and aldehydes to give lactones (**83**) and (**84**).¹⁸⁴ Aluminium chloride catalysis favours the 1 : 1 product (**84**), via a ketene pathway, while the large ring is the predominant product using e.g. $\text{TiCl}_2(\text{OPr}^i)_2$, where aryl halide enolates are implicated as intermediates.



Addition of trimethylsilyl cyanide to (*E*)-1,1,1-trifluoro-4-ethoxybut-2-en-2-one (**85**) yields 1,2- and 1,4-adducts, (**86**) and (**87**), both useful materials for onward synthesis of trifluoromethyl compounds.¹⁸⁵ The regioselectivity is solvent- and temperature-dependent, and strikingly affected by the nature of the catalyst employed: several bases give 100% yields of 1,2-adduct, while a range of Lewis acids lead exclusively to the 1,4-adduct.



Fluoride catalyses the addition of a trimethylsilyldiazoacetate, $\text{TMS}-\text{C}(=\text{N}_2)\text{CO}_2\text{Et}$, to benzaldehyde to yield an α -diazo- β -hydroxy ester, $\text{PhCH}(\text{OH})\text{C}(=\text{N}_2)\text{CO}_2\text{Et}$.¹⁸⁶

Formaldehyde undergoes a Cannizzaro-type reaction in high-temperature/high-pressure water (250 °C/4 MPa), without added hydroxide or other catalyst.¹⁸⁷ Classically, methanol product yield is not expected to exceed 50%, but values of up to 70% were obtained, with relatively little formic acid. The detection of carbon dioxide suggests that the formic acid that is produced then reacts as an 'oxidized aldehyde,' according to $\text{H}_2\text{CO} + \text{HCO}_2\text{H} \rightleftharpoons \text{H}_3\text{COH} + \text{CO}_2$. Carbon monoxide was not detected.

Substituent and solvent effects on the Kabachnik–Fields reaction of the dialkyl hydrogenphosphite–cyclohexylamine–benzaldehyde system have been reported; kinetic analysis shows evidence of a hydroxyphosphonate intermediate.¹⁸⁸ Kinetics are also reported for several substituted benzaldehydes, probing for evidence of an alternative imine intermediate,¹⁸⁹ and for salicylaldehyde, which *does* proceed via an imine (as the hydroxyphosphonate is unstable).¹⁹⁰ When the dialkyl hydrogenphosphonate reactant is changed to a phosphonate, the rate and mechanism of the reaction are significantly altered.¹⁹¹

trans-Propargylic oxiranes have been prepared by stereoselective addition of 3-(trimethylsilyl)propargyl chloride to aldehydes and ketones.¹⁹² Epoxyalkynes are formed stereoselectively via indium-promoted coupling of α -chloro sulfides to aldehydes.¹⁹³

Catalytic asymmetric dienylation of achiral aldehydes has been achieved using buta-2,3-dienylstannane and a chiral Lewis acid.¹⁹⁴

Enolization and Related Reactions

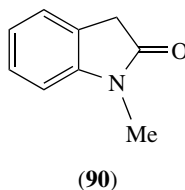
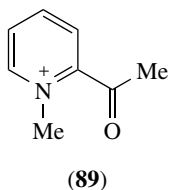
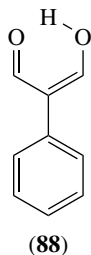
A new *ab initio* semi-classical technique for the calculation of tunnelling effects has been demonstrated for the case of the interconversion of the (degenerate) enols of malonaldehyde via intramolecular proton transfer; the method incorporates tunnelling into first principles molecular dynamics.¹⁹⁵ The use of density functional theory to model transition states in this reaction has also been described,¹⁹⁶ even the most advanced levels of theory meet substantial difficulties in such systems.

The possibility that the intramolecular hydrogen bond in the enol of 2-phenylmalonaldehyde (**88**) is a single potential well (i.e. a symmetric bonding situation) has been discounted, for chloroform and pyridine solvents, by ¹H and ¹³C NMR isotopic perturbation experiments which indicate two equilibrating tautomers.¹⁹⁷

Intrinsic rate constants for proton transfer from 2-acetyl-1-methylpyridinium ion (**89**) to secondary alicyclic amines have been measured in water and 50:50 aqueous

DMSO, at 20 °C.^{198a} This ketone is complicated by having a significant hydrate content ($K_h = 0.044$), and forms its hydrate anion at high pH. The compound is very acidic ($pK_a = 11.18$ at 25 °C), and its $\log k_0$ value of 0.92 is lower than that of any sterically unhindered carbon acid (except those of nitroalkanes). Rate constants for deprotonation by hydroxide are also reported, and discrepancies in the results of Frey^{198b} are put down to, in the main, an incomplete kinetic treatment of their raw data. The results are discussed in the context of Kresge's rate–equilibrium correlation for simple ketones and aldehydes.^{198c}

Keto–enol–enolate rate and equilibrium constants have been reported for *N*-methylindoline-2-one (90), its 2-thione, and its 2-selone, i.e. a lactam, a thiolactam, and a selenolactam.¹⁹⁹ As an example, the 'ketone' tautomer of the thione has an acidity constant of 8.93, and that of its 'enol' is 4.05, giving a tautomerization constant, pK_E , of 4.88.



Tautomeric equilibria have been measured for the highly strained ketones, Tip_2COR ($\text{Tip} = 2, 4, 6\text{-triisopropylphenyl}$), for methyl and *t*-butyl as R groups, and for the corresponding aldehyde ($\text{R} = \text{H}$).²⁰⁰ In hexane at 77.5 °C, $K_{\text{enol}} = 0.11, 0.0011, \text{ and } 90$, respectively. The enol tautomers also undergo oxidative cyclization to give benzofurans, losing an isopropyl group in the process.

The keto–enol equilibrium constant of benzoylacetone in water is perturbed in the presence of β -cyclodextrin, from a value of 0.62 to 5, and also in sodium dodecyl sulfate micelles, in both cases by preferential binding of the enol tautomer.²⁰¹ Thermodynamic parameters from temperature studies of the equilibrium give more information about the structures of the complexes; for example, the enol penetrates further into the cavity of the cyclodextrin, as confirmed by ^1H NMR spectroscopy. Nitrosation of benzoylacetone is slowed in the presence of the cyclodextrin, consistent with a protective effect arising from the strong binding to the enol.

Wirz has reviewed his work with Kresge on the generation of unstable tautomers by flash photolysis, and the subsequent kinetics of conversion to the stable tautomer.^{202,203} The enols of ketones and aldehydes, of carboxylic acids and esters, of ketenes, and the keto tautomers of phenols are described. The ratios of forward and reverse rate constants yield tautomeric constants over 30 orders of magnitude. A Marcus treatment yields an intrinsic barrier of $57 \pm 2 \text{ kJ mol}^{-1}$ for oxygen-to-carbon proton transfer. Possible evidence for protonation of n, π^* -excited triplet ketones is presented.

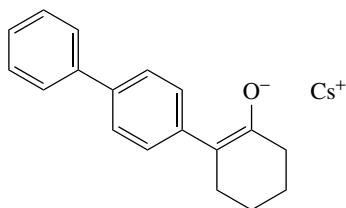
Enolates

Although kinetic protonation of many delocalized carbanions (including enolate anions) and of enols often takes place on the less hindered face (typically giving the less stable stereoisomer), an example of kinetic protonation on the more hindered side has been engineered via intramolecular proton transfer.^{211a,b}

Conformational issues in the enantioselective deprotonation of 4-*t*-butylcyclohexanone by chiral lithium bases have been explored using a series of rigid tetrahydroisoquinolines.²¹²

Aliphatic aldehydes have been butylated enantioselectively using *n*-butyllithium and chiral lithium amides.²¹³ Mixed lithium amide–Bu^{*n*}Li complexes gave a faster asymmetric reaction, compared with Bu^{*n*}Li in the form of its tetramer.

The caesium enolate (**94**) of 2-biphenylcyclohexanone exists in a monomer–dimer equilibrium in THF ($K_{\text{dimer}} = 1.9 \times 10^3 \text{ l mol}^{-1}$), but the monomer is more reactive towards alkylation.²¹⁴ Relative reactivities of several alkylating agents are reported, and only products of alkylation at the conjugated carbon were isolated.



(94)

The enolate salts, $\text{H}_2\text{C}=\text{CH}(\text{OM})$, have been studied at various levels of theory for all of the alkali metals.²¹⁵ Several structural and thermodynamic parameters are reported, and the effect of the restriction of enolate resonance by attachment of the cation is described.

α -Chlorination of ketones can be achieved via kinetic formation of enolate, using lithium diisopropylamide, followed by treatment with *p*-toluenesulfonyl chloride, acting as a source of 'Cl⁺'.²¹⁶

Enantioselective deprotonation of cyclic ketones has been reviewed (62 references).²¹⁷

Oxidation and Reduction of Carbonyl Compounds

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

The enol tautomers of 1-(2',4',6'-trialkylphenyl)-2-methyl-1,3-diketones form a range of alkene, epoxide, ether, and hydroperoxide products on reaction with singlet oxygen.²¹⁸ The product distribution is substantially affected by the solvent, apparently owing to the disruption of intramolecular hydrogen bonding of the enols in polar solvents.

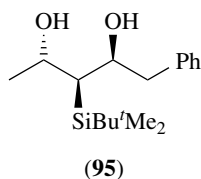
Kinetic and EPR studies have delineated the steps involved in the oxidation of D-ribose and 2-deoxy-D-ribose by chromium(VI), via chromium(V) intermediates, the distribution of which depends on the acidity of the solution.²¹⁹

Rates of oxidation by platinum(IV) have been reported for a range of aldoses, and for amino and methylated sugars.²²⁰

In kinetic studies of the oxidation of erythrose sugars by *N*-chlorobenzenesulfonamide in alkaline medium,²²¹ solvent isotope effects and product distributions suggest an enolate mechanism.

Synthetic applications of the oxidation of carbonyl compounds by organo-hypervalent iodine reagents have been reviewed (209 references).²²²

The carbonyl group of α -silylated aldols can be reduced stereoselectively with hydride reagents to yield 2-silylated 1,3-diols [e.g. (95)].²²³ Diols which are configured *syn,anti* [such as (95)] undergo highly regio- and stereo-selective Peterson olefination.

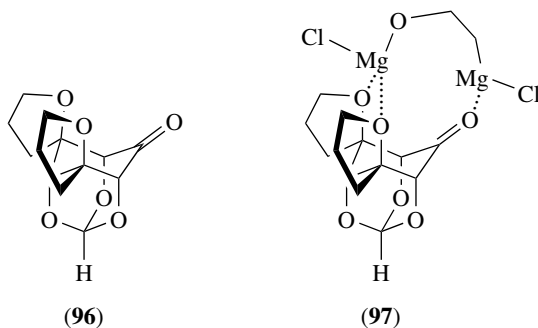


The unexpected finding that reduction of *cis*-2,6-dimethylcyclohexanone with sodium borohydride in methanol gave predominantly the *axial* alcohol prompted a detailed investigation of the reaction. Rates of epimerization versus reduction are compared, and the discrepancies arising are probed by molecular modelling.²²⁴ The study was also extended to the *trans*-reactant, and to lithium aluminium hydride as an alternative reductant.

The flowing afterglow-triple quadrupole technique has been used to measure the diastereoselectivity of the reduction of a range of cyclohexanones by silicon hydride ions in the gas phase.²²⁵ Strikingly, the axial or equatorial preferences in these 'intrinsic' diastereoselectivities are consistently similar to results in condensed phase.

β -Oxo carboxylic acids have been reduced to the β -hydroxy compounds in up to 99% *ee*, via neighbouring-group control.²²⁶

Ketone (96) is a C_2 -symmetric, rigid structure with five oxygen substituents, all axial. It provides an interesting model for tests of stereoelectronic and other effects in hydride reduction and nucleophilic addition, and in particular, the cumulative effects of multiple α - and β -alkoxy substituents.²²⁷ Standard NaBH_4 or LiAlH_4 reduction of the ketone gives an equatorial hydroxy group, the product of equatorial hydride attack, and $\text{Zn}(\text{BH}_4)_2$ gave the same result, ruling out a chelation route in this case. Allylmagnesium bromide gives allylation in the equatorial position, presumably preceded by magnesium complexation of the carbonyl oxygen. In contrast, addition of the Normant reagent, $\text{ClMg}(\text{CH}_2)_3\text{OMgCl}$, gives the opposite stereochemistry: this is proposed to occur via a 'chelation steering,' with the oxy-magnesium binding to the β -alkoxy oxygens on the upper face, setting up axial attack of the Grignard [as in (97)].



Reduction of a highly strained quinone does not yield a hydroquinone structure; rather, an adjacent aromatic ring is reduced, resulting in release of strain.²²⁸ Evidence for transient formation of the hydroquinone, and for double-reduction to replace the carbonyls with sp^3 centres, is presented.

A 1,4-asymmetric reduction of a γ -keto sulfoxide has its stereoselectivity reversed on addition of a lanthanide triflate.²²⁹

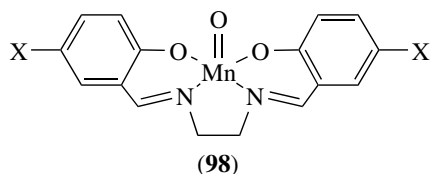
N-Formylamines can be prepared by the Leuckart reaction, a reductive amination of carbonyl compounds by reaction with formamide and formic acid. Evidence for an unprecedented intramolecular transamidation in the mechanism of enantioselective Leuckart reaction of 2-norbornanone with a (1-norbornyl)acetamide is presented.²³⁰

The mechanisms of the selective reduction of the carbonyl group of α,β -unsaturated carbonyl compounds have been reviewed (45 references),²³¹ and an enantioselective reduction of ketones using a bifunctional chiral oxazaborolidine catalyst has been reported.²³²

The Exterior Frontier Orbital Extension model, described earlier under *Regio-, Enantio-, and Distereo-selective Aldol Reactions*, can also be applied to predict stereoselectivity of carbonyl reduction.⁴²

Other Redox Reactions

Kinetics of the oxidation of a range of aliphatic aldehydes by benzyltrimethylammonium tribromide ($\text{PhCH}_2\text{NMe}_3\text{Br}_3^-$) have been measured in aqueous acetic acid.²³³ Based on the results and several control experiments, the mechanism appears to involve rapid equilibrium complex formation between the hydrate of the aldehyde and tribromide ion, followed by rate-determining C–H bond breaking to give the protonated acid, which rapidly deprotonates. When the anion is changed to chlorobromate (Br_2Cl^-), the mechanism switches to involve slow hydride transfer from the hydrate to the anion.²³⁴ Using similar experiments, the oxidations of *meta*- and *para*-substituted benzaldehydes by oxo(salen)manganese(V) complexes (**98**) were examined.²³⁵ Despite systematic variations of the substituents on the benzaldehyde and on the salen, and excellent Taft and Hammett plots, the results in this case did not conclusively distinguish between the mechanistic possibilities.



Substituted benzaldehydes are oxidized by quinolinium dichromate in DMF containing HCl, with electron-releasing substituents accelerating the reaction ($\rho = -0.90$).²³⁶ The first step, hydrogen abstraction, is rate-determining: the deuterium solvent isotope effect is 5.14 at 333 K.

The kinetics of the oxidation of *ortho*-substituted benzaldehydes by pyridinium chlorochromate have been analysed in terms of a multi-parameter equation, to allow separation of the 'ortho' or steric effect from the inductive and resonance effects.²³⁷

Also reported are the kinetics of the reaction of ozone with benzaldehydes in acetic acid,²³⁸ and of osmium(VIII)-catalysed oxidation of formaldehyde by alkaline periodate.²³⁹

A unusual oxidative decarbonylation has been reported in the photochemistry of bicyclo[2.2.2]octenone.²⁴⁰

A clean hydrogen-transfer reduction of aldehydes and ketones to the corresponding alcohols has been reported.²⁴¹ In a typical experiment, propan-2-ol is employed as reductant and solvent in an autoclave at 220–230 °C and 4–5 MPa. Although formally similar to Meerwein–Ponndorf–Verley reduction, the reaction requires no catalyst, which tends to cut down on side-products.

Tetramethoxyl-*p*-benzoquinone undergoes charge-transfer and subsequent substitution reactions with piperidine, and with morpholine, with the kinetics being first order in both acceptor and donor.²⁴²

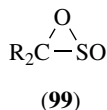
4-Alkyl analogues of NADH form 2 + 3-adducts with *p*-benzoquinone in the presence of scandium(III) triflate in acetonitrile;²⁴³ the rate behaviour shows that the Sc³⁺ ion catalyses the electron transfer.

For oxidation of acetophenone oximes by VO₃⁻, see under *Oximes*. Oxidation of thioketones is described later.

Reactions of Thiones

Thioketones, R₂C=S, can be oxidized to sulfoxes, R₂C=S=O, and further oxidized to, ultimately, the ketones, R₂C=O (+SO₂). Hydrogen peroxide can effect both reactions with catalysis by methyltrioxorhenium (MeReO₃). The kinetics of the oxidation sequence have been studied for a range of symmetrically disubstituted thiobenzophenones, and for thiocamphor.²⁴⁴ The first step is favoured by electron-releasing substituents (Hammett $\rho = -1.12$), whereas the second process, which is slower, exhibits a U-shaped Hammett plot. Hence it appears that the sulfine oxidation involves a mechanism in which the direction of electron flow in the transition state changes with the electron demand of the substituents in the reactants. The first step of the second reaction converts the sulfine to sultine (99) and/or sulfone (R₂CSO₂). Although the

transient sultine could not be directly observed, its onward reaction to ketone should produce SO, the evolution of which was confirmed by a trapping experiment.



Vinylcarbenoids react with thioketones to give vinylthiocarbonyl ylids, which can be cyclized to give a range of heterocycles.²⁴⁵

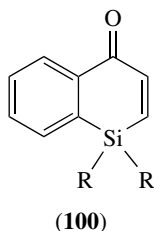
Semiempirical calculations have been used to model the mechanism of the reaction of *N*-(*p*-nitrobenzoyl)thiazolidine-2-thione with glycine.²⁴⁶

The mechanisms of the fluorescence quenching of aromatic thiones by various species have been reviewed (50 references).²⁴⁷

pK_a values for substituted diethylsulfamoyl 9-acridinethiones, acting as NH acids, have been reported;²⁴⁸ the Hammett correlation showed a weak sensitivity to substituents.

Other Reactions

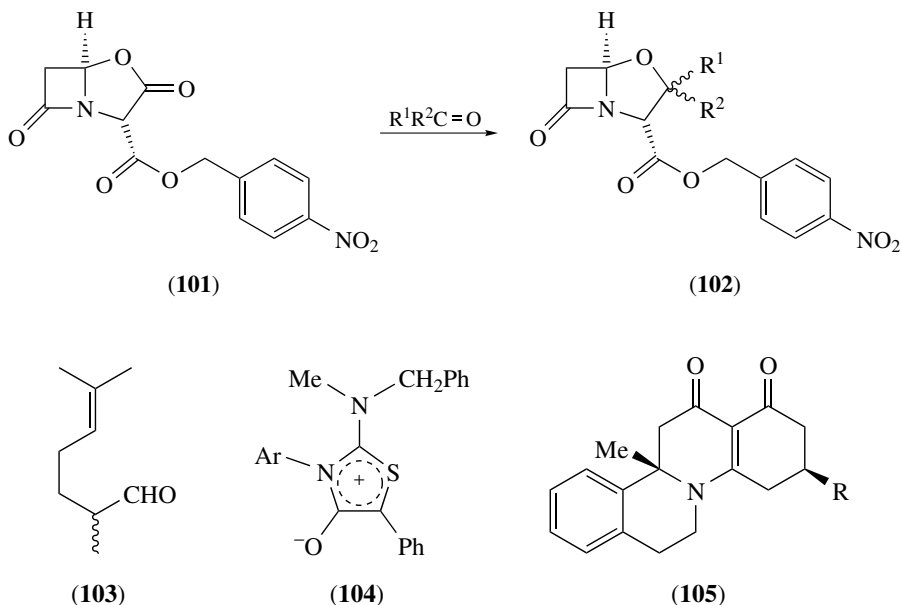
Two benzosilacyclohexadienones (**100**; R = Me, Ph) have been prepared and their reactivities characterized.²⁴⁹ These new cyclic β -silyl- α,β -unsaturated ketones undergo stereoselective Diels–Alder reactions, cyanocuprate addition to the carbonyl, and a Michael–Mukaiyama addition with an ethoxysilyloxy ketene acetal.



Oxapenamams (**102**) substituted in the 2-position are obtained by thermolysis of the β -lactam-based oxazolidinone (**101**) in the presence of aldehydes or ketones, via a ring-opened azomethine ylid, and subsequent cycloaddition.²⁵⁰

Unusual 2 + 1-adducts of citronellal (**103**) and oligo(hydroxy)benzenes are formed via acid-catalysed condensation, apparently via cyclization of the aldehyde, and subsequent carbocation formation via loss of hydroxide.²⁵¹

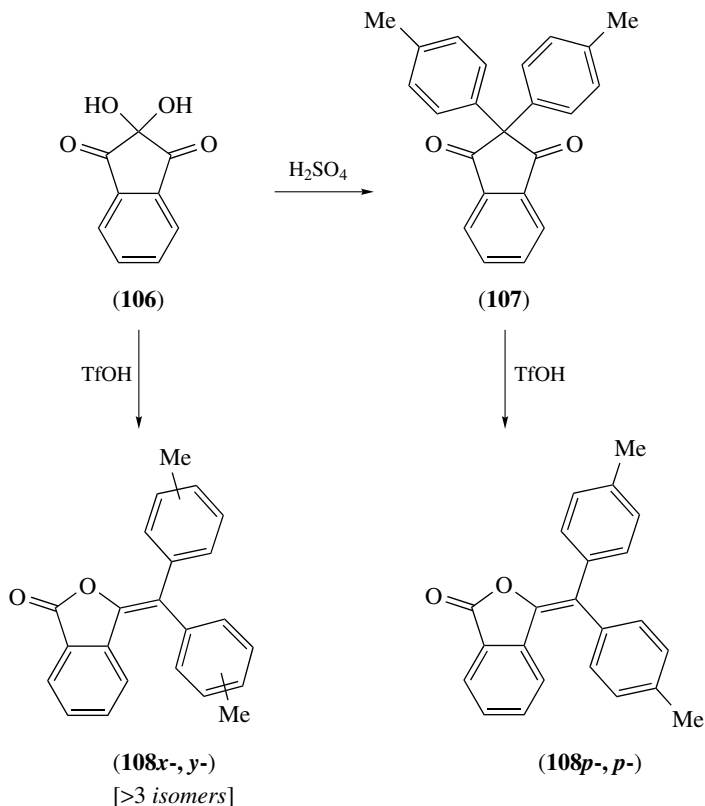
2-Aminothioisomunchnones (**104**) are mesoionic species; they cannot be represented by Lewis structures lacking charge separation. Two such dipoles (Ar = Ph, *p*-O₂NC₆H₄) have been found to react with benzaldehydes to produce β -lactams, apparently via 3 + 2-cycloaddition.²⁵²



1-Methyl-3,4-dihydroisoquinoline is annelated by a 5-(R-substituted) 2-acylcyclohexan-1,3-dione (a prochiral β,β' -triketone) to give the 8-azasteroid (**105**).²⁵³ The stereoselectivity of the reaction has been explored and explained.

Ninhydrin (**106**), the 2,2-diol or hydrate of indanetrione, reacts with aromatic compounds to form 2,2-diaryllindane-1,3-diones: the reaction is catalysed by sulfuric acid.²⁵⁴ For the example of toluene as aromatic reactant, the product (**107**) has both methyls *para*. Further reaction to give a 3-(diarylmethylene)isobenzofuranone (**108p-p-**) occurs on treatment with triflic acid. However, direct reaction of an arene such as toluene gives non-regioselective formation of the isobenzofuranone as a mixture of more than three isomers (**108x-y-**). A mechanistic scheme is proposed to account for the difference in product distribution, with the superacidic nature of anhydrous triflic acid suggested to allow diprotonation of the substrate. In the case of catalysis by sulfuric acid, the rearrangement of (**107**) to (**108p-p-**) is proposed to involve ring opening and re-closure.

Piperid-3- and -4-ones can be converted to the corresponding diphenylpiperidines with benzene and triflic acid.²⁵⁵ Evidence for reaction through the *O,N*-diprotonated reactant is presented. The reaction works for *N*-alkyl substrates, for tropinone and quinuclidine, and for acetals of the ketones, and indeed for acetals of the β -carbon of an *N*-alkylpiperidine. This electrophilic chemistry has been extended to biologically important α -keto acids, $RCOCO_2H$ ($R = COMe, CH_2CO_2H, CH_2CH_2CO_2H,$ and CH_2Ph).²⁵⁶ Typical intermediates and products include the *gem*-diphenyl group, with or without dehydrative decarbonylation. Dicationic intermediates are suggested to be involved in both routes.

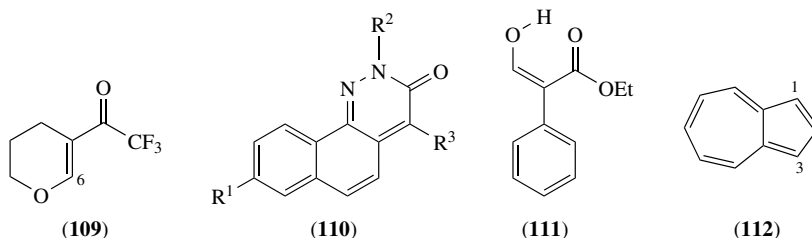


5-Trifluoroacetyl-3,4-dihydro-2*H*-pyran (**109**) reacts with nucleophiles at C(6) to give ring-opened products, $\text{NuCH}=\text{C}(\text{COCF}_3)(\text{CH}_2)_3\text{OH}$.²⁵⁷ Some of the amino products (e.g. $\text{Nu} = \text{NEt}_2$) are unstable, and undergo intramolecular nucleophilic additions to give tetrahydropyrans. Reactions with Grignards, hydrazine, hydroxylamine, and triethyl phosphite are also reported.

Syntheses and mechanisms are proposed for the preparation of a series of 4,4a,5,6-tetrahydro- and 5,6-dihydro-benzocinnolinones and their subsequent dehydrogenation and amination to give new benzo[*h*]cinnolines (**110**; $\text{R}^3 = \text{H}$) and their 4-amino derivatives ($\text{R}^3 = \text{NH}_2$), all starting from an appropriately substituted α -tetralone.²⁵⁸

Reaction of ethyl diazoacetate with benzaldehyde gives a β -keto ester product, $\text{PhCOCH}_2\text{CO}_2\text{Et}$, using tin(II) or tin(IV) catalysts. With trimethylsilyl triflate, however, the major product is the α -formyl ester [as its enol (**111**)], via a 1,2-aryl migration.²⁵⁹

Azulene (**112**) is easily formylated in the 1- (or 1- and 3-) position(s). Decarbonylation of such azulene intermediates has now been reported under mild conditions: reaction with pyrroles in acetic acid at ambient temperature.²⁶⁰ Thus formylation of azulene is now a feasible strategy for protection of its five-membered ring.



Decarbonylative functionalization of aldehydes and deacylative functionalization of ketones has been achieved via homolytic-induced decomposition of their unsaturated peroxy acetals.²⁶¹

Formaldehyde reacts with nitrosobenzene (PhNO) to yield *N*-phenylformohydroxamic acid, PhN(OH)CHO. The primary kinetic isotope effect in mixed solvents is altered on addition of small amounts of salt, an effect also seen in water at higher salt concentrations,²⁶² suggesting the involvement of chloride ion in C–H bond breaking.

Large-ring-fused tetrazoles have been prepared via reaction of ketones with *in situ* generated triazidochlorosilane; the mechanism has been delineated via the isolation of a stable diazido intermediate, which, when heated, gives the product tetrazole.²⁶³

Bromo- and chloro-malonaldehyde react with adenosine in water to give etheno- and ethenoformyl-adenosine; the kinetics and mechanistic alternatives are described.²⁶⁴

The reactivity of furo[2,3-*b*]- and furo[3,2-*b*]-pyrrole aldehydes with malonitrile, and with a 1,3-dione, have been described.²⁶⁵

α -Chloro- α,β -enones have been synthesized from diazodicarbonyls and acid chlorides, using a rhodium(II) catalyst.²⁶⁶

α -Amido ketones have been converted into 2-aminocyclobutanols with high stereoselectivity, using a Yang photocyclization.²⁶⁷

α -(*p*-Methoxybenzyloxy)ketones, R¹COCH(OPMB)R², undergo a base-promoted 1,2-shift to yield α -(*p*-methoxybenzyl) α -hydroxy ketones, R¹COCOH(PMB)R².²⁶⁸ Formal inversion of configuration is observed in this Curtis-type rearrangement, which undermines hypotheses involving radical pair separation/recombination.

Peroxonitrite (ONOO⁻) is generated intracellularly from NO and superoxide anion. Ketones have been found to catalyse its decomposition via dioxirane intermediates.²⁶⁹ Decomposition of Caro's acid (peroxymonosulfuric acid, H₂SO₅) is similarly catalysed. Kinetics of the decomposition catalysed by acetones with strongly electron-withdrawing substituents (e.g. fluoro, 1,1,1-trifluoro and hexafluoro) show evidence of the involvement of the ketone hydrate (i.e. the 1,1-diol) and its anion.²⁷⁰

The reaction of bifunctional carbonyl compounds with Lawesson's reagent, giving phosphorus heterocycles via ring closure, has been reviewed (23 references).²⁷¹

The preparation, reactions, and synthetic utility of *N*-alkylidenesulfinamides (sulfinimines), including chiral cases, have been reviewed.²⁷²

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