CHAPTER 1

Reactions of Aldehydes and Ketones and their Derivatives

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Formation and Reactions of Acetals and Related Species

A series of pyridinium cations with electron-withdrawing substituents on the ring catalyse acetalization of aldehydes and other protection reactions, such as the formation of dithianes, dithiolanes, dioxanes, and dioxolanes. The best catalyst works at 0.1 mol%, outperforming a Brønsted acid with a $\text{pK}_a$ of 2.2.

DFT has been used in the development of a general equation relating the activation energy of an intramolecular proton transfer to $r$ (the distance between the reacting centres) and $\alpha$ (the hydrogen-bonding angle). The equation has been applied to intramolecular general acid catalysis of five of Kirby’s acetals (e.g. 1; $X = \text{NH, O}$). Reaction rates correlate with $r^2$ and $\sin(180^\circ - \alpha)$; that is, acetals with short $r$ values and $\alpha$ close to $180^\circ$ (forming a linear hydrogen bond) are more reactive.

Cyclic hemiacetals (2) have been prepared stereoselectively in a 2 : 1 reaction of 4-formylbenzoates and aromatic enals ($\text{trans-Ar–CH=CH–CHO}$), using catalysis by $N$-heterocyclic carbenes (NHCs).

A dual acid-catalyst system has been employed for enantioselective addition of alkenyl and aryl boronates to chromene acetals (3). The Lewis–Brønsted combination of a lanthanide triflate and a tartaric acid monoamide gives $ee$ up to 97%.

The gas-phase elimination kinetics of several $\beta$-substituted acetals have been measured in the range 370–441 °C and in the presence of a radical inhibitor. Two different concerted four-membered transition states are proposed, leading to either the alcohol and vinyl ether (the latter decomposing to alkene and aldehyde) or alkane and alkyl ester.

Methylenecyclopropylcarbinols such as (4) react with acetals to give 3-oxabicyclo[3.1.0]hexanes (5); an intramolecular Prins-type mechanism is proposed.

Iron(III) chloride or bromide has been used to catalyse Prins cyclization/halogenation of alkynyl acetals, using an acetyl halide as halogen source.
Deacetalization of acetals, R\(^1\)CH(OR\(^2\))\(_2\), in the presence of trifluoroacetic acid has been shown to be viable without water. Although water is a by-product, alcohols are not, and a hemiacetal is not an intermediate. Rather, a hemiacetal TFA ester [R\(^1\)–CH(OR\(^2\))–OCOCF\(_3\)] is formed, followed by carbonyl production with two TFA ester byproducts, F\(_3\)CCO\(_2\)R\(^2\). The latter process renders the reaction irreversible. The two esters are produced at separate points in what is essentially a cascade mechanism. All intermediates have been identified by NMR. The new reaction has been dubbed ‘acidolysis’ to distinguish it from the more familiar acid-catalysed hydrolysis.

**Reactions of Glucosides**

4,6-\(O\)-Benzyldene acetals of glycopyranosides (6) have been oxidatively cleaved to the corresponding hydroxy-benzoates (7\(a/b\)) using dimethyldioxirane under mild conditions, and in high yield. Appropriate choice of the neighbouring protecting group gives regioselectivity, with a preponderance of (7\(a\)) or (7\(b\)) of \(>99\%\), as desired. The balance of electronic and steric effects in the best groups – chloroacetyl and TBS (\(t\)-butyldimethylsilyl) – is discussed.

The stereo- and regio-selectivity of Lewis-acid-catalysed reductive ring-opening of 4,6-\(O\)-benzyldiene acetals have been studied by kinetics, including primary and secondary isotope effects, leading to identification of a range of mechanisms in solvents of varying polarity, and in protocols with Brønsted acid additives. It is hoped that this will lead to new reducing agents, where reactivity and selectivity can be fine-tuned by choice of borane, solvent, Lewis acid, and temperature.
Glycoside hydrolases can give $10^{17}$-fold rate enhancements, and estimates of their dissociation constants from their transition states are as low as $10^{-22}$ mol dm$^{-3}$. Such affinity has encouraged mimicry, and a number of criteria have now been advanced to assess whether a natural or man-made glycosidase inhibitor is a true TS mimic.\textsuperscript{12}

A new dicyanohydrin-\(\beta\)-cyclodextrin acts as an artificial glycosidase, hydrolyzing aryl glycosides up to 5500 times faster than the uncatalysed reaction.\textsuperscript{13} Michaelis–Menten parameters are reported and compared with other modified cyclodextrins.

An investigation of nucleophilic substitutions of 2-deoxyglycosyl donors indicates that the more nucleophilic the oxygen nucleophile used, the less stereo-selective the reaction becomes.\textsuperscript{14} This erosion of stereo-chemical control is attributed to the rate of the stereochemistry-determining step approaching the diffusion limit, when the two faces of the prochiral oxocarbenium ion are subject to nucleophilic addition to afford a statistical mixture of diastereomers.

Recent advances in understanding mechanisms of chemical \(O\)-glycosylation have been reviewed.\textsuperscript{15} pH-rate profiles have been constructed and analysed for glycosylation reactions of a range of aromatic amines.\textsuperscript{16}

Oxime formation from sugars can be slow, but nucleophilic catalysis by aniline (at 100 mM) can increase rates up to 20-fold, and glycosylamine formation has to be watched.\textsuperscript{17}

A DFT method has been applied to scan the potential energy surface of furanosyl oxocarbenium ions.\textsuperscript{18} The results suggest that the preferred oxocarbenium ion conformation is not a consistent predictor of product stereochemistry.

A chiral Brønsted acid, a BINOL-phosphoric acid, activates trichloroacetimidate glycosyl donors with \(\beta\)-selectivity.\textsuperscript{19}

An account describes the mechanistic investigations that have led to a fuller understanding of the use of the 4,6-\(O\)-benzylidene acetal as a control element in glycosylation, giving direct access to \(\beta\)-mannopyranosides in high yield and selectivity.\textsuperscript{20}

A rhodium(II)-carbene-promoted activation of the anomeric C–H bond of carbohydrates has been used to provide a stereospecific entry to \(\alpha\)- and \(\beta\)-ketopyranosides.\textsuperscript{21}

Three unnatural methyl \(\alpha\)-septanosides (8), with the 3- and 5-hydroxyls \(ax\text{-eq}, eq\text{-ax}\), and \(eq\text{-eq}\) have been synthesized, and their rates of hydrolysis measured by \(^1\)H NMR at 50 °C in 0.5 mol dm$^{-3}$ DCl.\textsuperscript{22} The hydroxyl orientation affects the rate, with equatorial being more electron withdrawing than axial. Comparison with rates for analogous methyl \(\alpha\)-pyranoside structures shows that, while the inherently less stable seven-membered sugars react about two orders of magnitude faster, the rank ordering is the same.
Reactions of Ketenes

Keto-ketenes \((R^1R^2\text{C}≡\text{C}=\text{O})\) homodimerize to \(\beta\)-lactones (e.g. 9), thereby providing an important way of accessing such compounds. Catalysis by tributylphosphine has been investigated by NMR, and evidence for tetravalent phosphonium enolate intermediates (10) is presented: they can be trapped as their TMS ethers or by reaction with 4-chlorobenzaldehyde (to give a \(\beta\)-lactone). Such enolates may prove useful in other synthetic methodologies. There was no evidence for pentacovalent phosphorus intermediates.

\[
\begin{align*}
\text{(9)} & \quad \text{(10)} \\
\end{align*}
\]

DFT investigation of Staudinger 2 + 2-cycloaddition of a ketene and an imine, catalysed by NHCs, favour the ‘ketene-first’ mechanism, that is, it is the ketene that is initially activated by the NHC. This mechanism persists even when variation in the electrophilicity of the imine leads to stereodivergence in the experimental results. NHCs also promote the chlorination of unsymmetrically disubstituted ketenes, \(R^1R^2\text{C}=\text{C}=\text{O}\); the products are typically \(\alpha\)-halo esters \([R^1R^2\text{C}(\text{Cl})=\text{CO}_2R^3]\) under the conditions employed. With chiral NHCs, modest \(ee\)s of up to 61% are seen.

Dimerization and trimerization reactions of thiocetaldehyde and dimerization of thioketene have been studied by computation.

Formation and Reactions of Nitrogen Derivatives

Synthesis of Imines

The affinities of a wide-ranging array of imines for hydride, proton, and electron have been measured by titration colorimetry and by electrochemical methods, in acetonitrile. Thermodynamic ‘characteristic graphs’ are then introduced, linking the energies of the processes for each imine: each graph is intended to give the ‘molecular ID’ of the imine, facilitating prediction of likely reactions and mechanisms thereof.

The mechanism of Schiff base formation between pyridoxal analogues and aldehydes has been studied by DFT.

\(P–N–P\) ‘pincer’ complexes of ruthenium catalyse a new imine synthesis, from an alcohol and an amine, with evolution of hydrogen.

Formylpyridines react with tris(hydroxymethyl)aminomethane \([(\text{HOCH}_2)_3\text{CNH}_2, \text{‘TRIS’}]\), to give 1,3-oxazolidines (e.g. 11), which can equilibrate with their acyclic tautomers, that is, Schiff bases. Anomeric and hydrogen-bonding effects have been studied in these systems, including the adduct derived from pyridoxal. Oxazolidines such as (12) – derived from TRIS and a benzaldehyde – have been prepared and then
ring-opened under acetylating conditions. X-ray crystal data and computations indicate a strong endo anomeric effect stabilizing a conformation that leads to regioselective ring opening to give imine (rather than $N$-acetyloxazolidine). Imine-oxazolidine equilibria are also reported, and a per-$O$-acetylated imine, ($\text{AcOCH}_2)_3\text{C}–\text{N}=\text{CHAr}$, in the para-nitro case.\footnote{31}

An alkyl or aryl group, $R^1$, in a 2-iminothiazole (13) can be exchanged with that in an isothiocyanate, $R^4\text{N}=\text{C}=\text{S}$, in toluene at 105 °C.\footnote{32} The position of equilibrium in this reversible reaction is mainly dependent on the electronic properties of the exchanging groups (i.e. $R^1$ and $R^3$) and has been used to empirically compare the electrophilicity of various isothiocyanates.

2-Substituted benzimidazoles have been prepared by condensation of various aldehydes with 1,2-phenylenediamine, using copper(I) triflate catalyst, in refluxing acetonitrile.\footnote{33}

\section*{The Mannich Reaction}

Organocatalytic asymmetric Mannich reactions have been reviewed, focussing on proline derivatives,\footnote{34} as have Mannich preparations of alkyl- and cycloalkyl-amines.\footnote{35}

The autocatalysis previously seen in enantioselective Mannich reactions catalysed by $\text{L}$-proline and related species has been reinvestigated, using both the products themselves and close structural mimics.\footnote{36}

The 1-ethyl-3-methylimidazolium salt of ($S$)-proline acts as an ionic liquid (IL), which gives ‘three 99s’ performance (yield/de/ee) in a one-pot three-component Mannich reaction.\footnote{37} The reaction shows excellent chemo- and regio-selectivities, the precursors are cheap, the process tolerates moisture, and it can often be conducted at −20 °C.

A diastereoselectivity switch has been engineered in the direct Mannich reaction of glycine imines, $R^1\text{O}_2\text{C}–\text{CH}_2–\text{N}=\text{CR}^2\text{R}^3$, with $N$-(8-quinolyl)sulfonyl imines (14).\footnote{38} Steric and electronic tuning of the $R$ groups of the glycine imine switches the selectivity from syn-$\alpha$-$\beta$-diamino acids (for benzophenone-type imines) to anti- (for electron-rich aldimines). An Fe-sulfos-Cu(I) chiral catalyst gives ees of 99% in many cases.

An anti-selective reaction of aldehydes with $N$-sulfonyl imines exploits hydrogen bonding involving a 4-hydroxypyrrolidine catalyst and an external Bronsted acid.\footnote{39} DFT methods have been used to study diastereoselective reactions of ketimine with aldehyde, using both $\text{L}$-proline and ($S$)-1-(2-pyrrolidinylmethyl)pyrrolidine, catalysts that give opposite diastereoselectivities.\footnote{40}

Ferrocenyl cation, as its PF$_6^−$ salt, catalyses Mannich reaction of benzaldehyde, aniline, and cyclohexanone to give $\beta$-aminoketone (15), with some anti-preference,
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under solvent-free conditions. Tests of two-reactant combinations indicate that the reaction proceeds initially via imine rather than aldol formation.

Bench-stable α-amido sulfones have been used to generate N-Boc amino-protected imines, which then undergo in situ Mannich reactions with glycine Schiff-bases, using a cinchonidine–thiourea catalyst, to give α,β-diamino acid derivatives with close to 100%. In a similar strategy, a highly diastereo- and enantio-selective aminocatalytic Mannich reaction of aldehydes with N-carbamoyl imines involves their generation in situ from such α-amido sulfones.

DFT-calculated ees and des compare well with observed values for anti-Mannich and syn-aldol reactions catalysed by axially chiral amino sulfonamides.

While chiral phosphoric acids such as 3,3′-disubstituted BINOLs have been known to catalyse direct Mannich-type reaction of aldmines with 1,3-dicarbonyls, such catalysts can be contaminated by group I/II metal cations. Deliberate introduction of such cations, especially calcium, confirms that the metal salts may be the ‘true’ catalysts, giving higher yields and ee in some cases.

Enantioselective Mannich reactions of diethyl fluoromalonate with N-Boc aldmines using chiral bifunctional organocatalysts give (β-aminoalkyl)fluoromalonates in 93–97% ee, and bifunctional amine–thiourea catalysts derived from rosin give high ee and de in reaction of lactones with such imines.

N-Sulfonylcarboxamides of proline catalyse Mannich reaction of cyclic ketones with N-protected iminoglyoxylate, with de/ee up to 94/99%. Enamine intermediates have been examined by DFT.

The first catalytic, enantioselective vinylogous Mannich reaction of acyclic silyl dienolates (17) has been reported. Using protected imines (16), ees up to 98% have been achieved (R1 = H), and more highly substituted products (18, R1 = Me) can be prepared diastereoselectively. A second-generation BINOL-based phosphoric acid catalyst developed for the process has been studied by NMR, and a crystal structure of the imine-bound catalyst was obtained, shedding light on the facial selectivity of the reaction.

A Yb/K heterobimetallic catalyst and a chiral amide ligand promote nitro-Mannich (aza-Henry) reactions in up to 86% ee.

Addition of Organometallics

Advances in copper-catalysed enantioselective addition of dialkylzincs to imines have been reviewed back to 2000.
Nickel(II) and a spiro-chiral phosphine catalyse the three-component coupling of imines, diethylzinc, and aromatic alkynes with ee up to 98%, and with good chemoselectivity, to give useful allylic amines.\(^{52}\)

Diimines (19; \(R = \text{Ph, 2-pyrrolyl, 2- and 4-pyridinyl, 2,2'}\text{-bithiophen-5-yl}\)) have been prepared from \((R,R)\)-1,2-diaminocyclohexane and aromatic aldehydes.\(^{53}\) Addition of organolithiums and allylzinc proceeds in high yield and \(de\) (except for the 2-pyridine case), giving diamines with four chiral centres. The latter have also been tested as enantioselective catalysts for the Henry reaction.

Quantitative structure–reactivity relationships (QSSR) have been used to examine enantioselectivity in the addition of organolithiums to imines.\(^{54}\)

Chiral \(\alpha\)-chboro \(N\)-\text{-}t\text{-}butanesulfinyl ketimines (20) react with Grignards to give chiral aziridines with \(de\)/\(ee\) up to 96/98%\(\); the stereoselectivity is opposite to that found for imines without the \(\alpha\)-chboro substiuents, presumably due to chlorine coordination of the incoming Grignard.\(^{55}\)

The reactions of Grignard reagents with imines have been contrasted for catalytic and stoichiometric amounts of titanium alkoxide reagents.\(^{56}\) The former favours alkylation, while the latter gives reductive coupling, with distinctive mechanisms for each, as shown by studies using deuterium-labelled substrates.

Chiral phosphinoylimines have been prepared in high yield and good \(de\) by addition of Grignards to new \(P\)-chirogenic \(N\)-phosphinoylimines.\(^{57}\)

For more references to Grignards and imines, see under ‘Addition of Other Organometallics, Including Grignards’ below.

**Other Arylations, Alkenylations, and Allylations of Imines**

Rhodium-diene complexes catalyse arylation of \(N\)-tosyl ketimines by addition of sodium tetraarylborates. Using a chiral diene renders the process highly enantioselective.\(^{58}\)
Enantioselective formal alkenylations of imines, catalysed by axially chiral BINAP dicarboxylic acids, have been carried out using vinylogous aza-enamines.\textsuperscript{59} As the latter can be oxidized to nitriles, the route can allow access to enantiomerically enriched $\gamma$-amino $\alpha,\beta$-unsaturated nitriles, and thus to synthetically useful chiral $\gamma$-amino acids.

In the triphenylphosphine-catalysed reaction of alkyl propiolates with $N$-tosylimines, a stable phosphonium-enamine zwitterion (21) of proven importance in the mechanism has been isolated and characterized by X-ray crystallography.\textsuperscript{60} Deuterium-labelling experiments have identified several hydrogen-specific processes, none of which limit turnover, but they are highly medium dependent.

\[ \text{Ar} \equiv \text{CO}_2\text{R} + \text{TsN}^- \quad \text{PPh}_3 \]

$N$-protected $\alpha$-imino esters, for example, Pg-$N=\text{CH–CO}_2\text{Et}$, have been alkynylated with terminal alkenes using copper(I) triflate and a PYBOX ligand (22).\textsuperscript{61} Surprisingly, excess ligand does not raise the ee, but excess copper does, and a switch in metal-to-ligand ratio alone can reverse the ee. A modest positive non-linear effect was observed, and it is suggested that changing the metal-to-ligand stoichiometry may alter the coordination geometry at copper, and thus the transition state.

Enantioselective addition of terminal alkynes to imines and their derivatives has been reviewed, including in situ examples, that is, three-component reactions of terminal alkynes, aldehydes, and amines.\textsuperscript{62}

Chiral phosphinoylimines undergo highly diastereoselective alkynylation with aluminium acetylides, but lithium or magnesium alkynes give poor results.\textsuperscript{63}

An alkylzinc-mediated enantioselective synthesis of $N$-tosyl-($E$)-(2-en-3-ynyl)amines has been developed, working well with various $N$-tosylaldimines.\textsuperscript{64}

A review covers diastereo- and enantio-selective alkynylation of imines and iminium ions.\textsuperscript{65}

\textit{Reduction of Imines}

Chiral 1,3-diamines have been accessed by diastereoselective reduction of enantiopure $N$-$t$-butanesulfinylketimines (23, prepared from the corresponding diaryl ketone).\textsuperscript{66} The reduction can be 99 : 1 diastereoselective in either direction, depending on substrate and conditions. X-ray crystallography of reactants and products and NOESY-NMR studies point to unusual directing effects of the ortho-substituent in controlling the selectivity.
A chiral phosphoramidite ligand has been used to achieve good enantioselectivity in iridium-promoted hydrogenation of benzophenone N–H imines, Ar–C(=NH)–Ph, affording chiral diarlmethylamines without the need for N-protection. Several ortho-substituted substrates gave particularly high ee.

Advances in enantioselective reduction of C=N bonds have been reviewed, focussing on the use of metal-free chiral organocatalysts with Hantzsch esters as hydride source.

Reductive amination of carbonyl compounds – via transfer hydrogenation of their imine derivatives – has been achieved with cyclometalated iridium complexes. Ammonia–borane (H$_3$N–BH$_3$) has been employed in a mild, metal-free transfer hydrogenation of imines. A concerted double-hydrogen-transfer mechanism is proposed, backed up by deuterium kinetic isotope effects, Hammett correlations, and ab initio calculations. Hydrogenation of other unsaturated systems is being followed up.

**Iminium Species**

Kinetics of the reactions of iminium ions (pre-generated from cinnamaldehyde and secondary amines) with cyclic ketene acetals were studied by UV–visible spectroscopy. Second-order rate constants have been used to derive values of the electrophilicity parameter, $E$ ($-10 < E < -7$), and these have been analysed using a correlation equation, $\log_{10}k = S(E + N)$, where $S$ and $N$ are nucleophilicity parameters. The equation is then found to predict rate constants for reactions of the iminium ions with a range of other species, such as pyrroles, indoles, and sulfur ylides.

The intermediacy of an iminium ion, Me$_2$N+=CH$_2$, in the nitrosative cleavage of triethylamine to N-nitrosodimethylamine (Me$_2$N–NO) has been explored in a DFT study designed to elucidate how carcinogenic N-nitrosamines form from tertiary amines.

Reaction of dimethyl sulphate with DMF gives methoxymethylene-$N,N$-dimethyliminium salt, Me$_2$N+=CH(OMe)–O$_3$S–Me. It acts as an acid promoter of Staudinger synthesis of 2-azetidinones ($\beta$-lactams) from imines and substituted acetic acids. Under base catalysis, the carboxylate is proposed to react with the iminium salt to produce an activated ester, which breaks down (again with base catalysis) to yield the corresponding ketene, which is the immediate reactant with the imine.

A review surveys the development and potential of iminium ion catalysis, using ions formed by the condensation of chiral secondary or primary amines with $\alpha,\beta$-unsaturated aldehydes or ketones, in a variety of cyclo- and conjugate-addition reactions.

**Other Reactions of Imines**

Palladium(II) and rhodium(I) catalysts and chiral disphosphate ligands allow addition of phenylboronic acid, and of phenylboroxine, to N-tosylimines, in up to 99% ee. Azomethine imines (24) undergo 1,3-dipolar cycloaddition to homoallylic alcohols, giving trans-pyrazolidines (25) with excellent regio-, diastereo-, and enantioselectivities and good yields. A tartrate auxiliary and a Grignard in excess complete
the protocol, with generation of the chloromagnesium salt of the homoallylic alcohol being essential to the mechanism.

An unexpected reaction of aromatic aldimines (26) with a difluoroenoxysilane gives access to 2,2-difluoro-3-hydroxy-1-ones (28) – the Mukaiyama aldol-type product – via an amine (27).\(^{77}\) Zinc triflate promotes the reaction, and \(^{18}O\)-labelling and other experiments suggest that water is required to form the product (28).

3,4-Dihydroisoquinoline (29) undergoes aza-Henry reaction with excess nitromethane at ambient temperature to give the corresponding 1-(nitromethyl)tetrahydroisoquinoline (30), an unstable species that is trapped by acylation or alkylation, leading to Reissert-like products via an overall one-pot three-component reaction.\(^{78}\) Evidence for reaction via the methyleneazinic acid tautomer of nitromethane (31) is presented.

A vinylogous imine intermediate (33), generated in situ from an arylsulfonyl indole (32), undergoes enantioselective Michael addition to malonitrile, using a chiral thiourea catalyst, to give useful 3-indolyl derivatives (34).\(^{79}\) DFT has been used to study aziridination of diazoacetate with syn- and anti-imines in the presence of a chiral bisoxazoline-copper(I) catalyst.\(^{80}\)

\(^{trans}\)-2,3-Disubstituted aziridines (36) have been prepared from \(N\)-sulfinylaldimines (37) and \(2-(\text{para-tolylsulfinyl})\)benzyl iodide (35) in high \(ee/de\). Whether the intermediates are benzyl halocarbenoids or benzyl carbamions has been examined using DFT.\(^{81}\)

The previously reported reaction of diarylmethyl imines with diazoacetates to give \(cis\)-aziridines (using chiral VANOL or VAPOL ligands) has now been complemented...
by conversion of diazoacetamides to the corresponding trans-aziridines, again with high de, ee, and yield.\textsuperscript{82}

Systematic investigation of aziridination of benzhydryl-type imines, R–CH=N–CHAr\textsubscript{2}, has been undertaken, varying the imine aryls and using VANOL- and VAPOL-derived chiral boroxinates.\textsuperscript{83} Typical ees of 96–97\% were obtained using 2,4-dimethyl-3-methoxy as the Ar groups, and for these substrates their high activity allowed the conventional diazoacetate ester reagent to be replaced by a diazoacetamide, an option that is not really viable for simple benzhydryls (i.e. Ar = Ph). While varying the aryls varies the aziridine products, the latter are easily converted to N–H aziridines.

2-Methylazaarenes such as 2,6-lutidine (38) undergo palladium-catalysed benzylic addition with N-sulfonyl aldimines, showing a powerful C–H activation effect and giving access to heteroarylethylamines (39); a stereoselective version is being explored.\textsuperscript{84}

Organocatalytic asymmetric Strecker reactions have been reviewed.\textsuperscript{85} Chiral BINOLs and amino alcohols have both been used as enantioselective catalysts for Strecker reaction of achiral N-phosphinoyl imines with diethylaluminium cyanide.\textsuperscript{86}

Enantioselective titanium-catalysed cyanation of imines has been carried out rapidly at room temperature.\textsuperscript{87}
Chiral mono- and di-meric manganese(III) salen complexes catalyse Strecker addition of TMSCN to \(N\)-benzylimines at \(-55^\circ\text{C}\) in the presence of 4-phenylpyridine-\(N\)-oxide.\(^8\) The dimeric auxiliary is more effective \((ee > 99\%)\), and the catalysts are recyclable.

Hydrolysis of the Schiff base, \(N\)-salicylidene-\(meta\)-chloroaniline, has been studied from pH 3 to 12 at 303 K and also at other temperatures to yield thermodynamic parameters.\(^9\)

Chiral phosphoric acids catalyse asymmetric peroxidation of imines, \(R^2-\text{CH} = N-R^1\), to give amine-peroxides with the chiral centre between the functional groups \((\text{40})\), using organic hydroperoxides, \(R^3-\text{OOH}\).\(^{10}\)

Recent interest in the intermolecular carbon radical addition to the C=N double bond of imines, hydrazones, and oxime ethers has been reviewed, including stereoselective approaches.\(^{11}\)

A catalytic asymmetric \(exo^{\prime}\)-selective \([3+2]\) cycloadDITION of iminoesters \((\text{41})\) to nitroalkenes yields highly functionalized proline esters \((\text{42})\).\(^{12}\)

For a homocoupling of aromatic imines, see under ‘Benzoin Condensation and Pinacol Coupling’ below. For a nucleophilic perfluoroalkylation of imines, see under ‘Addition of Organozincs’ below.

**Oximes, Hydrazones, and Related Species**

FT-ICR mass spectrometry has been used to measure gas-phase acidities of ring-substituted \((E)\)-acetophenone oximes.\(^{13}\) Substituent trends are the same as in DMSO solution, indicating that solvation stabilization has a consistent effect, but that there is no specific solvent effect on any particular substituent.

The use of \(O\)-substituted hydroxylamines and oximes as electrophilic amino-transfer agents has been reviewed.\(^{14}\)

2-Isoxazolines have been prepared enantioselectively by conjugate addition of oximes to \(\alpha,\beta\)-unsaturated aldehydes, with anilinium catalysis.\(^{15}\)

\((O)\)-2-(Acyl)vinylketoximes \((\text{43})\) have been made as their \((E)\)-isomers by regio- and stereo-specific addition of ketoximes \((R^1R^2C=\text{NOH})\) to acylacetylenes \((\text{Ph} = \text{C} = \text{C} = \text{COR}^3)\) under mild conditions \((\text{DCM/r.t./10 mol% Ph}_3\text{P}).\(^{16}\) Slow build-up of the \((Z)\)-material over time indicates that the \((E)\)-isomer is a kinetic product.

A gold complex catalyses cyclization of \(O\)-propioloyl oximes \((\text{44})\), giving good yields of 4-benzylideneisoxazol-5(4\(H\))-ones \((\text{45})\) after transfer of the arylidene
group, but crossover experiments indicate that the arylidene ‘migration’ is in fact intermolecular.  

Triphenylphosphine and carbon tetrachloride, together with catalytic DBU and Bu₄NI, effect oxime ether formation (from oxime and alcohol) in refluxing acetonitrile.  

Among reports involving Beckmann rearrangement, N-imidoylbenzotriazoles (46) have been prepared in one pot in high yield from ketoximes, R¹–C(R²)=NOH, by reaction with mesyl chloride in the presence of a base and subsequent addition of benzotriazole. A kinetic study of the rearrangement of cyclohexanone oxime to e-caprolactam in aprotic solvents has been carried out, using trifluoroacetic acid as catalyst. Bromodimethylsulphonium bromide (Me₂S⁺Br Br⁻) catalyses rearrangement of ketoximes in refluxing acetonitrile, in the presence of zinc chloride. Rates of rearrangement of cyclohexanone oxime para-toluenesulphonate in eleven solvents have been described by a three-parameter linear correlation involving polarizability, electrophilicity, and solvent molar volume. Rearrangement of cyclooctodocene oxime into ω-laurolactam has been followed by an ‘in situ’ multinuclear solid-state NMR method, and in a batch reactor process, using IL media.  

NiCl₂·6H₂O catalyses coupling of aldoximes with amines to give amides; the oxime can be prepared in situ from the corresponding aldehyde. 18O-Labeling studies have been used to probe the mechanism: a label in the oxime is not incorporated into the amide.  

The combination of triflic anhydride and a 30% excess of triphenylphosphine dehydrates aldoximes to nitriles at 0°C in high yield in minutes, using 2 equiv. of triethylamine base in DCM. 1H, 13C, 19F, and 31P NMR studies indicate that the reagent combination equilibrates to a mixture of (Ph₃P⁺) OTf Tf⁻ and (Ph₃P⁺)₂O-2Tf⁻, with the former acting as oxygen activation and dehydration reagent.  

Indium trichloride catalyses hydration of nitriles to amides: in refluxing toluene, acetaldoxime can be used as a water surrogate. The by-product – acetonitrile – is already known to be required for some amide-to-nitrile protocols.  

Reports of oxidative deoximation back to carbonyl include an account of the kinetics of deoximation of a series of oximes of 3-alkyl-2,6-diphenylpiperidin-4-one (47) by pyridinium fluorochromate, which indicate steric crowding as the major influence. Rates of deoximation of aldoximes and ketoximes by morpholinium chlorochromate have been measured in DMSO, showing first-order dependence on both substrate and oxidant; for acetaldoxime, 19 solvents were examined. Quinolinium fluorochromate deoximates ketoximes in aqueous acetic acid, with a first-order dependence on both substrate and oxidant. Oximes have also been deoximated by aerial oxidation, using
manganese(I) porphyrins as catalysts and benzaldehyde as oxygen acceptor, in toluene at 50 °C. A radical trap stops the reaction, and the presence of a manganese-oxo porphyrin was confirmed by UV–vis spectra. The oximes of 2-nitrobenzaldehyde and pyridine-2-carboxaldehyde gave nitrile product; that is, ‘benzaldehydes’ with electron-withdrawing groups in the ortho-position divert in this way.

Organoceriums have been added diastereoselectively to chiral aldehyde hydrazones derived from 1-aminoprolines; resulting hydrazines can be cleaved to give enantiomerically enriched amines in protected form. The advantages of organoceriums over Grignards or organolithiums are discussed.

Chiral N-amino cyclic carbonate hydrazones (‘ACC’ hydrazones, e.g. (48), with a rigid carbamate derived from camphor) undergo α-alkylation via deprotonation by LDA. DFT has identified the features of the azaenolate intermediate that give rise to stereoselectivity. The calculations predict higher stereoselectivity than previously reported by experiment, and a modified experimental method has now yielded the higher values.

Indium and a chiral ammonium catalyse allylation of N-benzoylhydrazones to give homoallylic amines in high yield and up to 99% ee, at room temperature in methanol.

Tetrasubstituted alkenes (49) have been accessed by coupling of N-arylsulfonylhydrazones with aryl halides, using palladium(II) catalysis.

Arylation of α-chiral ketones has been achieved by converting them to tosylhydrazones, then cross-coupling them with aryl halides, using palladium(0). Enantiopurity is maintained, avoiding the epimerization problems found with many other approaches.

Chiral α-hydrazino acids (50) have been accessed by asymmetric hydrocyanation of hydrazones with TMSCN; an O-silylated BINOL-phosphate formed in situ acts as auxiliary, giving α-hydrazononitriles in a Strecker-like process, with subsequent acid hydrolysis yielding (50).
A range of $\alpha$-amido-$\alpha$-aminonitrone (51) can react to form three classes of products – 1,2,5-oxadiazin-4-ones, amidines, and dibenzo[$d,f$][1,3]diazepines – all of which retain the core structure. The products were identified by X-ray crystallography, which also pointed out unusual features, such as an exceptionally long $C_{sp^2}-C_{sp^2}$ single bond (arrowed), up to 1.54 Å, and a very high ‘trigonal’ angle of 131° for $N_{sp^3}-C_{sp^2}-N_{sp^2}$, as well as NH···O and NH···N intramolecular hydrogen-bond-like interactions. These features, together with DFT calculations, have been used to help elucidate the operative mechanisms.117

For oxime formation from carbohydrates, see under ‘Reactions of Glucosides’ above.

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

Reviews of Organocatalysts

General reviews include coverage of chemoselectivity in reactions involving asymmetric aminocatalysis,118 the roots of asymmetric aminocatalysis over the past century, championing the seminal contributions of Knoevenagel in the 1890s,119 current approaches to improving asymmetric organocatalysts via supramolecular interactions,120 and recent developments in aldolase-type organocatalytic direct reactions in water.121

Chiral BINOL-phosphoric acid catalysis has been reviewed,122 as has the emerging field of chiral phosphine oxides as organocatalysts of, for example, reductive aldols.123 The use of NHC catalysts in aldehyde reactions has been reviewed,124 as has been the regio- and stereochemistry of the aldol, with a survey of methodologies up to the present.125

No Barrier Theory and Marcus Theory have been applied to the rates of aldol addition reactions of representative aldehydes and ketones.126 The use of kinetic isotope effects in probing the mechanisms of stereoselective reactions has been surveyed (84 references).127 Many slow reactions not considered suitable for continuous flow processing techniques are now being reassessed under high-temperature/pressure conditions.128

Asymmetric Aldols Catalysed by Proline and its Derivatives

Reviews of asymmetric aldol reactions include an account of those proceeding via enamines using organocatalysts,129 their application to total synthesis of natural products in the last 5 years,130 and a survey of direct asymmetric aldols (357 references), which covers both organocatalytic and metal-based catalysts, noting the still low reactivity of many of the catalysts developed to date.131

In reports of proline-catalysed aldol reactions, the central role of enamine intermediates has been underlined by their direct observation by NMR. E-Configured s-trans enamines (52) are detected: in DMSO, EXSY-NMR shows them arising from oxazolidinones rather than from iminium-type intermediates. The oxazolidinone-enamine equilibrium is not affected by additional water (in small amounts) or by the amount of catalyst.132 A computational study has compared the enamine (Houk–List) and
oxazolidinone (Seebach) mechanisms, with the latter being found to be inadequate for predicting the stereochemical outcome. Another DFT study has focussed on the scope for oxazolidinone intermediates, and this method has also been used to investigate further the enamine mechanism for reactions involving acetone. A coherent mechanistic rationale has been put forward for differences in kinetic behaviour in enamine reactions such as aldol, amination, and aminooxylation, with a particular focus on auto-inductive effects and on the catalytic effects of additives. DFT has also been used to identify the origin of the enantioselectivity in the aldol reaction of benzaldehyde and acetone as catalysed both by proline derivatives and by 2-azetidine carboxylic acid.

New prolinamide catalysts of the aldol reaction of para-nitrobenzaldehyde with acetone have been reported. Calix[4]arene-prolinamide organocatalysts give yields/de/ee up to 99/97/70% in directalds of aromatic aldehydes with cyclohexanone.

List’s proline-catalysed stereoselective intramolecular aldols of 1,7-dicarbonyl compounds have been studied by DFT, with a polarizable continuum model employed for solvent effects. The enantioselectivity is found to arise from a key electrostatic contact between the forming alkoxide and the proline. The origin of the diastereoselectivity is typically more complex, especially for dialdehydes.

The application of reaction progress kinetic analysis to the proline-catalysed aldol has been described. The possible roles of imidazolidinone intermediates or by-products in aldol reactions catalysed by prolinamides (R = H, NO₂) has been studied by NMR and X-ray characterization of these species.

Four prolinamides have been designed with enhanced acidity (EWG = Ac, Ms, Tf, and Ts) and the potential for multiple N–H···O hydrogen bonding. The mesylate gave the best performance in terms of yield/de/ee in a test aldol: 94/94/>98%, while the tosylate may involve an aryl-stacking stabilization of the transition state.

Two new catalysts (alcohol and the corresponding ketone) have been developed for direct aldol addition in the presence of water. Prepared from trans-4-hydroxy-L-proline and the steroid isosteviol, the strategy involves a hydrophilic catalytic group (the acid of proline), a lipophilic pocket (the isosteviol skeleton), and an assisting functional group (the remote alcohol/ketone). With only 1 mol% loading, yield/de/ee of up to 99/98/99% has been achieved for a cyclohexanone–araldehyde aldol at room temperature. Effects of solvent, water, temperature, and substrate structure have been studied.
Ethylene and propylene carbonate, readily prepared from epoxides and carbon dioxide, are effective solvents for proline-catalysed aldols, giving yields/dee up to 99/100/99%. Choice of carbonate solvent and whether or not to use water co-solvent has to be matched to substrates, and in particular to their polarity.\textsuperscript{145} Intramolecular aldols of cyclic diketones are catalysed by proline, and List’s studies of the effect of incorporation of a 4-fluoro substituent in the cis- or trans-position has been studied by DFT. It finds that fluorine changes pathways as well as transition states: a low energy epimerization (after the C–C bond forming process) affects product distribution.\textsuperscript{146} \textit{N}-(para-Dodecylphenylsulfinyl)-2-pyrrolidinecarboxamide (56) is one of the best anti-aldol catalysts to date, with yields/ee/de up to 98/99/98%, low catalyst loading, mild conditions, and convenient solvents (or none). A DFT study has now identified the origins of the diastereoselectivity in non-classical hydrogen bonds between the sulfonamide, the electrophile, and the catalyst enamine that favour the anti-Re aldol transition state.\textsuperscript{147} An L-prolinethioamide catalyses aldols in water at 0°C, with yields/ee up to 98/99\.\textsuperscript{148} Strong non-linear effects are observed in proline-catalysed aldols when an achiral thiourea catalyst is also employed in non-polar solvents: with an ee as low as 5% for the proline, 40% ee and 94% de are observed in the products.\textsuperscript{149} The role of the thiourea co-catalyst in such reactions has been investigated. Examining the reaction of acetone with 4-substituted benzaldehydes, non-linear effects are observed (%ee\textsubscript{aldol} versus %ee\textsubscript{proline}), but these are markedly dependent on the nature of the aromatic substituent. Results from \textsuperscript{1}H-NMR and ESI-MS suggest that the main role of the thiourea is not that of producing a soluble proline-thiourea hydrogen-bonded complex.\textsuperscript{150} IL-tagged amino acid derivatives – 1,2,3-triazolium salts linked to lysine or proline – give high yields/ee/de in direct aldols: the lysine surprisingly outperformed the proline.\textsuperscript{151} \textit{(S)}-Prolinamides with a trans-4-ester moiety bearing an IL group give excellent yields, des and ees in aldol reactions in water.\textsuperscript{152}
A chiral solvent effect has been seen in proline-catalysed aldols in aqueous propylene carbonate: when enantiopure (R)-propylene carbonate (57) is used with (R)-proline, they constitute a ‘matched pair’ with high delee, whereas (S)-proline/(57) is a mismatch.\textsuperscript{153}

\[
\begin{align*}
\text{O} & \hspace{1cm} \text{O} \\
\text{O} & \hspace{1cm} \text{O} \\
\text{(57)} & \hspace{1cm} \text{(58)} & \hspace{1cm} \text{(59)}
\end{align*}
\]

Racemic \(\alpha\)-acylphosphinates undergo cross-aldol reaction with acetone to give diastereomeric \(\alpha\)-hydroxyphosphinates (58), because of the phosphorous chiral centre. Using proline catalyst, high \(ee\)s and \(de\)s have been achieved.\textsuperscript{154}

Efficient direct \(\alpha\)-hydroxymethylation of ketones in homogenous aqueous solvents has been reported: a bis-prolinamide-zinc complex promotes aldol reaction with aqueous formaldehyde in good yield and up to 94\% \(ee\).\textsuperscript{155}

\textit{Other Asymmetric Aldols}

A virtual screening method has been demonstrated as a rapid computational tool for prediction of potential asymmetric aldol organocatalysts, throwing up several new classes such as \(\beta\)-amino acids and hydrazides for testing.\textsuperscript{156} Amino amide catalysts that exploit a double hydrogen-bonding activation of carbonyls give high \(ee\)s.\textsuperscript{157} L- Tryptophan catalyses reaction between cyclohexanone and aldehydes in water; DFT has been used to identify the precise role of the indole substituent in stabilizing the transition state.\textsuperscript{158}

A siloxy-serine facilitates \textit{syn}-selective direct aldols in an IL: the recyclable catalyst gives \textit{delee} up to 88/94\% under mild conditions.\textsuperscript{159} A simple chiral diamine – picolylamine (59) – is an excellent organocatalyst for aldol reactions in water.\textsuperscript{160}

The combination of a primary–tertiary diamine and a Brønsted acid enables \textit{syn}-selectivity in cross-aldols of aldehydes: \(de = 92\%\). A chiral diamine (60), with triflic acid, renders it enantioselective too: \(ee = 87\%\), and it works for glycolaldehyde donors.\textsuperscript{161}

\[
\begin{align*}
\text{Bn} & \hspace{1cm} \text{NH}_2 & \hspace{1cm} \text{NEt}_2 \\
\text{O} & \hspace{1cm} \text{O} \\
\text{THN} & \hspace{1cm} \text{NHTf} \\
\text{(60)} & \hspace{1cm} \text{(61)} & \hspace{1cm} \text{(62)}
\end{align*}
\]

Direct addition of enolizable aldehydes to \(\alpha\)-halo thioesters gives \(\beta\)-hydroxy thioesters via reductive soft enolization, with \textit{syn}-selectivity, whereas conventional
conditions (amide bases) with esters or thioesters gives anti-product. The
conditions are mild (MgI$_2$/PPh$_3$/DCM), and the addition step is under kinetic control.

Several stereoselective aldol reactions of $\beta$-siloxy methyl ketones with aldehydes
have been developed using super-silyl stereo-directing groups such as $-$Si(TMS)$_3$, including examples of both 1,5-syn- and 1,5-anti-control. DFT analysis of the influence of $\beta$-substituents has been used to explain substrate-based 1,5-syn-stereocontrol in boron-mediated aldol reactions of $\beta$-alkoxy methylketones.

Quinidine thiourea catalyses the asymmetric aldol reaction of unactivated ketones
with activated carbonyl compounds via an enolate intermediate: it is suited to cases
where the enamine-based organocatalysis does not work well.

A chiral bifunctional thiourea catalyses aldol addition of $\alpha$-isothiocyanato imides
to $\alpha$-ketoesters in good $ee$ and fair $de$, giving access to $\beta$-hydroxy-$\alpha$-amino acid derivatives.

**Mukaiyama and Vinlyogous Aldolds**

$N,N$-Bis(trifluoromethanesulfonyle)squaramide ($61$) is a bench-stable and strong
Brønsted acid. It catalyses a wide range of aldehyde reactions: Mukaiyama aldol,
Mukaiyama Michael, Hosomi–Sakurai allylation, and an intramolecular carbonyl-ene
reaction of a 6-enol. In reactions with silylated substrates, it appears that ($61$) acts
to directly protonate the carbonyl compound, rather than catalysing routes involving
silylated Brønsted acid.

An (R)-BINAP platinum(II) complex catalyses enantioselective reaction of aldehydes
with ketene silyl acetals, for example, Me$_2$C=CH(Me)OTMS in DMF. The complex undergoes a dimer/monomer equilibrium in this solvent: the monomer is
apparently more catalytic.

A new series of $C_2$-symmetric chiral ligands ($62$; $R$=H, Me, Bu, etc.) has been
synthesized. Complexed with europium(III), aldehydes can be activated in aqueous
media, with the lanthanide still having vacant sites for hydration. In addition, the lanthanide complex facilitates luminescence-decay measurements. Tested as catalysts
of Mukaiyama aldols in ethanolic water, $\beta$-hydroxy carbonyl products were obtained
in high yields and $de/ee$ up to 96%, at temperatures as low as $-25$°C. The use of luminescence measurements allowed binding of benzaldehyde to be observed (indirectly)
via decreases in the water-coordination number of the europium cation.

A stereoinduction model has been used to explain an unexpected syn-selectivity in
the Mukaiyama aldol addition of crowded enolsilanes to $\alpha$-chboroaldehydes.

Pentafluorophenylammonium trifluoromethanesulfonimide, $F_5C_6-NH_3^+-NTf_2$, promotes Mukaiyama aldol and Mannich reactions using ketene silyl acetals with ketones and oxime ethers, respectively. $^1$H-NMR and other investigations suggest in situ formation of trimethylsilyl bistriflimide, Tf$_2$NTMS, as the active catalyst.

A stereoinduction model has been used to explain the unexpected syn-selectivity in
the Mukaiyama aldol addition of sterically demanding enolsilanes to $\alpha$-chboro aldehydes.
Vinyllogous Mukaiyama aldol reactions of enals with vinylketene silyl $N,O$-acetals ($63a/b$) give $1,7-$ ($64a$) and $1,6,7-$ ($64b$) -remote asymmetric inductions in TiCl$_4$-mediated experiments at low temperature.$^{173}$ Specific addition of small amounts of water (but not other protic species such as alcohols or acetic acid) gives a remarkable acceleration using ent-$64a$, and it is found for a variety of aldehydes. Possible double activation by water and titanium(IV) is considered, or water may break up TiCl$_4$ aggregates.

\[
\begin{align*}
\text{(63a; R}^1 = \text{H;}
\text{63b; R}^1 = \text{Me)}
\end{align*}
\]

Pyrrole- and furan-based dienoxy silanes ($65; X = O, N$-$\text{Boc})$ undergo ‘uncatalysed’ vinyllogous Mukaiyama aldol reaction in methanolic salty water at 40$^\circ$C, in open air, giving high des.\textsuperscript{174} The furan system is syn-selective (giving $66-O$), whereas anti-product ($66-N$-$\text{Boc})$ is found for pyrroles, although this switch appears to be steric in origin (i.e. due to the bulk of the Boc), rather than being due to the change of heteroatom per se. The precise roles of water as both solvent and ‘catalyst’ are discussed in the context of the reaction not being wholly homogenous, but involving dispersed droplets of lipophilic reactants.

\[
\begin{align*}
\text{(66-N-Boc)} & \quad \text{H}_2\text{O} \quad \text{(65)} \quad \text{(66-O)}
\end{align*}
\]

\textit{Other Aldol and Aldol-type Reactions}

A DFT study of the catalysis of the intramolecular aldol of acyclic keto-aldehydes by a bifunctional guanidine organocatalyst ($67$, 1,5,7-triazabicyclo[4.4.0]dec-5-ene, TBD) examined the model substrate 6-oxoheptanal.$^{175}$ Two steps are involved: concerted proton abstraction/proton donation to enolize the substrate (with internal enolization of the ketone operative), followed by C$-$C bond formation concerted with proton
transfer from enol to aldehyde, shuttled across the non-bridgehead nitrogens of (67). Alternative nucleophilic and enamine mechanisms have been explicitly ruled out by the calculations.

The aldol condensation of acetaldehyde in water has been studied under environmental conditions at high pH, as it may play a role in the degradation of organic matter in hyperalkaline conditions. Analysis of the kinetics suggests that the reaction is first order in substrate, hydroxide, and carbonate, in contrast to earlier studies suggesting a second-order base dependence, with the authors claiming that they have better avoided interference by a competing Cannizzaro process.

Benzamidine catalysis of an aldol reaction can be switched on and off reversibly with carbon dioxide, without affecting substrate or products.

Carbanions of 3-chloropropyl phenyl sulfones containing carbonyl and imino groups (e.g. 68) in the ortho-position add intramolecularly to these groups to give aldol-type anions. Subsequent intramolecular 1,5-substitution of chlorine gives tricyclic tetrahydrofurans, pyrrolidines, and cyclopentanes.

Halogenotin hydrides, Bu₂SnXH (X = Cl, I), catalyse a reductive aldol reaction of enones to give β-hydroxyketones in good de, using a Ph₂SiH₂/alcohol promoter system.

A strategy for controlling enantio- and diastereo-inductions in a sequential hydroformylation-aldol process involves selection of an appropriate combination of a chiral metal catalyst and a chiral organocatalyst.

A silver(I)-BINAP complex catalyses asymmetric aldol reaction of alkenyl trichloroacetates with α-keto esters. The reaction is also promoted by dibutyltin dimethoxide, Bu₂Sn(OMe)₂, a species that can be regenerated by addition of methanol. The catalysts also work for the reaction of diketene and methyl benzoylformate.

Enolizable aldehydes, R₁R₂CHCHO, undergo an asymmetric Meerwein–Ponndorf–Verley–Aldol etherification reaction in methanol, giving highly functionalized products (69) with defined configurations at adjacent quaternary and tertiary centres. (−)-Menthyl-TMS is used as auxiliary, and trifluoroacetic acid is required as a catalyst. Aldehyde ‘dimerization’ to Tishchenko esters is catalysed by sodium hydride. While NaH is usually considered a base, it can reduce aldehydes to sodium alcoholates, and this is proposed as the first step; detection of alcohol by-product supports such a mechanism.

Heteroaryl aldehydes undergo Evans–Tishchenko coupling with β-hydroxyketones using a samarium catalyst at −15 °C: high yields and de are obtained. At ambient temperature, a retro-aldol aldol Tishchenko process competes.
An asymmetric direct vinylogous aldol reaction of unactivated γ-butenolide (70) with aldehydes gives the corresponding 5-(1′-hydroxy) derivatives in high yield/ee (93/83%), using a cinchona-alkaloid-based thiourea organocatalyst.\textsuperscript{185}

A model reaction of an enal (71) and an enone (72) to give stereoselective synthesis of a \textit{trans}-cyclopentene (73), catalysed by an NHC, was studied by DFT methods.\textsuperscript{186} The complex mechanism involves an initial Breslow intermediate attacking the enone to give an enol-enolate, the point where the \textit{trans}-stereochemistry of (73) is determined. An intramolecular aldol condensation, extrusion of the NHC, and elimination of carbon dioxide feature in the later steps.

Asymmetric homoaldols have been reviewed.\textsuperscript{187} Homodimerization of 2-cyclohexanone, catalysed by \textit{l}-proline, proceeds via a two-step imine/enamine addition or concerted Diels–Alder cycloaddition: the former is preferred.\textsuperscript{188} A silver(I) complex of a chiral quinoxaline-diphosphine gives ee up to 99% in a nitroso aldol of alkenyl trichloroacetates to give α-amino-oxy ketones.\textsuperscript{189} A tin methoxide co-catalyst is also required, presumably to convert the substrate into a tin enolate, which then adds nitrosobenzene.

The $\textit{O}$-nitroso aldol reaction of nitrosobenzene with enolizable aldehydes is promoted by the TMS ether of diphenylprolinol, using \textit{para}-nitrobenzoic acid as a Brønsted acid co-catalyst, with ee of about 100%. The α-oxyaldehyde adducts produced are readily converted \textit{in situ} to α-oxyimines, and thence to 1,2-aminoalcohols via treatment with Grignards, the latter process exhibiting des > 90%.\textsuperscript{190}

\textbf{The Henry (Nitroaldol) Reaction}

A supramolecular chiral host, per-6-amino-\textit{β}-cyclodextrin, gives ‘all-99s’ performance (yield, de, ee) for a Henry reaction in aqueous acetonitrile, and is readily recyclable without loss of activity.\textsuperscript{191} Thiourea, flanked by proline and cinchonidine substituents, gives up to 96% de and ee in conjugate addition of ketones/aldehydes to nitroalkenes.\textsuperscript{192} Copper catalysis is widely used. A high level of stereocontrol of three contiguous stereogenic centres has been achieved using a complex of copper(I) chloride and a chiral sulfonyldiamine in a Henry reaction of (\textit{R})-2-phenylpropanal and nitroethane.\textsuperscript{193} Copper(II) complexes of chiral secondary diamines derived from 1,2-diaminocyclohexane catalyse reaction in 2-propanol at $-30^\circ$C in the presence of Hunig’s base, \textit{i}-\textit{Pr}_2\text{NEt}: examples of high yield/de/de are recorded.\textsuperscript{194} Combining diamine and bis(sulfonamide) auxiliary strategies, ligand (74) – in combination with copper(II) – gives yields/ee up to 99/99%.\textsuperscript{195} High \textit{syn}-selectivity with a
copper(II)-bisimidazoline has been rationalized in terms of the chiral environment around the metal, as seen in the X-ray structure.\textsuperscript{196}

Tetramethylenediamine (TMEDA) catalyses the nitroaldol of a range of aldehyde types under mild, solvent-free conditions.\textsuperscript{197} Two reviews cover advances in the asymmetric Henry reaction, focussing on organocatalysts\textsuperscript{198} and copper catalysts with chiral ligands.\textsuperscript{199}

For other references to the Henry reaction, see under ‘Other Reactions of Imines’ above.

\textit{The Baylis–Hillman Reaction and its Morita-variant}

The titanium-tetrachloride-promoted Baylis–Hillman reaction of methyl vinyl ketone and acetaldehyde in the absence of base has been studied by DFT, carefully dissecting the alternatives at each of the three main steps: chloride transfer to give a chloroenolate, titanium-mediated aldol, and elimination of HCl or HOTiCl$_3$.\textsuperscript{200}

All other reports deal with the Morita–Baylis–Hillman (MBH) reaction.

An amino-acid-derived phosphino-thiourea catalyses an intramolecular reaction in up to 84\% ee, converting \(\omega\)-formyl-\(\alpha,\beta\)-unsaturated carbonyl compounds to cyclic adducts.\textsuperscript{201}

Brucine N-oxide and proline have been developed as a dual-catalyst system for asymmetric MBH reactions of vinyl ketones: the former activates the vinyl ketones to provide enolates via conjugate addition, while the proline forms iminium intermediates with electron-deficient aryl aldehydes.\textsuperscript{202}

Enantioselective MBH reactions and their aza-variants have been carried out with trifunctional organocatalysts featuring a Brønsted acid and base and a Lewis base; counterion effects are significant.\textsuperscript{203}

The mechanism and stereoselectivity of the reaction between formaldehyde and methyl vinyl ketone has been investigated by DFT for \(N\)-methylprolinol (75), a bifunctional catalyst. Of the two steps – C–C bond formation and hydrogen migration – the latter is accelerated by water, leaving the former determining the rate and the stereochemistry.\textsuperscript{204}

A detailed mechanistic investigation highlights key deficiencies in the use of B3LYP calculations for this reaction and substitutes the MO6-2X DFT computational method.\textsuperscript{205} The failure to accelerate the reaction with higher temperatures has been explained by VT (variable temperature) experiments and MP2 calculations: the equilibrium shifts towards the reactants even with moderate increases in temperature. The authors also examine two key alternative mechanisms for proton transfer: Aggarwal’s protic route and McQuade’s aprotic one. They are found to be typically
in competition, with the mechanistic balance depending on both the amount of protic species present and on the reaction progress (early or late stage). Phenol- and auto-catalysis are also accurately modelled.

A highly enantioselective reaction of isatins (76) yields 3-substituted 3-hydroxy-2-oxindoles (77): this is the first ketone/acrolein example of a catalytic asymmetric MBH. A chiral β-amino ether auxiliary with a pendant hydroxyquinoline gives ee's up to 98% and high yields, in dichloromethane at $-20^\circ$C.

An enantioselective aza-MBH reaction of unactivated methyl acrylate has been developed. While a simple Lewis acid such as lanthanum(III) triflate was ineffective, the corresponding isopropoxide – in combination with a bis-BINOL and some DABCO – worked for a range of $N$-diphenylphosphinoyl imines, with yields up to 99% and ee's up to 95%. The reaction also worked for isomerizable alkyl imines. Initial rate and kinetic isotope studies suggest the Brønsted basicity of the metal catalyst, rather than its Lewis acidity, is crucial, as is the nucleophilicity of the lanthanum enolate intermediate.

The asymmetric MBH and its aza-variant have been reviewed, especially the use of bi- and multi-functional chiral catalysts derived from BINOL and BINAP and from cinchona alkaloids.

A primary–tertiary diamine catalyses reaction of vinyl acetate with aldehydes, apparently via a bifunctional cooperative catalysis involving an enamine-quaternary ammonium intermediate.

Amphiphilic $N$-alkylimidazoles catalyse reactions in water, without organic solvent.

An account of the roles of chiral phosphine organocatalysts of asymmetric MBH and related reactions emphasizes their multifunctionality.

**Allylation and Related Reactions**

A chiral dinuclear cadmium amino acid complex is an efficient water-compatible Lewis acid catalyst for chemo-, regio-, and diastereo-selective allylation of aldehydes.

Chiral aryl methyl sulfoxides, Ar–S*($=O$)–Me, activate asymmetric allylation of aldehydes with allyl trichlorosilanes, giving high ee and de and non-linear effects; the latter suggest that two sulfoxides are coordinated to silicon in the transition state. Enantioselective allylation of aldehydes by diastereomeric bis(tetrahydroisoquinoline)
N,N'-dioxides with allyl trichlorosilane exhibit dramatic and as yet unexplained solvent effects on the ee. Axially chiral bis(amine-oxides) give ees up to 99% in Sakurai–Hosomi allylation of α,β-unsaturated aldehydes with allyl trichlorosilane.

A bulky BINAP-phosphoric acid catalyses allylboration of aldehydes with yields and ees up to 99%. It works for a wide range of substrates, and crotylation works too. The high reactivity is ascribed to protonation of the allylboronate by the phosphoric acid.

Nickel-catalysed borylative coupling of dienes and aldehydes is remarkably affected by the use of P(TMS)$_3$ as phosphine ligand: relative to many other phosphines, regioselectivity is reversed, and de is enhanced. The effect bears comparison with ‘super-silyl’ stereodirection with the −Si(TMS)$_3$ group (see under ‘Other Asymmetric Aldols’ above). $^{31}$P NMR and steric arguments suggest that the effect is electronic in nature.

A mild indium-mediated Barbier-type allylation of aldehydes using an allyl halide has been reported using a simple chiral amino-alcohol: high yields and ees are obtained (and des when extended to crotylation), and a wide variety of other functionality is tolerated. Carried out in dipolar aprotic media such as THF, with a pyridine as Lewis base, the active allylating intermediate appears to be an allyllindium(III) species. Indium(0) persists throughout the reaction, indicating that the indium halide by-product disproportionates.

The samarium Barbier reaction – the coupling of alkyl halides and ketones by SmI$_2$ – is dramatically accelerated by HMPA. A kinetic and computational investigation has been undertaken to pin down the cause. Although addition of HMPA increases the reducing power of samarium(II), the key finding is that it activates the carbon–halide bond.

NMR and deuterium-labelling experiments have been used to explore the mechanism of rhodium-catalysed coupling of allylic, homoallylic, and bishomoallylic alcohols with aldehydes and N-tosylimines. The reactions, which can involve isomerization of the alkenols and then give aldol- and Mannich-type products, require activation by a strong base (t-BuOK), which promotes routes via alkoxides rather than via rhodium hydrides.

An ene-type coupling of aldehydes and conjugated dienes gives dienyl homoallylic alcohols, using a Pd/diphosphine/Et$_3$B catalytic system. The reaction occurs selectively at the more electron-rich double bond of the diene.

Chiral benzylic trifluoroborate salts, Ar$^1$Ar$^2$C*(Me)–BF$_3$–K$^+$, react with aldehydes to give homoallylic alcohols, with dearomatization of one of the aryl rings. Thus benzylic boron reagents behave as if they were allylic.

Desulfinative allylations of aldehydes and ketones have been carried out using alk-2-enesulfonyl chlorides and silyl alk-2-enesulfinites, H$_2$C=C(R)−CH$_2$SO$_2$−X (X = Cl, TMS), using palladium(II) catalysis.

The Horner–Wadsworth–Emmons Reaction and Other Olefinations

Z-Selective HWE-type reactions of aldehydes (and of acetophenone) employ a phosphorane reagent, L$_2$P–CH$_2$CO$_2$Et, where L = a bidentate naphthol.
Silver catalyses carbonyl olefination using electron-rich siloxyalkynes such as 1-siloxy-1-propyne or -hexyne to give trisubstituted unsaturated esters. An alternative to the HWE, the process is mild and chemoselective: neither esters nor ketones in substrates react.\textsuperscript{225}

A new compound, difluoromethyl 2-pyridyl sulfone (78) acts as a \textit{gem}-difluoro-olefination agent for aldehydes and ketones.\textsuperscript{226} A fluorinated sulfinate intermediate (79) in the reaction is relatively stable: it is observable by $^{19}$F NMR and trappable with methyl iodide. It loses sulfur dioxide to give the \textit{gem}-difluoro-alkene and 2-pyridone.

![Diagram of compounds 78 and 79]

Formaldehyde and propene, and substituted variants thereof, are the subject of a DFT study of carbonyl-ene reactions examining 12 Lewis acid catalysts.\textsuperscript{227} The substituent effects observed are very different from those seen for the Diels–Alder reaction.

For a review of the HWE and Wittig reactions, see under ‘The Wittig Reaction’ below.

**Alkynylation**

Reviews of asymmetric alkynylation cover enantioselective addition of terminal alkynes to aldehydes,\textsuperscript{228} catalysis by zinc triflate and two-point chiral ligands,\textsuperscript{229} and enantioselective addition of alkynes to ketones.\textsuperscript{230}

Deuterium-labelling NMR studies have been used to explore the catalysis of direct alkynylation of aldehydes using chiral ruthenium-bis(oxazolinyl)phenyl complexes.\textsuperscript{231}

Copper(II) complexed with an axially chiral bis-phosphine ligand catalyses propargylation of aldehydes with yields and $ee$ up to 99\%,\textsuperscript{232} and cobalt porphine co-catalysts enhance $ee$ in Nozaki–Hiyama propargylation of aldehydes.\textsuperscript{233}

Almost complete regiocontrol of nickel-catalysed reductive coupling of aldehydes and alkynes has been achieved: a cyclopropenylidene ligand favours reaction at the less hindered end of the alkyne, while use of an NHC reverses this,\textsuperscript{234} and a DFT study has examined nickel-catalysed reactions of this type: steric effects predominate for simple alkynes, but a more complex behaviour is observed for enynes and conjugated 1,3-diynes.\textsuperscript{235}

The dilithium salt of a chiral BINOL catalyses alkynylation of ketones by trimethoxysilyl-alkynes in fair to good $ee$.\textsuperscript{236}

**Benzoin Condensation and Pinacol Coupling**

Benzils have been prepared from benzaldehydes using an NHC catalyst under metal-free conditions.\textsuperscript{237} The one-pot method uses an azolium salt and DBU in DMF at
Viability of cyanide-catalysed benzoin condensation without protic assistance has been shown in a DFT study to follow a mechanism similar to the original Lapworth proposal.\textsuperscript{238}

As part of a mechanistic investigation of aldehyde umpolung via the use of NHCs, the keto form of the Breslow intermediate (80) has been synthesized, isolated, and purified, being formed from a triazolylidene and propanal.\textsuperscript{239} With rigorous exclusion of oxygen, it can be studied by NMR, and addition of catalytic amounts of acid (TFA or \textit{para}-tosic acid) do not result in detectible tautomerization to either its enaminol or enol forms. A second aldehyde can convert the intermediate (80) to a spirocyclic dioxolane (81), a ‘resting state’ in the catalysis. Although this reaction is reversible, the activation energy of 67 kJ mol\textsuperscript{−1} (for the reverse) helps account for the sluggishness of aliphatic aldehydes.

![Chemical structure](image)

A new chiral triazolium salt is a precursor to an NHC catalyst of a cross-benzoin of heteroaromatic aldehydes with trifluoromethyl ketones. The reaction appears to be under kinetic control, and gives moderate ee, substantially improved by recrystallization.\textsuperscript{240}

Ytterbium(III) triflate catalyses pinacol homocoupling of aldehydes and ketones and imine-coupling for aromatic imines (including an intramolecular case), in the presence of magnesium and TMSCl. Diastereoselectivities up to 100% were recorded for several classes. Reaction conditions are mild (THF or DCM reflux), and the \textit{de} can be altered by addition of tetraglyme, which could block off five coordination sites on the metal cation.\textsuperscript{241}

\textbf{Michael Additions}

The asymmetric Michael addition continues as a very active field, particularly with proline-derived catalysts. An ‘amphibian’ organocatalyst (82), containing proline incorporated into a hexahydropyrrolo[2,3-\textit{b}]indole skeleton, catalyses addition of aldehydes to nitroalkenes with high yield and \textit{de/ee} up to 98/99\%.\textsuperscript{242} Compound (82) features a bowl-shaped conformation, high geometry control over an enamine with efficient face-shielding, and a chiral pocket, allowing asymmetric reaction in both water and organic solvents.

Complete enantio-pair sets of diastereomeric spiro-lactams and spiro-diamines (83; \(X = \text{C}=\text{O}, \text{CH}_2\); \(R = \text{H}, \text{Boc}, \text{and the enantiomers at the spirocentre}\) have been
Reactions of Aldehydes and Ketones and their Derivatives

Prepared and isolated, all from l-proline, with absolute stereochemistry being determined by X-ray crystallography. High yields and de/ee have been obtained for the test reaction of addition of valeraldehyde to β-nitrostyrene. Thus the catalysts allow either enantiomer of the syn-Michael product to be favoured, even though all catalysts are sourced from the one (readily available) enantiomer of proline. Recyclable chiral IL (84), derived from DABCO and l-prolinol, gives yields/de/ee up to 100/98/97% for both aldehyde and ketone substrates, while pyrrolidinyl sulfone (85) gives up to ‘all-98’s’ results for ketones in aqueous solution.

New aminal-pyrrolidines (86), derived from cis-4-phenoxy-l-proline, have a modular aminal system at the 2-position, bearing two bulky (R1) groups that block one face of the proline. This gives a synergistic bifunctional enamine catalysis. They give excellent enantiocontrol in α-functionalization of linear and branched aldehydes and ketones, including examples of Michael and α-amination additions.

(S)-Prolinol silyl ether (87) acts as a surfactant-organocatalyst at room temperature in water containing 20 mol% formic acid and a catalyst loading of 2 mol%: the good de/ee results achieved fall sharply if the dodecyl chain is omitted. Silylation closer to the pyrrolidine (e.g. 88) is also highly effective.

Mentions of other proline-based catalysts include (with de/ee): C3-symmetric tris-prolinamines (98/98%), proline-BINAP-sulfonimides with Brønsted acid cocatalysis for addition to ketones (98/96%), a proline-BINOL thiophosphoramidite (98/99%), pyrrolidinyl-camphors in direct addition to aldehydes and ketones.
(96/99%), and a series of proline-derived catalysts optimized for addition of oxyaldehydes (66/96%).

As seen for aldols, the urea or thiourea moiety has been extensively used, often with proline; for example, bifunctional catalyst (89a) can potentially donate two urea hydrogen bonds during addition of ketones to nitroalkenes, but it proved to be a poorer catalyst than benzyl-catalyst (89b) with only one urea NH. A DFT study suggests that (89a) does indeed form a rigid complex with the nitro group of the substrate, but that this retards the approach of the enamine intermediate. The result serves as a caution for approaches to catalyst design that merely maximize the number of hydrogen bonds to the catalyst.

![Diagram of catalyst structures](image)

Thiourea examples include (with yield/de/ee) a thiourea incorporating BINOL and a prolinamide for conjugate addition of ketones to alkylidene malonates without solvent at ambient temperature (95/98/99%), a thiourea with a chiral amine attached with bifunctional catalysis supported by $^1$H NMR and ESI-MS data (98/–/99%), a thiourea bearing both proline and quinone groups (96/–/98%), and an achiral thiourea added (non-covalently) to proline, dubbed ‘self-assembly of organocatalysts’ (99/94/76%). A bifunctional thiourea with pendant amine and saccharide gives Michael-type addition of $\alpha,\beta,\gamma,\delta$-nitrodienes to ketones (99/94/76%), with exclusively 1,4-addition (not 1,6-): the products lead readily to trans- and cis-(3R)-5-substituted 3-pyrrolidinecarboxylic acids.

Examples of catalysts other than proline include the lithium salt of O-$t$-butyldiphenylsilyl L-serine (addition of malonates to enones), the lithium salt of $l$-phenylalanine (addition of aldehydes to nitroalkenes), and bifunctional primary amines such as Noyori’s Ts-DPEN ligand (addition of acetone to nitroalkenes).

Diastereoselectivity in additions to chalcones has been modelled by DFT for the case of [(diphenylmethylene)amino]acetonitrile (Ph$_2$C=N–CH$_2$–CN), a representative C–H acidic Schiff base, and for benzylideneacetophenone (Ph–CH=CH–CO–Ph). The results show the factors that give rise to high de for the chalcones, but a typical alkyl case such as H$_2$C=CH–CO–Bu-t gives zero de.

A domino Michael/Henry reaction has allowed preparation of medicinally important bicyclo[3.2.1]octanes (e.g. 90) from achiral reactants, for example, $\beta$-nitrostyrene and phenyl cyclohexylcarboxylate-2,4-dione. The example contains four contiguous stereocentres, including two quaternaries. Prepared with yield/de/ee of 93/98/94%, the reaction is catalysed by a thiourea (91) bearing a chiral cinchona alkaloid on one side and a substituted phenyl on the other. Evidence for multiple activation of the reactants
suggests hydrogen bonding between (i) the conjugate acid of the amine and the nitro group of the styrene, (ii) the thiourea and the Michael donor, and (iii) unusually, a phenyl C–H (arrowed) and the Michael donor.

In another variant, pyrrolo[1,2-α]indole-2-carbaldehydes (92) have been constructed in a one-pot domino aza-Michael/aldol reaction by N-alkylation of indole-2-carbaldehydes with α,β-unsaturated aldehydes. The TMS ether of diphenylprolinol gives high ee.

Dialkylphosphine oxides have been added to α,β-unsaturated enones in a zinc-mediated phospha-Michael process catalysed by a variant of Trost’s dinuclear catalyst, in up to 99% ee. The addition has also been applied to N-sulfinylimines in up to 99% de.

Miscellaneous Condensations

A synthesis of Tröger’s base from anilines and formaldehyde in an IL at ambient temperature has thrown up two new putative intermediates, bicycle (93) and tricycle (94), both being identified by X-ray crystallography.

1,1,3,5-Tetramethyl-4-oxo-2,6-diphenylpiperidinium triflate (95) has been prepared in four steps, starting with a Mannich reaction of benzaldehyde. It is an excellent catalyst for Biginelli synthesis of hydroxysemibicamines from the building blocks of an aldehyde, a β-dicarbonyl, and a (thio)urea. The possible intermediacy of N-acylimines is discussed.

Anthranilic acids, salicylaldehydes, and alkyl isocyanides undergo a novel Ugi-type process to give 2-[(2-alkylamino)benzofuran-3-yliden]benzoic acids (96). The high-yielding one-pot reaction, carried out in water, is proposed to involve initial salicylidenimine production followed by isocyanide attack, leading to formation of a nitrilium-amino-carboxylate intermediate, attack by phenol, and final aerial oxidation.

Multi-substituted cyclohexa-1,3-dienes (97) have been prepared via a multi-component domino reaction of aryl ketones (ArCONMe), aromatic aldehydes
Primary 1,2-diamine catalysis was achieved with the simplest possible catalyst, 1,2-diaminoethane.

Pictet–Spengler condensation of phenethylamines (98; R = H, OMe) with carbonyls has been achieved under mild conditions (DCM/ambient) to give tetrahydroisoquinolines (99). Catalysed by calcium bis-1,1,1,3,3,3-hexafluoroisopropoxide, Ca[OCH(CF₃)₂]₂, the reaction is unremarkable for aldehydes but is unprecedented for unactivated ketones, which have previously required two steps: imine formation, then cyclization.

Cyclic vinylogous acyl triflates (‘VAT’s’, e.g. 100) undergo addition of stabilized carbanionic nucleophiles to give a ketone aldolate intermediate (101), which undergoes ring opening to give an alkynyl-tethered ketone (102), still activated for further reaction via α-deprotonation. The process – dubbed ‘VAT-Claisen’ – differs from the classic Claisen because C–C bond cleavage is irreversible. Some labelling studies
and preliminary mechanistic details are reported in addition to practical examples that show the ease of the reaction when the electron-withdrawing group is an ester, a phosphonate, a phosphine oxide, etc.

Modified Knoevenagel condensation of malonic acid and aldehydes, using $N$-methyl-morpholine as catalyst, gave $(E)$-$\beta,\gamma$ unsaturated acids with high $\beta,\gamma$-regioselectivity and exclusive $(E)$-stereoselectivity.$^{273}$

**Other Addition Reactions**

A computational study has compared hydration of acetone in the gas phase and in water solvent: the former involves concerted processes avoiding zwitterionic transition states, whereas solvation in the latter allows hydrogen transfers to be asynchronous.$^{274}$

Asymmetric nucleophilic 1,2-addition to C=O and C=N bonds has been reviewed.$^{275}$

**Addition of Organozincs**

Enantioselective organozinc-catalysed additions to carbonyl compounds using chiral amino-alcohol auxiliaries have been reviewed.$^{276}$

Further investigations of Soai’s autocatalytic addition of diisopropylzinc to pyrimidine aldehydes (103) to give highly enantiopure alcohol (104) in high $ee$ from a catalytic quantity of (104) in very low initial $ee$, show intriguing results. An inverse temperature dependence on reaction rate is accompanied by a very long induction period, which is longer at higher temperature. Changing from 298 to 263 K, the rate increases 20-fold. A similar behaviour is observed over a range of concentrations, starting enantio-purities, and R groups and when the zinc alkoxide of (104) is used as catalyst. Low-temperature NMR techniques including COSY, ROESY, and DOSY (diffusion spectroscopy) have been used to probe the species present, with the last technique suggesting that a tetrameric zinc alkoxide and equilibria related to it can
help explain both the dormancy and the inverse-temperature kinetic effect. The mechanism of this reaction has also been investigated by DFT.

A chiral amino-phosphinite (105) – a trityl aziridine derivable from L-serine – catalyses arylation of benzaldehydes to diarylmethanols in the presence of diethylzinc; yields/ee are up to 97/93%. An enantioselective catalyst series for ethylation of arylaldehydes in the presence of titanium(IV) consists of two BINOLs joined by a propyl ether bridge, with additional substituents on the bridge. Yields and ees of 99/80% have been achieved. NMR and CD titrations, ESI-MS experiments, and semiempirical PM6 calculations have been used to characterize the immediate catalytic species.

New enantiopure pyridyl alcohols derived from terpenes contain conformationally flexible biaryl axes: alkylzincation of the hydroxide then freezes the conformer equilibrium to give enantioselective catalysts of addition of dialkylzincs to benzaldehyde. 2D-NMR and computations support the analysis.

An X-ray and Hammett study of oxazolidine ligands derived from (1R,2S)-ephedrine and their catalysis of addition to aldehydes has helped tease out structural, electronic, and steric effects involved. A parent chiral 1,1′-bisisoquinoline ligand and its mono-N-alkyl, -acyl, and -sulfonyl derivatives give significantly different ees; X-ray crystal structures show that the superficially similar compounds have peculiar structural features. Other reports reveal that BINOL substituted in the 3-position with various nitrogen heterocycles gives high yield and ee on addition to benzaldehyde in the presence of titanium tetraisopropoxide, a series of 1,3-aminoalcohols based on both cis- and trans-2-benzamidocyclohexane-carboxylic acids give good ee/ee on addition to araldehydes, and readily accessible ligands derived from (+)-ketopinic acid are effective catalysts.

Felkin control of nucleophilic addition of α-silyloxy aldehydes has been realized in a general method that promotes chelation control. A wide range of organozincs RZnX adds with high de (90 → >95%) in the presence of halides or triflates. The role of chelation is supported by NMR studies, the dramatic catalysis by RZnX, and the higher diastereoselectivity observed for larger alkyl substituents on the aldehyde’s α-carbon.

Imines, aldehydes, and ketones (R1R2C=NX, X = O, NPh) have been nucleophilically perfluoralkylated with sulfones, PhSO2R_F (R_F = CF3, C2F5), to give adducts R1R2R_F-C—XH, using alkoxide. Ketones, disulfides, and diselenides can be trifluoromethylated with diethyl trifluoromethylphosphonate, (EtO)2P(=O)CF3, again in the presence of alkoxide.

### Arylations

Among reports of asymmetric arylation of araldehydes with arylboronic acids, a new BINAP bearing a phosphine and a fluoroalcohol (106), when complexed with rhodium(I), gives to 92% ee. The corresponding catalysts with two hydrogens or two methyls on the alcohol carbon give zero or low yield and ee under comparable conditions. New chalcogen peptides including selenide catalyse in up to 91% ee. Amino alcohols derived...
from sugars such as d-xylose give yields/ee up to 97/96%: PM3 calculations support the mechanistic analysis.\textsuperscript{292} A DFT study of the rhodium(I)-mediated arylation (in the absence of base or water) has identified an internal base mechanism, with migratory insertion of the aldehyde into the rhodium(I)-aryl bond as the rate-limiting step.\textsuperscript{293} A cobalt(II)-chiral diphosphine combination gives high ees.\textsuperscript{294}

In a novel aryl coupling reaction, 2-phenylpyridine can be arylated (in the 2′-position: see 107) by an oxidative decarbonylative coupling of an aromatic aldehyde, \( \text{ArCHO} \), using a rhodium(I) catalyst and \( t \)-butyl peroxide as oxidant.\textsuperscript{295}

DFT has been used to investigate intermediates in organo-singly occupied molecular orbital (SOMO) catalysis of \( \alpha \)-arylation of aldehydes, focussing on the cyclized radical cation intermediates.\textsuperscript{296} Metal-catalysed \( \alpha \)-arylation of carbonyl compounds has been reviewed (130 references).\textsuperscript{297}

Aromatic trifluoromethyl ketones condense with arenes in superacid solution (\( \text{F}_3\text{C}–\text{SO}_3\text{H} \)), giving 1,1,1-triaryl-2,2,2-trifluoroethanes.\textsuperscript{298} The mechanism and synthetic scope of the reaction has been studied, including competing side and intramolecular reactions.

For enantioselective addition of alkenyl and aryl boronates to chromene acetals, see under ‘Formation and Reactions of Acetals and Related Species’ above.

\section*{Addition of Other Organometallics, Including Grignards}

While des in addition of chiral oxiranyllithiums to arylaldehydes are often low, completely stereoselective reactions can be achieved in suitably matched pairs of organolithium and a ‘remote’ sulfinyl group on (S)-2-\( \text{para} \)-tolylsulfinylbenzaldehyde (108) to give 2,3-epoxy alcohols.\textsuperscript{299}

A BF\textsubscript{2} complex (109) undergoes chemoselective addition of organolithiums to give 1,3-dioxo-BF\textsubscript{2} complexes (110) under mild conditions.\textsuperscript{300} Starting from an ethyl 3-oxopropanoate, the process yields 1,3-diketones (after cleavage of the boron).
A DFT study of the reaction of 1-propynyllithium (as a model for an \(sp\) organolithium) with formaldehyde has considered aggregation of the lithium reagent up to the hexamer and the relative nucleophilicity of the \(sp/sp^2/sp^3\) lithiated carbons by comparing vinyl- and methyl-lithium. Nucleophilicity order may not follow the acidity order (\(sp > sp^2 > sp^3\)).

2,2′-Oxy-bis(\(N,N\)-diethylethanamine) (BDMAEE, 111), a tridentate ligand for magnesium, and aluminium trichloride have been employed as regulators of asymmetric BINOL-catalysed arylation of aldehydes by aryl Grignards. BDMAEE inhibits the undesired background reaction promoted by Lewis-acidic MgX\(_2\) species, while aluminium chloride assists in the transfer of \textit{in situ} generated aryl intermediates to aldehydes.

The possibility that Grignard reactions with carbonyl compounds can compete in the presence of water, phenols, carboxylic acids, and other protic reagents has been tested, and moderate yields of Grignard adducts can be achieved, especially with allylmagnesium bromide and benzylmagnesium chloride. Although the effect may be partly due to the protic species being scavenged by electrophilic magnesium species, this effect can be obviated by carrying out intramolecular competitions, that is, by having a carbonyl and hydroxyl present in one substrate.

Clean addition of Grignards, RMgX, to ketones has been achieved using a triple catalyst/reagent system, ZnCl\(_2\)·Me\(_3\)Si–CH\(_2\)MgCl-LiCl (10/20/110 mol%). Mechanistic investigation suggests that stabilized mixed salts [R(Me\(_3\)Si–CH\(_2\))\(_2\)Zn]⁺[Li]⁻[MgX\(_2\)]\(_m\)[LiX]\(_n\) form \textit{in situ}. These can act as catalytic alkylating agents through increased nucleophilicity in their anions, while the cation can act as a Lewis-acidic activator of carbonyls. High yielding in THF at 0\(°\)C in a few hours with minimal by-products, the reaction can be used not only for aldehydes (unsurprisingly) but also for aldmines (to give secondary amines).

A 1 : 2 mole ratio of a Grignard and titanium tetraisopropanoxide has been used to alkylate or arylate aldehydes, with a BINOL catalyst giving \(ees > 90\%\); the method may be a useful alternative to use of organozincs.

For other articles on Grignards, see under ‘Addition of Organometallics’ above.

**The Wittig Reaction**

The Wittig reaction and variants such as the Horner–Wadsworth–Emmons (HWE) have been reviewed, as has the scope for phosphine-catalysed reactions and ‘cleaning up’ the reaction by replacing stoichiometric phosphorus species with catalytic reagents.

Stepwise and concerted mechanisms have been examined by DFT for a simple diastereomeric aldehyde (112) undergoing Wittig reaction with triphenylphosphonium ylide (Ph\(_3\)P=CH\(_2\)) in THF, and \textit{in vacuo}. A scandium carbene complex (113) has been prepared from a geminal dianion precursor, [Ph\(_2\)(S=)P–]\(_2\)C\(_2\)\(^{2–}\) (Li\(^+\))\(_2\), by salt metathesis on ScCl\(_3\)(THF)\(_3\). The X-ray structure and Natural Bond Orbital (NBO) analysis suggest it should behave as a nucleophilic carbene, with double \(\sigma + \pi\) donation towards the metal centre. Addition of benzophenone to the complex gives the expected alkene via a ‘scandia-Wittig’ reaction, further confirmed by the trapping of a rare \(\mu^3\)-oxo-Sc
species. A new but related yttrium carbene (114; R = CH₂SiMe₃) has been characterized by X-ray crystallography. Reaction with benzophenone gives an adduct (114; R = OC(CH₂SiMe₃)₂Ph₂). However, it does not quite behave as an ‘yttria-Wittig’ intermediate, ... but it does effect regioselective ortho-C–H activation and subsequent C–C and C–O bond-forming steps give iso-benzofurans and hydroxymethyl-benzophenones.

An equilibrium between a phosphonium dienolate (115a) and a vinylogous ylide (115b) has been described. In reactions between ethyl 2-methyl-2,3-butadieneoate [H₂C=¿C=C(Me)–CO₂Et] and aryl aldehydes using 1 equiv. of a trialkylphosphine, these intermediates are formed, with the balance depending on the presence or absence of a Lewis acid and on the nature of the phosphine. In one case, a rare vinylogous Wittig olefination is observed, while the other proceeds to vinylogous aldol addition via an unusual 1,2-aryl phosphorus-to-carbon migration.

Ruthenium-catalysed synthesis of the alkenes by decarbonylative coupling of aldehydes with alkynes has been described in both inter- and intra-molecular versions.

Hydrocyanation, Cyanosilylation, and Related Additions

An unusual reversal of enantioselectivity in the proline-catalysed α-amination of aldehydes with diethylazodicarboxylate (DEAD) is observed on addition of tertiary amines such as DBU, but the mechanistic cause is as yet unclear.

In other direct α-aminations by azodicarboxylates, proline–thioureas catalyse with yields and ee up to 99% within a few minutes, 5 mol% of a pyrrolidinyl-camphor catalyst gives yields and ee in the high 90s in reactions taking 5–10 minutes at 0°C, and similar pyrrolidine-camphor organocatalysts give close to 100% ee in some cases, the last work for more demanding α,α-disubstituted aldehydes, albeit with lower ees. A stable aminal (116) gives de/ee up to 86/98% and also catalyses Diels–Alder reactions.

trans-3- and 4-Butoxy-L-proline have been used as catalysts of unsymmetric α-amination of aldehydes and ketones.
Amination of aldehydes in water has been modelled using MO molecular dynamics simulations on the formaldehyde/ammonia reaction: $\text{H}_2\text{C}=\text{O} + \text{NH}_3 \rightarrow [\text{H}_3\text{N}^+–\text{CH}_2–\text{O}^-] \rightarrow \text{H}_2\text{N}–\text{CH}_2–\text{OH}$. Two hundred water molecules have been explicitly used in the calculations, comparing the direct (concerted) versus stepwise mechanisms, with the results favouring the latter (i.e. reaction does occur via the zwitterion, $\text{H}_3\text{N}^+–\text{CH}_2–\text{O}^-$).

A TEMPO-derived oxo-ammonium salt (117) has been used to achieve metal-free direct aminooxidation of aldehydes, with the reaction rendered asymmetric using a BINAP-based chiral amine catalyst. A proline organocatalyst ion tagged with an ee imidazolium accelerates $\alpha$-aminooxidation of aldehydes and ketones in ILs in up to 99% ee.

Sibi’s iron(III)-catalysed $\alpha$-oxyamination of aldehydes (118) by TEMPO to give $\alpha$-chiral aldehydes (119) in up to 90% ee was claimed as an example of SOMO-organo-catalysis by the imidazolidinone (120). A reinvestigation now suggests that a more traditional two-electron process – the enamine mechanism – operates. Kinetic, spectrometric, and spectrophotometric techniques – and in particular a radical-clock investigation – give a comprehensive picture supporting the enamine route.

Asymmetric salen complexes of vanadium, titanium, and aluminium have been used as catalysts of addition of TMSCN to aldehydes, with their Lewis acid and/or base properties activating the aldehyde and/or cyanide. As the extents of the relative catalyses is not always evident (from their structures), a Hammett analysis was undertaken. Acid catalysis correlates with a large and positive reaction constant, but smaller values were found for Lewis bases. Evidence of a mechanistic switchover was seen for the $[\text{Al(salen)}]_2\text{O/Ph}_3\text{PO}$ system: the Lewis base contribution increases as the aldehyde becomes more electron deficient. This also suggested it would work for ketones, which it did.

A kinetic study of three aluminium-based BINOL catalysts of asymmetric addition of TMSCN to benzaldehyde shows orders of one and zero in reactants, respectively. A common mechanism of Lewis base and Lewis acid activation of the respective
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... reactants is outlined and extended to a magnesium-based catalyst. Control experiments monitored by NMR indicate that the rate independence of the aldehyde concentration is due to its involvement only after the rate-determining step rather than the alternative possibility of a catalyst-aldehyde complex at constant concentration (i.e. saturation kinetics).

Chiral manganese(II) bis-salen complexes catalyse cyanohydrin formation from aldehydes with sodium cyanide in up to 99% ee.

Two cooperative catalyses, in which two chiral titanium-salen catalyst centres are linked, allow asymmetric cyanation of aldehydes with catalyst loadings as low as 0.005 mol%; the latter reports up to 99% yield and 97% ee and turnovers >170 000.

Direct catalytic asymmetric γ-addition of allyl cyanide to ketones is promoted by a soft Lewis acid/hard Brønsted base combination, and the efficiency has been enhanced by the addition of a phosphine oxide as a hard Lewis base. A ‘hard–hard’ interaction is proposed, wherein the action of the hard Brønsted base (a lithium phenolate) is augmented. VT-NMR data and kinetic studies of initial rates were used to support the mechanism.

A simple NHC catalyst promotes a new intramolecular cross-coupling of aldehyde-nitriles (121) to give access to 3-aminochromones (122).

Hydrosilylation, Hydrophosphonylation, and Related Reactions

Progress in the application of NHC complexes of metals to the hydrosilylation of ketones has been reviewed.

In a copper-catalysed hydrosilylation, a bowl-shaped phosphorane catalyst accelerates reduction of bulky ketones preferentially, to the point of leaving aldehydes untouched.

Asymmetric hydrosilylations reported include the following: a chiral BINAP-phosphepine liganded to copper(II) gives up to 96% ee for a wide range of ketones, without requiring base or fluoride activation; chiral cyanobis(oxazoline)rhenium(V)-oxo complexes give ees up to 99% for ketones and imines; a chiral tridentate bis(oxazolinylphenyl)amine complexed with iron(II) or cobalt(II) works for ketones and enones; DFT has been used to explore the mechanism of catalysis by copper(I) hydrides bearing phoshpine ligands; N-(2-pyridoyl)diarylprolinols act as Lewis base catalysts for conversion of α-imino esters to α-amino esters in yields/ee of up to 97/93%; a new 1-glycosyl-1H-triazole-based P,N-ligand, complexed to rhodium; and ketimines react enantioselectively using the readily accessible auxiliary (1R,2S)-1,2-diphenyl-2-formamidoethanol as Lewis base.
α-Aminophosphonic acid derivatives have been prepared diastereoselectively by hydrophosphonylation of N-diphenylphosphinylimines, R–CH=N–P(=O)Ph₂, using (R,R)-TADDOL-phosphite (123), derived from tartaric acid.341

Enolization and Related Reactions

In a kinetic study of the effect, if any, of the critical phenomena on reaction mechanism, iodination of acetone in isobutyric acid–water mixtures shows pseudo-zero-order kinetics and a critical slowing down, but the mechanism is not affected by criticality.342

2-Adamantanone (124), when deprotonated in the gas phase, gives its β-enolate anion (125), a species that can also be independently prepared if the 4-TMS derivative of the ketone is desilylated with fluoride.343 DFT studies suggest that the order of stability of the conjugate bases of (124) – that is, the ‘positional’ anions – is β > γ > α > δ. An attempt to generate the γ-enolate (by loss of carbon dioxide from a carboxylate in the γ-position) only yielded the ring-opened α-enolate isomer (126).

A review examines the scope for extending the reactivity of enolates from vinylogation to alkynylogation.344 A wide-ranging review examines metal enolates: their structure and spectroscopy and their role in many reaction types.345

A DFT study of keto-enol tautomerism of 1-phenylazo-2-naphthol and related compounds indicates that the quinone form is generally more stable and is further stabilized by electron-withdrawing groups. Solvent effects are small.346

A new protocol for intramolecular stereoselective protonation of enolates derived from aldehydes has been reported.347

The microscopic role of water as a catalyst in keto-enol tautomerism of acetone has been accessed via vacuum-UV photo-ionization. Gas-phase IR spectra of clusters containing a few molecules generated in this way have been correlated with IR spectra calculated using Gaussian™. Both proton-relay and ‘catch-and-release’ mechanisms are considered, with calculations favouring the latter.348

α-Halogenation, α-Alkylation, and Other α-Substitutions

A proline-functionalized chiral IL has been employed in asymmetric α-alkylation of ketones, giving yield/de/ee up to 99/98/87%.349

Levulinic acid and its esters (MeCOCH₂CH₂CO₂R; R = H, Me, Pr, Bu) brominate in the 3-position, predominantly, in imidazolium ILs, using molecular bromine. In organic solvents, 5-bromination is the major route.350 Small, variable amounts of
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3,5-dibromo-product are isolated in both solvent types. The IL may help equilibrate towards the thermodynamically stable 3-product: transferring a product mixture from organic solvent to IL causes a net shift (in the absence of bromine). The IL cation may also favour equilibration towards the more stable internal enol. Addition of urea to the IL switches the balance back towards the 5-product, possibly by hydrogen bonding to the carbonyl, causing disruption of interactions with the IL.

The use of molecular iodine to effect mild and metal-free α-iodination of carbonyl systems has been reviewed, emphasizing its dual role: it can catalyse enolization, as well as the more well-known subsequent reaction with the enol.\textsuperscript{351}

Aldehydes have been α-alkylated stereoselectively by four stable carbocations, using MacMillan’s imidazolidinone catalysts and lutidine as base.\textsuperscript{352} An unusual reversal of the configuration of the product was observed in the case of tropyl cation.

α-Arylpropanals are α-alkylated by diaryl bromomethanes using chiral primary aminothiourea derivatives in up to 94% ee.\textsuperscript{353} Kinetic isotope effects, Hammett plots, and competition studies all point to an $S_N\,1$ mechanism.

Functionalized chiral ILs derived from proline catalyse $S_N\,1$ α-alkylation of aldehydes and ketones with yield/de/ee up to 99/98/97% over a wide range of carbonyl types.\textsuperscript{354}

Cobalt(II), combined with a chiral bis(salen) ligand, catalyses α-fluorination and α-chlorination of β-ketoesters in good ee.\textsuperscript{355}

Organocatalytic α-alkylation of aldehydes has been reviewed.\textsuperscript{356}

New BINOL-derived crown ethers catalyse trifluoromethylation of 2-naphthyl aldehyde by TMS–$\text{CF}_3$ in the presence of base, with modest ee.\textsuperscript{357}

A combined organometallic–organocatalytic approach has been employed to achieve stereoselective α-alkylation of aldehydes with allylic alcohols, using the MacMillan catalyst and indium(III).\textsuperscript{358}

Aldehydes have been α-alkylated by propargylic alcohols using a cooperative strategy of organocatalyst and ruthenium complex, in high ee.\textsuperscript{359}

A useful preferential activation of a C–F bond over a C–I bond has been achieved, reacting trifluoromethyl iodide with the lithium enolate of an α-substituted carbonyl compound. The latter can be a ketone, ester, or amide, and $\text{CF}_2\text{I}$ is added exclusively at the α-carbon (in preference to $\text{CF}_3$) in most cases.\textsuperscript{360}

Oxidation and Reduction of Carbonyl Compounds

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

Alkyl arylformates, Ar–CO–CO$_2$R, have been reduced enantioselectively in acetonitrile using conformationally restricted NADH peptidomimetics in the presence of magnesium cation.\textsuperscript{361} Magnesium is proposed to coordinate the ketoesters and the peptidomimetic, with remote groups in the latter stereomodulating the reaction.

Enantioselective reduction of ketones has been carried out using catecholborane and a chiral thiourea-amine.\textsuperscript{362} The amine is proposed to complex the boron, enhancing B–H nucleophilicity, while the thiourea activates the carbonyl through hydrogen bonding.
Chiral iron(II)-bis(isocyanide) complexes catalyse transfer hydrogenation of aromatic ketones in up to 91% ee.\(^{363}\) The iron activates the ketone, with hydride transfer probably occurring via imine intermediates.

A dynamic kinetic resolution in the hydrogenation of racemic \(\alpha\)-arylxyketones gives \(ee\) up to 99/98%, using a chiral ruthenium complex as catalyst.\(^{364}\)

While asymmetric hydrogenation of functionalized ketones such as \(\beta\)-ketoesters by BINAP-RuX\(_2\) complexes is well established, a new review has focussed on the approaches required to achieve this for simple, unfunctionalized ketones such as acetone.\(^{365}\)

An amino-tetrazole ligand (127), in combination with Ru-BINAP, catalyses asymmetric hydrogenation of ketones.\(^{366}\)

![Image of ligand structure](image)

The use of iridium complexes in asymmetric hydrosilylation, transfer hydrogenation, and hydrogenation of ketones has been reviewed.\(^{367}\)

An l-proline-derived amino amide, together with ruthenium(II), catalyses transfer hydrogenation of ketones in water, with yields/\(ee\) up to 95/90%, with the aid of tetrabutylammonium bromide as a phase-transfer catalyst.\(^{368}\)

Aromatic ketones have been reduced enantioselectively using samarium metal and iodine in isopropanol.\(^{369}\)

**Other Reduction Reactions**

The kinetics of the Meerwein–Ponndorf–Verley reduction of a range of aldehydes and ketones have been measured, using boron triethoxide catalyst.\(^{370}\) Aliphatic substrates, but not aromatics, were reduced at room temperature. The reaction is also chemoselective, in that unsaturation in the substrates is not reduced.

Ketones have been reduced under hydrothermal conditions in the presence of NaOH at 300 °C, using formic acid for transfer hydrogenation; catalysis by water is considered.\(^{371}\)

**Oxidation Reactions**

Sulfides are poor catalysts of sulfonium-ylide-mediated methylene transfer to aldehydes, for example, conversion of benzaldehyde to styrene oxide. Ylide formation is the problematic step, and a new protocol uses methyl triflate to alkylate cyclic thiolanes, to allow aldehyde epoxidation. An asymmetric version has also been trialled.\(^{372}\)

Several reports describe direct conversion of aldehydes to acid derivatives: for example, they are oxidized to esters organocatalytically under mild conditions, using cooperative catalysis by an NHC to chemoselectively acylate in the presence of amines. Yields are high, and typically ester formation exceeds amide by \(>99 : 1\).\(^{373}\) Aldehydes
with electron-withdrawing groups, including heterocyclic aldehydes, can be directly converted to esters in aqueous alcoholic solution, using I₂/NaNO₂.\textsuperscript{374} Lanthanide metal amides catalyse convenient direct synthesis of amides from aldehydes; cyclopentadienyl ligands are not required.\textsuperscript{375}

1,3-Dicarbonyls have been oxidized by hydrogen peroxide, using a quaternary ammonium iodide catalyst.\textsuperscript{376} Cerium(IV) catalyses oxidative coupling of 1,3-dicarbonyls in acetonitrile/methanol/water mixtures, giving 1,4-diketone derivatives in high yield.\textsuperscript{377}

Cetyltrimethylammonium permanganate is a useful oxidant under solvent-free conditions, performing 1,2-dihydroxylation of alkenes, oxidation of aldehydes and ketones, and also regeneration of such carbonyl functionalities from their oximes.\textsuperscript{378}

A supramolecular micellar effect has been claimed to explain a diastereo- and enantio-selective Baeyer–Villiger oxidation of cyclobutanones with hydrogen peroxide and a cobalt(salen) catalyst in water: the system is inactive in organic solvents.\textsuperscript{379}

Kinetics of the oxidation of 36 monosubstituted benzaldehydes by morpholinium chlorochromate has been studied in a range of organic solvents.\textsuperscript{380}

The kinetics of oxidation of substituted benzaldehydes by benzyltrimethylammonium fluorochromate has been studied in protic solvents at 303 K.\textsuperscript{381} Rates are first order in substrate, oxidant, and hydronium, and Exner and Hammett plots have been constructed and thermodynamic parameters extracted from results at four temperatures.

For an oxidative decarbonylative coupling of aldehydes, see under ‘Arylations’ above.

**Atmospheric Reactions**

For the reaction of ozone with formaldehyde, the singlet and triplet potential energy surfaces have been explored by DFT.\textsuperscript{382} Reaction proceeds mainly via singlet states, leading to HCO and HO₃.

The possibility that a single water can catalyse reaction of acetaldehyde and hydroxyl radical under tropospheric conditions has been contraindicated by computation.\textsuperscript{383}

Quadropole MS and FT-IR techniques have been used to measure the rates of reaction of chlorine atoms with acetone in the gas phase over a range of temperature and pressure.\textsuperscript{384} Hydrogen abstraction to give HCl predominates, with formation of acetyl chloride contributing >0.1% of the reaction flux.

**Other Reactions**

In a rhodium-catalysed C–H activation/β-carbon elimination strategy, the strain energy of cyclobutanes and azetidines has been exploited to insert a tethered aldehyde, expanding four-membered rings to eight-membered enones.\textsuperscript{385}

Claims for synthesis of diazirinone (128) – a metastable adduct of N₂ and CO – have been challenged.\textsuperscript{386}

\(O\)-protected glycolate derivatives of \(N\)-1-(1’-naphthyl)ethyl-\(O\)-\(t\)-butylhydroxylamine (129) have been alkylated to give \(\alpha\)-substituted derivatives in high \(de\);
subsequent reduction cleaves off enantiopure α-alkoxy-, α-substituted-β-alkoxy-, and α,β-dialkoxy-aldehydes (130; R³ = H). Useful alternative products have also been obtained via methyllithium cleavage or aldol sequences.

A new pentacycle, chromeno[2′,2′:4,5]imidazo[2,1-α]isoquinoline (131), has been prepared from an ammonium salt (isoquinoline quaternized with chloroacetonitrile) and salicylaldehyde, via a novel cascade Kröhne condensation.

Vinylidenecyclopropanes (132) undergo a novel domino carbolithiation with conjugated ynones when treated with LDA in THF, to give hydroxy-diyne-dienones (133). Control experiments have been used to probe the mechanism.

β-Hydroxy and β-amino esters, R¹−CH(X)−CH₂−CO₂R² (X = OH, NHTs) have been prepared in high yield and ee from enals, R¹−CH=CH−CHO, using a combination of amino- and NHC-catalysis, with low loadings of the two catalysts, in a one-pot procedure tolerant of air and moisture.

N-Tosylhomoallylic amines react with aldehydes in an aza-Prins synthesis of piperidines, or pyrrolidines, using indium trichloride as Lewis acid promoter. A detailed mechanistic investigation has examined the factors that favour 5- versus 6-membered product, and also the origins of the stereoselectivities observed.

5-Hydroxy-1,3-diketones (134) have been prepared from reaction of an acid chloride (RCOCl) with 2 equiv. of acetone in the presence of LiHDMS. Subsequent cyclization yields 2,3-dihydro-4H-pyran-4-ones (135) when mediated by anhydrous
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indium(III) chloride. In situ FT-IR spectroscopy has proved useful in exploring the latter reaction. Dry conditions are essential, or else InCl₃ precipitates as its trihydrate.

Smiles rearrangements of \( \text{PhO(CH}_2)_n\text{O}^- \) anions, including the \( n = 3 \) case that produces phenoxide, ethylene, and formaldehyde, have been studied in the gas phase by \(^{18}\text{O}\)-labelling studies and by computation.

Natural secondary \( \alpha \)-amino acids (136) have been coupled with alkynes in an aldehyde- or ketone (137)-induced tandem decarboxylation, with the loss of CO₂ and H₂O. In formation of the amine-alkyne products (138), the carboxylate carbon has been replaced by the alkyne, and the nitrogen has been ‘alkylated’ by the carbonyl reactant. Copper(I) iodide is a catalyst, presumably via a copper acetylide. The regioselectivities observed have been investigated by computation.

Favorskii rearrangement of \( \alpha,\alpha' \)-dibromodibenzyl ketone has been studied in the gas phase by tandem MS and theoretical methods, using alkali cations.

Metal triflates catalyse the oxa-Pictet–Spengler reaction of aldehydes with \( \beta \)-arylethanols to give isochroman rings.

A rhodium-catalysed hydroacylation of cyclopropenes with aldehydes, catalysed by chiral ferrocenyl-phosphine auxiliaries, efficiently desymmetrizes them. This use of cyclopropyl strain energy to activate a C–H bond proceeds with \( ee \)s often >99% and \( de \)s of up to 95%, and high yields.

An attempted hydroamination reaction between 2-(2-phenylethynyl)aniline and acetone catalysed by an iridium complex yielded an unexpected vinyl indole derivative.

Labelling studies, isolation of an intermediate, and DFT calculations have been used to identify a likely mechanism via an imine intermediate.

A DFT study of the reactions of representative aromatic and aliphatic nitroso compounds with formaldehyde to give hydroxamic acids has looked at the gas phase (where a stepwise mechanism predominates), and at acetonitrile and water solvents, where solvent effects are found to be modest.

A kinetic study of the reaction of aryl nitroso oxides and methyl vinyl ketone in acetonitrile at 295 K finds that only the trans-oxides react; a Hammett \( \rho \) value of 1.11 ± 0.08 was determined.
A DF MBA (a difluoromethylbenzylamine such as 3-tolyl-CF$_2$–NEt$_2$), facilitates regioselective synthesis of $\beta$-fluoro-$\alpha,\beta$-unsaturated ketones by deoxyfluorination of unsymmetrical $\beta$-diketones.$^{401}$

Pyrrolo[2]indoles can be prepared by acid-catalysed condensation of acetone or acetophenones with activated 3-substituted-4,6-dimethoxyindoles (139).$^{402}$

$\alpha$-Alkylated aldehydes (141) have been prepared enantioselectively by alkylation of 2,2,6-trialkylpiperidines (140).$^{403}$ The origins of the 1,4-asymmetric induction, which are predominantly steric, have been derived by computation.

For other mentions of Prins-type reactions, see under ‘Formation and Reactions of Acetals and Related Species’ above.

References

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