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Preface

The present volume, the forty-seventh in the series, surveys research on organic reaction mechanisms described in the available literature dated 2011. In order to limit the size of the volume, it is necessary to exclude or restrict overlap with other publications that review specialist areas (e.g., photochemical reactions, biosynthesis, enzymology, electrochemistry, organometallic chemistry, surface chemistry, and heterogeneous catalysis). In order to minimize duplication, while ensuring a comprehensive coverage, the editor conducts a survey of all relevant literature and allocates publications to appropriate chapters. While a particular reference may be allocated to more than one chapter, it is assumed that readers will be aware of the alternative chapters to which a borderline topic of interest may have been preferentially assigned.

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

We are pleased to have retained for ORM 2011 our current team of experienced authors who have contributed to ORM volumes for periods of 6–33 years.

However, it is unfortunate that steps taken to reduce progressively the delay between title year and publication date were thwarted by very late arrival of a chapter for this volume. Nonetheless, we hope to regain our optimum production schedule soon.

I wish to thank the staff of John Wiley & Sons and our expert contributors for their efforts to ensure that the review standards of this series are sustained, particularly during a period of substantial reorganization of production procedures.

A. C. K.
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CHAPTER 1

Reactions of Aldehydes and Ketones and their Derivatives

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Formation and Reactions of Acetals and Related Species

Carbohydrate-based benzylidene acetals (e.g. 1) undergo reductive ring opening.\(^1\) In a deuterium-isotope study of this process, stereoselectivity is retained using AlD\(_3\), via the rare S\(_{\text{N}i}\) mechanism (internal nucleophilic substitution). The reagents BD\(_3\cdot\)THF and Et\(_3\)SiD involve S\(_{\text{N}1}\)-like routes.\(^2\)\(^3\)

\[
\text{Ph} \quad \begin{array}{c}
\text{O} \\
\text{BnO} \\
\text{BnO} \\
\text{OMe}
\end{array} \\
\text{OH}
\]

(1)

\[
\begin{array}{c}
\text{OH} \\
\text{O} \\
\text{F}_3\text{C} \\
\text{R}
\end{array} \\
\text{F}_3\text{C}
\]

(2)

\[
\begin{array}{c}
\text{OH} \\
\text{O} \\
\text{F}_3\text{C} \\
\text{Me} \\
\text{Ar}
\end{array} \\
\text{F}_3\text{C}
\]

(3)

Complementary protocols can convert the ethyl hemiacetal of trifluoroacetaldehyde (2, R = Et) to either anti- or syn-4,4,4-trifluoro-1-aryl-3-hydroxy-2-methyl-1-butanones (3). Using an enamine, \(\text{trans-Me-CH=CN(Ar)NR}_1\text{R}_2\), anti-selectivity is achieved, whereas an imine, \(\text{Et-C(Ar)=NR}_3\) gives the syn-product. Conditions are mild (typically \(-15\) or \(-72\) °C), with the product being freed with 10% HCl in both cases. Examples with hydrate as reactant (i.e. 2 with R = H) and with CHF\(_2\) instead of CF\(_3\) are also reported.\(^2\) A chiral tetrazolyl pyrrolidine renders the reaction enantioselective.\(^3\)

A review examines neighbouring group participation involving the oxygen atom of \(O,O\)- or \(O,N\)-acetals.\(^4\)

2-(4-Substituted-phenyl)-1,3-dithiane anions (4, R = H, OMe, Cl, CN) have been reacted with alkyl iodides in dimethyl sulfoxide (DMSO). Evidence for an \(S_{\text{RN}1}\) process has been presented, via radicals and radical ions, the latter being susceptible to C–S bond fragmentation.\(^5\)

The formal alkyne Prins reaction of mixed \(N,S\)-acetals generated from homopropargylamines has been studied and compared to that of \(N,O\)-analognes. The cycloisomerization is catalysed by gold(I), with significant thioether participation in the mechanism, consistent with the thiophilicity of such gold species.\(^5\)

A BINOL-phosphoric acid catalyses addition of thiols to \(N\)-acylaldimines, giving \(N\)-acylated \(N,S\)-acetals (5) with yields and \(ee\) of up to 99%.\(^7\)
Reactions of Aldehydes and Ketones and their Derivatives

Reactions of Glucosides

An efficient, stereocontrolled synthesis of \( \alpha \)- or \( \beta \)-1-\( C \)-alkyl-imino-\( L \)-arabinols (6) depends on the nucleophilic addition of pentose-derived imines generated from enantiopure \( t \)-butanesulfinamide. The stereoselectivity of this key step can be controlled either by the sugar moiety or by the stereogenic sulfur centre.

Both anomers of the methyl glycoside (7) of 6-\( O \)-benzyl-\( N \)-dimethylmaleoyl-\( D \)-allosamine are glycosylated exclusively on \( O(3) \) when reacted with the trichloroacetimidate of peracetylated \( \alpha \)-\( D \)-galactopyranoside (8). A density functional theory (DFT) study has investigated the regioselectivity of both anomers, identifying strong hydrogen bonds in both reactions. The explanation of the regioselectivities achieved in this analysis proved transferable to related cases in the literature.

Product-based evidence for remote participation of a 4-\( O \)-acyl group in a gold(I)-catalysed glycosylation has been further probed by deuterium labelling studies. 2-\( C \)-Branched carbohydrates undergo mild glycosidations and selective anomerizations using gold(III) bromide catalysis. Acid–base-catalysed activation of a glycosyl donor, and activation of a glycosyl acceptor by \( \text{PhBF}_2 \) (or \( \text{Ph}_2\text{BF} \)), has been used to set up hydrogen-bond-mediated intramolecular S\(_N\)2-type glycosidation, typically with high anomeric selectivity. The use of stereoelectronic effects to determine oxocarbenium- versus \( \beta \)-sulphonium-ion-mediated glycosylations has been described.

The influence on reactivity and selectivity of having glycosyl donors in ‘unusual’ conformations has been reviewed (118 references), covering both glycosylation and glycoside hydrolysis. Examples involving conformations enforced by special protecting groups, tethering, anhydro-bridging, steric hindrance, and so on are described. The mechanism of chemical glycosylations has been reviewed (135 references), emphasizing evidence for and against oxocarbenium ions.

Evidence for a very short-lived oxocarbenium species in an enzymatic glycosyl transfer that proceeds with retention of configuration has been obtained via QM/MM
metadynamics simulations. Computational studies probing such intermediacy have examined the stability of the methoxymethyl cation in water: a simulation estimates its lifetime at 1 ps.

Mechanisms of glycosyltransferases have been reviewed. 1-β-O-Acyl glucoside conjugates of phenylacetic acids have been synthesized, and their acyl migration and hydrolysis kinetics have been compared with the corresponding acyl glucoronides.

The isomerization of glyceraldehyde [HOCH2CH(OH)CHO] to dihydroxyacetone at the surface of Lewis acidic zeolites has been studied theoretically, focusing on the rate-determining 1,2-hydride shift involved.

The mechanism of the entry of fructose into the Maillard reaction (a series of sugar/amino acid processes in vivo) has been studied by DFT: the order of reactivity for the isomers is predicted as α- > β- > open-chain. Heyns rearrangement products are most favourable under basic conditions, possible under neutral conditions, but unfeasible at or below glycine’s isoelectric point. Kinetic and activation parameters have been reported for the corresponding glucose/proline reaction.

A kinetic study of the reductive opening of the diphenylmethylen acetal in methyl 2,3-O-diphenylmethylene-α-l-rhamnopyranoside has been compared to earlier quantum calculations.

The 1,2-dicarbonyl sugar, 3-deoxy-d-erythro-hexos-2-ulose (9, 3-deoxy-d-glucosone) degrades to (salts of) the isomeric 3-deoxy-d-ribo- and -arabino-hexonic acids (10; 1:6 ratio) at pH 7.5/37°C, as shown by selective 13C- and 2H-labelling and 13C-NMR. Evidence for a 1,2-hydrogen shift mechanism is presented: DFT calculations suggest that the hydrogen moving from C(1) to C(2) is almost neutral (rather than hydridic). Mechanisms involving acyclic and cyclic routes are considered, with the experimental data fitting the latter better.

Kinetic studies of four monosaccharides locked in a 2,5-B-conformation as xyloside mimics (e.g. 11) indicate that they hydrolyse 10^2 to 10^4 times faster in acid than unlocked xylosides, and the α-anomers are much more reactive than the β-anomers. It is suggested that much of the energy penalty going from chair to TS has already been paid in such substrates.

Effects of neighbouring-group participation in the acid-catalysed hydrolysis of 2-O-substituted methyl glucopyranosides have been studied kinetically: ‘arming’
non-participating groups and ‘disarming’ (carbonyl-containing) ones show only modest differences.26

For more references to Glucosides, see section titled ‘Formation and Reactions of Acetals and Related Species’.

Reactions of Ketenes

Asymmetric Staudinger synthesis of β-lactams from an imine and a ketene has been studied computationally for the N-heterocyclic carbene (NHC)-catalysed reactions in the literature. Focusing on the stereoselective step of imine reacting with a zwitterionic NHC/ketene intermediate, qualitative agreement with the sense and magnitude of stereoselectivities has been obtained, such that the method has predictive value for future NHC selection.27 An experimental and theoretical investigation into stereoselective control for Staudinger cases using monosubstituted ketenes (with electron-acceptor substituents) reacting with cyclic and acyclic imines highlight the imine attacking the ketene from the exo-side to generate zwitterionic intermediates. For linear imines, these can isomerize and then undergo conrotatory ring closure. This isolates the key factors as the attacking direction of the imine and control of isomerization (where relevant).28

Ynamides, \( \text{R}^1-\text{C}≡\text{C-N(R}^2)\)-EWG, undergo an unprecedented dimerization in the presence of a gold(I) complex, ultimately yielding a cyclopentadiene (12, for the example of \( \text{R}^1=\text{Bn, R}^2=\text{Hexyl, EWG=Ts} \)), via a keteniminium intermediate (13). This [3+2] cyclodimerization occurs in 98% yield at 40°C in 30 min. While the alkynophilic nature of gold is well known, the reaction is noteworthy for one ynamide partner playing a nucleophilic role, and the other electrophilic.29

\[
\text{Ts} \quad \text{Bn} \\
\text{C}_6\text{H}_{13} \quad \text{Bn} \\
\text{N} \quad \text{C}_5\text{H}_{11} \quad \text{N} \\
\text{Ts} \quad \text{R}^1 \quad \text{Au} \\
\text{N}^+ \quad \text{EWG} \\
\text{R}^1 \quad \text{R}^2
\]

(12) \hspace{1cm} (13)

For more references to Ketenes, see section titled ‘Other Oxidation Reactions’.

Formation and Reactions of Nitrogen Derivatives

Imines: Synthesis, and General and Iminium Chemistry

\( \text{N} \)-Chloroamines (e.g. 14), on treatment with strong bases such as potassium \( t \)-butoxide or lithium diisopropylamide (LDA), give 2-aza-allyl anions (15) that can undergo \( \pi 4s + \pi 2s \) cycloadditions with alkenes to give pyrrolidines. Imines can also be accessed by dehydrochlorination of (14), under modified conditions.30

Taking imine activation as an example, the relative roles of proton transfer/ion-pairing versus hydrogen bonding have been probed for Brønsted acid catalysis. Taking simple diaryl ketimines and aldmines as model substrates and
diphenylphosphate as acid, $^1$H–$^{15}$N magnetization transfer NMR studies facilitate the study of the acid–imine complexes, and the relative proportions of the OH···N and O···HN forms of these complexes and the relative hydrogen-bond strengths.\(^{31}\)

Iminium activation in catalytic enantioselective conjugate additions has been reviewed.\(^{32}\) A major review examines the development of catalytic enantioselective formation of C–C bonds by addition of imines and hydrazones, over the past 10 years (493 references).\(^{33}\)

C,N-Cyclic azomethine imines undergo an inverse-electron-demand 1,3-cycloaddition with electron-rich alkenes: using a BINOL-derived diacid catalyst, excellent chemo- and enantio-selectivities have been reported.\(^{34}\) Asymmetric alkylation of cyclic azomethine imines has been carried out using copper(I) and a chiral Brønsted acid as catalysts.\(^{35}\)

The Mannich reaction and its variants have been reviewed, mainly focussing on asymmetric catalysis thereof.\(^{36}\) Catalytic, enantioselective, vinylogous Mannich reactions have also been reviewed, covering both direct and silyl dienolate methods.\(^{37}\) Another review surveys Mannich-type reactions of nitrones, oximes, and hydrazones.\(^{38}\)

A pyrrolidine-thiourea-tertiary amine catalyses asymmetric Mannich reaction of N-Boc-imines (e.g. Ph-\(\text{CH}=\text{N-Boc}\)) with ethyl-4-chloro-3-oxobutanoate to give highly functionalized product (16). Addition of triethylamine leads to one-pot intramolecular cyclization to give an O-ethyl tetronic acid derivative (17).\(^{39}\)

Simple disubstituted pyrrolidines (18) have proved to be excellent catalysts for anti-Mannich reactions of aldehydes and glyoxylate imines, \(\text{para-MeO-C}_6\text{H}_4\text{-N}=\text{CH-CO}_2\text{Et}\), giving yield/de/ee performance up to 90/92/99\% at 0°C, with comparable results for ketones; (18) is a neat modular species, providing aminocatalysis via the NH, a hydrogen-bond-donor directing group (the triflamide), and an ethereal site for steric tuning of catalysis.\(^{40}\)

4-Piperidones (19) have been prepared from ketones (MeCOCH₂R) and aromatic imines (\(\text{Ar}^1\text{-N}=\text{CHAR}^2\)) via a double Mannich reaction and tandem cyclization. The I₂-induced room temperature reaction is highly stereoselective, giving only one of four possible isomers. Chelation and hydrogen-bonding effects have been invoked to explain the specificity.\(^{41}\)
A three-component Mannich-type reaction of a diazo compound, Ph-C(=N₂)-CO₂Me, a carbamate, BnO₂CNH₂, and an imine, PhCH=NPh, gives access to both syn- and anti-α,β-diamino acid derivatives (20). Co-catalysed by Rh₂(OAc)₄ and BINAP-derived phosphoric acids, the reaction involves diastereoselectively switchable enantioselective trapping of proton carbamate ammonium ylide intermediates. High levels of chemo-, diastereo-, and enantio-selectivities were achieved.

cis-2-Aminocyclopropanols (21, in N,O-diprotected form) have been prepared in high de by reaction of N-t-butylsulfinyl ketimines [Ar¹-C(Me)=N-SO-Bu-t] and aryl acylsilanes (Ar²-COSiR₃), via a Brook rearrangement/Mannich reaction.

A wide-ranging enantio- and diastereo-selective reaction of imines and aldehydes gives anti-Mannich product. For example, PhCH₂CH₂CH=NTs reacts in brine with both aliphatic and aromatic aldehydes. A simple diaryl prolinol TMS ether serves as chiral catalyst; N-nosyl imines can also be employed.

A chiral diphosphinyl ferrocene, together with copper(I), catalyses enantioselective addition of Grignards to cyclic enones, giving chiral magnesium enolates. These in turn can be added to N-protected imines directly or through in situ transformation to silyl enol ethers. This Mannich reaction of chiral enolates is diastereoselective.

α-Fluoro-β-ketoesters undergo Mannich reaction with N-Boc-aldimines in up to 99% ee, giving the β-aminated derivatives, using chiral palladium complexes.

DFT has been used to probe the effects on stereoselectivity of an α-amino acid catalyst on a Mannich reaction of cyclohexanone and a β-amino acid catalyst as well.

The asymmetric vinylogous Mannich has been reviewed.

Aromatic aldmines undergo asymmetric vinylogous Mannich reactions with α-angelica lactone (22), using a chiral N,N'-dioxide liganded to scandium(III).

Malonic acid half thioesters, RSOC₂H₂-CO₂H, undergo decarboxylative Mannich reactions with N-tosylaldimines enantioselectively, using a chiral bicyclic guanidine catalyst. Nucleophilic addition is proposed to precede decarboxylation, support by MS and DFT evidence.

A typical Petasis-type boronic Mannich reaction involving a styryl boronic acid, dibenzylamine, and α-hydroxypropanal has been probed mechanistically by DFT and appears to involve intramolecular transfer of the styryl group.

A review of the aza-Diels–Alder reaction suggests that it proceeds via the Mannich–Michael process, as against a concerted mechanism, when using electron-rich dienes. Mannich intermediates being observed is the main argument. Progress in metallo- and organo-catalysis of the transformation is also described.
Stereoselective ‘Name’ Reactions of Imines

The asymmetric Strecker reaction has been reviewed (142 references). In an asymmetric Strecker addition of TMSCN (trimethylsilyl cyanide) to ketimines, PhC(R)=N-PMP (PMP, para-methoxyphenyl), using a chiral urea organocatalyst, the ee is 94% when R = CF3. Changing to a CHF2 group, it drops slightly to 87%. However, for R = CH3, no ee is seen. Yield is unrelated, being 97, 73, and 97% respectively, although the methyl case reacted slower. A hydrogen bond between fluorine and one of the catalyst’s urea NH’s is proposed.

Amine-functionalized tridentate sulfynyl ligands catalyse aza-Henry reactions in high yield and ee. Chiral fluoroalkyl α,β-unsaturated N-t-butanesulfinyl ketimines undergo aza-Henry reaction with nitromethane with yield/de up to 98/90%, using potassium carbonate as base, at room temperature. New bifunctional thiourea glucosamines catalyse nucleophilic additions to nitroolefins, and to imines, in good ee.

While the electrophilic nature of cyclic N-sulfonylimines (e.g. saccharin derivatives, 23) has been applied in Mannich and other processes, their first use as direct nucleophiles in an asymmetric Michael addition to α,β-unsaturated aldehydes has now been reported. Using diaryl prolinols or their silyl ethers as catalysts, ees up to 99% were obtained.

A phosphine sulfonamide derived from l-threonine promotes aza-Morita–Baylis–Hillman (aza-MBH) reactions of sulfynylimines in up to 96% yield and 97% ee. A review describes the synthesis of chiral amines under mild conditions via catalytic asymmetric aza-MBH reactions. Proline/DABCO (1,4-diazabicyclo[2.2.2]octane) co-catalysis of enantioselective aza-MBH reactions gives good to high yields and up to 99% ee.

A mass spectrometry technique – ESI(+)-MS/(MS) – has been used to probe solution-phase DABCO-catalysed aza-MBH reactions of N-sulfonylimine (24) with methyl acrylate to give aza-adduct (25). A unique bis-sulfonamide intermediate (26) was intercepted, which – if central to the process – requires a revision of the generally accepted mechanism. A new mechanistic proposal does fit better with some features of aza-MBH reactions.

A spiro-organocatalyst (27) bearing convergent Brønsted acid and Lewis base moieties catalyses aza-MBH reaction of α,β-unsaturated ketones with N-tosyl benzaldimines at sub-zero temperatures. A highly chemo- and diastereoselective three-component reaction of an imine, alkyl vinyl ketone, and imide is catalysed by triphenylphosphine. The first two reactants are
Reactions of Aldehydes and Ketones and their Derivatives

combined via an aza-BH process, followed by Michael addition of phthalimide (or succinimide).\textsuperscript{64}

A diastereoselective [4+1]-annulation of phthalaldehyde and an N-Boc-imine gives a \textit{cis}-2-amino-3-hydroxyindanone (28). Catalysed by simple thiazolium NHCs, the process may involve a tandem aza-benzoin/aldol.\textsuperscript{65}

\textit{Synthesis of Aziridines from Imines}

\textit{N}-Acyl imines undergo enantioselective aza-Darzens reaction with 3-chloropentadione to give highly functionalized aziridines (29), with a vaulted biphenanthrol (VAPOL) magnesium phosphate catalyst.\textsuperscript{66} \textit{N}-\textit{t}-Butanesulfinimines, R\textsubscript{1}R\textsubscript{2}CH=\text{N-SO-}\textit{Bu}-\textit{t}, undergo high-yielding aza-Darzens reactions with ethyl bromoacetate, giving aziridines with \textit{de} typically >98%. The imines can be derived from aldehydes or ketones.\textsuperscript{67}

\textit{N}-Boc imines are sufficiently activated to react with both \textit{\alpha}-diazo esters and \textit{\alpha}-diazo-\textit{N}-acyl oxazolidinones to give trisubstituted aziridines with high yield, \textit{de}, and \textit{ee}.\textsuperscript{68}

DFT has been used to study the copper(I)-catalysed aziridination of imines by diazoacetate.\textsuperscript{69}
Arsenic ylides, $R^1R^2C^-\text{As}^+\text{Me}_3$, react with functionalized imines (e.g. aldimine ester, MeCH=$\text{N}CO_2\text{Me}$) to give the corresponding aziridines. Analogous to the corresponding phosphorus ylides, unstabilized, semistabilized, and stabilized versions can be employed, using $R^1 = \text{H}$, Ph, or COMe, respectively, with the latter two giving trans-selectivity. DFT studies reveal weak C-H···O hydrogen-bonding interactions and steric effects that may control the selectivity of this ‘arsena-aza-Wittig’-type process.\textsuperscript{70}

A DFT study has probed the mechanism of aziridination of benzaldehyde by a guanidinium ylide (30) to give 2,3-disubstituted $N$-benzyl-protected aziridines (31). The reaction involves initial addition to give oxaspirocyclic intermediate (32), which fragments. A more detailed study of $p$-substituted benzaldehydes looked at four transition states for different facial approaches, leading to Hammett plots of $(\Delta G^\ddagger_{\text{H}} - \Delta G^\ddagger_{\text{X}})$ versus $\sigma_X$ with $\rho$ values in the range 4–5.\textsuperscript{71}

\begin{center}
\begin{align*}
\text{Bu}^\prime\text{CO}_2 & \quad \text{PhCHO} \\
\text{Bn} & \quad \text{N}^+ \\
(30) & \quad \text{Ph} \\
\text{Bu}^\prime\text{CO}_2 & \quad \text{Bn} \\
\text{N} & \quad \text{N} \\
(32) & \quad \text{N} \\
\text{Bu}^\prime\text{CO}_2 & \quad \text{Ph} \\
(31)
\end{align*}
\end{center}

A multi-component catalytic asymmetric aziridination of aldehydes employs a protected amine and ethyl diazoacetate as reactants and an $(S)$-VAPOL boroxinate catalyst, giving aziridine-2-carboxylic esters in up to 99% ee. It works for some cases where preformed imines failed.\textsuperscript{72}

Stereoselective epoxidation and aziridination of carbonyl groups and imines have been reviewed.\textsuperscript{73}

**Addition of Organometallics**

\textit{P-Chirogenic phosphinoylimines} (33) have been synthesized and undergo diastereoselective addition of Grignards.\textsuperscript{74}

\begin{center}
\begin{align*}
\text{R} & \quad \text{P} \\
(33) & \quad \text{R} \\
\text{Bu}^\prime & \quad \text{S} \\
(34)
\end{align*}
\end{center}

Organometallics have been added diastereoselectively to $N$-(\textbf{t}-butanesulfinyl)-$\alpha$-fluorenimines (34) to give the corresponding amines. The sense of diastereoselection can be switched by changing the organometallic from a Grignard to an organozincate.\textsuperscript{75}
Aryl Grignards add to chiral N-alkyl (or N-aryl) benzenesulfinylimines, PhCH=NSOR/PhCH=NSOAr, in high yield and de, to give chiral diaryl amines (in protected sulfinyl form). A comparative study of the use of the familiar t-butane or p-toluene groups at sulfur with 2,4,6-triisopropylbenzene finds that the latter is significantly superior in yield and de and that results are somewhat better at room temperature versus $-40^\circ$C.76

A rhodium(I) catalyst has been used to directly add aryl C–H to the C=N bond of an N-sulfonyl aryl aldimine. Such hydrocarbon activation avoids the drawbacks of the Grignard alternative (i.e. need for organohalide and magnesium) or the related directed ortho metalation protocol.77 Benzyl zinc reagents have been added to N-t-butanesulfinyl imines to give the corresponding protected amines with yields and de up to 98%. The Knockel-type addition is enhanced by magnesium chloride.78

Enantioselective Alkylations and Additions of Other C-nucleophiles to Imines

Enantioselective addition of C-nucleophiles to imines and hydrazones has been reviewed (1998–2009),79 another review describes the synthesis of α-branched amines by nucleophilic addition of unstabilized carbanions, including application in stereoselective reactions.80

Imine reactions catalysed by BINOL-phosphoric acids have been modelled, using DFT calculations; the model can predict the correct enantioselectivity for a wide range of reactions in the literature, based on the E/Z preference of the transition state, and the catalyst-nucleophile orientation.81

Mono-fluorobenzyl carbanions can be stabilized by an ortho-sulfinyl group (35), which, if homochiral, reacts with N-p-tolylsulfinylimines (36) with complete stereoselectivity. The sulfinyl auxiliaries can then be removed with t-butyllithium without benzylic epimerization, giving enantiopure β-fluoro-β-phenethylamines (37).82

A short review examines nucleophilic trifluoromethylation of C=N bonds: imines, hydrazones, and nitrones, together with iminium cations and azomethine imines, mainly focusing on the Ruppert–Prakash reagent, TMS-CF$_3$.83

Enantiomerically pure syn-1,2-diaryl-1,2-sulfonylamines have been prepared by the addition of a benzyl carbanion, (S)-o-(tolysulfinyl)-PhCH$^-\text{-SMe}$, to N-aryl arylide-amine:es the ‘remote’ sulfinyl group controls the stereoselectivity (de and ee typically >98%) and can be removed afterwads from the product using t-butyllithium.84

Lithium enolates of ketones have been added to a sulfinylimine, F$_3$C-CH=NSO-Bu-t, in high yields and with de often >98%, to give β-trifluoromethylated β-amino
ketones. The reaction is readily scaled, and mild acid treatment yields the free amine if required.85

New chiral phosphorus-olefin bidentate ligands give high ees in the rhodium-catalysed addition of organoboroxines to N-sulfonylimines to give α-substituted amines.86

Arylations, Alkenylations, and Allylations of Imines

Imines of benzaldehyde that have been protected (or activated) with diarylphosphinyl groups, Ph-CH=NP(=O)Ar2, are enantioselectively arylated by aryl boronic acids, using rhodium(I) liganded with a chiral amidophosphane.87 The effects of varying the bulk of the aryl substituents on the phosphorus of the substrate are complex: ee is not severely impacted (indeed, it is sometimes improved), but reactivity falls, but so also does competing hydrolysis of the imine.

Rhodium–diene complexes catalyse highly enantioselective arylation of aliphatic N-tosyl- (or N-nosyl)-aldimines, using arylboronic acids.88 Activated N-t-butanesulfinyl ketimines have been arylated by rhodium-catalysed addition of arylboroxines.89

A rhodium(I) chloride with chiral diene ligands catalyses addition of potassium organotrifluoroborates (K+ ArBF3−) to N-sulfonyl ketimines, effecting C-arylation in good to excellent yields, and ee’s up to 99.5%.90

N-Sulfinyl aldimes undergo Friedel–Crafts reaction with indoles in up to 99% ee, using a copper(II)-bis(oxazoline) catalyst.91 An organocatalytic asymmetric aza-Friedel–Crafts alkylation of naphthols with N-sulfonylimines has been developed, giving yields and ees up to 99%.92

Enantioselective addition of metal alkynylides to imines has been reviewed.93

Electron-deficient alkenes have been prepared by stereoselective olefination of N-sulfonyl imines with stabilized phosphonium ylides. Nitrile stabilization of the ylide leads to α,β-unsaturated nitrile products with Z selectivity, whereas ester-, amide-, and ketone-stabilized substrates give E products. The selectivity is suggested to arise from the different rates at which the diastereomeric betaine intermediates form the corresponding 1,2-azaphosphetanes, supported by NMR and MS studies.94

α-Carbanions of imines have been applied as nucleophiles in palladium-catalysed allylic alkylations. Base and counterion effects have been exploited to tune the chemo- and regio-selectivities of these processes, including branched versus linear products.95

Homoallylamides have been prepared enantioselectively by adding stable accessible (pinacolato)allylborons to N-phosphinoylimines; the latter can be aryl-, heteroaryl-, alkyl-, or alkenyl-substituted. Chiral NHC-copper(I) catalysts give ees up to 97%.96 N-Acyl aldimes undergo Hosomi–Sakurai addition of allyltrimethylsilane in up to 98% ee, using chiral Brønsted acid catalysis. syn-Diastereoselective crotylations are also reported.97

The imine-ene reaction has been studied by DFT for the model case of methanimine, H2C=NH, and propene; a wide range of catalyses by Lewis acids are covered.98
Reduction of Imines

Catalytic asymmetric hydrogenation of C=N functions has been reviewed,\(^9\) as has asymmetric transfer hydrogenation, covering the principal types of catalyst, as well as hydrogen sources.\(^1\) Although turnover frequencies for organocatalysts are still lower than metal systems, the other advantages of the former are described. Other reviews include enantio- and diastereo-selective reduction including cases involving in situ imine generation,\(^2\) and an account of asymmetric direct and transfer hydrogenation focusing on substrate structure, identifying difficult substrate classes, and relevant catalytic cycles.\(^3\)

Aromatic ketimines are reduced enantioselectively to amines (50 atm \(H_2/toluene/65\,^\circ\)C/24 h), using a cooperative catalysis involving Knolker’s iron complex and a BINOL-derived hydrogen phosphate auxiliary, with \(^{31}\)P-NMR evidence supporting the bifunctional catalysis.\(^4\) A phosphine-free chiral cationic ruthenium complex catalyses enantioselective hydrogenation of \(N\)-alkyl ketimines, including many heretofore problematic substrates.\(^5\)

\(\text{o-Hydroxybenzophenone imines (38), easily formed from benzophenones in ammonia-saturated methanol, can be reduced enantioselectively using a chiral binaphthyl phosphoric acid and a Hantzsch ester as reductant.}\(^6\)

\[
\begin{align*}
\text{O}^+ H & \quad \text{N}^- H \\
R^1 & \quad \text{N} \quad R^2
\end{align*}
\]

(38)

Evidence for low-valent and trimeric titanium alkoxide species in the reaction of phenylsilane and titanium(IV) isopropoxide has been obtained from NMR, MS, and DFT studies and has been used to interpret the results in the use of these reagents for diastereoselective coupling of imines. Coupling of, for example, \(N\)-benzylideneaniline gives exclusively the (±)-diamine product, with no meso-isomer. A trimeric biradical intermediate is proposed.\(^7\)

Other Reactions of Imines

Salicyl \(N\)-thiophosphinyl imines (39) undergo novel domino annulations with certain sulfur ylides (40, \(R^2 = \text{CO}_2R/\text{COR}/\text{CH}=\text{CHCO}_2H, R^3 \text{typically} = \text{H}\)) to give highly substituted \(\text{trans-2,3-dihydrobenzofurans (41)}\) in high yield and \(de\).\(^8\) After formation of the N-C bond, an otherwise likely kinetic preference for aziridine formation is suppressed by steric hindrance.
The kinetics of hydrolysis of 1,1-bis(1H-imidazol-1-yl)methanimine and its methyl derivatives have been studied.\textsuperscript{108} The rates of hydrolysis of several pyridyl imines have been measured in buffered aqueous methanol.\textsuperscript{109}

Aldimines (R<sub>1</sub>-CH=NR<sub>2</sub>) have been phosphinated with diphenylphosphine oxide to give α-amino phosphine oxides (42) in up to 99% ee, using a chiral magnesium phosphate catalyst.\textsuperscript{110,111}

An \textit{ab initio} and DFT study has examined the mechanisms of and interactions present in radical additions of imidoyl and thioyl radicals to methanimine, H<sub>2</sub>C=NH.\textsuperscript{112}

Sugar-derived imines have been converted to β-lactams via a diastereoselective reaction with bromoesters mediated by indium and sonication.\textsuperscript{113}

For more references to Imines, see sections titled ‘Formation and Reactions of Acetals and Related Species’, ‘Reactions of Glucosides’, ‘Reactions of Ketenes’, and ‘Other Oxidation Reactions’.

**Oximes, Hydrazones, and Related Species**

Kinetics of the synthesis and aminolysis of 2,4-dinitrophenyl and 5-nitropyridine N-hydroxy oxime derivatives have been studied spectrophotometrically in acetonitrile.\textsuperscript{114}

The reaction of several cholesterol-related oximes with 2-chloroethylamine in the presence of methoxide ion gives the corresponding oxime ethers; DFT calculations indicate an oximate anion intermediate.\textsuperscript{115}

O-Vinyl- and O-allyl-oximes have been rearranged to pyrrole derivatives.\textsuperscript{116}

Several nitrile-forming eliminations are described: eliminations from (E)-2,4,6-trinitro-benzaldehyde O-benzoyloximes promoted by secondary alcohols in acetonitrile proceed via an irreversible (E1cb) mechanism, whereas the 2,4-dinitro case involves E2. The mechanistic switch is associated with a 470-fold rate increase and underlines the carbanion-stabilizing ability of the 2,4,6-trinitrophenyl group in aprotic solvent.\textsuperscript{117}

A related review of mechanistic studies on base-promoted elimination from (E)- and (Z)-arylaldehyde O-benzoyloximes has examined solvent and base effects, stereochemistry, and variations in the β-aryl group.\textsuperscript{118} A kinetic study of elimination of nitrile from (E)-2,4,6-trinitrobenzaldehyde O-pivaloyloxime has been carried out in acetonitrile, with catalysis by secondary amines.\textsuperscript{119} An ionic liquid with Lewis acid sites in both anion and cation catalyses dehydration of aldoximes to give nitriles.\textsuperscript{120}

Hypervalent iodine reagents such as diacetoxyiodobenzene [Ph-I(OAc)<sub>2</sub>] oxidize α-oxo-aldoximes to α-oxo-nitrile oxides, whereas the corresponding ketoximes give nitrile oxides via oxidative cleavage of the carbonyl-imino σ bond.\textsuperscript{121}
Benzyl phenyl ketone oxime reacts with acetylene in superbasis (DMSO/KOH/130 °C) to give \( N \)-benzyl benzamide and \( N \)-vinyl-2,3-diphenylpyrrole, plus benzoic acid, via azirines and aziridine intermediates.\(^{122}\)

Beckmann rearrangement of oximes to amides can deviate to fragmentation to form nitriles and carbocations, if the latter possess reasonable stability. Both 1-substituted-phenyl-2-propanones and 3-substituted-phenyl-2-butanones in aqueous solvents give both products, and calculations have been used to probe the mechanisms. In borderline cases, a dynamic path bifurcation from a single transition state is claimed.\(^{123}\)

Kinetic evidence for such a dynamic path bifurcation in the mechanism of the Beckmann rearrangement has also been presented for reactions of oxime sulfonates (43, \( R^1/R^2 = H/Me \)). In addition to the rearrangement product (amide), these substrates can also fragment (to alcohols), with the bifurcation in the mechanism apparently occurring after the rate-determining transition state.\(^{124}\)

\[
\begin{align*}
\text{(43)} & \\
\begin{array}{c}
\text{R}^1 \\
\text{R}^2 \\
\text{X} \\
\text{NOSO}_2\text{Ar}
\end{array} & \\
\text{Pr} & \\
\text{P} & \\
\text{O} & \\
\text{O} & \\
\text{PO} & \\
\text{Pr}
\end{align*}
\]

Propylphosphonic anhydride (44, “T3P”\(^{\circledR} \)) catalyses Beckmann rearrangements: ketoximes give amides (84–95% yield) and aldoximes give nitriles (87–99%).\(^{125}\)

A complex of pivaloyl chloride (Me\(_2\)C-CO-Cl) and DMF quickly converts ketoximes to amides/lactams at room temperature. The complex is proposed to be of the Vilsmeier–Haack-type, that is, Cl-Me\(_2\)\(^+\)\(\text{N}=\text{CH}-\text{O}_2\text{C}-\text{Bu}-t \), in equilibrium with a cation, Me\(_2\)\(^+\)\(\text{N}=\text{CH}-\text{Cl} \), which reacts with the oxime.\(^{126}\)

Neutral solutions of gold(III) bromide catalyse transoximations at ambient temperature: the reaction is so mild that \( \alpha \)-stereocentres are unepimerized, and most functional or protecting groups are unaffected, and reactions such as Beckmann or dehydration do not occur. Free gold(III) is essential, as the formation of gold nanoparticles (so useful for other chemistries) inactivates the metal. For deoximation, a protocol with diacetyl provides a cheap oxime acceptor.\(^{127}\)

The rates of deoximation of oximes using cetyltrimethylammonium dichromate in the presence of acetic acid and a cationic surfactant is sensitive to the concentrations of all four substances; substituent effects are also reported. The oxidant preferentially oxidizes oxime over hydroxyl groups.\(^{128}\)

2-Mercaptobenzoylhydrazones of aryl aldehydes, 2-HS-C\(_6\)H\(_4\)-CONHN=CH-C\(_6\)H\(_4\)-X (X = 3- or 4-substituent), exist as \( E/Z \) isomers in DMSO and also tautomerize to cyclic benzo-1,3,4-thiadiazepines; log\(K_T\) correlates with \( \sigma_X \).\(^{129}\)

A method for asymmetric \( \alpha,\alpha \)-bisalkylation of a ketone having both \( \alpha \)- and \( \alpha' \)-protons has been described. For the example of acetone, a chiral \( N \)-amino cyclic carbonate hydrazone derivative (45) is treated sequentially with two alkylation agents;
subsequent acid hydrolysis gives the bisalkylated ketone (46) in up to 98% ee. The process involves complex-induced syn-deprotonation, with the attacking amide nitrogen coordinated to a lithium being steered by the lithium that further coordinates to the carbonyl oxygen, reversing LDA’s normal preference of removing the less hindered of two protons of similar acidity.130

As formaldehyde hydrazones are particularly stable towards hydrolysis or polymerization, they can be used in water, a solvent that enhances the reactivity of the azomethine carbon for nucleophilic addition to α-keto esters, to give highly functionalized tertiary alcohols. A significant solvent isotope effect points to the active participation of water as an acid catalyst.131

DFT calculations have probed electronic effects in the reaction of 2-arylhydrazono acetic acid with pyruvic acid to give (2Z)- and (2E)-3-aryl acrylic acids.132

Rearrangement of 11 (Z)-arylhydrazones of 5-amino-3-benzoyl-1,2,4-oxadiazole to give 2-aryl-5-phenyl-(2H-triazol-4-yl)ureas has been studied in toluene, with catalysis by TFA or piperidine, and compared to earlier results in more polar media.133,134

The kinetics of the aceto phenone-phenylhydrazone reaction has been studied for a variety of solvents and ketone ring substituents.135

N-Tosylhydrazones, R1R2C=NNHTs, undergo a palladium-catalysed amidation with isocyanides (CN-R3) via a ketenimine intermediate in the presence of water. This allows access to amides, R1R2HC-CONHR3, from carbonyl compounds via a one-carbon extension.136

Conjugated enynes have been accessed by palladium-catalysed oxidative cross coupling of N-tosylhydrazones (or diazoesters) with terminal alkynes, via an unusual alkynyl migratory insertion of a palladium carbene; Z enynes are generally favoured.137

Iron(III) catalyses a green decomposition of sulfonylhydrazones, Ar(R)C=NNHTs, to give sulfones, ArCH(R)-SO2-Ar, in refluxing dioxane in the presence of base, with only water and nitrogen as by-products.138

Acylhydrazones, R1CH=N-NHCOR2, undergo stereoselective Mannich reactions with silyl ketene acetics to give β-hydrazido esters, using activation by a chiral silicon Lewis acid. Alternatively, the use of silyl ketene imine gives a β-hydrazido nitrile.139

Enantioselective (S)-1-amino-2-methoxymethylpyrrolidine (SAMP) hydrazone alkylation of aldehydes and ketones is the subject of a computational study, providing a useful screening method for possible new candidates.140
C–C Bond Formation and Fission: Aldol and Related Reactions

Reviews of Aldols and General Reviews of Asymmetric Catalysis

General reviews include the direct aldol,141 aldol and related processes,142 the Zimmerman–Traxler TS model used to explain the stereochemistry of the aldol condensation,143 catalysis of direct asymmetric aldols by prolinamides versus prolinethioamides,144 the catalytic asymmetric aldol reaction in aqueous media (considering both organometallic and organocatalytic approaches),145 the use of BINAP oxide in enantioselective direct aldols,146 and the use of metal enolates as synthons.147

Wider reviews include advances in acyclic stereocontrol148 and mechanisms of aminocatalysis focusing mainly on α-, β-, and γ-functionalizations of aldehydes and reactions of α,β-unsaturated aldehydes, catalysed by secondary amines.149

The use of NHC catalysts to generate homoenolates for C–C bond formation has been reviewed (56 references), including enantioselective cases.150

N-Triflyl phosphoramides derived from BINOL are highly acidic chiral Brønsted acids, and they are powerful catalysts for enantioselective C–C and C–X bond-forming reactions. Their design, structural features, and applications since their development in 2006 have been reviewed.151

The use of C₂-symmetric N,N′-dioxide amides in a wide variety of chiral ligand-/metal-catalysed or organocatalysed asymmetric reactions has been reviewed.152

Other reviews include chiral spiro catalysts153 and the organic and carbohydrate chemistry relevant to biomass.154

Asymmetric Aldols Catalysed by Proline and its Derivatives

The direct proline-catalysed aldol in the presence of water has been screened with water-compatible Lewis acid cocatalysts. Chlorides of zinc’s group proved best, and the optimized formation of anti-products in >99% ee was obtained with L-proline/ZnCl₂ in 4:1 DMSO/water.155 Adding cobalt(II) chloride as a co-catalyst to L-proline-promoted direct aldols substantially improves selectivity, giving yield/de/ee up to 93/96/99%. Cobalt(II) is proposed to preorganize two prolines.156

A rare chemo- and stereo-selective cross-aldol between aliphatic aldehydes, catalysed by proline and an axially chiral amino sulfonamide, links a simple aldehyde with an α-chloroaldehyde: the chemoselectivity arises from the steric instability of the enamine derived from the haloaldehyde.157

Simple N-proline-based dipeptides catalyse direct aldols of aldehydes with a wide range of ketones, giving yield/de/ee up to 99/>98 (syn)/97%, at room temperature in brine, with 2,4-dinitrophenol as co-catalyst.158 A simple organocatalyst, the methyl ester of (S)-proline-(S)-phenylalanine, promotes high-yielding aldols with up to 95% ee and 82% de (anti-) under solvent-free conditions at −20°C. Lack of solvent should maximize substrate–catalyst noncovalent interactions.159
In model aldol reactions, yield/de/ee performance of up to 100/94/97% has been achieved using prolinamide-thiourea catalysts in toluene at −20 °C.\(^\text{160}\) Chiral prolinamide-thioureas catalyse direct aldols in high yield/de/ee.\(^\text{161}\)

New \(\text{L}\)-prolinamide derivatives [47, \(X = \text{C}=\text{O}\) or \(\text{S}(=\text{O})_2\)] efficiently catalyse aldols in water (\text{anti/syn} = 97/3; \(ee\) up to 99%) and are easily recycled.\(^\text{162}\)

![Chemical Structures](images)

Prolinamides bearing 2-hydroxy-3-aminopinane units catalyse aldols of cyclic ketones with aromatic aldehydes in good yield/de/ee.\(^\text{163}\)

A simple trifunctional \(\text{L}\)-prolinamide (48) based on 8-aminoquinoline catalyses enantioselective aldols of aromatic and aliphatic aldehydes with acetone.\(^\text{164}\) \(\text{L}\)-Proline-anilide (49) is a simple and cheap organocatalyst of direct aldols, giving yield/de/ee up to 99/98/99% in large-scale reactions, and is readily recoverable and reusable.\(^\text{165}\)

Proline anthranilamide-based pseudopeptides act as bifunctional catalysts for direct aldols, giving good yields and de/ee up to 99/96%.\(^\text{166}\)

Zinc(II) increases the rate and stereoselectivity of the \(\text{L}\)-prolinamide-catalysed aldol reaction of acetone and \(p\)-nitrobenzaldehyde. An NMR and ESI-MS study suggests that zinc, as well as having an accelerative effect, also inhibits the non-stereospecific base-catalysed reaction by reducing the basicity of prolinamide nitrogen.\(^\text{167}\)

Screening of a range of modified prolines (mainly bearing sulfur functionality) as catalysts for the aldol of acetone and araldehyde has identified \(N\)-sulfinyl amide (50) as giving yields/\(ee\) up to 82/95%, substantially better than proline for this class of reaction.\(^\text{168}\)