CHAPTER 1

Reactions of Aldehydes and Ketones and their Derivatives

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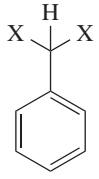
Formation and Reactions of Acetals and Related Species

Benzyl-*gem*-diacetate (**1**, X = OAc) is remarkably water stable: it does not solvolyse in water at 25 °C over a year. In contrast, its diazide and dihalide analogues (**1**, X = N_3, Cl, Br) spontaneously cleave in an S_N1 process to give benzaldehyde (via an α-azido or α-halo benzyl carbocation). Reasons put forward for this stability include (i) C−O bond energy, (ii) nucleophilicity, (iii) anion hydration energy, and (iv) geminal and hydrogen-bonding effects in the diacetate.[1]



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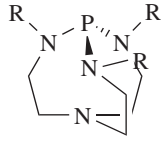


(**2**)

A proazaphosphatrane (**2**, R = *i*-Pr) catalyses the addition of TMS-1,3-dithiane to aldehydes.[2]

Reversible nucleophilic addition of secondary alcohols to ketones to form hemiacetals has been achieved by *in situ* binding of neighbouring Brønsted and Lewis acid activators. The strategy holds promise for molecular recognition of alcohols, and UV–vis monitoring of the process suggests a basis for optical sensors of alcohols.[3]

The mechanism of the acid-catalysed cyclization of 4-hydroxybutanal to yield the hemiacetal, 2-hydroxy-THF (tetrahydrofuran), has been studied via B3LYP calculations for the gas phase, and for water solvent (using a polarized continuum model). Un- and proton-catalysed reactions are highly energetic, while routes involving hydronium and hydronium-plus-water are comparably low in energy. A water-catalysed route is also quite accessible.[4]

Synthesis and applications of chiral dithioacetal derivatives have been reviewed in a chapter of *Organosulfur Chemistry in Asymmetric Synthesis*.[5] Another review deals (*de*) with the deprotection of acetals under mild and neutral conditions, in particular the (*ee*) selective deprotection of those derived from aldehydes (as against ketones).[6]

Weakly basic carbon nucleophiles have been added to Fmoc-protected acyl iminium ions. Starting from an Fmoc-protected *N*,*O*-acetal (AcO−CH_2−NHFmoc), a Lewis acid generates the iminium ion ($H_2C{=}NH^+$−Fmoc), and then addition of the nucleophile yields the product (Nu−CH_2−NHFmoc). The combination of mild Lewis acids [e.g. zinc(II) chloride] and weak *C*-nucleophiles prevents the loss of Fmoc protection.[7]

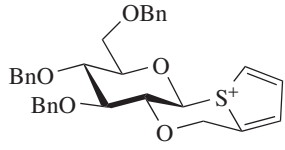
A self-assembled supramolecular host catalyses acetal hydrolysis in *basic* solution, giving accelerations of up to 980 over the background rate. Initial binding of the acetal substrate is driven by the hydrophobic effect, and – although the hydrolysis remains acid catalysed in the cavity – the mechanism changes from *A*-1 to *A*-2, with $\Delta S^{\neq}$ being negative, and an inverse solvent kinetic isotope effect (KIE) is observed.[8]

A gold(0)/silver(I) catalyst system combines acetals [e.g. **1**, X = OEt] with alkynes to give propargyl ethers. A three-component one-pot version substitutes aldehyde and triethyl orthoformate for the acetal. Gold alkynilides are proposed as intermediates.[9]

For hemiacetals of pyridinium ketones, see the section titled 'Miscellaneous Additions'.

Reactions of Glucosides and Nucleosides

A 2-*O*-(thiophen-2-yl)methyl protecting group has been used to achieve stereoselective synthesis of α-glucosides. Neighbouring group participation via an intermediate β-thiophenium ion (**3**) is proposed to account for the selectivity, which is greater for more hindered substrates.[10] (de)



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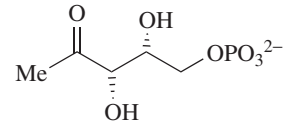


(**4**)

Conversion of 1-deoxy-D-xylulose 5-phosphate (DXP, **4**) to methyl-D-erythritol 4-phosphate is catalysed by DXP reductoisomerase: the enzyme is essential in many pathogens, but the pathway is absent in mammals, so it is an antibacterial target. Secondary KIEs suggest a retroaldol/aldol mechanism, a finding that should support drug design.[11] (de)

A major review of glycoside bond formation reflects demands for improved syntheses of biologically important oligosaccharides and glycoconjugates (313 references). Focussing on key principles of regio- and stereo-controlled bond formation, particularly on ion-pair generation and memory effects therein, and on conformation-dependent reactivity, improvements are predicted to come not from leaving group variation but from a deeper mechanistic focus.[12] (de)

The effect of a substituent at O(3) of *N*-acetylglucosamine acceptors on the relative reactivities at the 4-OH position has been examined for a series of sugars bearing β- or α-linked D- or L-saccharide substituents at O(3), and also for simpler groups such as acyl or carbonate protection at the same position.[13]

Mannosylation of various acceptors bearing a range of electron-withdrawing groups at O(3), O(4), or O(6) positions was found to be β-selective except where donors had 3-*O*-acyl and 6-*O*-acetyl groups. The α-directing effect of these latter cases is ascribed to remote participation.[14] (de)

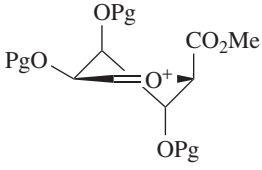
Glycosylation of mannuronate ester donors is highly selective, surprisingly giving 1,2-*cis*-linked products. A remote C(5)-carboxylate ester stereodirecting effect has been invoked; the group is suggested to prefer the axial position in the oxocarbenium intermediate. Model compounds have been used to test the hypothesis.[15] (de)

A strategy of using 2,6-disubstituted benzoates as neighbouring groups to enhance diastereoselectivity in β-galactosylation has proved effective. Using mesitoyl groups (2,4,6-trimethylbenzoyl), β-galactopyranose-1,3-β-galactopyranose linkages have been prepared, with good diastereoselectivity and with suppression of the transesterification often found for benzoyl- and pivaloyl-protected glycosyl donors. Although mesitoyl is difficult to hydrolyse (requiring lithium hydroxide at 80 °C), placing an electron-withdrawing group in place of the 4-methyl substituent may facilitate milder deprotection conditions.[16] (de)

Selectivities in nucleophilic substitutions of tetrahydropyran acetals have been investigated. Results for weak nucleophiles generally conformed to known S_N1 stereoelectronic models, but with strong nucleophiles, stereoselectivities tend to depend on reaction conditions, particularly if the counterion was non-coordinating. Such deviations have been attributed to the rates of addition to oxocarbenium ions approaching the diffusion limit. With triflate counterion, however, S_N2-like pathways became accessible, typically giving the opposite stereoisomer(s). Thus the S_N2 processes can be synthetically complementary.[17] (de)

β-*O*-Aryl glycosides have been formed with high diastereoselectivity in the absence of a directing group (DG) such as ester at C(2). The method uses a palladium(II) complex, $Pd(MeCN)_4(BF_4)_2$, to activate glycosyl trichloroacetimidate donors at room temperature. Working for D-glucose, D-galactose, and D-xylose donors, it also tolerates a wide range of phenols with electron-donating or -withdrawing groups, or hindrance (e.g. 2,6-dimethyl). Rearrangement of the product to *C*-aryl glycosides – seen with some other methods – is not observed.[18] (de)

The stereodirecting effect of the glycosyl substituent at C(5) has been investigated experimentally and computationally for a series of D-pyranosyl thioglycoside donors. An axially positioned C(5) carboxylate ester can stabilize the $^3H_4$ half-chair conformer of the oxocarbenium ion intermediate (**5**) by donating electron density from its carbonyl function. Benzyloxymethyl behaves similarly, but with less stabilization.[19] (de)



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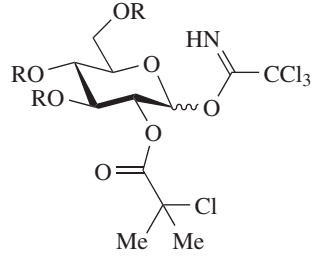

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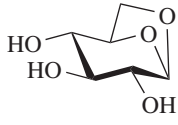


(**7**)

2-Chloro-2-methylpropanoic ester acts as a steering group in the Schmidt glycosidation reaction. Glycosidation of bulky alcohols with the donor (**6**) takes place under

mild, acidic conditions with the trichloroacetimidate group being replaced by alkoxy with β-selectivity, and without formation of orthoester by-product. Mild saponification cleaves off the ester.[20] (de)

Methyl β-D-glucoside undergoes thermal degradation to give levoglucosan [or 1,6-anhydro-β-D-glucose, (**7**)], with loss of methanol. A theoretical investigation of the mechanism has identified a conformational change, followed by an intramolecular nucleophilic substitution at the anomeric carbon in one step, that is, without an oxocarbenium ion intermediate. Direct homolysis was ruled out, as $\Delta G^{\circ\ddagger}$ is less than the C(1)−O(1) bond energy.[21]

In a study of the use of 2,3-anhydro sugars in glycoside bond synthesis, the mechanism of 2-deoxy-2-thioaryl glycoside formation has been investigated by QM calculations, NMR (nuclear magnetic resonance), and α-deuterium KIEs for a thioglycoside with D-xylo stereochemistry. All the results point to an oxocarbenium ion intermediate, rather than an episulfonium ion.[22]

For saccharides with an unprotected OH at C(4)/C(6) *and* O/S/Se substitution at the anomeric position, DAST (diethylaminosulfur trifluoride, Et_2NSF_3) can fluorinate at the latter position, migrating the group there to C(4)/C(6). While some saccharides yielded a mixture of normal and migration products, others yielded exclusively β-glycosyl fluorides (i.e. the migration product only), making the reaction potentially synthetically useful.[23] (de)

Anomeric O-alkylation/arylation has been used to form 2-deoxy-β-glycosides with high stereoselectivity. The experiments were chosen to show the importance of the β-effect, separate from the substituent at C(2).[24] (de)

The roles of protons and acetyl cations in sulfuric-acid-catalysed acetolysis of acylated methyl L-ribofuranosides (and anomerizations of reactants and products) have been studied kinetically by ^{1}H NMR.[25]

Phenylthioglycosides bearing 2,3-*trans*-carbamate or -carbonate rings are anomerized (β- to α-) by boron trifluoride in acetonitrile, but not in ether. The solvent effect is probably polarity driven, as the reaction involves a zwitterionic intermediate.[26] (de)

Roles for nucleophilic and solvent water have been investigated computationally to study the thermodynamics and kinetics of the hydrolysis of the *N*-glycosidic bond in deoxythymidine glycol.[27]

A reaction scheme for the interaction of lower monosaccharides with formaldehyde has been derived from the analysis of the kinetics and products of condensation of formaldehyde with glycolaldehyde, and with glyceraldehyde, in neutral and alkaline media. Roles of phosphates and of magnesium oxide were investigated.[28]

For reaction of a fructose-derived hydrazone, see the section titled 'Oximes, Hydrazones, and Related Species'.

Reactions of Ketenes and Ketenimines

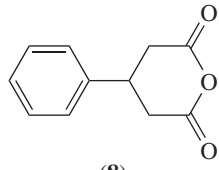
Catalytic, asymmetric reactions of ketenes and ketene enolates have been reviewed (159 references).[29] (de) (ee)

β-Trifluoromethyl-β-lactones have been prepared enantioselectively by a cycloaddition of a ketene to a trifluoromethyl ketone, via *N*-heterocyclic carbene (NHC) catalysis, using a chiral triazolium salt.[30] (de) (ee)

An investigation of torquoelectronic effects in the Staudinger synthesis of β-lactams from a ketene and an imine has observed the torquoelectronically disfavoured products predominantly for the first time, allowing the scope and limitations of the torquoselectivity approach to be delimited.[31] (de)

The amination reaction of ketene with ammonia has been studied in the gas phase, and in acetonitrile and benzene solvents, by calculation. As expected, the uncatalysed gas-phase process involves breakdown of enol amide as the rate-determining step. However, the use of $(NH_3)_2$, that is, catalysis by additional ammonia, sees the rate-determining step switch to enol amide formation (not previously found). In polar acetonitrile, zwitterions come into play.[32]

Lewis acids such as boron trifluoride etherate catalyse the one-pot formation of 3-phenyl-glutaric anhydride (**8**) from benzaldehyde and ketene; the intermediate 3-phenylpropiolactone can be isolated. Acetophenones also undergo the reaction, with the *p*-nitro case stopping at the lactone, presumably because its BF_3-catalysed ring opening would yield $p\text{-}O_2N{-}C_6H_4{-}C^+(Me){-}CH_2CO_2{-}BF_3^-$, a relatively unstable benzylic cation.[33]

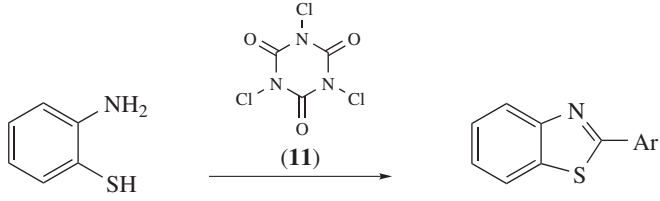


(**8**)

Formation and Reactions of Nitrogen Derivatives

Synthesis of Imines

A range of 2-arylbenzothiazoles (**10**) have been prepared by condensation of 2-aminothiophenol (**9**) with aromatic aldehydes, ArCHO. Trichloroisocyanuric acid (**11**) efficiently catalyses the reaction at room temperature.[34]



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

The use of a protic ionic liquid, ethylammonium nitrate (EAN), as an *additive* to reaction solvents has been tested for a range of reactions, including imine formation from aromatic aldehydes, where EAN can perform dual roles of Brønsted acid and nucleophile.[35]

A recognition-mediated aza-Wittig reaction allows imine formation in dry $CDCl_3$ from an iminophosphorane and an aldehyde, without production of water. The imine bond is formed reversibly under kinetic control in a protocol suited to dynamic covalent control. The method is compared with traditional imine formation by condensing an amine and aldehyde.[36]

Substituent effects on the thermodynamic stability of imines formed from glycine and benzaldehydes have been studied to help shed light on the catalytic activity of pyridoxal-5′-phosphate. Iminium-to-imine pK_a measurements for *ortho*- and *para*-hydroxy- and aza-substituents provide evidence for stabilization by an intramolecular hydrogen bond in an aqueous solution, and for a similar strength hydrogen bond in pyridoxal.[37]

The deoxygenation of carbohydrate-derived nitrones by tributylphosphine to give cyclic imines has been reinvestigated by DFT (density functional theory). Evidence for an azaoxaphosphetane intermediate, resulting from nucleophilic addition of phosphorus to the iminyl carbon, is discussed.[38]

The competition between cyclization and bisimine formation in the reactions of 1,3-diamine and aromatic aldehydes has been investigated experimentally and computationally. Cyclization – to form the hexahydropyrimidine – is favoured by the less nucleophilic amine, and by electron-withdrawing groups on the aryl ring.[39]

N-Phosphonyl β-amino Weinreb amides have been prepared in high yield and with high diastereoselectivity by treating chiral *N*-phosphinyl imines with the lithium enolate of *N*-methoxy-*N*-methylacetamide.[40] (*de*)

The structure, synthesis, and synthetic applications of *t*-butanesulfinimines have been reviewed (128 references). Although these chiral amino intermediates give high levels of stereoselectivity, the sense of stereoinduction is not readily predictable. The review presents models that address this problem.[41] (*de*) (*ee*)

Synthesis and applications of chiral sulfoximines[42] and of chiral sulfinamides[43] have been reviewed in *Organosulfur Chemistry in Asymmetric Synthesis*. (*de*) (*ee*)

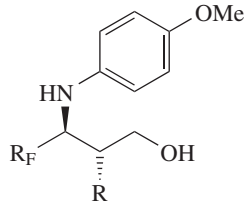
The Mannich Reaction

Direct catalytic asymmetric Mannich reactions have been reviewed;[44] another review examines the use of both organometallic catalysts and metal-free organocatalysts in such reactions,[45] while a third survey of this topic focuses on stereocontrolled assembly of both *syn*- and *anti*-α,β-diamino derivatives (37 references).[46] (*de*) (*ee*)

anti-γ-Fluoroalkyl-γ-amino alcohols (**12**) have been prepared from the corresponding fluoroalkylimine and aldehyde ($R-CH_2CHO$), via an asymmetric Mannich reaction using a proline derivative (α,α-diphenylprolinol TMS ether) as the organocatalyst.[47] (*de*) (*ee*)

Combining BINOL (1,1-bi-2-naphthol) and cinchona alkaloid motifs into one chiral catalyst for an asymmetric vinylogous Mannich reaction of α,α-dicyanoolefins with *N*-sulfonyl alkylamines yields high diastereo- and enantioselectivities for the process, and the adducts allow access to chiral β-, γ-, or δ-amino compounds.[48] (*de*) (*ee*)

A silyl dienolate (**13**) derived from dioxinone undergoes a highly regio- and diastereo-selective vinylogous Mannich-type reaction with a chiral *N*-*t*-butanesulfinyl



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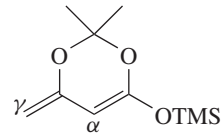


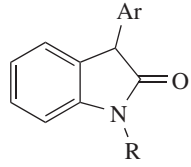
(**13**)

imino ester [$RO_2C{-}CH{=}N{-}S^*(=O)$-*t*-Bu] to yield γ- or α-product, with regio- (*de*)
selection by appropriate choice of a Lewis acid catalyst.[49]

A silver(I)-catalysed vinylogous Mannich reaction of aldimines with 2-TMSO-furan gives yields up to 91% with up to 98% *de* and 81% *ee* using chiral phosphine- (*de*)
Schiff base ligands. These optimum results were obtained using benzyl alcohol as a (*ee*)
stoichiometric additive.[50]

A direct *anti*-selective catalytic asymmetric Mannich-type reaction of α-ketoanilides (*de*)
(as homoenolate synthetic equivalents) with imines gives yields up to 99% with up to
98% *de* and 95% *ee*, using chiral dinickel-salen catalysts.[51] (*ee*)

A BINOL-derived phosphonium salt is an effective chiral phase-transfer catalyst of (*ee*)
asymmetric Michael and Mannich reactions of 3-aryloxindoles (**14**).[52]



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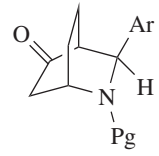
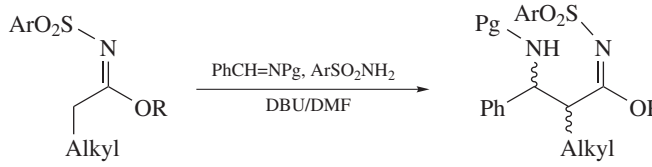


(**15**)

A *para*-dodecylphenylsulfonamide-modified proline acts as an asymmetric catalyst of the reaction of protected aromatic imines (ArCH=N-Pg) with cyclohexenone to give (*de*)
isoquinuclidines (**15**) in good yield, 99% *ee*, and >99 : 1 *exo/endo* ratio. A similar (*ee*)
reaction with aliphatic imines yields closely related *endo*-bicyclo[2.2.2]octanes with
up to 91% *ee*.[53]

A highly stereoselective Mannich-type reaction of thioamides with *N*-(diphenyl- (*de*)
phosphinoyl)imines employs a soft Lewis acid/hard Brønsted base strategy.[54] (*ee*)

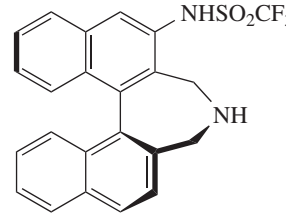
A new nucleophile, sulfonylimidate, has been introduced for Mannich addition to imines, including imines generated *in situ*. The type of sulfonylimidate used (**16a**) features (i) acidification of the α-position by the sulfonyl, (ii) stabilization of the imine by the alkoxy substituent, and (iii) fine-tuning of electronic and steric effects by variation of the substituent on the aryl ring. In a typical reaction, imine and sulfonamide combine with (**16a**) to give (**16b**), with high *anti*-selectivity. Kinetic studies indicate that (*ee*)
C−C bond formation is *not* rate determining, rather it is the deprotonation of (**16a**) by DBU.[55] Alkaline earth cations catalyse the reaction, with the choice of metal, in some cases, allowing selectivity reversal.



(**16a**) (**16b**)

In like vein, alkaline earth cations, as alkoxide salts, have been used to catalyse direct Michael, aldol, and Mannich additions: the latter gives good diastereoselectivities, with some examples showing a switch from *anti*- to *syn*-selectivity on changing the solvent.[56] (*de*)

A new BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl)-derived amino sulfonamide (**17**) catalyses direct Mannich and cross-aldol reactions, the former being catalysed *anti*-selectively and the latter being *syn*-selectively. Many enantioselectivities are >99%.[57] (*de*) (*ee*)



(**17**)

A copper(II) complex of a C_2-symmetric N,N'-dioxide catalyses the enantio- and diastereo-selective Mannich-type reaction of glycine Schiff bases with aldimines.[58] (*de*) (*ee*)

Chiral binaphthyls with a chiral pendant amino(thio)urea are excellent catalysts for asymmetric Mannich reactions of β-keto esters and *N*-Boc aldimines, giving β-amino-β-ketoesters with diastereo- and enantio-selectivities of up to 100 and 99%, respectively.[59] (*de*) (*ee*)

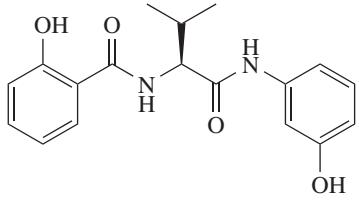
α-Hydroxy aldehydes bearing a protecting group, Pg−O−CH_2CHO, have been added enantioselectively to (phenylmethylene)benzamides, PhCO−N=CH−Ph, to yield PhCO−NH−*CH(Ph)−*CH(O−Pg)−CHO, i.e. protected α-hydroxy-β-benzoylaminoaldehydes. Using (*R*)-proline catalysis, good yields and enantio- and diastereo-selectivities of up to 99 and 90%, respectively, have been achieved. The products facilitate assembly of the anti-cancer drug, paclitaxel, and analogues.[60] (*de*) (*ee*)

Electrophilic Mannich-type reactions of α-cyano ketones with *N*-Boc aldimines have been catalysed by a chiral bifunctional urea, yielding up to 100% *de* and 99% *ee*.[61] (*de*) (*ee*)

NHCs catalyse enantioselective Mannich reactions of α-aryloxyacetaldehydes. Addition of carbene to the aldehyde causes elimination of an aryloxy anion and formation of an enol/enolate at the same time. With an activated imine present, Mannich reaction gives a β-amino acyl azolium intermediate. But the aryloxy (*ee*)

anion can 'rebound', re-entering the catalytic cycle, to regenerate the catalyst and a β-amino ester.[62]

The use of structural dynamics, such as that found in enzymes (and especially allosteric ones), has been demonstrated with an asymmetric organocatalyst (**18**). Complexation of (**18**) with scandium(III) gives a new catalyst for Mannich-type reaction (*de*) of α-cyanoketones with *N*-Boc imines (*de*/*ee* = 90%-*anti*/91%), whereas the use of (*ee*) erbium(III) reverses the diastereoselectivity (88%-*syn*) while maintaining the enantioselectivity (99%).[63]



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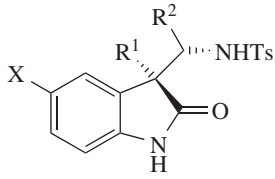


(**19**)

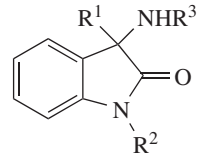
Trimethylchlorosilane promotes aza-Mannich reaction of enecarbamates (as nucleophiles) and aromatic *N*-Boc aldimines (as electrophiles), with *E*-selectivity in the β-amino enecarbamate products.[64]

N-Tosyl-araldimines (R^2−CH=NTs) undergo an *anti*-Mannich-type reaction with *N*-unprotected 3-substituted 2-oxindoles to yield side-chain-functionalized products (*de*) (**19**, X = H, Br; R^1 = Me, CH_2Ar; R^2 = Ar) with yields up to 90% with up to 90% *de* and 89% *ee*, using a cinchona alkaloid catalyst.[65] *N*-Tosyl-vinylaldimines (R^2 = (*ee*) vinyl) also work.

A strategy of generating a nucleophile via decarboxylation has been exploited in a (*de*) decarboxylative Mannich-type reaction. A copper(I)-catalysed extrusion of CO_2 from an α-cyano carboxylic acid sets up nucleophilic attack on an aldimine, allowing access (*ee*) to β-amino acid precursors with good diastereoselectivity and enantioselectivity.[66]

Addition of Organometallics, and Other Alkylations and Allylations

Grignard reagents (R^1MgBr) have been added diastereoselectively to chiral imines derived from isatin, to yield 3-substituted 3-aminooxindoles (**20**, R^2 = protecting (*de*) group, R^3 = chiral group). Such control of chirality at a quaternary centre derived from a ketimine is typically challenging.[67]



(**20**)

Addition of chloro- or iodo-methyllithium to aldimines allows access to β-chloro-amines and aziridines. A diastereoselective variant has also been developed.[68] (*de*)

BINAP-derived phosphoric acids catalyse radical addition to aldimines (at carbon), yielding chiral amines with up to 84% *ee*. The enantioselectivity was little affected by the *N*-substituent or the nature of the radical precursor.[69] (*ee*)

Aromatic or aliphatic aldimines can be cross-coupled directly with an allylic alcohol, without the need to protect or prederivatize the alcohol; that is, neither activated imines nor organometallic allyl reagents are required. The products are homoallylic amines. Coupling agents required are relatively straightforward: chlorotitanium(IV) triisopropoxide and cyclopentyl magnesium chloride. Enantiopure allylic alcohols react enantioselectively.[70] (*ee*)

Several BINAP-monophosphanes complexed with silver(I) catalyse enantioselective allylation of aldimines.[71] (*ee*)

Titanium-mediated reductive cross-coupling of aliphatic imines with allylic and allenic alkoxides has typically been problematic with Ti(O-*i*-Pr)$_4$/RMgX systems, but replacement of the Grignard component with *n*-BuLi gives a much cleaner process. Diastereoselective examples are also described.[72] (*de*)

Vinylic amino alcohols have been prepared with up to 99% *de* and 98% *ee* by benzoyloxyallylation of chiral sulfinyl imines.[73] (*de*) (*ee*)

A strategy of using simple amino acid hydrogen bonding to introduce chirality into metal catalysis has been tested, using the copper-catalysed coupling of an alkyne and an imine, to give a propargylamine. Using *N*-Boc proline and simple phosphine additives as ligands for copper(I), yields and enantioselectivities in the 90s have been achieved, using a wide range of amine starters.[74] (*ee*)

A H_8-BINOL-derived phosphoric acid catalyses enantioselective α-alkylation of enamides, Ar−C(=CH$_2$)−NHCOPh, with indolyl alcohols, to give β-aryl 3-(3-indolyl) propanones with yields and enantioselectivities up to 96%.[75] (*ee*)

Reduction of Imines

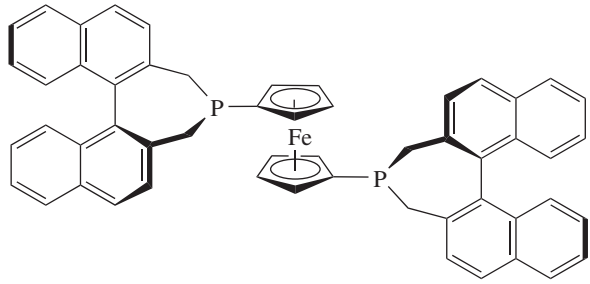
Organocatalytic imine and alkene reductions have been reviewed,[76] as have transfer hydrogenations of imines, focussing on catalysts and mechanisms.[77]

A spiro-phosphine-oxazoline ligand gives excellent enantioselectivity in an iridium(I)-catalysed hydrogenation of imines derived from ketones.[78] (*ee*)

Unsubstituted imines formally derived from ketones, R^1−C(=NH)−R^2, have been hydrogenated with high enantioselectivity, using iridium complexed with a (5,5′)-ferrocenyl-BINAPhane (**21**). The imine reactant can be conveniently obtained by (R^2-)alkylation of the appropriate nitrile, R^1−C≡N. The enantioselective imine reduction allows access to chiral amine products without the use of protecting groups.[79] (*ee*)

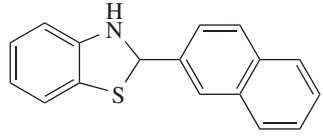
(1*S*,2*R*)-1-Amino-2-indanol, together with ruthenium(I)-*para*-cymene, catalyses transfer hydrogenation of *N*-(*t*-butanesulfinyl)imines in 2-propanol. The diastereoselective reduction of the imines followed by sulfinyl removal yields chiral primary amines with up to 99% *ee*. The process does require scrupulously dry conditions.[80] (*de*) (*ee*)

2-Naphthylbenzothiazoline (**22**) is an efficient reducing agent for transfer hydrogenation of ketimines; combined with a congested BINOL-phosphoric



(**21**)

acid, enantioselectivities of up to 98% and yields of up to 97% were obtained. (*ee*) Compound (**22**) could also be generated *in situ* from 2-aminothiophenol (**9**) and 2-naphthylcarbaldehyde.[81]



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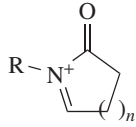


(**23**)

$B(C_6F_5)_3$ catalyses hydrogenation of bulky imines under metal-free conditions. This process has been investigated quantum-chemically, including study of formation of 'frustrated' complexes, both inherent and thermally induced.[82]

1,1′-Binaphthyldiamine-based Lewis bases have been used as organocatalysts for the trichlorosilane reduction of *N*-aryl and *N*-alkyl ketimines.[83] (*ee*)

Chiral amines have been prepared by trichlorosilane reduction of ketimines promoted by a chiral Lewis organobase. A three-component version, starting with ketone (*ee*) and amine precursors of the imine, has also been developed.[84]

Lewis basic formamides, derived from *N*-methyl valine, catalyse reduction of (*ee*) imines by trichlorosilane with up to 91% *ee*.[85]

Iminium Species

Asymmetric conjugate addition of oxindoles to enals has been achieved via iminium (*de*) ion catalysis using a novel BINAP-derived bifunctional primary amine thiourea to (*ee*) control the configuration of adjacent tertiary and quaternary centres.[86]

A chiral thiourea has been employed as an anion binder, producing good enantioselectivities in the addition of indoles to cyclic *N*-acyl iminium ions (**23**, $n = 1, 2$) derived from α-hydroxylactams. The protocol was uniquely effective using chloride (*ee*) counterion: its binding to the chiral thiourea catalyst, simultaneous with ion pairing to (**23**), may bias the indole's approach.[87]

The structures of enamine and iminium ion intermediates arising in organocatalytic applications of diarylprolinol ethers have been studied by X-ray crystallography,

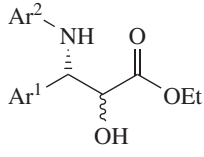
backed up by DFT calculations and nOe NMR (nuclear Overhauser effect nuclear magnetic resonance) studies. A detailed analysis of the (*E*)- and (*Z*)-conformers of both enamines and iminium ions is included.[88] (ee)

See also *N*,*O*-acetals and iminium ions[7] in the section titled 'Acetals'.

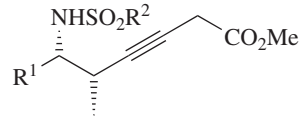
Other Reactions of Imines

α-Chiral primary amines have been deracemized via a one-pot, two-step cascade reaction involving ketone intermediates, catalysed by ω-transaminases.[89] A review has surveyed conjugated imines and iminium salts as versatile acceptors of nucleophiles (77 references), covering double nucleophilic additions of α,β-unsaturated aldimines, additions using alkynyl imines, 'umpoled' reactions of α-imino esters, and iminium salts as electrophiles.[90] Progress in nucleophilic radical addition to imines has been reviewed.[91] (de)

Dirhodium(II) acetate, $Rh_2(OAc)_4$, catalyses a three-component reaction – ethyl diazoacetate, water, and a diaromatic aldimine, $Ar^1{-}CH{=}N{-}Ar^2$ – to give β-aryl isoserine derivatives (**24**) in good yields with high diastereoselectivities. The first two reactants combine in the presence of rhodium to give a highly nucleophilic oxonium ylide which is then trapped by the imine.[92] (de)



(**24**)



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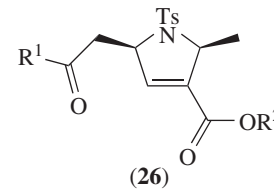


(**26**)

In a three-component reaction of an aldehyde (R^1CHO), a sulfonamide ($H_2NSO_2R^2$), and a chiral allenylsilane, the first two form an *N*-sulfonylimine *in situ*, which then reacts *syn*-selectively with the allenylsilane to yield a *syn*-homopropargylic sulfonamide (**25**). Chirality transfer from the allenylsilane is >97%.[93] (de) (ee)

Dienes, activated with ketone and ester functions at each end, react with imines to give functionalized 3-pyrrolines (**26**). The phosphine-catalysed reaction shows *de*s up to 98%.[94] (de)

Hydroboration and diboration of imines have been reviewed.[95]

Enantioselective addition of boronates, $R^1{-}B(OBu)_2$, to acyl imines, $R^2{-}CH{=}N{-}COR^3$, yields optically active amides, $R^1R^2CH^*{-}NHCOR^3$. A chiral bisphenol catalyst is employed, and MS mechanistic studies suggest an acyclic boronate intermediate.[96] (ee)

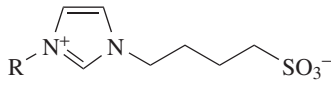
The pyridylalanine moiety has been used to catalyse enantioselective allenoate additions to *N*-acyl imines.[97] (ee)

Thioureas with pendant chiral amine and amide groups catalyse addition of nitroesters to *N*-carboalkyloxy imines with up to 81% *ee*. The catalysts are proposed (ee)

to control attack of the enolic form of the nitroester through a hydrogen-bonding network, a route explored via AM1 calculations.[98]

A guanidine-thiourea bifunctional organocatalyst gives up to 98% *de* and 99% *ee* in an aza-Henry reaction of imines with nitroalkanes.[99] Catalytic enantioselective aza-Henry (nitro-Mannich) reactions have been reviewed (71 references).[100] Thiophosphorylimines, PhCH=N-P(=S)R_2 (R = Ph, OEt), undergo aza-Henry reaction with nitromethane, using tetramethylguanidine catalyst, without solvent. A chiral thiourea catalyst renders the process enantioselective.[101] Chiral guanidines have been used as enantio- and diastereo-selective catalysts of the aza-Henry reaction. A second generation of related bis-guanidines are also effective, and in one case with a dramatic reversal of enantioselectivity.[102]

Zwitterionic molten salts (**27**, R = H, Me) act as catalytic 'internal' ionic liquids, giving solvent-free one-pot diastereoselective synthesis of *syn*-β-nitroamines via aza-Henry reaction, at room temperature.[103]



(**27**)

2-Imidazolines and imidazoles have been formed by intramolecular aza-Wittig ring closure of *N*-acylated azido sulfonamides.[104]

Organocatalysed Strecker reactions have been reviewed (61 references).[105] Another review dealing with the catalytic enantioselective Strecker reaction also covers the Reissert reaction of imines.[106]

Enantioselective Strecker cyanation of aldimines with TMSCN (trimethylsilyl cyanide) has been achieved, using a lanthanum(III)-BINAP-disulfonate catalyst. As HCN is known to be the actual cyanide source in these processes, protic additives were tested, and semi-stoichiometric amounts of acetic acid optimized both yield and enantioselectivity.[107]

The mechanism of the chiral BINOL–phosphoric-acid-catalysed Strecker reaction of *N*-benzyl imines has been studied computationally. A reversal of enantioselectivity, relative to *N*-aryl imines, is not because of differences in the steric bulk of aryl versus benzyl substituents, but rather because of an *E*/*Z*-switch in the imines.[108]

Asymmetric cyanation of aldehydes, ketones, aldimines, and ketimines by TMSCN or ethyl cyanoformate (NC−CO_2Et) as cyanide donor has been studied, using a catalyst derived from the combination of a cinchona alkaloid, titanium tetraisopropanoxide, and an achiral biphenol. Yields and enantioselectivity >99% have been achieved.[109]

A high-yield, high-enantioselectivity Strecker reaction of ketimines with TMSCN employs a chiral sodium phosphate derivative of BINOL as the catalyst.[110]

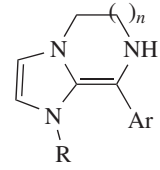
Imines have been hydrocyanated enantioselectively, using chiral thiourea organocatalysts. An experimental and computational re-investigation suggests that, rather than the thiourea directly activating the imine, it promotes proton transfer from hydrogen isocyanide to imine to generate diastereomeric iminium ion/cyanide ion pairs that are bound to the catalyst through multiple non-covalent interactions. Collapse of the ion pair yields the α-aminonitrile product.[111]

The reagent combination, *para*-$MeO \cdot C_6H_4-O^-Na^+/Me_3SiCH_2CO_2Et$, promotes addition of alkyl nitriles to unactivated aldimines, to yield aminonitrile products. For the example of acetonitrile, the reaction is thus a *C*-cyanomethylation of imines, and is transition metal free. Autocatalysis is also observed.[112]

A heterobimetallic complex of a chiral Schiff base has been used to catalyse enantioselective α-addition of isocyanides to a range of aldehyde types.[113] (*ee*)

An acid-promoted reaction of imines and isocyanides yields 3-aminoindoles and substituted indoxyls, via an 'interrupted Ugi reaction'. A recently reported triflyl phosphoramide, $(PhO)_2P(=O)NHS(=O)_2CF_3$, is a particularly efficient Brønsted acid catalyst of the process.[114]

Unactivated imines undergo base-induced intramolecular cyclization with NHCs to give Breslow-type intermediates (**28**, $n = 2, 3$), allowing access to new heterocycles.[115]



(**28**)

Electronic and steric effects have been investigated in the regioselectivity of the reactions of *N*-substituted 1,4-benzoquinone imines with arenesulfinic acids.[116]

The aza-Darzens reaction, synthesizing aziridines via nucleophilic attack of carbene equivalents on imines, has been reviewed (56 references).[117] (*de*) (*ee*)

Aldimines derived *in situ* from anilines and phenylglyoxal ($PhCH_2CHO$) undergo aza-Darzens reaction with ethyl diazoacetate to yield *cis*-aziridines with up to 97% *ee*, using a congested BINAP-phosphoric acid chiral catalyst.[118] (*ee*)

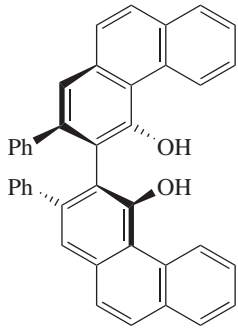
A boroxinate-based Brønsted-acid derivative of the chiral catalyst, VAPOL [**29**, 2,2′-diphenyl-(4-biphenanthrol)], has been implicated as the active catalyst in a catalytic asymmetric aziridination of aldimines with ethyl diazoacetate.[119] (*ee*)

N-Tosylaldimines have been nitro-aziridinated with 1-bromonitroalkanes in a one-pot reaction with both yields and *Z*-selectivity up to 92%.[120] (*de*)

N-Boc-protected araldimines react with diazoacetamides [$HC(=N_2)-CONHR$] to give aziridines *trans*-selectively, with enantioselectivities up to 98%, using a congested BINAP-phosphoric acid catalyst.[121] (*de*) (*ee*)

Ferrocenylimines derived from ferrocenecarboxaldehyde and a range of α-amino acids have been cyclized stereoselectively to either *cis*- or *trans*-oxazolidin-5-ones (**30**). Kinetic control (at $-78\,^\circ C$) gives *trans*-product, while close to room temperature, the thermodynamic *cis*-oxazolidinone is formed.[122] (*de*)

Imines have been reacted with substituted maleic anhydrides to give polycyclic lactams, with some diastereo- and regio-control. Aldimines react via an acylation/Mannich route, while ketimines follow a new acylation/aza-Michael process.[123] (*de*)



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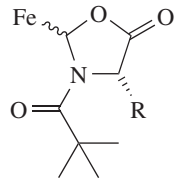
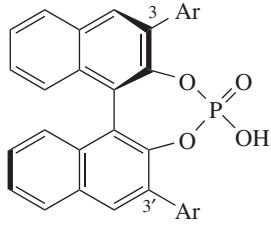


(**30**)

A theoretical study of hydrolysis of a formamidine bearing a modified cytidine has probed solvent effects on the balance between C−N and C=N attack.[124]

DFT calculations have been used to examine the asymmetric hydrophosphonylation of aldimines by dialkyl phosphites, catalysed by an (*R*)-BINOL-derived phosphoric acid. A nine-membered cyclic zwitterionic TS has been identified, with the catalyst providing Brønsted acid activation of the aldimine and Lewis base nucleophilic activation of phosphite.[125] (*ee*)

Hydrophosphorylation of aldimines with diisopropyl phosphite is rendered enantioselective with a series of (*R*)-BINOL-derived phosphoric acids (**31**). DFT studies have been used to probe the enantioselectivities as a function of the 3- and 3′-substituents, with the sterically demanding 3,5-$(F_3C)_2$−C_6H_3 substituent being particularly effective.[126] (*ee*)



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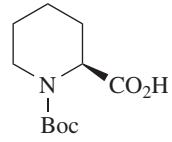


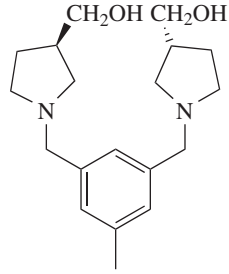
(**32**)

Production of chiral amines by enantioselective hydrosilylation of imines derived from ketones has been reviewed.[127] (*ee*)

A range of chiral Lewis bases have been derived by amidations of L-pipecolinic acid (**32**). They activate trichlorosilane to allow hydrosilylation of *N*-phenyl ketimines with good enantioselectivities. The roles of aryl–aryl and hydrogen-bonding interactions between catalyst and imine in producing the stereoselectivity are discussed.[128] (*ee*) (*ee*)

A C_2-symmetric bis(prolinol) (**33**) gives up to 95% *de* and 92% *ee* in nucleophilic addition of TMS-acetylene (Me_3Si−C≡CH) to *N*-phosphinoylimines derived from a variety of aldehyde types. Four equivalents of diethylzinc are required to give the (*de*)

products, *N*-phosphinoyl propargylamines still bearing a TMS group. A mechanism involving initial reaction of four diethylzincs with (**33**) – giving pairs of *N*,*O*- and *O*-coordinated zincs – is proposed based on ^{31}P NMR monitoring.[129] (*ee*)



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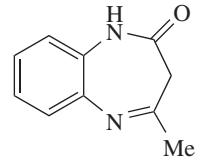
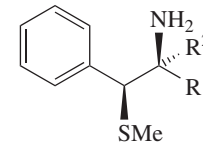


(**34**)



(**35**)

The mechanism of hydrazinolysis of 4-methyl-2,3-dihydro-1,5-benzodiazepin-2-one (**34**) has been studied by DFT. Hydrazine attacks the azomethine bond, leading to cyclization to form a pyrazole ring (3-methylpyrazol-5-one). Subsequent ring opening of the diazepine ring yields *ortho*-phenylenediamine; this last step is rate determining.[130]

An enantioselective two-carbon homologation has been developed, using enecarbamate derivatives and hemiaminal ethers, to yield 1,3-diamine derivatives. The enecarbamate acts as an acetaldehyde anion equivalent, and a chiral BINAP-phosphoric acid is used to activate the hemiaminal ether; the latter may be aromatic or aliphatic. Diastereoselectivities are modest, but enantioselectivities are good.[131] (*de*) (*ee*)

Enamines have been trifluoromethylated using TMS–CF_3 to give α-CF_3-substituted amines. The reaction is catalysed by HF, generated *in situ* from KHF_2 and an acid (TFA or triflic acid). Initial *N*-protonation is followed by transfer of CF_3^- from the silicon reagent. In addition to simple enamines derived from aldehydes and ketones, substrates bearing an ester group at the β-position (i.e. >N−C=C−CO_2R) also work.[132]

Tertiary enamides have been added intramolecularly and enantioselectively to ketones, to give functionalized γ-lactams, using a chiral chromium(III)-salen catalyst.[133] (*ee*)

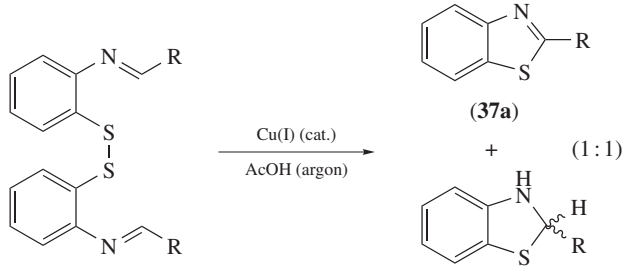
Alkaline earth alkoxides catalyse diastereo- and enantio-selective addition of sulfonylimidates to araldimines, with the diastereoselectivity being solvent-switchable in some cases.[134] (*de*) (*ee*)

Stereoselective addition of α-methylsulfonyl benzyl carbanions to *N*-sulfenylketimines allows stereoselective access – after desulfinylation – to α,α-dibranched β-sulfanyl amines (**35**).[135] (*de*)

β-Amino ketones, formed with stereocontrol over three consecutive stereogenic centres, were prepared from dialkylzincs, cyclic enones, and *N*-(*t*-butylsulfinyl)imines using chiral BINAP-phosphoramidite ligands. The β-amino ketones were then subjected to Baeyer–Villiger (BV) oxidation to give a range of aminolactones.[136] (*de*) (*ee*)

Optically pure β-fluoroalkyl β-amino acid derivatives have been prepared by reacting fluorinated imines with sulfinylated benzyl carbanions, the latter acting as synthetic equivalents of chiral ester enolates. Diastereoselectivities of up to 98% are reported.[137] (de)

Bisimine disulfides such as (**36**, R = phenyl, substituted phenyl) undergo an unusual redox reaction, catalysed by copper(I) under oxygen-free conditions, to give a benzothiazole (**37a**) and its 2,3-dihydro derivative (**37b**). Failure to trap any free sulfur electrophiles led to the somewhat unlikely oxidation of Cu(I) by the S−S bond [yielding Cu(III)], with subsequent hydrogen transfer leading to overall disproportionation of (**36**) to (**37a**) and (**37b**). However, MS and KIE experiments support this route.[138]



(**36**) (**37a**) (**37b**)

For the Staudinger synthesis of β-lactams from imines,[31] see the section titled 'Reactions of Ketenes and Ketenimines'.

For aza-(Morita)-Baylis–Hillman (MBH) reactions of imines, see the section titled 'The Baylis–Hillman Reaction and its Aza-, Morita-, and Sila-variants'.

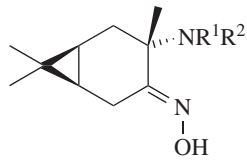
Oximes, Hydrazones, and Related Species

Theoretical and experimental approaches to the chemistry of hydroxylamines, oximes, and hydroxamic acids have been reviewed,[139] as have rearrangements of these three functional group classes.[140]

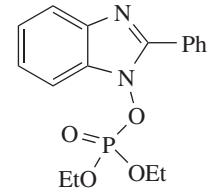
para-Toluenesulfonyl chloride, previously used as a stoichiometric dehydrogenation reagent for conversion of ketoximes to amides via the Beckmann rearrangement, has now been found to be effective as a catalyst, giving yields up to 99% with loadings as low as 1%.[141] A range of ketoximes undergo Beckmann rearrangement in ionic liquids, via Lewis acid catalysis. Seventeen solvents were studied, allowing the effects of the cation and the anion on the reaction rate and product composition to be assessed, as well as that of the hydrophobicity and hydrogen-bonding ability of the ionic liquids.[142]

Oximes have been converted to allylic oxime ethers using, for example, Ar−CH(OAc)−CH=CH_2, with loss of acetic acid. The reaction is both regioselective (giving predominantly the branched ether) and – with an iridium-pybox complex as the catalyst – enantioselective.[143] (ee)

α-Substituted caran-4-one oximes (**38**) undergo a Mannich-type three-component condensation with formaldehyde and secondary amines, resulting in α'-aminomethylation.[144]



(**38**)



(**39**)

Chiral aliphatic nitro compounds have been converted to thiooximes and to ketones, without racemization at an adjacent chiral centre; the latter conversion is catalysed by gold tribromide in neutral water, *in situ*. This Nef-type procedure failed with a large number of other metal halides.[145] (*ee*)

Phosphoric acid diethyl ester 2-phenylbenzimidazol-1-yl ester (**39**) is an efficient reagent for dehydration of aryl aldoximes to the corresponding nitriles.[146]

The ionic liquid, [pmim]BF_4 (1-pentyl-3-methylimidazolium tetrafluoroborate), dehydrates aldoximes to nitriles at 90 °C, presumably by coordination of the C(2)−H of the imidazolium with the hydroxyl of the oxime.[147]

Bromodimethylsulfonium bromide ($Br-S^+-Me_2$ Br^-) is a new and effective reagent for dehydration of both amides and aldoximes, to yield nitriles, driven by 'triple condensation' of DMSO (dimethylsulfoxide) plus two molecules of HBr. A base is not required. Room temperature is sufficient for oximes, whereas amides require chloroform reflux. Both mechanisms are proposed to involve oxygen attack on sulfur; for the amides, this is suggested to be from the iminol tautomer.[148]

In an interesting 'transhydration' reaction, nitrile can be converted to amide, coupled to acetaldoxime forming acetonitrile, using palladium diacetate and triphenylphosphine as catalysts. Palladium(II) is proposed to coordinate the nitrile, enhancing the electrophilicity of the latter's carbon, setting up nucleophilic attack by the oxime. Acetaldoxime is an effective 'water surrogate', and is cheap, and the acetonitrile by-product is easily separated.[149]

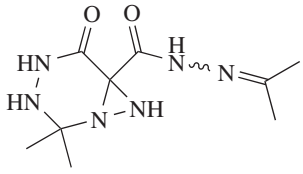
Ketoximes, $R^1R^2C{=}NOH$, have been converted to thioamides, $R^1C(=S)NHR^2$, using $PSCl_3$, a reagent that can induce Beckmann rearrangement and capture the intermediate nitrilium ion. The C-to-N migrating group is always that anti to the oxime's hydroxyl.[150]

The kinetics of the oxidative hydrolysis of benzaldoxime and several *para*-substituted derivatives by pyridinium fluorochromate are first order in oxime, oxidant, and hydronium ions. Temperature and solvent effects have also been determined.[151]

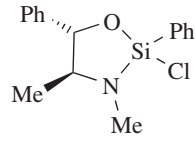
Kinetic studies over a range of temperatures, and with a range of acid and metal-ion catalysts, have been used to characterize the mechanism of the oxidative recarbonylation of ketoximes by bispyridinesilver(I) dichromate in aqueous ethanol.[152]

Diaziridine-3,3-dicarboxylic acid dihydrazide reacts with acetone to form (*E*)/(*Z*)-isomeric monohydrazones (**40**). While the product mixture shows no NMR change in refluxing d_6-acetone, isomerization *is* evident in d_6-DMSO.[153]

α-Amino-β-halo-esters have been prepared in high yield, with high diastereo- and enantio-selectivities, from a hydrazone and ethyl diazoacetate. The tandem process (*de*)



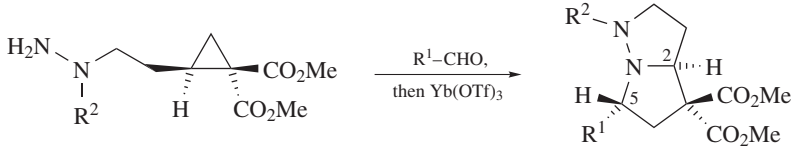
(**40**)



(**41**)

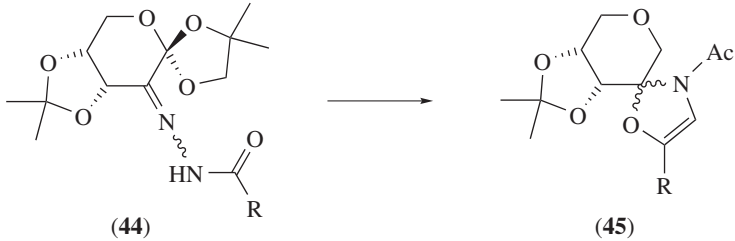
involves an aza-Darzens reaction to give an aziridine, followed by ring opening. A silane Lewis acid (**41**), chosen to catalyse the aziridine formation, unexpectedly also activated it towards ring opening.[154] (*ee*)

Hydrazinoethyl 1,1-cyclopropanediesters (**42**) react with aldehydes to yield fused bicyclo pyrazolidines (**43**, *trans*-isomer at the 5-position). Diastereoselectivity is elegantly achieved: reversing the order of addition of aldehyde and catalyst gives the *cis*-isomer. The switchover is explained in terms of the effects of ring opening in each protocol: formation of the (*E*)-aza-iminium ion (aldehyde-then-catalyst) gives the *trans*-adduct, while the (*Z*)-aza-iminium ion (catalyst-then-aldehyde) gives the *cis*-.[155] (*de*)



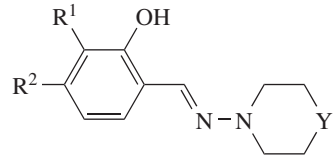
(**42**) (**43**)

Isomeric fructose-derived hydrazones (**44**) have been prepared and converted to oxadiazoles (**45**); the latter were then tested for anti-tumour activity. Isomers (**44**) are interconverted thermally in solution, and by acetic acid. Heterocyclization to form products (**45**) can be achieved with acetic anhydride: *N*-acetyl-(**44**) isomers have been isolated as intermediates of this process.[156]



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

Hydrazones derived from salicylaldehydes and *N*-amino-piperidine or -morpholine (**46**, Y = CH_2 or O) undergo nucleophilic trifluoromethylation at the imine carbon, using the Ruppert–Prakash reagent, Me_3SiCF_3. Pre-treatment with $BF_3{\cdot}OEt_2$ and



(**46**)

allyl-TMS gives an *O*,*N*-chelate difluoroboron complex; that is, the phenolic OH of (**46**) directs the trifluoromethylation.[157]

The kinetics of oxidation of a series of 3-alkyl-substituted 2,6-diphenylpiperidin-4-ones by pyridinium fluorochromate have been measured in aqueous acetic acid. The fast acid-catalysed reactions give ketone as the product.[158]

The nucleophilic addition–condensation reaction of thiosemicarbazide with 4-chlorochalcone has been studied theoretically.[159]

Rearrangements of hydrazones and semicarbazones have been reported.[160]

For an imine hydrazinolysis,[130] see the section titled 'Other Reactions of Imines'. For a review of allylation of *N*-acylhydrazones, see the section titled 'Allylation and Related Reactions'.

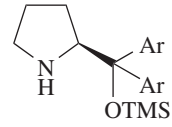
C–C Bond Formation and Fission: Aldol and Related Reactions

Reviews of Organocatalysts

Organocatalytic reports have grown geometrically in recent years, and are the subject of several general reviews, many focussing on the reactions of this section. Significant themes include use of proline-derived and NHC catalysts, and of aqueous and ionic liquid solvent systems. Asymmetric catalysis with chiral primary amine-based organocatalysts has been reviewed (89 references) up to late 2008, emphasizing that the explosive growth in the area in recent years has meant that mechanistic understanding has lagged behind developments of new catalysts, and indeed new reactions to exploit them.[161] (*de*) (*ee*)

Other reviews cover (i) the use of chiral amines in asymmetric organocatalysis;[162] (ii) the use of NHCs and metal complexes thereof as catalysts;[163] (iii) organocatalysis, and, in particular, aminocatalysis of asymmetric functionalizations of aldehydes and ketones (50 references);[164] (iv) asymmetric organocatalysis by chiral Brønsted bases (122 references), concentrating on C–C and C–X bond-forming reactions (X = N, O, S, P);[165] (v) recyclable stereoselective catalysts (633 references), focussing on new solvent systems in particular, together with recommendations for further progress;[166] (vi) symmetric organocatalysis of aldol, Michael, Mannich, and iminium-type cycloadditions;[167] and (vii) the state of the art in asymmetric induction 2003–2007 (439 references) using aldol as a case study.[168] (*de*) (*ee*) (*de*) (*ee*) (*de*) (*ee*)

A theoretical study of the enantioselectivity induced by α,α-diarylprolinol TMS ethers (**47**) as catalysts in α-functionalization of aldehydes, via enol intermediates, examines seven cases: Michael-aldol condensation, Michael addition, Mannich reaction, amination, sulfenylation, fluorination, and bromination at the α-position.[169] (*ee*)

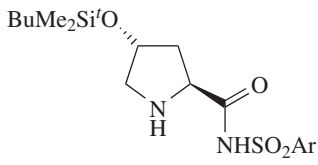


(**47**)

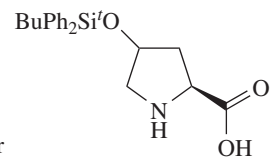
Asymmetric Aldols in Water, Brine, and Mixed Aqueous Solvents

Considerable attention has been focussed on aldols in water, and also in brine, though many cases may not be truly homogeneous reactions, with evidence for the organic materials forming a microphase, giving a concentration advantage, often accentuated by salt. Many also use proline and its derivatives, or other amino acids or peptides. (*ee*)

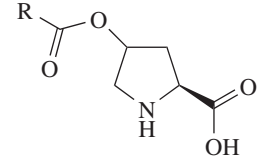
trans-4-TBDMS-oxy-substituted proline-sulfonamides (**48**) catalyse direct aldol reactions of cyclic ketones with aromatic aldehydes in water at ambient temperature: yields up to 99% with 98% *de* and 99% *ee* were achieved. Vigorous stirring was required, with the reaction probably occurring in an organic microphase. The TBDMS group may help to form a hydrophobic pocket, such as is found in aldolase antibodies.[170] (*ee*)



(**48**)



(**49**)



(**50**)

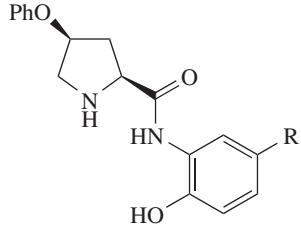
4-(*t*-Butyldiphenylsilyloxy)pyrrolidine-2-carboxylic acid (**49**, stereochemistry not specified) catalyses the cross-aldol reaction of ketones with β,γ-unsaturated ketoesters in water, allowing construction of quaternary carbon centres with up to 99% *ee*, and high diastereoselectivity.[171] (*de*) (*ee*)

New 4-substituted acyloxyprolines (**50**, stereochemistry not specified) catalyse direct asymmetric aldols between cyclic ketones (cyclohexanone and cycloheptanone) and substituted benzaldehydes, in water. Hydrophobic R groups in (**50**) gave the best diastereo/enantio-selectivity.[172] (*de*) (*ee*)

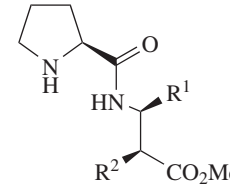
In a rational approach to design hydrophobic organocatalysts for direct aldols in water, *cis*-4-hydroxy-prolinamide was modified by incorporation of a hydrophobic phenoxy group at the 4-position and a pendant phenol at the amide (**51**, R = H/Me/*t*-Bu). The last of these gave excellent yields of up to 99% with up to 98% *de* and 97% *ee*.[173] (*de*) (*ee*)

An O-silylated serine catalyses *syn*-selective aldol reactions in water; up to 88% *ee* were achieved for this isomer.[174] (*de*) (*ee*)

A chemo-, diastereo-, and enantio-selective cross-aldol addition between enolizable aldehydes has been developed, using histidine as the catalyst. Carried out in water at (*de*)



(**51**)

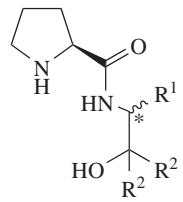


(**52**)

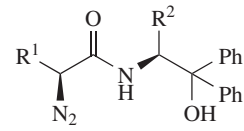
ambient temperature, the ability of histidine to differentiate between various aldehydes allows construction of defined-configuration quaternary stereogenic centres.[175] (*ee*)

Proline-β^3-amino-ester dipeptides (**52**, R^1 = various natural α-amino acid side-chains, R^2 = H, NH_2, NHTs) have been prepared from L-proline and β^3-L-amino acids, both readily available in enantiopure form. They catalyse direct aldols in water and in brine, with good yields and diastereo- and enantio-selectivities, particularly those bearing tyrosine or tryptophan side-chains.[176] (*ee*) (*ee*)

A series of L-prolinamides have been prepared by further functionalization at the amide nitrogen, adding on a chiral alcohol that is otherwise hydrophobic (**53**, R^1 = alkyl/Ph/Bn = R^2). They catalyse aldol reactions stereoselectively in several solvents, but give enhanced rates and up to 98% *de* and 99% *ee* in water. The aldol products – β-hydroxy ketones – allow access to β-amino alcohols diastereoselectively.[177] (*de*) (*ee*)



(**53**)



(**54**)

Four prolinamides, formed from proline and (*R*,*R*)-diphenylethyl diamine, give yields of up to 99% with up to 96% *de* and 97% *ee* in direct aldols in brine, using 2,4-dinitrophenol as a co-catalyst, and a 1% loading of each catalyst.[178] (*ee*)

A range of aminoalcohols (**54**), derived from amino acids, catalyse asymmetric aldol reactions of aldehydes and ketones in brine solution, without an organic co-solvent. Good yields and excellent stereoselectivities were obtained (98% *de*, >99% *ee*) using the diisobutyl catalyst (**54**; R^1, R^2 = *i*-Bu). 2,4-Dinitrophenol co-catalyst is required to achieve these results (and reasonable reaction times), but its precise role is not identified.[179] (*ee*)

A chiral β-amino sulfonamide catalyses direct aldols of aldehydes with ketones to give *anti*-products in 85–93% *ee*, in brine solution.[180] (*de*) (*ee*)

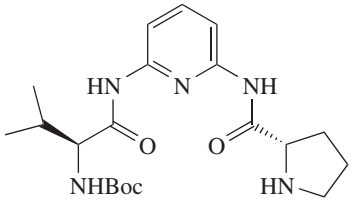
BINAP-prolinamide catalysts of aldol condensations give high yield and diastereo- and enantio-selectivities in ionic liquid-water systems.[181] (*de*) (*ee*)

A new series of pyrrolidinyl-camphor organocatalysts give yields of up to 99% with up to 98% *de* and 99% *ee* for direct aldols in either organic solvents or water.[182] (*de*) (*ee*)

Asymmetric Aldols Catalysed by Proline Derivatives in Other Solvents

In addition to the examples of proline-based catalysts above, many others have been investigated in non-aqueous systems. L-Proline-derived catalysts of aldol, Mannich, and conjugate addition reactions have been reviewed,[183] as has catalysis by proline itself.[184] (*de*) (*ee*)

While some bifunctional catalysts can suffer an acid–base self-quenching problem, a new enamine–metal Lewis acid system gets around this. A tridentate ligand tethered with a secondary amine [e.g. (**55**)] binds copper(II), producing a catalyst that gives high yields and enantio- and diastereo-selectivities in reactions of ketones. The design brings the metal Lewis acid into close proximity with the chiral secondary amine (a prolinamide), without self-quenching.[185] (*de*) (*ee*)



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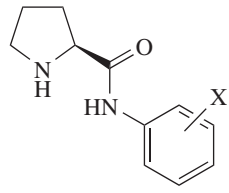


(**56**)

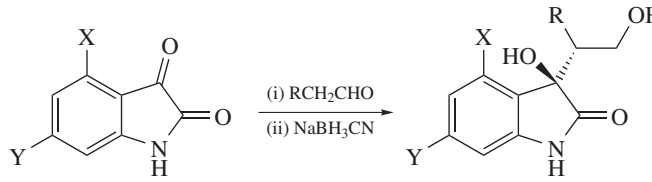
A kinetic study of proline-catalysed intermolecular aldol reactions, including measurement of deuterium isotope effects, suggests formation of an iminium species (rather than an enamine) in the rate-determining step.[186] (*ee*)

A series of *N*-aryl-L-prolinamides (**56**) in which incorporation of electron-withdrawing group(s) enhances the amide N−H acidity have proven to be highly diastereo- and enantio-selective catalysts of aldol reactions of cyclohexanone and a range of aldehydes. The best catalyst was the pentafluorophenyl (i.e. **56**: $X = F_5$); notably, X-ray crystallography showed that its aromatic ring was almost orthogonal to the amide, while a more representative case (X = 3,5-dinitro) showed coplanarity.[187] (*de*) (*ee*)

Catalysts derived from *N*-(2-hydroxyphenyl)-(*S*)-prolinamide have been electronically tuned to optimize their performance in aldol reactions. Product enantioselectivities correlate well with Hammett constants.[188] (*ee*)

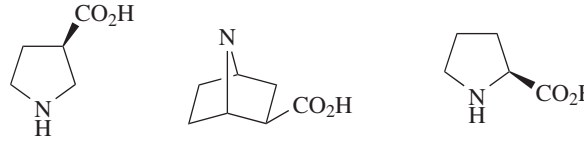
N-(Heteroarenesulfonyl)prolinamides have been used as organocatalysts of a crossed aldol reaction of isatin (**57**, X = Y = H) and its 4,6-dihalo derivatives (**57**, X = Y = Cl, Br, I) with aldehydes. Many reactions show enantioselectivities in the high 90s, and subsequent reduction gives convolutamydine derivatives (**58**) which are potent anti-cancer natural products.[189] (*ee*)

Enantiopure 7-azabicyclo[2.2.1]heptane-2-carboxylic acid (**60**) has been assessed as a constrained analogue of L-β-proline (**59**) in the aldol reaction of acetone with *para*-nitroacetophenone, and it was indeed found to give higher enantioselectivity, (*ee*)



(**57**) (**58**)

though not as good as L-proline (**61**) itself. The DFT calculations comparing (**59**), (**60**), and L-proline (**61**) indicate that constraining the pyrrolidine ring can modify the geometry of the carboxylic acid in such a way as to improve the enantioselectivity. The interpretation is supported by excellent agreement between observed and calculated enantioselectivities.[190]



(**59**) (**60**) (**61**)

Higher turnover number and up to 99% *ee* have been achieved in the direct aldol reaction catalysed by *cis*-4-hydroxy-L-proline by means of an imidazolium ion tag attached to C(4).[191] (*ee*)

L-Proline (**61**) catalyses aldol addition of acetone to β-substituted α-ketoesters: the dynamic kinetic resolution process gives up to 98% *de* and *ee*.[192] (*de*) (*ee*)

The DFT B3LYP calculations on proline- and prolinamide-catalysed aldol addition of acetone to isatin (**57**, X, Y = H) support the role of trace water in enhancing the enantioselectivity. Explicit incorporation of water in the TS reproduces the observed enantioselectivity.[193] (*de*)

An ionic-liquid-supported proline derivative catalyses the direct asymmetric aldol reaction of acetone with aldehydes.[194] Dendrimers bearing pyridine-2,6-dicarboxamide dendrons terminated by L-prolinamides give fair to good diastereo- and enantioselectivities in model aldol reactions.[195] (*ee*) (*de*) (*ee*)

Although *N*,*N*′-bis[3,5-bis(trifluoromethyl)phenyl]thiourea is achiral, its addition to aldols catalysed by L-proline (**61**) enhances the diastereo- and enantio-selectivities (up to 94 and >99%), via formation of a 1 : 1 host:guest complex. The complex is proposed to involve hydrogen bonding between the proline oxygens and the thiourea N−Hs, driven by the use of non-polar solvent. The stereoselection is in the same sense as with L-proline (**61**) alone.[196] 4-Substituted cyclohexanones have been desymmetrized with high diastereo- and enantio-selectivities via a simple direct aldol reaction catalysed by L-proline (**61**). Thioureas used as hydrogen-bond-donor catalysts substantially improve efficiency.[197] (*de*) (*ee*) (*de*) (*ee*)

For enamines/iminium ions in proline catalysis,[88] see the section titled ‘Iminium Species’.

For aza-MBH reactions of imines, see the section titled 'The Baylis–Hillman Reaction and its Aza-, Morita-, and Sila-variants'.

Other Asymmetric Aldols

Asymmetric synthesis of chiral cyclohexenones has been carried out using a BINOL-derived phosphoric acid catalyst to desymmetrize *meso*-1,3-diones.[198] (*ee*)

Direct observation of an enamine intermediate has been reported. The species was seen by crystallographic analysis of the adduct formed when an aldolase antibody reacts with a β-diketone derivative.[199] (*ee*)

Catalytic enantioselective aldol additions to ketone acceptors have been reviewed (57 references), highlighting strategies that have helped overcome the lower reactivity and decreased steric discrimination of ketones.[200] (*ee*)

A dipeptide, H-Pro-Thr-OH, with the threonine alcohol silylated, gives reasonable yields and enantioselectivities in aldols of acetone with a range of aldehydes, in chloroform solution.[201] (*ee*)

A series of tetrapeptides that are conformationally restricted so as to produce a β-turn motif have been tested as catalysts of aldol reactions of substituted aromatic aldehydes and cyclic and acyclic aliphatic ketones. The best – Val-D-Pro-Gly-Leu-H – gave an (*R*)-aldol in a test reaction of *para*-nitrobenzaldehyde with acetone in methanol, but gave (*S*)-product (with lower enantioselectivity) in DCM (dichloromethane), consistent with the β-turn being disrupted in the latter solvent.[202] (*de*) (*ee*)

A range of primary amine organocatalysts derived from natural primary amino acids which give only fair to good enantioselectivities for aldols (with long reaction times) gave higher yields and *ee*s quicker when 2,4-dinitrophenol was added as a co-catalyst. This 'remediation' of moderate catalysts by 2,4-DNP is substantially cheaper than catalyst re-design.[203] (*de*) (*ee*)

An acid–base catalyst system gives yields of up to 97% with up to 97% *de* and 99% *ee* in aldol reactions of α-hydroxy ketones. The auxiliary is a primary–tertiary diamine derived from amino acids, and a polyoxymetallate ($H_3PW_{12}O_{40}$) is used as Brønsted acid.[204] (*de*) (*ee*)

Quinidine alkaloids catalyse direct aldol reaction of hydroxyacetone with aldehydes with modest diastereo- and enantio-selectivities.[205] (*de*) (*ee*)

α-Alkylidene-β-hydroxy esters have been prepared via a barium-catalysed direct aldol. High enantioselectivities are obtained by exploiting a dynamic kinetic resolution.[206] (*ee*)

Dual-function aldolase models bearing amino acid and zinc(II) components catalyse direct aldols: both class I (Schiff base intermediate) and class II (Zn^{2+}-enolate) analogues have been prepared and tested. Complexation properties are also reported.[207] (*ee*)

Recent progress in the use of optically active metal-free organocatalysts has been reviewed, including cross-aldols, Friedel–Crafts reaction of indoles, hydrogenation of enones, Diels–Alder (diene–enone), and α,α-dialkylation of glycine Schiff bases.[208] (*de*) (*ee*)

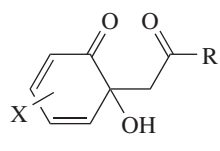
Dilithium binaphtholate catalyses direct aldols under mild conditions, without dehydration.[209] An aldol reaction between alkenyl trichloroacetates and aldehydes has been achieved using low catalytic levels of a chiral tin auxiliary.[210] A C_2-symmetric (*ee*)

N,*N*′-dioxide-scandium(III) complex promotes highly enantioselective direct aldols of α-ketoesters and diazoacetate esters.[211] Chiral rhodium(bis-oxazolinylphenyl) catalysts have been employed in a regioselective asymmetric direct aldol.[212] (ee) (de)

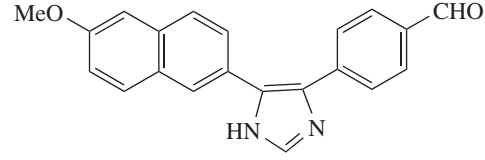
Samarium(II) iodide mediates dialdehydes undergoing a 'radical then aldol' cyclization cascade, generating four contiguous stereocentres with high diastereocontrol. In the unsymmetrical dials studied, it is proposed that one aldehyde function is pre-coordinated by samarium, and then reduced, while the other aldehyde 'waits in line'.[213] (de) (ee)

Other Aldol Reactions

Iron trichloride catalyses cross-aldol reactions of *ortho*-diketones (*ortho*-quinones) with methyl ketones (MeCOR); the products (**62**) can be thermally ring-expanded to tropone (cyclohepta-2,4,6-trienone) derivatives.[214]



(**62**)



(**63**)

α′-Hydroxyenones, easily prepared from aromatic aldehydes, can act as surrogates for α,β-enals in annulations that are catalysed by NHCs. Such α′-hydroxyenones, for example *trans*-Ar−CH=CH−CO−C(Me)$_2$−OH, are prepared by one-step aldol condensation (in this case, of ArCHO and commercially available 3-hydroxy-3-methylbutanone).[215]

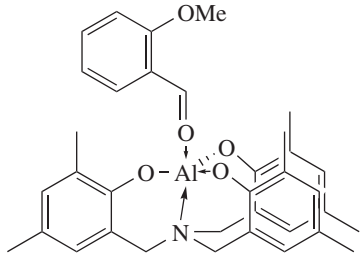
A fluorogenic aldehyde (**63**) has been developed for monitoring aldol reactions. Unlike the 6-methoxy-2-naphthaldehyde unit which is highly fluorescent in isolation, (**63**) is *non*-fluorescent, but aldolization 'turns it on', 800-fold. The formylbenzene moiety apparently acts as a quencher of the methoxynaphthyl component, so reacting the formyl group (in the aldol) removes the quenching effect.[216]

Inorganic ammonium salts with halide, acetate, and sulfate counterions catalyse direct aldols in water.[217] The acetate-promoted aldol-type reaction in glacial acetic acid has been investigated: ammonium acetate was particularly effective.[218]

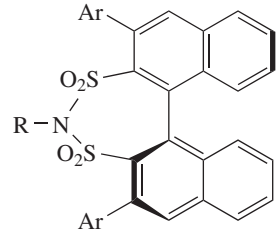
Mukaiyama and Vinylogous Aldols

A tricyclic aluminium alkoxide Lewis acid (**64a**) catalyses Mukaiyama aldol reactions, tolerating a wide range of aldehyde and enol silyl ether types. Despite the N−Al dative bond, the catalyst is a very strong Lewis acid (stronger than BF_3). An aldehyde complex (**64b**) has been isolated as intermediate. The strong catalysis observed is notwithstanding (**64a**) existing as an Al−O-linked dimer.[219] (de)

Chiral disulfonimide Brønsted (**65**, R = H) and Lewis (**65**, R = $SiMe_3$) acid catalysts have been employed as enantioselective catalysts of Mukaiyama aldol reactions, (ee)



(**64b**; **64a** = w/o aldehyde)



(**65**)

with the latter catalyst giving turnover numbers up to 8800. The directing role of the catalyst counterion (i.e. on loss of R^+) is discussed, including its possible wider role in asymmetric counterion-directed catalysis.[220]

In a survey of a range of hydrogen-bond-donor catalysts of a Mukaiyama aldol of silyl enol ethers, $Me_2N{-}C(OTBS){=}CHR$, with an acetyl phosphonate, $H_3C{-}CO{-}P(=O)(OMe)_2$, a TADDOL derivative ($\alpha,\alpha,\alpha',\alpha'$-tetraaryl-1,3-dioxolane-4,5-dimethanol) proved most efficient, giving 92% conversion in 10 h at −40 °C, and both diastereo- and enantio-selectivities up to 99%.[221] (*de*) (*ee*)

Ionic liquids based on thiazolium salts catalyse the Mukaiyama aldol between benzaldehyde and Danishefsky's diene.[222]

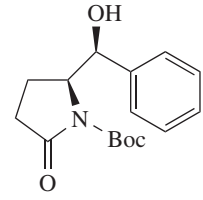
A mechanistic investigation of an enantioselective Mukaiyama reaction, consisting of a C−C bond-forming reaction and a silylation protection step, indicates that the enantioselectivity arises exclusively from the latter, via a kinetic resolution of the aldolate intermediate.[223] (*ee*)

A model compound has been designed to study the relative orientation of enol silane and carbonyl in a Mukaiyama aldol cyclization constrained to involve either *syn*-clinal or *anti*-periplanar orientation. The products are diastereomeric, allowing TS geometry to be correlated. Results for Lewis acids and fluoride are reported, the latter being independent of the nature of the cation. For tin(II) salts, the results *did* depend on the type of anion used.[224] (*de*)

Polyketide segments have been prepared via vinylogous Mukaiyama aldol reactions, with control of two new chiral centres.[225] *N*-Boc-2-silyloxypyrroles add to unsaturated aldehydes to give α,β-unsaturated-δ-hydroxylated-γ-butyrolactams [e.g. (**66**), from benzaldehyde]. Using a BINAP-derived bisphosphoramide catalyst, the vinylogous Mukaiyama aldol reaction gave 'three 99s' performance in terms of yield/diastereoselectivity/enantioselectivity in several cases, and is absolutely site selective (γ-addition only).[226] (*de*) (*ee*)

A highly diastereo- and enantio-selective copper-catalysed vinylogous Mukaiyama aldol has been reported.[227] (*de*) (*ee*)

t-Butyldimethylsilyl triflate, in combination with triethylamine, provides dual activation catalysis for intramolecular alkynylogous Mukaiyama aldol reaction of bicyclic alkanones tethered to alkynyl esters. The ring junction in the tricyclic allenoate product is formed with total diastereoselectivity.[228] (*de*)



(**66**)

A Mukaiyama–Michael reaction of (*Z*)-and (*E*)-silylketene acetals with a variety of α,β-unsaturated aldehydes exploits LUMO (lowest unoccupied molecular orbital)-lowering organocatalysis to achieve high diastereo- and enantio-selectivities.[229] (*de*)
BINAPO, a chiral phosphine oxide, catalyses enantioselective direct aldols. Using the reagent combination tetrachorosilane and Hunig's base (i-Pr_2NEt), the mechanism involves *in situ* formation of trichlorosilyl enol ethers.[230] BINAPO also catalyses aldol addition of ketene silyl acetals to benzaldehydes with moderate enantioselectivity.[231] (*ee*) (*ee*)

Enantioselective addition of *O*,*O*-ketene silyl acetals (derived from simple esters) to α-keto esters has been achieved using copper(II)–bis(oxazoline)complexes, dispensing with the need for the thioesters used in the Evans aldol. The new method is more tolerant of structural variation, and less subject to steric intolerance.[232] (*ee*)

Low-temperature and rapid-injection NMR techniques have been used to study the mechanism of Lewis-base-catalysed aldol addition. Taking the example of addition of the *t*-butylsilyl ketene acetal of *t*-butyl propanoate to 1-naphthaldehyde, ground and transition states have been correlated. A range of Lewis bases have been tested, including chiral ones giving both high and low selectivity.[233] (*ee*)

Other Aldol-type Reactions

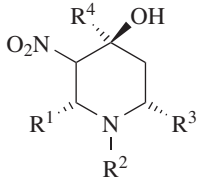
Asymmetric aldol-Tishchenko reactions of enolizable aldehydes, using a BINOL-Ti(O-t-Bu)$_2$/cinchona alkaloid complex as auxiliary, have been investigated kinetically, studying the interplay of the aldol/retroaldol process with the Tishchenko component.[234] (*de*) (*ee*)

Reaction of a nitroso compound with a carbonyl compound can give oxyamination ('*N*-product') or aminoxylation ('*O*-product'). (*S*)-Diphenylprolinol TMS ether catalysis gives the *N*-nitroso aldol product (>99 : 1 over *O*-), with 99% *ee*. The preference for the (*S*)-*N*-product has been investigated by computation, and the results favour an enol rather than an enamine intermediate, and specifically a *trans*-enol, which contributes to controlling the enantioselectivity.[235] (*ee*)

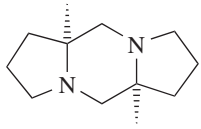
Camphor-annulated imidazolines catalyse asymmetric Henry reactions with up to 67% *ee*.[236] Copper(II) complexes of secondary diamines derived from *trans*-1,2-diamino-cyclohexane catalyse nitroaldol reaction of benzaldehyde and nitromethane at $-30\,^{\circ}C$, giving high yields, up to 99% *ee*, and moderate to good *anti*-diastereoselectivity, switching to *syn*- for aliphatic aldehydes.[237] A C_2-symmetric chiral diamine derived from isoborneol forms a copper(II) complex which catalyses nitroaldol reactions with yields of up to 95% and of up to 90% (*ee*) (*ee*)

ee.[238] Chiral tridentate ligands bearing hydroxyl, sulfinyl, and amino groups catalyse (*ee*) enantioselective nitroaldol reaction of nitromethane and benzaldehyde, giving yields (*ee*) of up to 90% with up to 98% *ee*.[239]

A one-pot asymmetric synthesis of substituted piperidines (**67**) employs a mild condensation of a nitroalkene (R^1 source), an amine (R^2), and an enone (R^3, R^4). Where chiral amines were used, a chirality induction through an unusual exocyclic (*de*) stereochemical control was observed. Mechanistic studies point to the irreversible (*ee*) Henry-aldol cyclization step as rate determining, which accounts for the piperidine diastereoselectivity.[240]



(**67**)



(**68**)

C_2-Symmetric diamine (**68**), complexed to copper(II), catalyses the Henry reaction of nitroalkanes with various aldehydes to give β-hydroxy nitroalkanes with yields up (*de*) to 97% with up to 42% *de* and 96% *ee*. Further steps give chiral aziridines.[241] (*ee*)

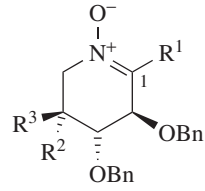
A chiral *P*-spiro tetraaminophosphonium salt mediates a direct Henry reaction of pyruvate esters with high diastereo- and enantio-selectivity.[242] Base-catalysed Henry (*de*) reactions of nitromethane with a variety of aldehyde types (and some aldehyde (*ee*) hydrates) show reversibility in alcohols. Equilibrium is also rapidly achieved in these solvents, and Triton B is a particularly effective catalyst.[243] The asymmetric Henry reaction has been reviewed, covering a range of types of chiral catalyst.[244]

Boron enolate aldol reactions of 1,2-*syn* β-alkoxy methyl ketones with achiral aldehydes result in excellent 1,5-*anti*-stereoinduction when the β-alkoxy protection is part of a benzylidene acetal. DFT and MP2 calculations have been used to examine the effects of the α-, β-, and γ-substituents, the β-alkoxy protecting group, the ligands (*de*) on boron, and so on.[245] (*ee*)

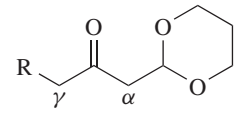
Non-terminal 7/6/5-alkynals undergo Brønsted-acid-catalysed intramolecular cyclization to give 7/6/5-membered cyclic enones; the reactions are essentially tandem alkyne hydration/aldol condensations.[246]

Carbohydrate-derived nitrones (**69**, $R^1 = CH_2OBn$) undergo β-elimination of the benzyloxy group at C(1) on treatment with samarium(II) iodide, giving a samarium(III) oxy-enamine intermediate. Reaction with carbonyl compounds yields aldol-type adducts, while protonation with water gives methyl product (**69**, $R^1 = Me$); that (*de*) is, overall transformation of a C−O into a C−C bond. The methyl group derives its H from H_2O (as confirmed by D_2O solvent, which gives $R^1 = CH_2D$).[247]

A simple primary–tertiary chiral diamine, *N*,*N*-diisopentyl-*trans*-diaminocyclohexane, catalyses direct aldol reactions of acetoacetals (**70**) with high (*de*) γ-regio-, enantio-, and diastereo-selectivity, using a Brønsted acid co-catalyst, (*ee*)



(**69**)



(**70**)

2,4-dinitrobenzenesulfonic acid. The transformation is equivalent to the direct aldol of a β-ketoaldehyde affording vinylogous-type aldol adducts.[248]

Metal-catalysed reductive aldol coupling of α,β-unsaturated compounds to aldehydes has been reviewed, focussing on cases with enolate intermediates.[249]

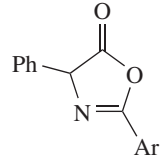
DFT has been used to probe the mechanism of the reaction of *endo*-2-bromoacetylisoborneol with prototypical aldehydes, RCHO (R = Me, Ph). The diastereoselective process involves an aldol-like reaction, followed by the formation of an epoxide. The terminal hydroxyl is vital for stereoselectivity.[250] (*de*)

Catalysts based on amino acids for asymmetric reactions in water have been reviewed (68 references), with particular emphasis on aldols, and hydrogenation of ketones.[251] (*ee*)

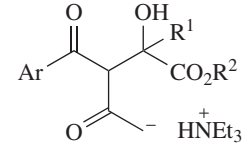
A catalytic carbanion reaction comparable to the direct aldol uses amide and ester equivalents (instead of aldehydes and ketones) to react with electrophiles in the presence of catalytic base. Strategies to overcome the α-proton pK_a barrier are discussed.[252]

A direct catalytic asymmetric aldol reaction of thioamides uses a soft Lewis acid/hard Brønsted base cooperative catalysis. The method has potential for accessing stereocontrolled synthesis of 1,3-polyols.[253] (*ee*)

Azlactones (**71**) undergo an enantioselective direct aldol-type reaction with vinyl ethers (e.g. $H_2C{=}CH{-}O{-}t$-Bu) using a chiral Brønsted acid catalyst to protonate the vinyl ether.[254] (*de*) (*ee*)



(**71**)



(**72**)

The rationale for control of aldol reactions that proceed via kinetic resolution has been explored, focussing on three stereocontrol elements: the diastereofacial selectivity of the aldehyde and of the ketone enol(ate), and the relative topicity of the coupling. Appropriate biasing for these elements should give kinetic resolution, implying that the enantioselectivity should be switchable if the sense of any one of the three elements is switched. The strategy has been tested in a series of Ti(O$-i$-Pr)$_4$-promoted boron enolate aldol processes.[255] (*de*) (*ee*)

Malonic acid half thio- and oxy-esters undergo decarboxylative nucleophilic addition reactions with ketone and aldehyde electrophiles in the presence of triethylamine. These decarboxylative ketone aldols, carried out under metal-free conditions, have been studied kinetically by using NMR, allowing identification of an intermediate (**72**, for the oxyester case), which occurs after nucleophilic addition but before decarboxylation.[256]

For reports on aza-Henry reactions,[99–103] see the section titled 'Other Reactions of Imines'.

The Baylis–Hillman Reaction and its Aza-, Morita-, and Sila-variants

Catalysis of the Baylis–Hillman (BH) reaction by phosphine derivatives has been reviewed.[257]

DFT calculations have been used to analyse the mechanism of the intramolecular BH reaction, considering catalyses by proline and by imidazole, and the role of water both in the presence and absence of these catalysts.[258] (ee)

Recent extensions of the MBH reaction have been reviewed (50 references); in particular, 'abnormal' cases have been discussed, such as double-, sila-, abnormal aza-, and tandem-MBH reactions.[259] (de) (ee)

A wide range of MBH reactions of conjugated nitroalkenes or nitrodienes with various carbonyl compounds have been reported, with the best results being obtained using DMAP (4-dimethylaminopyridine) catalyst in acetonitrile solvent. The role of DMAP is mainly ascribed to resonance stabilization of the initial zwitterionic intermediates. *E*/*Z*-Selectivities are discussed: they vary considerably with the type of carbonyl substrate.[260]

Anion catalysis of an MBH reaction has been achieved by coupling it to a 1,3-Brook rearrangement. Addition of γ-silylallenyl esters to aldehydes provides an entry point to [3.2.1]bicyclic natural products.[261]

Electrospray ionization mass spectrometry has been used to probe the mechanism of the MBH reaction, with key intermediates for the rate-determining step being intercepted and characterized.[262] Enantioselective MBH reactions have been reviewed, looking in particular at organocatalysts and at new mechanistic insights derived from electrospray ionization-MS/MS techniques.[263] (ee)

A chiral bifunctional phosphinothiourea catalyses MBH reactions of aromatic aldehydes with acrylates in excellent yields (up to 96%) with good enantioselectivities (up to 83%), under mild conditions.[264] (ee)

Chiral phosphinothioureas catalyse enantioselective MBH reactions.[265] A conjugate addition–elimination sequence has been developed to give protected allylic *syn*-1,3-diols which are MBH adducts.[266] The aza-BH reaction has been reviewed (210 references).[267] (ee) (de)

β-Amino carbonyl compounds bearing an α-alkylidene have been accessed via a highly enantioselective aza-BH-type reaction of α,β-unsaturated aldehydes with *N*-Boc- and *N*-Cbz-imines generated *in situ*.[268] (de) (ee)

In situ generated vinylaluminium reagents [e.g. i-$Bu_2Al{-}C(=CH_2){-}CO_2Et$] have been added to *N*-sulfinyl imines to give *N*-sulfinyl aza-MBH products

diastereoselectively; addition occurs from the least hindered direction. Hydrogenation of the products gives (protected) *anti*-α-alkyl β-amino esters.[269] (*de*)

A theoretical investigation of the MBH reaction and its aza-variant has focussed on the role of polar protic co-catalysts such as water, methanol, and formic acid, and in particular their ability to sustain relay proton transfer.[270]

β-Nitro-γ-enamines have been prepared from nitroalkenes and imines with yields up to 95% with up to 98% *de* and 91% *ee*. The tandem Michael addition/aza-Henry reaction is catalysed by a thiourea bearing a chiral diamine.[271] (*de*) (*ee*)

A sila-MBH reaction is proposed to overcome the formation of dimerization by-products under standard MBH conditions. This reaction of α-silylvinylaryl ketones with aryl aldehydes incorporates a 1,3-Brook rearrangement.[272]

Allylation and Related Reactions

The use of indium(I) and (0) catalysts for the allylation of ketones and *N*-acylhydrazones has been reviewed, including aqueous examples.[273]

Ketones and aldimines have been allylated using an allylboronic ester and the dimer of iridium(I)-cyclooctadiene chloride as the catalyst. Deuteration at the allylic position of the allylboronate results in scrambling, indicating vinyl shuttling on the iridium. This and other evidence indicates that a nucleophilic allyliridium(I) complex – activated by the diene ligand – attacks the ketone (or imine).[274]

Ruthenium trichloride catalyses allylation of aldehydes by allyl acetate in the presence of CO; water and triethylamine are also required, with CO_2 and acetic acid appearing as stoichiometric by-products. A mechanism is proposed which identifies the likely role of CO and water: their combination provides the stoichiometric reducing equivalent required, via the water gas shift reaction.[275]

The utility of Taft- and Charton-type steric parameters in correlating enantioselectivity of a reaction with ligand size has been examined for allylations of aldehydes and ketones, and a range of other reactions. Linear free energy relationships have been constructed by plotting the logarithm of the enantiomeric ratio against the steric parameters.[276] (*ee*)

An enantiospecific and *anti*-diastereoselective reaction of aldehydes with all-carbon-substituted α-chiral allylic stannanes uses bis(triorganostannyl)zinc reagents.[277] Aryl *t*-butyl sulfoxides promote enantioselective addition of allyltrichlorosilane to aldehydes.[278] (*de*) (*ee*)

Metal-mediated retro-allylation of homoallyl alcohols has been exploited to prepare allylmetals that are otherwise difficult to access. As the forward reaction (i.e. allylation of aldehyde) occurs under kinetic control, conditions have been sought to switch stereoselectivity. For example, a crotylzirconium reagent gives a *threo*-homoallyl alcohol at $-78\,^{\circ}C$, but *erythro*- at $25\,^{\circ}C$. The former occurs via a six-membered TS under kinetic control, but the latter involves isomerization via the retro-allylation process. Similar examples with a wide range of metals are reported.[279] (*de*)

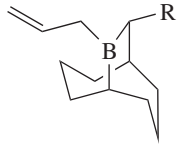
Diastereoselective synthesis of *anti*-tertiary homoallylic alcohols has been achieved by addition of allyltitanocenes to a range of ketones, with sterically hindered substrates giving complete diastereoselectivity.[280] (*de*)

Titanocene(III) complexes catalyse Barbier-type allylations, intramolecular crotylations (cyclizations), and prenylation of a range of aldehydes and ketones. Considerable mechanistic variation is seen in the reactions, many involving allyl radicals.[281]

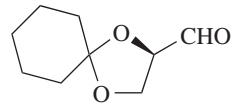
A phenyl-benzyl-carbinol-based auxiliary, readily accessible in both enantiomeric forms, has been developed for diastereoselective allylations of alkyl methyl ketones. (*de*)
Calculations support an oxocarbenium intermediate.[282]

A chiral diol-$SnCl_4$ complex acts as a protic catalyst for a range of highly enantio- (*de*)
and diastereo-selective allylations of aliphatic aldehydes.[283] (*ee*)

DFT calculations have been used to probe the origin of the enantioselectivity observed in allylboration of aldehydes and ketones, using Soderquist's chiral-substituted 9-borabicyclo[3.3.2]decanes (**73**, 'BBDs', R = TMS, Ph). Steric (*ee*)
interactions in the transition state are the main factors found, though more than one conformation of the BBD unit in the transition states must be considered.[284]



(**73**)



(**74**)

Allylboration of carbonyl compounds has been reviewed, focussing on stereoselective synthesis of homoallylic alcohols.[285] (*de*)

Asymmetric allylboration of ketones catalysed by chiral biphenols has been subjected to a kinetic and mechanistic study which has allowed the balance of rate and enantioselectivity to be optimized. The key role of added alcohols has been identified, (*ee*)
allowing isolated yield and enantioselectivity to reach 99% in some cases.[286]

DFT calculations indicate that BINAP-promoted enantioselective addition of allylboronates to ketones involves a cyclic Lewis-acid-activated boronate intermediate, and (*ee*)
not a Brønsted acid activation.[287]

Enamides and enol benzoates have been prepared under regio- and diastereo-control in a one-pot three-compound tandem Mitsonobu reaction/allylboration of aldehydes.[288] (*de*)

Dienals have been allylated enantioselectively using $Ni(cod)_2$ and chiral phosphonite (*ee*)
ligands, with allylboronic acid pinacol ester as the allylating agent.[289]

Silver(I) catalyses asymmetric Hosomi–Sakurai allylation of ketones using chiral (*de*)
allylsilanes, $R^1{-}CH{=}CH{-}{*}CH[Si(OMe)_3]{-}R^2$.[290] (*ee*)

(*R*)-Cyclohexylideneglyceraldehyde (**74**) undergoes Barbier-type crotylation diastereoselectively. Gallium metal in an ionic liquid solvent (butylmethylimidazolium bromide) gave the best results.[291] (*de*)

A regioselective allylation of aldehydes, and a regio- and diastereo-selective crotylation of aldehydes, has been developed.[292] (*de*)

A highly enantioselective α-crotylation of aldehydes, applicable to aliphatic substrates, involves a 'kinetic self-refinement': in each of the two steps of the reaction, (*ee*)
one stereoisomer is more reactive than the other, giving very high levels of geometric- and enantio-purity.[293]

An enantioselective crotylation of ketones using an auxiliary derived from norpseudoephedrine undergoes an unusual inversion for the pentenylation reaction. DFT calculations have been used to explain the effect, and to successfully match the selectivities of the corresponding hex- and hept-enylations.[294] (ee)

Olefinations and Ene Reactions

A kinetic study has allowed the direct comparison of nucleophilic reactivities of Horner–Wadsworth–Emmons carbanions and Wittig ylides with reference electrophiles (benzhydrylium cations and related quinine methides). Counterion ($Li^+/Na^+/K^+$) effects are also examined, in addition to reactions with other electrophiles, allowing existing nucleophilicity scales to be made more comprehensive.[295]

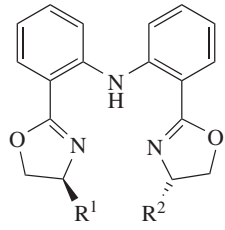
Aromatic aldehydes (ArCHO) react with organozinc halides (RCH_2ZnX, R = Ph, alkyl; X = Br/Cl/I) to give (*E*)-alkenes, ArCH=CHR, using a simple Lewis acid, aluminium trichloride.[296]

α-Fluoroacrylates have been prepared stereoselectively from aldehydes and ketones, using ethyl dibromofluoroacetate (Br_2FCCO_2Et), and diethylzinc as the mediator. The reaction with aldehydes is an *E*2-type process, while ketones react via *E*1*cb*. The aldehydes also give β-hydroxy-α-bromo-α-fluoro-esters as by-products, with some control over the product balance being achievable.[297] (de)

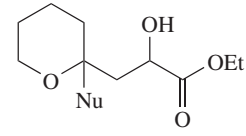
An (*S*)-BINOL/Ti(O−*i*-Pr)$_4$ system brings about enantioselective vinyl addition of vinylaluminium to ketones.[298] (ee)

Aryl aldehydes have been olefinated via a ruthenium-catalysed decarbonylative addition of terminal alkynes. The alkene products were predominantly *trans*- and some chemoselectivity was observed; aliphatic aldehydes did not react.[299]

A range of tridentate chiral ligands (**75**) give useful yields, excellent regioselectivity, and high enantioselectivities in chromium(III)-catalysed homoallenylation of aldehydes.[300] (ee)



(**75**)



(**76**)

Carbonyl olefin metathesis is known for cases with the two functional groups conjugated in one molecule. It has been reviewed, assessing the scope for non-conjugated and, indeed, intermolecular reactions and catalysis.[301]

2-Methylenetetrahydropyran undergoes a three-component coupling with an activated aldehyde or ketone, and a secondary nucleophile, to give 2-(tetrahydropyran-2-yl) alcohols [e.g. (**76**), using ethyl glyoxolate and triethylsilane: Nu = H]. Catalysed (de)

by a Lewis acid such as titanium tetrachloride, the reaction shows some diastereoselectivity, has been extended to allyl as a nucleophile (using allyl-TMS), and provides access to tetrahydropyranyl ketide derivatives found in natural products.[302]

Addition of simple alkenes to a range of carbonyl types, using catalysis by group 10 metals, has been reviewed.[303]

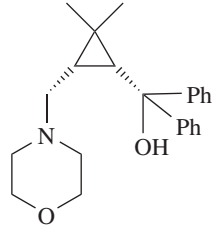
Alkynylations

Rhenium catalysis of the reaction of alkynes and allenes with 1,3-dicarbonyl compounds has been reviewed.[304] A proazaphosphatrane [$P(PhCH_2NCH_2CH_2)_3N$, **2**, R = Bn] acts as a Lewis base catalyst for the synthesis of propargyl alcohols and MBH adducts via aldehyde alkynylation, using TMS-alkynes.[305]

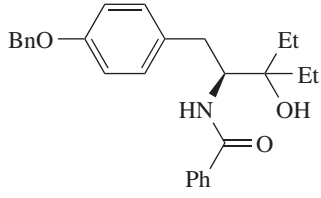
Indium(III) chloride catalyses a highly effective three-component reaction of a terminal alkyne ($R^1-C\equiv CH$), an aldehyde (R^2-CHO), and a secondary amine (HNR^3R^4), to give a propargylamine [$R^1-C\equiv C-C(R^2)-NR^3R^4$] with water as the only by-product. The indium may play several roles: in addition to C−H activation (converting the alkyne to an indium complex with the release of HCl, a catalyst for immonium salt formation from the aldehyde and secondary amine), it may act as a Lewis acid to make the aldehyde more electrophilic.[306]

The enantioselective addition of alkyne nucleophiles, including metal alkynylides, to prochiral ketones, aldehydes, and imines has been reviewed.[307] (ee)

A cyclopropyl amino alcohol (**77**), in combination with zinc, catalyses highly enantioselective alkynylations of aldehydes, without the need for titanium reagents.[308] (ee)



(**77**)



(**78**)

A series of diarylated BINOLs and their H_4- and H_8-analogues have been prepared and tested as catalysts of alkynylation of aldehydes to give propargyl alcohols. All reactions were promoted by $ZnEt_2/Ti(O-i\text{-}Pr)_4$, and gave up to 99% *ee*. Products with an appropriately placed alkene were taken onto cycloalkenes via ring-closing metathesis.[309] (ee)

A β-amido alcohol (**78**) derived from L-tyrosine, complexed with titanium(IV), catalyses enantioselective addition of methyl propiolate to aliphatic and aromatic aldehydes, to give γ-hydroxy-α,β-acetylenic esters with up to 94% *ee*.[310] (ee)

A mandelamide, readily prepared from mandelic acid and phenethylamine [both (*S*)-], catalyses enantioselective addition of terminal alkynes to aromatic (ee)

aldehydes in the presence of dimethylzinc.[311] A copper(I)-pybox ligand effects an enantioselective construction of chiral β,γ-alkynyl α-amino acid derivatives from three components: ethyl glyoxylate, *para*-anisidine, and alkynes.[312] *N*-Alkylation of diphenylprolinol with a mesitylmethyl group gives a good enantioselective catalyst for addition of alkynylzinc to aldehydes.[313] Diastereoselective addition of carbonyl compounds to 1,6-enynes is catalysed by gold(I). The cycloaddition produces 2-oxabicyclo[3.1.0]hexanes.[314]

(*ee*) (*ee*) (*de*)

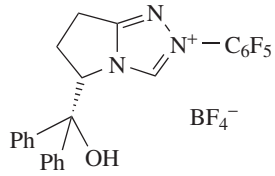
Benzoin, Stetter, Pinacol, Barbier, and Reformatsky Reactions

Bicyclic tertiary alcohols bearing quaternary stereocentres at two adjacent bridgehead positions have been synthesized via an intramolecular crossed benzoin reaction catalysed by NHCs. Some cases show near-perfect stereoselection, with diastereo- and enantio-selectivities >99%.[315]

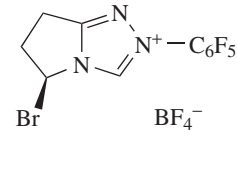
(*de*) (*ee*)

Precatalyst (**79**) – a progenitor of an NHC – has been employed in benzoin condensations, giving yields up to 100%, and some enantioselectivities >99%, using a base such as a carbonate or triethylamine, at room temperature. Notable design features include a diphenylprolinol chiral motif, including a hydrogen-bond-donor alcohol, and an acidifying pentafluorophenyl substituent on the triazole.[316] A new class of chiral triazolium ion gives up to 62% *ee* in the benzoin condensation. Evidence for hydrogen bond donation by the catalyst in the stereocentre-forming step is presented.[317]

(*ee*) (*ee*)



(**79**)



(**80**)

The asymmetric intramolecular Stetter reaction has been reviewed, concentrating on the use of chiral triazolium salts as organocatalysts.[318]

(*ee*)

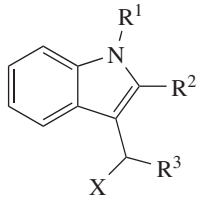
Building on recent advances in NHCs based on imidazole, a Stetter reaction has been developed using a triazolinylidene carbene, with chiral induction built into the catalyst (**80**). Glyoxamides have been reacted with alkylidene α-ketoamides as Michael acceptors, to give 1,4-dicarbonyls in good to excellent yields, and enantio-, and diastereo-selectivities.[319]

(*de*) (*ee*)

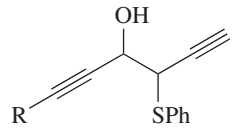
3-(1-Arylsulfonylalkyl)indoles (**81**, X = SO_2Ph) have been used as electrophiles in an umpolung reaction of aldehydes (ArCHO), using an NHC catalyst. This intermolecular Stetter-type reaction gives α-(3-indolyl) ketones (**81**, X = COAr) in high yields, for a wide range of substrates, under mild conditions. A chiral triazolium salt used as NHC renders the reaction enantioselective.[320]

(*ee*)

Nugent's reagent – $Cp_2Ti(III)Cl/Mn$ (prepared from titanocene dichloride and manganese dust) – unexpectedly promotes pinacol coupling of ketones, with some



(**81**)



(**82**)

diastereoselectivity. The titanocene plays a dual role, coordinating to the Lewis acid to facilitate single-electron transfer from the reductive metal (Mn; Zn also works) and also providing a template responsible for the stereoselection observed. (*de*) A cheap catalytic version was also reported: 0.2 equivalent of titanocene plus excess manganese also works if a titanocene-regenerating reagent is supplied (e.g. TMSCl/2,4,6-collidine).[321]

Samarium(II) triflate mediates diastereoselective pinacol coupling of (*Rp*)-2-diphenylphosphanyl ferrocenecarbaldehyde.[322] A pinacol-type intramolecular (*de*) reductive coupling of a ketone with a pendant *t*-butanesulfinyl imine at the δ-position gives *trans*-1,2-vicinal amino alcohols with 74% *de* and 98% *ee*, using samarium(II) iodide. A ketyl cyclization mechanism via single-electron transfer, rather than via an (*de*) anionic pathway, is supported by mechanistic experiments and the stereochemical outcomes.[323] (*ee*)

2-Oxaspiro-[4,5]decanes and -[4.4]nonanes have been prepared by Prins-pinacol annulations of alkene diols and a wide range of aldehydes and ketones.[324]

While indium-promoted reactions are often accelerated in water, Barbier coupling of propargyl aldehydes (R−C≡C−CHO) with α-chloropropargylphenyl sulfide (to give diyne **82**) is faster in *N*-methylformamide. The *syn*-isomer can be converted to (*de*) the corresponding epoxydiyne, while the *anti*- can be dehydrated to the ene(sulfide)-diyne.[325]

Progress in aqueous Reformatsky reactions has been reviewed, including the mechanism and applications.[326]

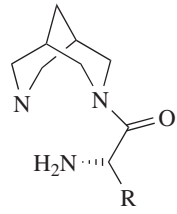
Michael Additions

DFT and *ab initio* methods have been used to probe the mechanism of organocatalysed Michael addition. Using pyrrolidine as a model secondary amine, the enamine pathways proved more accessible than those involving iminium routes.[327]

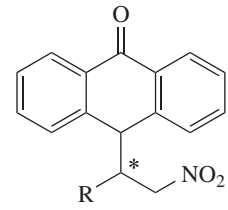
Chiral primary–secondary diamines based on bispidine (e.g. **83**, R = Ph, Bn) catalyse Michael addition of ketones to alkylidene malonates and nitroalkenes with yields (*de*) up to 99% and 98% *de* and 97% *ee*. Mild conditions and water or no solvent are (*ee*) employed.[328]

Pyrrolidine–pyridine catalysts used in Michael addition reactions of ketones to (*de*) chalcones yield the 1,5-diketone products with up to 98% *de* and up to 100% *ee*.[329] (*ee*)

An organocatalytic Michael reaction desymmetrizes *meso*- and prochiral ketones by direct addition to nitroolefins, with yield and diastereo- and enantio-selectivities up to



(**83**)



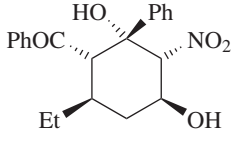
(**84**)

95% and 98 and 96%, respectively. The best catalyst is pyrrolidine (derived from proline) with a pendant *ortho*-hydroxynaphthamide as a hydrogen bond donor/acceptor.[330]

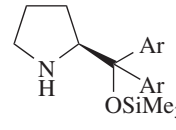
Bifunctional thiourea-tertiary amines catalyse Michael addition of anthrone to (*E*)-nitroalkenes, R−CH=CH−NO_2, to give the corresponding adducts (**84**, R = alkyl, Ph, naphthyl, furyl, etc.) in yields up to 97% with up to 94% *ee*, under mild conditions.[331] (*ee*)

A range of proline-derived catalysts have been tested on Michael addition of β-nitrostyrene to isovaleraldehyde, using ionic liquids as solvents. Good diastereoselectivities and modest enantioselectivity were obtained. Diastereoselectivity decreased with increasing temperature, but the thermal effects on the enantioselectivities were more complicated.[332] (*de*) (*ee*)

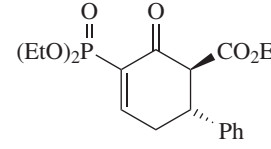
Synthesis of cyclohexanes with control of five stereocentres has been achieved: for example, (**85**) has been prepared from *trans*-pent-2-enal, dibenzoylmethane, and nitromethane, using a diarylprolinol catalyst, with 96% *de* and 99% *ee*. The one-pot synthesis proceeds via Michael addition followed by a tandem inter–intra double Henry reaction.[333] (*de*) (*ee*)



(**85**)



(**86**)



(**87**)

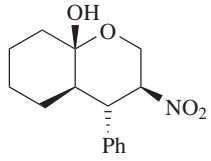
A Michael-type conjugate addition of aldehydes to vinyl sulfones shows modest diastereoselectivity. It is also highly enantioselective when diarylprolinol silyl ethers (**86**) are used as catalysts.[334] (*de*) (*ee*)

Optically active 3-(diethoxyphosphoryl)-2-oxocyclohex-3-ene-carboxylates (**87**) have been prepared with diastereo- and enantio-selectivities in the 90s, via a domino Michael–Knoevenagel condensation using a diaryl prolinol ether as the organocatalyst, starting from ethyl 4-(diethoxyphosphoryl)-3-oxobutanoate and an α,β-unsaturated aldehyde.[335] (*de*) (*ee*)

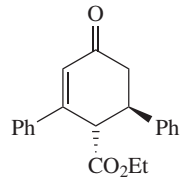
Recent advances in bifunctional iridium and ruthenium catalysts for enantioselective Michael and amination reactions have been reviewed.[336] (*ee*)

A domino Michael ketalization allows preparation of tetrahydropyrans with four contiguous chiral centres fused onto a cyclohexane (e.g. **88**). Starting from

a nitrostyrene alcohol such as *trans*-PhCH=C(NO_2)−CH_2OH (prepared via BH reaction of nitrostyrene and formaldehyde), reaction with cyclohexanone gives 62% yield and 97% *ee*, using a pyrrolidine-triazole catalyst (derived from L-proline), and TFA.[337] (*ee*)



(**88**)



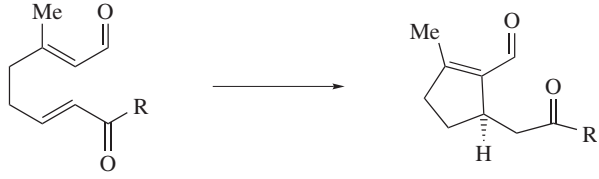
(**89**)

Benzoylacetates and α,β-unsaturated ketones undergo Michael-aldol-dehydration to give highly functionalized cyclohexenones. For example, ethyl benzoylacetate ($PhCOCH_2CO_2Et$) reacts with benzylideneacetone (PhCH=CHCOMe) to yield enone (**89**). Chiral primary–secondary diamine catalysts give fair diastereoselectivity, and yields and enantioselectivities of 99%.[338] (*de*) (*ee*)

Amphoteric amino aldehydes undergo a novel aza-Michael/aldol domino process, giving aminohydroxy α,β-unsaturated aldehydes in high yield and diastereoselectivity.[339] (*de*)

A diarylprolinol TMS ether with heavy aromatic buttressing catalyses a tandem Michael addition–Wittig reaction of *trans*-enals with (3-carboxy-2-oxopropylidene)-triphenylphosphorane (Ph_3P=$CHCOCH_2CO_2$−*t*-Bu) to yield cyclohexenone esters with 98% *de* and 99% *ee*. Lithium perchlorate and DABCO (1,4-diazabicyclo[2.2.2]octane) are also required.[340] (*de*) (*ee*)

An intramolecular Rauhut–Currier reaction creates a C−C bond between appropriately tethered Michael acceptors. A new enantioselective version (**90** → **91**) uses proline-derived catalysts to form electron-rich dienamines as key intermediates. The host catalyst was a diarylprolinol TMS ether with the four *meta*-positions CF_3 substituted (i.e. the commercially available Jørgensen–Hayashi catalyst). Although the aldehyde function is formally untouched, it is proposed to form an enamine with the catalyst, setting up controlled cyclization.[341] (*ee*)



(**90**) (**91**)

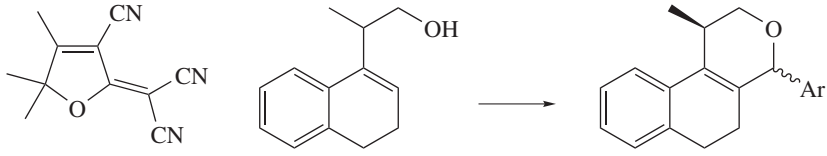
Miscellaneous Condensations

The titanium-promoted Knoevenagel condensation of dimethyl malonate and aldehydes has been studied by DFT and a range of spectroscopic techniques. The initial

deprotonation of malonate is favoured by the acidifying effect of titanium(IV) coordination. The following aldol condensation is promoted by titanium coordination of both the enolate and aldehyde. Then, elimination of water is favoured by formation of a titanyl complex.[342]

A kinetic study of the condensation of salicylaldehyde with diethyl malonate in toluene, catalysed by secondary amines such as piperidine, indicates that the Knoevenagel mechanism operates.[343] Chloride, when associated with soft organic cations, can catalyse the aldol and Knoevenagel condensations. A softness/hardness mismatch between cations and anions is suggested to enhance the nucleophilicity of chloride.[344]

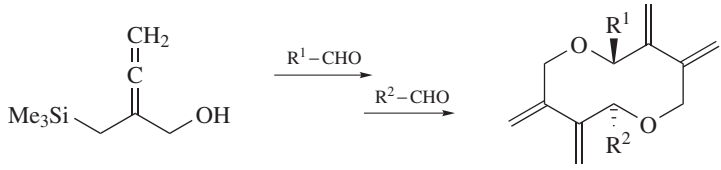
Synthesis of 2-dicyanomethylene-4,5,5-trimethyl-2,5-dihydrofuran-3-carbonitrile (**92**) from 3-hydroxy-3-methyl-2-butanone and malonitrile has been studied by DFT. Magnesium ethoxide lowers the activation barrier by 103 kJ mol^{-1}.[345]



(**92**) (**93**) (**94**)

Homoallylic alcohol (**93**) reacts with benzaldehydes to yield hexahydrobenzo[*f*]-chromenes (**94**, mixture of diastereomers) in an iodine-catalysed Prins cyclization. (*de*) Ketones also work [giving spiro-products, and changing the hydroxyl in (**93**) to tosylamino sets up the corresponding aza-Prins process] to give isoquinolines. Some of these reactions show useful diastereoselectivities.[346]

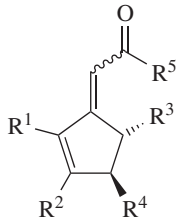
Entropically disfavoured 1,6-dioxecanes (e.g. **95**) have been prepared from a hydroxy(allenylmethyl)silane (**96**) and aromatic aldehydes via an intermolecular double Prins-type cyclization. Low-temperature NMR experiments provide evidence (*de*) of oxonium-ion intermediates, and extension to crossover experiments (i.e. $R^1 \neq R^2$) sheds light on the electronic effects of substituted benzaldehydes.[347]



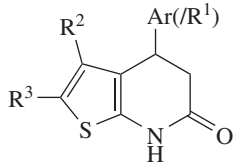
(**96**) (**95**)

A vinylogous Nazarov construction of cyclopentenone derivatives (**97**) has been developed, starting from acyclic cross-conjugated trienones.[348] (*de*)

The Biginelli synthesis of pyrimidines, from benzaldehyde, acetoacetate, and urea (or thiourea), has been investigated by ESI-MS and -MS/MS, supported by DFT calculations. The intermediates identified support the iminium mechanism, with little



(**97**)



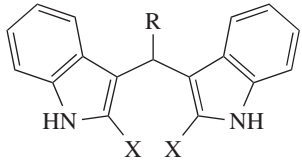
(**98**)

sign of Knoevenagel- or enamine-type intermediates: calculations suggest that the latter routes are higher in energy.[349]

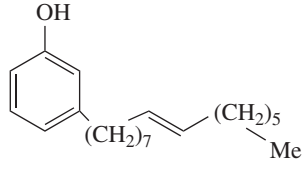
A new cascade reaction has been used to combine carbonyl compounds with malononitrile to give 1,1,2,2-tetracyanocyclopropanes. The reaction is quite general: for example, a cyclic ketone gives spiro-product at the 3-position.[350]

7-Aryl(or alkyl)-substituted 6,7-dihydro-4*H*-thiazolo[4,5-*b*]pyridine-5-ones (**98**) have been prepared in a three-component condensation of unstable derivatives of 2,4-diaminothiazole (generated *in situ*), an aldehyde, and Meldrum's acid.[351]

Bis(indolyl)methanes (**99**) have been prepared in very high yields using a few minutes of microwave radiation in an ionic liquid, starting from indoles (X = H, Me) and an aromatic or aliphatic aldehyde (RCHO). No catalyst is required.[352]



(**99**)



(**100**)

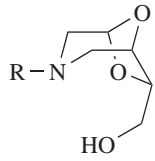
Cardanol (**100**), derived from cashew nuts, has been reacted with formaldehyde at 90–120 °C, using *para*-toluenesulfonic acid to catalyse novolac synthesis (i.e. formation of a phenol-formaldehyde-type resin). Rate data and thermodynamic properties are reported, and the polymeric products have been characterized.[353]

Other Addition Reactions

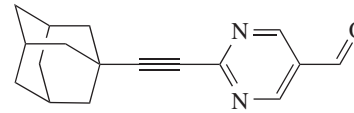
Addition of Organozincs

New chiral amide alcohols derived from camphor catalyse enantioselective addition (*ee*) of diethylzinc to benzaldehyde.[354]

Chiral bicyclic 1,4-aminoalcohols (**101**), in which the *N*-substituent is easily varied, catalyse enantioselective addition of diethylzinc to benzaldehyde. However, the (*ee*) reactions are slow, to the extent that the background racemic reaction (whose extent varies by commercial diethylzinc batch) has to be corrected for.[355]



(**101**)



(**102**)

A new asymmetric autocatalyst for Soai's diisopropylzinc reaction has been reported. The adamantyl derivative (**102**) gives up to 99% *ee* and also major amplifications, for example, 3.1 → 92.1% *ee*, in one reaction cycle. To ensure identical conditions, a parallel synthesizer system was used. The reaction has also been used to measure small enantioselectivities, via back-calculation from a detectable amplified result.[356] (*ee*)

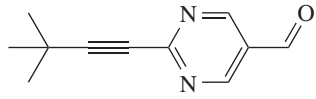
In the addition of diethylzinc to benzaldehyde, placing oxygenated side-chains – ether or acetal – on the nitrogen of ephedrine or pseudoephedrine has little effect on the enantioselectivity achieved.[357] A C_2-symmetric bis(imino-alcohol) derived from pinanone gives up to 99% *ee* in the same reaction.[358] Three *N*,*N*-dialkylated γ-aminoisoborneols, with varying degrees of oxygenation incorporated in the nitrogen's alkyl groups, have been tested as chiral ligands for the process: a pincer role for the oxygenated side-chain, activating and directing diethylzinc, is discussed.[359] Fair enantioselectivities were achieved using ephedrine catalysts bearing *N*-(pyridylmethyl) substitution.[360] (*ee*) (*ee*) (*ee*)

A C_2-symmetric BINOL derivative with flanking *para*-nitrophenol moieties catalyses titanium(IV)-mediated addition of diethylzinc to aromatic aldehydes with up to 89% *ee*.[361] A camphor-derived β-aminoalcohol gives up to 94% *ee* in addition of diethylzinc to aliphatic and aromatic aldehydes, taking 15 min at ambient temperature.[362] The amide of 2-furoic acid and (1*S*, 2*R*)-(+)-norephedrine adds diethylzinc to aromatic and heteroaromatic aldehydes with up to 99.8% *ee* in toluene in 24 h at 0 °C.[363] Chiral tridentate ligands bearing hydroxyl, sulfinyl, and aziridine groups catalyse diethylzinc addition to aryl and alkyl aldehydes with yields and enantioselectivities of up to 99% and 97%, respectively,[364] and a range of amino alcohols derived from (*S*)-6-chloronicotine give high enantioselectivities and good yields for a variety of aldehydes.[365] Chiral sulfinamido-sulfonamides give fair diastereo- and enantio-selectivity in addition to aldehydes with Ti(O−*i*-Pr)$_4$.[366] (*ee*) (*ee*) (*ee*) (*ee*) (*de*)

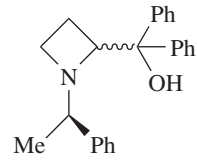
Amino alcohols derived from (−)-β-pinene catalyse dimethyl- and diethyl-zinc addition to benzaldehyde with 99% *ee*. A closely related auxiliary, derived from the same synthetic route, gives the opposite enantioselectivity, obviating the need to carry out a parallel synthesis from the (unnatural) (+)-β-pinene.[367] (*ee*)

Two formally achiral amino acids, glycine and α-methylalanine, can, nevertheless, possess chirality if partially deuterated. Both are found in meteorites, and in an isotopically enriched state (at least relative to terrestrial sources). Soai has now tested his pyrimidine aldehyde (**103**) on α-*d*-glycine and α-methyl-d_3-alanine as 'slightly chiral' auxiliaries: in the presence of diisopropylzinc, both produce highly enantio-enriched isopropyl pyrimidyl methanol. Yields and enantioselectivities are all in the 90s. The (*ee*)

large amplification of chirality found has implications for theories of the origin of homochirality in biology.[368]



(**103**)



(**104**)

Among dimethylzinc additions, a chiral ferrocenyl β-amino alcohol catalyses addition to aromatic aldehydes with up to 97.5%, without the need for other metals,[369] and a chiral amidoalcohol based on *cis*-cyclopropane adds to α-ketoesters with up to 81% *ee*.[370] (*ee*)

Organozincs have been added enantioselectively to ketones, using grafted isoborneosulfonamide polymers.[371] (*Z*)-α,α,β-Trisubstituted allylic alcohols have been prepared with high diastereo- and enantio-selectivity by coupling appropriate vinylzincs with prochiral aldehydes.[372] (*ee*) (*de*)

A diastereodivergent addition of allenylzincs to aryl glyoxylates depends on the method used for making the allenylzinc reagent. Aryl stacking in the TS of one of the routes (but not the other) may account for the result.[373] (*de*)

Chiral β-aminothiols proved superior enantioselective catalysts of alkynylzinc addition to aldehydes than the corresponding amino alcohols; yields were also typically higher.[374] (*ee*)

A range of diastereomeric azetidino amino alcohol pairs (**104**) have been prepared (separately) and tested as catalysts of addition of alkynylzinc to aromatic aldehydes. The configuration of the azetidine ring controlled the absolute stereochemistry of the product, while appropriate matching of the configuration of the side-chain centre boosted the enantioselectivity.[375] (*ee*)

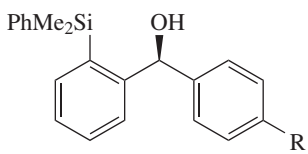
α-Trifluoromethylation of ketones via silyl enol ethers has been carried out using diethylzinc with a rhodium catalyst. A highly reactive ethylrhodium complex, derived from diethylzinc and $RhCl(PPh_3)_3$, was identified as a key intermediate. The method has been extended to α-trifluoromethylation of other carbonyl functions.[376]

Arylations

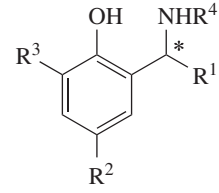
Recent advances in the enantioselective catalytic arylation of aldehydes, imines, and α,β-unsaturated carbonyl compounds have been reviewed.[377] Rhodium(I)-cyclooctadiene catalyses addition of arylboronic acids to aldehydes.[378] A chiral bis(phosphoramidite) derived from two linked BINOL units chelates ruthenium(II) to produce an enantioselective catalyst for arylation of aldehydes by arylboronic acids.[379] (*ee*) (*ee*)

Benzaldehyde – *ortho*-masked with a silyl group – has been arylated to give diarylmethanols (e.g. **105**) with up to 99% *ee*, using potassium aryltriolborates, catalysed by

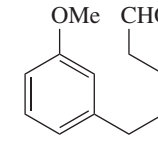
nickel bis(cyclooctadiene) and a duphos auxiliary. The steric tuning provided by the silyl group is critical for the high enantioselectivity, with the mask readily removable by protodesilylation (CsF/aqueous DMF reflux/quantitative).[380] (*ee*)



(**105**)



(**106**)



(**107**)

Thiophenyl methanols, $Ar^1{*}CHOHAr^2$ (Ar^1 = phenyl, substituted phenyl, naphthyl, furyl; Ar^2 = 2-thiophenyl), have been prepared with up to 96% *ee*, via asymmetric addition of thiophenylboronic acid to aldehydes in the presence of diethylzinc. Induction employed chiral *para*-Schiff-base alcohols derived from amino acids.[381] (*ee*)

Simple chiral aminophenols (**106**) catalyse arylation of aryl aldehydes by arylboronic acids with up to 99% *ee*.[382] (*ee*)

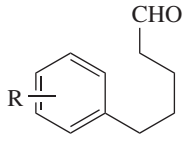
Aluminium reagents of the form $AlArEt_2(THF)$ efficiently arylate aldehydes under mild conditions, with high enantioselectivity, using a titanium(IV) complex of (*R*)−H_8−BINOL as a chiral catalyst. A similar protocol for ketones uses (*S*)-BINOL as auxiliary.[383] (*ee*)

A range of phenylaluminium reagents, $AlPh_nEt_{3-n}L$ (n = 1–3, L = Et_2O, THF, $Ph_3P{=}O$, or DMAP), have been prepared and characterized in solid state and in solution. In the presence of a chiral titanate complex and $Ti(O{-}i\text{-}Pr)_4$, the ethereal aluminium reagents arylate aldehydes with up to 94% *ee*; $AlPh_3{\cdot}THF$ was particularly effective. Neither the DMAP nor triphenylphosphine oxide complexes worked.[384] (*ee*)

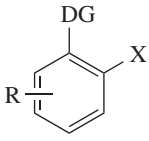
δ-Phenylaldehydes bearing a *meta*-methoxy group (**107**) undergo a Friedel–Crafts-type *α*-arylation to give the corresponding bicyclic aldehyde with high enantioselectivity, using a chiral imidazolidinone catalyst, and $Fe(phen)_3^{3+}$ as the oxidant, via 'SOMO' (singly occupied molecular orbital) catalysis.[385] *δ*-Phenylaldehydes without such a methoxy (**108**) also work, using chiral amines (with up to 95% *ee*) and ceric ammonium nitrate as the oxidant. An enamine intermediate is proposed, followed again by single-electron transfer.[386] (*ee*) (*ee*)

Arenes with a DG in (**109a**, X = H) can be acylated by aryl aldehydes to yield diaryl ketones (**109b**, X = COAr), using palladium(II) acetate in xylene at 120–130 °C, with air as the oxidant. The DG – 2-pyridyl, 2-pyridyloxy, or 2-pyridoyl – is palladated on nitrogen, activating the arene C−H. Although the DG limits the substrates, the method does allow direct access to ketones from aldehydes.[387]

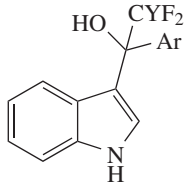
Iodine catalyses Friedel–Crafts alkylation of arenes ($Ar^1{-}H$) by aldehydes: aromatic aldehydes (Ar^2CHO) give triarylmethanes ($Ar^1_2Ar^2CH$), while aliphatic aldehydes (RCHO) give the corresponding diarylalkanes (Ar^1_2CHR).[388]



(**108**)



(**109a**: X = H;
109b: X = COAr)



(**110**)

Boron trifluoride monohydrate acts as an efficient catalyst for hydroxyalkylation of aromatics with aromatic aldehydes and dicarboxaldehydes, giving triarylmethanes, diarylmethylbenzaldehydes, and anthracenes in excellent yields. A good catalyst and less expensive than many superacids, it is also an effective protosolvating medium.[389]

Di- or tri-fluoromethyl-indolyl-phenylethanols (**110**, Y = H, F) have been prepared directly from indole and an appropriate ketone ($ArCOCYF_2$), using guanidine catalysis in water. This Friedel–Crafts-type alkylation gives near-quantitative yields. Conventional acid catalysis (to protonate/activate the ketone) gave poor results. Base catalysis, to activate the indole, was also unsatisfactory until guanidines were tested.[390]

Addition of Other Organometallics, Including Grignards

Synthetic methods for the preparation of alkanols by addition of organometallics to aldehydes and ketones have been reviewed.[391]

2-Thienylation of aryl alkyl ketones has been carried out with up to 97% *ee*, using tris(2-thienyl)aluminium · THF and an (*S*)-BINOL-titanate catalyst. Aliphatic ketones generally give poor enantioselectivities.[392] (*ee*)

Attachment of phosphite and phosphoramidite moieties to a furanoside framework yields a ligand for the nickel-catalysed addition of trialkylaluminium. High yields and enantioselectivities of up to 84% were reported.[393] (*ee*)

Rhodium(I) catalyses 1,2-addition of chiral secondary and tertiary alkyl potassium trifluoroborate salts, $R-CH^*(Ph)-BF_3^- K^+$, to araldehydes (ArCHO) to yield benzylic alcohols, $Ar-CH^*(OH)-CH^*(Ph)-R$, with complete stereoretention. β-Hydride elimination is avoided: a mechanism consistent with this is proposed.[394]

Asymmetric addition of achiral organo-magnesium or -lithium reagents to achiral aldehydes or ketones has been reviewed (77 references).[395] (*ee*)

The reaction of cyclopentadienyl organometallics with aliphatic ketones can be 'metal-tuned' for reduction or addition. When CpMgBr is used, reduction results, without C–C bond formation. But addition of zinc chloride diverts the reaction to Grignard, giving tertiary alcohols with complete diastereoselectivity.[396] (*de*) (*ee*)

A chiral α-pyrrolidinyl ketone can be arylated or alkylated diastereoselectively by Grignard reagents. The role of *N*,*O*-complexation of magnesium in controlling the result is discussed.[397] (*de*)

A theoretical study of the reaction of Grignard reagents (MeMgCl and MeMgBr) with acetone in diethyl ether confirms that the monomeric route is too energetic to

apply. The study suggests that the generally accepted cyclic dimer route does *not* operate, rather the dimer is linear. Given the strong solvent coordination present, a cluster of solvent molecules were incorporated into the calculation.[398]

Enantioselective Grignard addition to aldehydes, using (*S*)-BINOL/Ti(O−*i*-Pr)$_4$ catalysis, has been achieved using a Grignard *deactivation* strategy. Addition of bis[2-(*N*,*N*-dimethylamino)ethyl] ether ($Me_2N-CH_2CH_2-O-CH_2CH_2NMe_2$) allowed enantioselective addition with alkylmagnesium bromides, in particular; *i*-BuMgBr gave >99% *ee*. The additive may work by successfully suppressing the racemic background reaction.[399] (*ee*) (*ee*)

For Grignard addition to imines,[67] see the section titled 'Addition of Other Organometallics, Including Grignards'.

The Wittig Reaction

1,3-Dienes and 1,3,5-trienes have been prepared in water using semi-stabilized allyl ylides, with sodium hydroxide as the base, starting from aldehydes and enals, respectively. Fair to good *E*-selectivity is found.[400]

Two new stable phosphonium sila-ylides are promising as sila-Wittig reagents.[401]

DFT calculations have been employed to probe three possible pathways in the reaction of chloral with 2-methoxy-4*H*-1,3,2-benzodioxa-phosphorin-4-one.[402]

For a comparison of nucleophilic reactivities of Horner–Wadsworth–Emmons carbanions and Wittig ylides,[295] see the section titled 'Olefinations and Ene Reactions'. For an aza-Wittig[36] and an intramolecular aza-Wittig,[104] see the sections titled 'Synthesis of Imines' and 'Other Reactions of Imines', respectively.

Hydrocyanation, Cyanosilylation, and Related Additions

A mechanistic study of the asymmetric addition of TMSCN to aldehydes using VO(salen)X complexes (X = counterion, e.g. F or NCS) has been used to help design better asymmetric catalysts. Using kinetic and MS studies, parallel mono- and bimetallic pathways have been distinguished. The latter case involves cooperative catalysis by two vanadiums in different oxidation states, allowing simultaneous activation of aldehyde and cyanide reactants. The roles of counterion and molecular oxygen are also described.[403] (*ee*)

A chiral salen vanadium oxide catalyses cyanohydrin synthesis with up to 93% *ee* in propylene carbonate.[404] (*ee*)

Enantioselective enzyme-catalysed synthesis of cyanohydrins has been reviewed.[405] (*ee*)

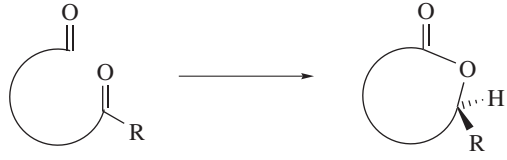
A multi-method theoretical study has probed the mechanism and enantioselectivity of hydrocyanation of aromatic aldehydes with a peptide catalyst, *cyclo*[(*S*)-His-(*S*)-Phe]. A dimer is found to be the catalytic species, with one imidazole delivering the nucleophile, and the other acting as an acid.[406] (*ee*)

Cyanohydrins derived from aldehydes and ketones have been hydrated to give amides, using platinum-phosphinite and molybdocene catalysts. Rates of hydration were slow, and a range of kinetic studies indicated cyanide poisoning of the catalysts. Under the conditions employed, the amide products were *not* subsequently hydrolysed.[407]

Methyl cyanoformate [Me−OC(=O)CN] adds to benzaldehyde enantioselectively, using a recyclable cinchonidine salt and triethylamine. This cyanoformylation is quantitative for aromatic and heteroaromatic aldehydes, with up to 96% *ee*, but less successful for aliphatic or α,β-unsaturated substrates.[408] (ee)

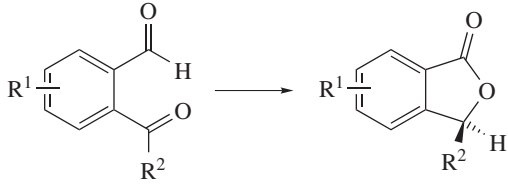
Chiral Lewis bases, such as natural products bearing a quinoline residue, catalyse enantioselective acetylcyanation of α-oxo esters by acetyl cyanide. Lewis acids and methanol also accelerate the reaction, which proceeds via racemic addition of cyanide followed by a dynamic kinetic resolution.[409] (ee)

A theoretical and experimental study has been undertaken of the mechanism of a highly enantioselective preparation of seven-membered lactones (**112**) via a rhodium-catalysed intramolecular ketone hydroacylation. This selective C−H activation process is believed to involve (i) rhodium(I) oxidative addition into the aldehyde C−H bond (of reactant **111**), (ii) insertion of the ketone C=O into the rhodium hydride, and (iii) C−O bond-forming reductive elimination. KIEs and Hammett plots, supported by DFT, indicate *step (ii)* as rate determining.[410] (ee)



(**111**) (**112**)

ortho-Ketoaldehydes (**113**) have been converted to phthalides (**114**) enantioselectively via the rhodium-catalysed ketone hydroacylation with a chiral diphosphine auxiliary. Counterion effects are important in the process, as some favour competing decarbonylation.[411]



(**113**) (**114**)

Hydrosilylation, Hydrophosphonylation, and Related Reactions

Substituted benzaldehydes and phenyl ketones have been hydrosilylated using triethylsilane, with $B(C_6F_5)_3$ as the Lewis acid catalyst, in a range of solvents. But metal(III) triflates (Bi, Al, Ga, Sc) change the chemoselectivity: the products are now dibenzyl ethers (and benzylated solvent, for benzene/toluene), with negligible hydrosilylation. With the borane catalyst, a dibenzyl ether is also formed when acetonitrile is the solvent. It is proposed that the triflate system allows the incipient silylcarboxonium

ion a longer lifetime, allowing it to react with the hydrosilylation product, and thus give the ether. For the $B(C_6H_5)_3/R_3SiH$ system, dibenzyl ether formation is believed to be favoured by equilibrium formation of silylnitrilium ion ($MeCN^+-SiR_3$) from MeCN.[412]

A new chiral phosphoramidite has been derived from BINOL complexes with rhodium, iridium, and palladium to produce enantioselective catalysts for a range of transformations, including hydrosilylation of ketones.[413] (ee)

A new mechanism for rhodium-catalysed hydrosilylation of ketones has been proposed. DFT calculations support a silylene intermediate, requiring the use of a secondary silane. The mechanism is also consistent with the observed inverse KIE.[414] The metal silylenes proposed as key intermediates help to explain the rate enhancement observed when dihydrosilanes (R_2SiH_2) are used instead of monohydrosilanes (R_3SiH).[415] (ee)

Thioureas bearing the (*S*)-α-phenethyl group catalyse enantioselective hydrosilylation of acetophenone by polymethylhydrosiloxane.[416] (ee)

For a reduction of ketones and imines exploiting silicon chirality in a hydrosilylation, see the section titled 'Regio-, Enantio-, and Diastereo-selective Reduction Reactions'.

A chiral tetraaminophosphonium phosphite has been detected at low temperature by NMR, and has been employed as an efficient enantioselective catalyst for hydrophosphonylation of aldehydes.[417] (ee)

α-Ketoesters have been hydrophosphonylated enantioselectively using thiourea organocatalysts bearing a cinchona alkaloid auxiliary.[418] (ee)

Mono(α-hydroxy)phosphines, $R^1_2PCH(OH)R^2$ (R^1 = Ph, CyHx; R^2 = H, Et, Bn, Ph), have been prepared under solvent-free conditions from the appropriate phosphine (R^1_2PH) and aldehyde (R^2CHO). The reaction is reversible, and stabilities of the materials have been studied in DMSO, Et_2O, and MeOH. They react with cinnamaldehyde in DMSO (except for R^2 = H) to give mono- and di-phosphines, $R^1{}_2PCH(Ph)CH_2CHO$ and $R^1{}_2PCH(Ph)CH_2CH(PR^1{}_2)OH$, and the starter aldehyde, R^2CHO. Several intermediates were characterized, and rates and equilibria measured.[419]

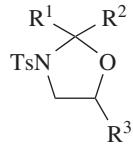
Miscellaneous Additions

Carbonyl destabilization by positive charge is evident in pyridinium ketones which show considerable hydrate and hemiacetal contents in water and methanol, respectively. Equilibrium constants were measured for acetyl and benzoyl cases of *N*-methylpyridinium at the 2-, 3-, and 4-positions. Using ^1H NMR, the 4-isomers had the highest values: 21% and 58%, respectively. Polar substituent constants, σ^*, for 2/3/4-pyridinium were calculated from the equilibrium constants.[420]

DFT calculations have been used to study the mechanism of hydration of four 'heavy' ketones with Si=S, Si=Se, Ge=S, and Ge=Se double bonds. All reactions proceed via an easily formed complex which then isomerizes via a four-membered TS with barriers of 18, 18, 35, and 40 kJ mol^{-1}, respectively.[421]

2-Alkyl-*N*-tosylaziridines react with aldehydes or ketones to give 5-alkyl-1,3-oxazolidines (**115**, R^1, R^2 derived from aldehyde or ketone, R^3 = substituent from

aziridine). Scandium(III) triflate catalyses the reaction, and regioselectivity for the 5-position is enhanced when the carbonyl substrate contains a substituent that can coordinate the catalyst and direct the aldehyde/ketone.[422] (*de*)



(**115**)

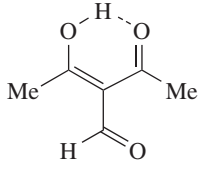
A nickel(0) precatalyst, combined with an NHC, activates ketones and aldehydes towards addition of organoborate esters.[423]

Enantioselective addition of alkyl propiolate to aliphatic aldehydes in the presence of $Et_2Zn/Ti(O-i\text{-}Pr)_4$ uses a H_8-BINOL catalyst.[424] (*ee*)

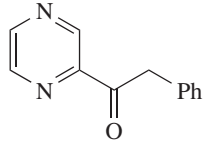
Recent advances in stereoselective hydroboration of carbonyl compounds have been reviewed.[425] (*ee*)

Enolization and Related Reactions

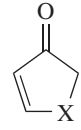
The tautomerization of 3-formyl-acetylacetone ($Ac_2CH-CHO$) has been studied by low-temperature NMR (to move the equilibria into the slow exchange regime), backed up by *ab initio* and DFT calculations in the gas phase and a continuum solvent model. A deuterated freon mixture, $CDClF_2$:CDF_3 (1 : 1), was employed: in addition to allowing access to measurements at 120 K, its dielectric constant is highly temperature dependant. The ketone tautomer was not observed over the range studied, with the 'acetylacetone' enol (**116**) and its degenerate enol predominating (ca 80% at 293 K), plus some enolization of the formyl group. The predominant tautomer (**116**) has the stronger hydrogen bond, as indicated by its chemical shift (19.3 ppm at 123 K). The equilibrium between enols is barely affected by change in dielectric constant: (**116**) goes only up to 86% at 123 K.[426]



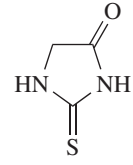
(**116**)



(**117**)



(**118**, X = O, S)



(**119**)

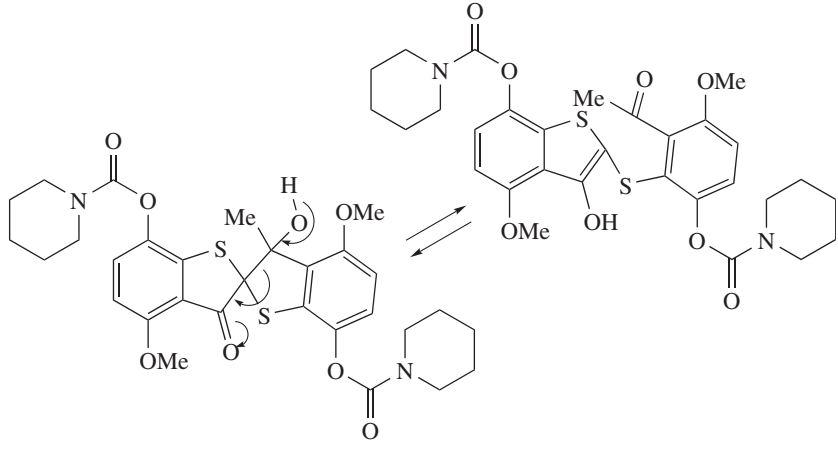
Enolization of phenylacetylpyrazine (**117**) is catalysed by acid, base, and metal ions in aqueous solution. Unusually, metal ions are more efficient catalysts: $k_{Zn}/k_H = 600$. This is in sharp contrast to tautomerization of the related 2-phenacylpyridine (2-$Py-CH_2COPh$), with a rate ratio of 0.0065. Kinetic and equilibrium experiments

have been carried out to fully characterize K_T and K_a values for (**117**), leading to the conclusion that differences in thermodynamic driving force can explain the contrast between the two substrates: in particular, the greater basicity of pyridine versus pyrazine.[427]

Deprotonation of 3(2*H*)-furanone and -thiophenone (**118**) by a series of delocalized carbanions, and by cyanide, exhibits evidence of disproportionately high aromaticity in the TS. MP2/6-31+G** calculations of several aromaticity parameters suggest that its development is more advanced than proton transfer, and that this lowers the intrinsic barrier to the reaction. Nevertheless, this barrier-lowering effect is substantially smaller compared to cases with 'fully aromatic' products, that is, deprotonation of protonated benzene or of cyclopentadiene.[428]

Proton transfer processes in 2-thioxoimidazolidin-4-one (**119**) involve a competition between keto-enol and thione-thiol tautomerizations. DFT calculations have been used to probe both the direct and water-assisted processes.[429]

Two diastereomers of 3′-hydroxy-4,4′-dimethoxy-3′-methyl-3-oxo-7,7′-bis(piperidino-carbonyloxy)-2,2′-spiro-bi[2*H*,2′*H*,3*H*,3′*H*-benzo[*b*]thiophene] (**120a**) equilibrate via an open-ring 3-hydroxybenzothiophene (**120b**) bearing a pendant acetyl group. The spiro form is more stable, despite the latter's aromaticity. The combined processes can be considered as linked keto-spirol and keto-enol tautomerizations. Acid-catalysed transformations of (**120a**) are also reported.[430]



(**120a**) (**120b**)

Substituent effects in keto-enol tautomerization of aliphatic ketones have been modelled using the MP2 method. Addition of one water molecule to the process was unfavourable, but two molecules lowered the barrier in all cases studied.[431]

The keto-enol tautomerization of 2-nitro-cyclohexanone appears to be anomalously fast in ionic liquids, based on solvent permittivity (when compared to the rates in common organic solvents). However, when more parameters are considered (polarizability, hydrogen bond acidity, cohesive pressure), a single linear solvent energy

relationship for both types of media can be constructed, negating any suggestion of a special 'ionic liquid effect'. It is noteworthy, however, that the TS structure becomes more enolate-like in ionic liquids, with a Brønsted β value close to unity.[432]

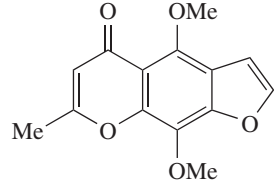
The relative C−H acidities of four functional groups – ketones, amides, esters, and acid fluorides – have been assessed in the gas phase by two computational methods. Acetone, acetonitrile, acetic acid, and acetyl fluoride were used as models (considering only their methyl acidities). The resonance and inductive effects were calculated using a vinylogue extrapolation, and by a block-localized wave function. While trends varied somewhat between methods, resonance was a bigger effect in all cases, and the combined effects gave excellent agreement between the methods, with fluoride > ketone ≈ ester > amide.[433]

A computational study has examined negative charge development at the α-carbon of the lithium enolate of acetaldehyde. Starting from the well-known tetrameric lithium enolate aggregate, a range of solvents have been attached to a single lithium. σ-Bonded complexes result in −0.5 a.u. charge on carbon, whereas π-bonded ones such as benzene give a higher charge (−0.7). High C=C double bond character is, nevertheless, observed.[434]

Bridgehead lithiation–substitution of bridged ketones, lactones, lactams, and imides has been tested by experiments and rationalized by B3LYP and NBO calculations. The reaction was feasible for several [$x.y.1$] systems, for example, $x = 3$, 4; $y = 2$, 3, but did not work where the sum of the bridging atoms was 5. The anions formed sometimes behaved like bridgehead enolates, whereas others were better described as α-keto carbanions.[435]

A key issue with enols as ambident nucleophiles is the relative rate at carbon versus oxygen, which can be settled in appropriate cases by knowing the product ratio. A method has now been reported for cases where only one final product is obtained. In the case of nitrosation, the *C*-reaction proceeds via rate-limiting electrophilic attack, whereas *O*-reaction involves rate-determining proton transfer, and the nucleophilic and general-base catalyses can be distinguished.[436]

A semi-empirical study of the hydrolysis of khellin (**121**, a furanochromone) indicates an enolate mechanism, leading to khellinone formation in basic media, and ω-acetokhellinone in acid.[437]



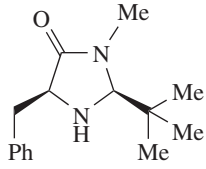
(**121**)

Allylic alcohols have been isomerized to aldehydes via the enol, using an iridium hydrogenation catalyst.[438]

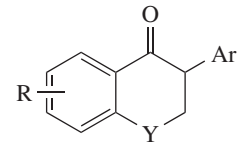
α-Halogenation, α-Alkylation, and Other α-Substitutions

A short review describes recent advances in organocatalysed direct asymmetric α-halogenation of carbonyl compounds.[439] (*de*) (*ee*)

In a 'linchpin' strategy of asymmetric catalysis, an enantio-enriched α-chloroaldehyde has been prepared, allowing access to many synthons: α-chloro and -cyano alcohols, α-amino and -hydroxy acids, and terminal aziridines and epoxides. Using organo-SOMO catalysis, a cheap chloride source such as NaCl is reacted with an aldehyde using a one-electron oxidant and chiral catalyst (**122**). Subsequent conversion to epoxide is also demonstrated: both reactions give >90% *ee*.[440] (*ee*)



(**122**)

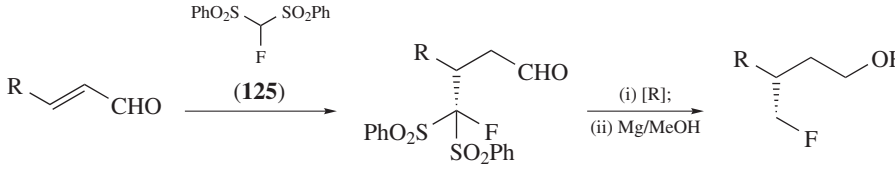


(**123**)

The kinetics of the bromination of 5-substituted 2-hydroxyacetophenones by phenyltrimethylammonium tribromide have been reported.[441]

Isoflavanones [3-aryl-chroman-4-ones, (**123**, Y = O)] and protected 3-phenyl-2,3-dihydroquinolin-4(1*H*)-ones (**123**, Y = N-Pg) have been alkylated at the 3-position with up to 92% *ee*, using a new cinchonidine-derived phase-transfer catalyst.[442] (*ee*)

A highly enantioselective formal addition of fluoromethyl anion to α,β-unsaturated aldehydes (**124**) has been achieved using fluorobis(phenylsulfonyl)methane (**125**) and a diarylprolinol ether organocatalyst. The immediate product aldehyde (**126**) can be oxidized to give the corresponding carboxylic acid. Alternatively, reduction to the alcohol can be followed by removal of the sulfonyl groups to give the γ-(fluoromethyl) derivative (**127**) of the alcohol.[443] (*ee*)



(**124**) (**126**) (**127**)

Nucleophilic difluoromethylenation of aldehydes and ketones has been carried out using the reagent $(EtO)_2P(=O)CF_2SiMe_3$, under mild conditions.[444]

Evidence for activation via a hydrogen bond is presented in a highly enantioselective sulfenylation of β-ketoesters catalysed by an α,α-diaryl prolinol.[445] (*ee*)

β-Nitroaldehydes have been prepared with good enantioselectivity and fair diastereoselectivity, from aldehydes and nitronates, via α-nitroalkylation with oxidative organocatalysis. Evidence for competing *syn*- and *anti*-selective mechanisms is discussed.[446] (de) (ee)

A proline-catalysed enantioselective α-aminoxylation of aldehydes and ketones with nitrosobenzene has been reported.[447] (ee)

Enantioselective proline-catalysed α-aminoxylation of aldehydes with nitrosobenzene is accelerated by addition of a bifunctional urea, $PhNHCONHCH_2CH_2NMe_2$. The rate enhancement appears to relate to stabilization of an oxazolidinone intermediate by the urea, increasing the rate of enamine formation. This is backed up by failure of the urea to work in the case of prolines incapable of forming oxazolidinones. The finding has been extended to other enamine cases: for example, the urea further accelerates a Mannich reaction which is proline catalysed.[448] (ee)

$P(i\text{-}PrNCH_2CH_2)_3N$ (**2**, R = *i*-Pr) efficiently catalyses addition of trimethylsilyl–acetonitrile ($TMS-CH_2CN$) to aldehydes under mild conditions, giving β-hydroxynitriles in up to 95% yield (after acid workup).[449]

Direct enantioselective hydroxymethylation of aldehydes with formaldehyde – to give α-substituted β-hydroxyaldehydes – is catalysed by diphenylprolinol TMS ether. The products were typically not isolated, but converted to more readily isolable derivatives such as the hydroxy acids, with yields and enantioselectivities of up to 94 and 99%, respectively. Alternatively, the aldehyde group could be retained 'as is' if the hydroxyl was protected on formation.[450] (ee)

For a study of α,α-diarylprolinol TMS ethers (**47**) as enantioselective catalysts in α-functionalization of aldehydes,[169] see the section titled 'Reviews of Organocatalysts'. For an α-trifluoromethylation of ketones using diethylzinc, see the section titled 'Addition of Organozincs'.[376]

Oxidation and Reduction of Carbonyl Compounds

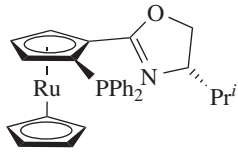
Regio-, Enantio-, and Diastereo-selective Reduction Reactions

Enantioselective hydrogenation of a range of ketone types has been reviewed, with an emphasis on diphosphine-ruthenium(II) catalysts.[451] (ee)

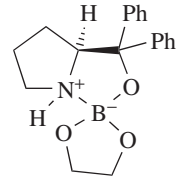
Aryl alkyl ketones have been reduced by asymmetric transfer hydrogenation using 2-propanol and a pseudo-dipeptide complexed to ruthenium(II), with good yields, short reaction times, and enantioselectivities >99% in some cases. Rate constants have been determined for individual steps. KIEs show that hydride transfer is rate determining: none were found for proton transfer. Lithium cation is catalytic. A bimetallic outer-sphere mechanism is proposed.[452] (ee)

Ruthenocenyl phosphinooxazoline ligand (**128**) catalyses near-quantitative hydrogenation of aromatic ketones, with up to 98% *ee*.[453] (ee)

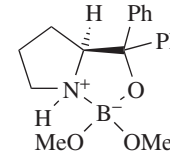
A benzimidazole with a chiral amino side-chain at C(2) acts as a bidentate ligand for ruthenium(II), inducing up to 99% *ee* in catalytic hydrogenation of aryl ketones. Substrate/catalyst ratios of up to 50 000 are effective and the system is air-stable, and unusually for this type of catalyst it works in non-polar and polar solvents.[454] (ee)



(**128**)



(**129**)



(**130**)

trans-$RuH_2(H_2N{-}CMe_2{-}CMe_2{-}NH_2)$[(*R*)-BINAP] catalyses hydrogenation of ketones by hydrogen gas in benzene solution. The mechanism is proposed to involve rapid transfer of hydride (from the ruthenium) and proton (from the amine) to the carbonyl of the ketone, yielding alcohol product and an unsaturated ruthenium by-product. The latter then splits dihydrogen, regenerating the catalyst. A KIE of 2.0 was measured for the reduction of acetophenone, using H_2 then D_2, with DFT predicting 2.1.[455] (*ee*)

Matching and mismatching effects have been examined in doubly chirally axial catalysts of the enantioselective hydrogenation of ketoesters.[456] (*ee*)

Spiroaminoborate (**129**, derived from diphenylprolinol) catalyses borane reduction of furyl-, thiophene-, chroman-, and thiochroman-containing ketones with up to 99% *ee*. Several enones were also reduced, albeit with lower enantioselectivity.[457] The closely related (non-spiro) aminoborate (**130**, also from diphenylprolinol) is comparably enantioselective: 1 mol% loading gives up to 99% *ee* for prochiral ketones. The X-ray crystal structure of (**130**) shows a dimer, linked by two N−H···OMe hydrogen bonds.[458] (*ee*) (*ee*)

C_2-Symmetric chiral bis-hydroxyamides induce borane reduction of prochiral ketones with yields up to 99% with up to 97% *ee*.[459] (*ee*)

β-Chlorodiisopinocampheylborane reduces arylalkyl ketones enantioselectively. A ^{13}C KIE method has been used to probe the desymmetrization. Comparison of experimental and computed KIEs highlight the roles of non-bonded interactions, directed orbital interactions, and hydrogen tunnelling.[460] (*ee*)

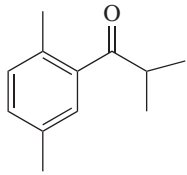
β-Isopinocampheyl-9-borabicyclo[3.31]nonane (Alpine-Borane) gives close to 100% *ee* in the reduction of *d*-benzaldehydes, but an in-depth investigation of this phenomenon found a correlation breakdown between observed and calculated rates for 2,6-dimethyl benzaldehydes. The loss of selectivity suggests breakdown of Alpine-Borane, implicating a non-selective reduction by 9-BBN.[461] (*ee*)

Prochiral ketones have been reduced by borane dimethyl sulfide with yields and enantioselectivity up to 99.8%, using a chiral oxazaborolidine derived from norephedrine.[462] (*ee*)

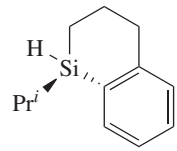
Borane-mediated enantioselective reduction of prochiral ketones promoted by amino alcohols derived from pinene has been investigated by DFT.[463] (*ee*)

Recent advances in enzyme-catalysed reduction of carbonyl compounds have been reviewed.[464] A combined quantum and molecular mechanics study of the reductive half-reaction of aldehyde oxidoreductase highlights the roles of a glutamic acid residue.[465] (*ee*) (*ee*)

Deuterium KIEs have been used to explore the role of non-bonding interactions in the enantioselection of the Corey–Bakshi–Shibata reduction of 2,5-dimethylphenyl isopropyl ketone (**131**).[466] (ee)



(**131**)



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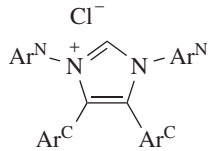


(**133**)

Ab initio molecular dynamics simulations have been used to probe the mechanism of sodium borohydride reduction of ketones in methanol, and, in particular, the origin of diastereoselectivity has been examined with reference to the experiment. Evidence for sodium cation complexation at the carbonyl is discussed.[467] (de)

Exocyclic enaminones (>N−C=C−C=O) have been hydrogenated enantioselectively using an iridium(IV)/I_2/chiral phosphine protocol.[468] (ee)

Direct asymmetric reductive amination of ketones has been achieved with hydrogen as the reductant, using a cooperative metal-Brønsted acid catalyst.[469] (ee)

The origin of enantioselectivity in the organocatalytic reductive amination of α-branched aldehydes has been investigated by computation.[470] (ee)

A silicon-stereogenic silane (**132**) has been used for stereoinduction by single-point binding. It reduces ketones via $B(C_6F_5)_3$-mediated hydrosilylation, with fair to good stereoselection. However, no asymmetric induction was seen for imines, a finding put down to different reaction pathways for the reduction steps in ketones versus imines.[471] (de) (ee)

Other Reduction Reactions

Precursors to tetraaryl-NHCs (**133**) combine with iridium(I)-cyclooctadiene to give excellent catalysts for transfer hydrogenation. A systematic study of variation of the Ar^N and Ar^C substituents indicates that the former are more important in the control of catalysis. Hammett treatments indicate a greater sensitivity to substituents on Ar^N, somewhat complicated by X-ray crystallographic evidence that none of the rings are close to being coplanar with the triazolium.[472]

Ruthenium(II), complexed with a tridentate ligand – a pyridine bearing a benzimidazole and a pyrazole – catalyses transfer hydrogenation of ketones and aldehydes in air, using 2-propanol. Many reactions were near-quantitative in seconds with turnover factors approaching 10^6 h^{-1}.[473]

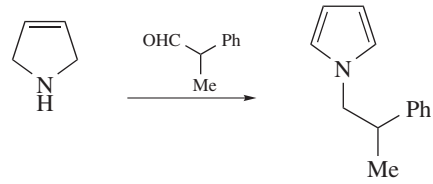
Three iron(III) complexes have been reported as catalysts for reduction of a wide variety of carbonyl types by sodium borohydride in acetonitrile under mild aprotic conditions: $FeCl_3(Py)_4$, $FeCl_3[(NH_2)_2CO]_6$, and $FeCl_3[(NH_2)_2CS]_6$.[474]

Reduction of benzophenones by samarium(II) iodide has been studied by stopped flow kinetics. Electron transfer takes place within the mixing dead time, typically

being quantitative. Post-transfer kinetics have been analysed, which indicates that the radical anion of benzophenone is in equilibrium with a Streitwieser dimer. The latter protonates ca 10 times faster than the monomer. In the absence of a proton donor, the radicals couple.[475]

The hydration/internal disproportionation of glyoxal (OHC−CHO) to give glycolic acid (HO−CH_2−CO_2H) has been studied by DFT calculations for the case of Al(III) catalysis.[476]

N-Alkylpyrroles (e.g. **135**) have been prepared via an intermolecular redox amination between 3-pyrroline (**134**) and 2-phenylpropanal. The highly atom-efficient reaction (no redox reagents are required) works for a variety of aldehydes, ketones, and lactols.[477]



(**134**) (**135**)

Reductive cross-coupling reactions of carbonyl and imine functions, as a route to *β*-amino alcohols, have been reviewed (122 references).[478] *de* *ee*

Triethylborane promotes rhodium(I)-catalysed reductive coupling of aldehydes with conjugated dienes, to give homoallyl alcohols.[479]

Cyclopent-2-enone has been reductively coupled at C(2) with aromatic aldehydes, using diphenylmethylsilane as a hydride donor, and a chiral ruthenium(II) phenylbis(oxazoline) ('Phebox') catalyst. The resulting *β*-hydroxy ketones are obtained *anti*-selectively (up to 96%), with up to 93% *ee*.[480]

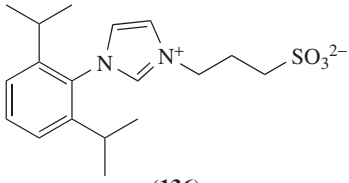
Oxidation Reactions

Oxidation of substituted benzaldehydes by butyltriphenylphosphonium dichromate in DMSO exhibits kinetics which are first order in the oxidant and second order in the hydronium ion. Charton's tri- and tetra-parametric equations (LDR and LDRS) have been used to correlate the substituent effects. KIE and solvent effects are also reported.[481]

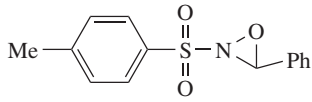
A non-linear (V-shaped) Hammett plot has been observed in the kinetics of oxidation of substituted benzaldehydes by pyrazinium chlorochromate in acetic acid solution. The reaction is catalysed by oxalic acid, and inhibited by manganese(II).[482]

The kinetics and mechanism of the oxidation of 2-hydroxynaphthaldehyde by alkaline *N*-bromosuccinimide have been studied in aqueous solution, with fractional orders being observed in the alkali and substrate, while the rate is first order in NBS.[483]

Aryl aldehydes bearing electron-withdrawing groups have been oxidatively carboxylated with water, using an NHC catalyst precursor (**136**). The imidazolium bears a pendant sulfoxyl which is believed to deliver an activated water to the carbonyl (subsequent to carbene attachment to the aldehyde).[484]



(**136**)



(**137**)

Kinetics of oxidation of six aliphatic aldehydes by morpholinium chlorochromate are first order in each of aldehyde, oxidant, and hydronium ions, and show a substantial primary KIE: $k_H/k_D = 5.95$ for MeCDO at 298 K. Solvent effects have also been measured, and a hydride ion transfer mechanism is proposed.[485]

Cyclic and aryl alkyl ketones have been conveniently oxidatively cleaved by quinolinium dichromate in 20% aqueous acetic acid solution, to give carboxylic acids.[486]

Cyclopentanone and cyclohexanone are oxidized by alkaline hexacyanoferrate(III), with rhodium(III) chloride acting as a catalyst. While the kinetics are first order in ketone and hydroxide, raising the concentrations of oxidant and catalyst results in the achievement of rate maxima, followed by retardation: these behaviours are explained in terms of pH-dependent processes.[487]

Two catalysts, mercury(II) and *N*-bromophthalimide (NBP), have been studied by kinetics of the oxidation of butanone by iodine monobromide (IBr) in acetic–perchloric acid mixtures. The former is proposed to involve an enol–Hg(II) complex reacting with IBr in the rate-determining step, while acid-catalysed enolization is rate determining in the NBP reaction, with the enol then reacting rapidly with NBP.[488]

Kinetics of oxidation of long-chain ketoacids by quinolinium dichromate in acid medium are first order in the substrate, oxidant, and acid,[489] and the kinetics of oxidation of cyclic ketones (ring size 5–8) by quinolinium fluorochromate in perchloric acid show the same orders. The ring size–reactivity relationship is discussed.[490]

trans-2-(*para*-Methylphenylsulfonyl)-3-phenyloxaziridine (**137**) α-oxidizes aldehydes to their (*S*)-α-hydroxy aldehyde analogues. Yields and enantioselectivities are fair, (*ee*) but are improved with proline as the catalyst, and more so with α-methylproline and α-methylproline tetrazole.[491]

KIEs have been measured for the hydroxylation of acetaldehyde by cytochrome *P*4502E1. With values around 5, this is typical of a hydrogen abstraction process; its temperature variation implies that quantum tunnelling is significant.[492]

A new mechanism for the cerium-catalysed α-hydroxylation of β-dicarbonyl compounds has been proposed, following ^{18}O-labelling evidence proving O_2 is the direct source of the hydroxyl oxygen, and water does not play a role. The true mechanism is yet to be firmly established; a possible peroxo-dimer route is discussed.[493]

Substituent effects in the BV oxidation of acetophenones have been studied theoretically, using formic and trifluoroacetic acids as catalysts, and the corresponding peracids as oxidants.[494]

Calculations on the mechanism of the BV oxidation of cyclohexanone by hydrogen peroxide indicate a two-step concerted process, with rearrangement being rate determining. Catalysis by phenol involves activation of *both* reactants by hydrogen bonding. Calculated rate constants are compared with experiment.[495]

One-pot BV oxidation of cycloalkanones has been achieved via *in situ* generation of hydrogen peroxide from secondary alcohols and molecular oxygen, using AIBN and *N*-hydroxyphthalimide as catalysts.[496]

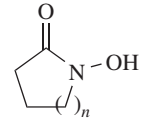
The kinetics of BV oxidation of benzil (1,2-diphenylethanedione) have been studied, using periodate, lead tetraacetate, peracids, hydrogen peroxide, and hydroperoxides as oxidants. Cerium(IV) has also been probed as an example of a one-electron oxidant.[497]

A supramolecular approach to enantioselectivity has been employed in the BV oxidation of cyclohexanones in water, using hydrogen peroxide and a Pt(II) catalyst.[498] (de) (ee)

The kinetics of the oxidation of aldonitrones by quinolinium chlorochromate in aqueous DMF (dimethylformamide) have been followed iodometrically, displaying first-order dependence on the substrate and the oxidant, and fractional order in the hydronium ion. The reaction also shows catalysis by oxalic acid (first order), and this and other features allow a mechanism to be proposed.[499]

An unusual intramolecular Cannizzaro reaction involving 2,6-diaminoanilines and glyoxal (ethanedial) exploits neighbouring group participation: no Lewis acid or strong base is required.[500]

Cyclobutanone and cyclopentanone react with *N*-hydroxybenzenesulfonamide ($PhSO_2NHOH$) under basic conditions to give the ring-expanded hydroxamic acid (**138**, $n = 1, 2$). A mechanistic study points towards the *N*-anion of $PhSO_2NHOH$ adding to the ketone to give a tetrahedral intermediate, which eliminates benzenesulfinic acid to give a *C*-nitroso alcohol, which tautomerizes to (**138**).[501]



(**138**)

For the BV oxidation of a β-amino ketone,[136] and an imine disproportionation,[138] see the section titled 'Other Reactions of Imines'. For oxidation of a semicarbazone,[158] see the section titled 'Oximes, Hydrazones, and Related Species'. A hydration–disproportionation of glyoxal (ethanedial)[476] is described in the section titled 'Other Reduction Reactions'.

Atmospheric Reactions

DFT and CCSD calculations on the oxidation of aldehydes by ozone (O_3) support two main channels: formation of hydrotrioxide [HC(=O)OOOH, for the example of formaldehyde], and formation of a five-membered ring (a tetraoxolane). The calculated barriers suggest that oxidation of aldehydes by ozone is too slow to be important in atmospheric chemistry. It is noted that the contrast in aldehyde versus alkene reactivity is mainly down to thermodynamics: the aldehyde reaction is moderately endothermic, while the alkene reaction is exothermic by ca 50 kcal mol^{-1}.[502]

A theoretical and experimental investigation of ozonolysis of benzaldehyde at low temperature suggests that its hydrotrioxide, PhC(=O)OOOH, should not be detectable

by NMR above −80 °C, despite claims to the contrary. It *is* involved in the mechanism, but is too unstable to detect. Another possible intermediate, the cyclic tetraoxide (i.e. the tetraoxolane) is less stable again, but the authors suggest that both might be detectable by IR matrix techniques.[503]

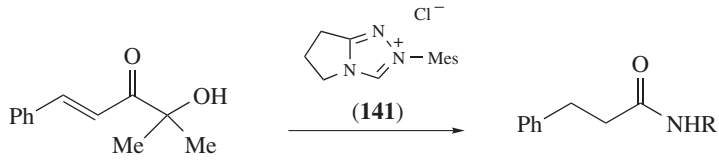
The kinetics and mechanism of the reaction of chlorine atoms under ambient (but oxygen-free) conditions have been studied by FT-IR. The results are consistent with the acyl radicals that are generated reacting almost exclusively with oxygen under atmospheric conditions.[504]

Other Reactions

Several reports describe formal ketone-to-amide conversions. A heterobimetallic lanthanide/sodium phenoxide reagent combination, $[Sm(OAr)_4][Na(DME)_3]$, amidates aldehydes with amines at room temperature. The best phenolate was 2,6-dimethylphenoxide. A samarium-sodium cooperative mechanism is proposed.[505]

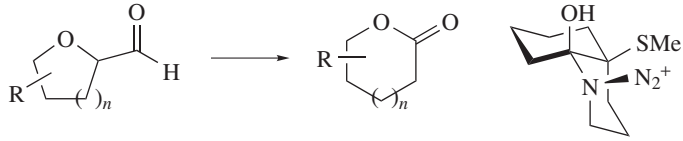
Aqueous ammonia and iodine bring about conversion of a wide variety of methyl ketones (or methyl carbinols) to primary amides at 60 °C in about an hour, with iodoform as by-product. A tandem mechanism is proposed: the Lieben iodoform reaction triiodinates the substrate, then – in a Haller–Bauer process – ammonium attacks the carbonyl to give a tetrahedral zwitterion, which eliminates CHI_3.[506]

α'-Hydroxyenones (e.g. **139**) undego catalytic amidation with primary amines. Formation of the amide product (**140**) requires a triazolium NHC precursor (**141**), and a 1,2,4-triazole co-catalyst. No stoichiometric reagents are required, the method is mild, and the only by-product is acetone. The method has advantages over using α,β-unsaturated aldehydes, which can be difficult to prepare, and can be complicated by imine formation with the amine.[507]



(**139**) (**140**)

Oxacycloalkane-2-carboxaldehydes (**142**, $n = 0, 1, 2$) can be ring-expanded to lactones (**143**) via catalysis by NHCs derived from imidazoliums.[508]

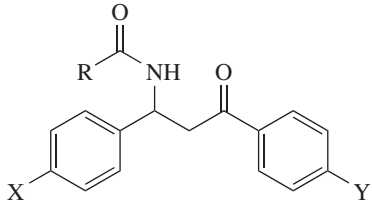


(**142**) (**143**) (**144**)

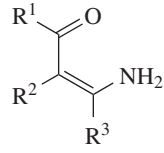
The regiochemistry of the intramolecular Schmidt reaction of 2-azidoalkylketones (to give lactams) can be controlled with a thioether substituent adjacent to the ketone.

The effect is explained in terms of through-space stabilization between the diazonium cation and the ring nitrogen's *n* electrons in the intermediate (**144**).[509]

A range of β-amido ketones (**145**) have been prepared in a one-pot combination of an X-substituted benzaldehyde, a Y-substituted acetophenone, a nitrile (RCN), and acetyl chloride, with yields of 50–84%, using a new Brønsted acid ionic liquid, 1-methyl-imidazolium hydrogen sulfate. Reaction conditions are mild, the solvent is reusable, and a wide range of functional groups are tolerated.[510]



(**145**)



(**146**)

A wide range of (*Z*)-ketoenamines (**146**) have been prepared in good yields from carbonyl compounds, R^1COCHR^2, and nitriles, $R^3{-}C{\equiv}N$. A rhenium heptahydride, $ReH_7(PPh_3)_2$, catalyses the process: it activates the α-CH bond of the ketone, setting up nitrile insertion. $N{-}H\cdots O{=}C$ hydrogen bonding is believed to favour (*Z*)-product. The method avoids self-condensation of either reactant.[511]

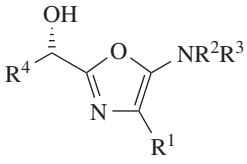
Among processes involving isonitriles, new multi-component reactions of cyclobutanones with isonitriles have been reported, including an Ugi reaction of cyclobutanone itself, and a Passerini reaction of tetramethylcyclobutane-1,3-dione.[512]

Passerini three-component reactions of strong carboxylic acids (R^1-CO_2H, $pK_a < 2$), isocyanides ($R^2{-}N^+{\equiv}C^-$), and aldehydes ($R^3{-}CHO$) yield α-acyloxycarboxamides ($R^1CO_2CHR^3{-}CONHR^2$) and/or products of a Ugi-type process, α-acylaminocarboxamides ($R^1CONR^2{-}CHR^3{-}CONHR^2$). Formation of the latter product is associated with the stronger carboxylic acids: *in situ* Brønsted-catalysed reaction of the isocyanide and aldehyde yields an imine that participates in the Ugi reaction. This adds another process to the increasing palette of isocyanide reactions.[513]

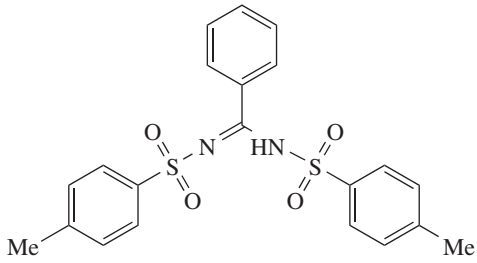
A chiral BINAP-phosphoric acid has been reacted (2 : 1) with diethylaluminium chloride, to give a bis(phosphate)Al(III) chloride. It catalyses enantioselective α-addition of isocyanides ($^-C{\equiv}N^+$-CHR^1-$CONR^2R^3$) to aldehydes (R^4-CHO) to give 5-aminooxazoles bearing a chiral alcohol (**147**). The Passerini-type reaction can be carried out at $-20\,^\circ C$ with 5 mol% catalyst, giving yields up to 95 with up to 87% *ee*.[514]

Heteroaromatic aldehydes and ketones (ArCOR) have been rearranged to α,α-difluoroalkyl heteroaryl ethers, $Ar{-}O{-}CF_2R$, using xenon difluoride and HF/pyridine.[515]

Sulfonamides can be *N*-alkylated with primary alcohols, using a convenient copper(II) acetate/potassium carbonate/air reagent system. A copper 'hydrogen-borrowing' mechanism is proposed (similar to ruthenium-catalysed amination of



(**147**)



(**148**)

alcohols), via the aldehyde and imine. For the reaction of benzyl alcohol and *para*-toluenesulfonamide, a 1 : 2 intermediate (**148**) was identified by MS.[516]

The nucleophilic reactivities of primary and secondary amines with *para*-quinone methides (to give the corresponding *para*-hydroxy benzylamines) have been studied kinetically in acetonitrile.[517]

A chiral rhodium complex catalyses reaction of a range of α-aryl-α-diazo ketones with activated olefins, to give cyclopropyl ketones with up to 90% *de* and 98% *ee*.[518] (*de*) (*ee*)

A Favorskii rearrangement of a *meso*-dihaloketone is catalysed by amines; L-proline derivatives give slight diastereoselectivity.[519] (*de*)

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