CHAPTER 1

Reactions of Aldehydes and Ketones and their Derivatives

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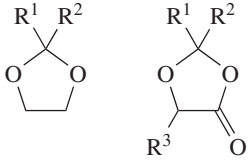
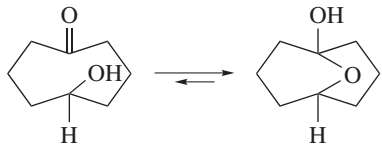
Formation and Reactions of Acetals and Related Species

Ketones and aldehydes can be conveniently protected as their cyclic acetals (**1**) using ethylene glycol and 5 mol% iodine.[1] HI is believed to be the actual catalyst, but it gives low yields in small-scale reactions, probably because the acidity is difficult to control. The reaction can be extended to using an α-hydroxy acid instead of an α-diol, giving 'lactonic acetal' protection (**2**). Examples include mandelic and lactic acids (i.e. $R^3 = Ph$ and Me) and, when the reactions are carried out in THF, they show some diastereoselectivity.



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



(**3**) (**4**)

The rearrangement of 5-hydroxycyclooctanone (**3**) to its hemiacetal (**4**) has been studied computationally.[2] A concerted intramolecular nucleophilic addition process is demonstrated.

gem-Diacetates, $R^1CH(OAc)_2$, and α-chloroalkyl esters, $R^1CH(Cl)OCOR^2$, have been prepared from aldehydes, R^1CHO, using $Zn(OTf)_2.6H_2O$ as catalyst, together with acetic anhydride or an acid chloride, R_2COCl.[3] Yields are high under solvent-free conditions at room temperature. Ketones also react, but in very low yields.

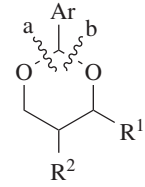
gem-Diacylates of aromatic aldehydes have been prepared under solvent-free conditions, using anhydrides and tetrabutylammonium tribromide as catalyst.[4] Deprotection can be achieved with the same catalyst on addition of methanol. The reaction proceeds via protonation of aldehyde, nucleophilic attack of the anhydride, and further nucleophilic attack on the hemiacylate intermediate, followed by regeneration of anhydride. Electron-donating groups in the aldehyde favour reaction, to the extent that such aldehydes can be chemoselectively protected in a substrate which also contains an aldehyde with an electron-withdrawing group. Such selectivity is also readily accomplished in *de*protection. All the *gem*-diacylals studied were more stable in base than in acid, but the order of stability is the same in both types of media. This reflects the fact that stability correlates with steric crowding around the carbonyl carbon, and *not* with the pK_as of the corresponding acids.

α,α-Diacetyl ketene dibenzylthioacetal reacts, under strongly basic conditions, with arylaldehydes in a deacylation–condensation sequence.[5]

A transition-state analogue for an acetal hydrolysis has been used to select and amplify the production of a macrocycle from a dynamic combinatorial library of disulfides in water. The macrocycle gives a modest acceleration of the acetal hydrolysis reaction.[6]

Terminal isopropylidene acetals can be hydrolysed using I_2 in acetonitrile; similar protection in non-terminal positions is untouched.[7]

Unsymmetrical cyclic benzylidene acetals (**5**) undergo reductive ring opening to give either a primary (path a) or secondary alcohol (path b).[8] $Cu(OTf)_2$ has been employed as a regioselective catalyst, using borane or trialkylsilanes as reductant, the former favouring path a, and the latter path b. The copper(II) triflate has dual functions: it is a Lewis acid, and its binding to the reductant brings about the regioselectivity.



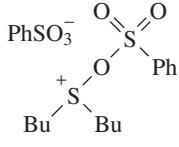
(**5**)

Reactions of Glucosides and Nucleosides

S_N2 reactivity is dramatically reduced at the primary C(6) position of *galacto*-configured pyranoses, relative to their *gluco* isomers. The low reactivity is widely attributed to dipole–dipole interactions in the transition structure, but *ab initio* calculations on model compounds suggest that the energy attributable to such interactions is not sufficient to explain the reactivity difference,[9] whereas rotameric populations and reaction path curvature are.[10]

The nucleosidation mechanism of five-membered glycals promoted by *N*-iodosuccinimide, to give 2′-deoxy-2′-iodo-β-nucleosides, has been investigated by semiempirical methods.[11]

In glucosides, hemiacetal hydroxyl activation/substitution can be achieved using a sulfonic anhydride and a nucleophile, plus a base as acid scavenger.[12] The reaction is catalysed by dibutyl sulfoxide ($Bu_2S{=}O$), and shows evidence of sulfur-covalent catalysis. Using benzenesulfonic anhydride [$(PhSO)_2O$], it is proposed to involve initial formation of a sulfonium sulfonate (**6**), the S(IV) centre of which then reacts with



(**6**)

the sugar hydroxyl to give glycosyl sulfonate (Gluc–O–SO_2Ph). ^{18}O incorporation experiments and ^{13}C–$^{16/18}$O isotopic NMR chemical shift perturbations have been used to probe the mechanism, which also shows evidence of a glycosyl oxosulfonium intermediate, Gluc–O–S^+–Bu_2.

New DISAL (methyl 3,5-*di*nitro*sal*icylate) glycosyl donors have been prepared and used to carry out β-selective glycosylations under neutral conditions.[13] (*de*)

Glycosylation using trichloroacetimidates [Gluc–C(=NH)–CCl_3] has been carried out in ionic liquids based on imidazolium salts.[14] Switching from non-coordinating anions in the solvent (PF_6^-, BF_4^-) to triflate anion gave a reversal of stereoselectivity, indicating that triflate counterion from the solvent is sufficiently nucleophilic to interact with the oxonium ion intermediate. (*de*)

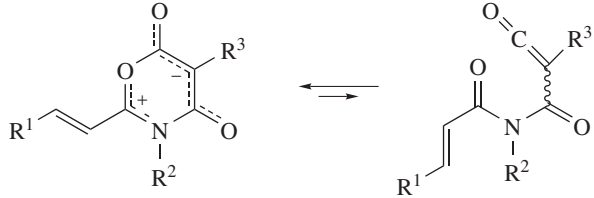
trans-2,3-*O*-Carbonate protection of glucopyranosyl donors leads to good β-selectivity in glycosylations, in the absence of neighbouring group or solvent participation.[15] (*de*)

A β-cyclodextrin bis(cyanohydrin) acts as an artificial glycosidase, giving k_{cat}/k_{uncat} ratios of 200–2000 in the hydrolysis of aryl glycosides. The electron-withdrawing effect of the cyano groups is proposed to acidify the geminal hydroxyls.[16] A further paper shows Michaelis–Menten kinetics for the hydrolyses,[17] with accelerations up to 8000. The behaviour is consistent with general acid catalysis of the bound substrate, with the cyanohydrin OH as catalytic group. An analogue with only one cyanohydrin function is also a good catalyst, and its action is compared with that of natural glycosidases, where a protonating carboxylic acid is the catalytic function.

Diazeniumdiolate anions as leaving groups at the anomeric position of carbohydrates can act as prodrugs, releasing NO upon hydrolysis by a glycosidase.[18]

Reactions of Ketenes

The energy surface linking ketene (**7**, several conformers), the corresponding oxazinium olate (**8**), and related imidoylketenes, oxo-ketenimines, and their cyclization products has been calculated.[19] Whereas (**8**) ring opens easily at room temperature, (**7**) is not directly observable, as its energy is ca 10 kcal mol^{-1} above (**8**). Many of the reactions in this manifold are pseudopericyclic in nature.



(**7**) (**8**)

Enantio-enriched enol esters – potential precursors of enantiopure α-arylalkanoic acids – have been prepared by asymmetric coupling of ketenes with aldehydes, using a chiral ferrocene bearing a dimethylaminopyridine function.[20] (*ee*)

Formation and Reactions of Nitrogen Derivatives

Imines: Synthesis, Tautomerism, Catalysis

A large-scale, robust enantioselective synthesis of β-substituted-β-amino esters from aldehydes via imine formation with a chiral amine has been reported.[21] (*ee*)

A wide range of kinetic and thermodynamic parameters have been measured for the formation and hydrolysis of Schiff bases derived from pyridoxal 5′-phosphate and L-tryptophan over a range of pH and temperature.[22]

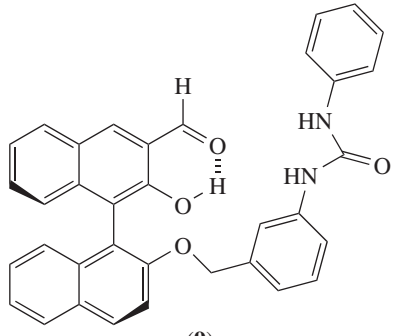
In a study of imine formation from aldehydes in aqueous solution, formation constants have been correlated with three parameters: the pK_a and HOMO energy of the amine and the LUMO energy of the aldehyde.[23]

Sodium dodecyl sulfate micelles accelerate condensations of *p*-dimethylaminocinnamaldehyde with a range of substituted anilines.[24]

Indolizidines have been prepared by cyclization of trimethylsilylmethylenecyclopropylimines.[25]

A linear solvation energy relationship (LSER) study of tautomerism in aromatic Schiff bases and related azo compounds indicates that the aminoenone tautomer is always the more polar, and is specifically favoured by proton donor solvents (binding to the second lone pair of the carbonyl). Effects of aromatization and benzo fusion are also discussed.[26]

A BINOL-derived chiral aldehyde (**9**) with three hydrogen bond-donating groups has been prepared.[27] It can recognize chiral 1,2-amino alcohols by reversible formation of imines. Experimental and computational results suggest that the stereoselective recognition depends on the imine bond, a resonance-assisted hydrogen bond to the imine nitrogen, and further hydrogen bonds to the oxygen of the alcohol. (*ee*)



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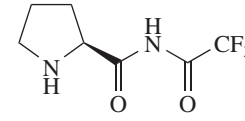


(**10**)

The Mannich and Nitro-Mannich Reactions

Chiral palladium complexes have been employed as enantio- and diastereo-selective catalysts of a Mannich-type addition of β-keto esters to aldimines and imino esters, in a strategy which activates both reactants.[28] (*ee*) (*de*)

anti-Selective direct enantioselective Mannich reactions use a BINAP-derived axially chiral aminosulfonamide as organocatalyst.[29] (*ee*)

An enantioselective nitro-Mannich reaction of alkyl- and aryl-benzylimines gives β-nitroamines in high *ee*, using a chiral copper(II)–bisoxazoline catalyst, with the products affording 1,2-diamines by reduction.[30] (*ee*)

A simple pyrrolidine imide (**10**), derived from L-proline, brings about the direct formation of α,β-unsaturated ketones from unmodified ketones and aldehydes under mild conditions.[31] Mechanistic investigation suggests a Mannich elimination process, rather than an aldol route.

Diastereoselective Mannich-type reactions between ketene silyl acetals and chiral sulfinimines using simple metal-free Lewis bases such as tetraalkylammonium carboxylates have been reported. The sulfinimine can even be generated *in situ* (from aldehyde and a chiral sulfonamide), using cesium carbonate, followed by addition of ketene silyl acetal at $-78\,^{\circ}$C, and as little as 1 mol% of catalyst.[32] (*de*)

syn-Diastereoselective Mannich-type reaction of α-phenylseleno chlorotitanium enolates with aromatic aldimines gives α-phenylseleno-β-amino esters.[33] (*de*)

A direct enantioselective Mannich synthesis of β-amino-α-oxyaldehydes – from unmodified β-oxyaldehydes and anilines – uses L-proline to give high *de*s and *ee*s.[34] (*de*) (*ee*)

Fluorinated γ-amino alcohols have been prepared in moderate yield, but high *de* and very high *ee*, using a proline-catalysed cross-Mannich reaction of fluorinated aldimines with aliphatic aldehydes, followed by $NaBH_4$ reduction.[35] (*de*) (*ee*)

A chiral thiourea catalyses enantio- and diastereo-selective addition of nitroalkanes to *N*-protected imines.[36] (*de*) (*ee*)

Enantiomerically pure β-nitroamines of enolizable aldimines and ketimines have been accessed via a diastereoselective aza-Henry reaction of *N*-sulfinylimines and nitromethane.[37] The reaction is catalysed by sodium hydroxide, but also by tetrabutylammonium fluoride, the latter species giving an inversion of stereochemistry. An $O^- \cdots {}^+N$ contact ion pair is proposed in the ammonium-catalysed route. (*de*) (*ee*)

Addition of Organometallics

Barbier-type *C*-alkylation of imines can be carried out with alkylstrontium halides generated from strontium metal and alkyl halide.[38] *N*-Alkylation competes, and RSrI is strongly nucleophilic, as shown by α-alkylation of imines derived from enolizable aldehydes.

trans-1,2-Diaminocyclohexane ligands have been used as enantioselective catalysts for the asymmetric addition of methyllithium[39] and aryllithiums[40] to aromatic imines. (*ee*)

A kinetic study of the addition of *n*-BuLi to a chiral aliphatic aldimine has explored the roles of TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine) and solvents (toluene, diethyl ether) on relative rates and diastereoselectivity.[41] Evidence for four mechanisms was obtained, including monomeric and dimeric *n*-BuLi cases, and a cooperative TMEDA–Et_2O pathway. Hence the roles of chelation, aggregation, and cooperative solvation all need to be considered when solvents and additives are varied in such reactions. (*de*)

Copper-catalysed enantioselective addition of diorganozincs to phosphinoylimines has been reported,[42] as has enantioselective addition of diethylzinc to *N*-acylaldimines.[43] (*ee*)

Asymmetric addition of organometallic reagents to imines, to produce useful optically active amines, has been reviewed.[44] (*ee*)

Enantioselective exocyclic, endocyclic, and acyclic α-*p*-tolylsulfinyl ketimines have been reacted with Et_2AlCN.[45] The cyclic substrates exhibit good yield and diastereoselectivity, but the acyclic cases are complicated by imine–enamine equilibria. (*ee*) (*de*)

Grignard addition to an enantiopure *t*-butylsulfinimine shows a dramatic reversal in diastereoselectivity when the solvent is changed from DCM to THF, probably due to a mechanistic switch away from chelation.[46] (*de*)

Chiral ferrocenoylpyrrolidines catalyse the highly enantioselective addition of diethylzinc to *N*-sulfonylimines in the presence of copper(II) triflate.[47] (*ee*)

Whereas *N*-tosylimines do not coordinate diethylzinc well in polar solvents (and thus tend to give ethylated product), solvents such as toluene favour coordination, leading to reduction of the imine to secondary amines under mild conditions, via a β-hydrogen transfer mechanism.[48]

Other Alkylations, Arylations, and Allylations of Imines

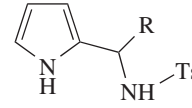
α-Sulfinyl carbanions exhibit high stereoselectivity in reactions with achiral imines, with the magnitude and direction of the *ee* dependent on the electron density at nitrogen.[49] (*ee*)

Nitrile-stabilized anions, generated for example by lithiation of benzyl cyanide and propionitrile, have been added diastereoselectively to aromatic aldimines.[50] Acid workup gives β-cyano amines. Alternatively, addition of RX gives β-R-substituted-β-cyanoamines. The factors determining *de*s in both reaction versions have been investigated. (*de*)

Recent advances in asymmetric additions of dialkyl reagents to imines have been reviewed.[51]

Arylboronic acids have been added diastereo- and enantio-selectively to (a) sulfinyl aldimines and (b) phosphinoyl aldimines, using rhodium(I) catalysts.[52] These two methods should prove useful in preparing α-branched amines. (*de*) (*ee*)

N-Tosyl aldimines, RCH=N–Ts, add regioselectively to the C(2) of pyrroles, to give pyrrole sulfonamides (**11**), using copper(II) triflate as catalyst.[53]



(**11**)

Anisidine imines of aldehydes, *p*-$MeOC_6H_4$–N=CHR (R = Ar, alkyl) can be allylated with *anti*-selectivity, using triethylborane and a Pd(II)–phosphine catalytic system, avoiding metallic or metalloid allylating agents.[54] The imines can be conveniently formed *in situ*. (*de*)

A highly stereoselective benzylation has been developed: α,α-dibranched β-phenylpropylamines and -ethanolamines can be synthesized in any desired configuration (*de*)

by reaction of *o*-sulfinylbenzyl carbanions with *N*-sulfinylketimines, followed by desulfinylation.[55]

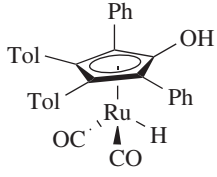
Synthesis of diarylmethylamine derivatives, Ar^1–CH(Ar^2)–$NHSO_2$–C_6H_4-*p*-NO_2, has been achieved enantioselectively using rhodium-catalysed arylation of imines with arylboroxines.[56] (*ee*)

Reduction of Imines

Catalytic asymmetric hydrogenation of prochiral Schiff bases has been reviewed.[57] (*ee*)

A catalytic asymmetric *in situ* reduction of N–H imines has been achieved in a sequence in which trifluoroacetophenones, $ArCOCF_3$, are first converted to silylimines [using $LiN(SiMe_3)_2$], and then on to give trifluoromethylated amine salts, Ar–$C(CF_3)$–NH_2.HCl, in good to excellent yield and *ee*.[58] The intermediate N–H imines can be isolated via methanolysis of the N–Si bond, while the enantioselective reduction can be carried out using a chiral borane auxiliary. (*ee*)

The mechanism of Shvo's hydroxycyclopentadienyl ruthenium hydride (**12**) reduction of imines has been studied using isomerization and deuterium scrambling experiments.[59] The rate-determining step is found to change from electron-deficient to electron-rich imines. A more detailed mechanistic investigation involving intramolecular trapping of a coordinatively unsaturated intermediate indicates hydrogen transfer can occur outside the metal coordination sphere.[60]



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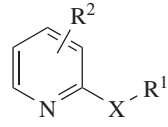

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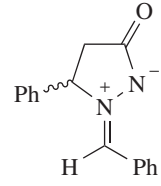


(**14**)

1-Substituted-1-(pyridine-2-yl)methylamines (**13**, X = ∗$CHNH_2$) have been prepared diastereoselectively by the reduction of enantiopure *N*-*p*-toluenesulfinyl ketimines [X = C=N– ∗ S(=O)-*p*-tolyl].[61] (*de*)

See also reduction of imines with diethylzinc under *Addition of Organometallics* above, and ionic hydrogenation of *Iminium Species* below.

Iminium Species

Racemic azomethine imine (**14**) has been kinetically resolved using a copper(I)-catalysed 3 + 2-cycloaddition, with a chiral co-catalyst.[62] (*ee*)

DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) conveniently oxidizes ketene silyl acetal (**15**) to give α-alkoxycarbonyl iminium salt (**16**).[63] Subsequent reaction with nucleophiles gives amino ester derivatives, Nu–CH(NBn_2)–CO_2R. Grignards

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

are typical nucleophiles, and the two reactions can be done in one pot, under mild conditions.

The scope and mechanism of ionic hydrogenation of iminium cations have been investigated for a CpRuH catalyst bearing a chelating diphosphine.[64] The mechanism involves three steps: hydride transfer (from the catalyst) to form an amine, coordination of H_2 to the resulting ruthenium cation, followed by proton transfer from the dicoordinated H_2 to the amine. The cationic intermediate [e.g. CpRu(dppm)(η^2-H_2)$^+$] can be used to hydrogenate enamines provided that the latter are more basic than the product amine. The relative reactivity of C=C and C=N bonds in α,β-unsaturated iminium cations has also been investigated. (*ee*)

Imine Cycloadditions

Regio- and enantio-selective additions of nitrile amines (R^1–C≡N^+–N^-–R^2, from the hydrazonyl bromide) to enones allows access to dihydropyrazoles close to enantiopurity, via a 3 + 2-cycloaddition.[65] (*ee*)

Sodium iodide catalyses a regioselective cycloaddition of cyclopropenes with imines, to give *cis*-vinylic aziridines.[66] (*de*)

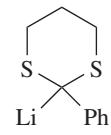
Lewis acids, especially rare earth triflates, are efficient catalysts of 1,3-dipolar cycloadditions to imines, Ar–^{1}CH=N–Ar^2.[67] (*de*)

Other Reactions of Imines

Recent advances in catalytic asymmetric addition to imines and other C=N systems have been reviewed.[68] (*ee*)

[*N*-(*p*-Tolylsulfonyl)imino]phenyliodinane, PhI=NTs, is a well-known nitrene precursor.[69] It has now been used to imidate aldehydes (i.e. RCH=O → RCH=NTs) using a ruthenium(II) catalyst and triphenylphosphine. Ph_3P=NTs formation is proposed to occur, followed by aza-Wittig reaction.

2-Lithio-2-phenyl-1,3-dithiane (**17**) has been employed in a new umpolung asymmetric addition of *N*-sulfinylimines, using a Lewis acid catalyst (Et_2AlCl). The high *de*s obtained open up a new route to enantiopure α-amino ketones.[70] (*de*)



(**17**)

Aldimines can be trifluoromethylated at the imine carbon using Me_3SiCF_3 in dimethyl formamide at $-20\,^{\circ}C$, using a lithium carboxylate as catalyst.[71] It is proposed that the carbon–silicon bond of the reagent is activated via formation of a lithium silicate bearing carboxylate and DMF ligands on silicon. A similar process has been used for *diastereoselective* addition to *sulfinyl*imines.[72] (de)

Strecker-type reaction of TMS cyanide with chiral sulfinimines gives diastereoselective cyanations at the imine carbon, at $-78\,^{\circ}C$ in DMF, using simple metal-free Lewis base catalysts such as tetraalkylammonium carboxylates.[73] (de)

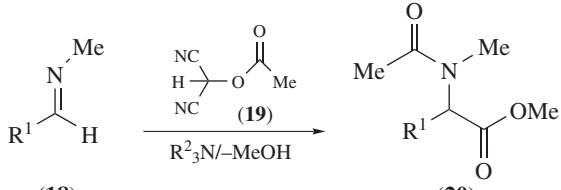
N-Tosylimines are alkynylated by aryl acetylenes in acetonitrile; the reaction is promoted by zinc bromide and Hunig's base (*N*,*N*-diisopropylethylamine).[74]

Vinyl aziridines have been prepared *trans*- and diastereo-selectively by reaction of *N*-*t*-butylsulfinylimines with telluronium ylides.[75] (de)

Enantioselective synthesis of β-lactams from enolate and imine components uses a bifunctional Lewis acid/nucleophile strategy.[76] A chiral nucleophile is used to form a zwitterionic enolate, and a metal ion coordinates the imine. The postulated mechanism is supported by kinetic, spectroscopic, and molecular modelling evidence. (ee) (de)

Chiral carbamoylsilanes, TMS–CO–N(Me)R*, have been added diastereoselectively to aldimines, giving α-aminoamides.[77] (de)

Simple *N*-alkylated imines, e.g. *N*-methylaldimine (**18**, R^1 = aryl, alkyl), undergo nucleophilic addition using a masked acyl cyanide reagent [**19**, where the masked group = $-C(CN)_2-O-$] with C–C bond formation to give an α-amido ester (**20**).[78] This mild conversion does not require 'pre-activation' (i.e. incorporation of an activating group in the substrate) or 'post-activation' (i.e. Brønsted or Lewis acid, or metallic species).



(**18**) (**20**)

An enantioselective Strecker cyanation of ketoimines exploits Lewis acid–Lewis base bifunctional catalysts.[79] (ee)

Chiral ketimines derived from (*R*)-glyceraldehyde have been cyanated in high *de*.[80] (de)

Catalyses of the addition of HCN to methanimine by formamidine and by formamide has been studied computationally.[81]

A BINOL-derived phosphoric acid derivative has been used as a catalyst in the enantioselective synthesis of α-amino phosphonates via hydrophosphonylation of imines with diisopropyl phosphite.[82] (ee)

A direct stereoselective addition of an activated imine to β-keto phosphonates in the presence of a chiral copper(II) catalyst has been developed.[83] (de)

Tetrakis(dimethylamino)ethylene (TDAE) combines with CF_3I to give a nucleophilic trifluoromethylation reagent which is effective with *N*-tosylaldimines and *N*-tolylsulfinimines, the latter case being diastereoselective.[84] (*de*)

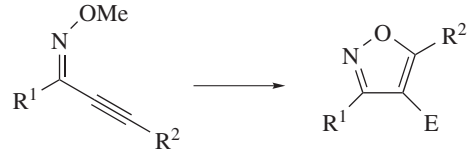
Regioselectivity control in the double nucleophilic addition of ketene silyl acetals to α,β-unsaturated imines has been reported.[85]

Silyl ketene imines have been acylated asymmetrically by anhydrides: evidence for a silyl-free nitrile anion intermediate is discussed.[86] (*ee*)

An *aza-Baylis–Hillman* reaction of *N*-sulfonated imines is described below.

Oximes, Hydrazones, and Related Species

2-Alkyn-1-one *O*-methyl oximes (**21**) undergo electrophilic cyclization with a range of reagents, E–X (e.g. I_2, Br_2, ICl, PhSeBr), to give substituted isoxazoles (**22**).[87]



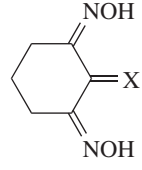
(**21**) (**22**)

O-Allylation of oximes yields *O*-allylated oxime ethers, whereas *N*-allylation gives the corresponding nitrone isomer, using an allylic carbonate or acetate as electrophile.[88] With Pd(II) catalysis and carbonate leaving group, *O*-allylation occurs without base, whereas the acetate substrate requires K_2CO_3 or Et_2Zn as base. To form nitrone product selectively, a Pd(II) Lewis acid catalyst was employed.

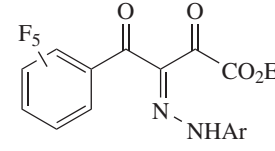
Base-catalysed nitrosation of acetone by *t*-butyl nitrite to give 1-hydroxyimino-2-oxopropane [$H_3C–C(=O)–CH=NOH$] has been studied by *ab initio* methods.[89] Using a sodium enolate route, the cation participates to give *Z*-isomer, whereas a 'naked enolate' calculation results in the *E*-product being favoured. (*de*)

Under the relatively mild conditions of chlorosulfonic acid in toluene, ketoximes undergo Beckmann rearrangement, whereas aldoximes dehydrate to nitriles.[90]

Hydrolysis of cyclohexane-1,2,3-trione-1,3-dioxime (**23**, X = O) and its 2-imine (X = NH) has been studied in perchloric acid solution.[91] The mechanism is proposed to involve a protonation pre-equilibrium, followed by slow water addition to protonated and non-protonated forms. Oxime protonation pK_as have been calculated.



(**23**)



(**24**)

Using a BINOL auxiliary with allylindium and indium metal, hydrazones have been allylated enantioselectively,[92] to give homoallylic amines in up to 97% *ee*. (ee)

3-Arylhydrazono-2,4-dioxo-4-pentafluorophenyl butanoates (**24**) react with hydrazine (or phenylhydrazine); unexpectedly, pyridazine-5,6-dione derivatives are produced.[93]

The use of neutral coordinate organocatalysts such as DMF, sulfoxides, and phosphine oxides to activate allyltrichlorosilane in allylation of acylhydrazones has been reviewed.[94] (de)

The kinetics of the oxidation of piperidinone thiosemicarbazones by chloramine-T have been studied in acetic/perchloric acid media.[95]

Nucleophilic additions to chiral α-alkoxy and α-amino nitrones have been reviewed, focusing on tuning of Lewis acid catalysts and protecting groups so as to exert stereocontrol in producing hydroxylamines and ultimately useful amino acids, amino alcohols, and nucleoside analogues.[96] (ee)

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

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

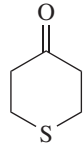
'Modern Aldol Reactions' contains several pertinent reviews: (i) catalytic enantioselective aldols with chiral Lewis bases;[97] (ii) the aldol–Tishchenko reaction;[98] (iii) titanium–enolate aldols;[99] (iv) crossed aldols mediated by boron and silicon enolates;[100] (v) amine-catalysed aldols;[101] and (vi) aldols catalysed by antibodies.[102] (ee)

Other reviews deal with aldol additions of group 1 and 2 enolates,[103] direct catalytic asymmetric aldol reactions catalysed by chiral metal complexes,[104] the exploitation of 'multi-point' recognition in catalytic asymmetric aldols,[105] and recent progress in asymmetric organocatalysis of aldol, Mannich, Michael, and other reactions.[106] (ee)

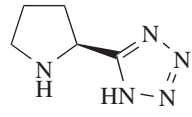
Hartree–Fock and density functional theory (DFT) calculations have been used to probe the enantioselectivity of the direct aldol reaction of acetone and 2,2-dimethylpropanal, catalysed by (*S*)-proline, in DMSO solution.[107] (ee)

Carefully matched acid and base catalysis has been used to select the pyrrolidine–*p*-nitrophenol combination as an efficient organocatalyst for direct aldol reactions.[108]

Direct intermolecular aldol reactions, catalysed by proline, between tetrahydro-4*H*-thiopyranone (**25**) and racemic aldehydes exhibit enantiotopic group selectivity and dynamic kinetic resolution, with *ee*s of >98% in some cases.[109] (ee)



(**25**)



(**26**)

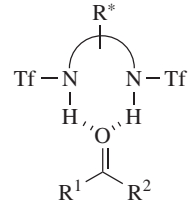
The role of assistance by water in the direct asymmetric aldol catalysed by amino acids has been studied in DMSO and in DMF.[110] (ee)

Structure–activity relationships have been probed in (*S*)-histidine-based dipeptides employed as organocatalysts for direct asymmetric aldol reactions, focusing on intramolecular cooperation between side-chain functions: H–Leu–His–OH proved particularly useful.[111] (*ee*)

Enantioselective aldolization using 5-pyrrolidin-2-yltetrazole (**26**) – in which the carboxylic acid of proline has been replaced by its well-known pharmacophore – has been modelled by DFT.[112] The calculations indicate that the large charge buildup on the carbonyl oxygen during C–C bond formation is stabilized by hydrogen bonding by the tetrazole NH. (*ee*)

4-Substituted prolines – typically with additional chiral centre(s) in the substituent – have been found to be much more enantioselective than proline itself in aldol reactions.[113] (*ee*)

Bis-sulfonamides have been used to activate carbonyl compounds through hydrogen bonding.[114] Bis-triflamides or -nonaflamides of readily available chiral diamines act as chiral Brønsted acid catalysts – through structures such as (**27**) – giving good to high yields and *ee*s in representative carbonyl additions such as Mukaiyama aldol, hetero-Diels–Alder, and Friedel–Crafts reactions. (*ee*)



(**27**)

Simple dipeptides bearing a *primary* amino N-terminus catalyse direct asymmetric intramolecular aldol reactions in up to 99% *ee*.[115] These simple catalysts such as L-Ala-L-Ala and L-Val-L-Phe can also promote the asymmetric formation of sugars, further suggesting a possible role in prebiotic chemistry. (*ee*)

DFT methods have been used to explore the nature of the transition states giving rise to stereoselectivity in intramolecular aldol cyclizations catalysed by amino acids.[116] Proline and primary amino acids are compared, identifying the factors explaining why proline is better in some cases, but not always. (*ee*)

Asymmetric aldol reactions promoted by chiral oxazaborolidinones can achieve high *ee* with critical quantities of THF, typically a 4–5-fold excess over the borane.[117] *Ab initio* calculations on Lewis acid–aldehyde–solvent complexes have been used to rationalize such results: extended hydrogen bonding networks have been identified. (*ee*)

β-Hydroxyaldehydes, with an intervening quaternary centre, have been synthesized enantioselectively by direct aldol reactions of α,α-dialkylaldehydes with aromatic aldehydes, using a chiral bifunctional pyrrolidine sulfonamide organocatalyst.[118] (*ee*)

A 'DYKAT' (dynamic kinetic asymmetric transformation) approach has been taken to *de novo* synthesis of triketide- and deoxy-sugars from racemic β-hydroxyaldehydes.[119] Using proline as catalyst, the process involves continuous amino acid-mediated racemization of the acceptor β-hydroxyaldehyde in combination with direct (*de*)

selective aldol addition, also catalysed by the proline; *de*s >90% and *ee*s up to 99% (*ee*) are reported.

Dicyclohexylchloroborane mediates aldol reactions between chiral aldehydes and a (*de*) chiral ketone; the reaction exhibits double diastereoselection.[120]

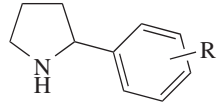
Evidence for chair-like transition states in aldol reactions of methyl ketone lithium enolates has been obtained from deuterium-labelled enolates.[121]

A divergent synthesis of 2-amino-1,3-diols has been reported, using a diastereoselective aldol addition to α-amino-β-silyloxyaldehydes.[122] (*de*)

Samarium(II) iodide mediates highly stereoselective aldol reactions of acylaziridines (*de*) with aldehydes, typically accompanied by ring opening, producing useful β-amino-β'-hydroxy derivatives.[123]

Boron-mediated ketone–ketone aldol reactions have been described, using boron enolates formed with dicyclohexylboron chloride and triethylamine.[124] Following (*de*) addition of the acceptor ketone to form a boron aldolate, oxidation with peroxide yields the aldol product.

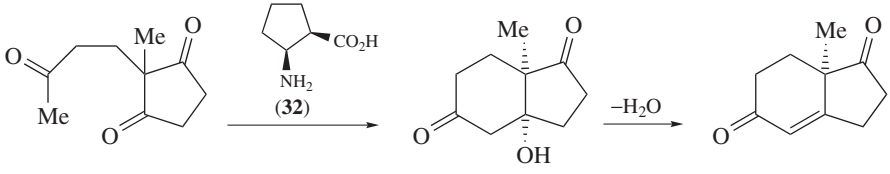
Several reports deal with aqueous media. Acid–base catalysis by pure water has been explored, using DFT, for the model aldol reaction of acetone and acetaldehyde.[125] A Hammett correlation of nornicotine analogues (**28**) – a series of *meta*- and *para*-substituted 2-arylpyrrolidines – as catalysts of an aqueous aldol reaction shows $\rho = 1.14$.[126] Also, direct aldol reactions have been carried out in water enantioselectively, (*ee*) using protonated chiral prolinamide organocatalysts.[127]



(**28**)

Intramolecular Aldols

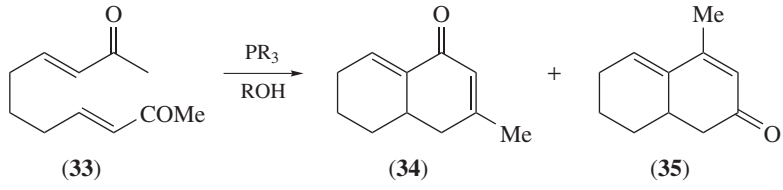
Triketone (**29**) undergoes an intramolecular aldol reaction – the Hajos–Parrish–Eder–Sauer–Wiechert reaction – to give (**30**) and subsequently enone (**31**), in high *ee* with (*ee*) the stereochemistries indicated being found for D-proline catalysis.[128] Now a homochiral β-amino acid, (1*R*,2*S*)-cispentacin (**32**) has been found to give comparable *ee*, and indeed does so for the cyclohexyl substrate also.



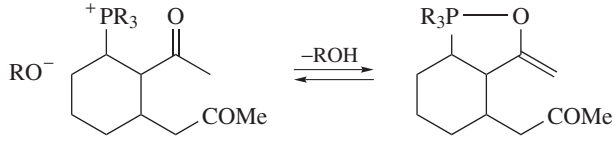
(**29**) (**30**) (**31**)

The roles of proline and primary amino acids in intramolecular aldol cyclizations are compared in the previous section.

Symmetrical bisenone (**33**) undergoes an intramolecular vinylogous Morita–Baylis–Hillman reaction, followed by intramolecular aldol cyclization to give dienone products (**34**) and (**35**).[129] An 83% yield was obtained in 1 day at ambient temperature, with a dramatic 94:6 preference for the cross-conjugated product (**34**). After the first cyclization, it is proposed that the phosphonium unit of the Michael adduct (**36**) reacts with the adjacent carbonyl to give regioselective deprotonation (**37**). Evidence presented includes the observation that, although the reaction can be carried out without phosphine (i.e. just using RO^-/ROH), the opposite regioselectivity results.



(**33**) (**34**) (**35**)

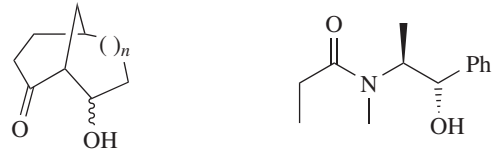


(**36**) (**37**)

1,6-Dialdehydes have been converted to cyclopentene carbaldehydes via an intramolecular asymmetric aldol cyclodehydration, using hydroxyamino acids as catalysts.[130] (*ee*)

Ring-size effects have been examined in a diastereoselective intramolecular aldol cyclization.[131] (*de*)

endo-X-Hydroxybicyclo[3.*n*.1]alkan-2-ones (**38**) can be accessed via an intramolecular aldolization of a cyclohexanone with an appropriately tethered aldehyde in the 4-position.[132] Using 4-(trialkylsilyloxy)prolines as catalysts, the octanone ($n = 1$, $X = 7$) and nonanone ($n = 2$, $X = 8$) systems have been synthesized in good yield, with up to 94% *ee*, and >98% *de*. (*ee*) (*de*)



(**38**) (**39**)

Five- and six-membered β-hydroxylactones have been synthesized diastereo- and enantio-selectively from α,β-unsaturated esters bearing a ketone tethered as the ester R group, in an intramolecular reductive aldol reaction catalysed by chiral bisphosphine complexes of copper(I).[133] (*de*) (*ee*)

Methyl trichlorosilyl ketene acetal reacts with aromatic and aliphatic ketones (the former enantioselectively), using chiral pyridine bis-*N*-oxide catalysts.[134] Computations and an X-ray crystal structure of a catalyst–$SiCl_4$ complex have helped to elucidate the mechanism. (*ee*)

(*S*,*S*)-(+)-Pseudoephedrine proprionamide (**39**) has been employed as a chiral auxiliary in asymmetric acetate aldol reactions.[135] (*de*)

A new thioester aldol reaction which uses a half-thioester (PhSOC–*CHMe–CO_2H) of methylmalonic acid and a copper–bis(oxazoline) catalyst is highly enantio- and diastereo-selective, while also being mild and tolerant of protic functional groups and enolizable aldehydes.[136] (*ee*) (*de*)

Mukaiyama and Vinylogous Aldols

Catalytic, enantioselective, vinylogous aldol reactions have been reviewed, from the first report in 1994 to date.[137] Many examples from natural products are given, and the remaining problems – especially the need to push beyond dienolates derived from esters – are highlighted. (*ee*)

Ab initio calculations indicate that a model uncatalysed Mukaiyama aldol reaction – that of formaldehyde and trihydrosilylenol ether – proceeds via a concerted pathway involving a twist-boat six-membered transition state.[138] A wide range of substituents on both reactants have been explored, and some combinations give rise to particularly low barriers, hopefully identifying cases that should work below room temperature.

Regio-, enantio-, and diastereo-selective vinylogous aldol additions of silyl dienol ethers to aldehydes use a Lewis base (a chiral bis-BINAP-phosphoramide) to activate a Lewis acid (silicon tetrachloride).[139] (*de*)

A variety of Brønsted acid sources – benzoic acid, silica gel, 3 Å molecular sieves – catalyse vinylogous aldol reactions of *O*-silyl dienolates, under solvent-free conditions.[140]

A range of chiral pre-organized diols have been studied to assess their potential to catalyse vinylogous Mukaiyama aldol reactions enantioselectively via hydrogen bonds.[141] (*ee*)

Simple Mukaiyama aldol and Diels–Alder reactions catalysed by cationic silicon Lewis acids show significant counterion effects.[142]

The vinylogous Mukaiyama aldol reaction of 2-(TMS-oxy)furans with methacroleins, catalysed by boron trifluoride etherate, has been studied experimentally and computationally, to identify the factors behind observed diastereoselectivities.[143] (*de*)

Using a chiral 4-dimethylaminopyridine–ferrocenyl catalyst, acyclic silyl ketene acetals react with anhydrides to furnish 1,3-dicarbonyl compounds containing all-carbon quaternary stereocentres in good yield and *ee*.[144] Evidence for dual activation (anhydride → acylpyridinium, and acetal → enolate) is presented. (*ee*)

Catalytic, enantioselective addition of silyl ketene acetals to aldehydes has been carried out using a variant of bifunctional catalysis: Lewis base activation of Lewis acids.[145] The weakly acidic $SiCl_4$ has been activated with a strongly basic phorphoramide (the latter chiral), to form a chiral Lewis acid *in situ*. It has also been extended to vinylogous aldol reactions of silyl dienol ethers derived from esters. (*ee*) (*de*)

The Aldol–Tishchenko Reaction

A direct aldol–Tishchenko reaction of aromatic aldehydes with ketones proceeds with stereocontrol of up to five contiguous centres in a chain, using titanium(IV) *t*-butoxide and cinchona alkaloids.[146] A tricyclic transition state is proposed to explain the high degree of stereoselection. (*ee*) (*de*)

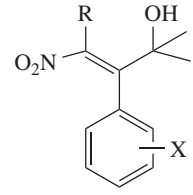
A *syn*-2-amino alcohol, complexed with Yb(III), catalyses the aldol–Tishchenko reaction of aliphatic ketones with aromatic aldehydes to give *anti*-1,3-diol monoesters with three adjacent stereocentres in high yield, *de*, and *ee*.[147] (*de*) (*ee*)

The aldol–Tishchenko reaction has been reviewed.[98]

Nitrile/Nitro/Nitroso Aldols

A direct enantioselective cross-aldol-type reaction of acetonitrile with an aldehyde (RCHO) has been reported, giving β-cyano alcohol product, R–CH*(OH)–CH_2–CN, in up to 77% *ee*.[148] CH_3CN, acting as an acetate surrogate, is chemoselectively activated and deprotonated using a soft metal alkoxide (CuO–Bu^t) in a strong donor solvent (HMPA), with a bulky chiral diphosphine as auxiliary. (*ee*)

The formation of tertiary 3-nitroallylic alcohols (**40**) via attack of nitromethanide anion ($RCHNO_2^-$) on the corresponding 2-chloroisopropylbutyrophenone has been studied in DMSO and HMPA.[149] Gibbs free enthalpies for various steps have been estimated, using gas-phase values and transfer enthalpies where necessary. Carbanion addition was assigned as the rate-determining step.



(**40**)

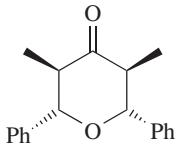
A regio- and enantio-selective nitrosoaldol synthesis, using an achiral enamine and nitrosobenzene, employs an asymmetric TADDOL catalyst.[150]

Other Aldol-type Reactions

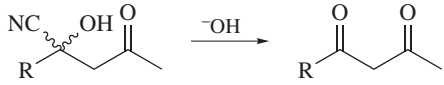
A diastereoselective titanium–enolate aldol reaction of (*S*)-1-benzyloxy-2-methylpentan-3-one has been reported.[151] (*de*)

The Maitland–Japp synthesis of highly substituted tetrahydropyran-4-ones[152a] (e.g. **41**, from pentan-3-one and two benzaldehydes) has been re-explored and generalized into a one-pot diastereoselective preparation.[152b] (*de*)

Proline catalyses an aldol-type addition of acyl cyanides (RCOCN) to acetone to give β-ketocyanohydrins (**42**); sodium hydroxide treatment gives the corresponding 1,3-diketone (**43**), by elimination of HCN.[153]



(**41**)

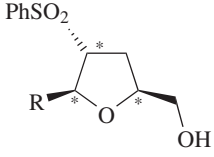


(**42**) (**43**)

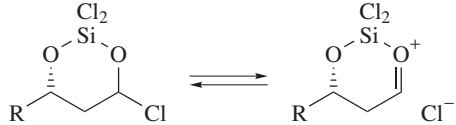
Palladium enolate chemistry has been exploited to perform a range of catalytic enantioselective reactions on carbonyl substrates, including aldol, Michael, Mannich-type, and α-fluorination.[154] (*ee*)

A rhodium bis(oxazoline) catalyst gives high *ee* and *anti*-selectivity in reductive aldols.[155] (*ee*) (*de*)

2-Substituted 3-phenylsulfonyl-5-hydroxymethyl-THFs (e.g. **44**) have been prepared chemo-, regio-, and diastereo-selectively via reaction of a γ,δ-epoxycarbanion with aldehydes, RCHO.[156] The initial aldol-type addition is non-diastereoselective, but reversible. The subsequent cyclization *is* selective, and exerts overall thermodynamic control. (*de*)



(**44**)



(**45a**) (**45b**)

An asymmetric catalytic halo-aldol reaction of β-iodoallenoates with aldehydes has been reported, using a chiral salen-aluminium chloride catalyst.[157]

Crossed aldol reaction between an aromatic aldehyde and the TMS enolate of another aldehyde proceeds smoothly in wet or dry DMF using a lithium carboxylate as Lewis base catalyst.[158] One-pot conversion to 1,3-diols using sodium borohydride as reductant gives up to 87% yield. A similar report, using tetrabutylammonium *phenolates* as Lewis bases, is *diastereoselective*.[159] (*de*)

Pyridine-*N*-oxide is an efficient Lewis-base catalyst for aldol reactions of trimethylsilyl enolate with both aryl and alkyl aldehydes in DMF at room temperature, tolerating a wide variety of sensitive substituents in the substrate.[160]

Trialkylsilyl enol ethers of acetaldehyde undergo enantioselective aldol addition to aromatic aldehydes, giving the aldol product in protected form.[161] Using a chiral BINAP-derived phosphoramide as Lewis base catalyst gives *ee*s up to 96%. $SiCl_4$ is required, a chlorohydrin intermediate (**45a**) is proposed, and NMR evidence suggests this exists as a 1:1 mixture of diastereomers. This masked aldol adduct presumably contributes to the high *ee*s, by preventing side reactions. Intermediate (**45a**) can also be intercepted at low temperature with nucleophiles: addition of *t*-butyl isocyanide gave a lactone (diastereoselectively), and a hydroxyamide by-product, both representing synthetically useful processes. It is proposed that the nucleophile attacks and displaces chloride (S_N2 process), or alternatively – in an S_N1-type process – an oxocarbenium species (**45b**) forms first. (*de*) (*ee*)

Carbon kinetic isotope effects have been measured in an exploration of the mechanism of the Lewis base-catalysed enantioselective crossed-aldol reaction of aldehydes.[162] The trichlorosilyl enolate of isobutyrophenone, $Me_2C{=}CHOSiCl_3$, was reacted with substituted benzaldehydes in chloroform–dichloromethane from −78 to −45 °C, using a chiral BINAP-derived phosphoramide catalyst. Aldolization is rate determining, and extraction of Arrhenius activation parameters indicates large, negative $\Delta S^{\neq}$ values, with a relatively small enthalpic barrier. This is true for both electron-rich and electron-poor benzaldehydes, despite the fact that a Hammett plot of the enantiomeric ratio is V-shaped, showing a dramatic switchover at $\sigma \approx 0$. Various scenarios for this divergent selectivity are discussed. After initial and reversible binding of the Lewis base to the silyl enolate, the two fundamental reaction steps are binding of aldehyde, followed by aldolization. On balance, the authors favour aldolization being both rate- and stereo-determining, even as selectivity changes. (*ee*)

Pinacol-type Coupling

The samarium–*N*-bromosuccinimide combination reductively dimerizes carbonyl compounds.[163] This pinacol-type coupling gives diols in 60–80% yield, with some diastereoselectivity; the by-product from simple reduction (i.e. alcohol) is typically 5–10%. The conditions suggest a single electron transfer to give carbonyl radical anion, which then self-couples. Even congested ketones such as benzophenone and fluorenone worked well. (*de*)

Samarium metal, in the presence of various additives such as ammonium chloride or bromide, induces reductive dimerizations of aromatic ketones to give 1,2-diols, with some diastereoselectivity, and with some alcohol (i.e. reduced ketone) by-product.[164] The *syn*-selectivity observed in many cases may be due to samarium chelation of the oxygens. (*de*)

Synthetically useful β, γ–δ, ε-doubly-unsaturated quaternary carbinols have been prepared enantioselectively via regioselective reductive coupling of 1,3-enynes with ketones.[165] (*ee*)

Samarium(II) iodide mediates diastereo- and enantio-selective pinacol coupling of chiral α-ketoamides.[166] (*de*) (*ee*)

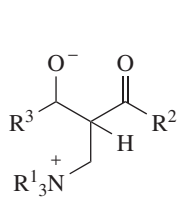
The Baylis–Hillman Reaction and its Aza and Morita Variants

The widely accepted mechanism of amine catalysis of the Baylis–Hillman reaction involves:

1. nucleophilic addition of the amine to the enone to give enolate, followed by
2. attack on the aldehyde to give a second zwitterionic intermediate (**46**), which
3. eliminates to product.

Step 2 is considered rate limiting, and autocatalysis can also be observed. Protic solvents can accelerate the reaction, perhaps by hydrogen bonding, but the enolate should be a better acceptor. A kinetic study has re-examined these issues, and finds (*ee*)

step 3 to be rate limiting in the initial phase, switching to step 2 as product (and hence autocatalysis) builds up.[167] The findings should help guide the design of asymmetric catalysts, especially those bearing hydrogen bond donors tethered to the nucleophile. In particular, alkoxide intermediate (**46**) can exist as four diastereomers, not all of which will have the hydrogen bond donor optimally placed for selective proton transfer.



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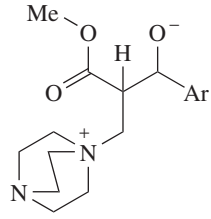

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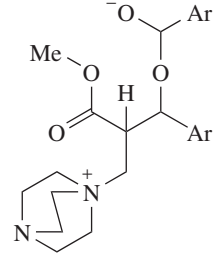


(**48**)

Based on reaction rate data, including primary and secondary kinetic isotope effects, a new mechanism has been proposed for the Baylis–Hillman reaction of arylaldehydes, using diazabicyclooctane as catalyst.[168] Starting from methyl acrylate ($H_2C{=}CHCO_2Me$) and DABCO, addition gives a zwitterionic intermediate, and a subsequent reaction with aldehyde gives another zwitterion (**47**). To this point, the mechanism coincides with that which is currently widely accepted. However, based on a finding of second-order behaviour in aldehyde and other evidence, the formation of hemiacetal-type intermediate (**48**) is proposed, with its breakdown to products – involving α C–H bond-breaking – being rate determining. The proposers discuss how the mechanism answers a wide range of puzzling observations about the reaction in a variety of media, and with various catalysts/additives.

Baylis–Hillman reactions of benzaldehyde and its 2-nitro derivative with α,β-unsaturated esters and nitriles have been carried out in water at pH 1 ($T = 0$ or 25 °C), with tertiary amine catalysts.[169]

N,*N*,*N*′,*N*′-Tetramethylethylenediamine (TMEDA) has been compared with DABCO in its catalysis of the reaction in aqueous medium.[170]

An air-stable ferrocenyl–dialkylphosphine is an effective catalyst for the Baylis–Hillman reaction; chiral analogues have also been developed to render it enantioselective.[171] (*ee*)

An enantioselective reaction of α-hydroxymethyl acrylates, using a bis-oxazoline chiral catalyst, gives the equivalent of formaldehyde aldol products in good yield and *ee*.[172] (*ee*)

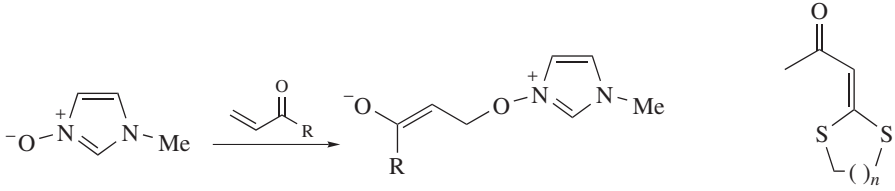
A highly enantioselective intramolecular version, catalysed by proline, undergoes an inversion of enantioselectivity on addition of imidazole.[173] The imidazole substantially increases the reaction rate: it is proposed to act as a co-catalyst, hydrogen bonding to the proline's acid hydrogen, blocking a reactant face which is otherwise available in the proline-only route. (*ee*)

Baylis–Hillman (and aza-BH) reactions have been reported for *N*-tosyl aldimines and aryl aldehydes with 3-methylpenta-3,4-dien-2-one, $H_2C{=}C{=}C(Me)COMe$.[174]

An NMR kinetic study of a phosphine-catalysed aza-Baylis–Hillman reaction of but-3-enone with arylidene–tosylamides showed rate-limiting proton transfer in the absence of added protic species, but no autocatalysis.[175] Brønsted acids accelerate the elimination step. Study of the effects of BINOL–phosphinoyl catalysts sheds light not only on the potential for enantioselection with such bifunctional catalysis, but also on their scope for catalysing racemization. (*ee*)

Bifunctional catalysis, using a phenolic BINAP–phosphine, is proposed in the enantioselective aza-BH reaction of *N*-sulfonated imines with cycloalk-2-en-1-ones.[176] (*ee*)

1-Methylimidazole 3-*N*-oxide (**49**) catalyses the Morita–Baylis–Hillman reaction at room temperature under solvent-free conditions; addition to the enone reactant to give a zwitterionic enolate (**50**) is proposed, followed by reaction with aldehyde.[177]



(**49**) (**50**) (**51**)

A dual catalyst combination of pipecolinic acid and *N*-methylimidazole gives 84% *ee* in a Morita–BH cyclization.[178] (*ee*)

N-Sulfonated imines undergo enantioselective aza-Morita–Baylis–Hillman reactions with methyl vinyl ketone, using a BINAP-derived phosphine Lewis base.[179] (*ee*)

The α-carbon atom of α-oxoketene dithioacetals (**51**, $n = 1, 2$) reacts with aromatic aldehydes to give 1:1 and 2:1 adducts, i.e. Baylis–Hillman and 'double-Baylis–Hillman', using mediation by titanium tetrachloride.[180]

An intramolecular vinylogous Morita–Baylis–Hillman reaction, followed by intramolecular aldol cyclization,[129] is described under *Intramolecular Aldols* above.

Allylation and Related Reactions

Lewis acid-catalysed allylboronate additions to aldehydes have been reviewed.[181]

An allylboronate derivative of tartaric acid developed for enantioselective allylation of aldehydes is readily recyclable without losing selectivity.[182] (*ee*)

A chiral pyridine–bisoxazoline ('PYBOX') ligand has been combined with indium (III) triflate to produce an enantioselective catalyst for allylation of a wide variety of aldehydes in ionic liquids;[183] *ee*s of >90% were obtained, and extraction and reuse of the catalyst–ionic liquid combination saw this figure hold up to >80% on the fourth recycle. (*ee*)

A chiral BINOL–indium(III) complex has been used to catalyse the addition of allyltributylstannane to aldehydes in high *ee*.[184] (*ee*)

Aldehydes can be allylated with allyltributylstannane using cerium(III) chloride in acetonitrile, a method particularly suitable for substrates bearing acid-sensitive groups.[185]

Enantioselective addition of allylstannane to straight-chain aldehydes has been achieved using a chromium–salen catalyst.[186] (*ee*)

Carboxylic acids promote the allylation of aldehydes by allyltributylstannane.[187] In the case of crotylation, some regioselectivity can be achieved by an appropriate choice of acid. (*de*)

A proline-derived *N*-oxide catalyses enantioselective allylation of aldehydes, using allyltrichlorosilane at ambient temperature.[188] (*ee*)

A terpene-derived pyridine *N*-oxide catalyses the asymmetric allylation of aldehydes with allyl- and crotyl-trichlorosilane at $-40\,^{\circ}C$, and the *ee*s hold up well even at ambient temperature.[189] (*ee*)

Chiral BINOL–indium(III) complexes have been employed in several enantioselective allylations: (i) in the ionic liquid, hexylmethylimidazolium–PF_6, for aldehydes,[190] (ii) a moisture tolerant version, for a wide variety of aldehyde types,[191] and (iii) a recyclable example, useful for aromatic, aliphatic, and α,β-unsaturated ketones.[192] (*ee*)

Indium mediates a highly enantioselective Barbier-type allylation of both aromatic and aliphatic aldehydes, using a chiral ethanolamine auxiliary, readily recoverable by acid extraction.[193] Barbier coupling of aldehydes can be carried out in water using tin(II) chloride, with cobalt(II) acetylacetonate as catalyst.[194] (*ee*)

In a gallium-mediated allyl transfer process, bulky gallium homoallylic alkoxides have been retro-allylated to generate (*Z*)- and (*E*)-crotylgallium reagents stereospecifically.[195] Immediate reaction with aromatic aldehydes gives *erythro*- and *threo*-homoallylic alcohols. (*de*)

Aldehydes have been allylated with allyltributyltin, using supramolecular catalysis in acidic water at $60\,^{\circ}C$.[196] Using β-cyclodextrin as catalyst with all species at a 1 mmol level, high yields were obtained in a few hours. The catalyst, which can be recycled effectively, hydrogen bonds the aldehyde oxygen within the cavity.

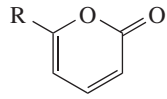
Palladium-catalysed asymmetric α-allyl alkylation of acyclic ketones has been reported: allyl enol carbonates of a wide range of ketones undergo allyl transfer in high yields and *ee*s at room temperature.[197] (*ee*)

A regio- and enantio-selective palladium-catalysed allylic alkylation of ketones has been reported, using allyl enol carbonate chemistry in which a CO_2 unit tethers the allylating agent to the nucleophile.[198] (*ee*)

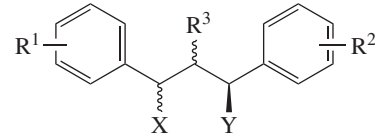
Catalytic asymmetric vinylation of ketones has been achieved. Vinylzinc reagents have been generated by hydrozirconation of terminal alkynes which are then transmetallated with zinc.[199] A titanium(IV) complex of a *trans*-cyclohexane-bis(sulfonamide) provides chiral catalysis; it also facilitates dienylation of ketones, with *ee*s also >90% in this case. (*ee*)

Enantioselective alkenylation and phenylation of aldehydes has been carried out using a chiral CuF complex.[200] (*ee*)

Phosphine-catalysed annulation between aldehydes (RCHO) and ethyl allenolate ($H_2C{=}C{=}CHCO_2Et$) gives 6-substituted 2-pyrones (**52**), proceeding via a zwitterionic enolate.[201] The product is derived from the *E*-intermediate, which is favoured by the use of sterically demanding trialkylphosphines, such as tri(cyclopentyl). However, overdoing the phosphine bulk with, for example, the tri(*t*-butyl) derivative gives no yield. (*de*)



(**52**)



(**53**)

Quaternary stereocentres in β-keto esters have been deracemized in an enantio-convergent decarboxylative allylation process, catalysed by palladium(II).[202] One catalyst is involved in both C–C bond-breaking and -making steps. (*ee*)

The Horner–Wadsworth-Emmons and Related Olefinations

Epimerizable aldehydes clearly undergo intermolecular Horner–Wadsworth–Emmons olefination with trimethyl phosphonoacetate, by using the weak base, lithium hexafluoroisopropoxide [$LiOCH(CF_3)_2$], as catalyst.[203] (*de*) (*ee*)

A *Z*-selective alkenylation reaction produces α-fluoro-α,β-unsaturated esters. Using the anion of an α-fluoro-α-organoselanylacetate, $R^1Se–CHF–CO_2Et$, to react with an aldehyde or ketone ($R^2R^3C{=}O$), it results in formation of an alcohol selenyl ether, $R^2R^3C(OH)–CF(SeR^1)–CO_2Et$.[204] Acid treatment then eliminates a molecule of R^1SeOH to give $R^2R^3C{=}C(F)–CO_2Et$. (*de*)

Ketones can be olefinated with ethyl diazoacetate in the presence of triphenylphosphine, using methyltrioxorhenium as catalyst.[205]

Synthetically useful Lewis acid-promoted reactions of araldehydes (R^2–Ar–CHO) with styrenes have been investigated.[206] Using boron halide reagents gives a variety of 1,3-diarylpropanes (**53**). For example, boron trihalides give the corresponding 1,3-dihalo derivatives (**53**, X = Y = Cl, Br, I), while phenylboron dichloride gives the 3-chloropropanol (**53**, X = Cl, Y = OH), with the *anti*-isomer predominating (88% *de*). NMR evidence suggests an oxyboronchloride intermediate [(**53**), X = O–B(Cl)–Ph, Y = Cl] for this reaction; presumably a similar intermediate ($X = OBCl_2$) would operate in the BCl_3 reaction. *trans*-β-Methylstyrene, in the presence of BCl_3, gave 1,3-dichloro-2-methyl product, with some diastereoselectivity. (*de*)

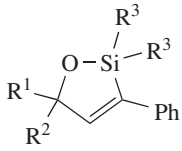
PYBOX complexes of scandium(III) triflate act as enantio- and diastereo-selective catalysts of ene reactions, including examples with trisubstituted alkenes.[207] (*de*) (*ee*)

Cyclic alkenyl ethers have been prepared by intramolecular *O*-vinylation of β-keto esters using a pendant vinyl bromide, with copper(I) catalysis.[208]

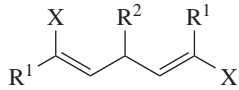
Alkynylations

A short review reports high *ee*s in the alkynylation of aromatic aldehydes, using BINAP derivatives bearing amino alcohol ligands.[209] (*ee*)

Aldehydes and ketones (R^1COR^2) undergo an unusual tandem alkynylation and *trans*-hydrosilylation with alkynylsilanes (e.g. $Ph–C{\equiv}C–SiHR^3_2$) to give oxasilacyclopentenes (**54**).[210] A mild alkoxide initiator is required.



(**54**)



(**55**, X = Cl, Br)

Anhydrous iron(III) halides catalyse coupling of alkynes and aldehydes.[211] Simple terminal alkynes, $R^1C{\equiv}CH$, react with aldehydes, R^2CHO, to give (*E*,*Z*)-1,5-dihalo-1,4-dienes (**55**). In contrast, non-terminal arylalkynes give (*E*)-α,β-unsaturated ketones. The catalysts also promote standard Prins cyclization of homoallylic alcohols. Studies of intermediates and of alkyne hydration – together with calculations – all support FeX_3 complex formation with alkyne as the activating step.

Alkynyl nucleophiles, $(R^1O)_3Si{-}C{\equiv}C{-}R^2$, have been added to aldehydes, ketones, and imines, using a strong Lewis base, KOEt.[212] Evidence for ethoxide attack at silicon, to give a hypervalent silicate intermediate, which then coordinates with the carbonyl (or imine), is presented. ^{29}Si NMR is particularly informative: when R^1 = OEt, the alkyne silicon shows up at -72 ppm [similar to $(EtO)_4Si$ at -80 ppm], but a new peak is seen very far upfield at -126 ppm, beyond a similar known silicate, $(EtO)_4SiPhK$ at -117 ppm, and indeed close to $(EtO)_5Si^-$, at -130 ppm.

Aldehydes and ketones have been alkynylated using indium(III) and Hunig's base (Pr^i_2NEt) as catalysts.[213] IR and NMR evidence support a dual-activation role for indium: it is a Lewis acid for the hard electrophile (carbonyl compound), and has sufficient π-coordination ability for a soft nucleophile such as a terminal alkyne. For the latter substrate, the amine then assists proton abstraction.

Dimethylzinc promotes the addition of phenylacetylene to aldehydes and ketones, to give propargyl alcohols.[214] The process works at room temperature, without added ligands. The role of the carbonyl group as 'ligand' has been investigated: calculations suggest that acetone can coordinate, causing the linear and non-polar dimethylzinc to bend, with an associated increase in basicity of the methyl group.

Using triethylaluminium and a quinine auxiliary, phenylacetylene has been added enantioselectively to unactivated acetophenones.[215] (*ee*)

An open-chain sugar has been alkynylated with 1,2-*syn* selectivity, using acetylides in the presence of zinc(II) chloride.[216] (*de*)

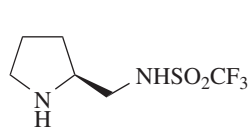
Michael Additions

Enantioselective Michael additions of aldehydes to enones using imidazolidinones as organocatalysts show evidence of enamine intermediates.[217] Several co-catalysts – mainly phenols – raise the yield and/or *ee*. (*ee*)

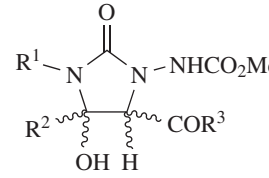
Glycine imine esters, $Ph_2C{=}N{-}CH_2{-}CO_2R$, undergo asymmetric Michael addition to enones using an ether–water phase-transfer system.[218] A chiral ammonium salt, in conjunction with cesium carbonate, gives high *ee*s. (*ee*)

Diphenylprolinol methyl ether catalyses the enantioselective Michael addition of simple aldehydes to simple enones.[219] (*ee*)

Organocatalyst (**56**), a pyrrolidine sulfonamide derived from L-proline, catalyses the direct Michael addition of aldehydes to nitrostyrene with high *ee* and *de*, apparently exploiting its bifunctional (acid–base) nature.[220] (*ee*) (*de*)



(**56**)



(**57**)

Diazenes, R^1–NHCON=N–CO_2Me, have been reacted with 1,3-dicarbonyl compounds ($R^2COCH_2COR^3$) to give a convenient synthesis of highly substituted 2-imidazolin-2-ones (**57**); the products are easily dehydrated in the presence of acid.[221] Intermediate Michael adducts are isolable.

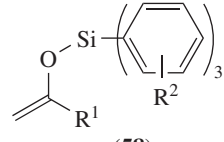
An intramolecular asymmetric Michael addition of aldehydes and ketones – to give cyclopentanals – gives the otherwise disfavoured *cis*-products when catalysed with antibody 38C2, the first commercially available catalytic antibody.[222] One case gave 99% *de*, 98% *ee*. (*de*) (*ee*)

Other Addition Reactions

General and Theoretical

CH/π hydrogen bonds in organic reactions have been reviewed, including major sections on diastereoface- and enantioface-discriminating reactions.[223] (*de*) (*ee*)

The nucleophilic reactivities of silyl enol ethers (**58**, R^1 = alkyl) and silyl ketene acetals (**58**, R^1 = *O*-alkyl) have been measured for the triphenylsilyl ($R^2 = H_5$) substrate, and its perfluoro analogue ($R^2 = F_5$), using benzhydrylium cations as reference electrophiles.[224] The triphenyl compound is 10 times less reactive than its trimethyl equivalent, but the perfluorination causes the C=C nucleophilicity to drop by 3–4 orders of magnitude. The new compounds have been placed on scales of nucleophilicity taken from the literature.



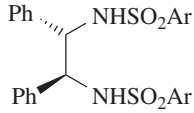
(**58**)

A computational study of hydride addition to a range of carbonyl compounds suggests that most of the negative charge resides on hydrogens, and not on the carbonyl oxygen.[225]

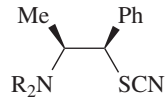
Proton affinities of a variety of simple ketones, α-diones, and α-keto esters and lactones have been calculated by a variety of methods and compared with experiment.[226]

Addition of Organozincs

A range of simple bis-sulfonamides (**59**) give mediocre *ee*s of ca 20% in the enantioselective addition of diethylzinc to benzaldehyde at low reaction conversion, but – in a striking example of auto-induction – the catalyst evolves to give *ee*s up to 79% at completion.[227] The reactions are carried out under standard titanium(IV) isopropoxide conditions, and the mechanism of auto-induction is proposed to involve interaction of isopropoxides on the titanium with the alkoxide of the product. Replacement of isopropoxide in the titanium reagent with bulkier (but achiral) alkoxides allows the *ee* to be raised further. Thus in this case the enantioselectivity of the catalyst can be optimized by varying achiral ligands, considerably more convenient than having to optimize enantiopure ones.



(**59**)



(**60**)

A study of enantioselective additions of diethylzinc to benzaldehyde, using chiral carboline and oxazolidine auxiliaries, has examined the requirements to allow the conformations of the free ligands to be related to the *ee*s and transition states, given that several steps intervene.[228]

Cyclic derivatives of 1,2- and 1,3-amino alcohols have been trialled as chiral catalysts in the addition of diethylzinc to benzaldehyde.[229] Enantioselective addition of diethylzinc to benzaldehyde is the subject of other reports,[230,231] including the use of triazinyl-BINOLs as enantioselective catalysts of addition to araldehydes, using Ti(IV) tetraisopropoxide.[232] Two optically active amino thiocyanate derivatives (**60**) of (−)-norephedrine act as aprotic ligands for enantioselective addition of diethylzinc to aldehydes in up to 96% *ee*.[233] The *ee* drops drastically if the −SCN group is changed to −SR.

Synthesis of a series of *N*-sulfonylated amino alcohols and their use as ligands of titanium(IV) in enantioselective addition of diethylzinc to aldehydes has been described.[234]

Aryl stacking effects in the transition state appear to play a role in the enantioselective addition of di*methyl*zinc to benzaldehyde when an *N*-benzylmandelamide–Ti(IV) complex is used as catalyst.[235]

While β-amino alcohols have been widely studied as chiral auxiliaries, a series of (*S*)-amino alcohols – built into norbornane frameworks – have been examined as catalysts of enantioselective addition of dialkylzincs to benzaldehydes.[236]

Chiral bis-sulfonamides have been employed as catalysts of enantioselective addition of a range of organozincs to simple aryl ketones, in *ee*s up to 99%, using Ti(IV) tetraisopropoxide methodology.[237]

Catalytic asymmetric addition of functionalized alkylzincs to ketones and enones has been reported.[238] Functional groups include esters, silyl ethers, alkyl chlorides, and alkyl bromides, with *ee*s >99% in some cases.

N-Acylethylenediamine ligands, derived from Boc-protected amino acids, catalyse the enantioselective addition of vinylzinc reagents to aldehydes.[239] (ee)

β-Amino thiols derived from (*S*)-valine catalyse the enantioselective addition of alkenylzincs to aldehydes.[240] Enantioselective addition of alkynylzincs to aldehydes has been described.[241] (ee)

Pyrrolidinylmethanols derived from (*S*)-proline have been employed in the zinc-catalysed addition of arylboronic acids to aromatic aldehydes, giving *ee*s up to 98%.[242] An arylzinc species is generated via a boron–zinc exchange, avoiding the need for expensive diphenylzinc. (ee)

BINAP-derived 1,2-amino alcohols catalyse the enantioselective phenylalkynylation and phenylation of aromatic aldehydes by zinc reagents.[243] (ee)

A BINOL-dicarboxamide catalyses the enantioselective phenylation of aldehydes by ethylphenylzinc.[244] (ee)

DFT calculations have been used to probe the mechanism of enantioselective addition of diphenylzinc to aldehydes, and in particular the enhanced selectivity which accompanies addition of di*ethyl*zinc to the system.[245] (ee)

Chiral diarylmethanols have been prepared enantioselectively by phenyl transfer to benzaldehydes, using $PhB(OH)_2$–$ZnEt_2$ and a new tertiary aminonaphthol auxiliary.[246] (ee)

A catalytic enantioselective arylation of arylaldehydes employs a chiral *β*-amino alcohol and a boronic acid–diethylzinc exchange reaction to generate the reactive arylzinc species.[247] (ee)

Addition of Other Organometallics

Potassium trifluoro(organo)borates such as $ArBF_3K$ couple with benzaldehydes to give carbinols using the catalytic combination of $Rh(H_2C{=}CH_2)_2Cl_2$ and Bu^t_3P, in toluene–water mixtures at 60 °C.[248] The reaction tolerates a wide range of functionality and works well for hindered benzaldehydes, and even for aliphatic aldehydes.

t-Butyl-'Amphos' (Bu^t_2P–CH_2CH_2–NMe_3Cl) combines with $RhCl_3.3H_2O$ to give a recyclable catalyst for cross-coupling aldehydes with aryl- and vinyl-boronic acids in aqueous solution.[249]

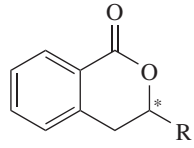
Aldehydes, R^1CHO, have been alkylated to give secondary alcohols, $R^1CH(OH)R^2$, using boranes, R^2_3B, and a nickel(II) catalyst.[250]

Formation of secondary alcohols, RCH(OH)Ar, from aldehydes and arylboronic acids, $ArB(OH)_2$, is catalysed by a range of palladium(0) complexes, but chloroform is required.[251] Palladium–chloroform complexes are equally effective, and evidence for $(Ph_3P)_2Pd$ being converted to palladium(II) intermediates, $(Ph_3P)_2Pd(X)$–$CHCl_2$, is presented (X = Cl, then OH).

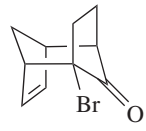
An enantioselective addition of trialkylaluminium to aldehydes uses chiral *α*-hydroxy acids as ligands.[252] (ee)

Molecular dynamics simulations have been used to predict solvent and temperature effects in the nucleophilic addition of *α*-chiral carbonyl compounds.[253] Prediction of diastereoselectivity 'break' temperatures (i.e. inversion points) has been achieved with fair accuracy by comparison with experimental data on *n*-BuLi addition. Dramatic differences are seen for additions to 2-phenylpropanol in pentane solvent, compared with octane. (de)

3-Substituted 3,4-dihydroisocoumarins (**61**) have been prepared enantioselectively by two diastereoselective processes: addition of aldehydes (RCHO) to laterally lithiated chiral 2-(*O*-tolyl)oxazolines, followed by lactonization.[254] (*ee*) (*de*)



(**61**)



(**62**)

sp^2- and *sp*-hybridized organolithiums have been added to a bridgehead bromo ketone (**62**).[255]

The diastereofacial selectivity of the addition of lithioacetonitrile to 2-phenylpropanol has been studied over a wide range of temperatures, solvents, and bases.[256] Eyring plots [ln(*dr*) vs 1/*T*], activation parameters, and inversion temperatures have been characterized. In some cases, the differential entropy of activation, $\Delta\Delta S^{\neq}$, plays an exclusive role in determining *anti*-selectivity. (*de*)

Grignard-type Reactions

Efficient alkylation of ketones to give tertiary alcohols has been achieved using magnesium 'ate' complexes such as R_3MgLi or RMe_2MgLi, the latter being an 'R'-selective reagent.[257] These alkylating species can be prepared from RLi and either RMgX or R_2Mg. The R group is much more nucleophilic than that of either RLi or RMgX, and R_3MgLi is less basic. A range of substrates show higher yields and fewer by-product problems compared with Grignards. The alkyl selectivity can be dramatic: benzophenone yields >99% ethanol product on treatment with $EtMe_2MgLi$. The same substrate with EtMgBr gives only a 14% yield, with 68% Ph_2CHOH by-product.

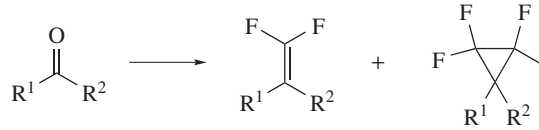
Organogallium reagents, R_3Ga, have been added enantioselectively to aldehydes, using $TiCl_4$ as a Lewis acid catalyst, with a chiral salan ligand.[258] (*ee*)

The Wittig Reaction

Quantum mechanical calculations in the gas phase and DMSO solution at different temperatures can highlight the hazards of standard 0 K gas-phase calculations.[259] For the Wittig reaction, a small barrier in the potential energy curve is transformed into a significant entropic barrier in the free energy profile, and the formally neutral oxaphosphetane intermediate is displaced in favour of the zwitterionic betaine in the presence of DMSO.

Stabilized ylides react with aldehydes in water to give Wittig products, sometimes with remarkable acceleration.[260] For example, pentafluorobenzaldehyde reacts with ester-stabilized ylide, $Ph_3P{=}CHCO_2Me$, at 20 °C in 5 min in 86% yield, with 99:1 *E*:*Z*-selectivity. Water's ability to stabilize the polar transition state of the reaction, and its participation in the reaction (as determined by deuterium exchange), are discussed. (*de*)

gem-Difluoroalkenes (**63**) have been prepared from aldehydes and ketones, using Wittig-type reactions.[261] Difluoromethylene phosphorus ylides are prepared using $Hg(CF_3)_2$ and NaI, together with a trialkyl-or triaryl-phosphine: reaction typically takes 2 h at 70 °C. Unexpectedly, tetrafluorocyclopropanes (**64**) were also formed, through *in situ* addition of difluorocarbene. In most cases, the use of Bn_3P gives (**63**) almost exclusively, whereas Ph_3P favours (**64**), as does higher temperature.



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

Hydrocyanation and Cyanosilylation

Mono- or di-lithium salts of (*R*)-BINOL give high yields and good *ee*s in cyanations of aromatic aldehydes.[262] Formation of an aqua (or alcohol) complex of the catalyst gives higher and reversed *ee*, and non-linear effects in some cases. (*ee*)

Asymmetric cyanohydrin synthesis from aldehydes using trimethylsilyl cyanide (TMSCN) has been carried out using a chiral Al(salen) complex–triphenylphosphine Lewis acid–base combination.[263] (*ee*)

An enantiopure cyanohydrin of 2-*p*-tolylsulfinylbenzaldehyde has been prepared using various metallic cyanating agents in the presence of Yb(III) or Y(III) triflate.[264] Sulfoxide coordination with the metal is implicated, supported by DFT calculations. (*de*)

Aldehydes, RCHO, have been cyanoethoxycarbonylated with ethyl cyanoformate, to give cyanohydrin-related products, $RCH^*(CN)OCO_2Et$, using a heterobimetallic chiral catalyst to achieve high *ee*s.[265] Kinetic studies have probed the roles of achiral additives in raising the yield and *ee*. (*ee*)

Lithium chloride is a convenient catalyst for cyanosilylation of a range of ketones and aldehydes by trialkylsilyl cyanide, under solvent-free conditions: the silylated cyanohydrin product can be directly distilled out.[266] As little as a microequivalent of catalyst proved effective. Evidence for nucleophilic chloride, generating a pentavalent silicon (**65**) as reactive species, is presented.

(**65**) (**66**)

Strong base (**66**, R = Me, pK_a of conjugate acid = 32.9) catalyses the cyanosilylation of aldehydes and ketones, using TMSCN in THF at 0 °C.[267] Even better results are obtained with isopropyl as R group, but the isobutyl case is a much poorer catalyst, indicating a very fine balance between basicity and steric bulk in the action of these catalysts.

A simple ionic liquid, octylmethylimidazolium (with PF_6^- counterion), promotes TMSCN addition to aldehydes in yields up to quantitative, in 1 day at room temperature. Environmentally friendly and recyclable, the solvent requires no Lewis acid or other activation.[268] The long-chain substituent and the nature of the counterion are important contributors to the high yield. Deprotection to give the product as cyanohydrin just requires an HCl–THF workup.

A BINOL–salen ligand catalyses the enantioselective addition of TMSCN to aldehydes at room temperature, in the presence of titanium(IV) isopropoxide.[269] (ee)

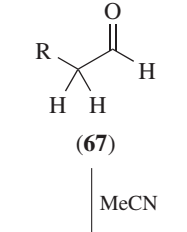
The source of enantioselection in the trimethylsilylcyanation of benzaldehyde using chiral Schiff base–titanium(IV) complexes has been investigated by computation.[270] (ee)

Cyanosilylation of methyl ketones has been carried out using diphenylmethylphosphine oxide and trimethylsilyl cyanide, generating a phosphorus isonitrile-type species, $Ph_2MeP(OTMS)(N{=}C{:})$, as the reactive intermediate.[271] A chiral oxazaborolidinium ion catalyst renders the reaction enantioselective. (ee)

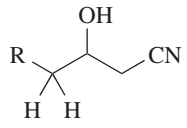
trans-Diaminocyclohexane-derived catalysts bearing a thiourea group are efficient enantioselective catalysts for the cyanosilylation of ketones.[272] A cooperative mechanism involving nucleophilic and electrophilic activation from the amino and thiourea components is proposed. (ee)

A simple amino acid salt, sodium L-phenylglycinate, catalyses the enantioselective cyanosilylation of ketones.[273] (ee)

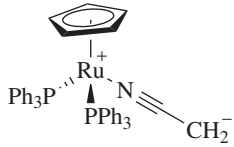
Despite acetonitrile's feeble acidity (pK_a ca 29) compared with enolizable aldehydes (**67**, pK_as 16–17), the combination of a simple ruthenium complex, $[RuCp(PPh_3)_2]^+$, and diazabicycloundecane (DBU) brings about a nitrile-selective deprotonation to give β-hydroxynitriles (**68**).[274] A mechanism is proposed in which DBU, aldehyde, and acetonitrile can displace triphenylphosphines, with the metal centre activating acetonitrile to convert it to an $NC–CH_2^-$ ligand (proposed intermediate, **69**). A nickel–diarylamidodiphosphine complex (**70**) also catalyses this transformation in the presence of DBU.[275]



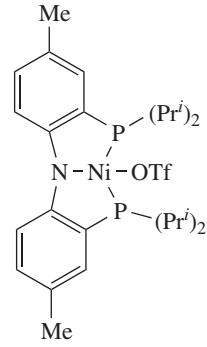
(**67**)



(**68**)



(**69**)



(**70**)

For other cyanations, see *Other Reactions of Imines* above.

Hydrosilylation and Hydrophosphonylation

Recent advances in the asymmetric hydrosilylation of ketones and imines have been reviewed.[276]

Hydrosilylation of ketones, and also of α- and β-keto esters and amides, has been achieved using polymethylhydrosiloxane in methanol, with various zinc(II) catalysts.[277] The reactions are faster than in aprotic solvents, and show some enantioselectivity with chiral diaminozincs. (*ee*)

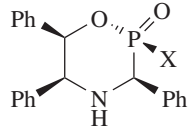
A salalen ligand (a hybrid salicylideneimine–salicylamine) has been coordinated to aluminium to serve as an enantioselective catalyst for aldehyde hydrophosphonylation of aldehydes.[278] (*ee*)

Miscellaneous Additions

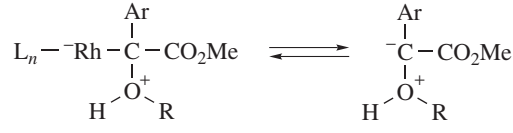
Catalytic enantioselective α-aminations and α-oxygenations of carbonyl compounds have been reviewed.[279] (*ee*)

The formaldehyde–sulfite reaction displays non-linear dynamics: it is a 'clock' reaction with a sudden pH excursion (from ca 7 up to 11).[280] The induction period in batch processes is explained by the internal buffer systems, HSO_3^-–SO_3^-. However, flow reactors also exhibit pH oscillations and bistability.

A 2*H*-2-oxo-1,4,2-oxazaphosphinane (**71**, X = H) can be added diastereoselectively to alkyl- or aryl-aldehydes or the corresponding aldimines to give alcohol [X = CH*(OH)R^1] or amine [X = CH*(NHR^2)R^1] products in high yield.[281] Nucleophilic and electrophilic activation strategies have been investigated to maximize the *de*. (*de*)



(**71**)



(**72a**) (**72b**)

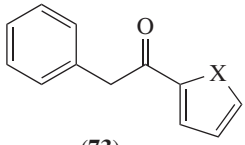
The Boyer reaction – a relative of the Schmidt process – involves 2-oxazoline formation from a 2-azidoethanol and an aldehyde (RCHO).[282] Using a 2-aryl-2-azidoethanol, a 2-oxazoline product and its 3-isomer are obtained using BF_3 catalysis. However, on using copper(II) triflate, an acetal, $RCH[OCH_2CH(Ph)N_3]_2$, resulted.

A three-component reaction of aryl diazoacetates, alcohols, and araldehydes (or araldimines) has been investigated, using a rhodium(II) catalyst.[283] The first two components combine in the presence of catalyst to produce a zwitterion (**72a**). Evidence for equilibration with an alcoholic oxonium ylide intermediate (**72b**) is presented. It is proposed that this species is trapped by electron-deficient araldehyde (or imine) to give new C–C bond formation.

α-Silyloxy ketones have been generated regiochemically in a new cross silyl benzoin reaction catalysed by cyanide.[284] Use of $La(CN)_3$ allows extension of the reaction to alkyl and α,β-unsaturated substrates. The mechanism – and in particular the reversibility of key steps – has been investigated.

Enolization and Related Reactions

The effects of cationic and zwitterionic micelles on the keto–enol tautomerism of 2-phenylacetyl-furan and -thiophene (**73**, X = O, S) have been studied in aqueous media.[285] While the micelles perturb the equilibrium only slightly, the apparent acidity of one or other tautomer is increased, as the micelles have an affinity for the enolate. The systems also show lowered 'water' rates at the minima of their pH–rate profiles, allowing an otherwise undetectable metal ion catalysis to be observed.



(**73**)

(**74**)

Solvent and concentration effects on keto–enol tautomerization have been investigated in DMSO–water mixtures and aqueous micellar solutions, for 2-acetylcyclohexanone and 2-acetyl-1-tetralone.[286] Dramatic rate increases aboves 60% DMSO content have been explained in terms of solvent structure: solvent polarity alone cannot rationalize the effect.

Using a transition state model for enolate formation and a database search, a thiourea with a pendant amine has been designed as a catalyst, and its ability to hydrogen bond the enolate of acetone explored.[287] Both in-plane and out-of-plane hydrogen bonds, to a lone a pair and the carbonyl π-bond, respectively, were considered.

Charge density analysis has been carried out for three reaction paths involving intramolecular hydrogen transfer: the keto–enol tautomerism of acetaldehyde, the pinacol rearrangement of protonated ethane-1,2-diol, and the unimolecular decomposition of methanediol, reactions involving H-transfer between C···O, C···C, and O···O atoms.[288]

A computational study of intramolecular proton transfer in acetylacetone has been carried out.[289] (ee)

A short review describes recent developments in the transfer of chirality within enolate alkylation reactions.[290] (ee)

Ketone dilithio α,β-dianion species (**74**) have been generated by the tin–lithium exchange reaction of the lithium enolate of β-tributyltin-substituted ketones.[291] Reaction with carbon electrophiles gives substituted ketones.

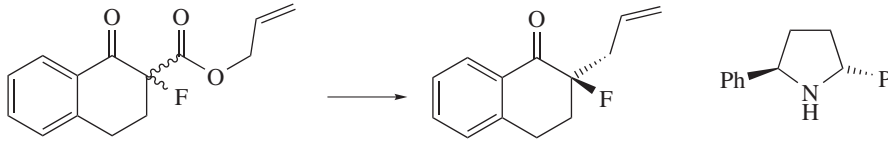
A range of asymmetric alkyl additions to ketones have been carried out using highly concentrated or solvent-free conditions to produce 'greener' conversion.[292] The loading of catalyst – a bis-sulfonamide – can be significantly decreased under these conditions. (ee)

Recent advances in catalytic asymmetric electrophilic α-halogenation of carbonyl compounds are described in two reviews.[293,294]. (ee)

Direct enantioselective catalytic α-fluorination of aldehydes has been carried out using *N*-fluorobenzenesulfonimide [F–N–$(O_2SPh)_2$] and a chiral secondary amine (an imidazolidinone) to provide enamine organocatalysis.[295] (ee)

Direct asymmetric α-fluorination of both branched and linear aldehydes has been carried out with a series of pyrrolidine-related catalysts.[296] (*ee*)

Chiral α-fluoro ketones (e.g. **75**) bearing a *gem*-allyl function have been prepared by catalytic enantioselective decarboxylation of the racemic allyl ester (**76**), using a range of palladium(II) catalysts.[297] (*ee*)



(**76**) (**75**) (**77**)

Protected sulfenylation reagents (Lg–S–Pg) α-sulfenylate aldehydes, using sterically encumbered chiral pyrrolidines as enantioselective organocatalysts.[298] (*ee*)

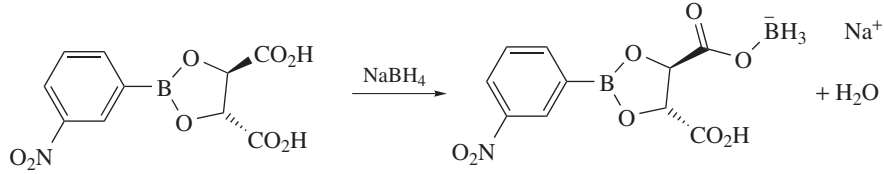
2,5-Diphenylpyrrolidine (**77**) catalyses the enantioselective α-chlorination of aldehydes.[299] Mechanistic and computational studies suggest that – in contrast to previously proposed mechanisms involving direct formation of the carbon-electrophile bond – *N*-chlorination occurs first, followed by a 1,3-sigmatropic shift of chlorine to the enamine carbon. The product iminium ion is then hydrolysed in the rate-determining step. (*ee*)

α-Ketol and related isomerizations – the isomerization of α-hydroxy ketones, aldehydes, and imines – have been reviewed up to 2002.[300]

Oxidation and Reduction of Carbonyl Compounds

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

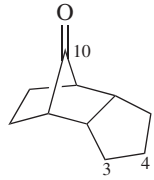
The reagent L-TarB-NO_2 (**78**), prepared from tartaric and *m*-nitrophenylboronic acids, asymmetrically reduces ketones in the presence of sodium borohydride.[301] Evidence for a monoacyloxyborohydride intermediate (**79**) is presented. (*ee*)



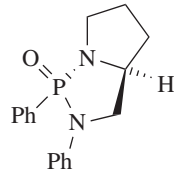
(**78**) (**79**)

(−)-Menthol catalyses the enantioselective reduction of ketones by $NaBH_4$ in diglyme: proton- and auto-catalytic possibilities are investigated, and trialkyl borate species generated during the reaction may also play a role in catalysis.[302] (*ee*)

The diastereoselectivities of the reduction of tricyclo[5.2.1.$0^{2,6}$]decan-10-one (**80**) and its 3,4-ene and 3-one derivatives have been measured, using $NaBH_4$ in methanol (*de*)



(**80**)



(**81**)

as hydride reducing agent.[303] The results are explained in terms of antiperiplanar and vicinal $\sigma \rightarrow \pi^*_{C=O}$ interactions, rather than hyperconjugative effects. Calculations have been employed to examine the effect of sodium complexation: the conformations of the complexes are argued as being possibly more important than those of the ground-state free ketones.

While chiral catalysts containing N–P=O moieties have been increasingly studied in borane-mediated asymmetric reduction of ketones, a study of a range of such species (e.g. **81**) indicates that the configuration at phosphorus plays little or no role in determining enantioselectivity, and indeed the stereochemistry at the phosphorus centre may be scrambled under the reaction conditions.[304] (*ee*)

$BH_3.Me_2S$ reduction of aryl alkyl ketones can be carried out with *ee*s up to 98% using 3 mol% of a chiral oxazaborolidine derived from (−)-β-pinene.[305] (*ee*)

Transfer hydrogenation of aromatic ketones has been carried out in high yield and *ee* using propan-2-ol and a catalyst generated *in situ* from an iridium(I) [or rhodium(I)] hydride and a *trans*-1,2-diaminocyclohexane ligand.[306] (*ee*)

A hindered BINAP–phosphoric acid catalyst allows the enantioselective reduction of ketimines via transfer hydrogenation.[307] Imines can be generated *in situ* from either aliphatic or aromatic ketones, with low catalyst loading. (*ee*)

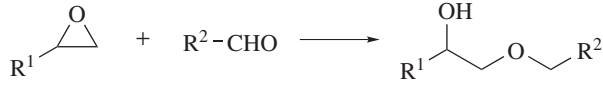
Substrate substituent effects on activity and enantioselectivity have been investigated in the enzymatic reduction of aryl ketones, using 24 recombinant ketoreductases.[308] (*ee*)

A recoverable fluorous prolinol catalyst has been developed for enantioselective reduction of ketones.[309] (*ee*)

A ruthenium centre, tethered to a 1-amino-2-sulfonamide auxiliary, catalyses transfer hydrogenation of ketones in high yield and *ee*.[310] (*ee*)

Other Reduction Reactions

Catalytic reductive coupling of epoxides (**82**, R^1 = alkyl) with aldehydes (**83**) yields β-hydroxy ethers (**84**), in a C–O bond-forming process involving yields up to 90%.[311] The reaction is catalysed by $(Ph_3P)_3RuCl$, a species which cannot reduce the aldehyde



(**82**) (**83**) (**84**)

in the absence of epoxides. Based on this and other evidence, ring opening *precedes* carbonyl reduction, a finding which opens up possibilities where the aldehyde could be replaced by other functional groups.

DFT has been used to explore the mechanism of reductive etherification of aromatic aldehydes by alcohols, using BH_3 as catalyst and reductant.[312] The reaction is suggested to proceed by addition (rate controlling), followed by reduction, and is expected to be feasible in polar solvents such as acetonitrile.

Stabilized nucleophiles have been added to allylic alcohols using 'catalytic electronic activation', in which a reaction has been designed where an alcohol is temporarily oxidized to a carbonyl compound.[313]

Aldehydes have been catalytically hydrogenated to alcohol products in a range of supercritical solvents under otherwise mild conditions.[314]

The redox chemistry of quinones has been reviewed in the context of hydrogen bonding, protonation, and supramolecular effects that can modify their reactivity.[315]

Ketonic decarboxylation, in which two molecules of acid are thermally converted to a symmetrical ketone plus carbon dioxide and water, has been reviewed.[316] Radical, β-keto acid, and concerted mechanisms are considered, with the reviewer favouring the last, albeit not conclusively. It is suggested that development of bifunctional catalysts may be the best way to improve the energetics of the process, and hence its synthetic utility and 'green' credentials.

The reagent combination $TiCl(O^iPr)_3$–$NaBH(OAc)_3$ performs reductive amination of aldehydes by electron-deficient and heteroaromatic primary amines, to give secondary amine.[317]

Oxidation Reactions

The relative rates and stereochemistry of epoxidation reactions of 5-substituted-adamantan-2-ones with two sulfur ylids (methylenedimethylsulfurane and its oxysulfurane analogue) have been studied in DMSO and in benzene.[318]

Oxidation of aliphatic aldehydes by quinolinium dichromate in aqueous acetic acid shows first-order kinetics in substrate and oxidant, and second-order with respect to H^+.[319] Hydrated aldehyde and protonated oxidant are suggested to be the reactive species, with Zucker–Hammett plots supporting proton abstraction by water in the slow step.

Oxidation of ketones by ceric perchlorate is catalysed by iridium(III) chloride, particularly in acidic media.[320]

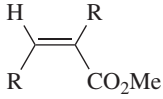
Oxidation of long-chain aliphatic aldehydes by quinolinium dichromate has been studied in aqueous acetic acid–sulfuric acid mixtures.[321]

The kinetics of the oxidation of cyclic ketones by Caro's acid (peroxomonosulfuric acid, H_2SO_5) are first order in both, and the pH–rate profile has been analysed in terms of contributions from HSO_5^- and SO_5^{2-}.[322] Similar results are found for aromatic aldehydes.[323]

Decomposition of Caro's acid is catalysed by acetone.[324] A kinetic study in aqueous alkaline medium indicates simple second-order kinetics. Nucleophilic addition of SO_5^{2-} to the carbonyl carbon leads to oxirane by reaction with another SO_5^{2-} to give

oxygen, sulfate, and regenerated ketone. Substituent effects are also described from results with other ketones.

Ketones, R–CH_2COCH_2–R, undergo *Z*-selective oxidation to give useful acrylates (**85**), using KOH and molecular iodine in methanol.[325] Evidence for the formation (*de*) of an α,α'-diiodoketone intermediate is presented, followed by a Favorskii-type rearrangement.



(**85**)

A mild oxidative one-carbon homologation of aldehyde to amide has been reported.[326]

Ketones and aldehydes have been economically α-hydroxylated (to give α-hydroxyacetals), using iodine in basic methanol.[327] Enolate formation and iodination to give α-iodocarbonyl is then followed by transformation into the hydroxyacetal, a dimethyl acetal under the MeO^-/MeOH conditions employed.

The tetraphenylmethane skeleton has been used to develop a series of hypervalent iodine(III) reagents, C–(C_6H_4-*p*-R)$_4$.[328] Starting from the tetraiodide (R = I), a diacetate, a bis(trifluoroacetate), and a hydroxytosylate have all been prepared [i.e. R = $I(OAc)_2$, $I(O_2C–CF_3)_2$, and I(OH)OTs, respectively]. In addition to being useful for general oxidations (alcohol to ketone, hydroquinone to quinone, etc.), the recyclable reagents catalyse α-tosyloxylation of methyl alkyl ketones *on the more hindered side*, an ostensibly unexpected result for such a bulky reagent.

The kinetics of the oxidation of D-galactose and D-xylose by an alkaline solution of sodium metaperiodate has been studied, using ruthenate ion (RuO_4^{2-}) as a catalyst.[329]

β,δ-Unsaturated alcohols undergo an oxidative esterification with aliphatic aldehydes in the presence of an iridium(I) catalyst and potassium carbonate.[330] Precoordination of the ene-alkoxide with iridium is proposed, followed by reaction with aldehyde. Although the 'ester yield' is high, a mixture of unsaturated and saturated esters is typically obtained, except for secondary alcohols.

Two new tetraphenylporphyrin (TPP) catalysts have been reviewed.[331] $Cr(TPP)^{III}$ triflate is highly regio- and stereo-selective in rearranging epoxides into aldehydes, while the iron perchlorate analogue affords the corresponding ketones.

Other Reactions

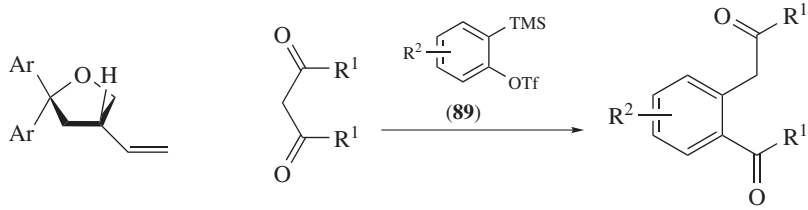
The use of carbohydrate-derived phosphorus ligands in asymmetric synthesis has been (*ee*) reviewed,[332] as has the potential for substrate-induced asymmetric catalysis.[333]

In atmospheric chemistry, kinetic isotope effects have been measured for the reaction of hydroxyl radicals with acetone using the relative-rate method over a range of temperatures.[334] Water vapour had relatively little effect on rates. Product studies have allowed partitioning of the reaction flux into routes that produce acetic acid directly, and secondary processes.

In a totally selective ring opening of amino epoxides with ketones, enantiopure (2*R*,3*S*)- and (2*S*,3*S*)-3-aminoalkane-1,2-diols have been prepared in high yield, total diastereoselectivity, and without epimerization, using $BF_3.Et_2O$ catalysis.[335] (*de*)

NMR experiments using ^2H- and ^{13}C-labelled substrates indicate that acetone and dimethyloxirane are *not* in equilibrium.[336] (*de*)

Thioketones such as 4,4′-dimethoxythiobenzophenone react with enantiopure (*R*)-2-vinyloxirane to give virtually enantiopure (*S*)-4-vinyl-1,3-oxathiolanes (**86**) in high yield, using mild Lewis acid conditions (SiO_2, DCM, 0 °C).[337] More hindered thioketones require a stronger Lewis acid (BF_3, −78 °C). The clear inversion at the oxirane C(2) indicates an efficient S_N2 mechanism. (*ee*)



(**86**) (**88**) (**87**)

Efficient *ortho*-difunctionalization of aromatics (**87**) can be achieved by insertion of arynes into the C–C σ-bonds of β-dicarbonyls (**88**), using a simple aryne source (**89**) under mild conditions.[338] The β-dicarbonyl reactant can be a dione (aromatic or aliphatic), or a diester (including dilactones). A mechanism involving the formation of a benzocyclobutane is proposed.

The mechanisms of asymmetric synthesis of aziridines from guanidinium ylides and arylaldehydes have been probed by varying *para*-substituents in the aldehyde.[339] Hammett plots show a mechanistic switchover going from electron-donating to electron-withdrawing groups. (*de*) (*ee*)

In a highly selective fluoroform-type reaction, 4-hydroxy-3,3-difluoromethyl trifluoromethyl ketones [$R^1R^2C(OH)–CF_2–CO–CF_3$] undergo base-promoted cleavage to give 3-hydroxy-2,2-difluoro acids [$R^1R^2C(OH)–CF_2–CO_2H$] and fluoroform.[340] The alternative products of cleavage on the other side of the carbonyl are not observed. DFT calculations are used to rationalize this preferential cleavage of a C(=O)–CF_3over a C(=O)–CF_2R bond in both the gas phase and solution.

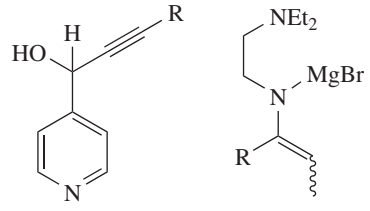
Samarium(II) iodide has been developed as a sub-stoichiometric promoter of Reformatsky-type additions of various α-halo substrates to aldehydes, giving several advantages over Co(0)–phosphine methods.[341]

An examination of the reactivity of carbonyl compounds with a Mitsunobu reagent, to produce a range of products, indicates that the steric and electronic properties of the carbonyl starter can give a high degree of control over product selection.[342] Particularly useful are conjugated ketones, which give 1,3-dienes containing nitrogen substituents.

The classical Biginelli synthesis of heterocycles from β-diketones, urea, and aldehydes has been extended by the replacement of the dione with a cycloalkanone.[343] The

one-pot reactions have also been carried out using thioureas, but these gave different products.

4-Pyridylpropargylic alcohols (**90**) are converted into (*E*)-propenones, with some propynone product, using pyridinium chloride in methanol at room temperature.[344] (de) Study of the progress of the reaction, and deuterium exchange results, point towards an allenol intermediate.



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

Magnesium enamides with a tethered nitrogen coordination site (**91**) undergo alkylation with alkyl chlorides or fluorides to give the corresponding α-substituted ketone, (de) with some diastereoselectivity, and tolerance of silyl groups elsewhere in the substrate.[345]

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