CHAPTER 1

Reactions of Aldehydes and Ketones and Their Derivatives

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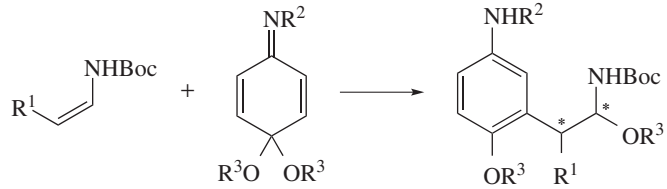
Formation and Reactions of Acetals and Related Species

Equilibria for the formation of hemiacetals from eight isomeric hexanals have been measured in methanol, and compared with the steric environment around the aldehyde.[1] Kinetic studies have also been carried out, and these suggest an early TS.

Catalytic asymmetric acetalization of aldehydes has been demonstrated, using large chiral BINOL-derived phosphoric acid catalysts: these are proposed to generate confined chiral microenvironments.[2] (ee)

A new enantioselective arylation of enecarbamates (**1**) has been developed, using a quinone imine acetal (**2**) as a functionalized surrogate aromatic, and an axially chiral BINAP-dicarboxylic acid catalyst.[3] The useful α-amino-β-aryl ether products (**3**) are formed in up to 99% *ee*, and *de*s often >90%, and are further transformable into chiral β-aryl amines and α-aryl esters. Mechanistically revealing observations include: (i) *trans*-enecarbamate switches the sense of asymmetric induction; (ii) the NH in (**1**) is critical, presumably for hydrogen bonding to catalyst: the NMe starter fails; and (iii) crossover experiments fail, implicating an intramolecular route. The proposed first step is a highly stereoselective C–C bond formation followed by aromatization (with elimination of R^3-OH), then re-addition of R^3-OH to the sidechain. (ee) (de)



(**1**) (**2**) (**3**)

A stable *N*,*N*′-diamidocarbene has been used to activate molecules with X–X homonuclear single bonds (where X = Br, O, S, C).[4] Br_2 yields a substituted tetrahydropyrimidinium salt, benzoyl peroxide yields diamidoacetal product, and various (de)

sulfides give the corresponding diamidothioacetals. For X = C, insertion into the (O)C–C(O) bond of diones was observed, and for cyclopropenone, insertion into the (O)–C–C bond occurred.

meta- and *para*-Substituted benzaldehyde acetals, X-C_6H_4–$CH(OBu)_2$, have been oxidized by *N*-bromosuccinimide in acetonitrile, to give the corresponding esters (and alkyl bromide).[5] Rates have been measured by the iodometric method, over a range of temperature. A primary kinetic isotope effect, k_H/k_D, is observed, indicating rate-determining C–H cleavage; a Hammett σ value of $1 \cdot 4$ and activation parameters are given.

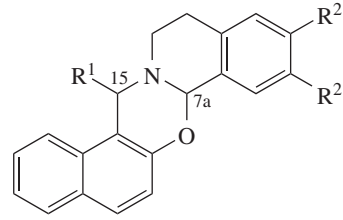
Kinetics of the oxidation of a range of aromatic acetals by *N*-chloronicotinamide have been measured in acetonitrile.[6]

The combination of triethylsilyltriflate with either 2,6-dimethylpyridine (2,6-lutidine) or 2,4,6-trimethylpyridine (2,4,6-collidine) effectively deprotects acetals of aldehydes under mild, neutral conditions, while leaving those of ketones unaffected.[7] Pyridinium-type salt intermediates are proposed.

The Prins reaction has been modelled using DFT (density functional theory), using an alkene ($RCH{=}CH_2$, R = Me or Ph), a formaldehyde dimer, and a proton-water cluster, $H_3O^+(H_2O)_{13}$. Both alkenes feature a concerted path to give the 1,3-diols. An unprecedented hemiacetal intermediate, HO–CH_2–O–CH(R)–CH_2CH_2–OH, was then identified: it undergoes ring closure to the 1,3-dioxane product.[8] Gas-phase Prins reaction of formaldehyde dimer with alkene has been studied computationally: it proceeds via a π-complex (without formation of any intermediate σ-complex).[9]

DFT calculations have been used to study the kinetic and thermodynamic parameters of the oligomerization of formaldehyde in neutral aqueous solution: linear and cyclic oligomers up to tetramer were examined, and implications for enolization and aldol reactions were also examined.[10]

A series of new naphtha[1,3]oxazino[2,3-α]isoquinolines (**4**, R^1 = H, Me, Ph, Ar; R^2 = H, OMe) have been prepared from 1-aminomethyl-2-naphthols and 3,4-dihydroisoquinolines.[11] The predominant diastereomer is *trans*- (at the 7a- and 15-positions), (*de*) but a surprising inversion at nitrogen can be observed by NMR (nuclear magnetic resonance). Computations support ring-opening at the C(7a)-oxygen bond, giving an iminium-phenolate intermediate.



(**4**)

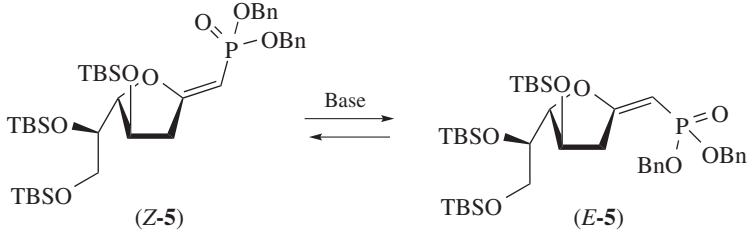
For other reports of acetals, see the section titled 'Miscellaneous Oxidative Processes' later.

Reactions of Glucosides

Proton affinities and pK_as have been calculated for various tautomers of D-glucose and D-fructose, and compare favourably with experimental measurements of the pH's of sugar solutions in water.[12]

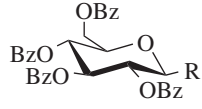
A review surveys the catalysts and mechanistic approaches to alter the reactivity of hydroxyl groups in carbohydrates, thus facilitating regioselective manipulation.[13]

exo-Glycals [e.g., (*Z*)-**5** and (*E*)-**5**] are glycosides with an exocyclic enol ether next to the oxygen of the ring, are useful synthons, and some have biochemical applications in their own right. However, the (*E*)-isomers have been inaccessible to date. In a treatment of the (*Z*)-species with strong base (aimed at further functionalization), *t*-BuLi at −78 °C surprisingly gave 34% conversion to the (*E*)-*exo*-glycal [(*E*)-**5**] with no by-products. A vinyl anionic intermediate was confirmed. Optimum isomerization employed 3 mol LiHDMS at ambient temperature for 10 min (to deprotonate), followed by −100 °C for 2 h, which favours the (*E*)-isomer.[14]



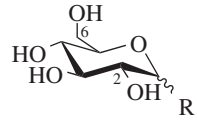
(*Z*-**5**) (*E*-**5**)

Several formic acid derivatives of a protected glucose have been prepared: *O*-perbenzoylated *C*-(*β*-D-glucopyranosyl)-formimidate [**6**, R = C(=NH)OEt], -formamidine [R = C(=NH)–NH_2], -formamidrazone [R = C(=NH–NHX)–NH_2, X = H or Ts] and -formyl chloride (R = COCl).[15] Designed to lead to 1,2,4-triazole derivatives of the sugar, they unexpectedly also gave 1,3,4-oxadiazole derivatives. DFT calculations have been used to investigate the alternative ring-forming pathways.



(**6**)

Chemo- and regio-selective functionalization of non-protected carbohydrates has been developed, allowing selective thiocarbonylation, acylation and sulfonylation of a particular carbohydrate in the presence of structurally similar carbohydrates, for example, anomers.[16] For example, sugar anomers (**7**) can be functionalized in the 6-position in up to 99% yield and 99% *β*-selectivity, using Me_2SnCl_2 as catalyst. Just switching the catalyst to Bu_2SnCl_2 gives comparable yields and *α*-selectivities in the 2-position. The mechanisms are discussed in terms of the steric approaches of the catalysts at the 1,2- versus 4,6-sites.

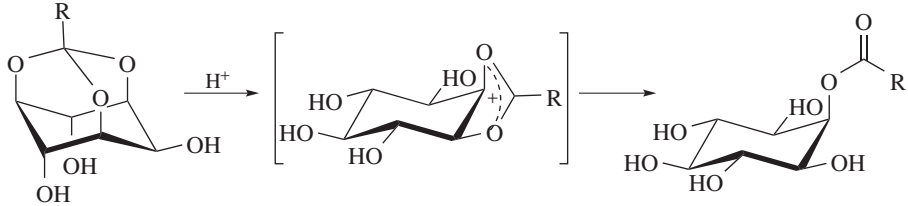


(**7**; $\alpha/\beta = 1/1$)

A DFT study of the acid catalysis of the mutarotation of erythrose and threose has looked at reaction in the gas phase, and in a continuum water model.[17] Sodium cation can act as an inhibitor, whereas borane acts as a Lewis acid catalyst. Brønsted acids H^+ and H_3O^+ are particularly effective, with the activation energy being further lowered using H_3O^+ with one bridging H_2O.

MP2 and B3LYP methods have been used to examine the mechanisms of the Lewis acid-catalysed isomerization and epimerization of xylose to xylulose and lyxose, respectively.[18]

myo-Inositol 1,3,5-orthoesters (**8**, R = Me, Pr, Ph, but *not* H) exclusively afford the corresponding 2-*O*-acyl *myo*-inositol products (**10**) via a 1,2-bridged five-membered ring dioxolanylium ion intermediate (**9**) observed by NMR.[19] If the orthoester (**8**, R = CH_3) is equilibrated in TFA-*d*, the R group becomes deuterated; however, if the free hydroxyls (either axial or equatorial) are benzylated, the benzyl CH_2s are not exchanged. Complete mechanisms are proposed for these processes.



(**8**) (**9**) (**10**)

Activation of *O*-glycosyl trichloroacetimidates as glycosyl donors typically requires moderately strong acids, such that a simple *N,N′*-diarylthiourea, ArNHC(=S)NHAr [e.g., Ar = 3,5-bis(trifluoromethyl), $pK_a = 8 \cdot 5$], would not be expected to catalyse the process.[20] However, it can act as a *co*-catalyst with simple Brønsted acids such as benzoic ($pK_a = 4$). The system gives significant rate and yield enhancements, and good selectivity for the β-anomer. A multiply hydrogen-bonded complex of reactants and catalysts is proposed. (*ee*)

An α/β-stereo- and diastereo-selective glycosylation method employs a glucosyl α-trichloroacetimidate and a chiral BINOL-derived phosphoric acid catalyst: the system selects the *R*-enantiomer of a racemic mixture of secondary alcohols.[21] (*ee*)

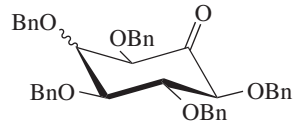
A mechanistic study of glycosylation using a prop-1-enyl donor in the presence of *N*-iodosuccinimide and triflic acid highlights one of the possible roles of TfOH: it could produce IOTf *in situ* to activate the prop-1-enyl group.[22] (*de*)

Highly stereospecific formation of *O*-alkyl glycosides has been achieved by 'native chemical ligation', in which a pendant alcohol at the anomeric centre is used to steer the reaction.[23] (*de*)

DFT has been used to identify a neighbouring-group participation step in a BF_3-catalysed glycosylation of a galactosyl donor.[24]

Glycosidase-like activity is reported for a cyclodextrin with one or two cyanohydrins incorporated on its secondary rim, with a rate acceleration of up to 1770.[25]

Studies of Grignard reactions and hydride reductions of *epi*- and *scyllo*-inososes (**11**) indicate that the diastereoselectivity is determined by the orientation of the β-hydroxyl group (or its derivative).[26]



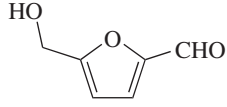
(**11**)

The rates of hydrolysis of *N*-acetyl-D-glucosamine (the monomer of chitin) have been measured in hydrochloric, perchloric and phosphoric acids: they depend on proton concentration, without counterion effects.[27]

Acid-catalysed hydrolysis of sucrose to glucose and fructose has been investigated by DFT, using a catalytic cluster, $H_3O^+(H_2O)_{13}$.[28] Considering protonations of the three ethereal oxygens, that at the bridging oxygen is relevant to the mechanism, but the calculations only find a slight preference for cleavage on the fructosyl side (over the glucosyl side).

Conversion of glucose, fructose and cellulose into *S*-hydroxymethylfurfural was studied under hydrothermal conditions, with both acid and base catalyses, with DFT calculations helping to scope out mechanistic possibilities.[29]

In situ ^{13}C-NMR spectroscopy has been used to investigate the kinetics and mechanism of the conversion of D-fructose into 5-hydroxymethyl-2-furaldehyde (**12**), and subsequent hydrolysis to formic and levulinic acids.[30] Following a study in three solvents [water, methanol and DMSO (dimethyl sulfoxide)] and temperatures from 30 to 150 °C, the production of the two useful acids is predicted to be favoured by hydrothermal methods.



(**12**)

The kinetics of oxidation of D-galactose by cerium(IV) in the presence of catalytic rhodium(III) have been measured in acid in the range 308–333 K.[31]

The rate of oxidation of galactose by *N*-bromophthalimide in the presence of acid has been measured at 308 K, and the effects of salts, phthalimide, mercury(III) and a cationic surfactant have been used to explore the mechanism.[32]

The carbon-Ferrier rearrangement, in which appropriately functionalized glycols react with a variety of *C*-nucleophiles at the anomeric carbon with loss of a C(3) substituent, has been reviewed.[33]

For the use of carbohydrates catalytically activated as acyl anions to act as formaldehyde equivalents, see the section titled 'Stetter Reaction' below.

Reactions of Ketenes

Synthesis of β-lactams via transition metal promoted Staudinger [2+2] cycloaddition of a ketene and an imine has been reviewed (63 references).[34] (ee)

Staudinger reaction of ketene and imine gives β-lactam, via [2+2] cycloaddition.[35] (de) Six-membered rings can potentially be formed using a second equivalent of ketene or of imine, via [2+2+2] processes. DFT has been used to probe annuloselectivity in forming such (N,O), (N,O,O) or (N,N,O) ring systems for a range of seven reactants with substituents which are EWG, EDG or bulky.

The Staudinger synthesis is catalysed by NHCs (*N*-heterocyclic carbenes), via Ye's possible 'ketene-first' or 'imine-first' mechanisms.[36a] To test these alternatives, four zwitterionic NHC adducts have been prepared: two using *N*-tosyl benzaldimine and two using diphenylketene.[36b] All four adducts had 1:1 stoichiometry and have been extensively characterized by ^{1}H- and ^{13}C-NMR, X-ray crystallography and catalytic tests. The imine-derived zwitterions proved poor catalysts, whereas those derived from diphenylketene replicated the free carbene catalysts, strongly supporting the 'ketene-first' route.

Gas-phase reaction of ketene and water to produce acetic acid – both uncatalysed and with catalysis by an additional water molecule – has been studied computationally: the reaction is found to be likely to occur in high-temperature combustion of biomass, but is negligible under ambient atmospheric conditions.[37]

Hydration of ketene to give acetic acid has been studied under atmospheric conditions, over a range of humidities.[38]

Formation and Reactions of Nitrogen Derivatives

Imines: Synthesis, and General and Iminium Chemistry

A DFT mechanistic study of the formation of Schiff bases from acetaldehyde in water has looked at two amines of biological importance: glycine and phosphatidylethanolamine, with an amine-phospholipid monolayer model being incorporated in the latter.[39] The rate-determining step was found to be dehydration of the carbinolamine intermediate in both cases. Relative free energies of the intermediates and transition states were lower (compared to butylamine as a reference amine), these effects being ascribed to the carboxylic group and phospholipid environment, respectively.

Amines react with primary alcohols to give imines under the influence of a 'pincer' complex, ruthenium(II)-PNP [PNP = 2,6-bis(di-*t*-butylphosphanylmethyl)pyridine].[40] DFT has been used to identify the mechanistic steps, and in particular the factors that favour imine as product, as closely related complexes yield amides.

Imine metathesis is often carried out at high temperature using a metal-based catalyst.[41] However, amine–imine exchange reactions of sterically unhindered reactants have been shown to proceed rapidly in non-aqueous organic solvent systems without such catalysts, or acids. *Ab initio* gas-phase calculations suggest that such

transiminations involve nucleophilic addition to the C=N bond in concert with proton transfer from the amine NH bond to the imine nitrogen in a highly imbalanced TS. Primary amines are highly efficient catalysts, and reported kinetic data is fully consistent with the mechanism outlined.

A kinetic and mechanistic study of the transaldimination of amino acids and aromatic amines with pyridoxal considers the geometric constraints on the aminal and Schiff base intermediates with respect to the pyridine ring plane of pyridoxal, and especially the influence of its *ortho*-hydroxy and -methylol substituents.[42]

Mayr has extended his electrophilicity scale to benzaldehyde-derived iminium ions through measurement of rate constants for their reactions with *C*-nucleophiles such as enamines, silylated ketene acetals and enol ethers.[43] With an *E* value of −9.27 for Ph–CH=NMe_2^+ (in a range from −8.34 to −10.69 for *para*-CF_3 and *para*-OMe, respectively), these iminium ions are 10 orders more reactive than the parent aldehydes. However, the values are restricted to *C*-nucleophiles: the iminium ions react 10^3–10^5 times faster with water and amines than these *E* values would predict. Such reactions benefit from the anomeric stabilization of *O*,*N*-acetals and *N*,*N*-aminals.

For more on such parameters, see DDQ (**140**) under the section titled 'Miscellaneous Additions' below.

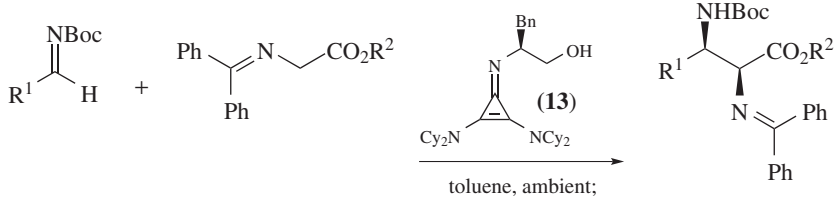
The use of chiral organocatalysts to produce enantioselective transformation of *N*-acyliminium ions has been reviewed.[44] (*ee*)

Vilsmeier–Haack formylations of acetophenones are slow in acetonitrile, even at elevated temperatures, but are markedly accelerated by Cu(II), Ni(II), Co(II) and Cd(II).[45] Second-order kinetics are observed. A ternary precursor, M^{II}:substrate:Vilsmeier reagent, is proposed.

Mannich, Mannich-type and Nitro-Mannich Reactions

The use of Mannich and aza-Henry reactions to synthesize *β*-nitroamines has been reviewed.[46]

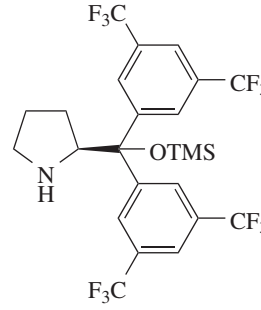
Readily available chiral cyclopropenimine (**13**) catalyses Mannich reactions of *N*-Boc-aldimines (**14**) and glycine imines (**15**), with yields/*de*/*ee* up to 97/98/95%.[47] The vicinal diamino stereoarray of the products (**16**) allows access to many useful derivatives, and the *t*-butyl ester of the product (**16**, $R^2 = Bu^t$) is amenable to acidic deprotection. In the proposed mechanism, the congestion caused by the cyclohexyl substituents in catalyst (**13**) is suggested to lock the stereocentre therein. (*ee*) (*de*)



(**14**) (**15**) (**16**)

A simple gold(I) NHC, 1,3-bis(diisopropylphenyl)imidazol-2-ylidene]AuNTf$_2$, catalyses Mannich reactions of *N*-protected imines with 1,3-dicarbonyls under mild conditions (DCM/ambient).[48] Using *N*-sulfonylimines, R^4-CH=N–PG, the reaction works in good yields for both *β*-ketoesters and *β*-diketones, affording protected *β*-amino-dicarbonyls, R^1-CO–CR^2(–CHR^4–NH–PG)–CO-R^3, in up to 62% *de*. (*de*)

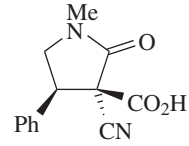
An *N*-Boc sulfone derivative has been used for *in situ* generation of an *α*-keto imine, which undergoes an asymmetric Mannich reaction, using a diarylprolinol silyl ether (**17**) as organocatalyst.[49] (*ee*) (*de*)



(**17**)

The proposed intermediates in proline-catalysed Mannich reactions have been studied computationally; enamines, iminium ions and oxazolidinones have been examined, and the transition states involved in their interconversion.[50] (*ee*)

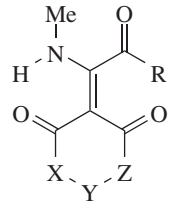
Highly substituted *γ*-lactams with three stereogenic centres, including one quaternary centre (e.g., **18**), have been prepared in good *de* from an imine and an anhydride (in this case, from *N*-methylbenzaldimine and cyanosuccinic anhydride).[51a] Computations suggest a Mannich reaction between the *E*-imine and the enol of the anhydride, followed by a transannular acylation. The results do not support an earlier iminolysis route.[51b] The stereoselectivity is determined by the Mannich step, with stabilizing C–H···O and hydrogen-bonding interactions being identified. (*de*) (*de*) (*de*)



(**18**)

An asymmetric one-pot sequential Mannich/hydroamination sequence involves a three-catalyst system: a chiral organocatalyst, BF_3 and a gold complex.[52] It converts an indole-imine into privileged spiro[pyrrolidin-3,2′-oxindole] structures in up to 91/97% yield/*ee*. (*ee*)

Treating enolizable cyclo-1,3-diketones with acyclic nitrones, R-CO-CH=N(Me)-O$^-$, allows access to *β*-enamino diones (**19**) in up to 99% yield, via a self-catalysed



(**19**)

Mannich-type reaction, followed by a spontaneous intramolecular reorganization.[53] The proposed mechanism is supported by a DFT analysis.

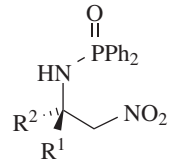
A Mannich-type reaction of *β*-keto ester with *C*-alkynyl imines generated *in situ* delivers asymmetric synthesis of propargylamines with two adjacent stereocentres organocatalytically.[54] (*ee*)

The potential for chiral silane-*gem*-diols to act as anion-binding catalysts has been explored in the case of acyl Mannich reactions.[55] (*de*) (*ee*)

Spirodiketones have been prepared in >99% *ee* via a redox-pinacol-Mannich cascade.[56] Controlling both the reversibility of the Mannich step and background catalysis by gold complexes are critical to minimizing racemization: low-temperature conditions and rapid isolation are essential in this regard. (*ee*)

The nitro-Mannich reaction has been reviewed (266 references), covering a variety of its manifestations: simple nitroalkane versus more functionalized nitro compounds, non-catalytic, metal ion- and organo-catalytic, conjugate and cycloadditions and so on.[57] (*ee*)

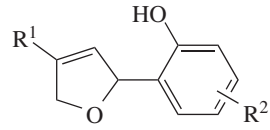
New chiral modular bifunctional iminophosphorane superbase organocatalysts allow metal-free enantioselective addition of nitromethane to otherwise unreactive ketone-derived imines.[58] The readily scalable reaction yields *β*-nitroamines (**20**) with a fully substituted carbon atom, in up to 95% *ee*. (*de*) (*ee*)



(**20**)

The Kabachnik–Fields (phospha-Mannich) reaction has been reviewed, including evidence for imine intermediates via *in situ* FT-IR studies.[59] Solvent-free microwave conditions are particularly effective, with little call for catalysts.

Functionalized 2,5-dihydrofurans (**21**) have been prepared by a Petasis borono-Mannich reaction, using a 4-substituted 1,2-oxaborol-2(5*H*)-ol and salicylaldehyde.[60] The amine-catalysed process combines a boronic-acid-based Mannich reaction with an intramolecular S_N2 cyclization.



(**21**)

Other 'Name' Reactions of Imines

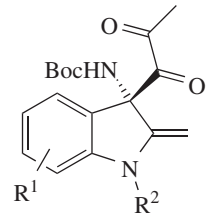
A review examines the use of carbohydrates as versatile starting materials for chiral auxiliaries in glycosylation, Mannich-type, stereoselective Strecker condensation and Ugi reactions.[61]

A theoretical investigation of a cinchona-alkaloid-catalysed Strecker reaction using $Ti(OPr^i)_4$ indicates that the rate-determining step is the isomerization of HCN to HNC, while the stereodetermination occurs at C–C bond formation.[62] (*ee*)

β-Amino-α-methylene carbonyl compounds have been prepared in up to 92% *ee* via an aza-Morita–Baylis–Hillman reaction.[63] *N*-Tosyl imines of β,γ-unsaturated α-ketoesters have been reacted with acrolein in the presence of two catalysts: β-isocupridine (a chiral quinolol containing a DABCO moiety) and a bifunctional BINOL (or a 3° amine-thiourea). NMR and MS evidence supports a self-assembly of the catalysts, giving a multi-functional supramolecular catalyst. (*ee*)

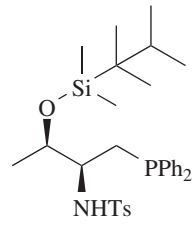
The kinetics of the aza-Morita–Baylis–Hillman reaction have been studied for a range of imine substrates in various solvents, using triphenylphosphine as catalyst, and *p*-nitrophenol as a Brønsted acid co-catalyst.[64] The effects of varying the phosphine:phenol catalyst ratio on the rate indicate interdependence between them. This and the solvent effects support reversible protonation of zwitterionic intermediates within the mechanism. ^{31}P-NMR and quantum calculations also support such a route.

An asymmetric aza-MBH reaction of isatin-derived *N*-Boc ketimines with methyl vinyl ketone has been developed, giving 3-amino-2-oxindoles bearing quaternary stereogenic centres (**22**), using chiral amine or phosphine catalysts.[65] (*ee*)



(**22**)

The L-threonine-derived phosphine-sulfonamide (**23**) is one of the best catalysts for the enantioselective aza-Morita–Baylis–Hillman reaction.[66] A DFT study has identified a key intramolecular N–H···O hydrogen-bonding interaction between the sulfonamide (*ee*)



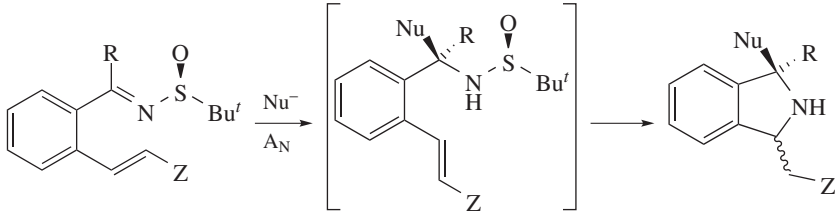
(**23**)

and enolate groups of the phosphonium enolate intermediate. This helps stereochemical control in both the enolate addition to imine and in the subsequent proton transfer step.

NHCs catalyse a one-pot synthesis of hydroxamic esters, via reaction of nitrosobenzenes, aldehydes and enals in an aza-benzoin-type process, followed by an internal redox esterification.[67]

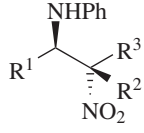
An enantioselective aza-benzoin reaction of enals with activated ketimines employs an NHC catalyst: incorporation of appropriate steric hindrance in the catalyst blocks competing reaction through the homo-enolate route.[68] (*ee*)

Sulfonimines (**24**) with a pendant *ortho*-Michael acceptor (Z = COR, CHO, NO_2, SO_2R) undergo nucleophilic addition (Nu = Ar, heteroAr, CN, allyl, propargyl, enolate; adduct = **25**); subsequent intramolecular aza-Michael reaction (IMAMR) yields 1,3-disubstituted isoindolines (**26**) in good yield and *de*.[69] *Cis*- and *trans*-products can be selected kinetically or thermodynamically, sometimes by choice of base. The products can be readily desulfonated. (*de*)

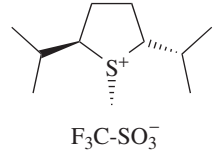


(**24**) (**25**) (**26**)

A multi-component aza-Henry reaction of an aldehyde (R^1CHO), aniline and a nitroalkane ($R^2R^3CHNO_2$) yields *β*-nitroamines (**27**) in high *de*, *ee*, and yield in brine, with an optimal rate at pH 5.5, using a hydrogen-bond donor (a chiral thiourea or squaramide), and a tertiary amine as Lewis base.[70] (*ee*) (*de*)



(**27**)

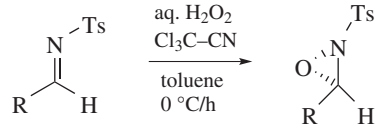


(**28**)

Synthesis of Azacyclopropanes from Imines

Terminal aziridines have been prepared in modest *ee* by methylene transfer to an *N*-sulfonylimine, using a simple chiral sulfonium salt (**28**) and a strong organic base.[71] (ee)

N-Sulfinyl imines (**29**) undergo highly enantioselective Payne-type oxidation to give oxaziridines (**30**) in high yields, using hydrogen peroxide and trichloroacetonitrile under mild conditions.[72] A *P*-spiro chiral triaminoiminophosphorane provides the asymmetry. The roles of the amide, Cl_3CCONH_2, and of the related anions, $Cl_3C–C(=NH)–O^-$ and $Cl_3C–C(=NH)–O–O^-$, in the mechanism are discussed. (ee)

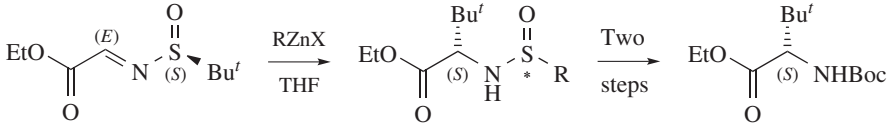


(**29**) (**30**)

A new method for enantioselective oxaziridination of aryl aldimines uses *meta*-chloroperbenzoic acid and a cinchona alkaloid derivative.[73] (ee)

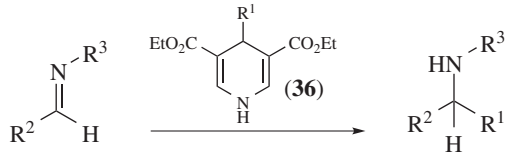
Alkylations and Additions of Other C*-Nucleophiles to Imines*

A novel migration-addition sequence has been found for enantioenriched *N-t*-butylsulfinyl iminoacetate (**31**) with functionalized benzylzinc bromide reagents, producing *t*-leucine derivatives (**32**) in up to 96% *de*.[74] Desulfurization and *N*-protection to give (**33**) can then be carried out in >98% *ee*. (ee) (de)



(**31**) (**32**) (**33**)

Imines (**34**) have been *C*-alkylated to give amines (**35**), in an unusual alkyl transfer arising from C–C cleavage.[75] Hantzsch ester analogues such as (**36**) can act as hydride-transfer agents, but they have now been used to transfer alkyl groups, using Brønsted or Lewis acid catalysts. Benzyl-substituted dihydropyridines (i.e., **36**, with $R^1 = Bn$) are particularly efficient. Evidence for a concerted transfer process is discussed.



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

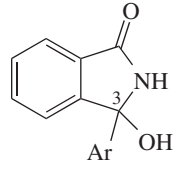
The alkylation of ambident enolates of a methyl glycinate Schiff base has been studied computationally.[76] Although the *E*- and *Z*-enolates have similar energy and geometry, and similar transition states with ethyl chloride, the *E*-enolate is substantially more stabilized by lithium cation.

The direct catalytic asymmetric addition of acetonitrile to *N*-thiophosphinoylimines, Ar–CH=N–P(=S)Ph_2, proceeds at 50 °C, using Barton's base [$(Me_2N)_2$–C=N–Bu^t], copper(I) and a Taniaphos chiral ligand; that is, using a soft Lewis acid-hard Brønsted base cooperative catalysis. Although the yield and *ee* are modest, the corresponding nitrile derivatives of amines, Ar–*CH(CH_2–C≡N)–NH–P(=S)Ph_2, are obtained.[77] Subsequent treatment with 4 *M* HCl in dioxane at 60 °C cleaves the thiophosphinoyl group (without racemization) to give the *β*-aminonitrile, Ar–*CH(CH_2–C=N)–NH_2. (*ee*)

Arylations, Alkenylations and Allylations of Imines

Enantioselective arylation of ketimines has been carried out using rhodium catalysis with chiral sulfur-olefin ligands: arylboronic acids are added in up to 99/99% yield/*ee*.[78] (*ee*)

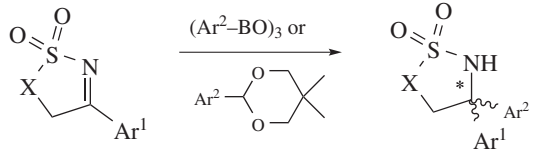
3-Aryl-3-hydroxyisoindolin-1-ones (**37**) can be further arylated at the 3-position with an arylboroxine and rhodium(I) catalysis: reaction proceeds via dehydration to give a cyclic *N*-carbonyl ketimine *in situ*, followed by addition.[79] (*ee*)



(**37**)

Enantioselective production of quaternary centres has been carried out in high yields via palladium-catalysed addition of arylboronic acids to cyclic ketimines.[80] (*ee*)

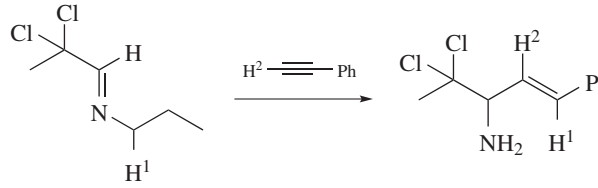
A range of cyclic ketimines (**38**, X = CH_2, O, NR) undergo rhodium-catalysed asymmetric arylation to give *gem*-diaryl sulfamidates or sulfamides (**39**) in up to 99% *ee*.[81] (*ee*) The products can be converted into *α*-tertiary chiral amine derivatives without loss of enantiomeric purity.



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

N-Alkyl-*α*,*α*-dichloroaldimines, for example, *N*-propyl (**40**), undergo Lewis-acid-catalysed vinyl transfer, using a terminal alkyne as vinyl donor, yielding geometrically

pure allylic β,β-dichloroamines (**41**).[82] The reaction features the acetylenic hydrogen unsurprisingly ending up *cis*- to the phenyl, but the other vinyl hydrogen in the product is derived from the *N*-alkyl group acting as a sacrificial hydrogen donor, with an unusual cleavage of an unactivated C–N bond.

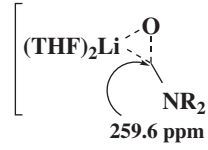


(**40**) (**41**)

Miscellaneous Additions to Imines

The lithium enolate of *t*-amyl acetate exists as a doubly chelated dimer in the presence of TMEDA (*N,N,N′,N′*-tetramethylethylenediamine).[83] Reaction with a simple aldimine such as *para*-F–C_6H_4–CH=N–Ph gives an *N*-lithiated β-amino ester as a monomer, observed by ^{6}Li- and ^{15}N-NMR. Kinetic studies by ^{19}F-NMR give a reaction order consistent with a TS of stoichiometry $[(ROLi)_2(TMEDA)_2(imine)]$, supported by DFT calculations. That such aza-aldol condensations involve dimeric mechanistic routes runs counter to many claims that monomers are more reactive.

Dialkylformamides and LDA (lithium diisopropylamide) react to give 'carbamoyl anions' (**42**, with contributions from *C*-lithiated anion and *O*-lithiated carbene forms).[84] (*de*) Addition of such anions to chiral *N*-sulfinyl ald- and ket-imines provides α-amino amides. The method avoids the 'unmasking' of the nucleophile found in other approaches. ^{13}C-NMR confirms the unusual nature of the carbon of the anion (**42**).



(**42**)

3,5-Disubstituted *N*-acyl-1,4-benzoquinone monoamines exhibit significant steric strain in the C=N–C fragment, in contrast to their *N*-arylsulfonyl analogues.[85] This results either in the bond angle exceeding 130° or in twisting of the double bond and loss of quinoid planarity. The increase in reactivity allows 1,2-addition of alcohols.

Lithiated ynamides react stereoselectively with chiral *N*-sulfonyl imides without Lewis acid catalysts.[86] Boron trifluoride etherate completely *reverses* the selectivity: a switch (*de*) from a chelated to an open TS is proposed.

A C(2)-selective nucleophilic addition of indoles to sulfonimines is catalysed by a $Co^{III}(C_6H_6)(Cp–Me_5)$ complex.[87]

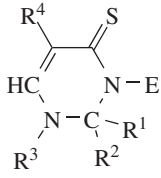
Lewis acids catalyse regio- and diastereo-selective additions of silyl dienolates to fluorinated sulfinylimines, R_F–CH=N–S(=O)–Bu^t, allowing access to new chiral α-fluoroalkyl amines.[88] (de)

Solution-phase DFT methods have been used to identify the source of the diastereoselectivity in sulfur ylide additions to chiral *N*-sulfinyl imines, which – upon ring-closure – yield terminal aziridines.[89] Ring closure is fast and irreversible, and (de) the control due to the sulfur configuration is augmented by a favourable interaction between the sulfinyl oxygen and iminyl hydrogen.

The stereochemistry of the addition of dialkyl phosphonates to the azomethine bond of pyridine-2,6-dicarboxaldimines and of isophthalaldimines, to give the corresponding aminophosphonates, has been studied, with the latter giving higher *de*.[90] For (de) bis(trimethylsilyl)phosphonate, the pyridine substrate gives comparable or better *de*.

N-Phosphinoyl and *N*-thiophosphinoyl ketimines, Ph–C(Me)=N–P(=X)Ph_2 (X = O and S), have been hydrophosphonylated in high yield and *ee* using a copper(I) catalyst liganded with a chiral diphosphino ethane.[91] In the case of the sulfur substrates, facile differentiated removal of the *thio*phosphinoyl group affords α-amino phosphonic acid derivatives, Ph–*C(Me)(NH_2)–P(=O)($OEt)_2$, that is, phosphonic acid analogues of enantio-enriched α,α-disubstituted α-amino acids. The reaction also accommodates alkyl, cycloalkyl and alkenyl substituents in place of the phenyl.

A multi-component reaction of a terminal alkyne, sulfur, electrophile (E–X) and carbodiimides, R^1R^2CH–N=C=N-R^3, produces 1,2-dihydrothiopyrimidines and 2,3-dihydropyrimidinthiones (**43**, R^4 derived from alkyne, E = H, alkyl).[92] The expected N=C cleavage of the diimide is accompanied by an unexpected C(sp^3)–H cleavage, such that the carbodiimide acts as sources of 'H' + 'R^1R^2-C–N' + 'C=N-R^3', with subsequent reorganization to give products.



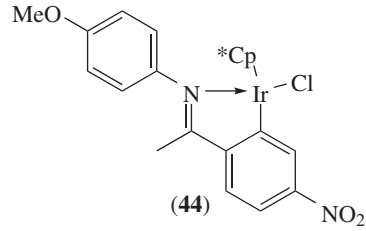
(**43**)

Reduction of Imines

An achiral iridium catalyst gives high yields in hydrogenation of imines derived from acetophenone, and also imines of aliphatic ketones.[93] An enantioselective version has (ee) been developed, using a chiral phosphoric acid as Brønsted acid. This gives *ee*s up to 98%, but at the expense of the reaction rate, slowed by the bulk of the BINOL-type phosphoric acid.

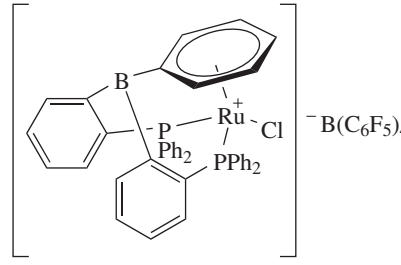
Enantioselective hydrogenation of imines has been achieved via a cooperative catalysis involving an iridium(I) organometallic and an organocatalyst, with low-temperature nOe- and DoSy-NMR techniques being used to characterize a key ternary complex.[94] (ee)

A cyclometallated iridium(III) catalyst (**44**) bearing an imine ligand catalyses hydrogenation of imines, typically in an hour at 0.05 mol% loading/20 atm H_2/75 °C.[95] It is selective for imines, is air-stable, and is probably turnover-limited by the hydride formation step.



(**44**)

A new Ru-η^6-arene complex (**45**) acts as a *C*-based Lewis acid catalyst for the hydrogenation of aldimines at ambient temperature via a 'frustrated Lewis pair' mechanism: with 102 atm H_2 in DCM at 25 °C, 1 mol% catalyst gives up to 99% amine in 8 h.[96] The catalyst and its mechanism have been extensively characterized by X-ray crystallography and NMR, including deuteration experiments with D_2 which prove that exchange is occurring *ortho*- and *para*- to the boron.

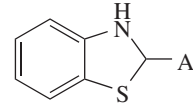


(**45**)

In another frustrated Lewis pair route, a highly enantioselective metal-free hydrogenation of imines uses a BINAP-derived diene as a 'ligand': hydroboration of the alkenes *in situ* with $HB(C_6F_5)_2$ generates a chiral bis-borane catalyst.[97]

Reduction of ald- and ket-imines, and α-imino esters, has been carried out by transfer hydrogenation using Hantzsch ester: molecular iodine is an efficient catalyst.[98]

2-Arylbenzothioazolines (**46**) are efficient reducing agents for the transfer hydrogenation of ketimines and α-imino esters: in the presence of a chiral BINOL-phosphoric acid catalyst, it affords the corresponding amines in high *ee*, following a similar mechanism

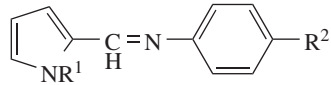


(**46**)

to (but superior than) using Hantzsch ester.[99] A DFT study has clarified the reasons for the high *ee*, which are mainly steric in origin, but including the scope for tuning the benzothiazoline's aryl substituent. The phosphoric acid's Brønsted site activates the imine, while its basic site coordinates benzothiazoline. (ee)

Other Reactions of Imines

Two series of *N*-pyrrolyl-2-methylene-aniline Schiff bases (**47**; $R^1 = H$, Me; $R^2 = H$, Me, OMe, OEt, Cl, Br) have been hydrolysed over a wide range of pH (−4 to +14), and pH-rate profiles generated: these are bell shaped, and mechanistic explanations are offered for each pH domain.[100]

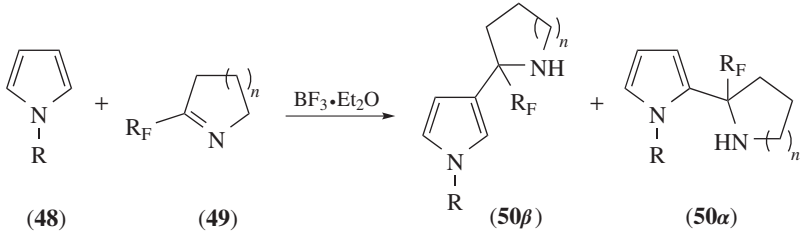


(**47**)

The kinetics of oxidation of a Schiff base, 5-chloro-2-hydroxy-4-methyl-acetophenoneanil, by cerium(IV) in aqueous sulfuric acid has been reported.[101]

Aromatic *N*-TMS-ketene imines undergo efficient aldol-type reaction with *O*-protected α-hydroxy aldehydes, giving *syn*-selectivity at ambient temperature, reversing at −78 °C to *anti*-.[102] Transfer of the TMS group from the ketene imine prevents retro-reaction. (de)

Pyrroles (**48**; R = H, Me) undergo Friedel–Crafts aminoalkylation with cyclic α-perfluoroalkylated imines (**49**; $R_F = CF_3$, C_2F_5; $n = 1$, 2, 3) to give α- and β-substituted pyrroles (**50***α*, **50***β*).[103] Catalysed by Lewis acids, the most high-yielding and regioselective results were obtained using boron trifluoride etherate in DCM at 0 °C over 5 days, giving 9% **50***α* to 87% **50***β* ($R_F = CF_3$; n = 1). The preference is thermodynamic, as a sample of pure **50***α* converts into **50***β* in the presence of $BF_3 \cdot Et_2O$. DFT studies identify the steric bulk of the trifluoromethyl group, as well as its specific electronic properties, as the main factors giving β-selectivity. (de)

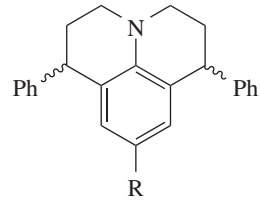


(**48**) (**49**) (**50***β*) (**50***α*)

The recently reported insertion of *N*-sulfonylaldimines into aryl C–H bonds, catalysed by rhodium(III), has been examined to determine the mechanism.[104] Key intermediates were isolated and their structures determined by X-ray crystallography.

The Povarov cascade reaction of an aniline, two moles of formaldehyde and two moles of styrene gives tricyclic (**51**).[105] Calix[4]- and calix[6]-arene sulfonic acids have been (de)

employed as catalysts, giving good yields and fair *de*s in a range of solvents, including water. MS evidence is provided for an iminium ion intermediate formed from the aniline and formaldehyde, as well as a later iminium ion, after the first styrene and second formaldehyde have been incorporated.

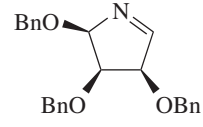


(**51**)

Rhodium(I) catalyses a dynamic kinetic asymmetric [3+2] annulation of aryl ketimines with racemic allenes, with good *E*/*Z*-selectivity and up to 98% *ee*.[106] (*ee*)

cis-Homoenolate equivalents have been generated from *cis*-enals using NHC catalysis: they react with α,β-unsaturated imines to form chiral cyclic ketone products.[107] Their reactivities and stereoselectivities contrast with the better known *trans*-enals. (*de*)

Ugi multi-component reactions of an amine, aldehyde, carboxylic acid and isocyanide (or the three-component variant with preformed imines) involve a Mumm rearrangement of an imidate in the final step, often considered the stereoselective step.[108] However, experimental and computational evidence for kinetic control has now been reported in Ugi reactions of a D-pentose-derived pyrroline (**52**). The selective step is the *formation* of the imidate by the addition of isocyanide to the intermediate iminium ion, with the conformation of the latter determined by its substitution pattern. (*de*)



(**52**)

A new 'split-Ugi' reaction is the subject of a short review (37 references).[109] The classical four-component reaction of aldehyde, primary amine, carboxylic acid and isocyanide has been modified using a *secondary* amine instead. This allows the Mumm-like rearrangement step to be avoided, freezing the reaction at the imino-anhydride intermediate, which is susceptible to alternative nucleophilic trapping.

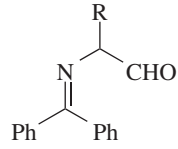
Oximes, Hydrazones and Related Species

Neighbouring halogen participation effects have been investigated for *peri*-chloro- and *peri*-bromo-substituted *O*-tosyl oximes under acid-catalysed Beckmann rearrangement conditions.[110] Evidence for stabilization of a nitrogen cation by nearby halogen is presented, including diversion of expected pathways.

A DFT study of organo-mediated Beckmann rearrangements recharacterizes the species as initiators, rather than true catalysts.[111] A self-propagating mechanism has been identified and shown to be energetically more favourable than previous proposals involving Meisenheimer complexes.

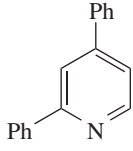
The oxime derived from the triterpenoid, oleanolic acid, has been studied under Beckmann rearrangement conditions.[112]

α-Imino aldehydes (**53**) based on benzophenone have been prepared by coupling benzophenone oxime with a *trans*-alkenyl boronic acid [R-CH=CH–$B(OH)_2$] followed by thermal [1,3]-rearrangement.[113] Evidence for a dissociative rearrangement is presented, and the products (**53**) can be used in Horner–Wadsworth–Emmons olefinations to produce γ-imino-α,β-unsaturated esters.



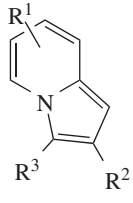
(**53**)

A [3+3]-type condensation of *O*-acetyl ketoximes and α,β-unsaturated aldehydes yields pyridines;[114] for example, Ph–(Me)C=N–OAc and *trans*-cinnamaldehyde (*trans*-Ph–CH=CH–CHO) give 2,4-diphenylpyridine (**54**) using copper(I) iodide as catalyst and a salt of a secondary amine; only a trace of the 2,6-product is observed. A synergistic copper/iminium catalysis is proposed: the oxime reacts with the copper iodide to give an iminyl copper species, Ph–(Me)C=N–Cu-X (i.e., N–O reduction), which tautomerizes to a copper(II) enamide, Ph–$C(=CH_2)$–NH–CuX, which then acts as a nucleophile towards the iminium ion (formed from the aldehyde and 2° amine).



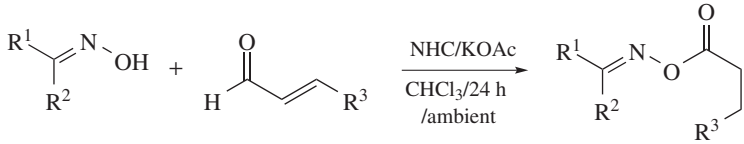
(**54**)

Imidazo[1,2-*a*]pyridines (**55**) have been prepared from an (R^1-)substituted pyridine and a ketone oxime ester, R^3-$CH_2C(R^2)$=N–OAc, via a copper-catalysed aerobic dehydrogenative cyclization.[115] The best yields were obtained with copper(I) iodide in the presence of lithium carbonate and air, in DMF at 95 °C.



(**55**)

Oximes (**56**) and α,β-unsaturated aldehydes (**57**) undergo a redox esterification to oxime esters (**58**) catalysed by a triazolium salt.[116] A wide variety of oxime and enal types are tolerated.

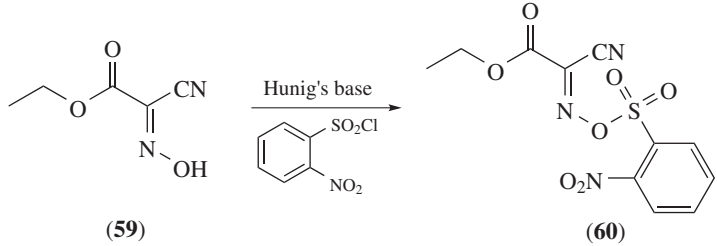


(**56**) (**57**) (**58**)

DFT has been used to investigate the mechanism of enantioselective borane reduction of *E*-acetophenone *O*-methyl oxime, using a stable chiral spiroborate ester.[117]

The Neber rearrangement of oxime *O*-sulfonates to 2*H*-azirines (or α-amino ketones, after aqueous acid workup) has been reviewed, together with the 'modified Neber', involving *N*,*N*,*N*-trimethylhydrazonium iodides.[118] With an excess of base, the α-amino acetal can be formed from the 2*H*-azirine via the unstable 2-alkoxy aziridine.

Oxyma [**59**, ethyl 2-cyano-2-(hydroxyimino)acetate] has been *O*-sulfonated, and the sulfonate ester (**60**) is an excellent catalyst for dehydration of oximes to nitriles.[119]



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

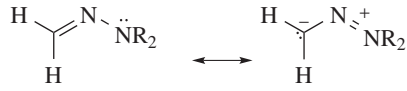
A kinetic study of nitrile-forming elimination from (*E*)-2,4-dinitrobenzaldehyde *O*-aryloximes has been carried out in acetonitrile, with catalysis by tertiary amines.[120] The Brønsted β value for this dehydration ranges from 0.83 to 1.0, with $|\beta_{lg}| = 0.41-0.46$. The results are consistent with a highly E_1cb-like TS.

Oxidative deoximation of aldo- and keto-oximes by tetraethylammonium chlorochromate in DMSO is first-order in oxime and oxidant, and the kinetic study was extended to 19 organic solvents.[121] Similar kinetic behaviour was found for imidazolium fluorochromate;[122] in the case of acetaldoxime, the same solvent survey was performed. Pyridinium fluorochromate as oxidant was also studied in DMSO.[123]

Iodine catalyses the condensations of 2-aminobenzohydrazide with aldehydes and ketones, to give hydrazones and quinazolines, respectively.[124]

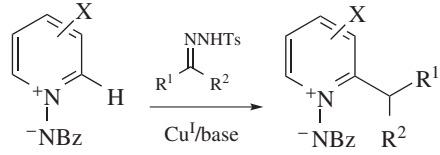
Formaldehyde hydrazones (**61a** ↔ **61b**), prepared by reaction of formaldehyde and *N*,*N*-dialkylhydrazones, can act as *C*- or *N*-nucleophiles.[125] Their reactivities have been measured by reaction with a range of benzhydryl cations, Ar_2CH^+, as reference electrophiles with known *E* values. Kinetic reaction of the carbocations at the (terminal)

nitrogen is followed by slower thermodynamic reaction at carbon, with second-order rate constants derivable for both processes. The results rationalize why Mannich salts, Vilsmeier reagents and nitrostyrenes react freely with hydrazones, whereas weaker electrophiles such as enones and aldehydes require catalytic activation.



(**61a**) (**61b**)

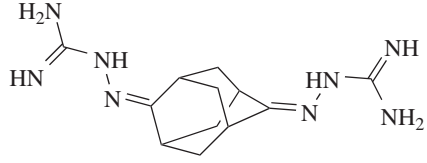
N-Iminopyridinium ylides (**62**) undergo direct C–H bond alkylation by cross-coupling with *N*-tosylhydrazones, using unliganded copper(I) iodide and lithium *t*-butoxide.[126] DFT calculations suggest a Cu carbene migratory insertion. Direct Cu carbene C–H insertion was ruled out by a diphenyldiazomethane control reaction which only gave (**63**) if the requisite base was present (the direct carbene process does not need base).



(**62**) (**63**)

A three-component cross-coupling of *N*-tosylhydrazones, terminal alkynes and allyl halides yields allyl allenes, using copper(I) catalysis: a copper carbene migratory insertion is proposed.[127]

A series of bis(guanylhydrazone) derivatives of the pentacycloundecane and adamantane skeletons (e.g., **64**) have been studied in the gas phase via ESI-MS/MS.[128] Elimination of neutral guanidine is a major fragmentation pathway, via cage opening of the hydrocarbon skeleton leading to carbocations. In some cases, elimination of CH_2N_2 is preferred. The results are interpreted in terms of a neighbouring-group effect, with close contact of two guanidines being crucial to determining the preferential pathway and suppressing dication formation.



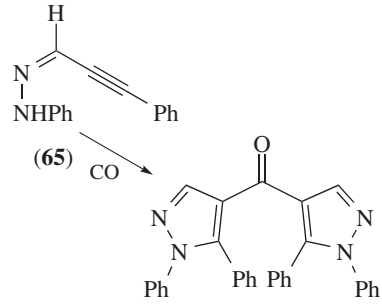
(**64**)

Formaldehyde *t*-butyl hydrazone, $H_2C{=}N{-}NH{-}Bu^t$, has been used as a formyl anion equivalent: it reacts with isatins to give functionalized 3-hydroxy-2-oxindoles.

BINAM-derived organocatalysts which provide dual activation – hydrogen-bond donor and acceptor – render the reaction which is high yielding and highly enantioselective.[129]

An enantioselective Strecker-type transformation of aliphatic *N*,*N*-dibenzylhydrazones, R-CH=N–NBn_2, to the corresponding hydrazino nitriles, R-CH(CN)–NH–NBn_2, uses a *t*-leucine-derived bifunctional thiourea catalyst, and the combination of TMSCN and phenol for *in situ* generation of HCN as cyanide source.[130]

α,β-Alkynic hydrazones (e.g., **65**) undergo an unusual cyclization-carbonylation-cyclization reaction in the presence of CO to give a bis-heterocyclic ketone (**66**), using a bis(oxazolinyl)palladium(II) complex to catalyse the coupling and *para*-benzoquinone (1.5 equiv) in methanol.[131]



(**66**)

trans-Enals (*trans*-R-CH=CH–CHO) have been reacted with various diazo compounds, X–C(=N_2)–CO_2–Y, to give *N*-acylhydrazones, R-CH=C(=O)–NH–N=C(X)–CO_2–Y, in up to 91% yield.[132] The reaction is NHC-catalysed and proceeds via an acyl anion pathway (and *not* via the competing homoenolate, enol or acyl azolium pathways). DFT calculations indicate that this fully regioselective reaction is under orbital control, whereas charge control would give homoenolate products.

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

Reviews of Aldols and General Reviews of Asymmetric Catalysis

The applications of primary and secondary amine-ureas and -thioureas in asymmetric organocatalysis have been reviewed (138 references),[133] as has the use of oxazolidinones as chiral auxiliaries in asymmetric aldols employed in total synthesis (193 references).[134] (*ee*) (*de*) (*de*)

A short review (63 references) surveys the fusion of asymmetric aminocatalysis and the vinylogy principle, considering activation via vinylogous nucleophilicity (i.e., HOMO-raising) and vinylogous electrophilicity (i.e., LUMO-lowering).[135] Examples of the development of dienamine, trienamine and vinylogous iminium activations are described, allowing for asymmetric functionalization of carbonyl compounds at their γ-, ε- and δ-positions, respectively. (*ee*) (*de*)

A short review (50 references) surveys the use of C–H···O non-classical hydrogen bonds in achieving stereocontrol.[136] (*ee*) (*de*)

A review describes the utility of a new class of helically chiral pyridines as asymmetric organocatalysts for propargylation of aldehydes, as well as for several other unrelated transformations.[137] (ee)

The topic of asymmetric ion-pairing catalysis has been extensively reviewed (142 references), over a wide range of reaction types.[138] While the directional effect of electrostatic attraction is not particularly strong, secondary non-covalent interactions can be exploited to build high stereoinduction. (ee) (de)

The mechanisms of action of a range of organocatalysts have been reviewed for a range of reaction types, focussing on the use of electro- and nucleophilicity parameters to tease out viable routes.[139]

Mechanisms in organocatalysis are the subject of a short review, with a particular focus on enamine and iminium catalysis.[140] (ee) (de)

The use of metal enolates in carbohydrate-based aldol reactions has been reviewed, questioning the preponderance of lithium and sodium versions and proposing a wider range of methodologies.[141] In other reviews, the use of titanium complexes bearing chiral ligands in enantioselective aldols has been surveyed,[142] and the use of asymmetric aldol and Mannich reactions in the preparation of α-amino acids via homologation of glycine Schiff bases has been described.[143] (de) (ee) (ee) (de)

Asymmetric Aldols Catalysed by Proline and Its Derivatives

ReaxFF, a reactive force-field approach, has been used to model the iminium-enamine conversion in the proline-catalysed self-aldol of propanol.[144] Quantum mechanical methods have been used to study the same step in the proline-catalysed aldol.[145] (de) (ee)

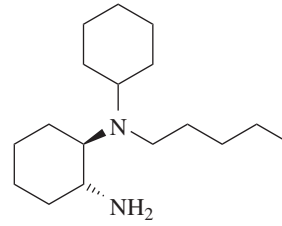
A study of a series of proline catalysts of the aldol suggests that steric hindrance at the α-position may shift the rate-determining step from C–C bond formation to formation of enamine.[146] Modifying the N–H acidity was also investigated. (de) (ee)

A DFT study has examined the chemo-, diastereo- and enantio-selectivities in direct aldol reactions between two enolizable aldehydes with different electronic nature.[147] Self- and cross-aldols are considered for catalysis by proline and by Maruoka's axially chiral amino-sulfonamide. Potential energy profiles for the formation of the enamine confirm that both catalysts can distinguish between 3-methylbutanal as an enamine component and an α-chloroaldehyde as a carbonyl component. The calculations reproduce the *anti*-product preference of the proline, and *syn*- for Maruoka's catalyst, and the experimental *ee*s. (ee) (de)

Direct asymmetric aldol reactions in aqueous media catalysed by phenolic prolinamides show enhanced *de* and *ee* when the catalysis is augmented by LiCl, $ZnCl_2$ or $SnCl_2$.[148] (ee) (de)

Asymmetric Aldols Catalysed by Other Organocatalysts

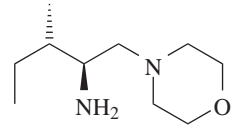
The simple *trans*-diamine (**67**) gives excellent enantio- and diastereo-selectivities in a variety of aldol reactions in ethanol: *de* is up to 98% *anti*, but it switches over to comparable *syn*-selectivity just by changing the solvent to water.[149] (ee) (de)



(**67**)

A direct aldol reaction of isatin with cyclohexanone is catalysed by 10 mol% of a simple primary-tertiary diamine (**68**, with 2,4-dinitrophenol Brønsted additive) in 90% yield, 64% *de* (*syn*), but a rather disappointing 10% *ee* (*syn*).[150] However, lowering the catalyst loading gives considerable improvement, with yield/*de*/*ee* of 93/86/82% at 1 mol%. A kinetic study shows that the enantioselectivity is approximately constant over a day at low loading, whereas the higher loading gives nearly as good an *ee* in the first hour, but it drops to the observed 10% after a day. The rationalization is that the high loading equilibrates faster (with respect to the retro-aldol): that is, the reaction swings from kinetic to thermodynamic control.

ee *de*



(**68**)

Substituent effects have been compared in 4-substituted benzaldehydes versus 4-substituted (phenylethynyl)benzaldehydes, 4-X-C_6H_4–C≡C-4-C_6H_4–CHO.[151] For example, changing a cyano substituent to methoxy in the former causes a 54-fold decrease in the rate of an aldol reaction, whereas the factor was only 1.4 in the latter series.

Pyruvic aldehyde dimethyl acetal, MeCO–$CH(OMe)_2$, undergoes enantioselective direct aldol reaction with isatin derivatives, using a bifunctional organocatalytic combination of a cinchona-derived primary amine and trichloroacetic acid.[152] *ee*

Glycosyl-α-aminotetrazoles efficiently catalyse enantioselective aldol reactions: DFT calculations have been used to identify the origin of the selectivity.[153] *ee*

New chiral spiro[4,4]-diphosphine oxides catalyse double-aldols of ketones with two molecules of aldehyde in good yield, *de* and *ee*.[154] *ee* *de*

The Mukaiyama Aldol

As part of a series, the Lewis base-catalysed Mukaiyama-directed aldol has been reviewed (57 references) on its 40th anniversary, focussing particularly on the work of

Mukaiyama himself, and of Denmark.[155] In addition to the development of its regio-, diastereo- and enantio-selectivities, its role as a proving ground for new concepts in catalysis is described. (ee) (de)

Examples of total syntheses involving the Mukaiyama aldol have been reviewed (60 references), emphasizing the mechanistic rationale determining the stereochemical outcomes.[156] A short review of the Mukaiyama aldol traces the development of strategies based on silicon, boron and tin(II) methodologies (51 references).[157] Base-catalysed Mukaiyama-type aldol additions have been reviewed (55 references), with the generation of nascent chiral enolates or cationic siliconium species being singled out for their roles in ensuring high selectivity.[158] (ee) (de) (ee) (de) (ee) (de)

β-Siloxy-α-haloketones have been prepared with high *anti*-selectivity via a Mukaiyama aldol of 'super-silyl' enol ethers, using the tris(trimethylsilyl)silyl (or TTMSS) group.[159] Most cases involve chlorine, but fluorine works too, and one-pot sequential double-aldol versions deliver β,δ-bis(super-silyl)oxy-α,γ-dihaloketones with control of four contiguous chiral centres. (ee) (de)

A mild, convenient, asymmetric Mukaiyama aldol process uses chiral iron(III) or bismuth(III) catalysts in water at 0 °C.[160] (ee) (de)

The Kobayashi modification of the Mukaiyama aldol, in which lanthanide Lewis acids are used in aqueous solution, is a very attractive high-yielding green process, but the role of water is not understood.[161] A computational study of the Eu^{3+}-catalysed reaction between TMS cyclohexenolate and benzaldehyde seeks to probe the possibilities. Does water act as proton source? Does it stabilize TMS dissociation? Does it stabilize the *syn*-TS? These questions are addressed and answered using the AFiR method (artificial force-induced reaction) to probe the energy surfaces for the two most likely europium clusters, $[Eu(H_2O)_8]^{3+}$ and $[Eu(H_2O)_9]^{3+}$. (de)

A *syn*-selective Kobayashi aldol reaction of acetals has been used for polyketide synthesis, with *de*s up to 98%.[162] (de)

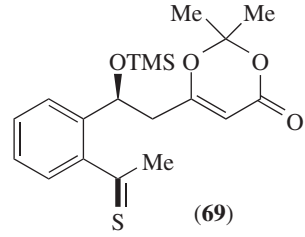
A bifunctional amine/thiourea catalyst gives high *ee* in a direct vinylogous aldol reaction of allyl ketones with isatins, giving biologically important 3-hydroxy-2-oxindoles.[163] (ee)

The direct vinylogous aldol additions of α,β-dichloro-γ-butenolides and -butyrolactams have been examined computationally, seeking to identify the origin of the observed diastereoselectivities and especially the reversal observed between the two systems.[164] In addition, reactions with *ortho*-substituted benzaldehydes have been compared with those with benzaldehyde itself. (de)

A versatile γ-vinylogous aldol reaction of a dioxinone-derived silyl enol ether, by enolate activation with an appropriate Lewis base, has been developed.[165] Using chiral 2-(methylsulfinyl)benzaldehyde, adduct (**69**) has been obtained in high *de* and *ee*. This 1,4-asymmetric induction features a dual role for the sulfinyl group: chiral inductor and activator of a silyloxydiene. (ee) (de)

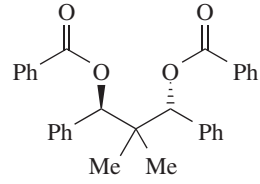
Other Asymmetric Aldols

Asymmetric aldol reactions between acetone and benzaldehyde use a chiral zinc(II) complex of aminoacyl 1,4,7,10-tetraazacyclododecane with pendant amino-acid sidechains.[166] (ee)



(**69**)

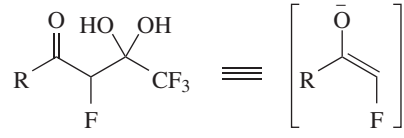
Sodium *t*-butoxide promotes reaction of isobutyrophenone, Ph–C(=O)–$CHMe_2$, with an excess of benzaldehyde (>4 mol), to give *anti*-1,3-dibenzoyloxy-2,2-dimethyl-1,3-diphenylpropane (**70**).[167] This easy access to a useful C_2-symmetric chiral 1,3-diol (*de*) occurs via sequential aldol-Tishchenko and Tishchenko reactions.



(**70**)

Malonic acid half thioesters, $HO_2C–CH(R^1)–CO–SR^2$ (R^1 = H/Me), undergo an enantioselective decarboxylative aldol reaction with aldehydes, using a chiral catalyst bearing a hydrogen-bond donor and acceptor.[168] *In situ* ESI-MS evidence supports (*ee*) a complex between the conjugate base of the substrate and the conjugate acid of the catalyst.

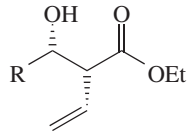
α-Fluorinated trifluoromethyl *gem*-diols (**71**) – prepared by fluorination of the corresponding β-diketone – act as the synthetic equivalent of a fluorinated enolate (**72**) in decarboxylative aldol additions, with the loss of trifluoroacetate.[169] In a demonstration (*ee*) reaction with isatins, 3-hydroxyindoles have been prepared in good yields and *ee*s.



(**71**) (**72**)

Syn-β-hydroxy-α-vinyl carboxylate esters (**73**) have been prepared via an enantio- and diastereo-selective reductive aldol of ethyl allenecarboxylate with a chiral (*ee*) α-trimethylsilyl borane.[170] A 1,4-hydroboration pathway is supported by DFT (*de*) and NMR.

The 'memory of chirality' concept has been employed in a strategy for the synthesis of chiral α,β-diamino- and α-amino-β-hydroxy ester derivatives via asymmetric imino-aldol and aldol reactions, starting from protected aminoesters.[171] The route can (*ee*) be extended to the enantioselective synthesis of aziridines.

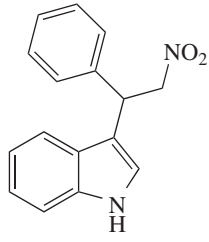


(**73**)

The Henry (Nitroaldol) Reaction

The scope, limitations and mechanisms of asymmetric Henry reactions catalysed by transition metal complexes have been reviewed.[172] (*ee*)

A green one-pot preparation of nitroalkenes has been developed: for example, benzaldehyde and nitromethane give pure nitrostyrene in 95% isolated yield in toluene, after 4 h reflux (or 79% without toluene).[173] A dual-catalyst system of iron trichloride and piperidine (both 10 mol%) simultaneously activates electro- and nucleophiles, without affecting many sensitive groups. The one-pot conditions can be extended by the addition of, for example, indole to give 3-alkylindole (**74**) via Michael addition of the initial nitrostyrene product. Similar one-pot tandem approaches yield 3-nitrochromenes and *N*-arylpyrroles.



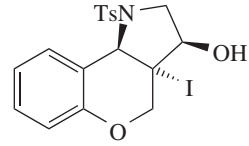
(**74**)

A Henry reaction in aqueous media gives *syn*-β-nitroalcohols under very mild conditions: reactions take a day or two, using phosphate buffer at neutral pH and ambient temperature.[174] Aromatic aldehydes work with comparable yields to aliphatics. (*de*)

Three closely related phenanthrolinylquinine ligands were tested for their ability to coordinate copper(II).[175] One did not form a complex, another gave an unexpected five-coordinate mode and the third catalysed a Henry reaction in high *ee*, being able to activate both aldehyde and nitroalkane. (*ee*)

Stereoselective synthesis of highly functionalized azatricycles (e.g., **75**) has been achieved by copper-catalysed Henry reaction of enals with nitromethane, zinc reduction of the nitro group and subsequent tosylation, followed by iodocyclization.[176] The iodine is easily removed afterwards by hydrogenation, or can be used to introduce other functionality, such as by epoxidation of the adjacent alcohol. (*ee*) (*de*)

A *syn*- and enantio-selective Henry reaction employs copper(II) acetate and a chiral β-amino alcohol catalyst.[177] (*ee*) (*de*)



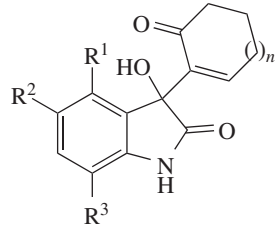
(**75**)

7-Oxo-hept-5-enals undergo an organocatalytic one-pot reaction with nitromethane to give trisubstituted cyclohexanols with three contiguous chiral centres: *de* of >98% is reported and *ee* up to 96%.[178] The process is a tandem Henry–Michael, followed by a tandem retro-Henry–Henry. Consistent with this sequence is the finding that the use of the racemic Henry product as substrate gives similar final results. (*ee*) (*de*)

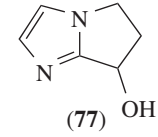
The Baylis–Hillman Reaction and Its Morita-variant

Recent advances in organocatalytic asymmetric Morita–Baylis–Hillman reactions and their aza-variants have been reviewed (112 references), with a particular focus on amine- and phosphine-catalysed routes, and bifunctional catalysis.[179] (*ee*) (*de*)

The catalytic effect of alkylmethylimidazolium ionic liquids as solvents for the Baylis–Hillman reaction has been investigated by DFT, using benzaldehyde, substrate and DABCO as base.[180] 3-Substituted 3-hydroxy-2-oxindoles (**76**, $n = 0$, 1) have been prepared in water via an MBH reaction of unprotected isatins with cyclic enones.[181] Bicyclic imidazolyl alcohol (**77**) is a particularly good catalyst, with its hydroxyl group proposed to stabilize the betaine intermediate.



(**76**)



(**77**)

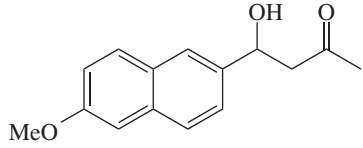
A hypervalent silicon complex, generated from silicon tetrachloride and a chiral phosphine oxide, acts as an enantioselective organocatalyst of the MBH reaction, by asymmetric delivery of a chloride anion as a nucleophile.[182] (*ee*)

Other Aldol and Aldol-type Reactions

DFT and Car–Parrinello molecular dynamics simulations have been used to study aggregation effects in model aldols, using the lithium enolates of acetaldehyde and acetone, with formaldehyde and acetone as electrophiles.[183] The core of the aggregates is Li_nO_n

clusters, and the structure tends towards the most favourable arrangement of the point charges in these clusters. Reactivity of enolates follows monomer ≫ dimer > tetramer. Positive cooperative effects for successive aldols in the aggregates are discussed.

Computationally designed retroaldolase RA-61 gives a 10^5-fold rate acceleration, largely attributed to non-specific interactions with the aromatic substrate.[184a] To test this, the rates of amine-catalysed retro-aldol cleavage of methodol (**78**) have been measured in simple micellar systems, consisting of a positively charged surfactant and a long chain amine.[184b] Acceleration by a factor of 9500 supports the hypothesis, as does a comparable result using bovine serum albumen as catalyst.



(**78**)

α-Alkyl-β-ketoesters undergo electrophilic amination, using nitrosoformate esters, O=N–CO_2R.[185] These highly reactive species can be formed *in situ* by copper(I)-catalysed aerial oxidation of *N*-hydroxycarbamates, allowing a nitroso aldol at ambient temperature.

A short review covers recent advances in the catalytic enantioselective Reformatsky reaction, while highlighting significant current challenges,[186] and the diastereoselective Reformatsky has also been reviewed (61 references).[187] NHC's catalyse Reformatsky reaction of aldehydes with α-TMS-carbonyls, to give β-hydroxycarbonyl compounds.[188] (*ee*) (*de*)

Allylation and Related Reactions

Allylboration of carbonyl compounds has been reviewed.[189]

DFT has been employed to probe the mechanisms of chiral BINOL-phosphoric-acid-catalysed allylboration and propargylation reactions, with a particular focus on whether the catalyst interacts with the pseudo-axial or pseudo-equatorial oxygen of the boronate.[190] (*ee*)

The role of boron trifluoride etherate in the allylboration of aldehydes using (*R*)-pinanediol has been studied computationally, considering the alternatives of attachment of BF_3 to the chiral ligand or to the aldehyde.[191] (*ee*)

Highly substituted enantiomerically pure allylboronic esters have been synthesized and added to aldehydes to give *E*-configured homoallylic alcohols exclusively.[192] (*ee*) (*de*)

DFT has been used to probe the mechanism of allylation of ketones by allylboronates in the presence of diethylzinc.[193] Results favour a double γ-addition stepwise route, rather than concerted Lewis acid. Diethylzinc is found to be weakly catalytic, with the addition of ethanol substantially accelerating the reaction via $Zn(OEt)_2$ catalysis, with $Zn(OH)_2$ and ZnF_2 efficiencies also being calculated.

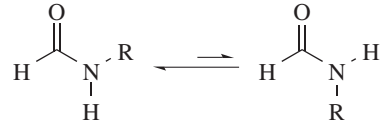
An allylation of aldehydes, (R-CHO, R = aryl, alkyl), with allylboronates in aqueous media reveals features unique to this solvent.[194] Using zinc(II) hydroxide catalysis, (*ee*) (*de*)

exclusive formation of α-addition products was observed, in contrast to organic media. A key allylzinc intermediate was identified by MS, and an asymmetric variant was developed using a chiral ligand. Extension to alkyl-, chloro- and alkoxy-allylation is described.

A new protocol has been introduced to improve selectivity in allylboration of aldehydes.[195] The readily available α-substituted allyl or crotyl pinacol boronic esters often give low *E*/*Z*-selectivity. Addition of *n*-butyllithium followed by trapping of alkoxide with TFAA generates an allyl *borinic* acid, which gives very high *E*-selectivity, and in some cases, this is the *opposite* of the standard conditions. The borinic ester intermediate was characterized by ^{11}B-NMR. (*ee*) (*de*)

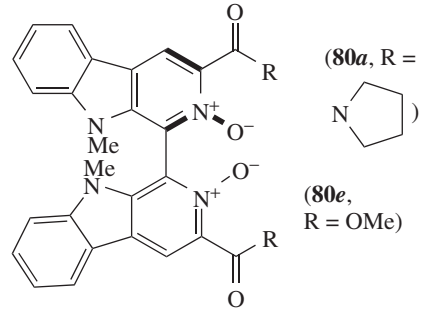
Chiral pyridine *N*-oxides catalyse asymmetric allylation of aldehydes with allyltrichlorosilanes.[196] Relatively small changes in the steric bulk of the *N*-oxide can switch the mechanism between dissociative and associative routes. The analysis is backed up by kinetic measurements and quantum chemical calculations. (*ee*) (*de*)

A structure–activity relationship has been developed for formamides which activate allyltrichlorosilane in the allylation of benzaldehyde.[197] In the case of secondary formamides (**79**), the *trans*-conformer (*trans*-**79**) predominates, but the *cis*- (*cis*-**79**) is suggested to be the reactive conformation. Solvent effects are also explored.



(*trans*-**79**) (*cis*-**79**)

A new axially chiral *N*,*N*′-dioxide di*amide* (**80*a***) gives up to 96% *ee* in allylation of aldehydes with allyltrichlorosilane.[198] However, the absolute configuration of the product is opposite to that found for the corresponding di*ester* catalyst (**80*e***); the latter also gives lower *ee*. Quantum methods used to model transition states suggest that the oxygens of the *N*-oxides of the di*ester* (**80*e***) are close together, forming one catalytic centre, while they are further apart in the di*amide* (**80*a***), and the amide C=O can also become involved. (*ee*)

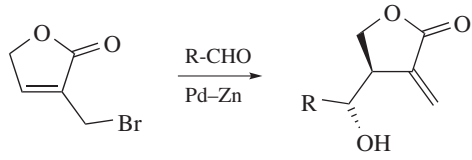


(**80*a***, R = N)

(**80*e***, R = OMe)

A theoretical investigation of the diastereoselectivity of the addition of (*E*)-2-butenyltrimethylsilane (*trans*-Me–CH=CH–CH_2–TMS) to ethanal has been carried out for the cases of electrophilic activation by H_3O^+ or BF_3, and nucleophilic activation by F^-.[199] (de)

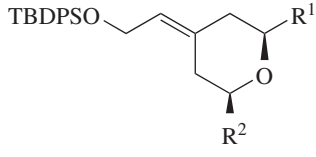
A diastereoselective Pd-catalysed allylation of aldehydes with 3-bromomethyl-5*H*-furan-2-one (**81**) allows the synthesis of *β*-(hydroxymethylaryl/alkyl)-*α*-methylene-*γ*-butyrolactones with *syn* relative configuration (**82**) for the first time.[200] (de)



(**81**) (**82**)

DFT has been used to investigate the highly regioselective 1:2 coupling of aldehydes and allenes catalysed by rhodium(I) complexes.[201] The initial steps appear to be oxidative coupling of the allenes, followed by allylation of the aldehyde.

Prins cyclization of *syn*-*β*-hydroxy allylsilanes with aldehydes gives *cis*-2,6-disubstituted 4-alkylidenetetrahydropyrans (**83**) as *sole* product regardless of the aldehyde (R^2) or allylsilane (R^1) substituent.[202] Complementary exocyclic stereocontrol can be achieved by reversing R^1 and R^2. With yields over 90%, >95:5% control on olefin geometry and a similar *cis*:*trans* ratio, the excellent stereoselectivity has been subjected to a DFT study. The products are related to natural bryostatins, and the method holds promise for other chiral pyranyl targets.



(**83**)

The Horner–Wadsworth–Emmons Reaction and Related Olefinations

The use of the Horner–Wadsworth–Emmons reaction for stereocontrolled olefin synthesis in the field of natural products has been reviewed in 2000–2013.[203] (ee) (de)

The modified Julia olefination of aromatic aldehydes with alkyl benzothiazol-2-yl sulfones has been investigated experimentally, and by DFT, with a view to identifying the origin of the high *E*-selectivity.[204] The reversibility of the addition is very variable, so the selectivity of the formation of the sulfinate intermediate also varies. However, the *syn*- and *anti*-sulfinates both eliminate in concerted processes (*syn*- and *anti*-periplanar, respectively), thus leading preferentially to (*E*)-alkene.

The mechanism of reaction of the silylated phosphorane, Bu_3P=CH–TMS, with *para*-substituted benzaldehydes, yielding cinnamylphosphonium salts, has been studied to

identify the factors affecting the stereochemical and kinetic outcome of the Peterson olefination.[205] The electronic nature of the aldehyde substituent affects the stereochemistry, while the Hammett correlation is strongly temperature dependent.

For another route to HWE products, see under the section titled 'Oximes'.

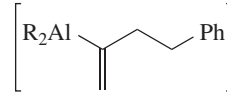
Alkynylations

A metal/organocatalytic direct alkynylation of aldehydes employs copper(I) *t*-butoxide in *t*-butanol, together with a prolinol bearing a pendant triphenylphosphine.[206] Yields and *ee* of up to 98/94% are rationalized in terms of copper chelation of organocatalyst (at N, O and P) and alkyne, further organized by O–H···O and sp^3-C–H···O hydrogen bonds, the latter being unusual in alcoholic solvent, but they are supported by QM calculations. (*ee*)

Enantioselective propargylation and allenylation of ketones and imines have been reviewed (53 references).[207]

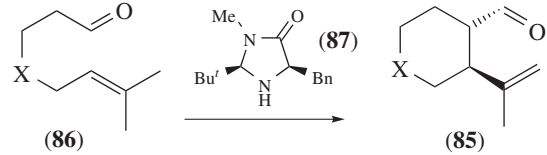
A DFT investigation of BINOL-catalysed asymmetric propargylation of ketones suggests that the activation mode is Lewis acid, not Brønsted.[208] (*ee*)

Terminal alkynes such as 4-phenylbutyne undergo nickel(II)-catalysed reaction with dialkylaluminium hydride to give vinylaluminium reagents (**84**), which react with aldehydes to give enantioselective formation of α-substituted secondary allylic alcohols, via H_8-BINOL catalysis.[209] The vinylaluminium alkyl groups are chosen in such a way that the reagent does not just directly reduce the aldehyde. (*ee*)



(**84**)

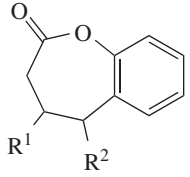
Asymmetrically substituted carbo- and hetero-cycles (**85**, X = CH_2, O, N-Ts) have been prepared via an intramolecular aldehyde α-alkylation of unactivated aldehyde-alkene precursors (**86**) using an amine catalyst (**87**), with transposition of the alkene double bond.[210] The α-carbonyl cyclization gives useful formyl and vinyl substituents on the ring and can be considered a 'homo-ene' process analogous to the well-known carbonyl-ene reaction. Exploring SOMO (singly occupied molecular orbital) catalysis, the initial step is proposed to involve condensation and amine addition with single electron loss, giving an enamine radical cation. (*ee*) (*de*)



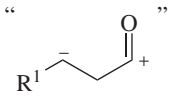
(**86**) (**85**)

2-Benzoxopinones (**88**) have been accessed enantioselectively via a formal [4+3] annulation.[211] A dual-activation strategy involves two Lewis bases: (i) an NHC to (*ee*) (*de*)

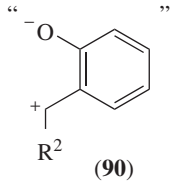
convert an enal, R^1-CH=CH–CHO, into a homoenolate equivalent (**89**), and (ii) fluoride anion, to activate an *ortho*-silyloxy benzyl bromide (bearing R^2) to give a transient quinone methide (equivalent to zwitterionic phenoxide, **90**). The method elegantly allows two highly reactive transient species to be generated and then to react enantioselectively with each other, while minimizing the side reactions that are available to both. A formal [4+2] variant unexpectedly yielded useful dihydrocoumarins.



(**88**)



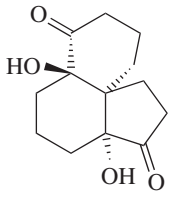
(**89**)



(**90**)

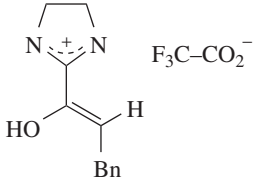
Stetter Reaction, Benzoin Condensation and Pinacol Coupling

NHC catalysis has been efficiently employed in an intramolecular crossed-benzoin reaction of symmetrical reactants.[212] This desymmetrization strategy can be applied to asymmetric synthesis with chiral NHCs. As an example, bis(acyloin) (**91**) containing three contiguous quaternary bridgehead chiral centres was synthesized and structurally characterized by X-ray crystallography.



(**91**)

NHC-catalysed umpolung reactions of both simple and α,β-unsaturated aldehydes have been studied by NMR spectroscopy and X-ray diffraction: key intermediates characterized include diamino enols, diamino dienols, azolium enolates, and the first report of an azolium enol (**92**).[213] Interconversion of these species has been followed by NMR kinetics, with mechanistic characterization further supported by DFT calculations.

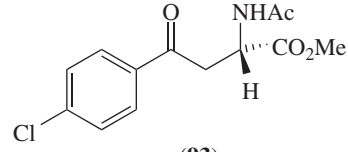


(**92**)

The intermolecular Stetter reaction of benzaldehyde and cyclopropene, catalysed by NHCs, has been modelled using DFT.[214] The roles of water and of bases such as DBU in affecting the free energy and controlling the diastereomeric ratio are examined. (*de*)

NHC catalysis of Stetter and benzoin reactions by triazolidenes has been investigated via *in situ* observation of intermediate 3-(hydroxybenzyl)azolium salts of the benzaldehyde substrates.[215] Equilibrium constants for their formation are reported, together with rate constants for hydrogen–deuterium exchange at the α-carbon.

p-Chlorobenzaldehyde undergoes an enantioselective Stetter reaction with *N*-acylamido acrylate, to give α-amido ester (**93**) in 95% *ee*, using potassium *t*-butoxide and a chiral NHC in toluene at 0 °C.[216] DFT evidence for explicit counterion binding is presented: a 24.2 kcal mol^{-1} stabilization is reported, relative to the pathway without K-coordination. (*ee*)

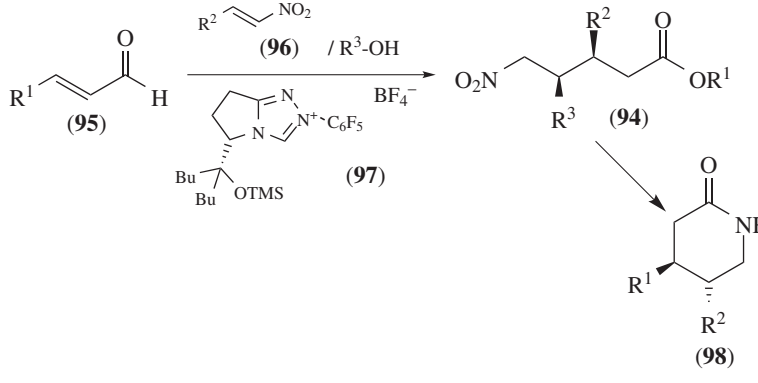


(**93**)

Carbohydrates have been catalytically activated as acyl anions to act as formaldehyde equivalents for a Stetter reaction.[217] The acyl anions are generated by NHC-catalysed C–C bond cleavage of carbohydrates via a retro-benzoin-type process.

NHCs catalyse an intramolecular Stetter reaction of methyl 4-(2-formylphenoxy)-2-butenoate in toluene to yield a chromanone.[218] A B3LYP/6-3IG** study identified the formation of the Breslow intermediate as the rate-determining step, followed by a Michael-type addition, which is the stereoselectivity-determining step.

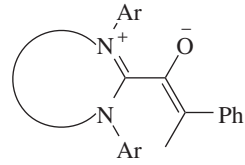
Previously unreported *syn*-diastereoselectivity in the synthesis of δ-nitroesters (**94**) from enals (**95**) and nitroalkenes (**96**) has been achieved, using an NHC (**97**, reminiscent of dialkylprolinol TMS ether) designed to avoid the established acyl anion/Stetter pathway and favour the homoenolate route.[219] The method has been further exploited in a mild and elegant one-pot synthesis of δ-lactams (**98**) from similar starters. (*ee*) (*de*)



Michael Additions

The continuing controversy over the mechanism of the stereoselective Michael addition as catalysed by diphenylprolinol silyl ether is the subject of a short review (12 references).[220] (*ee*) (*de*)

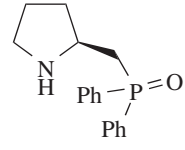
A series of azolium enolates (**99**; Ar = phenyl, mesityl) have been synthesized and characterized.[221] Their ambident reactivities have been measured by studying their reactions with benzhydryl cations, $Ar_2CH^{\oplus}$, in d_3-acetonitrile, using known electrophilicity parameters for the latter. NMR shows predominantly *O*-attack initially, with a switch to *C*-product over 1–2 days, with second-order rate constants for the two processes calculable. The azolium enolate reactivities have been compared with those of the corresponding free carbenes, and deoxy-Breslow intermediates.



(**99**)

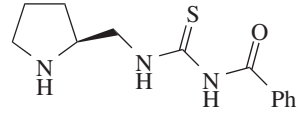
Highly functionalized 3,4-disubstituted lactones have been prepared in good *de*/*ee* via Michael addition of aryl methyl ketones to 2-furanones, using bifunctional catalysis by a simple chiral diamine and tosic acid: ESI-MS suggests that a catalytic monosalt forms.[222] (*ee*) (*de*)

An organophosphine oxide (**100**) derived from L-proline catalyses asymmetric Michael addition of chalcones to cyclic ketones, with yields/*ee*s/*de*s up to 91/99/98%.[223] A mechanism involving enamines is proposed, supported by ^{31}P-NMR and by the observation of a 1:1 chalcone:catalyst complex in the ESI-MS. (*ee*) (*de*)



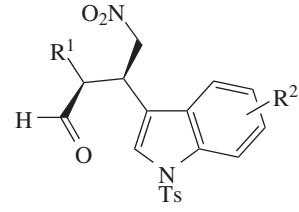
(**100**)

Benzoylthiourea-pyrrolidine (**101**), derived from L-proline, efficiently catalyses Michael addition of cyclohexanone to nitrostyrenes: *de*/*ee* values of over 98/99% have been achieved in the presence of 2,4-dichlorobenzoic acid as co-catalyst.[224] (*ee*) (*de*)



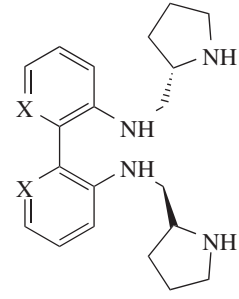
(**101**)

Optically pure 2-alkyl-3-(1*H*-indol-3-yl)-4-nitrobutanals (**102**) have been prepared in yield/*de*/*ee* up to 98/98/99% by Michael addition of aliphatic aldehydes, R^1-CH_2CHO, to *trans*-indolylnitroalkenes, using (*S*)-diphenylprolinol TMS ether as organocatalyst.[225] The products (**102**) are useful precursors to biologically active tryptamines. (*ee*) (*de*)



(**102**)

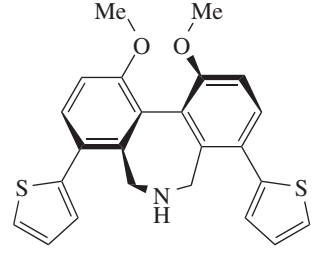
New C_2-symmetric but axially unfixed organocatalysts (**103**) derived from L-proline catalyse Michael addition of ketones and aldehydes with nitro-olefins, in the presence of acidic additives such as benzoic acid.[226] The excellent performance of up to 99/98/96% on yield/*de*/*ee* is ascribed to their likely bifunctional nature. (*ee*) (*de*)



(**103**, X = CH, N)

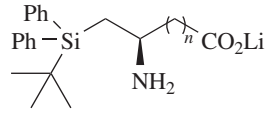
A new class of chiral squaramides give *de*/*ee* up to 98/99% as catalysts for Michael addition of nitroolefins to 1,3-dicarbonyls.[227] (*ee*) (*de*)

An unusual *anti*-selective conjugate addition of aldehydes to nitroalkenes is catalysed by a biphenyl-based chiral secondary amine (**104**).[228] An NMR study shows the diastereoselectivity arises in the C–C bond-forming step. (*ee*) (*de*)



(**104**)

A series of lithium salts of protected primary amino acids (**105**, $n = 0–2$) catalyse asymmetric Michael addition of malonates to 2-cyclohexen-1-one.[229] The β-amino salt ($n = 1$) gave higher *ee* than either the γ- or the α-. A mechanistic study using DFT has been carried out to identify how the β-amino salt better coordinates the imine intermediate and maximizes *ee*. (*ee*)

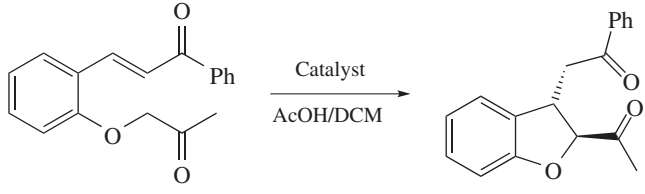


(**105**)

A DFT and ONIOM study has probed the mechanism of 1,4-Michael addition of malonitrile to unsaturated aryl ketones catalysed by 9-*epi*-amino-cinchona alkaloids.[230] The proton from an acidic additive is critical in the formation of the key ketiminium ion intermediate, with the protonated tertiary amine of the alkaloid activating the carbonyl via hydrogen bonding. The origin of the high *ee* is also explored. (*ee*)

An enantioselective Michael reaction of aldehydes and maleimides gives up to 99% yield and *ee*, using a cooperative catalysis by a chiral primary amine and triphenylphosphine.[231] Evidence for a supramolecular assembly of the catalysts is presented, including UV/visible, fluorescence, CD and NMR spectroscopy, and ESI-MS. (*ee*)

Keto-enone (**106**) undergoes an intramolecular Michael reaction, giving the pharmaceutically valuable *trans*-dihydrobenzofuran skeleton (**107**).[232] Using a bifunctional primary amine-squaramide catalyst, yield/*de*/*ee* of up to 98/94/>99% have been achieved. (*ee*) (*de*)

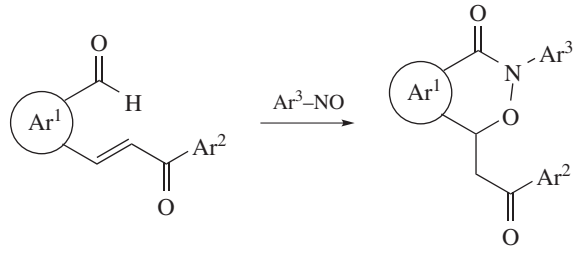


(**106**) (**107**)

The imidazolidinone-catalysed intramolecular asymmetric Michael addition has been studied by DFT.[233] The mechanism is identified as enamine formation followed by Michael addition (which is stereochemistry determining), followed by enol-keto tautomerization and hydrolysis. (*ee*)

An organocatalytic enantioselective direct vinylogous Michael addition of γ-butenolides to 3-aroyl acrylates has been reported.[234] (*ee*) (*de*)

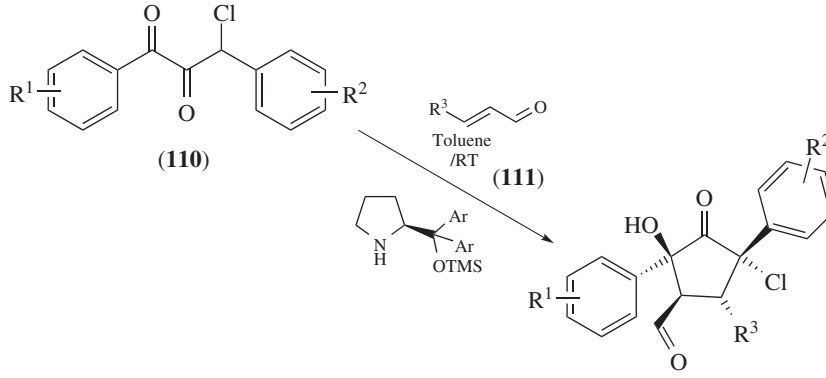
2-Aroylvinylarylaldehydes (**108**, Ar^1 = furyl, thiophenyl or pyridyl) react with nitrosoarenes to give heterocyclic ring-fused 1,2-oxazinones (**109**), using NHC catalysis.[235] Intermediate formation of *N*-hydroxylamides followed by intramolecular oxo-Michael addition is discussed.



(**108**) (**109**)

A tungsten-stabilized phosphinophosphonate, $(OC)_5WPH(Ph)–P(=O)(OEt)_2$, reacts with ethynyl- and diethynyl-ketones in the presence of LDA to give oxaphospholes and bisphospholes, that is, via nucleophilic attack in the Michael position.[236] (*ee*) (*de*)

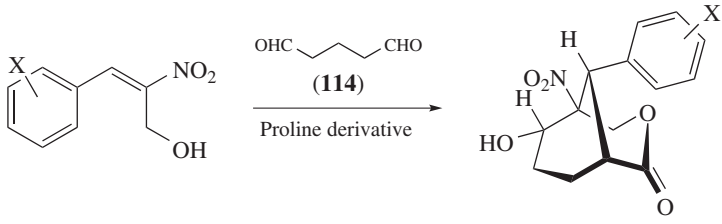
3-Chloro-1,2-diones (**110**) undergo a domino Michael/aldol with enals (**111**) to give highly functionalized cyclopentanones (**112**), using diaryl prolinol TMS ethers as organocatalysts.[237] The best *de*/*ee*/yield results were 90/94/97%. A fluoro-substrate gives a cyclopentenone product, that is, the dehydration equivalent of (**112**).



(**110**) (**111**) (**112**)

3-Oxabicyclo[3.3.1]nonan-2-ones (**113**) containing four consecutive stereogenic centres have been prepared in >99% *ee* by a cascade organocatalytic Michael-Henry acetalization-oxidation reaction of glutaraldehyde (**114**) and 3-aryl-2-nitroprop-2-enols (**115**).[238] The structures and absolute configurations of the products were confirmed by X-ray crystallography.

Aldehydes have been activated in the β-position by oxidative NHC catalysis.[239] This formal Michael acceptor strategy can produce highly functionalized lactones (using β-diketones) in high yield and *ee* with a chiral NHC. Mild conditions prevail, with a quinone as oxidant. (*ee*)

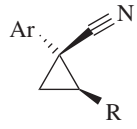


(**115**) (**113**)

Miscellaneous Condensations

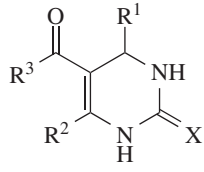
Knoevenagel reactions can be carried out at ambient temperature using an ionic liquid, dimethylethanolammonium acetate: it features wide substrate tolerance, and ease of workup and reuse.[240] Its catalytic effect has been demonstrated by a solvatochromic study which identifies dual functions: the cation hydrogen-bonds to the aldehyde, and the anion acts as acceptor to the active methylene substrate, facilitating the formation of carbanion.

A diastereoselective synthesis of cyclopropanes combines an aryl acetonitrile, $ArCH_2CN$, with an aldehyde, RCHO, to give 100% *cis*-product (**116**) as a racemic mixture of enantiomers.[241] The one-pot reaction shows yields of 45–93% covering a wide range of substrates: 'Ar' includes 3-pyridyl and 2-thiophenyl, and the aldehyde can be aromatic or aliphatic. The reaction sequence consists of a Knoevenagel condensation followed by a Corey/Chaykovsky cyclopropanation.



(**116**)

The Biginelli multi-component synthesis of 5-acyl dihydropyrimidin(thi)ones (**117**, X = S or O) from a (thio)urea, $[H_2N–C(=X)–NH_2]$, an aldehyde (R^1-CHO) and a β-ketoester (R^2-CO–CH_2–CO-R^3) has provided a wide range of anti-tumour candidates.[242] Using an ion-tagged iron catalyst – an imidazolium with $FeCl_4^-$ or $Fe_2Cl_7^-$ as counterion – the reaction can be carried out under ionic liquid conditions,



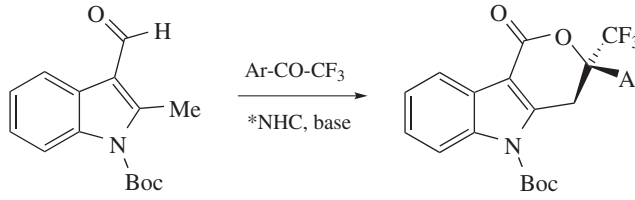
(**117**)

with the catalyst being recoverable and recyclable. A kinetic study indicates that the rate is independent of aldehyde and dione, but slows with excess urea, consistent with an iminium ion mechanism, and tending to rule out enamine or Knoevenagel routes. In another use of ionic liquids, two new benzothiazolium IL's have been prepared and tested as catalysts of the Biginelli.[243]

A detailed study of the Biginelli has varied acid catalysis (Brønsted vs Lewis), and also covered a wide range of solvents.[244] The yield is found to depend on the keto-enol equilibrium of the β-ketoester, a factor which in turn depends on the solvent. This control via an equilibrium is in turn facilitated by the catalyst, which can eliminate kinetic control.

Proline potassium salt is a superior catalyst for Friedlander annulations, compared to proline.[245] Copper(II) catalysis of the Friedlander reaction has been studied by DFT.[246]

Benzylic-type sp^3-centres of heteroaromatic aldehydes (e.g., the methyl of indole **118**) can be activated with chiral NHCs, via *ortho*-quinodimethane-type intermediates, allowing cyclization with trifluoromethyl aryl ketones to give lactones (e.g., **119**) in good yields and *ee*.[247] (*ee*)



(**118**) (**119**)

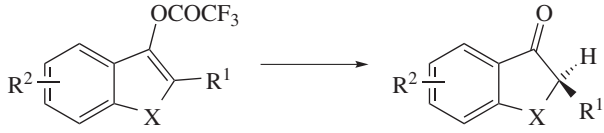
Other Addition Reactions

The use of transition metal catalysts to activate C–H bonds towards addition to C=O and C=N bonds has been reviewed (64 references), with a focus on mechanistic data and lacunae.[248] (*ee*)

pK_a values for a series of chiral Brønsted acids which are commonly used in organocatalysis, including phosphoric acids, *N*-triflylphosphoramides and bis(sulfuryl)imides, have been measured in dry acetonitrile, and compared with other common catalysts for which acidity is known in this solvent.[249] These classes have pK_as of 12–14, 6–7 and ca 5, respectively.

A range of cyclic alkenyl trifluoroacetates (**120**, R^1 = alkyl, allyl, benzyl; R^2 = H, 6/7-MeO; X = $-CH_2-$, $-OCH_2-$ and $-CH_2CH_2-$) undergo enantioselective protonation, using methanol as proton source and a chiral binaphthyl tin bromide methoxide as chiral catalyst, to give chiral ketones (**121**).[250] Pronounced nonlinear effects are observed in the *ee* and are rationalized in terms of monomer-dimer equilibria involving the catalyst. (*ee*)

An intrinsic reactivity index (IRI) has been developed, with a view to capturing electro- and nucleophilicity on a single scale, and using frontier molecular orbital data to access values.[251] A correlation of IRI with Mayr's *E* and *N* parameters is also described.

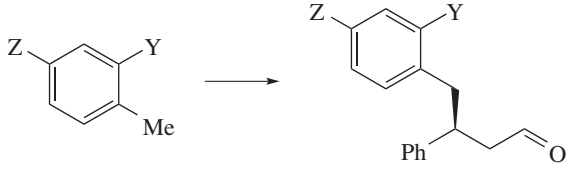


(**120**) (**121**)

1,4-Addition of nucleophiles to α,β-unsaturated carbonyl groups has been reviewed, considering acrylic amides or esters on a carbohydrate template as acceptors.[252] (*de*)

The stereochemistry of 1,2-elimination and proton transfer reactions of acyclic esters, thioesters and ketones has been reviewed (41 references), focussing on electronic factors and avoiding complications from aggregation effects.[253] While *anti*-stereospecificity (*ee*) can arise from concerted *E*2 processes, it is also regularly found in E_1cb_{irrev} reactions, (*de*) even though they proceed via equilibrated 'free' enolates. Negative hyperconjugation is invoked to explain the results, with hydrogen bonding also being significant in hydroxylic solvents.

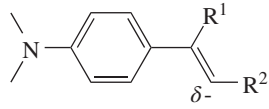
'Inert' aryl methanes (**122**, Y/Z = H/NO_2) have been activated as nucleophiles towards enals, using a chiral amine catalyst under mild conditions, giving enantioselective direct conjugate addition product (**123**) in high yield and *ee*.[254] (*ee*)



(**122**) (**123**)

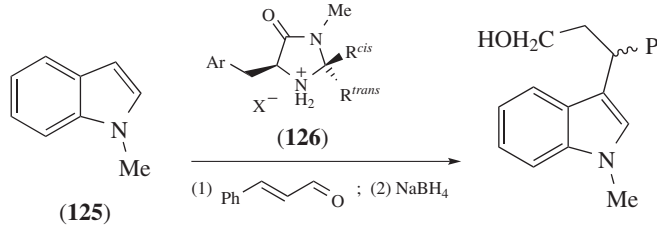
In a study of organocatalytic asymmetric conjugate addition (ACA) of nitroalkenes to aldehydes, ESI-MS has been used to identify intermediates and the stereoselective step.[255] Starting with quasi-enantiomeric reaction products, MS is used for back-reaction (*ee*) screening and supports the enamine mechanism (over the enol route). (*de*)

para-Vinylanilines (e.g., **124**) are proposed as a new type of nucleophilic synthon, an 'aromatic' enamine.[256] They undergo C–C coupling with aldehydes, R^3-CHO (when R^1 is also an aniline) to give 1,4-dienes, $Ar_2C{=}CH{-}CH(R^3){-}CH{=}CAr_2$.



(**124**)

Addition of 1-methyl-1*H*-indole (**125**) to cinnamaldehyde using McMillan's generation-I imidazolidinone catalyst (**126**, R = Me) gives – after reduction – enantiomeric alcohols (**127**).[257] In an unusual 'fluorine effect', changing the *cis*-methyl (R) (*ee*) group of the catalyst to fluoromethyl reverses the enantioselectivity.



Direct organocatalytic β-benzylation of α,β-unsaturated aldehydes using toluenes has been achieved under mild conditions of DCM/reflux, using *t*-butyldimethylsilyl-protected diphenylprolinol: *ee*s >99% are reported.[258] Typically, the toluene needs to be activated by a base such as triethylamine, and typically also needs two nitro groups (or one nitro and another EWG) to stabilize the benzyl anion intermediate. Dual activation is essential: without the prolinol, no reaction occurs, even with excess DMAP or DBU as base. (*ee*)

A range of NMR, IR and MS techniques have been brought to bear on the reaction of diphenylphosphine oxide with aromatic aldehydes and ketones, to give α-hydroxy-phosphine oxides.[259] Rate constants were correlated with the Hammett equation, for the aldehydes.

Trifluoroacetaldehyde hydrate, $F_3C–CH(OH)_2$, has been used as a trifluoromethyl source for nucleophilic trifluoromethylation of aldehydes and ketones, including hindered cases such as adamantanone.[260] Using DMF solvent at −50 °C, potassium *t*-butoxide is used to form the dianion of the hydrate, delivering trifluoromethyl anion, with significant stabilization by the solvent.

Triflic acid catalyses direct conjugate alkenylation of α,β-unsaturated ketones with styrenes, with some diastereoselectivity.[261]

NHCs catalyse hydroacylation of styrenes by aldehydes (RCHO), giving mainly β-keto-aromatics, $RCOCH_2CH_2–Ar$, with some α-isomer, RCOCH(Me)Ar; a wide variety of functionality in both reactants is tolerated.[262]

α,β-Unsaturated ketones have been directly accessed in high yields by coupling aldehydes and alkenes, using a simple copper catalyst ($CuCl_2$) and *t*-butyl hydroperoxide.[263]

A new amino-catalytic vinylogous cascade involves asymmetric 1,6-addition to linear 2,4-dienals with good *de*, high *ee* and selectivity for the δ-site, exploiting a vinylogous iminium ion strategy.[264] (*ee*) (*de*)

Silver(I) catalyses allenylation and propargylation of ketones and α-ketoesters, with product type easily selectable by choice of conditions.[265] (*ee*)

Addition of Organozincs

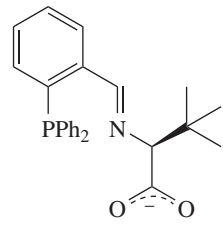
An achiral quaternary ammonium salt such as tetrabutylammonium bromide exerts a synergistic effect on addition of diethylzinc to aldehydes catalysed by a chiral phosphoramide.[266] In the presence of 10 mol% tetrabutylammonium bromide, the chiral catalyst can be lowered from 10 to 0.5 mol%, while retaining reactivity and *ee*. (*ee*)

New C_2-symmetric nickel complexes of α-amino amides catalyse enantioselective addition of dialkylzincs to aldehydes.[267] DFT studies suggest that the aldehyde carbonyl, rather than coordinating to the metal, is activated by an amino hydrogen which has been acidified by the nickel complexation. (*ee*)

Chelation-controlled diastereoselective addition to α-silyloxy aldehydes has been achieved using dialkylzincs and chlorotrimethylsilane: the chelation is promoted by *in situ* ethyl zinc chloride.[268] This autocatalysis means that stoichiometric amounts are not needed. (*de*)

A study of palladium-catalysed conjugate addition of diorganozincs to various enone types indicated that both Pd(0) and Pd(II) complexes could catalyse the reaction.[269] Phosphine ligands such as PPh_3 or PBu_3 were effective, but only at a 1:1 Pd:P ratio: a 1:2 ratio caused yields to collapse. The observation is consistent with a mechanism computed for the Pd(0) case, in which the enone is simultaneously coordinated to Pd(0) and R_2Zn: this undergoes oxidative addition to palladium with simultaneous transmetalation from Zn to Pd, followed by reductive elimination.

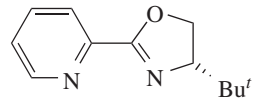
An enantioselective 1,6-conjugate addition of dialkylzincs to acyclic $\alpha,\beta,\gamma,\delta$-dienones is catalysed by copper and a triphenylphosphine with a pendant chiral imino-carboxylate, DIPPAM (**128**).[270] Small amounts of 1,4-adduct are also produced. The 1,6-ACA (asymmetric conjugate addition) has further been sequentially coupled to a 1,4-ACA version, with a reconjugation step in between. (*ee*)



(**128**)

Arylations

Enantioselective conjugate additions of arylboronic acids to β-substituted enones using a Pd(II) trifluoroacetate/(*S*)-*t*-BuPyOx (**129**) catalyst system have been further investigated by experiment and computation.[271] The palladium catalyst that might act as a Lewis acid to activate the enone has been ruled out. Instead, transmetalation from boron to palladium is followed by rate- and *ee*-determining carbopalladation of the olefin of the enone by a cationic Pd species and protonolysis of the resulting palladium-enolate. Knowledge of the mechanism has afforded improvements: addition of water and ammonium hexafluoro-phosphate accelerates the reaction, allowing lower catalyst loadings. (*ee*)

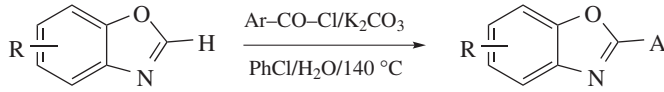


(**129**)

Optically active tertiary α-hydroxyesters have been accessed by rhodium-catalysed asymmetric 1,2-addition of arylboronic acids to aliphatic α-ketoesters.[272] Readily available chiral *N*-(sulfinyl)allylamines are efficient novel ligands, and reversals of regio- and enantio-selectivities can be achieved by tuning the olefin substituent between linear and branched versions. (ee) (de)

Seemingly disparate processes promoted by cationic sulfur(IV) species, such as direct ylide transfer to carbonyl derivatives and a sulfoxide-mediated arylation, have been found to have important mechanistic links, revealed through DFT studies and NMR kinetics.[273]

Benzo[*d*]oxazoles (**130**) undergo a base-promoted formal arylation using an aromatic acyl chloride, giving product (**131**) in up to 91% yield.[274] The reaction proceeds via *N*-acylation of oxazole to form an iminium intermediate, which hydrates to give a Lewis acetal, ring-opens, extrudes CO, ring-closes and then dehydrates. The reaction avoids the previous use of transition metal ion catalysis, and one example of an alkyl acid chloride is also reported.



(**130**) (**131**)

Addition of Other Organometallics

Aromatic aldehydes have been converted into the corresponding aryl phenyl ketone, using triphenylaluminium.[275] The latter reagent was generated from bromobenzene, aluminium chloride and magnesium. A tandem organoaluminium addition-Oppenhauer oxidation sequence is proposed. Pinacolone was used as an oxidant, and the organoaluminiums proved highly selective for aromatic aldehydes even with significant quantities of ketones in the system.

The Wittig Reaction

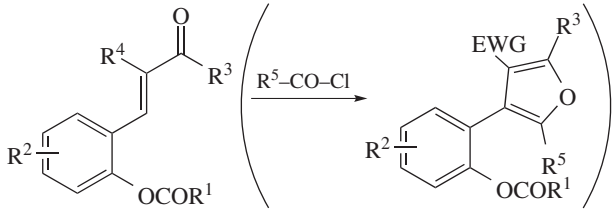
The mechanisms of the Wittig reaction have been reviewed (108 references), with the authors drawing a clear distinction between the well-established 'Li salt-free' reaction (with an oxaphosphetane as its first-formed and indeed only intermediate) and the 'Li-product' cases, where the precise mechanistic details are less clear.[276] (de)

The Wittig reaction has been carried out under very mild green conditions: weakly basic water, ambient temperature and overnight completion.[277] Employing silver carbonate to convert a phosphonium salt into an ylide, the reaction works for stabilized, semi-stabilized and non-stabilized ylides, using aromatic, heteroaromatic and aliphatic aldehydes (and an example of a ketone).

The anomalous *Z*-selectivity observed in Wittig reactions of *ortho*-substituted benzaldehydes has previously been ascribed to phosphorous-heteroatom interactions in the addition TS, but a DFT study identifies the cause as being primarily steric.[278]

The Wittig reaction has been rendered catalytic (in phosphane), using diphenylsilane to chemoselectively reduce a phosphane oxide precatalyst and a simple base: sodium carbonate or Hunig's.[279] *E*/*Z*-selectivity >95/5 is seen in many cases.

Reaction of simple aryl enones (**132**, $R^4 = H$) with acid chlorides gives benzofurans via a chemoselective intramolecular Wittig, using combined Bu_3P/Et_3N catalysis.[280] Incorporation of a significantly electron-withdrawing group (EWG, e.g., $R^4 = C{\equiv}N$, COPh) switches the reaction to produce 3-aryl-4-EWG-furans (**133**), whereas a donating group in the reactant (e.g., $R^4 = Me$) results in no reaction. DFT calculations have been used to probe the factors in the benzofuran versus aryl-furan alternatives.



(**132**) (**133**)

Olefinations of *P*-stabilized *C*-nucleophiles have been reviewed.[281]

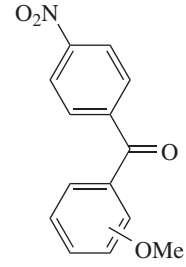
Phospha-alkenes can be prepared via the phospha-Wittig–Horner process.[282] Ketenes have been employed as reactants, leading to 1-phospha-allene products, in a mechanistic investigation which has offered X-ray crystal structures of key intermediates, allowing clarification of the route for the first time. An oxadiphosphetane intermediate undergoes exclusively P–P cleavage, followed by a [2,3]-sigmatropic rearrangement.

A computational study has examined the effects of substituents on the sulfur-Wittig reaction of $H_2S{=}CH_2$ with a range of formyl (O=CH-R) substrates: R = H, F, Cl, Me, OMe, NMe_2 and Bu^t.[283]

2-Hydroxyisoindole-, isoindoline- and indane-1,3-diones have been reacted with both stabilized alkylidenephosphoranes (e.g., acyl-methylenetriphenylphosphoranes) and also active ylides such as phosphacumulenes.[284]

Sodium chlorodifluoroacetate, $ClCF_2{-}CO_2Na$, undergoes a decarboxylative Wittig with aldehydes.[285] Three mechanisms had been proposed, involving difluorocarbene, phosphobetaine and chlorophosphonium acetate intermediates. The second mechanism has now been established, via isolation of the difluoromethylene phosphobetaine intermediate, $Ph_3P{-}CF_2{-}CO_2^-$, characterized by NMR, MS, elemental analysis and X-ray crystallography. The material is air- and water-stable, and is a useful ylide precursor, reacting with a range of aldehydes in NMP (*N*-methyl-2-pyrrolidone) at 80 °C, in 4 h.

In an unusual ketone homologation, attempted Wittig reaction of methyltriphenylphosphonium bromide with 2- (or 4-) methoxy-4′-nitrobenzophenone (**134**) using potassium *t*-butoxide as base unexpectedly yielded methyleneketones with the exclusion of triphenylphosphine.[286]



(**134**)

Hydrocyanation, Cyanosilylation and Related Additions

Zinc-catalysed asymmetric hydrosilylation of ketones and imines has been reviewed.[287] (*ee*)

A bidentate cyclopentadienyl-functionalized NHC complex of nickel(II) catalyses hydrosilylation of aldehydes, allowing quantitative reduction in 5 min at 25 °C.[288] A transient nickel hydride complex, (*Cp-NHC)NiH, is implicated as the active species.

Cyclic α-fluorinated ketones undergo solvent-assisted addition of TMSCN in DMF, giving TMS-promoted cyanohydrins in good yields and up to 91% *de*, with the *cis*-product predominating.[289] Interaction of the carbonyl of DMF with TMSCN is (*de*) proposed to activate the reagent, by weakening the Si–CN bond. Simple reduction of the product with lithium aluminium hydride affords the corresponding fluorinated 1,2-amino alcohols.

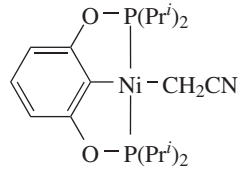
Hydrosilylation of ketones in high *ee* has been achieved under ambient conditions in toluene using a silane and a zinc catalyst in which the metal ion is chelated simultaneously by a chiral 1,2-diamine and a chiral 1,2-diol.[290] Although the catalyst could not be (*ee*) isolated in crystalline form, a combination of diethylzinc, diamine and diol shows evidence for it by ^{1}H-NMR, and addition of the silane results in a new peak at $\delta = 4.50$ ppm, consistent with Zn–H: this peak decreases on addition of ketone. CD spectra are also reported, and extensive DFT calculations support the hydride formation, as well as preorganization of substrate and catalyst via an N–H···O=C hydrogen bond.

DFT has been used to model the hydrosilylation of ketones catalysed by NHC–Cu(I) hydrides.[291] Using CuF as pre-catalyst, a four-centre metathesis TS is identified.

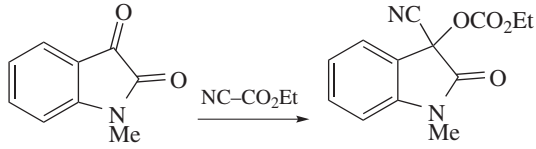
Nucleophilic 1,2-addition of silicon reagents to aldehyde has been achieved using copper(I) catalysts bearing axially chiral ligands: the α-hydroxysilane products are formed in >99% *ee* in many cases.[292] (*ee*)

Acetonitrile's weak acidity usually requires a strong base to activate it.[293] Transition-metal activation is an alternative, and a nickel catalyst (**135**) allows cyanomethylation of aldehydes by acetonitrile at ambient temperature under base-free conditions. The robust catalyst works at low loadings, without drying or degassing precautions.

Isatins (e.g., **136**) are considerably less reactive than simple ketones, and a successful enantioselective cyanoethoxycarbonylation protocol gave poor results for such substrates.[294a,b] A Lewis base–Brønsted acid cooperative enantioselective catalyst now (*ee*) allows reaction at ambient temperature with yields of adducts (**137**) and *ee*s in the



(**135**)



(**136**) (**137**)

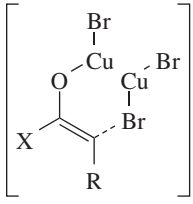
high 90's.[294c] The strategy allows simultaneous activation of the cyanoester (via the Lewis acid) and the isatin (via hydrogen bonding). (ee)

The mechanism and stereochemistry of hydrophosphonylation of α-ketoesters by dimethylphosphonate [H–P(=O)(OMe)$_2$] has been studied theoretically by the ONIOM method, for catalysis by cinchona-thioureas.[295] Deprotonation of the phosphonate is rate determining. It is followed by C–P bond formation (the stereo-controlling step) via nucleophilic addition, and then reprotonation (regenerating the catalyst). Multiple hydrogen bonds activate the substrates, facilitate charge transfer and stabilize transition states. (ee)

α-Aminations and Related Reactions

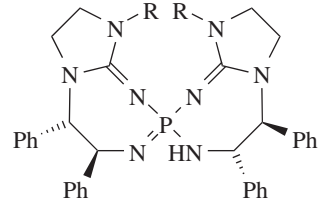
Electrophilic amination of carbanions, enolates and their surrogates has been reviewed.[296]

Aldehydes, ketones and esters, XCOCH$_2$R (X = H, alkyl, aryl, MeO, etc.), have been directly α-aminated via copper(II) bromide catalysis.[297] An α-bromo carbonyl species is proposed as intermediate (**138**), followed by nucleophilic displacement of the bromide by the amine. Done in air at ambient temperature and various solvents (DMSO is best), the intermediate (**138**) is proposed to generate transient XCOCH(Br)R. Amine attack, as well as giving product, releases HBr, and this – together with oxygen – converts CuBr by-product back to catalyst.



(**138**)

A series of neutral chiral bis(guanidine)iminophosphoranes (**139**, R = Me, Bu^t, Br, benzhydryl) have been prepared, and their hydrohalide salts have been characterized by X-ray crystallography.[298] They act as organosuperbase catalysts for enantioselective amination of ketones. (ee)

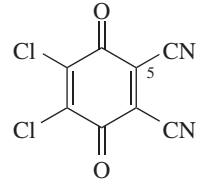


(**139**)

Regio- and enantio-selective hydroxyaminations of aldehydes have been achieved under metal-free conditions, using *in situ* generated nitrosocarbonyl compounds, O=N–CO_2R: the latter are generated by the dehydrogenation of suitable hydroxamic acid derivatives, HO–NH–CO_2R, using benzoyl peroxide/TEMPO as oxidant.[299] A BINAP-amine catalyst gives high yields and *ee*s up to 99%. Competing aminoxylation is typically undetected. (ee)

Miscellaneous Additions

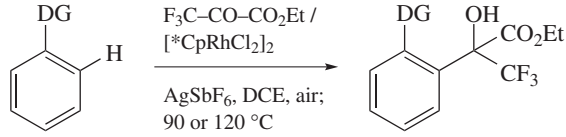
A kinetic study of reactions of 2,3-dichloro-5,6-dicyano-*para*-benzoquinone (**140**, DDQ) with silyl enol ethers, silyl ketene acetals, allylsilanes, enamino esters and diazomethanes has been carried out in acetonitrile and DCM, allowing correlations with nucleophilicity parameters for the latter species to be examined.[300] These are found to be 2–5 orders of magnitude larger than expected for Single Electron Transfer processes, supporting a polar mechanism for C–C bond formation at C(5). However, rate constants for *O*-attack *do* correlate well with calculated values assuming rate-determining SET.



(**140**)

Using an appropriate directing group in the aromatic (DG in **141**), rhodium-catalysed direct C–H bond addition to ketones has been achieved, giving a highly functionalized benzylic alcohol (**142**).[301] 2-Quinolyl is a particularly good directing group, affording tridentate rhodium coordination possibilities (N, O, O) in the TS. A Friedel–Crafts mechanism has been ruled out, and deuterium labelling in the aromatic results in exchange, indicating that the reaction is reversible.

Ab initio methods have been used to study the reaction of urea with formaldehyde.[302]

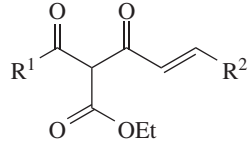


(**141**) (**142**)

Enolization, Reactions of Enolates and Related Reactions

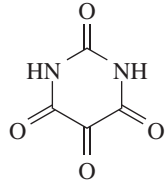
An exclusively computational method for obtaining enolization equilibrium constants in water has been described, based on gas-phase free energy changes, solvation energies and a correction for the latter via a parameterization scheme.[303] In some cases where computed and experimental values disagree, the authors identify concerns with the experimental values. For 37 reactions, the correlation shows a root-mean-square error of 1.3 kcal mol^{-1}. The report includes an examination of the relative stability of some *E*- and *Z*-enols.

Two β,β'-tricarbonyls (**143a**: R^1, R^2 = Ph, 2-furyl; **143b**: R^1, R^2 = Me, Ph) have been investigated by NMR and DFT in different solvents to characterize their keto-enol (and enol–enol) equilibria.[304]



(**143a, 143b**)

The tautomers, rotamers, anions and cations of alloxan (**144**) have been studied by DFT, with the 'tetraketo' form (shown) being the most stable in gas phase and solution.[305]



(**144**)

Ab initio and DFT methods have been used to study catalysis of keto-enol tautomerization of cyclopenta-1,3-dione in water, using a full solvation model, including a molecular dynamics simulation with 324 explicit waters.[306] The immediate involvement of water molecules lowers the barrier, but further waters have little effect, probably because the extensive hydrogen-bonding networks that might give optimal reaction are entropically disfavoured such that their contributions to the reaction rate are minimal.

A theoretical study has examined keto-enol tautomerism and other isomerization processes in pyruvic acid, $H_3C–C(=O)–CO_2H$.[307]

Keto-enol tautomerism has been studied by computation for a range of polyphenols such as resorcinol (1,3-dihydroxybenzene) and phloroglucinol (1,3,5-trihydroxybenzene).[308] In addition to the obvious favouring of enols associated with aromaticity, less obvious through-bond effects are also highlighted.

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

Organozinc halides have been used with a modified BINOL and $Ti(O^iPr)_4$ to carry out alkylation of aldehydes in up to 93% *ee*.[309] (ee)

An oxidative NHC catalysis has been developed for direct α-functionalization of simple aldehydes, with *ee* up to 99%, and good *de*'s, using a chiral NHC and a quinone oxidant.[310] (ee) (de)

Oxidation and Reduction of Carbonyl Compounds

Oxidation of Aldehydes to Acids

A kinetic study of the oxidation of six aliphatic aldehydes by tetrakis(pyridine) silver dichromate in DMSO indicates that it is first-order in both aldehyde and oxidant, and has a large primary kinetic isotope effect: 5.80 at 298 K (in the case of Me-CDO). Nineteen other organic solvents have also been studied.[311] Similar findings are reported using imidazolium fluorochromate in DMSO, again employing MeCDO for the primary KIE.[312]

Oxidation of 36 monosubstituted benzaldehydes by quinolinium fluorochromate was studied in this and 19 other solvents, with a large primary KIE for Ph-CDO,[313] and kinetic and thermodynamic parameters are given for oxidation of *para*-substituted benzaldehydes by imidazolium fluorochromate in the presence of tosic acid in various solvents.[314]

Rates of oxidation of benzaldehyde and of its 4-nitro derivative by pyridinium dichromate in aqueous acetic acid are first-order with respect to substrate and oxidant, and second-order in H^+.[315]

Kinetics of the oxidation of crotonaldehyde by tetraethylammonium chlorochromate have been measured in 50/50 aqueous acetic acid, including derivation of activation parameters.[316]

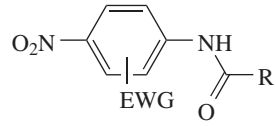
The Keggin-type phosphotungstic acid has been used to catalyse oxidation of substituted benzaldehydes by *N*-bromophthalimide in aqueous acetic acid, using mercury(II) as a scavenger.[317] Reaction rates are first-order in oxidant but fractional in aldehyde and phosphotungstate.

Oxidation of Aldehydes to Amides, Esters and Related Functional Groups

Alkali metal *t*-butoxides, hydrides and bis(TMS)amides efficiently catalyse Claisen–Tishchenko disproportionation of aldehydes to the corresponding carboxylic esters.[318] Potassium bases were more effective than sodium, and 18-crown-6 further accelerates the reaction. Kinetic studies suggest that the rate-determining step is a second-order concerted hydride transfer from a potassium hemiacetal to another molecule of aldehyde.

In an unusual oxidative amidation of tertiary amines (typically Ar–NMe_2) with aldehydes, R-CHO, amides are formed with the loss of an alkyl group … methyl in this case.[319] The amide product, Ar–N(Me)CO-R, is formed in good yield using iron(II) catalysis in refluxing acetonitrile, and *t*-butylhydroperoxide as oxidant.

A range of aldehydes, R-CHO, have been amidated using *para*-nitroaromatic azides, yielding anilides (**145**) in up to 94% yield.[320] Starting from the aniline, the azides are generated in THF at 0 °C, using *t*-Bu-ONO and TMS-N_3. Addition of aldehyde gives the amide, using a thiazolium salt and sodium *t*-butoxide as catalysts, apparently via catalytic radical transfer, with the azide dianion as intermediate.

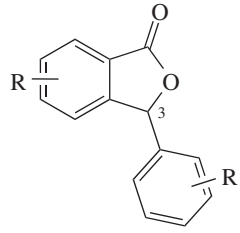


(**145**)

A mechanistic investigation of aerobic esterifications of aldehydes with alcohols using NHC catalysis indicates that it is the benzoin that undergoes oxidation, and not the Breslow intermediate, nor the NHC-aldehyde tetrahedral adduct.[321]

Aldehydes (R-CHO) undergo an *O*-selective addition of nitrosoarenes (O=N–Ar) catalysed by NHCs: this oxidative esterification yields R-CO_2–NHAr product in fair to good yields, with no C–N product [RCON(OH)Ar] in most cases.[322]

Substituted benzaldehydes can be self-coupled oxidatively to give C(3)-substituted phthalides (**146**), using a rhodium(III)/aniline dual catalysis.[323] The cascade *ortho*-C–H-activation/insertion/annulation sequence can also be used in a heterocoupling sense with a second aldehyde. The dual catalysis allows plenty of scope for generating an enantioselective version. (*ee*)



(**146**)

NHC's catalyse oxidative coupling of aldehydes (R^1-CHO) with *N*,*N*′-disubstituted carbodiimides (R^2-N=C=N-R^3) to give *N*-acylureas (R^1-$CONR^2$–CO–NHR^3) in ambient acetonitrile in the presence of air: yield is up to 93%, but is severely lowered under inert gas.[324] This and other control observations lead to a mechanism with carbene attacking aldehyde, giving a zwitterion (acyl anion) which attacks carbodiimide. However, some reaction flux may proceed via carboxylic acid or benzoin/acyloin routes.

Another oxidative synthesis of esters is described under the section titled 'Oximes'.

Baeyer–Villiger and Other Oxidation Reactions of Ketones

The regioselectivity of the BV (Baeyer–Villiger) reaction of cyclohexanone bearing α-methyl, α-fluoro- or α-trifluoromethyl substituents has been studied computationally.[325] The authors challenge the conventional understanding of migratory aptitude based on the ability to stabilize partial positive charge, that is, an effect on kinetic reactivity. While such an effect on the energy barrier appears to operate for CF_3, the CH_3 and F cases showed no difference in energy barriers, and structural stability operates in determining the most stable TS. The methyl case, in particular, shows a pronounced steric effect.

Benzaldehyde and isobutyraldehyde have been used as co-reductants in aerobic BV oxidation of cyclohexanone, catalysed by iron(III) porphyrins.[326] The dramatic difference in the yield of ε-caprolactone (96% for benzaldehyde and 11% for isobutyraldehyde) has been investigated kinetically, leading to elucidation of a mechanistic difference. The reaction with benzaldehyde involves a high-valent iron porphyrin, whereas the isobutyraldehyde version proceeds via peroxy isobutyric acid.

Kinetics of ruthenium(III)-catalysed oxidations of aliphatic ketones by *N*-bromosuccinimide in the presence of mercury(II) acetate have been measured in aqueous acid.[327]

Oxidation of pentan-3-one[328] and pentan-2-one[329] by iridium(III) chloride in aqueous perchloric acid has been studied in the presence of cerium(IV) perchlorate. Kinetic studies covered the range 293–308 K, with iridium in excess over cerium in excess over ketone. Kinetic order in each was determined, and for H^+. Ce^{4+} and $Ce(OH)^{3+}$ are implicated as catalytic species.

A short review describes a new transition-metal-free aerobic oxidative C–C cleavage of α-hydroxy ketones: a dimeric intermediate is implicated, with ^{18}O-labelling being used to probe the mechanism.[330]

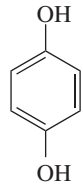
Cyclic acetone peroxides are an important class of home-made explosives, being easily prepared from household materials, but also highly unstable.[331] An experimental and DFT investigation of the uncatalysed reaction of acetone and hydrogen peroxide has identified key steps: (i) formation of the monomer, 2-hydroperoxipropan-2-ol, $HO–CMe_2–O–O–H$; (ii) polymerization and (iii) cyclization. DFT-generated reaction profiles match well with GC-MS, Raman and NMR observations over time.

Miscellaneous Oxidative Processes

The scope for catalysis by NHCs under oxidative conditions has been explored in a review (37 references), considering appropriate oxidants (inorganic, organic and dioxygen) consistent with carbenes.[332] (ee) (de)

The kinetics and mechanism of the oxidation of aromatic acetals by *N*-chloronicotinamide have been studied in acetonitrile.[333]

Nitrite (NO_2^-) catalyses mono-etherification of 1,4-hydroquinone (**147**) by methanol, via oxidation to the semi-quinone intermediate.[334] The reaction has been extended to other alcohols, and for substituted hydroquinones, reaction occurs exclusively at the less hindered phenol.



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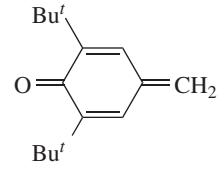
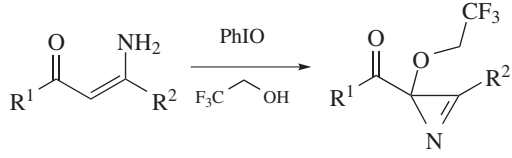


(**148**)

Butylated hydroxytoluene (BHT), a common anti-oxidant in drug formulations, can form a quinone methide (**148**) when oxidized.[335] Hydrolysis of this form has been studied over a range of pH in aqueous acetonitrile. Nucleophilic excipients in formulations may react with (**148**). The sole hydrolysis product is 3,5-di-*t*-butyl-4-hydroxybenzyl alcohol.

A range of enaminones and enamine carboxylic esters (**149**, R^1 = Ar, OMe; R^2 = Ar, alkyl, EtOCO) have been converted into highly functionalized trifluoroethoxylated 2*H*-aziridines (**150**), using iodosobenzene and trifluoroethanol (TFE).[336] This represents metal-free oxidative C–N and C–O bond formation. Evidence for a bis-TFE adduct of the promoter [i.e., Ph–I(O–CH_2CF_3)$_2$], and later enamine intermediates, is presented.



(**149**) (**150**)

For other reports of oxidation, see the sections titled ‘Acetals’ and ‘Glucosides’ above.

Reduction Reactions

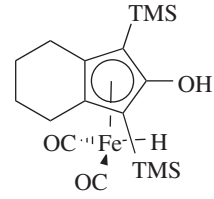
A simple protocol allows silver-catalysed hydrogenation of aldehydes in water: $AgPF_6$/40 atm H_2/*i*-Pr_2NEt (Hunig’s base)/100 °C gives up to 99% yield of alcohol in 24 h.[337]

A range of NHCs and bis-NHC-ruthenium complexes have been characterized and tested as catalysts for transfer hydrogenation of ketones in basic isopropanol.[338]

Use of ammonia borane ($H_3N{\rightarrow}BH_3$) to reduce ketones and imines has been studied by computational methods; evidence for concerted double-hydrogen transfer is advanced.[339]

Knölker’s catalyst (**151**) catalyses hydrogenation of ketones, and DFT calculations have identified five plausible mechanisms: two inner- and three outer-sphere. [340] One of the latter proved most viable, with the lowest free energy barrier, and also was consistent with kinetic results for acetophenone. It involves simultaneous proton and hydride transfer and suggests that further improvement will require simultaneous increase in polarization of CpO–H and Fe–H bonds.

Catalytic reductive amidation of hexanal with acetamide gives *N*-hexylacetamide, using (cyclooctadiene)rhodium(I) chloride dimer as catalyst, together with xantphos ligand and an acid co-catalyst.[341] NMR shows that acetamide adds nucleophilically to



(**151**)

hexanal, forming *N*-(1-hydroxyethyl)acetamide in equilibrium with both hexanal and the dehydrated unsaturated imides, with the presence of acid allowing all these species to equilibrate rapidly.

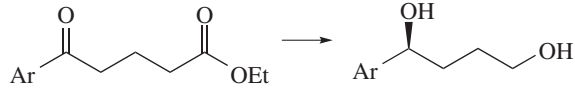
1,2-Bis(diphenylphosphino)ethane and its methane analogue have been reacted with a range of *ortho*- and *para*-benzoquinones, as well as *ortho*-naphtho-, phenanthrene- and acenaphtho-quinones.[342] A number of mechanisms are proposed to account for the variety of redox products formed.

While high crystallinity is often considered desirable in inorganic photocatalysts, ordered $CoMn_2O_4$ is a poor catalyst for hydrogen formation from methanol (in water).[343] In contrast, a highly disordered $Co_{1.28}Mn_{1.71}O_4$ phase is a good catalyst, even without co-catalysts present. Its wide absorbance range likely contributes to its efficiency, with strong absorbance over the entire visible spectrum, and also in the near-UV and -IR.

In a demonstration of a reductive amination in water, acetophenone reacts with anilines to give *N*-alkylated products, PhCH(Me)–NH–Ar, in high yield, using an iridium complex.[344] A bell-shaped pH-rate profile shows a maximum at ca 4–5: this may optimally protonate an imine intermediate, while leaving the ketone neutral. Excessively low pH would suppress imine formation. The reaction has been extended to other acetophenones and to acetone, and the aniline can be substituted with benzylamine or other alkylamines, and a test with a chiral amine gave >98% *de*. (*de*)

Stereoselective Reduction Reactions

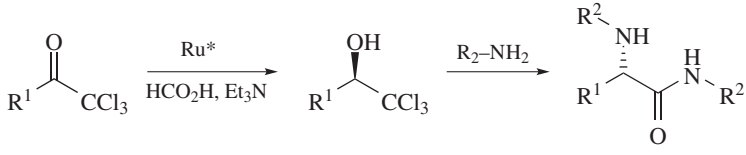
Chiral 1,5-diols (**153**) have been efficiently accessed by iridium-catalysed asymmetric hydrogenation of *δ*-aryl-*δ*-ketoesters (**152**).[345] A gas chromatographic study indicates initial ketone reduction, to the hydroxyl-ester. Loss of ethanol gives a *δ*-lactone intermediate, which is reductively reopened: this sequence is confirmed by generation of (**153**) when an authentic sample of the lactone is treated under the same conditions. (*ee*)



(**152**) (**153**)

Ruthenium(II) complexes containing a phosphine-sulfonate chelate catalyse hydrogenation of aryl ketones in fair to good *ee*, with significant co-catalysis by tertiary amines.[346] Key species have been characterized by X-ray crystallography and ^{1}H- and ^{31}P-NMR, including a ruthenium-hydride resting state and a -dihydride intermediate. (*ee*)

Trichloromethyl ketones (**154**) undergo smooth transfer hydrogenation in up to 98% *ee*, using a chiral ruthenium catalyst, to give the corresponding alcohol (**155**) in up to 97% yield.[347] Subsequent Jocic-type reaction with amines, again under mild conditions, gives chiral amino-amides (**156**).

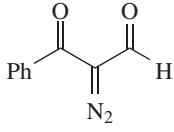


(**154**) (**155**) (**156**)

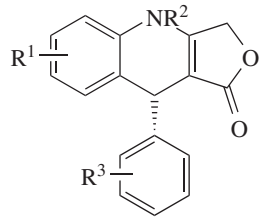
Other Reactions

The use of diazocarbonyls with acid catalysis under metal-free conditions has been reviewed (45 references), covering 1,3-dipolar cycloadditions, rearrangements, three-membered ring formation and Mannich-type and aldol reactions.[348]

Reactions of 2-diazo-3-oxo-3-phenylpropanal (**157**) with aldehydes and ketones of various types in the presence of triethylamine have been investigated, focussing on the electronic factors contributing to the chemoselectivities observed.[349]



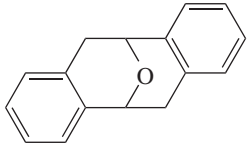
(**157**)



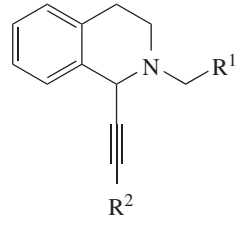
(**158**)

4-Aza-podophyllotoxins (**158**) have been prepared in a cascade reaction of tetronic acid with aldehydes and anilines.[350] A mechanistic investigation shows evidence for an electron-deficient aniline acting as a sacrificial component in the sequence.

Functionalized analogues of Kagan's ether (**159**) have been prepared via a one-pot cascade dimerization of *ortho*-alkynylbenzaldehydes in acetic acid, with aqueous HBF_4 catalysis.[351]



(**159**)

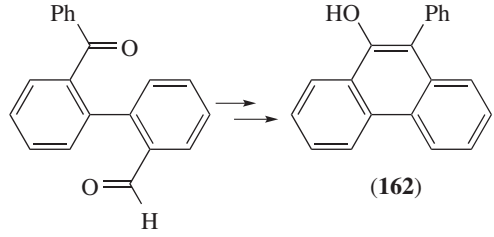


(**160**)

C(1)-Alkynylated tetrahydroquinolines (**160**) have been prepared from tetrahydroquinoline, an aldehyde (R^1-CHO) and an alkyne (R^2-C≡C–H), using copper(I) iodide at 50 °C in toluene.[352] The first two components are proposed to form an *exo*-iminium ion *in situ*, which isomerizes to the *endo*-iminium, which then adds copper acetylide. Alkynylation *can* take place at the *exo*-methylene, but up to 99% *endo*-selectivity is seen.

A computational study has been undertaken of the reaction between dimethyl perfluorododecanedicarboxylate and alkyl ketones, to give polyfluorinated tetraketones.[353]

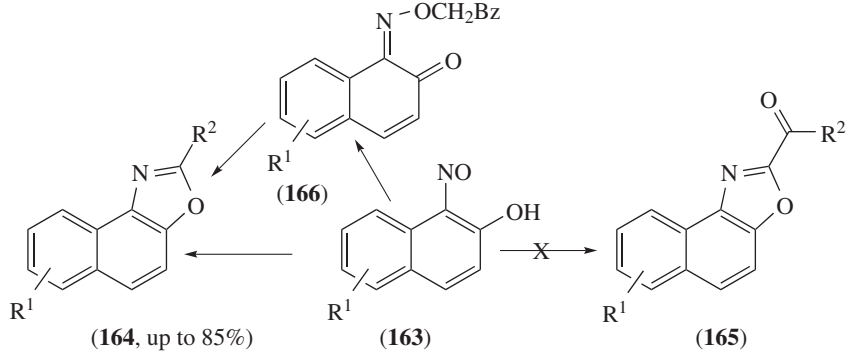
2′-Benzoyl-biphenyl-2-carbaldehyde (**161**) can be converted into a phenanthrol derivative (**162**), using tosyl hydrazide ($TsNHNH_2$) in toluene at 70 °C.[354] The reaction proceeds via selective formation of the *N*-tosylhydrazone at the aldehyde, followed by cyclization (using a strong base). The reaction is formally similar to a diazo-carbon



(**161**) (**162**)

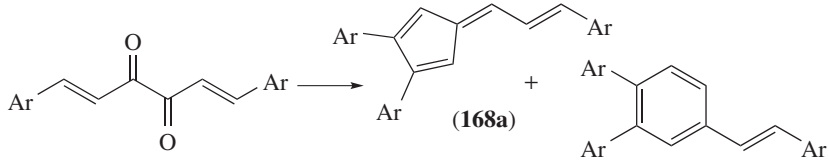
insertion, is generalizable to naphthols and hetereoatom-containing analogues and requires no catalyst.

1-Nitroso-2-naphthols (**163**) react with α-functionalized ketones, X-CH_2–COR^2 (X = Cl, Br, MsO, TsO, HO), under basic conditions to give exclusively 2-substituted naphtho[1,2-*d*][1,3]oxazoles (**164**) rather than ketones (**165**); that is, the reaction proceeds with an unexpected loss of the carbonyl group.[355] Strangely, using a reactant *without* carbonyl (e.g., $BrCH_2Ph$) or with an *extra* carbonyl (e.g., α-bromoacetophenone, $BrCH_2COCOPh$) gives the same product (i.e., **164**, R^2 = Ph). While the mechanism is not clear, it is proposed that (**163**), as its *O*-quinone oxime tautomer, reacts with α-bromoacetophenone to give oxime ether (**166**) – which can be isolated – followed by several intramolecular rearrangements, and concluding with the loss of formate.



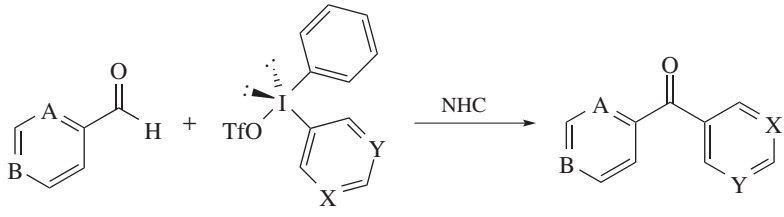
Another interesting arylation is described under the section titled 'Other Reactions'.

Cinnamils (**167**) undergo an unusual NHC-catalysed transformation to 2,3,8-triaryl vinyl fulvenes (**168a**), using two equivalents of sodium hydride, plus an *ortho*-terphenyl derivative (**168b**).[356] Crossover experiments employing two (different) cinnamil starters (**167**) have been used to probe the mechanism.



(**167**) (**168a**) (**168b**)

Complex heteroaryl ketones (**169**) have been prepared from heteroaldehydes (**170**) by exploiting the electrophilicity of diaryliodonium salts (**171**), with catalysis by a commercially available NHC.[357] The reaction works in DCM, at 0 °C or lower, in less than a day, using DMAP to generate the carbene and a protic additive (water or alcohol).



(**170**) (**171**) (**169**)

A mild metal-free nitrogenation of alkenes through C=C bond cleavage has been developed,[358] using inorganic nitrogen. Using phenyliodonium diacetate, $PhI(OAc)_2$, a styrene is converted into a benzonitrile, with the nitrogen being supplied by ammonium bicarbonate, and all in aqueous methanol at 36 °C, in 12 h. The corresponding benzaldehyde is proposed as an intermediate.

Unsymmetrical benzils, $Ar^1–COCO–Ar^2$, have been prepared via NHC-catalysed nucleophilic aroylation of *N*-phenylimidoyl chlorides, $Ar^1–C(Cl)=N–Ph$, by aromatic aldehydes ($Ar^2–CHO$), to give the imine, $Ar^1–C(=NPh)–CO–Ar^2$, followed by hydrolysis.[359] Conveniently done in one pot with sodium hydride in refluxing THF, the further *in situ* conversion of the benzils into 2,3-diaryl-quinoxalines and -pyrazines has been achieved by double-condensation with 1,2-diamines.

Pyrolysis of furfural under dilute and inert conditions yields (initially) furan and CO, by unimolecular decomposition.[360] Further processes produce a range of products including acetylene, formaldehyde and propyne. Benzaldehyde is more resistant to pyrolysis, eventually giving phenyl and hydrogen radicals plus CO, leading to benzene and CO as final products.

Aluminium chloride catalyses addition of amines to carbodiimides to give substituted guanidines, under mild solvent-free conditions.[361] *In situ* IR spectroscopy has been used to probe the mechanism.

Hartree/Fock- and MP2-calculations to the 6-311+G* level have been employed to study reaction of bromoform with cyclohexanone to give the dibromoepoxide, considering the alternatives of addition of dibromocarbene or tribromomethyl carbanion to the carbonyl.[362] Solvent effects are also explored.

The possible mechanisms of the cycloaddition of singlet silylenesilene ($H_2Si{=}Si$) and acetaldehyde have been probed by computation.[363]

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