

Reactions of Aldehydes and Ketones and their Derivatives

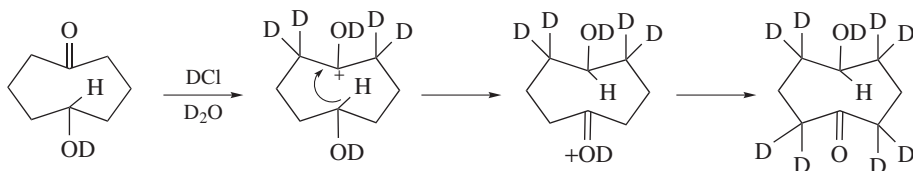
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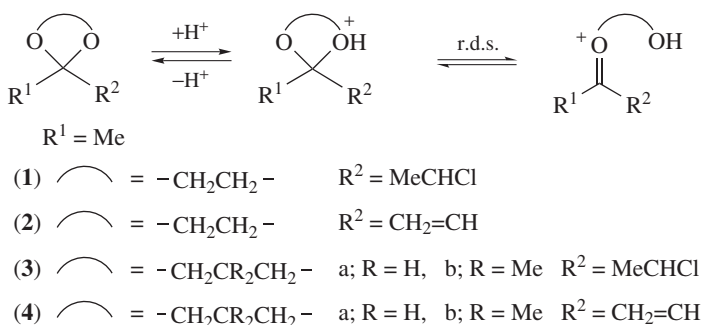
Formation and Reactions of Acetals and Related Species

An acid-catalysed 1,5-hydride shift via a tight six-membered ring transition state, of similar overall conformation to the starting structure, has been proposed to account for the deuterium exchange of eight out of twelve methylene hydrogen atoms of 5-hydroxycyclooctanone under acidic (Scheme 1) and basic conditions in D_2O , as revealed by 1H NMR measurements.¹ The reaction has been analysed by quantum chemical calculations and activation barriers have been determined for the catalysed and uncatalysed reactions.



SCHEME 1

Conformational, stereoelectronic, and resonance effects on the $A1$ mechanism have been invoked to explain the effects of ring size and substituents on rates of acid-catalysed hydrolysis of five- and six-membered ring cyclic diol-derived ketone acetals in mixtures of THF- d_8 and H_2O with DCl. The results for (1)–(4) reveal resonance effects for (2) and (4) and substantial stereoelectronic effects on ring conformation whereby alignment of the equatorial or pseudo-equatorial lone pair with the σ^* orbital of the breaking C–O bond can explain why a five-membered ring ethanediol-derived acetal strongly resembles a six-membered ring 2,2-dimethylpropanediol-derived acetal and why the corresponding cyclic propanediol-derived acetals hydrolyse faster than both of these.²

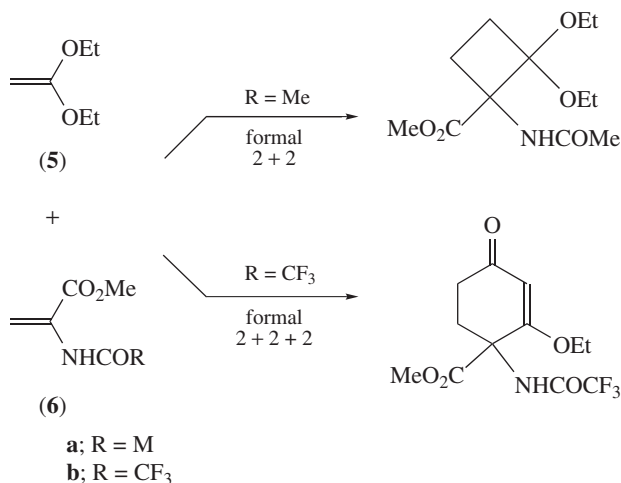


SCHEME 2

Chemoselective, quantitative transacetalization of aldehyde O,O - and O,S -cyclic acetals into the corresponding S,S -acetals in the presence of ketones or their acetals

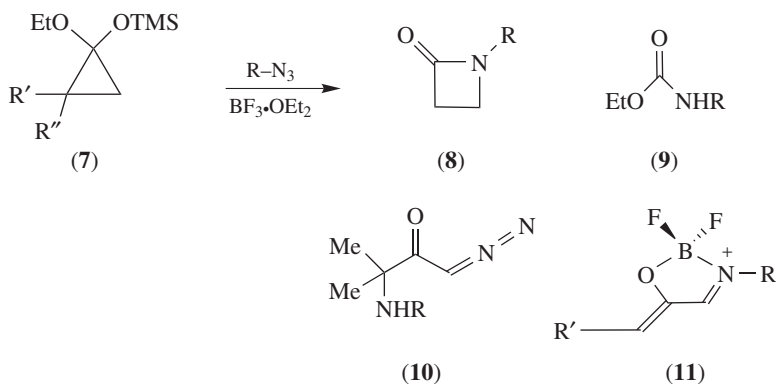
and oxathioacetals has been reported.³ The reactions were promoted using RSH or HSCH₂CH₂SH in DMF at room temperature, with cyanuric acid as the catalyst.

Ketene diethyl acetal (**5**) has been found to undergo Michael–Dieckmann-type reactions with 2-acylaminoacrylates (**6a**) and (**6b**) to give formal 2 + 2- and 2 + 2 + 2- cycloaddition products, respectively (Scheme 3).⁴ The results have been interpreted theoretically in terms of a polar stepwise mechanism.



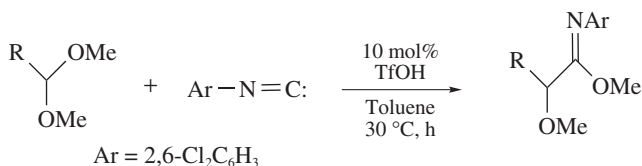
SCHEME 3

A study of the Lewis acid-mediated reactions of cyclopropanone acetals (**7**) with alkylazides has established that the product(s) obtained are markedly dependent on ring substituents R', R'', giving (**8**) and (**9**) [from azide addition to the carbonyl, followed by ring expansion or rearrangement, respectively], where R', R'' = H,H, (**10**) [from C(2)–C(3) bond cleavage of the corresponding cyclopropanone, giving oxyallyl cations that are captured by azides], where R', R'' = Me,Me, (**11**) [also the result of



C(2)–C(3) bond rupture, azide capture, and loss of nitrogen] where $R', R'' = \text{Ar}, \text{H}$, and **(8)** and **(11)**, where $R', R'' = n\text{-C}_6\text{H}_{13}, \text{H}$. Reasons for the contrasting behaviour have been discussed.⁵

The Brønsted acid-catalysed formal insertion of an isocyanide into a C–O bond of a diverse array of acyclic and cyclic acetals (Scheme 4) can be achieved in the presence of nitro, cyano, halogen, ester, and alkoxy groups, but the course of the reaction is highly dependent on the structure of the isocyanide; an electron-deficient aryl isocyanide is required to obtain the monoinsertion product, otherwise double insertion of two aryl isocyanide molecules may occur.⁶ The reaction of *t*-octyl isocyanide also induces a double incorporation, but the subsequent acid-mediated fragmentation leads to the 2-alkoxyimidoyl cyanide. The monoinsertion products, α -alkoxyimidates, can readily be hydrolysed to α -alkoxy esters, realizing the formyl carbonylation of an acetal.



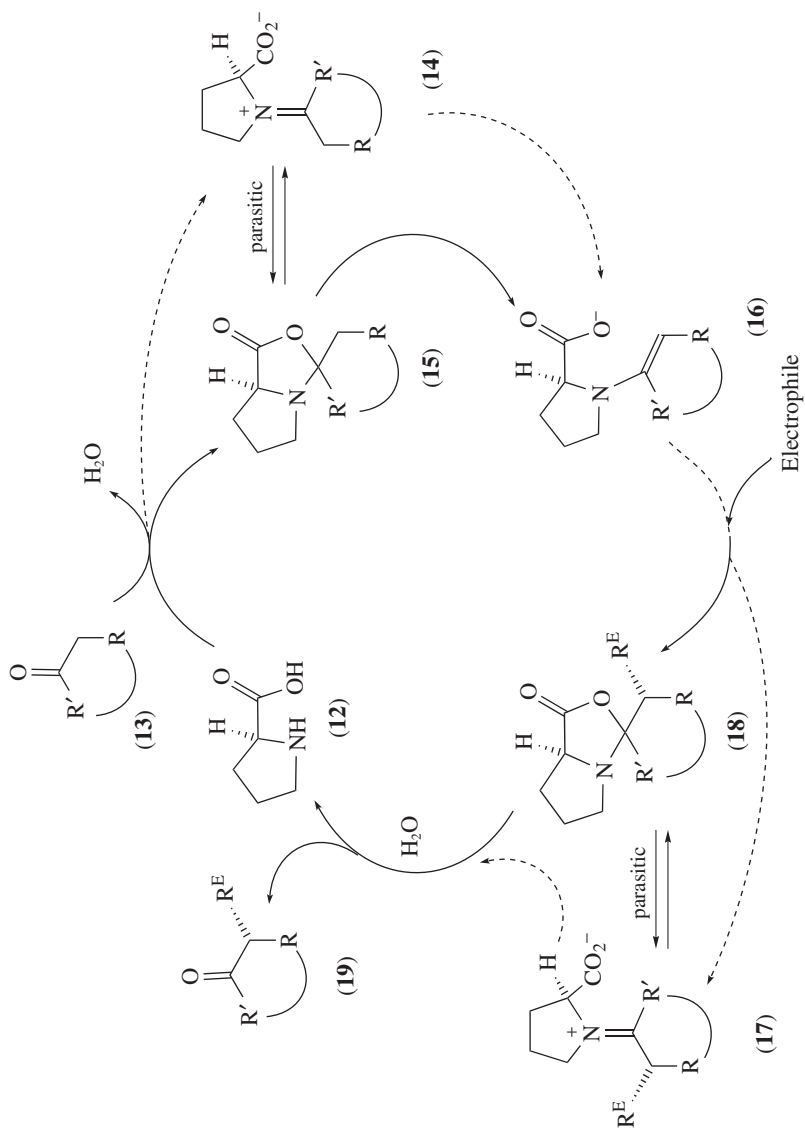
SCHEME 4

A detailed kinetic study of the pH dependence of the multistate reaction of 6-hydroxy-4'-(dimethylamino)flavylium hexafluorophosphate in aqueous solutions has revealed relatively slow hydrative formation of intermediate hemiketal species, from which *cis*- and *trans*-chalcones are obtained.⁷ Comparison with other flavylium compounds shows that the hydration process is affected by the amino group and that the hydroxyl group is implicated in tautomerization and isomerization reactions.

An experimental and computational (quantum chemical and FMO) study of ring-chain tautomerism of simplified analogues of oxidized and reduced isoniazid–NAD(P) adducts has identified when cyclic hemiamidal and keto-amide chain forms will predominate, respectively; the dependence on the aryl ring and on solvent polarity has been discussed.⁸

Pyrrolidine (20 mol%)-catalysed aldol reaction of trifluoroacetaldehyde ethyl hemiacetal with ketones or aldehydes at room temperature has been shown to afford the aldol products in good to excellent yields (up to 95%) and with much higher catalytic activity than piperidine. It is suggested that the reaction proceeds by rate-determining formation of intermediate enamine which is present in extremely low concentration during the reaction; the asymmetric aldol reaction with cyclohexanone catalysed by L-proline derivatives was also discussed.⁹

Scheme 5 depicts the generally accepted cycle (via the 'outer route' depicted by the dashed arrows) of proline-catalysed reactions of aldehydes and ketones with electrophiles, in which oxazolidinones **(15)** and **(18)** appear to play a role only as 'parasitic' species not involved in any steps for formation of product or reactive intermediates. A detailed study of oxazolidinones has now revealed direct evidence of the two



SCHEME 5

hitherto putative participants [iminium ion (**14**) and enamine (**16**)] in this catalytic cycle.¹⁰ However, the commonly accepted mechanism of the stereoselective C–C or C–X bond-forming reaction with the electrophile has been challenged. An alternative model has been proposed, whereby oxazolidinones play a pivotal role in the regio- and diastereo-selective formation of the intermediate enamino acid (**16**) [from (**15**) by elimination] and in the subsequent reaction with an electrophile [as the product (**18**) of *trans*-addition with lactonization]. (de)

Reactions of Glucosides and Nucleosides

The β/α selectivity found on coupling alcohols [on preactivation with 1-benzene-sulfinylpiperidine and $(\text{CF}_3\text{SO}_3)_2\text{O}$] with a series of 4,6-*O*-benzylidene-protected 2-*O*-benzyl gluco- and manno-pyranosyl thioglycosides, bearing 2-deoxy-2-fluoro and 3-deoxy-3-fluoro substituents, was found in all cases to be lower than for the corresponding simple 4,6-*O*-benzylidene 2,3-di-*O*-benzyl gluco- and manno-pyranosyl thioglycosides.¹¹ The high β -selectivity observed for 4,6-*O*-benzylidene 2,3-di-*O*-benzylmannopyranosyl donors has therefore been ascribed to compression of the O(2)–C(2)–C(3)–O(3) torsion angle on going from the intermediate covalent glycosyl triflate to the oxacarbenium ion, rather than to the electron-withdrawing effect of the C(3)–O(3) bond. (de)

Using three approaches (LFER analysis, X-ray crystallography, and computational modelling) it has been shown that NAG–thiazoline is a transition-state (TS) analogue for the human *O*-GlcNAcase-catalysed hydrolysis of β -glucosaminides whereas PUGNAc is either a poor TS analogue or a serendipitous binding inhibitor.¹² The study suggests that glycosidase inhibitors should be designed to exploit the late transition state poise of the *O*-GlcNAse-catalysed reaction, which features significant nucleophilic participation and little involvement of the leaving group.

Reactions of Ketenes

A DFT study of the nucleophilic addition of water to cyano- and methylcarboxyketene has been conducted at the B3LYP/6–31++G** level of theory.¹³ Results for the latter reaction in both the gas and solvated phase agree with the view (based on previous experimental data for ketenes obtained from malonates) that addition of water or alcohols occurs by a concerted pseudocyclic mechanism. The results are also in agreement with experimental data for addition to cyanoketene, for which solvent is essential since reaction occurs through a zwitterionic intermediate.

A detailed study of the effect of temperature on the stereoselectivity of Staudinger cycloaddition reactions between ketenes ($\text{R}^1\text{CH}=\text{C}=\text{O}$) and imines ($\text{R}^2\text{CH}=\text{NR}^3$) has revealed a notable dependence on the ketene substituent.¹⁴ Eyring plots are usually non-linear, but this does not necessarily indicate a change of the stereoselectivity-determining step. For most Staudinger reactions, the plots are concave, exhibiting isoinversion, and *cis*-selectivity decreases with increase in temperature. However, intramolecular p - π and π - π interactions between the ketene substituents and imine C-substituents complicate the behaviour. The temperature-dependent stereoselectivity (de)

of Staudinger reactions involving cyclic imines with different ketenes is not a consequence of competition between *exo* and *endo* attack on the ketene, but related to changes in rates of ring closure and isomerization of zwitterionic intermediates generated from the ketenes and imines during the reaction.

The highly reactive indanedione ketene has been found to cyclodimerize in the absence of nucleophiles to give a corresponding tetraoxo spiro-oxetanone in quantitative yield; reactions of this β -lactone with amines may be exploited in organic synthesis.¹⁵

Formation and Reactions of Nitrogen Derivatives

Imines: Synthesis, Tautomerism, Catalysis

A review of the history and perspective of chiral organic catalysts¹⁶ has focused on areas of iminium, enamine, Brønsted acid, and phase-transfer catalysis. Recent advances in the formation of carbon–nitrogen double bonds by the aza-Wittig reaction of phosphazene derivatives with several carbonyl compounds have been reviewed.¹⁷

Low loadings of a chiral copper catalyst have been used to promote highly diastereo- and enantio-selective addition of enesulfonamides to α -ketoaldehydes and azodicarboxylates; the product sulfonylimines $[R^3COC^*H(OH)C^*HR^2CR^1=NSO_2Ar]$ could be reduced diastereoselectively to biologically important chiral sulfonamides.¹⁸

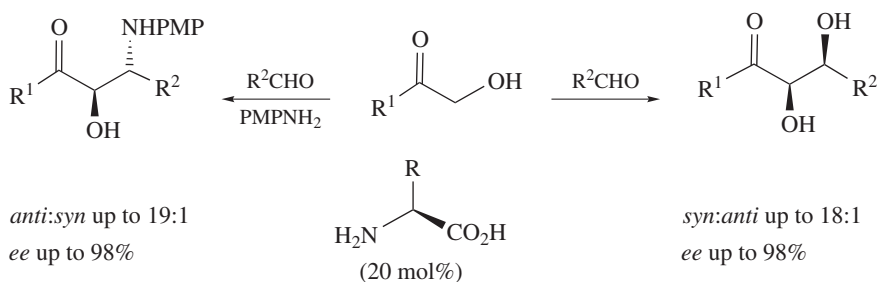
The kinetics and mechanism of the chain reaction of *N*-phenyl-1,4-benzoquinone monoimine with 2,5-dimethyl-1,4-hydroquinone in chlorobenzene have been studied and the product 2,5-dimethylquinone has been found to exert only a weak inhibiting effect; comparison with previous results for reaction of the imine with the 2,5-di-*t*-butyl-1,4-hydroquinone revealed a marked substituent effect on the kinetic parameters for this new class of chain reaction.¹⁹

The Mannich and Nitro-Mannich Reactions

Reviews have addressed ‘asymmetric catalysis for construction of quaternary carbon centres: nucleophilic addition on ketones and ketimines’,²⁰ and ‘organocatalytic asymmetric Mannich reactions: new methodology, catalyst design, and synthetic applications’.²¹

The *R*- and *S*-forms of the chiral product of an asymmetric Mannich reaction between propanone and *p*-MeOC₆H₄N=CHCO₂Et have been found to act as chiral catalysts for their own formation (autocatalysis); the catalytic cycle is believed to involve equilibria between hydrogen-bonded substrate–product complexes.²²

Organocatalysis has been used for the first time to form highly enantiomerically enriched *anti*-1,2-amino alcohols and *syn*-1,2-diols (Scheme 6) through direct asymmetric Mannich, Mannich-type, and aldol reactions involving unmodified α -hydroxy ketones in reactions catalysed by primary amine-containing amino acids.²³ The reactions exploit (*Z*)-enamines of α -hydroxy ketones in their bond-forming transition states and support the view that amino acid catalysis may have played a key role in asymmetric synthesis of the molecules of life.



SCHEME 6

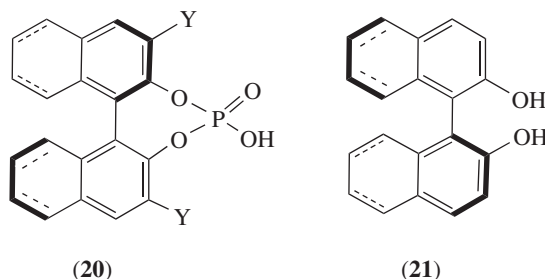
Amino acids have also been used to catalyse asymmetric *anti*-selective two-²⁴ and three-component²⁵ Mannich reactions of cyclohexanone and *O*-benzylhydroxyacetone, respectively, in aqueous solution, and reactions of *O*-TBS-hydroxyacetone with various *N*-tosylimines²⁶ in toluene at room temperature; good to excellent yields and very high diastereo- and enantio-selectivities (up to 99% *ee*) were reported in each case. (ee)

Addition of unmodified aldehydes to *N*-Boc-protected arylimines, catalysed by proline, has provided a means of one-pot asymmetric synthesis of Boc-protected β -amino aldehydes, β -amino acids, and γ -amino alcohols with excellent chemo- and enantio-selectivities in high yields with up to >19:1 *dr* and 93–99% *ee*.^{27,28} Proline has also been found to catalyse direct asymmetric α -aminomethylation of unmodified aldehydes on reaction with the formaldehyde-derived imine precursor MeOCH₂NBn₂.²⁹ Proline derivatives and chiral pyrrolidines were also screened for catalytic activity and the corresponding dibenzyl-protected γ -amino alcohols HOC*HRCH₂NBn₂ were isolated in high yields with up to 98% *ee* after *in situ* reduction. Thus, imine equivalents with a readily removable protective group can be used in organocatalytic Mannich-type reactions. Transition-state models have been proposed to account for the enantioselectivity observed. (ee)

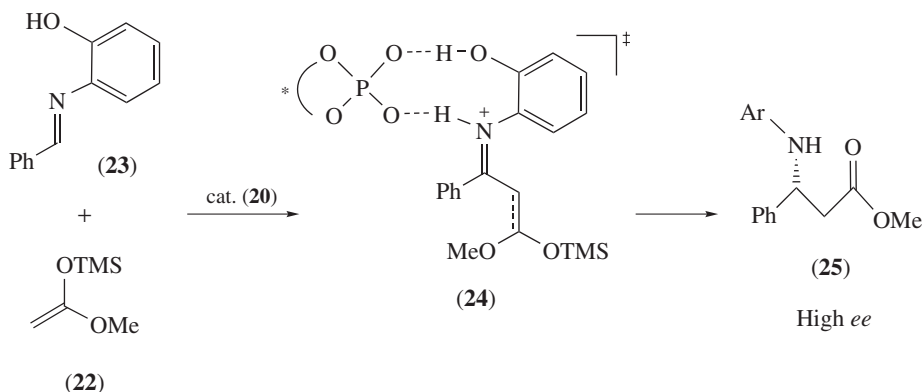
Conversion of aromatic and aliphatic aldehydes (RCHO) into optically active carbamate-protected aryl- and alkyl- β -amino acids has been achieved by a highly enantioselective Mannich reaction with *in situ* generation of otherwise unstable *N*-carbamate-protected imines (RCH=NBoc) from stable α -amido sulfones [RCH(SO₂Ar)NHCO₂R'], catalysed by a *Cinchona* alkaloid as organic catalyst without recourse to PTC.³⁰

Exploration of the catalytic efficacy of BINOL and its derivatives in Mannich reactions continues.^{31–34} Asymmetric catalysis by chiral Brønsted acids has been demonstrated in direct Mannich reactions promoted by BINOL-derived phosphoric acids (**20**) (cyclic diesters, where only one proton per catalyst is available).³¹ Computational and experimental studies have now revealed that the stereoselection is a consequence of exothermic formation of simple 1:1 H-bond associates between the bulky chiral catalyst and Boc-protected imines, thereby enantioselectively restricting the trajectory for attack of the nucleophile under kinetic control. Various phosphoric acids, prepared from BINOL and its H₈-BINOL derivatives (**20**), have been evaluated for catalysing the direct Mannich reaction;³² it has been found that reactions of cyclic (ee)

ketones with a wide range of aldimines occur in high yields with high *anti* selectivity (up to 98:2 *dr*) and excellent enantioselectivity (up to 98% *ee*) even in the presence of truly catalytic amounts of the phosphoric acid. (de)
(ee)



Mannich-type reactions of ketene silyl acetals (**22**) with aldimines (**23**) catalysed by (*R*)-BINOL (**20**) form β -amino esters (**25**) with good *syn* diastereoselectivity and high enantioselectivity (up to 96% *ee*), the best results being obtained where Y = 4-NO₂C₆H₄.³³ The *N*-2-hydroxyphenyl group of (**23**) is a requirement and density functional calculations (BHandHLYP/6-31G*) support a dicoordination pathway (rather than monocoordination alternatives) through a zwitterionic and nine-membered cyclic transition state (**24**) which favours *re*-facial selectivity, since *si*-facial attack is subject to steric hindrance by 3,3'-aryl substituents. (de)
(ee)

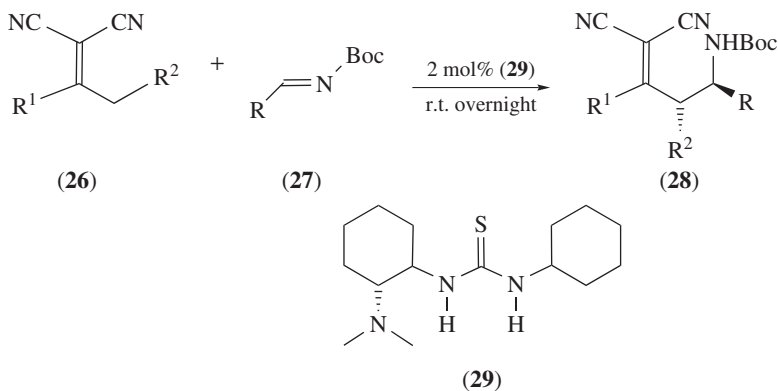


SCHEME 7

(*S*)-H₈-BINOL (**21**) has been identified as the optimal catalyst for formation of β -aminoaryl ketones in good yield and enantiomeric excess by Mannich reaction, in toluene at -30°C , between *N*-Boc imines (ArCH=NBoc) and morpholinoenamines derived from acetophenone.³⁴ (ee)

Direct-type Mannich reactions of amides R²CHCON(Boc)C₆H₄OMe-*o* with aldimines R¹CH=NP(O)Ph₂, using barium phenoxide as catalyst affords the expected

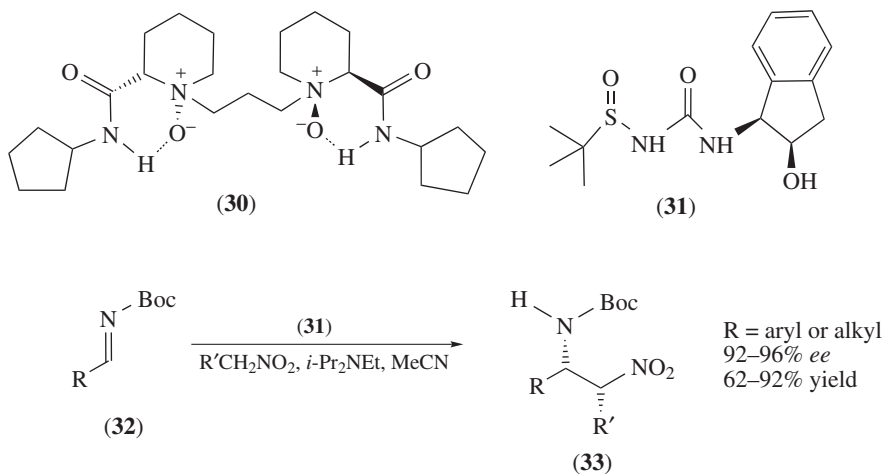
adducts with high *anti* selectivities (*syn:anti* up to 8:92).³⁵ The first direct asymmetric vinylogous Mannich reaction of α,α -dicyanoalkenes (**26**) and *N*-Boc-aldimines (**27**) has been promoted regioselectively by a thiourea-derived organocatalyst (**29**) (2 mol%, in toluene at room temperature) to give adducts (**28**) with high *de* (>99%) and *ee* (96–>99.5%).³⁶ The adducts have been formed using a broad array of substrates and can easily be converted to enantiomerically pure δ -amino acids.



SCHEME 8

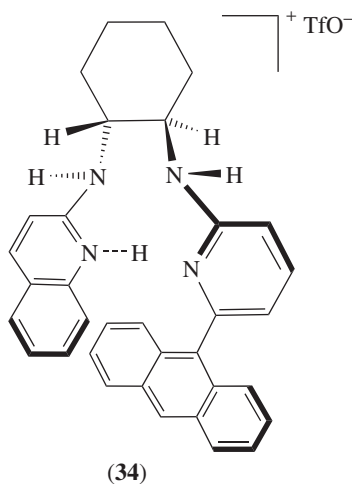
A multiparameter Koppel–Palm equation has been used to correlate the solvent dependence of the second-order rate constants found for Mannich reaction between methanal and butanal promoted by diethylamine in hydrophobic solvents;³⁷ solvent polarity, self-association, and electrophilic solvation power are important factors.

N,N-Dioxide–(Cu) complexes formed *in situ* from **(30)** and CuOTf have been used to catalyse the aza-Henry addition reaction of nitromethane to *N*-tosylaldimines, promoted by *i*-Pr₂NEt as base. The nitronate and imine are believed to associate with the



complex such that the former is positioned on the *Re*-face of the latter prior to enantioselective C–C bond formation (up to 93% *ee*), to give $\text{RC}^*\text{H}(\text{NHTs})\text{CH}_2\text{NO}_2$ in yields up to 99%.³⁸ Aza-Henry reactions have also been promoted by *N*-sulfinylureas [e.g. (31)], a new class of organocatalysts in which the sulfinyl group serves both as an acidifying agent and as a chiral control element.³⁹ The hydroxyl group of (31) was essential for the high enantioselectivity observed and changing the sulfinyl stereochemistry from *R* to *S* was disadvantageous. High enantioselectivity has been achieved not only for aromatic *N*-Boc-aldimine substrates (32, R = Ar) but also for aliphatic *N*-Boc-aldimines for which H-bonding catalysis has not been demonstrated previously. High enantioselectivities are reported for $\text{R}'\text{CH}_2\text{NO}_2$ having $\text{R}' = \text{H}$, Me and Ph and for unbranched and β -branched imine substrates.

Chiral proton catalysis, by unsymmetrical bis(amidine) complex (34), has also been reported for highly *anti*-diastereoselective and enantioselective (87–95% *ee*) additions of nitroacetic acid esters ($\text{NO}_2\text{CH}_2\text{CO}_2\text{R}$, R = Me, Et, Bn, *t*-Bu) to a range of ring substituted *N*-Boc-benzaldimines.⁴⁰



Nucleophilic addition of the masked acyl cyanide reagent dicyanomethyl *t*-butyldimethylsilyl ether $[(\text{CN})_2\text{CHOTBS}]$ to optically active *t*-butanesulfinimides ($\text{RCH}=\text{NSOBU-}t$) affords α -amino acid precursors in excellent yields and with high diastereoselectivities.⁴¹

Addition of Organometallics

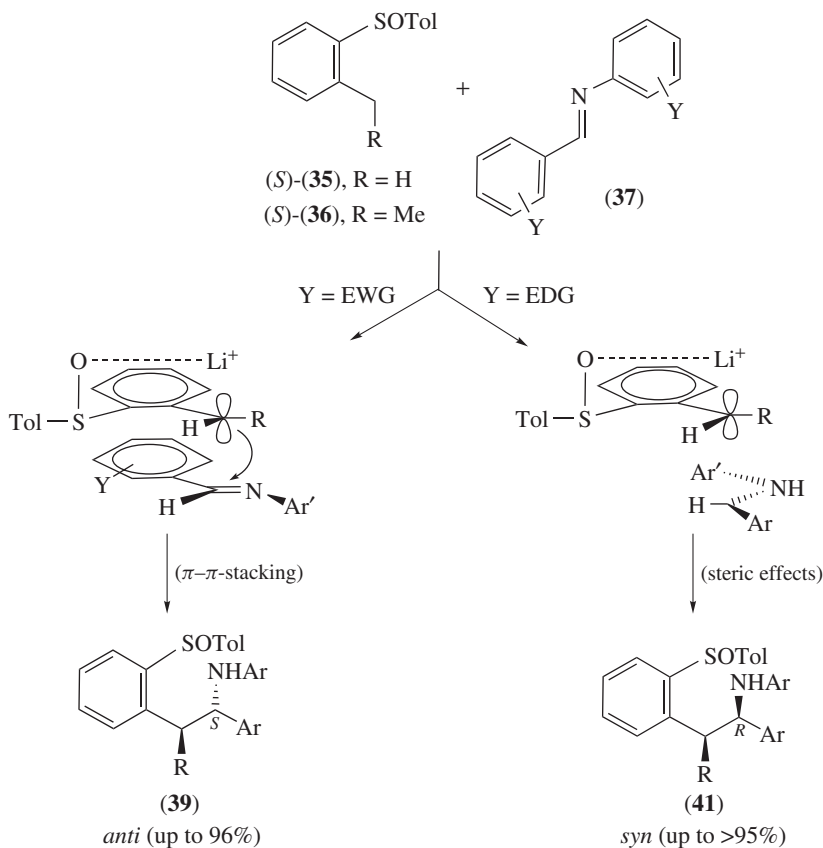
The reaction rates and yields of addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl)- and *N*-(benzenesulfonyl)-imines is improved markedly by a catalytic amount of a nickel complex such as $\text{Ni}(\text{acac})_2$ (0.1–5.3 mol%).⁴² Enantioselective addition of RZn to *N*-(diphenylphosphinoyl)imines has been achieved with up to 92% *ee* (R = Me, Et, *i*-Pr, *n*-Bu) in the presence of 0.5 equiv. of commercially

available *N*-benzyl-1-prolinol.⁴³ Reactions of such *N*-protected aromatic imines with Et_2Zn in toluene at room temperature have been promoted by chiral oxazoline ligands (prepared from aspartic acid) with up to 95% *ee* and 85% yield.⁴⁴

Other Alkylations, Arylations, and Allylations of Imines

The past decade has witnessed remarkable developments in the field of catalytic asymmetric iminoalkylation; these achievements have been reviewed.⁴⁵

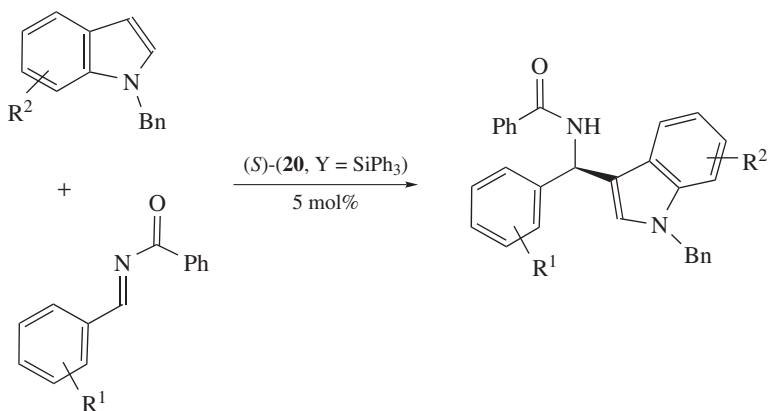
N-Arylarylideneamines (**37**) react with sulfinylbenzyl carbanions derived from 2-(*p*-tolylsulfinyl)toluenes (*S*)-(**35**), *R* = H and (*S*)-(**36**), *R* = Me to give epimeric mixtures at C(1) of 1,2-diarylethyl- and 1,2-diarylpropyl-amine derivatives, respectively, exhibiting at C(2) the same *S* configuration (completely controlled by the sulfinyl group).⁴⁶ The configuration at C(1) depends on the electron density of the ring adjacent to the iminic carbon atom and this can be modulated by π - π stacking interactions with the ring joined to the carbanionic centre. Thus, the stereoselectivity can be controlled by using appropriate substituents to modify the acceptor quality of the aryldenamine



SCHEME 9

ring; the highly selective formation of C(1) with *R* configuration is promoted by electron-donating groups since the stacking interaction is insufficient to overcome steric repulsion.

A highly enantioselective addition (90–97% *ee*) of *N*-benzylindoles to *N*-acylimines has been promoted organocatalytically by a hindered binol derivative (*S*)-(20, Y = SiPh₃) in high yields (89–99%) (Scheme 10);⁴⁷ the substrate versatility and the ease of removal of the protection from both nitrogens are notable. (ee)



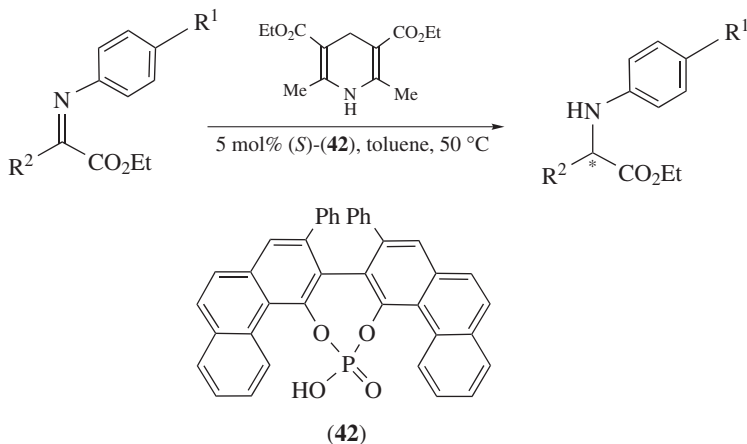
SCHEME 10

Asymmetric addition of alkynes to imines has been promoted: by copper(I)-bis(oxazoline) in water (up to 97% *ee*), using Ar¹CH=NR² and phenylethyne;⁴⁸ in one pot using Me₂Zn and terminal alkynes in combination with various aldehydes and *o*-methoxyaniline, in the presence of non-covalent recoverable chiral auxiliaries (enantiopure β -amino alcohols derived from norephedrine, giving up to 97% *ee*);⁴⁹ by diastereoselective addition of alkynyldimethylaluminium compounds to *N*-*p*-tolylsulfinylimines to give protected chiral propargylamines *p*-Tol-S*ONHC*HR¹ C=R² with high diastereoselectivity (up to 99% *de*), which is opposite to that obtained with lithium acetylide (as a probable consequence of chelation of both the N and O of sulfilimines to two different molecules of the organoaluminium reagent);⁵⁰ and by enantioselective reaction (*er* up to 96) of terminal alkynes with PG–N=CHCO₂R under the dual catalytic influence of a metal salt of a chiral phosphoric acid (20, Y=Ar).⁵¹ (ee)
(de)
(ee)

Reduction of Imines

Enantioselective hydrosilylation (by HSiCl₃) has been achieved for a broad range of ketimines using an L-proline-derived C₂-symmetric tetramide as a Lewis base catalyst to give up to 95% yield of R¹R²C*HNHAr with up to 86% *ee*,⁵² and for *N*-aryl- and *N*-benzyl-ketimines catalysed by chiral *N*-picolinoylamino alcohols to give secondary amines ArRC*HNHPG with up to 95% *ee*.⁵³ (ee)

Reduction of a range of α -imino ester substrates (derived from substituted aryl and alkyl keto esters) to the corresponding α -amino esters by Hantzsch ester has been promoted enantioselectively by chiral phosphoric acid catalysts such as BINOL acids (**20**); *ees* of 94–99% were achieved using the vaulted compound (**42**) derived from VANOL (Scheme 11).⁵⁴ (ee)



SCHEME 11

Iminium Species

Iminium chemistry has featured in a review of the history of chiral organic catalysts.¹⁶ (ee)

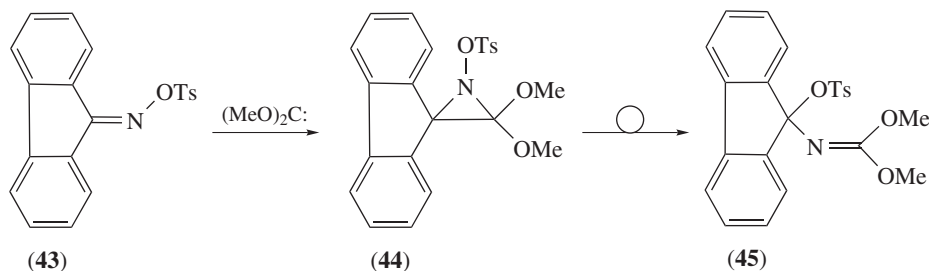
Activation parameters have been reported for C–C coupling reactions of silylated bis(oxy)iminium ions with a series of reference nucleophiles, and electrophilicities of the iminium species have been estimated as a guide to coupling behaviour.⁵⁵

Iminium ions, generated *in situ* from the corresponding *N,O*-acetals, have featured as electrophiles in a Morita–Baylis–Hillman-type reaction with a wide range of Michael acceptors, under the asymmetric influence of a chiral sulfide.⁵⁶ (ee)

Other Reactions of Imines

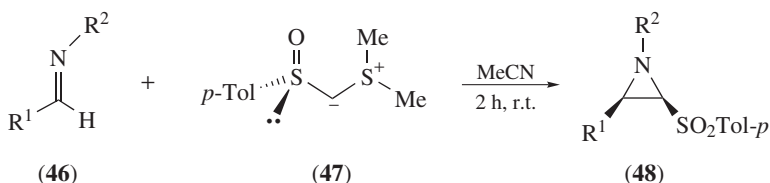
Conversion of *N*-(9*H*-fluoren-9-ylidene)-4-methylbenzenesulphonamide (**43**) to carbonimidoate derivative (**45**) on reaction with dimethoxycarbene (DMC) is believed to proceed by rearrangement of the intermediate aziridine cycloadduct (**44**); the corresponding benzylidene imine does not react with DMC under comparable conditions.⁵⁷

The reaction profile for aziridination of aldimine $\text{MeHC}=\text{NCO}_2\text{Me}$ by substituted sulfur ylides ($\text{Me}_2\text{S}^+\text{CH}^-\text{R}$) has been found, by density functional studies, to be highly dependent on the nature of the ylidic substituent.⁵⁸ Thus, diastereoselectivity (cisoid addition leading to *trans*-aziridines via *anti*-betaine) is controlled by the initial addition step for semistabilized ylides but the barrier for the elimination step holds the key for stabilized ylides. (de)



SCHEME 12

In order to obtain enantiomerically pure 2-substituted aziridines for versatile use in organic synthesis, a new type of chiral sulfur ylide, with an enantiopure sulfinyl group bound to ylidic carbon, has been reacted with *N*-tosylimines with full enantio- and diastereo-selectivity (Scheme 13); transoid approach of the ylide leads to *cis* aziridines (easily desulfinylated) via *syn*-betaine.⁵⁹ (ee) (de)



SCHEME 13

Asymmetric aziridination of *N*-*t*-butylsulfonylimino ester ($\text{EtO}_2\text{CH}=\text{NSO}_2\text{Bu-}t$) by chiral cyclic and acyclic aminosulfoxonium ylides $[\text{R}^1\text{R}^2\text{C}=\text{CHC}^-\text{S}^{*+}(\text{O})(\text{NMe}_2)\text{Ph}]$ forms the corresponding alkenylaziridine carboxylates with medium to high diastereo- and enantio-selectivity.⁶⁰ (ee) (de)

The Vilsmeier reagent ($\text{Me}_2\text{N}^+=\text{CHCl Cl}^-$) has been shown to act as a convenient activator for the one-step Staudinger reaction between imines and substituted ethanoic acids to give β -lactams under mild conditions.⁶¹

Acetyl cyanide has been used, in the presence of Jacobson's chiral catalyst, to form α -amidonitriles by asymmetric acylcyanation of aromatic and aliphatic *N*-benzylimines by an acyl-Strecker-type reaction in toluene at -40°C .⁶²

A chiral L-piperidinamide-derived *N,N*-dioxide generated *in situ* has been used to promote enantioselective (up to 92% *ee*) Strecker reaction of phosphinoylketoimines $[\text{R}^1\text{R}^2\text{C}=\text{NP}(\text{O})\text{Ph}_2]$ with TMSCN , in toluene under metal-free conditions, to give $\text{R}^1\text{R}^2\text{C}^*(\text{CN})\text{NHP}(\text{O})\text{Ph}_2$ from which α -aminonitriles are obtained; the dioxide catalyst can be recycled.⁶³ (ee)

A catalytic cycle has been suggested to account for a smooth cross-coupling reaction of aromatic aldehydes (R^1CHO) with unactivated imines ($\text{R}^2\text{CH}=\text{NR}^3$) to give α -amino ketones ($\text{R}^1\text{COCHR}^2\text{NHR}^3$), under the catalytic influence of a thiazolium-derived *N*-heterocyclic carbene.⁶⁴

The unexpected formation of stable 1:1 complexes on reaction of imines with *N*-iodosuccinimide has been reported.⁶⁵

Oximes, Hydrazones, and Related Species

Enantioselective borane reduction of *O*-benzyloxime ethers to primary amines has been achieved in up to 99% *ee* using BH_3 in THF catalysed by spiroborate esters derived from nonracemic 1,2-amino alcohols and ethylene glycol.⁶⁶ (ee)

The homogeneous elimination kinetics of thermal decomposition of benzaldoxime in the gas phase (to give PhCN and H_2O) at 350–400 °C and 56–140 Torr suggest that the rate-determining step features a concerted, semi-polar, four-membered cyclic transition state.⁶⁷

A mechanistic scheme has been proposed to account for the Hg(II)-catalysed rearrangement of a variety of acyclic and cyclic ketoximes into amides and lactams in acetonitrile under essentially neutral conditions.⁶⁸

A study of the kinetics and mechanism of oxidative regeneration of carbonyl compounds from oximes by quinolinium bromochromate (QBC) has established that the reaction is first order in both substrate and QBC, slower for ketoximes than aldoximes, and features nucleophilic attack by a chromate oxygen on the carbon in a cyclic transition state.⁶⁹

Second-order kinetics and activation parameters have been reported for uncatalysed reactions of amine nucleophiles with *O*-(2',4'-dinitrophenyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one oxime in aprotic solvents.⁷⁰

A theoretical study of *Z/E* selectivity in the oximation of α -haloacetophenones, using molecular mechanics (MM+) and semiempirical (AM1 and PM3) methods, has been reported.⁷¹ (de)

The equilibria of formation and dehydration of the carbinolamine intermediate in the reaction of benzaldehyde with hydrazine have been studied at pH 3–7 by polarographic techniques; values of *K* and *K_a* for component steps, as appropriate, have been reported.⁷²

A further study of reaction of ketone arylhydrazones with NO in CH_2Cl_2 to form C(1')-nitro azo compounds in high yield has established that nitration of asymmetric cyclic hydrazones occurs stereospecifically such that the nitro group the C(1')-atom and a substituent at C(2') lie on opposite sides of the ring; both cyclopentanone and cyclohexanone hydrazones give higher *trans:cis* ratios (up to >99:1) than for corresponding cycloheptanone derivatives.⁷³ (de)

Enantioselective addition of methyleneaminopyrrolidine ($\text{R}_2\text{NN}=\text{CH}_2$) to *N*-Boc-imines ($\text{ArCH}=\text{N-PG}$) has been achieved with up to 90% *ee* in the presence of chiral phosphoric acids (**20**, $\text{Y} = \text{Ar}$) derived from 3,3'-di(phenanthryl)-H₈-BINOL.⁷⁴ (ee)

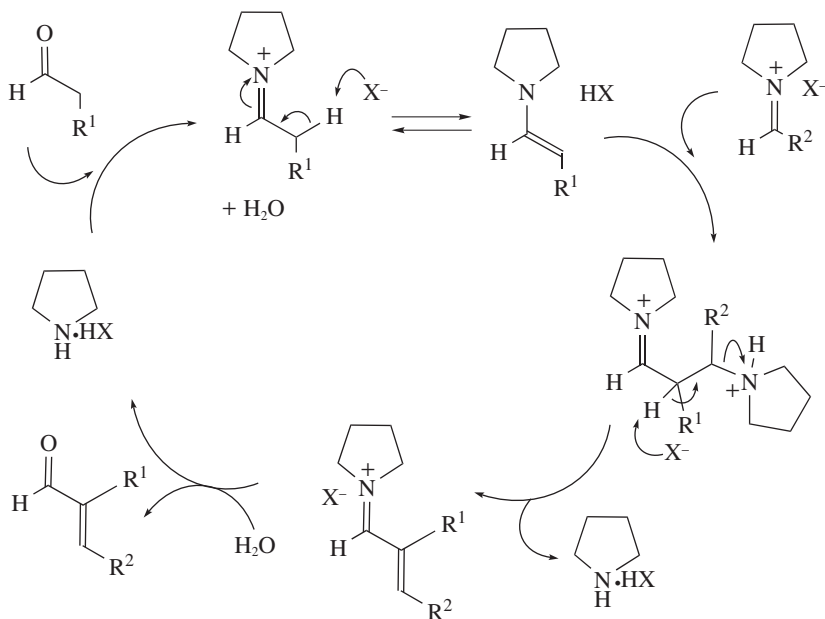
C–C Bond Formation and Fission: Aldol and Related Reactions

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

Reviews have featured asymmetric homoaldol reactions (including enantioselective additions via stereospecific deprotonation and α - and γ -deprotonations),⁷⁵ and also

application of proline as a chiral catalyst in asymmetric aldol reactions,⁷⁶ and progress in the study of such reaction mechanisms (inter- and intra-molecular cases).⁷⁷ (ee)

As a result of a systematic optimization study of the α -methylenation of aldehydes with methanal, a catalytic system, pyrrolidine *p*-(dimethylamino)benzoate, has been developed for the convenient preparation of α -substituted acroleins and for self-condensation of aldehydes.⁷⁸ Scheme 14 depicts the mechanism proposed to account for the kinetics, which reveal a second-order dependence on catalyst, saturation regarding the donor aldehyde, and an inverse rate relationship with methanal (where $R^2 = H$). Two amine molecules are required to activate the reaction partners, one as the enamine and the other as an iminium salt.



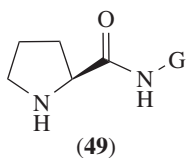
SCHEME 14

L-Proline has been used to promote asymmetric aldol condensation of *N*-substituted isatins with propanone,⁷⁹ *anti*-aldol formation (up to 99% *ee*) from cyclohexanones and substituted benzaldehydes under solvent-free conditions in a ball mill,⁸⁰ and organic solvent-free aldehyde–aldehyde and aldehyde–ketone direct aldol reactions (under dry and wet conditions, respectively) with excellent diastereo- and enantioselectivities.⁸¹ Aldol reaction ‘in water’, not merely ‘in the presence of water’, has been catalysed with good enantioselectivity for the first time, using Pro-NH₂,⁸² 19 other amino acids were found to be ineffective. Since the stereochemistry of self-aldol reaction of propanal is the same using Pro-NH₂ in water and proline in DMF, it is believed that the former catalyst activates the carbonyl group in the same way as does the carboxylic acid proton of Pro and an enamine mechanism applies. It has been (de) (ee)

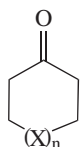
found that the amino acids Arg and Ile have higher catalytic efficiency than L-proline for direct aldol reactions in aqueous micelles and that the *syn:anti* diastereoisomer ratio can be tuned by proper choice of amino acid used.⁸³

Great interest has been shown in the efficacy of proline amide derivatives as stereodirecting catalysts for aldol reactions.^{84–103}

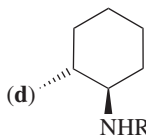
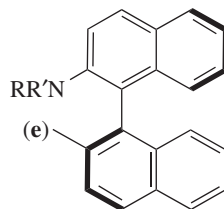
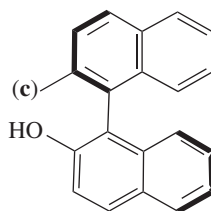
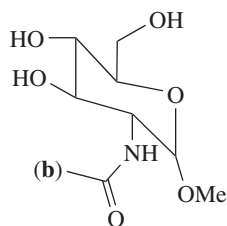
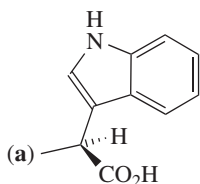
Reactions conducted under aqueous conditions have received particular attention.^{84–90} The L-proline-based dipeptide (**49a**) (20 mol% in water at 0 °C) has been found to catalyse direct aldol reaction of cyclic or acyclic ketones with aromatic, aliphatic, heteroaromatic, and unsaturated aldehydes in high yields (up to 94%) and good enantioselectivities (up to 97% *ee*).⁸⁴ (*R*)-Aldol has been formed in water with improved efficiency, relative to L-proline, using the L-prolineamido glucoside (**49b**) to couple 4-nitrobenzaldehyde and propanone. The enantiocontrol is reversed when methyl 2-(*L*-*t*-leucyloxy)- α -D-glucopyranoside is used as catalyst and generation of the transition state through reaction of enamine with a hydroxyl group on the glucoside auxiliary has been suggested.⁸⁵ Dioxane at 4 °C with water as an additive has been used for formation of aldols (up to >99: <1



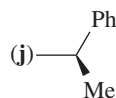
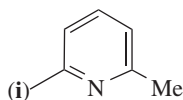
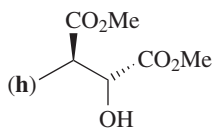
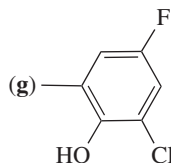
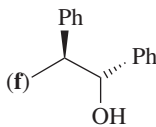
G = (a) – (j)



X = CH₂, O, S
n = 0, 1



R = *p*-TolCO



anti:syn, with up to 95% *ee*) by reaction of aromatic aldehydes with propanone and cyclic ketones, including (**50**), catalysed by (*S*)-NOBIN-L-prolinamide (**49c**).⁸⁶ Water was found to be a suitable solvent for the L-prolinethioamide-catalysed aldol reaction of various cyclic ketones (**50**) with aromatic aldehydes since reactions could be conducted without high ketone excess and the stereochemical effects of hydrophobic aggregation could be exploited to advantage using ‘salting-in’ and ‘salting-out’ techniques.⁸⁷

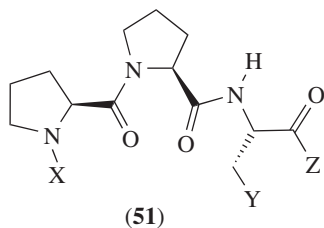
Direct aldol reactions of cyclohexanone with aromatic aldehydes, promoted with excellent *de* and *ee* (>90%) by the bifunctional organocatalyst (**49d**) (20 mol%) with HOAc (20 mol%), occur more efficiently in brine than in water.⁸⁸ 1,1'-Binaphthyl-2,2'-diamine-based (*S*)-prolinamides [e.g. (**49e**)], in the presence of stearic acid, have been used to promote direct aldol condensation of cyclohexanone and other ketones with different aldehydes in the presence of much water with good yields, high *de* and up to 99% *ee*;⁸⁹ other additives in combination with both *C*₁- and *C*₂-symmetric catalysts were also explored. Effective aqua-organocatalytic direct asymmetric aldol reactions promoted by acyclic amino acids, without the addition of organic solvents, and with control of stereochemistry modulated by organic base as co-catalyst, have been developed;⁹⁰ the possible role of aromatic amino acids as a chiral influence on prebiotic chemistry has been mentioned.

L-Prolinamide catalysts have also been used in polychloromethanes to promote highly diastereo- and enantio-selective aldol reactions of aldehydes with cycloketones (**50**), using *trans*-4-OSBT-(**49f**)^{91,92} and (**49g**),⁹³ and with methylthio- and fluoro-propanone, using (**49h**);⁹⁴ *de* and *ee* values of 95–99% were reported.

Experimental and theoretical studies support a transition state featuring hydrogen-bonding interactions of the amide N–H and the pyridine N from a single molecule of L-prolinamide catalyst (**49i**) with, respectively, the keto oxygen and the carboxylic acid hydroxyl of α -keto acids R²COCO₂H, to account for the reactivity and enantioselectivity (up to 98% *ee*) of the direct aldol condensation with ketones R¹COMe in toluene at 0 °C, to form α -hydroxy- γ -keto acid precursors of target 2-hydroxy- γ -butyrolactones.⁹⁵

Study of several analogs (**51**) of the tripeptide catalyst H–Pro–Pro–Arg–NH₂ (**51**, X = H, Y = CO₂H, Z = NH₂), in which the *N*-terminal secondary amine or the carboxylic acid in the side-chain of the aspartic acid residue is replaced with different functional groups, has revealed that these groups are important for effective catalysis of asymmetric aldol reactions.⁹⁶ Implications for the reaction mechanism are discussed.

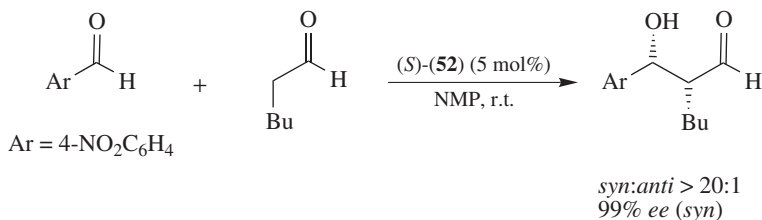
Excellent *de* and *ee* values (up to >99%) have been achieved for direct aldol reactions of cyclohexanone with aromatic aldehydes catalysed by *trans*-4-hydroxy-L-proline hydrazide–trifluoroacetic acid.⁹⁷



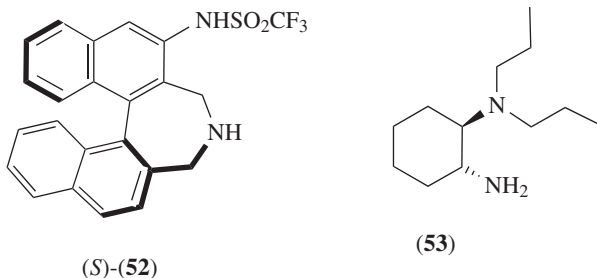
X = H, H·TFA, Ac, Me
 Y = CO₂H, SO₃H, CONH₂
 Z = NH₂, OMe

Enantioselective aldol reactions between propanone and aromatic aldehydes have been catalysed by *N*-toluenesulfonyl-L-prolinamide in ionic liquids; the results were comparable to those for the same catalyst in DMSO and for L-proline in ionic liquids.⁹⁸ A functionalized chiral ionic liquid containing the L-proline unit has been used to promote aldol condensation of aldehydes and ketones in [Bmim][BF₄] at room temperature.⁹⁹

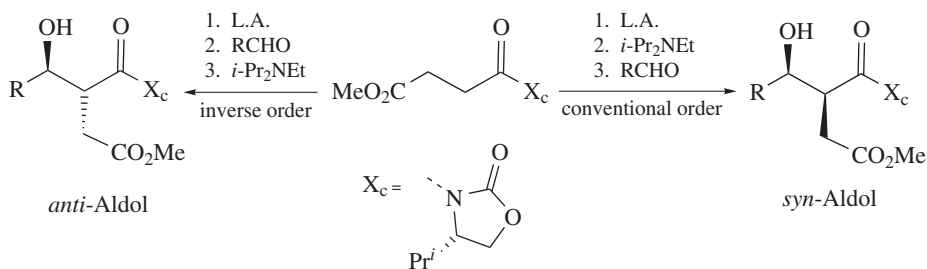
Chiral sulfonamide (**52**) has been found to catalyse the enantioselective direct cross-aldol reaction between two different aldehydes with formation of *syn* products (Scheme 15); this contrasts with the *anti* selectivity induced by L-proline.¹⁰⁰ *syn*-Aldols have also been formed preferentially (up to 98%) using a threonine-based catalyst (*O*-*t*-Bu-L-Thr) to promote reaction of unprotected¹⁰² and protected¹⁰¹ 1,3-dihydroxy- or protected¹⁰¹ hydroxypropanone with a variety of aldehydes, thereby emulating the L-rhamnulose 1-phosphate and D-fructose 1,6-diphosphate aldolases. A simple chiral primary-tertiary diamine (**53**), in combination with TfOH, has also been reported to be remarkably *syn* selective in promoting aldol coupling (of linear aliphatic ketones and aldehydes) with high regio-, diastereo-, and enantio-selectivity;¹⁰⁴ this is in contrast with the *anti* selectivity usually exhibited by secondary amine catalysts. However, a primary amine derived from cinchonine promoted the reaction of aldehydes with cyclic ketones to give 99% yields of *anti*-aldols with high *dr* (up to 9:1) and *ee* (up to 99%).¹⁰⁵



SCHEME 15



It has been found that by simply changing the addition sequence (Scheme 16), predominant *syn*- or *anti*-aldol product can be obtained from reaction of aldehydes



SCHEME 16

with chiral *N*-acyl-2-oxazolidinones promoted by Lewis acid (L.A.) (TiCl_4) and $i\text{-Pr}_2\text{NEt}$.¹⁰⁶

The ability of polyleucines of various lengths to act as enantioselective catalysts in aldol condensations between cyclohexanone and aromatic aldehydes strengthens the hypothesis that simple amino acid derivatives played a role in prebiotic catalysis.¹⁰⁷ (ee)

Thioamides have featured in three studies of direct aldol addition.^{87,103,108} The use of *L*-prolinethioamide derivative (**49**, with O instead of S), rather than (**49**) itself, with TFA, to catalyse direct asymmetric aldol reaction of propanone with 4-nitrobenzaldehyde has an appreciable effect on both the yield (up to 99%) and stereochemistry (up to 99% *ee*).¹⁰³ Over 20 acid additives were investigated and direct evidence of enamine–iminium catalysis was found; the C=S bond remains intact throughout the mechanism proposed. A chelated-chair transition state has been proposed to explain highly diastereoselective acetate aldol additions to RCHO observed using chlorotitanium enolates of mesityl-substituted *N*-acetyloxazolidinethione auxiliaries.¹⁰⁸ (de)

Desymmetrization of a centrosymmetric dialdehyde, by enantioselective aldol reaction with a range of ketone nucleophiles, has illustrated the synthetic potential of the approach to the synthesis of natural products having embedded centrosymmetric fragments.¹⁰⁹ (ee)

The regiochemistry of the $(\text{cyclohexyl})_2\text{BCl-Et}_3\text{N}$ -mediated aldol reactions of (1,3-dioxolan-2-yl)ethyl ketones, $\text{EtCOCH}_2\text{CH}_2\text{C}(-\text{OCH}_2\text{CH}_2\text{O}-)\text{R}$, with $\text{R}'\text{CHO}$ has been found to depend on both ketone structure and solvent; the predominant nucleophilic carbons in diethyl ether and pentane are C(2) and C(4), respectively.¹¹⁰

Although enantioselective intramolecular formation of bicyclo[4.3.0]nonane derivatives by aldol reaction of 2-methylcyclohexa-1,3-dione bearing a butanal group at C(2), catalysed by the trifluoroacetic acid salt of 2-(pyrrolidinylmethyl)pyrrolidine, is a rare combination of aldehyde as nucleophile and ketone as electrophile, the result is hardly surprising, given the marked preference usually observed for five- relative to seven-membered ring closures.¹¹⁰ (ee)

Mukaiyama and Vinylogous Aldols

Asymmetric vinylogous Mukaiyama aldol reactions have been reviewed,¹¹² the reaction allows efficient construction of polyketide frameworks using ketene acetals as the synthon for two acetate or propionate units.

A report has detailed comprehensive investigations of the scope and limitations of the Lewis base-catalysed SiCl_4 -mediated vinylogous aldol additions of ketone- and amide-derived silyl dienol ethers to various aldehydes, catalysed by chiral phosphoramides.¹¹³ Of note is the exceptionally high γ -site selectivity found for a variety of substituted dienyl units. Excellent enantio- and diastereo-selectivity is achieved from both ketone- and morpholine amide-derived dienol ethers on addition to conjugated aldehydes and reaction of the latter with aliphatic aldehydes was the highest yet found for the SiCl_4 -chiral phosphoramidate system. (ee)

Ab initio calculations (MP2/6-311+G**//B3LYP/6-31G*) have been used to study the mechanism of the metal chloride-promoted Mukaiyama aldol reaction between trihydrosilyl enol ether and methanal.¹¹⁴ The Lewis acid promotes a stepwise mechanism (in contrast to the concerted uncatalysed aldol reaction) for which the favoured route involves simultaneous C-C bond formation and chlorine atom shift in the first (rate-determining) step, for which a low activation energy (12 kJ mol^{-1}) has been calculated for TiCl_4 ; BCl_3 , AlCl_3 , and GaCl_3 are also predicted to be efficient catalysts since they strongly activate the electrophile. The reactions feature pretransition-state π - π complexation between enol silane ($\text{H}_3\text{SiOCH}=\text{CH}_2$) and ($\text{CH}_2=\text{O} \cdots \text{MCl}_n$). (de)

A study of ambido-, stereo-, and enantio-selectivity of the phosphoramidate-promoted aldol reactions of α -oxyaldehyde trichlorosilyl enolates with benzaldehyde has established that α -*t*-butyldimethylsilyloxy- α -deuterioacetaldehyde trichlorosilyl enolate reacts as an α -butyldimethylsilyl enolate rather than a trichlorosilyl enolate, with very high ambidoselectivity, excellent *anti* diastereoselectivity, but moderate *ee*.¹¹⁵ (ee)

The Aldol-Tishchenko Reaction

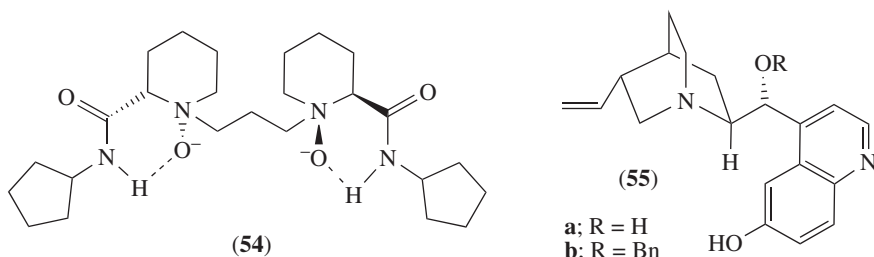
A review of the direct catalytic aldol-Tishchenko reaction has highlighted its role in overcoming the retro-aldol problem for aromatic donors and acceptors.¹¹⁶

Nitrile/Nitro/Nitroso Aldols

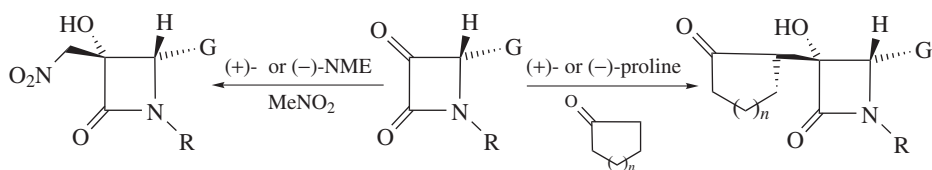
Recent advances in the catalytic asymmetric nitroaldol (Henry) reaction have been reviewed.¹¹⁷

Enantioselective Henry reactions of CH_3NO_2 with various aldehydes have been promoted by chiral amines associated with copper salts.¹¹⁸⁻¹²¹ Thus, a C_2 -symmetric diethyl *i*-Pr-bis(oxazoline)- $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ catalyst in *i*-PrOH at 25°C gave (*S*)- β -hydroxynitroalkanes with high chemical yields (up to 95%) and *ee* up to 97%.¹¹⁸ 2,6-Bis[*(S)*-4-isopropyl-1-phenyl-4,5-dihydro-1*H*-imidazol-2-yl]pyridine- $\text{Cu}(\text{OTf})_2$ (based on one of several easily tunable chiral bisimidazolines studied) with Et_3N in EtOH at room temperature gave the *R*-product from aliphatic and aromatic aldehydes with yields of 45-98% and 93-98% *ee*.¹¹⁹ Based on experimental observations and MM+ calculations, a possible catalytic cycle and transition state have been proposed to explain the excellent enantioselectivities (up to 96% *ee*) achieved using a variety of heteroaromatic, enal, and aliphatic aldehydes with a new $\text{Cu}^{\text{I}}\text{-[H}_4\text{]salen}$ catalyst in methanol.¹²⁰ Based on ^1H NMR, ESI-HRMS, and MM2 calculations, it (ee)

has been suggested that chiral *N,N*-diol (**54**) coordinates to Cu(I) via amide nitrogens and *N*-oxide oxygens in forming an effective catalyst for the asymmetric (up to 98% *ee*) Henry reaction with aromatic and heteroaromatic aldehydes and with α -keto esters;¹²¹ effective catalyst complexes could not be formed using Cu(I) with structures (**54**) lacking *N*-oxidation at one or both of the *N*-oxide sites.



The first organocatalytic highly enantioselective (*ee* up to 90%) nitroaldol reaction of α -ketophosphonates and nitromethane has been catalysed by cupreine (**55a**) and 9-*O*-benzylcupreine (**55b**) in THF; the products can be reduced to β -amino- α -hydroxyphosphonates with complete retention of stereochemistry.¹²² Organocatalytic direct aldol and nitroaldol reactions of enantiopure azetidine-2,3-diones with ketones and nitroketones have been promoted by proline and *N*-methylephedrine, respectively, to give 3-functionalized 3-hydroxy- β -lactams with good yields and total diastereoselectivities.¹²³ The substrate symmetry determines the asymmetric induction, which is unaffected by the chiral form of the catalyst used (Scheme 17).



NME = *N*-methylephedrine; $n = 0, 1$; R = aryl, alkyl; G = 2,2-dimethyl-[1,3]dioxolanyl

SCHEME 17

A DFT study of the mechanism and regioselectivity of the tandem *O*-nitroso aldol–Michael reaction of nitrosobenzene and cyclohexenone with a pyrrolidine-based catalyst has revealed that the energetics favour the *O*- rather than *N*-selective reaction route.¹²⁴

Enantioselective formation of quaternary stereogenic carbons can be achieved by aldol additions of silyl ketene imines, $R^1R^2C=C=N-TBS$, to aromatic aldehydes under the catalytic influence of a chiral phosphoramidate in the presence of $SiCl_4$, giving β -aryl- β -hydroxynitriles.¹²⁵

Other Aldol-type Reactions

DFT calculations have been applied to trace the elementary processes involved in base- and acid-promoted aldol condensations: $\text{MeRC}=\text{O} + \text{HO}^- + (\text{H}_2\text{O})_8$ ($\text{R} = \text{H}$ and Me) and $\text{MeCH}=\text{O} + \text{H}_3\text{O}^+ + (\text{H}_2\text{O})_8$.¹²⁶ The HO^- -promoted reactions have three elementary processes but the rate-determining steps for $\text{R} = \text{H}$ and $\text{R} = \text{Me}$ are C–H bond scission and C–C bond formation, respectively. The H_3O^+ -promoted reactions involve only two elementary processes, C–C bond formation being rate determining. The HO^- -promoted reaction of the aldehyde had the highest reactivity of the three reactions studied.

DFT-computed transition states have also quantitatively explained the surprising stereochemical outcome of boron aldol reactions of unsubstituted enol borinates with aldehydes, whereby *Si*-face attack on (*Z*)-enolates, via a chair transition state, is found to be in contrast with *Re*-face attack on unsubstituted enolates, via a boat transition state.¹²⁷ (de)

The stereochemistry of epoxyamide formation by Darzens condensation between α -haloamides and aldehydes has been controlled under the catalytic influence of a cobalt(salen) complex.¹²⁸ A change of diastereoselectivity from formation of *cis*- to *trans*-epoxides (with up to 50% and 43% *ee*, respectively) can be induced by changing the leaving group and base. (de) (ee)

Recent developments in the stereoselectivity and catalysis of the Reformatsky reaction, whereby aldehydes and ketones can be condensed with α -halocarbonyl compounds to form β -hydroxycarbonyl compounds asymmetric at both C_α and C_β , have been discussed.¹²⁹ (de)

4,7-Di-*t*-butylacenaphthenone has been used as a mechanistic probe in order to identify several factors that contribute to successful cyclotrimerizations of cyclic ketones;¹³⁰ it is particularly important to avoid dehydration of the initial dimer to a β,γ - rather than an α,β -unsaturated ketone.

Pinacol-type Coupling

Progress in pinacol coupling of aldehydes and ketones using low-valent titanium (known to give higher chemo- and stereo-selectivity) has been reviewed.¹³¹

A chiral Salan–Mo(VI) dioxo complex has been found to be an effective precatalyst for symmetric pinacol coupling of aromatic aldehydes to give chiral diols with high diastereo- and enantio-selectivity, up to 92:8 and 95%, respectively.¹³² The reaction proceeds via an intermediate of Mo oxidation state +4 (formed by successive reactions with TMSCl and zinc and confirmed by X-ray photoelectron spectroscopy), which facilitates radical coupling of two aldehyde molecules to form the favoured *S,S*-enantiomer of the *de*-isomer. (de) (ee)

An asymmetric catalytic redox system, featuring tethered bis(8-quinolinato)(TBOx) chromium (III/II) complexes, has been used to achieve high diastereo- and enantio-selectivity reactions of aldehydes in pinacol coupling (*de:meso* up to 98:2), asymmetric NH allylation (*anti:syn* up to 10:1, up to 99% *ee*), and asymmetric allenylation (up to 97% *ee*).¹³³ This has been attributed to the well-designed chiral environment of the ligands and the *cis*- β configuration of the Cr metal. (de) (ee)

The Baylis–Hillman Reaction and its Aza and Morita Variants

Reviews of the Baylis–Hillman reaction¹³⁴ and the aza-Baylis–Hillman reaction¹³⁵ have emphasized the importance of their synthetic applications. A minireview of the enantioselective Morita–Baylis–Hillman (MBH) reaction and its aza counterpart has summarized recent mechanistic insights and advances in the design of small-molecule organocatalysts for these important reactions; bifunctional catalysts in which both Lewis base and Lewis acid units are tethered to a chiral rigid backbone are particularly efficient.¹³⁶ (ee)

The mechanism of the Morita–Baylis–Hillman reaction has been explored computationally.^{137–139} Focusing on the reaction of methyl acrylate with benzaldehyde, catalysed by a tertiary amine, it has been shown that in the absence of a protic solvent deprotonation of the α -position, with intramolecular proton transfer to a hemiacetal alkoxide formed by addition of a second aldehyde molecule to the intermediate alkoxide, is rate determining, thereby explaining the second-order dependence on [ArCHO].¹³⁷ In contrast, in the presence of methanol, which lowers the activation energy by facilitating proton transfer from carbon to oxygen, a first-order dependence on [ArCHO] is predicted. It is argued that, since the energy for the transition state for addition of the amine–acrylate betaine adduct to the aldehyde is much lower than that for proton transfer, C–C bond formation should not be rate limiting, except perhaps for some aliphatic aldehydes or imines.

Likewise, *ab initio* and DFT studies of the mechanism of the MBH reaction have shown that rate-limiting intramolecular proton transfer occurs within the zwitterionic intermediate formed by reaction between ammonium enolate and the electrophile and that, for reaction between methyl vinyl ketone and benzaldehyde catalysed by DABCO, the activation for C–C bond formation is 20.2 kcal mol⁻¹ lower than for proton transfer.¹³⁸

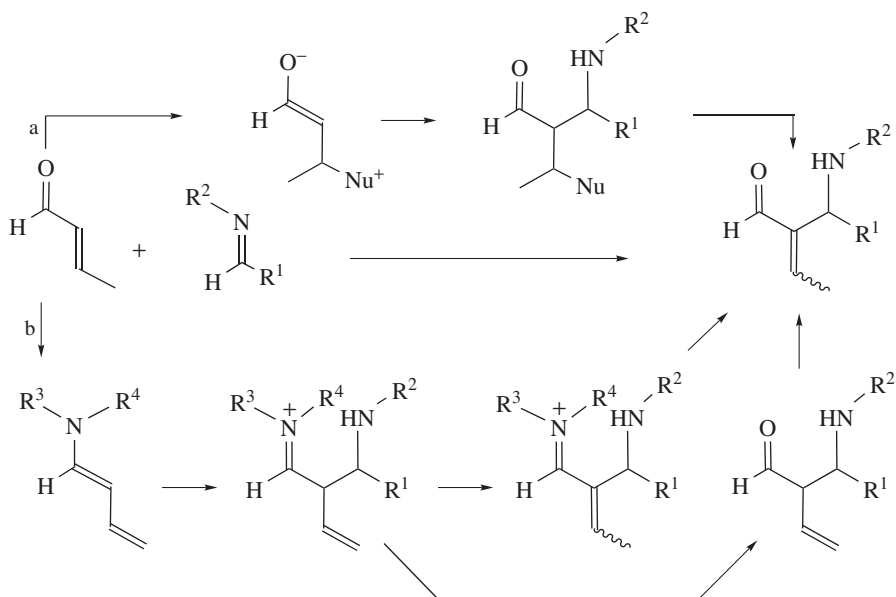
Hydrogen transfer has also been predicted [by investigation at the B3LYP/6–311+G(d) level, combined with Thomasi's IEF–PCM solvent model] to be rate determining for MBH reaction in CH₂Cl₂ involving 1,4-addition of PMe₃, aldol addition, hydrogen transfer, and elimination of product.¹³⁹

The presence of a small amount of water has been found to improve both the yield and rate of the aminocatalytic Baylis–Hillman reaction between methyl vinyl ketone and a variety of aldehydes in the presence of proline and imidazole; 10% aqueous DMF was found to be the optimal medium for a variety of substrates.¹⁴⁰ Shi's mechanism, featuring preformation of a quaternary imine on reaction of the keto group with proline, followed by pyrrolidine-catalysed C–C coupling, is assumed.

Highly substituted α,β -unsaturated ketones have been prepared by the *N*-heterocyclic carbene-initiated addition of α -hydroxypropargylsilanes to aldehydes as an efficient alternative to the standard MBH approach for synthesis of such compounds.¹⁴¹ Initial addition of the carbene to RCHO gives a nucleophilic alkoxide, which abstracts the silyl group to form a reactive allenolate; there follows aldol coupling with a further RCHO.

A Mannich-type reaction (of *in situ*-generated enamine)–isomerization sequence (Scheme 18, path b) has been proposed to explain the enantioselective formation (up to 99% *ee*) of β -aminocarbonyl compounds bearing α -alkylidene groups by reaction

of β -substituted α,β -unsaturated aldehydes and α -imino esters (*N*-*p*-methoxyphenyl) \textcircled{ee} in the presence of (*S*)-proline and imidazole under mild conditions.¹⁴² The mechanism circumvents the steric retardation (by the β -substituent) of Michael addition by the Lewis base catalyst in the aza-MBA mechanism (Scheme 18, path a). A similar mechanism has been considered in discussion of the highly enantioselective (93–99% *ee*) catalytic route to Boc protected aza-MBH-type products from the organocatalytic reaction between unmodified α,β -unsaturated aldehydes and *N*-Boc-protected aryl imines promoted by L-proline with DABCO.¹⁴³ \textcircled{ee}



SCHEME 18

Aza-MBH reactions between variously substituted *N*-(phenylsulfonyl)aldimines and conjugated dienes (activated by sulfone, ester, or ketone moieties) have been promoted by 3-hydroxyquinuclidine in DMF to form highly functionalized allylic amine derivatives with varying degrees of diastereoselection.¹⁴⁴ \textcircled{de}

Allylation and Related Reactions

DFT calculations at the PBE1PBE/DGDZVP level have revealed that transfer of methanal to the π -allyl group of bis- π -allylpalladium complex is favoured thermodynamically ($\Delta G = -1.4 \text{ kcal mol}^{-1}$) and involves nucleophilic attack of the allyl group on the aldehyde coordinated to the metal centre (with $\Delta G^\ddagger = 23.0 \text{ kcal mol}^{-1}$).¹⁴⁵ The results are consistent with the mechanistic proposal of Yamamoto *et al.*,^{146a} rather than Szabó,^{146b} which is also supported by the chemoselectivity found for allylation

The first enantioselective allylation of ketone enamines to give the products from addition to the more substituted position of an allyl electrophile has been developed.¹⁵⁷ The reactions feature substituted enol carbonates (*E*)-R¹CH=CHCH₂OCO₂R² and a BINOL phosphoramidite ligand L1 [20, Y = H; P(O)OH = P-N(R,S)-(CHPhMe)₂] as Ir(cod)(κ²-L1)(L1). (ee)

Under Pd(0)-Et₃B catalysis, vinyl epoxide has been found to behave amphiphilically towards aldehydes as a formal but-3-enyl 2-anion-1-cation equivalent reacting in one pot, by electrophilic α-allylation and nucleophilic carbonyl addition, to form the corresponding 2-vinylcyclobutanol.¹⁵⁸

Alkenylboronates have been used as a vinyl source in the asymmetric addition of an alkenylzinc reagent to aldehydes R'CHO, catalysed by a dendritic ligand in hexane-toluene, to form allylic alcohols R¹R²C=CR³C*H(OH)R'.¹⁵⁹ Asymmetric vinylation, to form (*E*)-allylic alcohols, has also been achieved by addition of alkenylzincs to aromatic and α-branched aliphatic aldehydes, catalysed by a bicyclic aminothiols.¹⁶⁰ (ee)

Alkynations

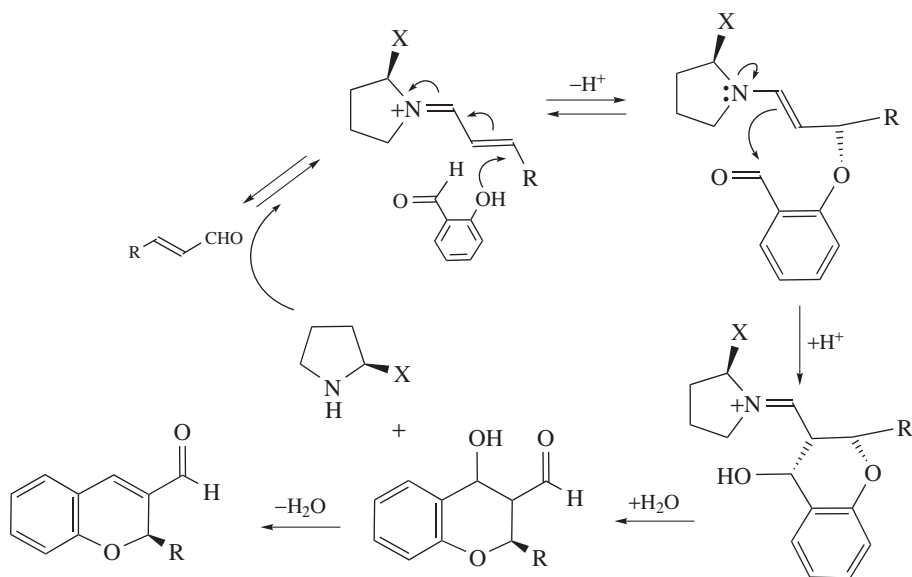
Study of addition of terminal alkynes to aldehydes and activated ketones promoted by rhodium-phosphine complexes has established that a mixture of 2-(di-*t*-butylphosphino)biphenyl and dicarbonylacetonatorhodium(I) provides a very effective catalyst system for the formation of propargylic alcohols under mild conditions tolerant towards many functional groups (including unprotected OH and CO₂H).¹⁶¹ However, since only low enantioselectivity is induced by the chiral phosphines, six modifications of the β-diketonate ligand have been evaluated; those bearing strong electron-withdrawing groups diminish catalytic activity whereas bulky and electron-rich derivatives are more efficient catalysts (in terms of rate and yield), which could perhaps be made enantioselective by incorporation of chiral substituents.¹⁶² (ee)

Asymmetric addition of 1-ethynylcyclohexene to both aromatic and heteroaromatic ketones has been achieved with up to 88% yield and 83% *ee* under the influence of a chiral Schff base-zinc complex of [*N*-(*S*)-(1,2,2-triphenylethan-2-ol)-1-naphthaldimine].¹⁶³ Phenylacetylene addition to linear or branched aliphatic aldehydes and vinylaldehydes has been promoted in THF or CH₂Cl₂ with 89–96% *ee* by Me₂Zn (2 equiv.) and a macrocycle catalyst incorporating two dihydroxy-1,1'-binaphthyl units held in a tetraimine ring.¹⁶⁴ (ee)

Michael Additions

Enantioselective (up to >99% *ee*) α-arylation of aldehydes (via intermediate enamines) by reaction with quinones organocatalysed by chiral pyrrolidine derivatives in H₂O or EtOH-H₂O has been studied.¹⁶⁵ (ee)

Domino oxa-Michael-aldol condensation reactions between salicylaldehyde derivatives and α,β-unsaturated aldehydes, with iminium activation organocatalysed by chiral pyrrolidine derivatives, proceed with high *ee* (83–98%) to give chromene-3-carbaldehydes (Scheme 20) in high yields.¹⁶⁶ (ee)



SCHEME 20

Highly enantio- and diastereo-selective tandem Michael–aldol reactions have been activated by hydrogen bonding of both donor and acceptor to a *Cinchona* alkaloid thiourea and used to create three stereogenic centres in a one-pot synthesis of chiral thiochromanes.¹⁶⁷ (de) (ee)

Ferrocenyl-substituted aziridinylmethanols have been used as chiral ligands with nickel to catalyse enantioselective conjugate addition of diethylzinc to enones; ligands with *S*-configuration at aziridine position 2 give the product with *R*-configuration, and vice versa.¹⁶⁸ (ee)

A direct intermolecular hydroacylation of *N,N*-dialkylacrylamides with both aliphatic and aromatic aldehydes has been catalysed by a cationic rhodium(I)–dppb complex; an acylrhodium intermediate stabilized by alkene chelation to rhodium is believed to feature in this new route to γ -ketoamides R¹COCHR²CHR³CONR⁴₂.¹⁶⁹

Other Addition Reactions

General and Theoretical

Computational approaches to asymmetric synthesis have provided valuable insight into mechanisms and the controlling electronic and steric effects; representative contributions of QM, MM, and QM/MM methods have been discussed.¹⁷⁰

Addition of Organozincs

Asymmetric addition of dimethylzinc to aldehydes has been induced by a new chiral fluorosulfonate ligand in quantitative yield with 96% ee,¹⁷¹ and by the titanium complex of (ee)

an axially dissymmetric fluorous ligand with 99% *ee*.¹⁷² The dihydroxy ligands were easily recovered in each case as a consequence of their high fluorine content.

Asymmetric addition of diethylzinc to aldehydes has continued to attract much attention.^{173–180} and has featured catalysis by: 3,3'-dipyridyl-BINOL ligands (especially applied to benzaldehydes and cinnamaldehydes);¹⁷³ dendritic BINOL ligands [applied to benzaldehyde, with and without Ti(OPr^{*i*})₄];¹⁷⁴ binaphthyl-containing salicyl hydrazones;¹⁷⁵ a new series of chiral *cis*-cyclopropane-based amino alcohols (which also promote phenyl transfer to aromatic aldehydes);¹⁷⁶ nickel complexes of simple chiral α -aminoamide derivatives (metal–ligand complexes with 1:1 and 1:2 stoichiometries afford the (*S*)- and (*R*)-alcohol, respectively, from benzaldehyde);¹⁷⁸ a ferrocenyl-substituted aziridinylmethanol in toluene, forming secondary alcohols in high yields and up to 99% *ee* at room temperature from aliphatic and aromatic aldehydes;¹⁷⁹ novel chiral sulfinamido alcohol ligands [from (*S*)-*t*-butanesulfinamide];¹⁷⁹ and a variety of camphor sulfonamide ligands (with up to 83% *ee*).¹⁸⁰

Reviews have featured kinetic investigations of the Soai reaction¹⁸¹ and the implications of such asymmetric autocatalysis with amplification of chirality on the origin of chiral homogeneity of biomolecules.¹⁸² The Soai reaction induced by chiral secondary alcohols as chiral initiators of the enantioselective alkylation of a pyrimidine-5-carbaldehyde by diisopropylzinc has been studied and the relationship between the absolute configuration of the initiator and the pyrimidyl alkanol has been discussed.¹⁸³ Numerical kinetic simulations have also been employed to determine why the enantioselectivity of Soai reaction induced by chiral β -amino alcohol catalysts is reversed if the reaction is conducted in the presence of their achiral analogues.¹⁸⁴ The effect of such reversal is to cause steep, abrupt transitions between opposed optically active states and is a further example of spontaneous mirror-symmetry breaking. The modelling indicates that the reversal can be caused by interaction between either (i) the chiral and achiral additives or (ii) the additives and the customary products of the Soai reaction. The latter suggestion, which constitutes reversible inhibition of the chirally selective autocatalysts, is able to explain further observations which reveal the remarkable sensitivity of this system to the initial presence of almost any chiral substance, even if catalytically inactive.

β -Hydroxysulfoximines have been used to catalyse the formation of diarylmethanols by asymmetric phenyl transfer (from Et₂Zn with either Ph₂Zn or Ph₃B) on to aromatic aldehydes with up to 93% *ee*.¹⁸⁵

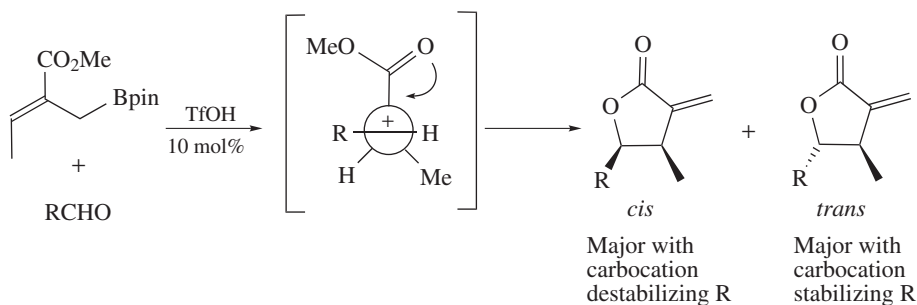
Other reactions of organozincs were mentioned above.^{147,154,160}

Addition of Other Organometallics

Reaction of aryl- or heteroaryl-boronic acids, R¹B(OH)₂, with aldehydes, R²CHO, in the presence of PdCl₂ and P(1-Nap)₃ affords carbinol derivatives, R¹R²CHOH, by a reaction that is versatile in its compatibility with functional groups and without the need to exclude air or moisture.¹⁸⁶

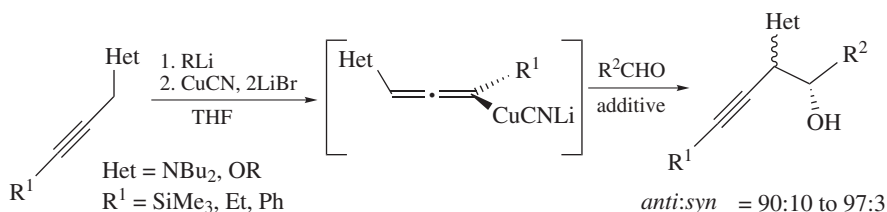
Arylation of aldehydes by $\text{ArB}(\text{OH})_2$ has been achieved smoothly using dirhodium(II) catalyst complexes with *N*-heterocyclic carbene ligands at the axial positions.¹⁸⁷ DFT calculations have helped to explain desirable stereoelectronic features of the optimum catalyst.

An intermediate carbocation has been proposed to account for the stereoselective formation of β,γ -disubstituted five-membered ring lactones with *exo*-methylene at the α -position following triflic acid-catalysed allylboration between 2-alkoxycarbonyl allylboronates and aldehydes (Scheme 21).¹⁸⁸ O^{18} -labelling confirmed that aldehydic oxygen is not incorporated in the lactone.



SCHEME 21

Anti-alkyl homopropargylic alcohols (which were inaccessible by tin chemistry) are obtained preferentially on addition of heteroallenyl copper reagents to aldehydes (Scheme 22); DFT calculations have shown that the observed reactivity order, $\text{SiMe}_3 > \text{Ph} > \text{Et}$, relates to the stability of the reactive allenic species compared to the less-stable propargylic isomer.¹⁸⁹



SCHEME 22

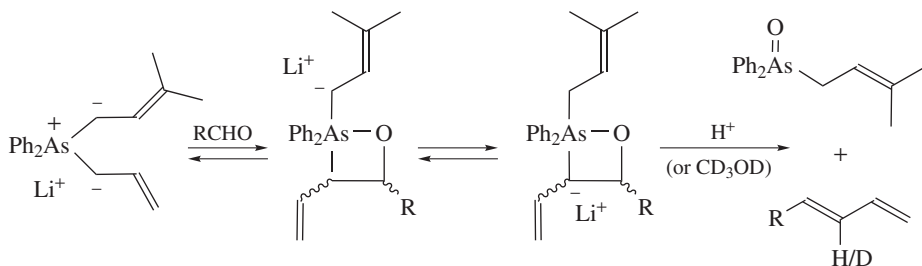
Grignard-type Reactions

It has been found, by study of the levels of diastereoselection attainable by addition of vinylmagnesium bromide to a selection of bicyclo[2.2.2]oct-5-en-2-one derivatives in de

the presence of various Lewis acids, that facial selectivity of the nucleophilic addition is influenced by the substituents and reaction conditions.¹⁹⁰

The Wittig Reaction

A study of the reactivity of aldehydes with semi-stabilized arsonium ylide anions has established suitable conditions for stereoselective formation of terminal (*E*)-1,3-dienes (with *E*:*Z* ratios ranging from 90:10 to 97:3).¹⁹¹ The ylide anions were generated by addition of *n*-BuLi (in THF at -35°C) to $[\text{Ph}_2\text{As}(\text{R})\text{R}']^+ \text{X}^-$, where R and R' are methyl, allyl, prenyl, or benzyl groups. The mechanism proposed for reaction of a dissymmetric arsonium bromide, for which allyl transfer predominates over prenyl transfer, is shown in Scheme 23; note that the result of deuterium quenching is consistent with the proposal. Analogous steps for the competing prenyl transfer are in equilibrium with those shown. (de)

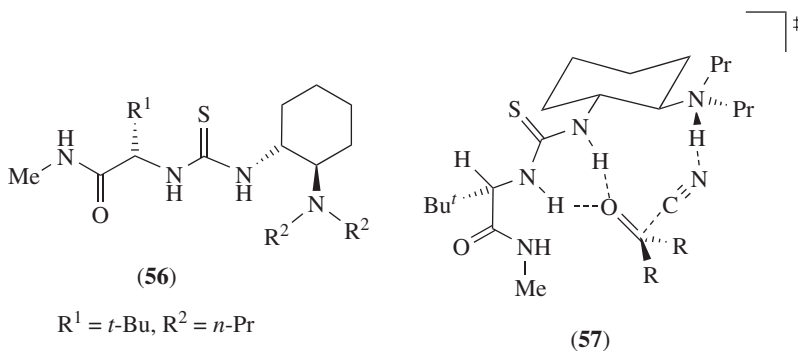


SCHEME 23

Hydrocyanation and Cyanosilylation

Reaction of pentafulvenone with hydrocyanic acid has been shown by theoretical calculations at the MP2/6-311+G**//B3LYP/6-311+G** level to involve two intermediates, thirteen transition states and eight products.¹⁹²

A very detailed theoretical and experimental investigation of ketone cyanosilylation catalysed by *t*-aminothioureas (**56**) has established a mechanistic basis for the



enantioselectivity observed.¹⁹³ Both the thiourea and the *t*-amine groups are involved cooperatively in the rate-limiting cyanide addition step, which features amine-bound HCN (formed initially as co-catalyst) adding to thiourea-bound ketone in a ternary transition structure (**57**). Computational analysis of that structure reveals a basis for enantioselectivity that involves binding of the ketone through both lone pairs with the catalyst. Further support for the mechanism comes from agreement between computed and calculated inverse isotope effects for reaction with HCN and DCN.

Enantioselective cyanosilylation of aldehydes (with up to 99% yield and 80% *ee* in CH₂Cl₂) has also been catalysed by a novel *N,N*-dioxide-Ti(OPr^{*i*})₄ bifunctional catalyst;¹⁹⁴ Lewis acid- and Lewis base-activated aldehyde and trimethylsilyl cyanide, respectively, feature in the proposed catalytic cycle.

Highly enantioselective ($\leq 91\%$ *ee* and $\leq 99\%$ yield) cyanoforylation of aldehydes with ethyl cyanofornate in *i*-PrOH-CHCl₃ has been catalysed by a mononuclear salen-Ti(OPr^{*i*})₄ complex generated *in situ*.¹⁹⁵

Hydrosilylation and Hydrophosphonylation

DFT calculations (B3LYP) combined with experimental observations suggest that the mechanism of hydrosilylation of aldehydes and ketones by a molybdenum(VI) complex, [MoCl₂O₂], involves initial Si-H activation, by 2 + 2-addition to Mo=O, giving a stable distorted-square-pyramidal hydride complex which coordinates weakly to the carbonyl oxygen in the next step.¹⁹⁶ Alternative stepwise (via an alkoxide) or concerted reduction pathways to silyl ether are then possible in the gas phase; however, solvation effects favour the former (classical) mechanism if HSiMe₃ is used as the silicon source. Comparable energetics suggest that a radical route could also apply in acetonitrile, in agreement with experiment.

Hydrosilylation of carbonyl compounds catalysed by (PPh₃)₂Re(O)₂I is also proposed to proceed by initial Si-H activation (by addition to Re=O, forming a stable siloxyrhenium hydride) followed by dative coordination of the carbonyl group which is then intramolecularly reduced (by Re-H insertion) to give a siloxyrhenium alkoxide; transfer of the silyl group from the siloxy to the alkoxy ligand (a retro-2 + 2-reaction) results in retention of the carbonyl oxygen in the silyl ether product and permits reassociation of the phosphine ligand displaced on initial carbonyl complexation.¹⁹⁷

In contrast, for hydrosilylation of aldehydes by Et₃SiH catalysed by oxo- and imido-rhenium(V) complexes Re(X)Cl₃(PR₃)₂ (X = O, NAr, and R = Ph or Cy), cycloaddition of silane across the Re=X multiple bond does not occur;¹⁹⁸ nor does the reaction proceed via Re(X)Cl₂(H)(PR₃)₂, which can be formed from the silane in high yield (in the absence of aldehyde), apparently via heterolytic cleavage of Si-H within a σ -adduct—thereby enabling release of Et₃SiCl. The problem is that although benzaldehyde has been shown to react with the rhenium hydride (X = O) to give the alkoxide Re(O)Cl₂(OCH₂Ph)(PPh₃)₂, with a kinetic dependence that is consistent with aldehyde coordination and subsequent insertion into the Re-H bond, the rhenium-alkoxide complex regenerates the rhenium-hydride complex in the presence of Et₃SiH. Hence the observed intermediates do not account for the predominant catalytic pathway, which is now believed to involve rate-determining silane activation by σ -adduct formation

cis to the Re=X bond (with displacement of PPh₃), followed by heterolytic Si-H cleavage induced by direct or indirect attack of the aldehyde on silicon.

HETPHOX ligands have been used to promote rhodium-catalysed asymmetric hydrosilylation of a range of substituted acetophenones with moderate enantioselectivities.¹⁹⁹ Rhodium complex-catalysed hydrosilylation of acetophenone in THF has been found to occur at high speed under dihydrogen pressure.²⁰⁰ (ee)

Miscellaneous Additions

Trifluoromethylation of ketones by (trifluoromethyl)trimethylsilane has been catalysed by cinchonidine-derived quaternary ammonium phenoxides with moderate to high enantioselectivity.²⁰¹ (ee)

A mechanism has been proposed for diastereoselective synthesis of 2-aryl-3-vinyl-2,3-dihydrobenzo[*b*]furans through a Sakurai reaction, whereby 2,3-dihydrobenzoxasilepins are condensed with aromatic aldehydes in the presence of BF₃;²⁰² a ring-opened allylfluorosilane intermediate is involved. (de)

Quantum-chemical calculations designed to predict the stereoselectivity of asymmetric ring expansion products of reactions between achiral hydroxyalkylazides and chiral 4-substituted cyclohexanones have been further refined to take account of solvent.²⁰³ (ee)

Remarkably high diastereoselectivity has been reported for reaction of hydride reducing reagents and Grignard reagents with 2-ketoaziridines, as a consequence of the orthogonal behaviour of the amine and ketone groups which would otherwise be incompatible.²⁰⁴ (de)

Enolization and Related Reactions

Two-directional elaboration of *O*-(tetrahydropyran-2-yl)-protected hydroxypropanone has been achieved by generating the enolate under thermodynamically controlled conditions (1.3 equiv. NAH, THF), conducting allylation or 2-propynylation regioselectively at the carbon bearing the protected group, and then effecting aldol addition of the methyl group to an aldehyde R'CHO.²⁰⁵ The allylation was also achieved with 50% *ee* (*S*) using a chiral protecting group. (ee)

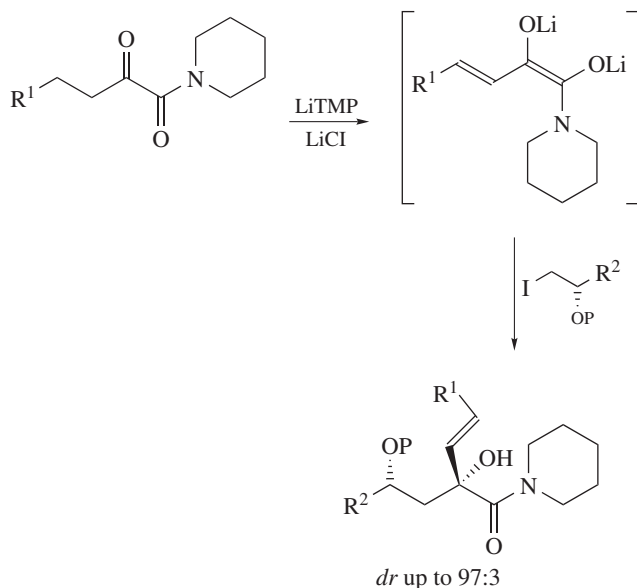
A novel method of synthesis of quaternary α -hydroxycarboxyl derivatives has featured alkylation of prochiral enediolates by chiral primary and secondary protected iodohydrin electrophiles which direct the observed diastereoselectivity (up to 97:3 in the case of dienediolates); the reaction (Scheme 24) is believed to proceed via a lithium-coordinated assembly of nucleophile and electrophile.²⁰⁶ (de)

Enantioselective organocatalytic protonation of silyl enolates has been promoted by *Cinchona* alkaloids and a latent source of HF.²⁰⁷

Oxidation and Reduction of Carbonyl Compounds

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

Asymmetric reduction of prochiral ketones, including recent advances, has been reviewed.²⁰⁸ (ee)



SCHEME 24

A quantum chemical study of the reduction of prochiral ketones by NaBH_4 has concluded that reduction of 4-methylcyclohexanone proceeds by a two-step path and features solvent (*i*-PrOH) participation in a six-membered ring transition state.²⁰⁹

A density functional study has identified competing enantioselective pathways for reduction of acetophenone by a chiral 1,3,2-oxazaphospholidine–borane.²¹⁰ (ee)

Spiroborate esters derived from non-racemic 1,2-amino alcohols and ethylene glycol have been found to be effective catalysts for the asymmetric borane reduction (up to 99% *ee*) of a variety of prochiral ketones with borane–dimethyl sulfide complex at room temperature.²¹¹ (ee)

A mechanistic investigation of the asymmetric Meerwein–Schmidt–Ponndorf–Verley reduction of ketones catalysed by BINOL– AlMe_3 –2-propanol has established, through ^1H and ^{27}Al NMR spectroscopy, that the catalytic precursor formed *in situ* is a BINOL-chelated, pentacoordinate aluminium species.²¹² The rate is unaffected by substrate concentration, depends inversely on 2-propanol, and shows an almost first-order dependence on aluminium. A systematic study of ligands has confirmed that a tetrahedral geometry around the aluminium is desirable, but also found that enantioselectivity is enhanced when pentacoordinate geometry can be achieved through a second point of coordination with the substrate, to the axial site of a pseudo-square pyramid. (ee)

A selective reductive amination of substituted cyclohexanones with primary amines using lithium borohydride has been shown to be selective toward formation of *trans* products; excess amine is used to ensure pre-equilibrium formation of imine, which is then attacked by borohydride preferentially from the axial direction.²¹³ (de)

Transfer hydrogenations of carbonyl compounds and alkenes catalysed by ruthenium(II)–*N*-heterocycle carbene complexes have been explored.²¹⁴ Excellent catalytic

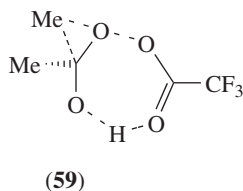
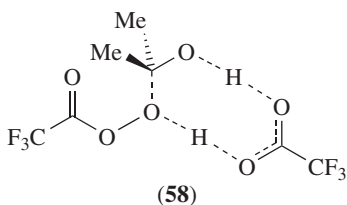
activities have been achieved for the reduction of cinnamaldehyde (with initial formation of the unsaturated alcohol) and several ketones using propan-2-ol–KOH as an H-donor.

Oxidation Reactions

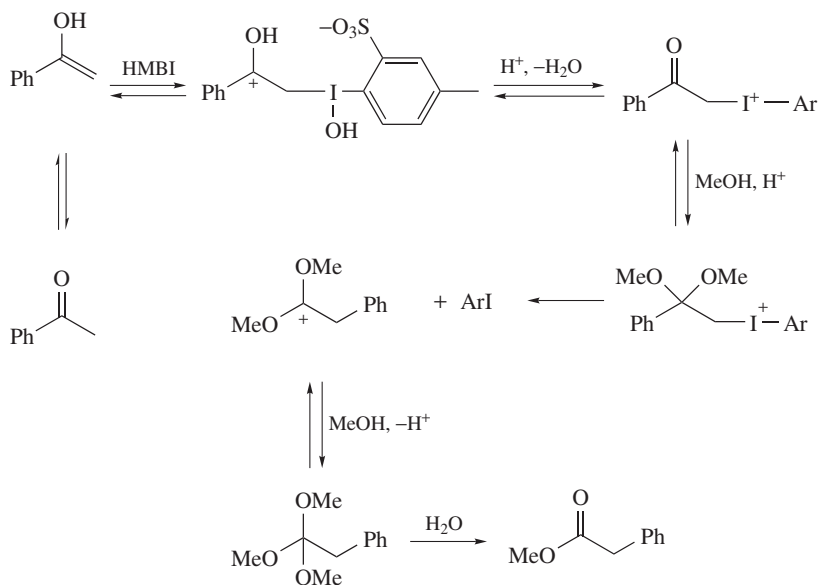
A kinetic investigation of the oxidation of 36 *meta*- and *para*-substituted benzaldehydes by $\text{Bu}_4\text{N}^+ \text{Br}_3^-$ in acetic acid has established that the reaction is first order in both aldehyde and oxidant and subject to a substantial deuterium isotope effect for PhCDO; the rates increase with increase in solvent polarity and correlate well with Charton's triparametric LDR equation.²¹⁵ An electron-deficient reaction centre features in the rate-determining step and steric acceleration by *ortho* substituents is found.

The kinetics of oxidation of six aliphatic aldehydes by quinolinium bromochromate (QBC) in DMSO reveal a first-order dependence on both aldehyde and oxidant and specific acid catalysis, such that $k_{\text{obs}} = a + b[\text{H}^+]$; the kinetic isotope effect ($k_{\text{H}}/k_{\text{D}} = 5.8$ at 298 K) for MeCDO is substantial.²¹⁶ Rate constants for reaction of MeCHO in 19 solvents have been analysed using multiparametric equations of Swain and Taft and found to correlate well with Taft's σ^* values, with negative reaction constant. A mechanism involving hydride ion transfer has been proposed.

Reaction of propanone with trifluoroacetic acid, catalysed by trifluoroacetic acid in dichloromethane, has been used as a model for a quantum chemistry study of the Baeyer–Villiger rearrangement, using three DFT methods (B3LYP, BH&HLYP and MPWB1K) and MP2.²¹⁷ The refined results allowed the calculation of the overall reaction rate coefficient using conventional transition-state theory, giving excellent agreement between experimental ($1.8 \times 10^{-3} \text{ l mol}^{-1} \text{ s}^{-1}$) and calculated ($1.00 \times 10^{-3} \text{ l mol}^{-1} \text{ s}^{-1}$) values at the MPWB1K level, thereby providing support for the mechanism recently proposed by the group; good agreement was likewise found on application of the DFT method to a larger system, cyclohexanone + trifluoroacetic acid. The currently accepted ionic mechanism for the Baeyer–Villiger reaction contrasts with the modelling results, which suggest that the reaction proceeds in two concerted steps. A strongly catalysed addition step is followed by an apparently uncatalysed migration step, for which transition states (58) and (59) apply, respectively.



A plausible mechanism (Scheme 25) has been suggested to account for the oxidative rearrangement of arylalkanones to alkyl 2-aryl esters effected by 1*H*-1-hydroxy-5-methyl-1,2,3-benziodoxathiole 3,3-dioxide (HMBI) (in MeOH, TMOF, H_2SO_4).²¹⁸



SCHEME 25

The procedure avoids the use of reagents which produce toxic metal salts or halogenated organics as by-products and is therefore an improvement on previous methods.

Electrospray ionization mass spectrometry has permitted the direct detection of the key intermediates on the catalysis cycle for direct organocatalytic α -halogenation of butanal by *N*-chlorosuccinimide promoted by *L*-prolinamide;²¹⁹ in contrast, the reaction with *N*-bromo- and *N*-iodo-succinimide occurs by direct *C*-halogenation.

Other Reactions

The α -hydroxyallylation reaction of carbonyl compounds²²⁰ and the Prins reaction²²¹ have been reviewed.

The reactions of formaldehyde with HO^\bullet and HO^- have been studied theoretically at the MP4 (SDTQ) level with the 6-311++G(3df,3pd) basis set. The most favourable reaction paths are production of H_2O (on reaction with HO^\bullet) and of H_2 (on reaction with HO^-).²²² The relative electrophilicity and relative nucleophilicity of cyclohexanone and its derivatives have been evaluated by DFT calculations at the B3LYP/6-311++G** level in order to determine the effects of substitution of B, N, O S, Se, and Si in the six-membered ring.²²³ Results of a quantum chemical study of the keto-enol tautomerism of *N*-aryl-3-oxobutane thioamides suggest that a three-stage intermolecular proton transfer between two molecules of amide occurs.²²⁴ A DFT study of the mechanism of Paal-Knorr pyrrole synthesis (from reaction of 1,4-dicarbonyls with amines) indicates that the preferred mechanism consists of formation and cyclization of a hemiaminal followed by a dehydration step.²²⁵

Hydrophobic environments in aggregated *N*-(2,6-diphenylphenyl)-*N*-mesitylammonium pentafluorobenzenesulfonates have been found to promote unusual dehydrative rate acceleration in condensation reactions and cyclization of 1,3,5-triketones.²²⁶

Kinetic and thermodynamic parameters for reactions of thiourea and its *N*-methyl and *N,N*-dimethyl derivatives with benzoquinones (chloranil and bromanil) in methanol have been reported.²²⁷ Intramolecular π - π interactions whereby remote substituents act to modulate conformational and reactive properties of quinones have been identified by theoretical calculations and related to the behaviour of ubiquinones in biological systems.²²⁸

The chemistry of pyrrolo[1,2-*a*]indole- and pyrido[1,2-*a*]indole-based quinones has been studied in order to determine the influence of the fused pyrrolo and indole rings on quinone methide and vinylquinone formation and fate and also on cytostatic and cytotoxic activity.²²⁹

The stereoselectivity of one-pot reactions of polycyclic 'cage' ketones with dimethoxycarbene, to form α -hydroxycarboxylic acid esters, suggests that the carbene adds to the *exo*-face.²³⁰ (de)

Rate constants have been determined for reaction of chlorine atoms with a series of C₄-C₆ ketones.²³¹

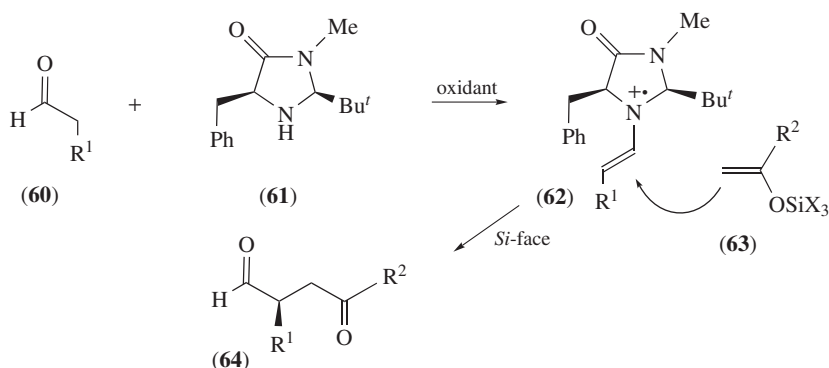
Quantitative kinetic analysis of rate constant-[cationic gemini surfactant] data for the ninhydrin-tryptophan reaction indicates that large micellar aggregates are responsible for rate enhancement.²³²

A synthetically useful method of coupling indoles and pyrroles to carbonyl compounds, which occurs with high chemoselectivity (functional group tolerability), regioselectivity [coupling occurs exclusively at C(3) of indole or C(2) of pyrrole] and stereoselectivity (substrate control), appears to occur by a single electron-transfer process requiring generation of an electron-deficient radical adjacent to a carbonyl, which is then intercepted by the indole or pyrrole anion.²³³ The conclusion is supported by Hammett analysis of kinetic results for reaction of C(5)- and C(6)-substituted indoles.

A new methodology for the synthesis of β -diketones RCOCH₂COCH₂R from aromatic α -bromo ketones RCOCH₂Br and EtZnCH₂I in CH₂Cl₂ is believed to proceed via a Reformatsky-type reaction of α -bromo ketone, followed by C-C bond sigma-tropic rearrangement of the aldolate intermediate; aliphatic α -bromo ketones form 2,4-disubstituted furans or *cis*-1,2-disubstituted cyclopropanols in moderate yields.²³⁴ A tentative reaction scheme has been proposed to account for the contrasting results.

Acid bromides can be prepared directly from aldehydes with Br₃CCO₂Et under radical conditions; reactivity is greatest for aromatic aldehydes bearing an electron-donating group.²³⁵

Organocatalytic singly occupied molecular orbital (SOMO) activation has been used to achieve the first asymmetric α -enolation of aldehydes and thereby enable direct access to enantioenriched γ -ketoaldehydes (**64**) from simple aldehydes, enolsilanes, and a commercial catalyst (**61**) (Scheme 26).²³⁶ The asymmetric induction observed is consistent with addition of the enolsilane (**63**) to the *Si*-face of the intermediate radical cation (**62**) formed by one-electron oxidation of a transient enamine intermediate. (ee)

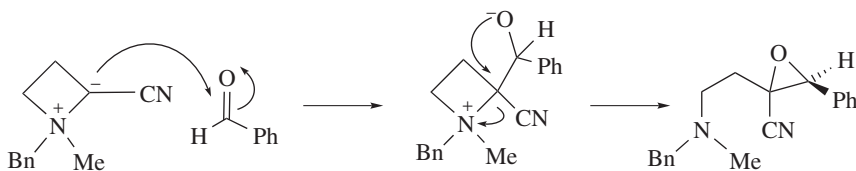


SCHEME 26

An intermediate enamine also features in the formation of α -phenylselenoaldehydes in high yields and up to 99% *ee* on reaction of *N*-(phenylseleno)phthalimide with aldehydes in the presence of a chiral secondary amine organocatalyst (TMS-protected α,α -diphenyl-2-pyrrolidinemethanol).²³⁷ (ee)

An experimental investigation of the epoxidation of benzaldehydes by sulfur ylides has determined $k^{12}/k^{13} = 1.026$ and $k^H/k^D = 0.93$ for isotopic substitution of the carbonyl carbon and aldehydic hydrogen, respectively; a Hammett $\rho = +2.50$ was determined for *para* substituents.²³⁸ The results are consistent with rate-determining carbanion addition.

As a consequence of inherent ring strain, azetidinium ylides have been found to effect facile diastereoselective epoxidation of aliphatic and aromatic aldehydes and ketones, giving rise to tri- or tetra-substituted epoxides (Scheme 27) that cannot be formed via classical ammonium ylide chemistry.²³⁹ (de)



SCHEME 27

Synthesis of enantiopure tetrahydrofuran-3-ols has been achieved by 5-*exo-trig* cyclization, whereby a δ -carbon radical (from tin hydride mediated deselenylation of 5-phenylseleno-3-oxapentanal) adds intramolecularly to the carbonyl group of an aldehyde.²⁴⁰

Mechanistic study of the role of homoleptic heavier alkaline earth amides, $M[N(\text{SiMe}_3)_2]_2(\text{THF})_2$ ($M = \text{Ca}, \text{Sr}, \text{Ba}$) as precatalysts for the dimerization of electron-

deficient aldehydes (RCHO) to the corresponding carboxylic esters (RCO₂CH₂R) (Tischenko reaction) is continuing.²⁴¹

A synthesis of naphthalene derivatives by rhenium-catalysed reactions of aromatic ketimines and aldehydes with dienophiles features initiation by C–H bond activation and aldehyde insertion followed by intramolecular nucleophilic cyclization, reductive elimination, elimination of aniline, Diels–Alder reaction, and dehydration.²⁴²

The scope and mechanism of formation of ketones (ArCOCH₂CH₂R and ArCOCHRMe) by intramolecular addition of aldehydes (ArCHO) to alkenes (RCH=CH₂) catalysed by Rh(I)–alkene complexes have been explored; kinetic and NMR studies have been used to establish the full catalytic cycle.²⁴³

A study of gas-phase lithium cation basicities of acetophenones has revealed a linear relationship with the corresponding proton basicities.²⁴⁴

Strecker and retro-Strecker reactions feature prominently in a strategy for enantioselective synthesis of amino acids RC*HNNH₂CO₂H via dissymmetric iminodinitriles RC*H(CN)NHC*(CN)R'R'' formed from chiral ketones R'R''CO, which can be recycled.²⁴⁵

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