

# Reactions of Aldehydes and Ketones and their Derivatives

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<b>Formation and Reactions of Acetals and Related Species</b> . . . . .	2
<b>Reactions of Glucosides and Nucleosides</b> . . . . .	3
<b>Reactions of Ketenes and Ketenimines</b> . . . . .	3
<b>Formation and Reactions of Nitrogen Derivatives</b> . . . . .	3
Imines: Synthesis and Tautomerism . . . . .	3
The Mannich Reaction . . . . .	5
Addition of Organometallics . . . . .	6
Other Alkylations and Allylations of Imines . . . . .	7
Reduction of Imines . . . . .	8
Iminium Species . . . . .	9
Other Reactions of Imines . . . . .	10
Oximes, Hydrazones, and Related Species . . . . .	13
<b>C–C Bond Formation and Fission: Aldol and Related Reactions</b> . . . . .	14
Stereoselective Aldol Reactions Using Proline Organocatalysts . . . . .	14
Other Stereoselective Aldol Reactions . . . . .	16
Mukaiyama and Vinylogous Aldols . . . . .	18
The Aldol-Tishchenko Reaction . . . . .	19
Nitro and Nitroso Aldols . . . . .	19
Other Aldol-type Reactions . . . . .	20
The Aza and Morita Variants of the Baylis–Hillman Reaction . . . . .	21
Allylation and Related Reactions . . . . .	22
Olefinations . . . . .	24
Alkynylations . . . . .	25
Michael Additions . . . . .	26
<b>Other Addition Reactions</b> . . . . .	27
General and Theoretical . . . . .	27
Addition of Organozincs . . . . .	27
Addition of Other Organometallics, Including Grignards . . . . .	29
The Wittig and Aza-Wittig Reactions . . . . .	30
Hydrocyanation, Cyanosilylation, and Related Additions . . . . .	30
Hydrosilylation and Related Reactions . . . . .	32
Miscellaneous Additions . . . . .	33
<b>Enolization and Related Reactions</b> . . . . .	36
$\alpha$ -Halogenation, $\alpha$ -Alkylation, and Related Reactions . . . . .	37

<b>Oxidation and Reduction of Carbonyl Compounds</b> . . . . .	38
Regio-, Enantio-, and Diastereo-selective Reduction Reactions . . . . .	38
Other Reduction Reactions . . . . .	41
Oxidation Reactions . . . . .	42
<b>Other Reactions</b> . . . . .	43
<b>References</b> . . . . .	44

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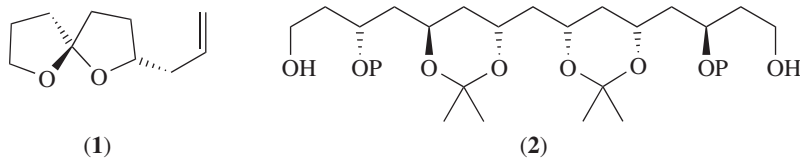
## Formation and Reactions of Acetals and Related Species

Chemoselectivities in the acetalization of *p*-nitro- and *p*-hydroxy-benzaldehyde have been studied for a range of bisnucleophiles, XCH<sub>2</sub>CH<sub>2</sub>Y (X, Y = OH, OH; SH, SH; SH, OH; and SH, NH).<sup>1</sup> The relative yields of products have been analysed in terms of atomic charges, Parr's global electrophilicity descriptor (*w*), and Pearson's hard-soft acid-base concept; such a global electrophilicity descriptor has also been used to explain acetalizations and thioacetalizations of substituted benzaldehydes, although it cannot handle steric factors.<sup>2</sup>

Pd[(-)-sparteine]Cl<sub>2</sub> catalyses the conversion of styrenes to their Markovnikov dialkyl acetals.<sup>3</sup> Deuterium labelling studies suggest an enol ether mechanism involving a Pd-H species.

The Eberlin reaction – polar acetalization and transacetalization in the gas phase – has been reviewed (249 references).<sup>4</sup> In addition to a detailed mechanistic treatment, several analytical applications are described, as are atmospheric pressure variants, relationships with condensed-phase reactions, and other gas-phase processes closely related to acetalization. Another review covers similar ground.<sup>5</sup>

Enantiopure 1,6-dioxaspiro[4.4]nonanes [e.g. (1)] have been prepared from an  $\alpha$ -hydroxy- $\omega$ -ene ketone, using a camphor-selenide auxiliary.<sup>6</sup>



Differentiation of 1,3-*anti*- and -*syn*-diols has been achieved via the selective hydrolysis of an *anti*-1,3-acetonide (2) containing an adjacent *syn*-acetonide.<sup>7</sup>

Gallium(III) chloride catalyses two useful reactions that employ isocyanides as a C<sub>1</sub> source: (i) an insertion into a C–O bond of an acetal and (ii) a 4 + 1-cycloaddition of  $\alpha,\beta$ -unsaturated carbonyl compounds. The catalysis appears to depend on the low affinity of GaCl<sub>3</sub> for heteroatoms.<sup>8</sup>

The reagent BH<sub>3</sub>.NMe<sub>3</sub>–AlCl<sub>3</sub> has been used to bring about reductive opening of acetals.<sup>9</sup> With mixed phenolic-benzylic acetal as reactant, the reagent acts regioselectively.

tively (in THF at 0 °C), yielding a benzylic ether and free phenol, probably because the borane first associates with the more basic benzylic oxygen. Conditions to bring about the inverse opening are being sought.

### Reactions of Glucosides and Nucleosides

A detailed experimental and computational study of the anomerization of glucose in water has been undertaken.<sup>10</sup> Following measurement of kinetic isotope effects (KIE) on rate constants for approach of  $\alpha$ -glucopyranose to its equilibrium with the  $\beta$ -anomer, these were converted into unidirectional KIEs using equilibrium isotope effects. Saturation transfer <sup>13</sup>C NMR spectroscopy then yielded the relative free energies of the transition states (TS) involved. Modelling, constrained by all the KIEs measured, then gave the anomerization TSs. Key findings include the observation that only one water molecule is required to participate, and that it must not hydrogen bridge OH(1) and O(5) simultaneously in either TS.

The mechanistic role of nucleotides in directing the growth of IR-emitting semiconductor nanocrystals has been investigated for a range of nucleotides, concentrations, stoichiometries, and temperatures.<sup>11</sup>

### Reactions of Ketenes and Ketenimines

A short review of the first 100 years of ketene chemistry covers haloketenes, Wolff rearrangements, stereoselective nucleophilic attack, dimerization, cycloadditions, ketene-Claisen and -Cope reactions,asketenes, and free radical processes.<sup>12</sup>

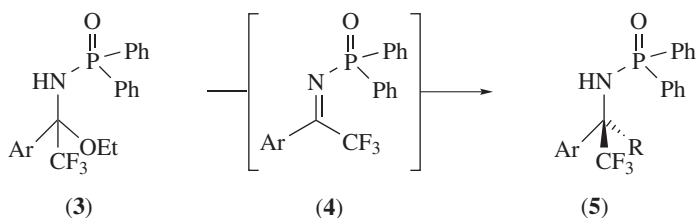
Two series of ketenimines, Ph-CH=C=N-Ph-*p*-R and *p*-R-Ph-CH=C=N-*i*-Pr, have been aminated with butylamine, with UV monitoring allowing rate measurement and hence construction of Hammett plots for each ring system.<sup>13</sup> Addition to the C=N bond to give vinylidenediamine intermediate is followed by tautomerization to amidine product. A switchover in rate-determining step is observed. Calculations indicate that the *N*-aromatic group provides significant electronic stabilization to the first TS.<sup>14</sup>

### Formation and Reactions of Nitrogen Derivatives

#### *Imines: Synthesis and Tautomerism*

Erbium(III) triflate is an efficient catalyst in the synthesis of aldimines, ketoimines, and enamines.<sup>15</sup> For aromatic imines, the problem of Michael addition found with the CeCl<sub>3</sub>/NaI-catalysed addition to unsaturated aldehydes is avoided.

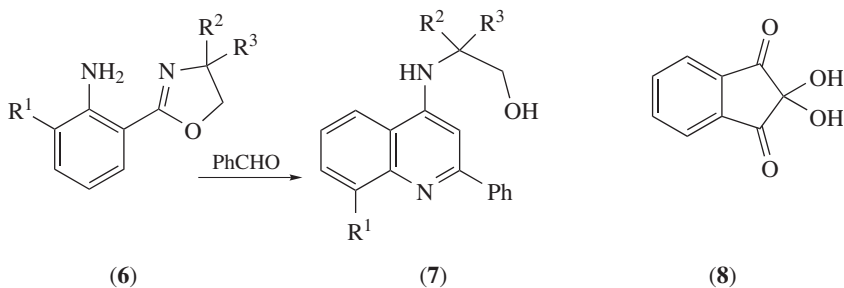
An *N*-phosphinoylhemiaminal (**3**) has been used as a precursor to trifluoromethylketimines (**4**); *in situ* alkylation with a dialkylzinc in the presence of a diphosphine monoxide auxiliary gives chiral  $\alpha,\alpha,\alpha$ -trifluoromethylamines (**5**) in high yield and *ee* up to 99%.<sup>16</sup>



The Skraup–Doebner–Von Miller synthesis of quinolines – involving condensation of an aniline with an  $\alpha,\beta$ -unsaturated ketone – has been investigated using  $^{13}\text{C}$ -labelled ketones in cross-over experiments: a complex fragmentation–recombination mechanism involving imine intermediates is indicated.<sup>17</sup>

In another synthesis of quinolines involving imine intermediates, *o*-oxazoline-substituted anilines (**6**) react with ketones in dry butanol reflux to give 4-amino-substituted quinolines [e.g. (**7**)], or 4-quinolones, using tosic acid as catalyst.<sup>18</sup> A mechanism involving ketoimine formation with subsequent tautomerization to give an enamine which attacks the oxazoline ring is discussed.

A related one-pot, three-component synthesis of  $\beta$ -amino carbonyl compounds has been achieved using a cascade reaction of anilines with aromatic aldehydes and car- (de)



An enantioselective one-pot, three-component imino-Reformatsky reaction has been reported.<sup>20</sup> Combining a benzaldehyde, an aniline, and an alkyl bromoacetate ester, (ee)

*ees* of up to 92% have been achieved in the  $\beta$ -amino ester product, using a recyclable *N*-methylephedrine as auxiliary. A nickel(II) salt and dimethylzinc are employed: the latter serves as dehydrating agent, reductant, and coordinating metal.

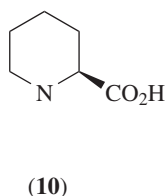
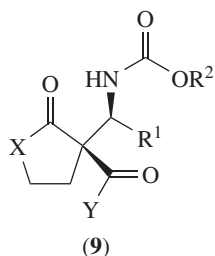
The kinetics and mechanism of the reaction of glycylglycine<sup>21</sup> and of valine<sup>22</sup> with ninhydrin (**8**) have been studied in aqueous micellar media.

*Cis*–*trans* isomerization in benzylideneaniline ( $\text{PhCH}=\text{NPh}$ ) has been found by computation to involve a single TS, and conformers leading to each isomer have been identified. However, kinetic selectivity of the two conformers depends on the reaction dynamics.<sup>23</sup>

### The Mannich Reaction

Most reports in this category deal with asymmetric processes. For example, classic Mannich reaction of unmodified ketones, aqueous formaldehyde, and aromatic amines produces  $\alpha$ -aminomethylation of the ketones in >99% *ee*, using L-proline as catalyst.<sup>24</sup> Methyl ketones regioselectively reacted on the methylene carbon. The method is simple, using wet solvents in the presence of air. (ee)

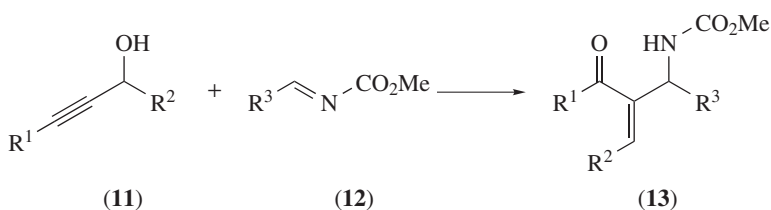
Direct Mannich reactions of cyclic 1,3-dicarbonyls with acyl imines,  $R^1\text{-CH=N-CO}_2R^2$ , gives  $\alpha$ -quaternary-carbon-bearing products (**9**; X = CH<sub>2</sub>, O; Y = Me, OMe, OEt) with yield/*de/ee* up to 98/90/99%, using cinchona alkaloid catalysts.<sup>25</sup> (de)  
(ee)



Mannich reactions between aldehydes and *N*-*p*-methoxyphenyl-protected  $\alpha$ -imino ethyl glyoxylate (PMP-N=CH-CO<sub>2</sub>Et) give high *ees* using (*S*)-pipecolic acid (**10**) as catalyst, but low *des*.<sup>26</sup> (*S*)-Proline also gives high *ee*, but also predominantly *syn* product. Calculations indicate that the transition structures involving the *s-cis*- and *s-trans*-enamine intermediates are much closer in energy in the case of catalyst (**10**). (de)  
(ee)

A highly enantioselective direct Mannich reaction of simple *N*-Boc-aryl and alkyl-imines with malonates and  $\beta$ -keto esters has been reported.<sup>27</sup> Catalysed by cinchona alkaloids with a pendant urea moiety, bifunctional catalysis is achieved, with the urea providing cooperative hydrogen bonding, and the alkaloid giving chiral induction. With yields and *ees* up to 99% in dichloromethane (DCM) solvent, the mild air- and moisture-tolerant method opens up a convenient route to *N*-Boc-amino acids. (ee)

Several other asymmetric Mannich-type processes have been described. Propargyl alcohols (**11**) undergo an addition to imines (**12**), to give 2-acylallylic carbamates (**13**), using an oxovanadium catalyst.<sup>28</sup> The reaction always gave the (*Z*)-enone, but a trial with a chiral propargyl alcohol showed virtually no enantioselectivity. (ee)



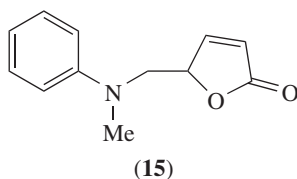
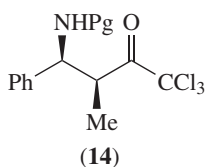
*N*-Sulfonylaldimines undergo Mannich-type addition to silyl enol ethers of ketones, giving  $\beta$ -amino carbonyl derivatives in up to 93% *ee* in the presence of a chiral ferrocene bearing *S*- and *P*-substituents complexed to copper(II).<sup>29</sup> (ee)

$\beta$ -Aminocarbonyl compounds have been prepared via Lewis base-catalysed Mannich reaction of TMS enol ethers and *N*-tosylaldimines,  $\text{ArCH}=\text{N}-\text{Ts}$ , with excellent *anti* selectivity in some cases.<sup>30</sup> (de)

A zinc-bis(BINOL) complex has been employed to effect chemoselective enolate formation from an  $\alpha$ -hydroxy ketone (in the presence of an isomerizable imine) to give a Mannich-type product in high *ee*.<sup>31</sup> (de)

Chiral *syn*- $\beta$ -amino esters have been prepared by addition of titanium ester enolates to aldimines containing an (*R*)- $\alpha$ -methylbenzylamine moiety.<sup>32</sup> (ee)

Benzaldimines bearing *N*-protection react diastereoselectively in a direct catalytic Mannich-type transformation with a trichloromethyl ketone donor,  $\text{Me}-\text{CH}_2-\text{C}(=\text{O})-\text{CCl}_3$ , using a Lewis base catalyst, lithium *p*-methoxyphenoxide, to give *syn*-amino ketone (**14**, in protected form).<sup>33</sup> Subsequent carbonyl reduction of (**14**) to give the carbinol sets up ring closure to azetidines, with the trichloromethyl moiety as the leaving group. (de)



Two redox-Mannich conversions have been described. A direct asymmetric reductive reaction produces three contiguous stereocentres with high chemo-, diastereo-, and enantio-selectivity.<sup>34</sup> An oxidative Mannich reaction has been employed to form a  $\gamma$ -aminoalkylbutenolide (**15**).<sup>35</sup> Starting with *N,N*-dimethylaniline, C-H oxidation yields iminium ion, which is then intercepted with 2-triisopropylsilylfuran as nucleophile. Carried out in T-HYDRO reagent (70% *t*-BuOOH in water) in the presence of air, dirhodium caprolactamate  $[\text{Rh}_2(\text{cap})_4]$  catalyses the reaction, giving yields of up to 95% in a few hours, using methanol co-solvent at 60 °C. Evidence for the intermediacy of the iminium ion includes rapid formation of  $\alpha$ -methoxyamine in the absence of the furan nucleophile. (de)

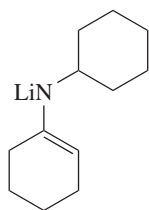
### Addition of Organometallics

Schiff bases,  $\text{Ar}^1-\text{CH}=\text{N}-\text{Ar}^2$ , that are unreactive with triethylaluminium alone undergo ethylation in the presence of cerium(IV); the reaction site is the methine.<sup>36</sup> The sterically sensitive reaction is favoured by electron-donating substituents. Excess  $\text{Et}_3\text{Al}$  is required, or cleavage to aldehyde and amine results.

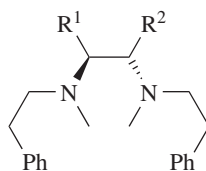
The structure of lithiated cyclohexanone *N*-cyclohexylimine (**16**) and its reactivity towards *C*-alkylation has been investigated experimentally and by DFT calculations.<sup>37</sup> (ee)

Formed from the imine using LDA in hexane, NMR studies reveal complex solvent-dependent distributions of monomers, dimers, and trimers in several ethereal solvents, although a mono-solvated dimer can be selected by appropriate choice of solvent. Study of *C*-alkylation rates suggests that both monomer- and dimer-based mechanisms operate. The lithioimines were compared with the isostructural lithium dialkylamides, but were shown to be *not* simply vinylogous analogues thereof.

(*S*)-*t*-Butylsulfinylferrocene has been added to a range of aryl- and alkyl-imines, via *o*-lithiation: some imines gave complete stereocontrol of the three stereocentres in the product, as shown by single-crystal X-ray analysis.<sup>38</sup> (de)



(16)



(17)

A pseudo- $C_2$ -symmetric tertiary diamine derived from (1*S*,2*S*)-(+)-pseudoephedrine (17,  $R^1 = \text{Me}$ ,  $R^2 = \text{Ph}$ ) has been prepared and tested in the enantioselective addition of methyllithium to aromatic imines.<sup>39</sup> It shows comparable *ee* and better reactivity than a genuinely  $C_2$ -symmetric relative [17,  $R^1, R^2 = -(\text{CH}_2)_4-$ ]. (ee)

A chiral rhodium(I)-diene complex catalyses the addition of dimethylzinc to *N*-tosylarylimines,  $\text{ArCH}=\text{NTs}$ , with *ees* up to 98%.<sup>40</sup> (ee)

$\alpha$ -Aldiminoesters,  $R^1-\text{N}=\text{CH}-\text{CO}_2R^2$ , undergo diethylzinc addition to give the corresponding  $\alpha$ -amino esters in high *ee* in the presence of a chiral titanium(IV) Lewis acid-Lewis base bifunctional catalyst.<sup>41</sup> (ee)

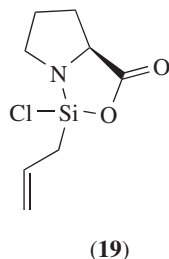
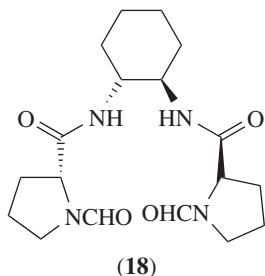
### Other Alkylations and Allylations of Imines

Primary alkyl radicals have been generated from alkyl iodides ( $\text{RCH}_2\text{I}$ ) using dimethylzinc and air as initiator; the radicals can then be used to alkylate *N*-tosylimines,  $\text{ArCH}=\text{NTs}$ , to give the corresponding amines,  $\text{ArCH}(\text{CH}_2\text{R})\text{NHTs}$ .<sup>42</sup> The latter process is promoted by  $\text{BF}_3$  etherate and catalysed by copper(II).

Di(*t*-butyl) tartrate has been used as an auxiliary to give asymmetric addition of alkynylzincs to nitrones, yielding optically active  $\alpha$ -substituted propargylic *N*-hydroxylamines.<sup>43</sup> Addition of product-like *N*-hydroxylamine boosted *ees* up to 95%. (ee)

A  $C_2$ -chiral bisformamide (18) derived from diaminocyclohexane catalyses the enantioselective allylation of simple aldimines, using allyltrichlorosilane in the presence of L-proline.<sup>44</sup> The more immediate allylating agent is, in fact, L-proline derivative (19), formed *in situ*, and observed by NMR and MS. (ee)

Phenols have been employed as directing groups in the enantioselective allylation of aldimines and ketimines using allylchlorosilane reagents.<sup>45</sup> (ee)



Ketoimines, including aromatic, heteroaromatic, and enolizable cases, have been allylated in a catalytic enantioselective process using CuF complexed with an axially chiral DuPHOS ligand and a non-toxic allylboronic pinacol ester as nucleophile.<sup>46</sup> Lithium isopropanoxide catalyses the reaction, and extensive <sup>11</sup>B NMR studies indicate that it does so by boosting formation of a copper alkoxyallylborate, H<sub>2</sub>C=CH-CH<sub>2</sub>-B(pinacol)<sup>-</sup>-<sup>+</sup>OR (R = *i*-Pr), which then reacts with copper(I) to generate allylcopper, H<sub>2</sub>C=CH-CH<sub>2</sub>-Cu, as immediate nucleophile. Addition of *t*-butanol gives even better results, through formation of a similar intermediate with R = *t*-Bu.

Regio- and stereo-selective allylation of sulfonylimines has been carried out with trifluoro(allyl)borates and allylstannanes, using 'palladium-pincer' complexes as catalysts.<sup>47</sup> *Syn* products predominate, in contrast to the corresponding reaction of aldehyde electrophiles; DFT calculations have been employed to probe the mechanistic differences.

### Reduction of Imines

Ruthenium and iridium are commonly used in catalysts for this reaction. A selectively deuterated hydroxycyclopentadienyl ruthenium hydride catalyst has been employed to probe the mechanism.<sup>48</sup> The relative rates of different steps determine whether the process is stereospecific (typically *trans*) or stereorandom.

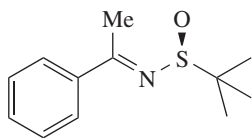
A water-soluble, recyclable ruthenium(II) complex including a chiral diamine ligand has been used for asymmetric transfer hydrogenation of cyclic imines and iminiums in water, with yields and *ee* up to 99%.<sup>49</sup>

Homogeneous catalytic hydrogenation of imines has been carried out using cationic iridium hydride catalysts.<sup>50</sup> The mechanistic possibilities are compared and contrasted with C=O hydrogenations.

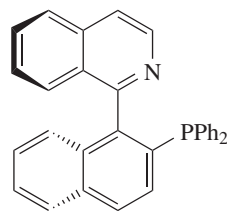
A new class of chiral phosphine-oxazolines act as ligands in iridium-catalysed asymmetric hydrogenation of imines, and of alkenes, giving *ees* up to 99%.<sup>51</sup>

Acyclic aromatic *N*-arylimines, Ar<sup>1</sup>-C(Me)=N-Ar<sup>2</sup>, have been reduced to the corresponding amine with up to 99% *ee*, using 1 atm of hydrogen and an iridium(I) catalyst bearing a chiral diphosphinoethane chelating ligand.<sup>52</sup>

Using cheaper metals, electron-deficient imines such as sulfinylimine (**20**) can be reduced by diethylzinc, using a chiral nickel(II) catalyst; yields and *des* >90% can be achieved.<sup>53</sup> Interestingly, ketones are unaffected by the process; many common reducing agents cannot so discriminate. <sup>1</sup>H NMR profiling indicates ethylene production, a



(20)



(21)

finding which supports an Et–Zn–N–C–Ni–Et intermediate, which eliminates the gas to give a nickel hydride which acts as immediate reductant of the carbon.

Formamides derived from L-pipecolic acid act as Lewis base organocatalysts for reduction of *N*-arylimines with trichlorosilane, giving yields and *ees* in the high 90s (ee) for a wide range of imine substrates.<sup>54</sup>

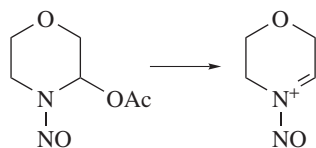
### Iminium Species

A QUINAP auxiliary (21), bound to copper(I), gives excellent enantioselectivity in the addition of terminal alkynes to isolated isoquinoline iminium cations.<sup>55</sup> (ee)

DFT calculations have been used to follow the formation of iminium ions from secondary amines and acrolein.<sup>56</sup> Energy barriers in the process can be lowered by incorporation of a heteroatom (N or O) in the  $\alpha$ -position of the amine, or an electron-withdrawing group (carbonyl or thiocarbonyl) in the  $\beta$ -position.

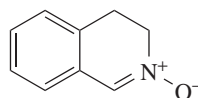
Pentafluorophenylation of iminium cations has been studied by DFT methods, and the experimental conditions have also been optimized.<sup>57</sup> Silane reagents, (F<sub>5</sub>C<sub>6</sub>)<sub>4–n</sub>SiF<sub>n</sub> (*n* = 1, 3) have been investigated, particularly with reference to their activation by weak Lewis bases. Pentafluorophenyl significantly stabilizes pentacoordinate silicon species, but as a group it is much more reactive in an apical than an equatorial position.

The synthesis and aqueous chemistry of  $\alpha$ -acetoxy-*N*-nitrosomorpholine (22) has been described.<sup>58</sup> It decomposes cleanly, with first-order kinetics, via an *N*-nitrosoiminium ion intermediate (23), with the pH–rate profile showing acid- and base-catalysed regions, and an extensive pH-independent region between 3 and 9, the latter being ca 100 times slower than its *C*-analogue, the corresponding piperidine derivative. Implications for the interaction of *N*-nitrosomorpholine with DNA are discussed.



(22)

(23)



(24)

Vinylzinc reagents have been added to 3,4-dihydroisoquinoline *N*-oxide (24) in up to 95% *ee*, using a chiral 2-aminoamide as auxiliary.<sup>59</sup> (ee)

Asymmetric catalysis of carbonyl transformations via iminium ion and enamine intermediates have been reviewed (35 references), including their recent merger in tandem iminium–enamine sequences.<sup>60</sup>

(ee)

### Other Reactions of Imines

Several of preparations of aziridines have been reported. The aza-Darzens reaction of an *N*-bromocyclohexanecarboxamide with *N*-diphenylphosphinylimines, ArCH=N–P(=O)Ph<sub>2</sub>, gives *cis*-aziridine derivatives, except if the aryl is *o*-substituted, which gives significant *trans* product, and even 100% *trans*- with *o*-CF<sub>3</sub>.<sup>61</sup> While steric factors play a role in this inversion of selectivity, electronic effects are also important: *o*-methyl gives a 50:50 ratio of products.

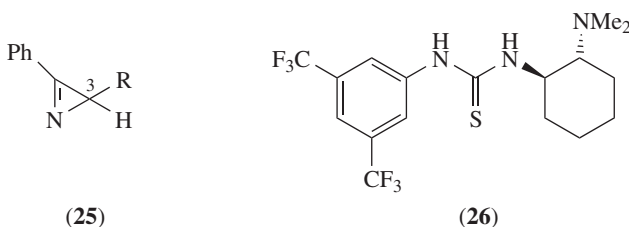
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A computational study has probed the origin of the diastereoselectivity in aziridine formation from sulfur ylides, Me<sub>2</sub>S<sup>+</sup>–CH<sup>–</sup>–R, and imines.<sup>62</sup> For semi-stabilized cases (R = Ph), betaine formation is non-reversible, so that selectivity is determined in the initial addition step. In contrast, for stabilized ylides (R = CO<sub>2</sub>Me), betaine formation is endothermic, and the elimination step becomes rate and selectivity determining.

(de)

Allylaziridines have been prepared in good yield by the action of allylindium reagents on azirines (e.g. **25**).<sup>63</sup> The C(3) substituent can control stereochemistry: hydroxy- (or acetoxy-) -methyl gives *cis*-allylation (via chelation with the indium reagent), whereas R = Me/Ph/CO<sub>2</sub>Et gives a *trans* result, presumably due to steric repulsion.

(de)



Enantioselective nucleophilic addition to imines has been carried out with a planar-chiral Lewis acid based on a 1,2-azaborolyl framework.<sup>64</sup>

(ee)

Addition and cyclization reactions of imines, catalysed by Brønsted acids, have been reviewed, including examples in water solvent and enantioselective cases.<sup>65</sup> Another review examines stereoselective nucleophilic additions to the C=N bond of aromatic azines (60 references).<sup>66</sup>

(ee)

(ee)

An enantioselective Strecker reaction involving Brønsted acid catalysis uses a BINOL-phosphoric acid, which affords *ees* up to 93% in hydrocyanations of aromatic aldimines in toluene at –40 °C.<sup>67</sup> The asymmetric induction processes in the stereoselective synthesis of both optically active *cis*- and *trans*-1-amino-2-hydroxycyclohexane-1-carboxylic acids via a Strecker reaction have been investigated.<sup>68</sup> A 2-pyridylsulfonyl group has been used as a novel stereocontroller in a Strecker-type process: *ees* up to 94% are suggested to arise from the ability of a chiral Lewis acid to coordinate to one of the sulfonyl oxygens.<sup>69</sup>

(ee)

(de)

(ee)

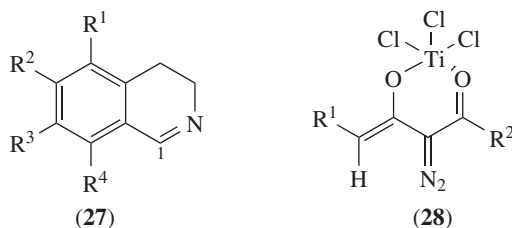
(ee)

The Strecker reaction of silyl cyanide ( $\text{H}_3\text{SiCN}$ ) with benzaldehyde *N*-methylimine ( $\text{PhCH}=\text{NMe}$ ), catalysed by an axially chiral 2,2'-bipyridine *N,N'*-dioxide has been explored computationally as a model for the corresponding reaction using  $\text{TMSCN}$ ,  $\text{PhCH}=\text{NCH}_2\text{Ph}$ , and a biquinoline dioxide.<sup>70</sup> The non-catalysed reaction is found to be concerted (via a five-membered ring TS), whereas the catalysis is stepwise, via a hexacoordinate hypervalent silicate. (ee)

A thiourea derived from hydroquinine (a cinchona alkaloid) acts as a general organic catalyst for asymmetric addition of stabilized nucleophiles to acylimines, giving secondary amine adducts in high *ee* and *de*. Sample reactions catalysed include asymmetric nitro-aldol and aza-Henry reactions.<sup>71</sup> Chiral thiourea (**26**) catalyses aza-Henry reactions of *N*-Boc-aldimines with nitroalkanes, giving *syn*- $\beta$ -nitroamines in high yield, *de*, and *ee*.<sup>72</sup> A bifunctional catalysis, with the thiourea *N*-Hs binding the nitro group and activating C–H deprotonation via the tertiary amine substituent, is discussed. (de) (ee) (de) (ee)

A cheap and efficient enantioselective aza-Henry reaction of nitromethane with a variety of *N*-protected arylaldimines has been reported.<sup>73</sup> Using zinc triflate and (–)-*N*-methylephedrine at  $-20^\circ\text{C}$ , yields and *ees* of up to 99% have been achieved with wide tolerance of aryl substituent in terms of both electronic nature and position. The auxiliary is also easily recycled. (ee)

Among addition reactions of imines, malonate esters have been added to dihydroisoquinolines (**27**) at C(1), to give the corresponding tetrahydro derivatives in high *ee*,<sup>74</sup> and enantiopure aromatic sulfoxides (prepared by *o*-directed metallation) have been added enantioselectively to imines.<sup>75</sup> (ee) (ee)

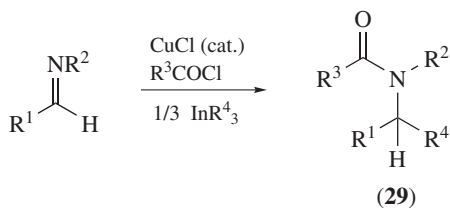


Titanium(IV) enolates derived from  $\alpha$ -diazo- $\beta$ -keto esters or ketones (**28**) efficiently add to  $\text{TiCl}_4$ -activated *N*-tosylimines to give the corresponding  $\delta$ -*N*-tosylamino derivative.<sup>76</sup> Subsequent diazo decomposition – catalysed by rhodium(II) or light – yields useful pyrroles or  $\gamma$ -lactams, respectively.

Scandium triflate catalyses a highly diastereoselective addition of imines to 1,1-cyclopropane diesters to give multi-substituted pyrrolidines.<sup>77</sup> (de)

Non-activated imines have been pentafluorophenylated with  $(\text{F}_5\text{C}_6)_3\text{SiF}$ ; protonation activates the imine, and chloride ions activate the silane.<sup>78</sup>

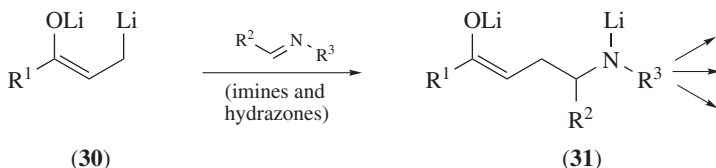
Highly substituted amides (**29**) have been prepared in a three-component reaction of an imine, an acid chloride, and trialkylindium.<sup>79</sup> Proceeding under mild conditions and high metal efficiency, the ‘alkyl’ group on indium can also be aryl, heteroaryl, or vinyl.



Carbonyls protected as azines or other C=N derivatives can be deprotected in seconds using HOF.MeCN, a reagent easily generated from dilute fluorine in water.<sup>80</sup> Sensitive groups such as cyclic acetals of ketones elsewhere in the substrate often survive. As the electrophilic oxygen in the reagent is derived from water, the method is easily adapted to produce isotopic oxygen labelling in carbonyls.

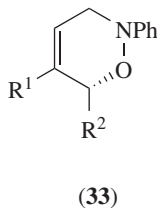
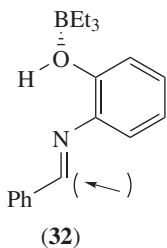
A study of the Staudinger synthesis of  $\beta$ -lactams from a diazo ketone, an acid chloride, and an imine (under basic conditions) has explored the *cis/trans* selectivity as a function of time, temperature, solvent, and the order of addition of reagents.<sup>81</sup>

Ketone dilithio- $\alpha,\beta$ -dianions (**30**, formed by treatment of  $\beta$ -stannylketones,  $\text{RCOCH}_2\text{-CH}_2\text{SnBuCl}_2$ , with 4 equiv. of BuLi) react with imines and hydrazone selectively at the  $\beta$ -anion portion to give dilithium enolate amides (**31**).<sup>82</sup> Subsequent reaction with electrophiles gives  $\gamma$ -amino ketones and related heterocycles.



Among reports related to radicals, *ab initio* calculations have been used to model intramolecular additions of acyl radicals to imines.<sup>83</sup> Imines and oxazolines bearing a pendant acyl radical at carbon have been cyclized to give 2-piperidones through a selective 6-*endo*-cyclization at nitrogen.<sup>84</sup> The acyl radical is generated via CO de insertion into a suitable precursor. A diastereoselective example is also reported.

Nucleophilic carbon radicals can *C*-alkylate imines, a process which is found to be substantially facilitated by an *o*-phenolic substituent as in e.g. (**32**).<sup>85</sup> The hydroxyl is ee presumed to stabilize an intermediate aminyl radical. An enantioselective version of the reaction is also reported.



## Oximes, Hydrazones, and Related Species

The Beckmann rearrangement of cyclohexanone oxime has been modelled kinetically, focusing on simulation of industrial conditions, and taking into account self-catalysis and the role of polymorphs.<sup>86</sup>

Chiral 1,2-oxazines (**33**) have been prepared from achiral ketones,  $R^1-CO-CH_2-R^2$ , via an  $\alpha$ -oximation step (with a tetrazolylpyrrolidine organocatalyst), followed by a Wittig reaction.<sup>87</sup> Subsequent N–O cleavage yields enantiopure *cis*-allylic alcohols bearing a pendant amine. (ee)

Aryl alkyl ketoxime ethers,  $Ar-C(R^1)=N-OR^2$ , have been reduced with borane-THF at ca 0 °C to give amines,  $Ar-^*CH(R^1)-NH_2$ .<sup>88</sup> A chiral BINAP with an  $O_3BN$  framework gives up to 98% *ee*. (ee)

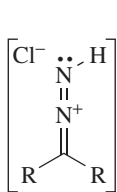
The kinetics of oxidative deoxygenation of aldo- and keto-oximes by 2,2'-bipyridinium chlorochromate (back to the parent carbonyl compounds) have been studied in DMSO, where the reaction is found to be first order in both oxime and oxidant.<sup>89</sup> The aldoximes proved more reactive, and rates correlated well with the Pavelich–Taft dual substituent equation. Following extension of the study to hindered cases, and to 18 other solvents (analysed by Taft and Swain multi-parameters), a cyclic intermediate is proposed for the rate-determining step. The same reaction order behaviour is found using the pyridinium version, and again electronic, steric, and solvent effects were examined.<sup>90</sup>

Electroanalytical techniques indicate the formation of two carbinolamine intermediates and one monohydrazone in the reaction of terephthalaldehyde with hydrazine at pH 7.3.<sup>91</sup>

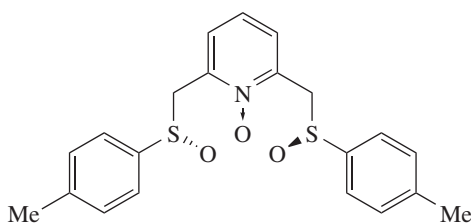
Reaction of hydrazones with iodine under basic conditions, to give azines, shows evidence of diazo intermediates that can be trapped with an internal alkene or alkyne function.<sup>92</sup>

Unsubstituted hydrazones of aromatic ketones and aldehydes have been converted in high yield to alkyl chlorides under Swern oxidation conditions, although the substrate actually undergoes a net reduction.<sup>93</sup> When the hydrazone is dideuterated, a deuterium ends up on the carbon, supporting the proposed intermediacy of cation (**34**), which tautomerizes and loses  $N_2$ , to give a carbocation which combines with the chloride. This experiment also suggests a convenient method to produce deuterium-labelled alkyl chloride from the corresponding aldehyde/ketone.

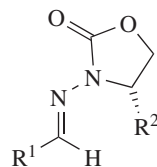
A new  $C_2$ -symmetric bis-sulfoxide/*N*-oxide (**35**; *R,R*-) promotes allylation of *N*-benzoylhydrazones with allyltrichlorosilane in up to 76% *ee*.<sup>94</sup> (ee)



(34)



(35)



(36)

Chiral *N*-acylhydrazones (**36**) – derived from an aldehyde (RCHO) and 4-benzyl-2-oxazolidinone – are sufficiently conformationally restricted to impart facial selectivity to C=N bond addition.<sup>95</sup> Using indium(III) triflate, they undergo highly diastereoselective fluoride-initiated allylsilane addition, i.e. the aza-Sakurai reaction. Mechanistic investigation suggests a dual activation process in which the hydrazone is electrophilically activated via formation of its indium complex, followed by nucleophilic attack by an allylfluorosilicate species, [(allyl)<sub>4</sub>SiF<sup>-</sup>], leading to homoallylic amine adducts. (de)

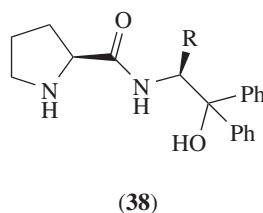
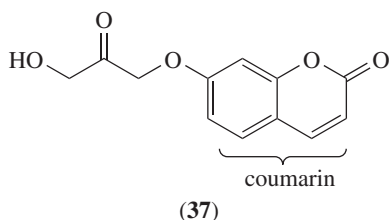
## C–C Bond Formation and Fission: Aldol and Related Reactions

### Stereoselective Aldol Reactions Using Proline Organocatalysts

The use of L-proline, amides derived from it, and related amino acids and small peptides as asymmetric organocatalysts for aldols – and indeed many other reactions mentioned elsewhere in this chapter – expanded hugely in 2006. A review deals with the direct aldol case.<sup>96</sup> (ee)

L-Proline catalyses direct aldols of trifluoroacetaldehyde ethyl (hemi)acetals, F<sub>3</sub>C–CH(OH)–OX (X = H, CH<sub>2</sub>CH<sub>3</sub>, CH<sub>2</sub>CF<sub>3</sub>), with ketones at room temperature to produce β-hydroxy-β-fluoromethylated ketones with *des* up to 96% and *ees* up to 91%.<sup>97</sup> (de) (ee)

Many reactions have also been carried out in water. The mechanisms of the reactions of acetone and 1,3-dihydroxyacetone using zinc–proline and related catalysts have been probed kinetically.<sup>98</sup> The former exhibits an enamine route, whereas the latter involves rate-limiting deprotonation of the α-carbon and formation of an enolate. An umbelliferyl ether of dihydroxyacetone (**37**) has been used as a fluorogenic probe for enolization, which may prove useful in screening of aldolases in water. (ee)



*trans*-4-Hydroxyproline is readily available in both enantiomeric forms. It catalyses direct aldols in water with high *de* and *ee*, as do several of its silyloxy analogues.<sup>99</sup> (de)

The first asymmetric direct aldol of 1,2-diketones and ketones, to give 2-hydroxy-1,4-diketones, has been reported.<sup>100</sup> L-Proline derivatives give high regio-, diastereo-, and enantio-selectivity in the reaction of 1-arylpropane-1,2-diones with simple ketones. (ee)

Several reports describe additives: for example, tertiary amine bases, weak acids, and strong acids have been examined, with limited effect, except for the strong acids, which stop the reaction completely.<sup>101</sup> C<sub>2</sub>-symmetric chiral diols substantially improve proline-catalysed *ee*, conversion efficiency, and yield in the reaction of acetone with benzaldehyde, with addition of (*S*)-BINOL giving further improvement.<sup>102</sup> (ee)

PEG [poly(ethylene glycol)] – a non-toxic and widely used solvent – has been successfully used with proline; no loss of activity was found when both PEG and proline were recycled 10 times.<sup>103</sup>

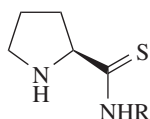
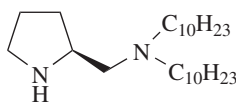
Several prolinamides have been examined: **(38)** catalyses the reactions of acetone with both aliphatic and aromatic aldehydes with *ees* up to 97%.<sup>104</sup> It is proposed that amide and alcohol groups simultaneously donate hydrogen bonds to the aldehyde, while the *gem*-diphenyl moiety's bulk orients the aldehyde's approach.

An L-prolinamide gives high regio-, diastereo-, and enantio-selectivity in direct aldols of *p*-nitrobenzaldehyde with chloroacetone, giving *anti*- $\alpha$ -chloro- $\beta$ -hydroxy ketones;<sup>105</sup> prolinamides with groups such as tetrazole or benzimidazole attached (via a methylene) to the amide nitrogen give *ees* up to 96% for acetone reacting with electron-deficient aromatic aldehydes.<sup>106</sup>

A range of prolinamides, some bearing one or more additional amino groups, have been developed as catalysts in water;<sup>107</sup> *o*-hydroxyaromatic substituents likewise give high selectivity in this solvent (and in neat ketone solution) for direct aldols of araldehydes with ketones.<sup>108</sup>

Sterically and electronically tuneable and bifunctional organocatalysts based on diamides derived from proline are particularly selective in reactions of heterocyclic ketones with aldehydes.<sup>109</sup>

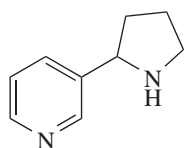
L-Prolinethioamides (**39**, R = alkyl including chiral alkyl), prepared from proline and amines, are effective in acetone–benzaldehyde reactions.<sup>110</sup> Mechanistic studies focused in particular on suppression of non-enantioselective side-reactions, and also on the role of the side-chain of the catalyst acting as hydrogen bond donor, especially as the thioamides (with their more acidic N–H protons) are more catalytic than their amide analogues.

**(39)****(40)**

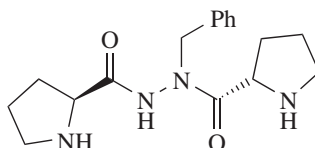
A range of proline derivatives have been employed as enamine-based organocatalysts of direct aldols in water, without organic co-solvent.<sup>111</sup> Using the reaction of cyclohexanone with benzaldehydes as a test bed, lipophilic diamine **(40)** in the presence of TFA proved to be an excellent bifunctional catalyst system, giving performance up to 99/90/99% in terms of conversion/*delee*. Alkyl chains of **(40)** make an organic microphase likely.

A computationally derived model for catalysis of the aqueous aldol by nornicotine **(41)** has been tested (by the same authors) via kinetic isotope effects (KIEs) and thermodynamic measurements.<sup>112</sup> A proton inventory indicates that the computational results are not conclusive, and a water molecule is involved in or before the rate-determining step.

New chiral  $\alpha$ -aminophosphonates related to proline catalyse enantioselective direct aldols; *syn* selectivity is also achieved on addition of bases such as DBU or DBN.<sup>113</sup>



(41)



(42)

*N'*-Benzyl-*N'*-prolylhydrazide (**42**), in its protonated form, gives high *ee* in the acetone–benzaldehyde reaction.<sup>114</sup>

A dendrimer bearing *N*-prolylsulfonamide catalytic groups achieves up to 99% yield, *de*, and *ee* in direct aldols in water.<sup>115</sup>

BINAM – the diamino analogue of BINOL – has been converted to its  $C_2$ -symmetric bis(prolinamide).<sup>116</sup> The latter acts as a recoverable catalyst of direct aldols in DMF–H<sub>2</sub>O at 0 °C, giving high *des* and *ees*. Butan-2-one showed significant regioselectivity, giving predominantly the iso product.

Multi-functional enantioselective catalysts for direct aldol and Mannich reactions have been prepared from (*S*)-proline and 2,2'-diaminoBINAP.<sup>117</sup>

Among the uses of other amino acids, L-tryptophan gives high *ees* and *des* in direct aldols of cyclic ketones and benzaldehydes in water;<sup>118</sup> hydrophobic and aryl-stacking effects have been considered in explaining the selectivities.

$\beta$ -Homoamino acids have been tested as enantioselective catalysts of intra- and inter-molecular aldols.<sup>119</sup>

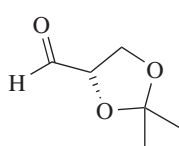
$\alpha$ - and  $\beta$ -amino acids, chiral primary amines, and small peptides have been investigated as organocatalysts of direct aldols in non-aqueous systems, with *ees* up to 99% in some cases.<sup>120</sup> Enantioselectivities were raised in some instances by the addition of water, suggesting a significant role for hydrogen bonding. The implications for the evolution of homochirality in sugars are discussed.

Small peptides – simple di- and tri-peptides with a primary amine at the N-terminus – catalyse the aqueous aldol between unmodified ketones and aldehydes with up to 86% *ee*.<sup>121</sup> This is dramatically different from the corresponding amino acid-catalysed reaction, suggesting that peptide formation may have been significant in the evolution of asymmetric synthesis. Addition of  $\alpha$ -cyclodextrin raised the *ee* further through the hydrophobic effect.

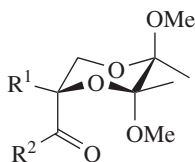
### Other Stereoselective Aldol Reactions

To address limitations in the use of glyceraldehyde acetonide (**43**) as a three-carbon chiral building block, butane-2,3-diacetal-protected glyceraldehyde (**44**, R<sup>1</sup> = R<sup>2</sup> = H) has been prepared. It undergoes diastereoselective aldol reactions with a range of carbonyl compounds: esters, thioesters, and ketones. The work has been extended to other derivatives such as the  $\alpha$ -substituted aldehyde (**44**, R<sup>1</sup> = Me, allyl) and the methyl ketone (**44**, R<sup>2</sup> = Me).<sup>122a,b</sup>

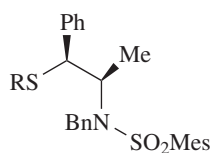
A highly diastereoselective aldol of an  $\alpha$ -CF<sub>3</sub>-substituted enolate has opened up a new route to trifluoromethyl-substituted chiral centres.<sup>123</sup>



(43)



(44)

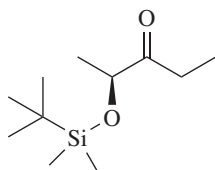


(45)

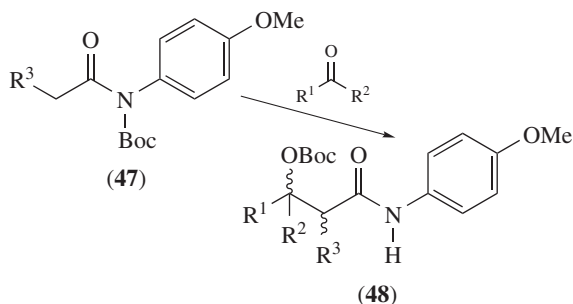
A new thiol auxiliary (**45**, R = COEt) participates in boron-mediated *anti*-aldol reactions with aldehydes with high yield and *de*.<sup>124</sup> Reaction of the product with nucleophiles displaces it (in the form of the thiol, **45**; R = H), converting the aldol product under mild conditions into esters, thiolates, phosphonates, alcohols, or acids. (de)

Hydrogen bonding and steric effects have been investigated in a theoretical study of the origin of the diastereoselectivity in the remote 1,5-stereoinduction of boron aldol reactions of  $\beta$ -alkoxy methyl ketones;<sup>125</sup> high levels of 1,5-*anti*-stereocontrol have been achieved in such reactions of  $\alpha$ -methyl- $\alpha$ -alkoxy methyl ketones, giving both Felkin and anti-Felkin products.<sup>126</sup> (de)

(*S*)-2-*t*-Butyldimethylsilyloxypentan-3-one (**46**), a lactate-derived chiral ketone, undergoes titanium-mediated aldols giving all-*syn* products in high *de*.<sup>127</sup> Low-temperature <sup>1</sup>H and <sup>13</sup>C NMR evidence suggests a likely TS to account for the selectivity. (de)



(46)



(48)

A highly *anti*-selective catalytic aldol reaction of amides with aldehydes has been reported.<sup>128</sup> The amide – specifically an *N*-Boc-aniside (**47**) – gives the aldol product (**48**) with the Boc group transferred to oxygen. Catalysed by barium phenoxides, the reduction proceeds under mild, convenient conditions (THF, 0 °C, 24–48 h), giving high yields and *des*. A wide variety of aldehyde types work (though aliphatics give low yields), and a trifluoromethyl ketone example is also reported, as are initial investigations of enantioselective cases. (de)

A catalytic enantio- and diastereo-selective aldol reaction of ketones with ketene silyl acetals, H<sub>2</sub>C=C(OTMS)–OMe, gives fair to good yields and *ee*.<sup>129</sup> With further substitution of the vinyl function, the reaction is diastereoselective, up to 97%. A highly developed catalyst/promoter protocol is employed: a copper(I) fluoride complex is combined with a Taniaphos auxiliary (a chiral ferrocenyldiphosphine), plus (EtO)<sub>3</sub>SiF. Evidence for the formation of species (EtO)<sub>4–n</sub>SiF<sub>n</sub> (*n* ≥ 2) as active (ee)

trapping silyl agents is presented. These intermediates appear to form more rapidly when  $K^+ PhBF_3^-$  is added, by direct reaction with  $(EtO)_3SiF$ .

A systematic study of methyl ketone aldol additions with  $\alpha$ -alkoxy and  $\alpha,\beta$ -bisalkoxy aldehydes has been undertaken, under non-chelating conditions.<sup>130</sup> With a single  $\alpha$ -alkoxy stereocentre, diastereoselectivity generally follows Cornforth/polar Felkin–Anh models. With an additional  $\beta$ -alkoxy stereocentre,  $\pi$ -facial selectivity is dramatically dependent on the relative configuration at  $\alpha$ - and  $\beta$ -centres: if they are *anti*, high *de* results, but not if they are *syn*. A model for such acyclic stereocontrol is proposed in which the  $\beta$ -alkoxy substituent determines the position in space of the  $\alpha$ -alkoxy relative to the carbonyl, thus determining the  $\pi$ -facial selectivity. (de)

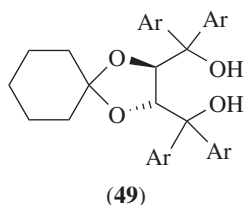
### Mukaiyama and Vinylogous Aldols

An aldol reaction of a trimethoxysilyl enol ether, catalysed by a lithium binaphtholate, shows *anti* diastereoselectivity and modest *ees* under dry conditions, but addition of water brings about *syn* adduct formation, with higher *ee*.<sup>131</sup> (de)

Silyl Lewis acid-induced Mukaiyama aldol reactions have attracted considerable mechanistic attention lately.<sup>132</sup> In a study which considers five mechanisms (including a new one), the effect of the conjugate base of the Lewis acid is examined. Considering three cases,  $^-NTf_2$ ,  $^-CTf_3$ , and  $^-OTf$ , the catalytic cycles are suggested to be significantly different between the low-nucleophilicity cases (the first two) and the relatively highly nucleophilic  $^-OTf$ . (de)

Scandium(III) and lutetium(III)<sup>133</sup> and zinc<sup>134</sup> complexes of  $C_2$ -symmetric pyridine–bis(oxazoline) (PYBOX) ligands are highly effective enantioselective catalysts of Mukaiyama aldol reactions. (ee)

A TADDOL derivative (**49**, Ar = 1-naphthyl) is a potent diastereo- and enantioselective catalyst; an X-ray structure of a complex of (**49**) with an aldehyde indicates (i) an intramolecular hydrogen bond in the catalyst and (ii) a hydrogen bond from catalyst to aldehyde.<sup>135</sup> It is therefore proposed that the asymmetric activation of the aldehyde arises from hydrogen bonding to a pre-organized catalyst. (de)



A chiral silver-based catalyst – formed from an amino acid and  $AgF_2$  – promotes efficient enantioselective addition of enolsilanes to  $\alpha$ -keto esters in THF at temperatures as low as  $-30^\circ C$ , with yields and *ees* in the high 90s.<sup>136</sup> (ee)

Chiral sulfoximines liganded to copper(II) give highly enantioselective vinylogous Mukaiyama-type aldol reactions under mild conditions.<sup>137</sup> A chiral sulfinyl group has been used to achieve 1,5- and 1,6-asymmetric induction in Mukaiyama aldols, using  $Yb(OTf)_3$  catalysis.<sup>138</sup> (ee)

### The Aldol-Tishchenko Reaction

A short review examines the current status and prospects for the direct asymmetric aldol-Tishchenko reaction, a process which allows for stereocontrol of three contiguous chiral centres in ‘three-aldehyde’ or ‘aldehyde–ketone–aldehyde’ reactant combinations.<sup>139</sup> (ee)

*anti*-1,3-Diols have been prepared in good yield and enantioselectivity, and high diastereoselectivity, by reaction of aromatic aldehydes with aliphatic or aromatic ketones.<sup>140</sup> The chiral ytterbium catalyst employed – derived from Yb(III) triflate and an ephedrine – promotes both the aldol reaction (through enolization) and the Evans–Tishchenko reduction of the aldol intermediate. (de)  
(ee)

### Nitro and Nitroso Aldols

The catalytic asymmetric Henry reaction has been reviewed.<sup>141,142</sup>

Chiral iminopyridines catalyse nitro aldol reactions with good *ees* in the presence of copper(II) acetate, without the need for exclusion of air or moisture.<sup>143</sup> A phenylalanine-derived Schiff base – also complexed to copper(II) – is also effective, with the advantage that product configuration is easily reversed (by using the enantiomeric phenylalanine).<sup>144</sup> (de)  
(ee)  
(ee)

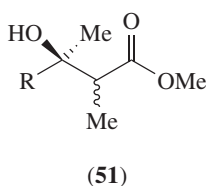
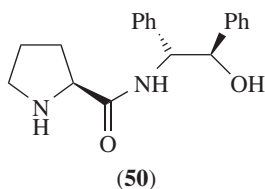
$\beta,\gamma$ -Unsaturated  $\alpha$ -keto esters such as *trans*-MeCH=CHCOCO<sub>2</sub>Et undergo enantioselective reaction with nitromethane, using new catalytic auxiliaries based on cinchona alkaloids.<sup>145</sup> Carried out at –20 °C in DCM, the organocatalysts give high conversion, predominantly reaction at ketone only (typically <5% of product involves simultaneous addition to the alkene), and up to 97% *ee*. (ee)

A diastereomeric guanidine–bisthiourea bifunctional organocatalyst gives high *ees* and *des* in nitroaldols in a biphasic system: toluene–water at 0 °C.<sup>146</sup> (de)

A dichloro[(-)-sparteine-*N,N'*]copper(II) catalyst in cold MeOH–Et<sub>3</sub>N gives good yields and *ees* of 73–79%.<sup>147</sup> (ee)

While metal–phosphine complexes can apparently catalyse the nitroaldol, it may be the free phosphine that is involved.<sup>148</sup> Testing of phosphines under metal-free conditions, and addition of extra phosphine in the presence of metal–phosphine complexes, have both been shown to catalyse the reaction.

In direct nitroso aldol reactions of  $\alpha$ -branched aldehydes, an L-prolinamide (**50**) catalyses to give  $\alpha$ -hydroxyamino carbonyl compounds which are otherwise disfavoured; *ees* up to 64% were found.<sup>149</sup> Another prolinamide derivative gives similar results in a nitrosobenzene reaction.<sup>150</sup> For proline-catalysed cases involving highly substituted cyclohexanones, DFT calculations have highlighted the roles of electrostatic and dipole–dipole interactions in the level of *de* achieved.<sup>151</sup> (ee)  
(ee)  
(ee)  
(de)



### Other Aldol-type Reactions

Migration of silyl groups from  $\alpha$ - to  $\beta$ -oxygen in a sodium aldol reaction has been reported.<sup>152</sup>

A cationic rhodium complex,  $[(\text{Me}_5\text{Cp})\text{Rh}(\eta^6\text{-benzene})]^{2+}$ , catalyses direct aldol condensation of ketones.<sup>153</sup>

A DFT study of enolborane addition of  $\alpha$ -heteroatom-substituted aldehydes has focused on the relevance of the Cornforth and polar Felkin–Anh (PKA) models for asymmetric induction.<sup>154</sup> Using chiral substrates,  $\text{MeCH}(\text{X})\text{CHO}$ , polar ( $\text{X} = \text{F}, \text{Cl}, \text{OMe}$ ) and less polar ( $\text{X} = \text{SMe}, \text{NMe}_2, \text{PMe}_2$ ) substituents have been examined. The former favour Cornforth TS structures, the latter PKA. TS preferences have been correlated with the relative energy of the corresponding rotamer of the uncomplexed aldehyde. An in-depth study of addition of (*E*)- and (*Z*)-enolborane nucleophiles to 2-methoxypropanal successfully predicts experimentally determined diastereofacial selectivities. (de)

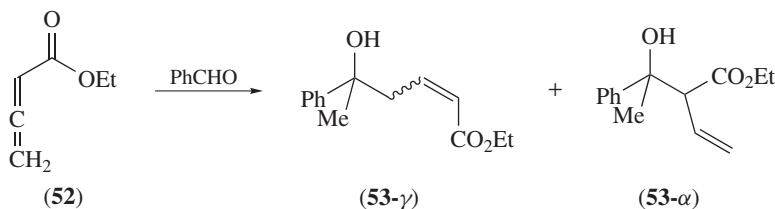
Direct aldol-type condensations of aldehydes with ethyl diazoacetate to give  $\beta$ -hydroxy- $\alpha$ -diazocarbonyl compounds,  $\text{R}-\text{CH}(\text{OH})-\text{C}(=\text{N}_2)-\text{CO}_2\text{Et}$ , are catalysed by tetrabutylammonium hydroxide.<sup>155</sup>

A nickel hydride complex,  $\text{NiHCl}(\text{diphenylphosphinoethane})$ , catalyses the tandem isomerization–aldolization reaction of allylic alcohols with aldehydes.<sup>156</sup> The atom-efficient process proceeds at or below ambient temperature with low catalyst loading, and works well even for bulky aldehydes. Magnesium bromide acts as a co-catalyst, and mechanistic investigations suggest that a free enol is formed, which then adds to the aldehyde in a ‘hydroxyl–carbonyl–ene’-type reaction. (de)

A domino reduction–aldol reaction of ketones with methyl acrylate produces tertiary alcohols bearing an ester group (**51**) in high *ee* and *de*.<sup>157</sup> Using a diphosphine-modified copper(I) fluoride complex in the presence of phenylsilane, the method avoids having to preactivate the nucleophile prior to the C–C bond-forming step. (de)  
(ee)

Three types of one-pot catalytic enantioselective reductive aldol reactions of ketones have been described,<sup>158</sup> giving fair to excellent *ees* with a BINAP auxiliary. (ee)

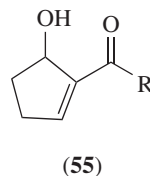
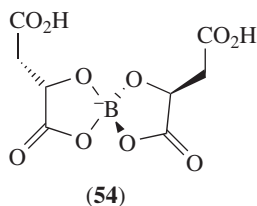
Reductive aldol reaction of an allenic ester (**52**) to a ketone such as acetophenone can give  $\gamma$ - (**53- $\gamma$** ) or  $\alpha$ -product (**53- $\alpha$** ).<sup>159</sup> Using as catalysts a copper salt and a range of chiral phosphines, together with phosphine additives such as the triphenyl or tricyclohexyl compounds, a highly selective set of outcomes can be achieved, e.g. (**53- $\gamma$** ) almost exclusively *cis*- with 99% *ee*, or – without additive – significant amounts of (**53- $\alpha$** ) can be formed (as a *syn-anti* mixture). A diastereoselective implementation of the latter has also been developed. (de)  
(ee)



New 4-substituted phenyl(bisoxazoline) ligands (PHEBOX ligands) have been complexed with rhodium and examined as enantioselective catalysts of the reductive aldol of acrylates and aldehydes.<sup>160</sup> The results have been compared with the corresponding pyridine-centred (PYBOX) ligand complexes.

### The Aza and Morita Variants of the Baylis–Hillman Reaction

Chiral solvents rarely induce significant enantioselectivity, but *ees* up to 84% have been achieved in an aza-Baylis–Hillman reaction.<sup>161</sup> Using an ionic liquid (IL), the anion of which is a dimalatoborate (**54**), it is suggested that the high enantioselectivity arises from strong ion-pair and hydrogen bond interactions with the zwitterionic intermediate of the reaction, i.e.  $\text{IL-B}^- \cdots \text{R}_3\text{P}^+ - \text{CH}_2 - \text{CH} = \text{C}(\text{Me}) - \text{O}^- \cdots \text{HO-IL}$ .



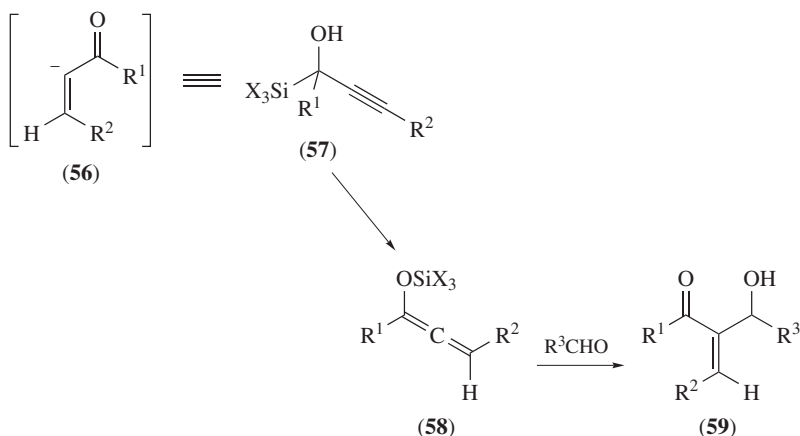
Chiral thiourea derivatives have been employed as catalysts; although yields are modest, *ees* up to 99% have been recorded.<sup>162</sup> For the DABCO-promoted reaction of an *N-p*-nitrobenzenesulfonylimine with methyl acrylate, a DABCO–acrylate–imine adduct was isolated as a key intermediate.

A new tandem Michael–aldol reaction of  $\alpha,\beta$ -unsaturated compounds bearing a chalcogenide or thioamide group with electrophiles has been reviewed.<sup>163</sup> The product  $\alpha$ -( $\alpha$ -hydroxyalkyl)enones – Morita–Baylis–Hillman (MBH) adducts – can be formed with significant stereocontrol when an optically active thione is used.

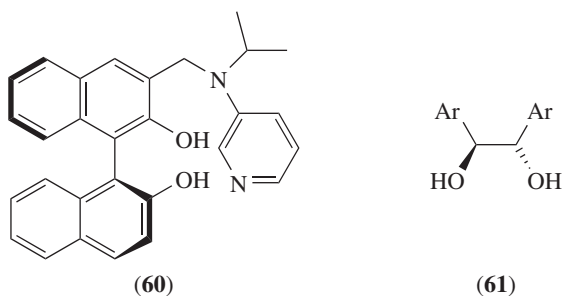
Enones with a pendant aldehyde,  $\text{RC}(=\text{O})-\text{CH}=\text{CH}-(\text{CH}_2)_2-\text{CHO}$ , have been cyclized via an intramolecular MBH reaction in a study of the influence of Michael acceptor stereochemistry on yield.<sup>164</sup> Using triphenylphosphine as catalyst, the *Z*-isomer consistently gave 2.5–8.5 times higher yield of the product (**55**), using reaction times of 1–3 days. It is unclear whether this is due to the relative accessibility of the  $\beta$ -positions of the isomers to the nucleophilic catalyst, or differential stability in the enolate intermediates.

A new ionic liquid – a dinaphthalene imidazolium salt – catalyses the MBH reaction.<sup>165</sup>

As an alternative to the MBH generation of  $\alpha$ -acylvinyl anions (**56**),  $\alpha$ -hydroxypropargylsilanes (**57**) can be used: 1,2-Brook rearrangement converts them to the corresponding silyloxyallene (**58**), using *n*-BuLi, and subsequent reaction with an aldehyde gives the highly functionalized  $\alpha,\beta$ -unsaturated carbonyl compound (**59**).<sup>166</sup> Using Lewis acid catalysts in DCM at  $-78^\circ\text{C}$ , highly selective versions of this reaction have been developed: with scandium(III) triflate, near-quantitative yields with an *E:Z* ratio of 1:20 result, and a chiral (salen)chromium(III) auxiliary gave 92% *ee*.



Chiral BINOL (**60**) is a bifunctional organocatalyst: in addition to the phenolic Brønsted acid groups, it has a Lewis base unit attached via a spacer moiety.<sup>167</sup> This particular combination holds the groups in a conformational lock, where they can doubly activate a substrate while giving a high level of stereocontrol. For this example of an aza-Morita–Baylis–Hillman reaction of an enone and an imine, yields up to 100% and *ees* up to 96% have been achieved. (ee)



### Allylation and Related Reactions

Camphor-derived glyoxylic oxime ethers have been allylated in high yield and *de* using allyltributyltin–Sn(OTf)<sub>2</sub>.<sup>168</sup> A diastereoselective allylation of an  $\alpha$ -ketoamide bearing a camphor-derived auxiliary, again promoted by tin(II) triflate, undergoes a *de* reversal when palladium(II) chloride is employed, as indicated by <sup>13</sup>C NMR and IR spectra.<sup>169</sup> Tin(II) chloride-mediated allylation of aldehydes and ketones has been found to be significantly more straightforward in an ionic liquid.<sup>170</sup> (de)

Chiral (salen)chromium(III) complexes catalyse the asymmetric allylation of a range of aldehyde types, using allylstannane reagents.<sup>171</sup> (ee)

BINOL-derived phosphoramidites are versatile ligands in palladium-catalysed umpolung allylation of aryl aldehydes mediated by diethylzinc.<sup>172</sup> The possible roles of allyl-zinc and -palladium species in the mechanism are discussed in detail. (ee)

A homoallyl alcohol has been used to generate an allylrhodium species via retro-allylation.<sup>173</sup> Subsequent reaction with an aldehyde (RCHO) yields the corresponding secondary alcohol, R-CH(OH)CH<sub>2</sub>-C(Me)=CH<sub>2</sub>, *in situ*. This can be isomerized in the same pot to yield saturated ketone, R-C(=O)CH<sub>2</sub>-CHMe<sub>2</sub>.

Pinacols (**61**) derived from a variety of aromatic aldehydes have been employed in enantio- and diastereo-selective allylations of aliphatic aldehydes.<sup>174</sup> Their allylboronate derivatives react under Lewis acid conditions (SnCl<sub>4</sub>) with a variety of aldehyde types, in good yield and *ee*. Even better results are obtained by addition of (**61**) as a Brønsted acid (auto)catalyst, via coordination/activation of the tin catalyst. (de)  
(ee)

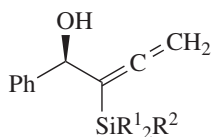
A combined experimental and computational approach has been undertaken to identify the origin of *syn/anti* diastereoselectivity in two types of crotylation reactions of aldehydes and ketones: (i) multi-component crotylations of simple aldehydes/ketones and (ii) acetal substitution reactions of aldehyde dimethyl acetals with *E*- and *Z*-configured crotyltrimethylsilane.<sup>175</sup> The stereochemical outcome is nearly identical in the two reactions, and the computational results suggest that this is due to near identical mechanisms: an S<sub>N</sub>1 process involving attack of *O*-methyl-substituted carboxonium ions by crotylsilane. (de)

Chiral phosphoramides have been developed as catalysts for asymmetric addition of allylic trichlorosilanes to aldehydes.<sup>176</sup> Although some *des* were high, *ees* were modest. Kinetic studies suggest dual mechanisms, and thus a route to the design of more highly selective catalysts. (de)  
(ee)

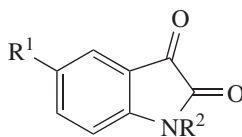
1,3-Dimethylallylation of (-)-menthone provides an allyl transfer agent for the highly enantio- and diastereo-selective pentenylation of aldehydes.<sup>177</sup> (de)  
(ee)

Trifluoromethyl ketones have been alkenylated, alkynylated, and phenylated in high *ee* using silane reagents and a chiral copper(I)-diphosphine complex.<sup>178</sup> (ee)

A chiral bis-oxazoline catalyses asymmetric Nozaki-Hiyama allenylation of aldehydes.<sup>179</sup> For example, benzaldehyde is converted to silylated allene (**62**) using a bromoalkynylsilane, BrCH<sub>2</sub>-C≡C-SiR<sup>1</sup><sub>2</sub>R<sup>2</sup>; the product is readily desilylated quantitatively without loss of *ee*. (ee)



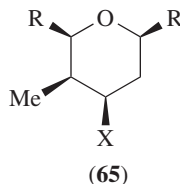
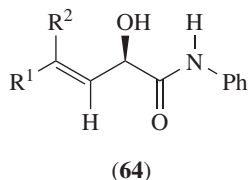
(62)



(63)

The ketone carbonyl of a series of isatins (**63**) undergoes enantioselective addition of aryl- and alkenyl-boronic acids, using a rhodium catalyst and a chiral phosphine.<sup>180</sup> (ee)

Enantiopure amide derivatives (**64**) of  $\beta,\gamma$ -unsaturated  $\alpha$ -hydroxy acids have been made by addition of a vinylsilane,  $R^2R^1C=CHSiMe_3$ , to *N*-phenylglyoxamide.<sup>181</sup> The reaction is catalysed by scandium(III) triflate complexed to a  $C_2$ -symmetric PYBOX ligand derived from (*R*)-norephedrine. (ee)



Optically active homoallylic alcohols,  $R^1CH(OH)CH_2CH=CHMe$ , react with aldehydes ( $R^2CHO$ ) to give 2,3,4,6-tetrasubstituted tetrahydropyrans (e.g. **65**,  $R = R^1$  and/or  $R^2$ ;  $X = OH, OAc, F, Cl, OTs$ ) in the presence of an acid catalyst,  $HX$ , via Prins cyclization.<sup>182</sup> (de)

New hydrophobic Brønsted acidic ionic liquids (HBAILs) have been prepared and used as organic catalysts of dehydration reactions in water, e.g. Prins cyclization of styrene derivatives with aqueous formaldehyde, to give 1,3-dioxanes.<sup>183</sup> (ee)

*Syn*- and *anti*-selective halo-Prins cyclizations of  $\delta,\epsilon$ -unsaturated ketones to give 1,3-halohydrins have been catalysed by Lewis acids, with *syn* selectivity correlating with acid strength.<sup>184</sup> (de)

In a carbonyl-ene reaction of ethyl glyoxylate with  $\alpha$ -methylstyrene catalysed by copper triflate-bisoxazoline complexes, *ees* of up to 100% have been achieved, but a dramatic switchover in stereochemistry is seen for an apparently minor change in bisoxazoline structure.<sup>185</sup> A change in the metal geometry is implicated. (ee)

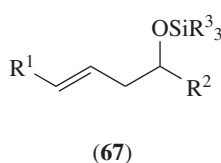
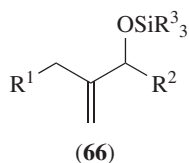
### Olefinations

Ruthenium(II)-salen complexes catalyse olefination of aldehydes by ethyl diazoacetate: yields and *E*-selectivities are good, with electron-deficient aldehydes reacting faster.<sup>186</sup>

A new synthesis of sterically hindered *o*-substituted tetraphenylethenes via McMurry olefination of the corresponding 2,2'-disubstituted benzophenones exploits electronic effects that dominate over steric considerations.<sup>187</sup>

Two recently developed coupling reactions of an alkene ( $R^1CH_2CH=CH_2$ ), an aldehyde ( $R^2CHO$ ), and a silyl triflate ( $R^3_3SiOTf$ ) yield an allylic (**66**) or homoallylic (**67**) alcohol (in protected form).<sup>188</sup> Employing nickel-phosphine catalysts, either product can be selected by small changes in the phosphine component. A mechanism distinct from that of Lewis acid-catalysed carbonyl-ene reactions is proposed and discussed.

Aldehydes,  $RCHO$ , have been reductively olefinated (to *trans*- $RCH=CHR$ ) using chromium dichloride and trichlorosilane, apparently via a novel chromium Brook rearrangement.<sup>189</sup> In one case, a *trans*-1,2-diol (a putative intermediate in such a mechanism) was isolated.



### Alkynylations

A  $C_2$ -symmetric bisoxazolidine–zinc complex catalyses alkynylation of aldehydes, giving propargyl alcohols in high yield and *ee*.<sup>190</sup> (ee)

Aldehydes and alkynes ( $RC\equiv CH$ ) have been reductively coupled via formal hydrochromation of the alkyne to give a 1-substituted ethenylchromium reagent,  $H_2C=C(R)Cr(III)$ , using a low-valent metal reagent,  $CrCl_2$ , in aqueous DMF.<sup>191</sup> Catalytic nickel(II)– $PPh_3$  is required to generate the organochromium species, probably through formation and transmetalation of  $H_2C=C(R)Ni(II)$ . Subsequent reaction with an aldehyde gives linear and branched  $\beta,\gamma$ -unsaturated alcohols.

Zinc-catalysed asymmetric alkynylation of  $\alpha,\beta$ -unsaturated aldehydes giving high yields and *ees* has been reported.<sup>192</sup> A dinuclear complex is proposed. (ee)

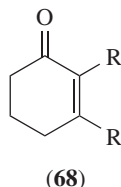
Carbonyl compounds have been alkynylated to give the corresponding propargyl alcohols, using TMS-alkynes and a base such as acetate or phenoxide ion.<sup>193</sup>

Ketones and aldehydes, including activated and enolizable substrates and those containing alcohol or carboxylic acid substituents, can be alkynylated using a rhodium(II) catalyst complexed with a bulky phosphine.<sup>194</sup>

A new cascade reaction of aromatic aldehydes with terminal conjugated alkynes produces a range of polycyclic aromatic hydrocarbons.<sup>195</sup> The effect of temperature on regioselectivity is discussed.

A complex of nickel(0) with an *N*-heterocyclic carbene catalyses coupling of  $\alpha$ -silyloxyaldehydes with alkynylsilanes, giving (deprotected) *anti*-1,2-diols in good yield and *de* >96%.<sup>196</sup> (de)

Cyclobutanones can act as 1-oxobutane-1,4-diyl units: they undergo intermolecular alkyne ( $RC\equiv CR$ ) insertion to give cyclohexanones (68), catalysed by  $Ni(cod)_2$ , apparently via a seven-membered nickelacycle.<sup>197</sup>



Reductive couplings of 1,6-enynes and aldehydes, catalysed by  $Ni(cod)_2$ , show regioselectivity effects that are switchable via addition of a phosphine.<sup>198</sup> Chelation control and steering effects due to the alkene tether have been invoked to explain this. (de)

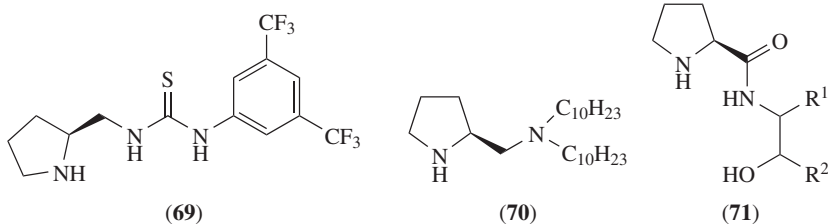
Favorskii ethynylation of acetone with acetylene in the presence of KOH is inhibited by dibenzo-18-crown-6, but not due to deactivation of acetone, as its aldol-like

condensation is accelerated under such conditions.<sup>199</sup> Rather, activation of acetylene by potassium cation is suggested to play an important role.

### Michael Additions

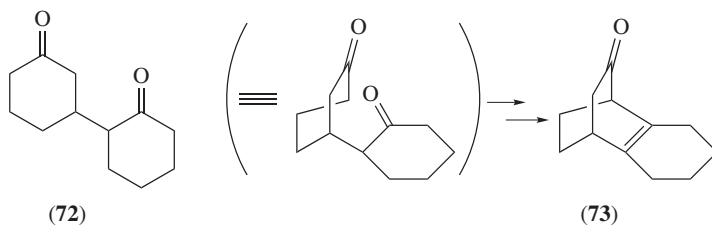
Direct catalytic Michael addition of aldehydes to nitrostyrenes proceeds in good yield, *syn* diastereoselectivity, and enantioselectivity (up to 82/90/99%, respectively) using a recyclable dendritic catalyst bearing chiral pyrrolidine moieties.<sup>200</sup> High-yielding enantio- and diastereo-selective direct Michael addition of ketones to nitroalkenes to give aldol products employ modular acyclic primary amino acid derivatives as catalysts.<sup>201</sup>

A pyrrolidine–thiourea organocatalyst (**69**) facilitates Michael addition of cyclohexanone to both aryl and alkyl nitroalkenes with up to 98% *de* and *ee*.<sup>202</sup> The bifunctional catalyst (**69**) can doubly hydrogen bond to the nitro group, leaving the chiral heterocycles positioned for cyclohexyl enamine formation over one face of the alkene.



A direct organocatalytic Michael reaction of ketones or aldehydes with  $\beta$ -nitrostyrene has been reported in brine solution, using a bifunctional catalyst system: proline-derived diamine (**70**) and TFA.<sup>203</sup> In some cases the conversion, yield, *de*, and *ee* all exceeded 95%. Results in water were poor, mainly due to polymerization, which is catalysed by amines. It is proposed that sodium cations stabilize the anionic intermediate formed from (**70**) and  $\beta$ -nitrostyrene, thus minimizing polymer formation. While organic co-solvent is not required, an organic-rich phase is proposed to concentrate the Michael reactants and catalysts, thus accelerating the reaction.

L-Prolinamides (**71**) with a pendant alcohol act as recoverable bifunctional catalysts of direct nitro-Michael addition of ketones to  $\beta$ -nitrostyrenes, giving *syn-des* up to 94% and *ees* up to 80%.<sup>204</sup> The pyrrolidine provides enamine catalysis, and the side-chain donors can hydrogen-bond the nitro oxygens.



Diketone (**72**) undergoes an acid-catalysed Michael–aldol reaction to give tricyclic ketone (**73**).<sup>205</sup>

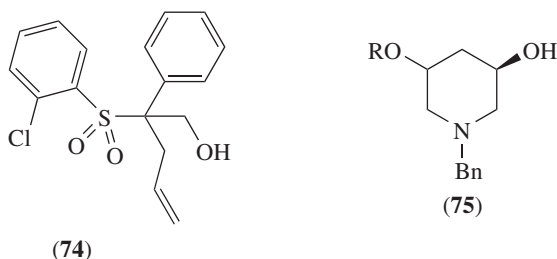
## Other Addition Reactions

### General and Theoretical

Recent developments in the asymmetric addition of aldehydes have been reviewed,<sup>206</sup> as have asymmetric catalysis using metal complexes<sup>207</sup> and nucleophile isotope effects.<sup>208</sup>

Natural bond orbital analysis of early and late TSs has been carried out to explore the factors involved in  $\pi$ -selectivity of nucleophilic addition to carbonyls.<sup>209</sup> Cieplak's  $\sigma \rightarrow \sigma^*$  hyperconjugation hypothesis (where  $\sigma^*$  is the incipient bond) is *not* supported by the results for early TSs, and evidence in favour of Felkin–Anh's  $\sigma^* \rightarrow \sigma^*$  hypothesis is weak. Late TSs are devoid of  $\sigma \rightarrow \pi_{\text{C=O}}^*$  interactions: here, the Cieplak model may be applicable.

Alcohol (**74**) undergoes an unusual extrusion of its hydroxymethyl group in the presence of sodium hydride.<sup>210</sup> That it is a reverse reaction of nucleophilic addition to formaldehyde was confirmed by trapping experiments for the latter. Relief of steric congestion is a likely cause, with the sulfinyl also helping to stabilize the incipient carbanion. The two factors combined help to reverse the equilibrium which normally favours attack on formaldehyde.



The atmospheric chemical kinetics of linear perfluorinated aldehyde hydrates,  $\text{C}_x\text{-F}_{2x+1}\text{CH}(\text{OH})_2$ , have been measured for  $x = 1, 3, \text{ and } 4$ , focusing on formation (from aldehyde, by hydration), dehydration, and chlorine atom- and hydroxyl radical-initiated oxidation.<sup>211</sup> The latter reaction is implicated as a significant source of perfluorinated carboxylic acids in the environment.

### Addition of Organozincs

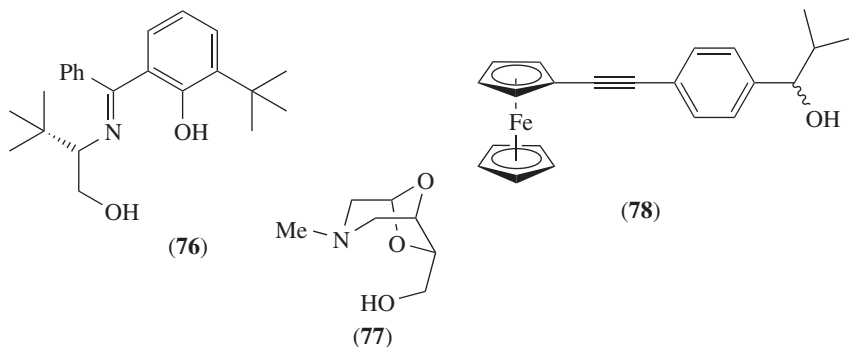
Most papers deal with diethylzinc. Chiral (3*R*,5*R*)-dihydroxypiperidines (**75**), derived from *trans*-4-hydroxy-L-proline, give up to 98% *ee* in its additions to benzaldehyde and heptanal.<sup>212</sup>

Cyclohexanols bearing 1-phenylethylamine attached via nitrogen in the  $\alpha$ -position have been tested as enantioselective catalysts of diethylzinc addition to benzaldehyde.<sup>213</sup>

A range of chiral bridged resorcinarene ‘bowls’ also catalyse this reaction: a mechanistic model suggests that the axial chirality of the receptor cavity, rather than a central chirality in the bridge, is responsible.<sup>214</sup> Theoretical predictions for the reaction have been calculated for a series of catalysts, using a rapid QSSR (quantitative structure–selectivity relationship); based on quantum molecular interaction fields, the predictions have since been tested by independent experiments.<sup>215,216</sup> Sterically congested ferrocenylaziridino-alcohol auxiliaries give up to 99.8% *ee*; evidence for a strong direct steric interaction with the substrate – which can even lead to inversion of configuration – is presented.<sup>217</sup>

$\gamma$ -Amino alcohols derived from (+)- and (–)- $\alpha$ -pinene act as catalysts for enantioselective addition of diethylzinc to aromatic aldehydes.<sup>218</sup> The *ee* is highly dependent on the *N*-substituent, and *ab initio* molecular modelling has been used to interpret this finding.

A chiral Schiff base with pendant phenol and alcohol functions (**76**) catalyses addition to aldehydes in cold hexane with up to 96% *ee*.<sup>219</sup> Non-linear effects on the *ee* suggest that zinc aggregation occurs, and NMR evidence indicates that both ethyl groups react with both hydroxyls in the catalyst.



A chiral [2.2]paracyclophane bearing a  $\beta$ -hydroxyamino side-chain catalyses enantioselective reaction with aromatic and  $\alpha,\beta$ -unsaturated aldehydes.<sup>220</sup> Comparison with simpler catalysts suggests that the new one exhibits cooperative effects between planar and central chiralities.

Unsymmetrical substitution of BINOL with a bulky group gives enhanced activity: 95% *ee* was achieved with <1 mol% loading of catalyst, compared with comparable conditions employing 20 mol% BINOL.<sup>221</sup>

In other diethylzinc studies, a neural network modelling approach has been used to predict the utility of new enantioselective catalysts,<sup>222</sup> norephedrine-derived ligands with three stereogenic centres catalyse enantioselective addition to aldehydes and to chalcones,<sup>223</sup> and a chiral sulfonamide ligand based on tartaric acid gives good *ees* in addition to both aldehydes and ketones.<sup>224</sup>

A new enantiopure constrained 1,4-amino alcohol (**77**) allows alkylation and also ethylation by zinc reagents with best *ees* of 70 and 98%, respectively.<sup>225</sup>

A commercially available chlorochromium–salen complex has been shown to be a good enantioselective catalyst for the addition of dimethylzinc to aromatic aldehydes, with yields up to 95% and *ees* up to 99%, using 2–4 mol% catalyst.<sup>226</sup> (ee)

(*R*)- and (*S*)-pyrimidyl alcohols (**78**), prepared from reaction of the corresponding pyrimidylaldehyde with diisopropylzinc, are also autocatalysts: starting from a near racemic ‘seed’, a large positive non-linear effect gives >99% *ee*.<sup>227</sup> (ee)

A mandelamide diastereomer catalyses addition of both aryl- and alkyl-zincs to heteroaromatic aldehydes in high yield and *ee*, giving heterocyclic propargyl alcohols, under otherwise metal-free conditions.<sup>228</sup> (ee)

A chiral H<sub>8</sub>-BINOL derivative catalyses an efficient direct enantioselective addition of diphenylzinc to both aromatic and aliphatic aldehydes, with particularly good results for straight-chain cases.<sup>229</sup> Aggregation phenomena in solution have been studied by NMR spectroscopy. (ee)

Chiral amino alcohols derived from BINAP have been employed as catalysts in a highly enantioselective addition of arylzincs (prepared *in situ*) to aldehydes.<sup>230</sup> (ee)

Recent progress in enantioselective addition of organozincs has been reviewed.<sup>231</sup> (ee)

#### Addition of Other Organometallics, Including Grignards

1,2-Additions of a range of organolithium reagents, RLi, ArLi, NC–CH<sub>2</sub>Li, RC≡CLi, and ArC≡CLi, show *ees* of 65–98%, using a chiral lithium aminosulfide auxiliary, superior to similar lithium amides with an ether instead of a sulfide, or without either chelator.<sup>232</sup> (ee)

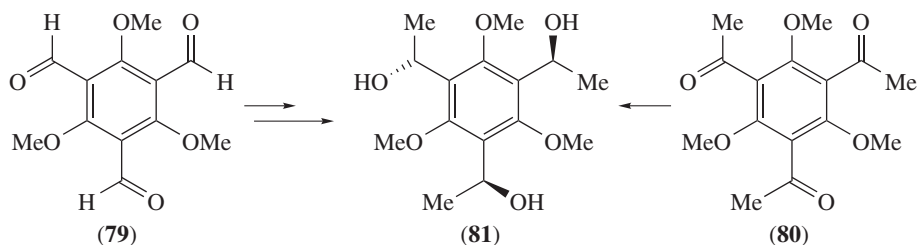
Lithium carbazoles have been added enantioselectively to aldehydes, giving heterocyclic carbinols.<sup>233</sup> (ee)

The preparation and synthetic applications of  $\alpha$ -lithio aldehydes and ketones and related compounds have been reviewed.<sup>234</sup>

Mixed lanthanide–alkali chlorides, LnCl<sub>3</sub>.2LiCl (Ln = La, Ce, Nd) can be readily prepared as 0.5 mol dm<sup>-3</sup> solutions in THF.<sup>235</sup> They act as improved promoters of addition of organomagnesium reagents to ketones, and also to aldimines, and in addition have been found to promote organolithium addition.

2,4,6-Trimethoxybenzene-1,3,5-tricarbaldehyde (**79**) and its keto homologue (**80**) involve three symmetry-equivalent carbonyl centres, each in a 1,5-relationship to their neighbours.<sup>236</sup> Two diastereoselective reactions have been performed: (i) the trial can be trimethylated to give triol (**81**) with methylolithium in THF, and (ii) the triketone can be reduced (to the same product), in both cases with >95% *de* (*anti*, *syn*). Chelation and steric (gearing) effects about the crowded aromatic core are discussed to explain the observed diastereoselectivity. (de)

A range of di- and tri-methoxybenzaldehydes, expected to give alkyl carbinols on treatment with alkylmagnesium bromides (RMgBr), instead gave the *di*alkyl carbinol, (MeO)<sub>2/3</sub>–C<sub>6</sub>H<sub>3/2</sub>–C(OH)R<sub>2</sub>.<sup>237</sup> It is proposed that the intended product is subject to an internal Cannizzaro-type oxidation process to give the ketone, allowing the Grignard to re-alkylate.



### The Wittig and Aza-Wittig Reactions

A detailed DFT study of the mechanism of the Wittig reaction has been carried out on a range of non-stabilized, semi-stabilized, and stabilized ylides: experimentally realistic results required explicit consideration of solvent effects, and practical large-scale systems which allow steric, electronic, and stereochemical effects to be captured.<sup>238</sup> Significant results for the non- and semi-stabilized systems include the necessity of considering the energy of the elimination TS in order to identify *E/Z* selectivity. Also, puckering of the addition TS depends not on ylide stabilization, but on 1,2-, 1,3-, and C–H ···O interactions. For stabilized substrates, puckering depends on dipole–dipole interactions: these determine the high *E* selectivity seen in such cases.

A QSAR (quantitative structure–activity relationship) approach has been taken to predicting stereoselectivity in the Wittig reaction.<sup>239</sup>

Pyrazolo[1,5-*a*]pyrimidines and imidazo[1,2-*b*]pyrazoles have been prepared from phosphine derivatives of 5-amino-3-phenylpyrazole in aza-Wittig reactions with selected  $\alpha$ -chloroketones.<sup>240</sup>

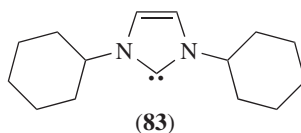
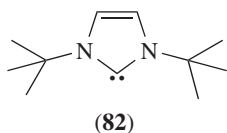
An enantioselective aza-Wittig strategy has been employed in the desymmetrization of prochiral 1,3-diketoozides, to produce  $\beta$ -quaternary azacycles.<sup>241</sup>

(*ee*)

### Hydrocyanation, Cyanosilylation, and Related Additions

A range of *N*-heterocyclic carbenes catalyse TMSCN addition to aldehydes (RCHO) to yield cyanohydrin TMS ethers, R–\*CH(OTMS)CN; acid treatment gives the cyanohydrins.<sup>242</sup> Mechanistic possibilities are discussed, and use of a chiral carbene gives a modest *ee*. Several other studies used such carbenes;<sup>243</sup> for example, a low loading of 0.01–0.5 mol% of 1,3-di-*t*-butylimidazol-2-ylidene (**82**) catalyses TMSCN addition to a wide range of aliphatic and aromatic aldehydes and ketones under mild, metal-free conditions, with a wide functional group tolerance.<sup>244</sup> Also, (**83**) gives comparable results, and has also been used to convert imines to aminonitriles.<sup>245</sup>

(*de*)



Diastereoselectivities in the tetrabutylammonium cyanide-catalysed cyanosilylation of cyclic  $\alpha,\beta$ -epoxyketones are dependent on ring size, with a switchover in selectivity between five-membered and larger rings being explained through computation of TSs.<sup>246</sup>

A range of Lewis bases catalyse the addition of TMSCN to aldehydes, with phosphines and amines the most efficient.<sup>247</sup> Kinetic studies indicate that the orders of aldehyde, Lewis base (LB), and TMSCN are 1, 1, and 0, suggesting an  $\text{Me}_3\text{Si-LB}^+\text{CN}^-$  ion pair as an intermediate. However, chiral phosphines and amines gave very low *ees*.

A chiral aluminium-salen- $\text{Ph}_3\text{PO}$  combination catalyses addition to ketones in up to 92% *ee*; the catalyst system essentially acts as a Lewis acid-Lewis base bifunctional system.<sup>248</sup> A similar chiral manganese(III)-salen- $\text{Ph}_3\text{PO}$  method is comparable.<sup>249</sup>

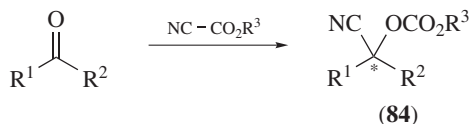
Another effective catalyst is 1,1,3,3-tetramethylguanidine, which works well at 0.1 mol% loading in solvent-free conditions at ambient temperature.<sup>250</sup>

Aliphatic aldehydes have been converted to their (*R*)-cyanohydrins using a biphasic system to accommodate hydroxynitrile lyase enzyme (from the Japanese apricot, *Prunus mume*) as the enantioselective catalyst.<sup>251</sup>

An alternative TS for asymmetric addition of cyanide to aldehydes catalysed by titanium-salen complexes has been proposed, based on a comparison with a related iron-salen complex for which a crystal structure is reported.<sup>252</sup>

High-yielding, high-*ee* cyanation has been achieved using a multi-component bifunctional catalyst system.<sup>253</sup> Aldehyde (RCHO) and nitrile (NC-CO<sub>2</sub>Et) react at -45 °C in DCM to give the corresponding cyanohydrin ethyl carbonate, R-<sup>\*</sup>CH(CN)-O-CO<sub>2</sub>Et. The catalyst used has *four* components: a chiral BINAP, (1*R*,2*S*)-(-)-*N*-methylephedrine, cinchonine, and titanium isopropanoxide. Evidence for all four being essential is presented.

Ketones have been enantioselectively cyanocarbonated to give tetrasubstituted carbon stereocentres (**84**), using cinchona alkaloid catalysts and cyano esters, with *ees* up to 97%.<sup>254</sup> A fall-off in *ee* at high conversions has been explained by a mechanism involving competing asymmetric processes, and significant retro-cyanation.

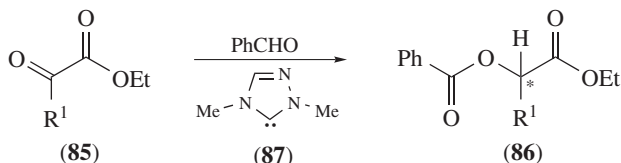


Aldehydes, RCHO, have been cyanophosphorylated with diethyl cyanophosphonate [NC-P(=O)(OEt)<sub>2</sub>] to give cyanohydrin *O*-phosphonates, R-<sup>\*</sup>CH(CN)-OP(=O)(OEt)<sub>2</sub>, in up to 98% yield and 97% *ee*, using a  $\text{YLi}_3(\text{BINAP})_3$  catalyst.<sup>255</sup>

DBU catalyses cyanoacylation of ketones, R<sup>1</sup>COR<sup>2</sup>, with aromatic acyl cyanides giving *O*-acyl cyanohydrin adducts, ArOCO-C(CN)R<sup>1</sup>R<sup>2</sup>, in fair to good yields in 2 h at ambient temperature.<sup>256</sup>

Hydroacylation of carbonyls or alkenes by aldehydes is well known. Hydroacylation of an activated ketone (**85**) by benzaldehyde has now been reported, giving a new asymmetric centre at the ketone carbon (**86**).<sup>257</sup> In a metal-free procedure, the reaction

is catalysed by *N*-heterocyclic carbenes, such as the triazole catalyst (**87**) shown. The reaction involves separate reduction and acylation steps, with the organocatalyst carrying out two key bond-forming processes. Whereas (**86**) is the major product in DCM, methanol solvent decouples reduction and acylation, giving the alcohol 'intermediate', Ph-<sup>\*</sup>CH(OH)CO<sub>2</sub>Me, as sole product.



The use of homogeneous carbonylation reactions for the synthesis of biologically important compounds has been reviewed, covering many methodologies, including direct use of carbon monoxide, and also hydroformylation and alkoxy- and amino-carbonylation, both inter- and intra-molecular.<sup>258</sup>

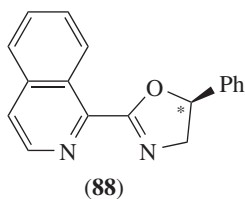
$\alpha$ -Amino- $\beta$ -keto esters have been prepared in high *ee* via catalytic electrophilic  $\alpha$ -amination of  $\beta$ -keto esters, using azodicarboxylate reagents and a chiral palladium complex as catalyst.<sup>259</sup> By immobilizing the catalyst in an ionic liquid, the system can easily be recycled. (ee)

The introduction of  $\alpha$ -heteroatom functionalization into an aldehyde or ketone is a very useful class of transformation. Performing it directly and asymmetrically, using organocatalysts, has been reviewed for reactions such as amination, oxygenation, halogenation, and sulfenylation (44 references).<sup>260</sup> (de) (ee)

Propanal has been enantioselectively hydroxylaminated with nitrosobenzene (Ph-N=O) to give a hydroxylamino alcohol, Ph-N(OH)-<sup>\*</sup>CH(Me)CH<sub>2</sub>OH, using an axially chiral BINAP secondary amine catalyst in THF at 0 °C, followed by methanolic treatment with sodium borohydride.<sup>261</sup> Yields up to 90% and *ees* up to 99% were recorded, and one-pot conversions to the corresponding  $\beta$ -amino alcohol or  $\beta$ -diamine are described. (ee)

### Hydrosilylation and Related Reactions

An enantioselective metal-free hydrosilylation of aromatic ketones (and also of their imines) employs a quinolyloxazoline (**88**), which brings about a relatively long-range induction.<sup>262</sup> (ee)

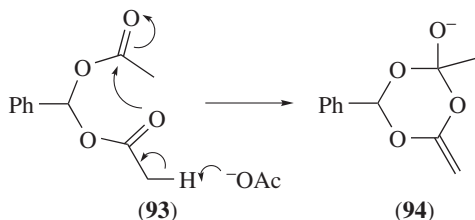




mechanism is discussed with an emphasis on the role of sulfur via comparison with the 2,5-dioxo compounds.

The TEMPO moiety (2,2,6,6-tetramethylpiperidine-1-oxyl) has been incorporated into acetoacetic derivatives to achieve *E*-selective Knoevenagel condensations, exploiting the steric hindrance that it causes.<sup>269</sup> In contrast, acylacetoamides (including Weinreb amides) produce *Z*-adducts. Downstream reductions of carbonyl groups in the products allow access to a variety of useful materials.

In a revisitation of the mechanism of the Perkin condensation, a strong argument is advanced against the common belief that acetate deprotonates acetic anhydride to give its enolate,  $\text{AcO}-\text{C}(\text{=CH}_2)-\text{O}^-$ .<sup>270</sup> The  $\text{p}K_a$  of acetic anhydride (estimated 20) is too high, acetate is too weak a base, and the enolate would probably decompose (to ketene and acetate) at the typical reaction temperature of 180 °C. This leaves a problem: what likely two-carbon nucleophile – a formal acetic acid dianion equivalent – is available? The *gem*-diacetate (**93**) is suggested; its simple enolate might be difficult to form, but a type of neighbouring group participation could generate anion (**94**) as nucleophile (for reaction with the second benzaldehyde). The finding that (**93**) can give cinnamic acid product at room temperature (in *t*-BuOK–THF) supports the hypothesis, in addition to pointing the way towards milder conditions.

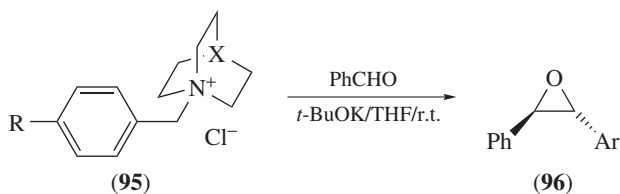


An isoborneol with a *cis*- $\alpha$ -amino group gives *ees* of up to 93% in addition of Reformatsky reagents to aldehydes.<sup>271</sup> (ee)

A wide range of benzocyclic ketones have been accessed by intramolecular arylation using aldehyde groups.<sup>272</sup> This intramolecular Friedel–Crafts-type acylation is promoted by iodonium species, using the reagent combination  $\text{IPy}_2\text{BF}_4\text{--HBF}_4$ .

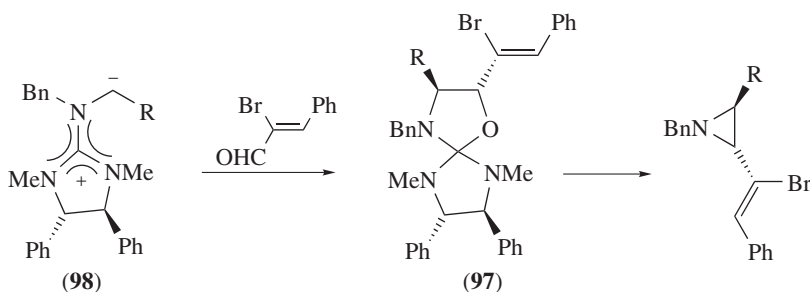
Chiral benzoylformate esters,  $\text{PhCOCO}_2\text{R}^*$ , react with diazomethane to give  $\alpha$ -oxiranyl esters, but *de* is typically negligible.<sup>273</sup> (de)

Aryl-stabilized ammonium ylides from deprotonation of (**95**; X = CH, N) react with benzaldehyde to give epoxides (**96**).<sup>274</sup> The diastereoselectivity is highly sensitive (de) to the nature of the amine and the ylide substituent, e.g. it reaches 99:1 *trans*:*cis*

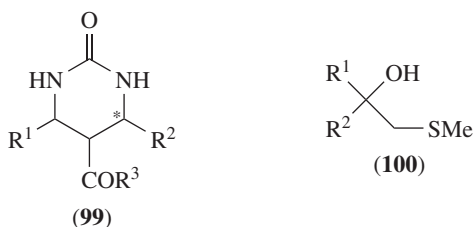


for  $R = CF_3$ . DFT calculations suggest that – although the ylide is a high-energy species – betaine formation is reversible, as the next step of ring closure also has a high barrier. Thus groups that stabilize the ylide and/or increase the barrier to ring closure (electron-deficient aryls) favour *trans* selectivity.

A spiro imidazolidine–oxazolidine intermediate (**97**) has been isolated in an aziridination of  $\alpha$ -bromocinnamaldehyde mediated by a guanidinium ylide (**98**).<sup>275</sup>



Biginelli synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones (**99**) from an aldehyde, a  $\beta$ -diketone, and urea is catalysed by L-proline methyl ester hydrochloride.<sup>276</sup> Although evidence strongly supports an enamine mechanism, the products were essentially racemic. (ee)

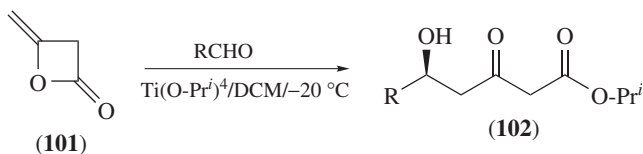


Corey–Chaykovsky reaction of a ketone  $R^1COR^2$  with  $Me_3S^+ I^- NaH$  in DMSO is a useful synthesis of epoxides, but a re-investigation in THF using *n*-BuLi as base gave significant amounts of  $\beta$ -hydroxymethyl thioether (**100**), in addition to epoxide.<sup>277</sup> This represents formal addition of  $Me_2S$ .

Di- and tri-substituted enamines of aldehydes have been generated under mild conditions (1 h, 0 °C, 1.2 equiv. of amine).<sup>278</sup> Although easily isolable, they can be conveniently employed *in situ*. The reaction is chemoselective (ketones present are not affected), it tolerates sensitive groups such as acetals and silyl ethers, and it works for both aliphatic and aromatic aldehydes.

Chiral Schiff bases derived from salicylaldehyde, when complexed to titanium(IV), catalyse enantioselective addition of diketene (**101**) to aldehydes ( $RCHO$ ;  $R = Ph$ , alkyl, alkenyl) to yield  $\delta$ -hydroxy- $\beta$ -keto esters (**102**), with up to 84% *ee*.<sup>279</sup> (ee)

2-Aryl aldehydes and ketones with an  $\alpha$ -substituent,  $Ar-CHMe-COR$  ( $R = H$ , Me), are sulfamidated to give  $\alpha,\alpha$ -disubstituted product,  $Ar-C(NHTs)Me-COR$ , by



chloramine-T.<sup>280</sup> In the case of the aldehydes, oxidation and removal of the tosyl group give access to  $\alpha,\alpha$ -disubstituted amino acids.

The Willgerodt reaction allows amide synthesis from aromatic aldehydes or ketones, using a secondary amine and a thiating agent. The mechanism of the more convenient Kindler modification, employing sulfur and morpholine, has been reviewed.<sup>281</sup>

Tetrakis(dimethylamino)ethylene (TDAE) has been used as a reagent for the nucleophilic perfluoroalkylation of aldehydes, ketones, imines, disulfides, and diselenides.<sup>282</sup> Analogous to trifluoromethylation with  $\text{CF}_3\text{I}$ , the reagents  $\text{C}_2\text{F}_5\text{I}$  and  $n\text{-C}_4\text{F}_9\text{I}$  ( $\text{R}_\text{F}\text{-I}$ ) give perfluoroalkylation in DMF solution. The aldehyde and ketone reactions give enhanced yields upon irradiation. TDAE is presumed to reductively cleave  $\text{R}_\text{F}\text{-I}$  to give  $\text{RF}^-$  and  $\text{I}^-$  (and  $\text{TDAE}^{2+}$ ).

The conjugate bases of amides, imides, and carboxylic acids have been used as Lewis acids for perfluoroalkylation of carbonyl compounds and aldimines, using  $\text{TMS-R}_\text{F}$  reagents ( $\text{R}_\text{F} = \text{CF}_3, \text{C}_2\text{F}_5, \text{and } n\text{-C}_3\text{F}_7$ ).<sup>283</sup>

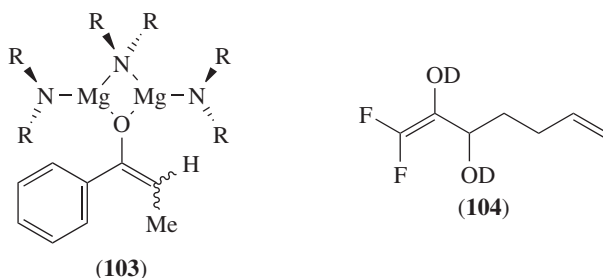
Catalytic asymmetric synthesis of enantiopure diaryl-methanols and -methylamines (important pharmaceutical intermediates) has been reviewed (76 references), focusing on (i) aryl transfers on to aryl-aldehydes and -imines and (ii) asymmetric reductions of diaryl-ketones and -ketoimines.<sup>284</sup> (ee)

Asymmetric synthesis of diarylmethanols can be achieved via rhodium-catalysed addition of arylboronic acids to benzaldehydes, using chiral mono- or bi-dentate phosphoramidites based on BINOL.<sup>285</sup> (ee)

Benzaldehyde undergoes nucleophilic arylation with phenyltrimethoxysilane,  $\text{PhSi}(\text{OMe})_3$ , to give diphenylmethanol in good yields under moderately vigorous conditions:  $\text{Bu}_4\text{N}^+\text{F}^-$  catalysis in refluxing acetonitrile.<sup>286</sup> However, this 1,2-addition process is completely switched to give methyl benzoate, the oxidative esterification product (at  $25\text{ }^\circ\text{C}$ ), by addition of a palladium–phosphinous acid catalyst. NMR evidence suggests that the siloxane may perform three functions: generating a Lewis acidic silicate to activate the aldehyde, while acting as methoxy donor and hydride acceptor.

## Enolization and Related Reactions

Magnesium bis(hexamethyldisilazide),  $\text{Mg}(\text{HMDS})_2$ , catalyses the enolization of ketones.<sup>287</sup> On addition to propiophenone in toluene at ambient temperature, a ca 3:1 *E*:*Z* mixture of enolates (**103**,  $\text{R}=\text{SiMe}_3$ ) is formed. These enolates, and an initial ketone complex, have been characterized by NMR, X-ray, IR, and UV–visible spectroscopy and computational studies. Kinetics of tautomerization have been measured, with proton transfer confirmed as rate determining ( $k_\text{H}/k_\text{D} = 18.9$  at 295 K). The significant temperature dependence of the primary isotope effect is indicative of tunnelling.



Enol (**104**), generated rapidly in acidic solution from a precursor acetal, shows remarkable stability:  $t_{1/2} > 3$  h in  $0.1 \text{ mol dm}^{-3}$  DCl in  $\text{CD}_3\text{OD}$  at 300 K, allowing its characterization by 2D NMR spectroscopy. A DFT study of a simple model, 2,2-difluoroethenol, indicates that there are significant differences in timing of the protonation TS compared with the non-fluorinated enol.<sup>288</sup>

Keto–enol tautomerization of 3-hydropyridazine derivatives has been investigated using DFT: the 2-hydropyridazin-3-one tautomer is typically found to be the most stable.<sup>289</sup>

Triethylgallium has been used as a non-nucleophilic base to generate enolates from ketones, both cyclic and acyclic, without forming carbonyl addition products.<sup>290</sup> The gallium enolates can then be *C*-benzoylated, and can participate in aldol reactions. Unsymmetrical ketones preferentially enolized at the methylene, under kinetic control.

Silyl enol ethers of decalones have been synthesized which allow stereoselective protonation of the corresponding enol to be initiated and followed kinetically.<sup>291</sup> Pendant groups have been placed so that the relative rates of intermolecular protonation and intramolecular protonation (by the proximate group) can be measured. Examples of groups which give one or other mechanism are detailed:  $\text{CO}_2^-$  and  $\text{CO}_2\text{H}$  typify the latter.

Commercially available amino acid derivatives have been tested as chiral proton sources for protonation of lithium enolates: catalytic *N*<sup>β</sup>-L-aspartyl-L-phenylalanine methyl ester gave an *ee* of 88%.<sup>292</sup>

A stereoselective enolate protonation has been achieved by changing the counterion of the chiral alkoxide base employed: the lithium alkoxide-generated enolate gives close to 90% of the  $\beta$ -epimeric ketone product, whereas the use of the potassium cation gives 99%  $\alpha$ -epimer.<sup>293</sup>

A chiral BINAP-diphosphine complexed to silver(I), with fluoride as counterion, catalyses the enantioselective protonation of TMS-enolates, giving ketones with a tertiary asymmetric  $\alpha$ -carbon in up to 99% *ee*.<sup>294</sup>

### *α*-Halogenation, *α*-Alkylation, and Related Reactions

Key advances in  $\alpha$ -fluorination which occurred in 2005, using both organo- and metallo-catalytic approaches, have been reviewed (21 references).<sup>295</sup>

A mild metal-free  $\alpha$ -iodination of ketones uses molecular iodine in a neutral reaction medium.<sup>296</sup> Aliphatic ketones react predominantly on the more substituted side, with

about 1 day at room temperature being sufficient. Aryl alkyl ketones require the solvent, dimethoxyethane, to be heated to reflux for a few hours. Iodine is proposed to act as a Lewis acid promoter of initial enolization of the ketone, while HI formation should give autocatalysis; pyridine stops the reaction.

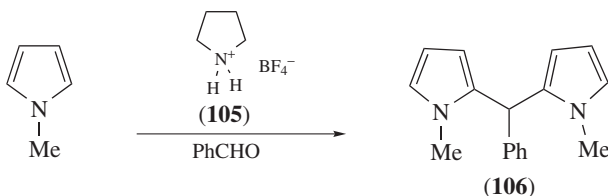
A new synthesis of pyrroles generates a 1,3-diketone by reacting a lithium enolate of a ketone with an acid chloride; *in situ* addition of a hydrazine yields, potentially, a tetrasubstituted pyrazole.<sup>297</sup> Tolerant of a wide range of functional groups, it is also easily adapted to rapid preparation of fused bicyclic pyrazole systems.

The utility of global and local reactivity descriptors to predict chemical reactivity and *C*- versus *O*-alkylation has been investigated for the case of lithium enolates.<sup>298</sup>

The origin of the dramatically increased enantioselectivity of  $\alpha$ -alkylation of aldehydes when 2-methylproline is substituted for proline as organocatalyst has been investigated using DFT.<sup>299</sup> (ee)

Direct catalytic intermolecular  $\alpha$ -allylic alkylation of aldehydes and cyclic ketones has been achieved using a one-pot combination of a transition metal catalyst, Pd(PPh<sub>3</sub>)<sub>4</sub>, and an organocatalyst: a secondary amine which facilitates enamine catalysis.<sup>300</sup>

Pyrrolidinium tetrafluoroborate (**105**) serves as an organocatalyst for the reaction of benzaldehyde with *N*-methylpyrrole, to give the corresponding dipyromethanes (**106**) under mild conditions.<sup>301</sup> Initial formation of an iminium ion by condensation of the aldehyde with the catalyst is proposed.



2-, 3-, and 4-pyridinecarboxaldehyde condense with benzene in F<sub>3</sub>C–SO<sub>3</sub>H (triflic acid), to give the *gem*-diphenyl product, PyCHPh<sub>2</sub>.<sup>302</sup> Substituted pyridine aldehydes also gave the reaction, and deactivated arenes (e.g. *o*-dichlorobenzene, nitrobenzene) also work. Even hydrocarbons such as adamantane work, in the presence of high-pressure CO, giving adamantanyl–CO–CH<sub>2</sub>Py derivatives. Evidence for the formation of dicationic intermediates (diprotonated pyridinecarboxaldehydes) is seen at low temperatures in superacid (FSO<sub>3</sub>H–SbF<sub>5</sub>) using <sup>13</sup>C NMR spectroscopy.

## Oxidation and Reduction of Carbonyl Compounds

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

An integration of readily available computational methods and visualization techniques has rendered a simple method to predict nucleophilic asymmetric induction of prochiral electrophiles.<sup>303</sup> Taking the examples of ketone and aldehyde reductions, electrostatic potential has been mapped on to the frontier orbital involved. A distinct difference in (de)

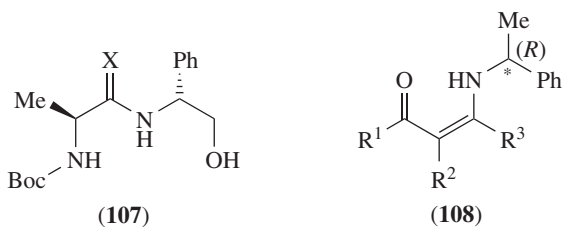
potential between the faces of the carbonyl has been used to predict the direction of nucleophilic attack.

In a probe for the presence of stereoelectronic effects in nucleophilic addition to 12 sterically unbiased ketones, calculations have identified subtle bond length differences in the C–Nu bond of the diastereomeric alcohol products, where  $\text{Nu}^- = \text{H}^-$  or  $\text{Me}^-$ .<sup>304</sup> The calculated differences are weak (<1%) but consistent: the bond is longer in the major product, acting as a ‘fossil record’ of the TS. Using microscopic reversibility, the easier bond to cleave (the longer one) is the easier to form. The effect bears comparison with the kinetic anomeric effect in sugars, where such bond length differences in calculation are borne out in X-ray crystal structures.

Asymmetric hydrogenation of ketones is one of the more common reduction methods, with ruthenium complexes often used as catalysts, a topic which has been reviewed.<sup>305</sup>

Noted results in this area include the following:  $[\text{RuCl}_2(p\text{-cymene})]$ -pseudo-dipeptide catalysts are markedly affected by alkali metal cations (calculations show that the higher *ee* associated with addition of lithium cation is due to a tighter TS);<sup>306</sup> a kinetic study of continuous homogeneous hydrogenation uses a chemical membrane reactor with a ‘polymer-enlarged’ chiral ruthenium catalyst while retaining *ee* and conversion from the batch process;<sup>307</sup> and Noyori’s catalyst system of *trans*-Ru(diphosphine) $\text{Cl}_2$ (diamine) plus base in propan-2-ol has been investigated in its chiral form (both ligands chiral): several inaccessible intermediates have been identified which shed light on the role of added base.<sup>308</sup> Ruthenium(II) catalysis with ferrocenylamino auxiliaries shows asymmetric contributions from both planar and carbon-centred chirality,<sup>309</sup> and terpene-derived  $\beta$ -amino alcohols complexed to the same metal centre give moderate *ees* for reduction of aryl alkyl ketones.<sup>310</sup> High *ees* are obtained when the ruthenium is complexed with two common chiral chelators: *trans*-1,2-diaminocyclohexane and BINOL-derived phosphines.<sup>311</sup>

A range of  $\alpha,\beta$ -unsaturated,  $\alpha$ -tosyloxy, and  $\alpha$ -substituted ketones have been reduced via asymmetric transfer hydrogenation using chiral ruthenium(II) and rhodium(III) complexes.<sup>312</sup> A chiral amide (**107**, X = O) promotes enantioselective transfer hydrogenation of aryl alkyl ketones, giving the (*S*)-secondary alcohols with modest *ee*, using the same two metal cations.<sup>313</sup> Switching from the simple  $\alpha$ -amino acid amide to its thioamide analogue (**107**, X = S) raises and reverses the selectivity, giving *R*-product with up to 97% *ee*. This dramatic switch may arise from a different coordination mode: simple thioamides have an N–H  $\text{p}K_{\text{a}}$  about 7 units below amides, so that the NH of the thioamide auxiliary is likely to be an acidic site, with the BocNH as a basic site.



2,2,2-Trifluoroacetophenones,  $\text{Ar}^1\text{COCF}_3$ , react with arylboronic acids,  $\text{Ar}^2\text{B}(\text{OH})_2$ , to give tertiary alcohols,  $\text{Ar}^1\text{Ar}^2-\text{*CHOH}$ :<sup>314</sup> the auxiliary is a phosphoramidite derived from BINAP, complexed to rhodium(I). A rhodium(III) chloride catalyst bearing a cyclopentadienyl ligand with a chiral cyclohexdiamine–monotosylate tether gives near quantitative conversion, with *ees* up to 99.5%.<sup>315</sup> Employing transfer hydrogenation methods – ammonium formate in water or formic acid–triethylamine – loadings of 0.5% catalyst give completion in typically a few hours at 28 °C. Trials with loadings as low as 0.01% took longer, naturally, but gave the same *ee*, indicating negligible background rates.

Perfluoroalkyl ketones have been reduced in high *ee* using a simple alkoxide; lithium (*S*)-1-phenylethoxide, for example, reduces 2,2,2-trifluoroacetophenone to its (*S*)-carbinol in 80% *ee* and 61% yield at 0 °C, with acetophenone produced as by-product.<sup>316</sup>

The asymmetric reduction of achiral ketones using borohydrides has been reviewed, particularly the use of sodium borohydride in combination with chiral Lewis acids.<sup>317</sup> Such a reduction of unsymmetrical benzophenones gives poor *ee* (0–46%), unless an *o*-fluoro substituent is present, where *ee* values range from 80 to 96%.<sup>318</sup> Aliphatic ketones have been reduced in high *ee*, using a tartrate-derived boronic ester and borohydride.<sup>319</sup> Enantiopure *syn*- $\gamma$ -amino alcohols have been prepared by reduction of chiral  $\beta$ -enaminoketones (**108**;  $\text{R}^1 = \text{Me, Ph}$ ;  $\text{R}^2 = \text{H, Cl}$ ;  $\text{R}^3 = \text{Me, CF}_3$ ) using sodium borohydride in acetic acid at 10 °C.<sup>320</sup> Molecular modelling, X-ray, and <sup>1</sup>H NMR data afforded absolute configurations. The acidic conditions convert the reactant to its protonated enolimine form, setting up boron attachment to oxygen, so that C=N reduction occurs first.

Chiral  $\text{C}_2$ -symmetric boron bis(oxazolines) act as enantioselective catalysts in the reduction of ketones promoted by catecholborane.<sup>321</sup> DFT calculations indicate that the stereochemical outcome is determined by such catalysts being able to bind both the ketone and borane reducing agent, activating the latter as a hydride donor, while also enhancing the electrophilicity of the carbonyl. X-ray structures of catalyst–catechol complexes are also reported.

(*S*)-Methyl lactate gives a poor *ee* in hydroboration of acetophenone, but  $\text{ZnCl}_2$  raises it.<sup>322</sup> A molecular orbital method has looked at the enantioselectivities associated with four oxazaborolidine catalysts acting on phenyl methyl ketone.<sup>323</sup>

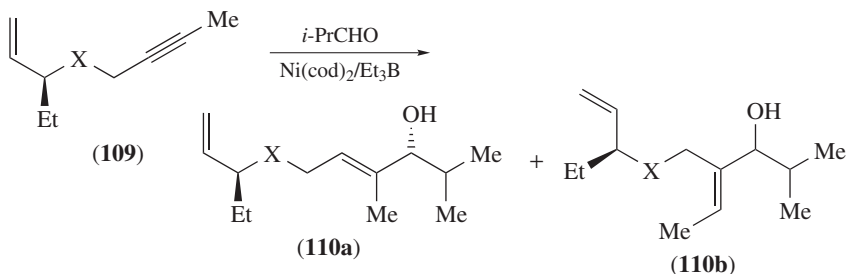
1-Ethylpyridinium tetrafluoroborate, a readily accessible ionic liquid, is an effective solvent for BINOL-promoted enantioselective reduction of aryl alkyl ketones by LAH.<sup>324</sup> A chiral diol modifies LAH reagents to give up to 98% *ee*.<sup>325</sup>

A new active-iron reducing system – iron(II) chloride tetrahydrate–excess lithium powder–5 mol% 4,4'-di-*t*-butylbiphenyl in THF – reduces ketones and imines.<sup>326</sup> Mono- and poly-cyclic ketones in particular are reduced with good to excellent *ee*.

Camphor-derived  $\alpha$ -ketoamides undergo two reactions with 98% yield and *de*: (i) allylation with allyltributylstannane and a Lewis acid catalyst and (ii) reduction with K-Selectride.<sup>327</sup> The stereoselectivity of the allylation can be reversed by appropriate change of Lewis acid.

Chiral 1,6-enynes (**109**,  $\text{X} = \text{O}$  or  $\text{CH}_2$ ) undergo nickel-catalysed reductive coupling with aldehydes to give regioisomers, **110a** and **110b**; regioselectivity is 95:5, with a

*de* of 90%.<sup>328</sup> However, addition of catalytic amounts of tri(cyclopentyl)phosphine completely reverses the regioselectivity to give >95% of **110b**, this time with no *de*. Three distinct mechanistic possibilities are discussed, with the authors favouring coordination of alkyne and alkene to the metal centre during the C–C bond-forming step (favouring **110a** with high *de*). The phosphine, however, can directly coordinate to the metal, disrupting this effect.



Developments in the enantioselective formation of tertiary alcohols via asymmetric addition to ketones have been reviewed.<sup>329</sup>

### Other Reduction Reactions

The kinetics and mechanism of hydride transfer between Michler's hydride and 2,3,5,6-tetrabromo-*p*-benzoquinone have been investigated spectrophotometrically, examining both solvent and pressure effects.<sup>330</sup>

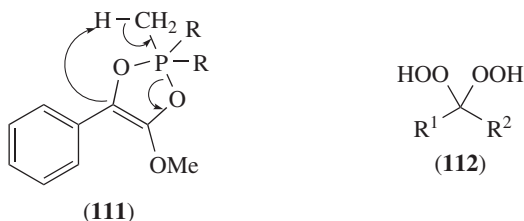
A remarkable reduction protocol reduces a wide range of oxygen functionality to hydrocarbon, including carboxylic acids, aldehydes, ketones, and all alcohols: (primary, secondary and tertiary). Using a simple silane (*n*-butyl or diethyl) and a Lewis acid catalyst, tris(pentafluorophenyl)borane, the reaction takes a few hours in DCM under argon.<sup>331</sup> Alkene functionality, nitro groups, and ethers are all unaffected, while phenols are merely silylated. Similar mechanisms are proposed for all reductions: hydride abstraction by boron with simultaneous oxygen attack on silicon, giving a silyloxy cation, followed by hydride return to carbon.

A dynamic kinetic resolution has been employed to achieve a catalytic asymmetric reductive amination of aldehydes.<sup>332</sup> Reductive amination of ketones and aldehydes by sodium triacetoxyborohydride has been reviewed, highlighting its advantage over other reagents.<sup>333</sup>

Reductive amination of ketones using *p*-anisidine and the Hantzsch ester for transfer hydrogenation is a low-yielding reaction in toluene at room temperature, but thiourea is an efficient catalyst, and yields of up to 94% are reported at 50 °C.<sup>334</sup> A mechanism involving thiourea hydrogen bonding to the intermediate imine is supported by *ab initio* calculations.

A variety of activated carbonyls such as  $\alpha$ -keto esters, benzils, cyclohexane-1,2-dione, and  $\alpha$ -ketophosphonates have been reduced to the corresponding  $\alpha$ -hydroxy compounds in THF at room temperature, using alkylphosphines (PMe<sub>3</sub> or PPhMe<sub>2</sub>).<sup>335</sup>

$^2\text{H}$ - and  $^{18}\text{O}$ -labelling experiments suggest that proton transfer from alkylphosphine occurs (via e.g. **111**), with aqueous workup releasing the product plus  $\text{R}_2\text{P}(=\text{O})\text{Me}$ .



A rhodium(I)-*N*-heterocyclic carbene complex has brought about a chemoselective decarbonylation, converting a cyclobutanone to the corresponding cyclopropane, while leaving an aldehydic substituent untouched.<sup>336</sup>

### Oxidation Reactions

Ketones,  $\text{R}^1\text{COR}^2$ , have been converted to their *gem*-dihydroperoxides (**112**) using a 'green' oxidant, aqueous 30% hydrogen peroxide, with iodine as catalyst.<sup>337</sup> The iodine may enhance the electrophilic character of the carbonyl carbon and/or the nucleophilicity of the hydrogen peroxide. The reaction has also been extended to acetals and aldehydes.

A new ionic liquid, 1-butyl-3-methylimidazolium tribromide can act as an oxidizing agent to convert alcohols to aldehydes and ketones.<sup>338</sup> In the case of benzyl alcohols and diols,  $[\text{Bmim}][\text{Br}_3]$  combines oxidizing and brominating properties in a one-pot synthesis of  $\beta$ -bromoethyl esters.

The kinetics of the oxidation of aromatic aldehydes by *N*-chloronicotinamide in aqueous acetic acid are first order in both reactants and in proton.<sup>339</sup> The effect of substituents has been studied, and data at different temperatures yield activation parameters.

Several reports deal with the action of heterocycle-chromate agents such as: quinolinium dichromate on five-membered heteroaldehydes<sup>340</sup> and quinolinium bromochromate on benzaldehydes,<sup>341,342</sup> all in acetic acid solution. The latter studies show a second-order dependence on proton concentration, acceleration by electron-withdrawing *para*-substituents, and a substantial kinetic isotope effect for the deuterated aldehyde.

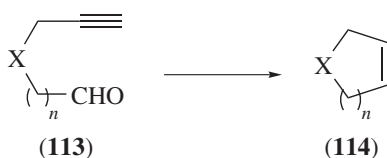
Oxidative amidation of aldehydes can be achieved with primary amine hydrochlorides,  $\text{CuI}$  as catalyst, and *t*-BuOOH as oxidant, probably via a carbinolamine intermediate.<sup>343</sup>

An experimental and theoretical study of the Baeyer-Villiger (BV) oxidation of ketones has examined its uncatalysed and acid-catalysed forms, and fluoro- and chloro-substituted substrates.<sup>344</sup> In assessing migratory aptitudes, fluoroalkyl groups are only slightly less favourable than alkyl (by 0.3/0.5 kcal mol<sup>-1</sup>, calculated/observed), whereas migration of a chlorinated substituent is significantly more difficult (ca 2.6 kcal mol<sup>-1</sup>).

Cyclohexanone and cyclopentanone monooxygenases have been used in the microbial BV oxidation of prochiral bicycloketones. A significant difference in behaviour of [3.3.0] and [4.3.0] substrates has been analysed by high-level DFT calculations.<sup>345</sup> Al–BINOL complexes catalyse the enantioselective BV oxidation of cyclobutanones to give the corresponding  $\gamma$ -butyrolactones in up to 84% *ee*.<sup>346</sup> Advances in the enantioselective metal-catalysed reaction have been reviewed, especially for lactone preparation.<sup>347</sup>

## Other Reactions

Terminal alkynals (**113**) of appropriate length ( $n = 1, 2$ ) and substitution [ $X = C(CO_2Me)_2, C(CH_2OR)_2, NTs,$  and others] have been cyclized with decarbonylation to cycloalkenes (**114**), using a ruthenium(I) catalyst.<sup>348</sup> In some cases, cycloisomerization to give conjugated aldehyde occurred. Both processes are believed to involve catalytic ruthenium vinylidenes.



Alkynals and alkynones have been alkylatively cyclized in a palladium(0)-catalysed *trans*-addition of organoboronic acids.<sup>349</sup>

3-Silyloxy-2-aldehydes can undergo hetero-Diels–Alder reaction with aldehydes to give useful heterocycles.<sup>350</sup> A model reaction,  $H_2C=C(OSiH_3)-N=CH_2$  with formaldehyde, has been explored theoretically. Lewis acids such as boron trifluoride catalyse the reaction by coordinating to the aldehyde oxygen, making the aldehyde more electrophilic. Concerted and stepwise mechanisms for this process are considered.

Aromatic aldehydes react with triphenylphosphine and trichloroacetic acid derivatives ( $Cl_3C-CO_2Et, Cl_3C-CN$ ) to give benzylidene dichlorides or  $\alpha$ -chlorocinnamates.<sup>351</sup> Substituent and reaction condition effects on chemo- and regio-selectivity are described.

A variety of ketones and aldehydes have been condensed with sulfones, using *t*-BuOK catalysis in *N,N*-dimethylacetamide solvent.<sup>352</sup> Typical results – for  $\alpha$ -methylcarbonyl compounds – include useful yields of the corresponding butadiene, whereas aromatic ketones give variations on the theme.  $\alpha$ -Tetralone, for example, gives naphthalene and its  $\alpha$ -methyl derivative (mainly the latter), but acetophenone interestingly gives some *p*-terphenyl.

Rates of alkaline hydrolysis of isatin (indane-2,3-dione) and its *N*-methyl derivative have been measured in a range of DMSO–water mixtures from 30 to 45 °C.<sup>353</sup> Analysis of activation parameters and rate variation with dielectric constant suggest selective solvation by water.

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