Aldehydes and ketones

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Reviewing the literature published between July 1993 and September 1994

1 Synthesis of saturated aldehydes and ketones

1.1 Redox methods

Oxidation of alcohols provides the simplest route to aldehydes and ketones and this remains an area of much activity. The use of tetrapropylammonium perruthenate (TPAP) has become well established and a review of oxidations with this reagent has appeared.[1] Despite the well established use of Cr^{VI} based oxidants, developments in this area continue to appear. Quinolium fluorochromate, $C_9H_7NH[FCrO_3]$, has been reported as a more soluble (in non-aqueous solvents), less acidic, but equally effective alternative to the corresponding pyridine based reagents.[2] Magnesium chlorochromate, which is very simple to prepare in either hydrated or anhydrous form, has been noted although there does not appear to be a significant advantage associated with its use.[3] Simplified procedures also continue to be of interest; including those based on supported reagents[4] and the use of sub-stoichiometric amounts of the chromium salt together with a co-oxidant, *e.g.* sodium percarbonate.[5] A similar strategy has been employed with a variety of other transition metal species. t-Butylhydroperoxide (TBHP) has been employed with reagents based on iron,[6] copper,[7] and osmium.[8] Interestingly, the last combination is selective for the oxidation of allylic alcohols; neither alkene dihydroxylation nor saturated alcohol oxidation is observed. Cobalt Schiff base complexes together with either ethyl-2-oxocyclopentanecarboxylate[9(a)] or 2-methylpropanal[9(b)] efficiently mediate the conversion of alcohols into the corresponding carbonyl compounds. With the former co-reactant allylic and benzylic hydrocarbons are also converted into the corresponding ketones. Similar catalytic systems for the aerobic oxidation of alcohols have been developed using ruthenium complexes together with a cobalt salt as oxygen activator.[10] These latter systems have a significant safety advantage in that they operate at sufficiently low partial pressures of oxygen to render air a viable working atmosphere. Related catalysts have also been employed to activate manganese dioxide for the oxidation of saturated alcohols.[11]

Primary and benzylic silyl ethers can be converted directly into the corresponding carbonyl compound in a heterogeneous process using silver or sodium perbromate.[12] The isomeric α-hydroxysilanes also undergo oxidative desilylation to afford aldehydes in good yields upon treatment with chromic acid in DMSO.[13]

Secondary alcohols can be oxidized in preference to primary alcohols on reaction with trichloromelamine.[14] Unlike other *N*-halo oxidants the formation of α-haloketones is not a problem although with this reagent diols tend to afford lactones. Similar selectivity is achieved with HOF.MeCN and in this case the oxidation of primary/secondary diol combination occurs smoothly to afford the hydroxyketone with competing lactone formation not being a problem.[15] The relatively low temperatures counterbalance the high acidity of the medium so that acid labile substrates can be oxidized with few problems.

The efficient oxidation of primary alcohols and allylic methylene units to aldehydes and enones respectively can be achieved using perfluorobenzeneselenic acid or the related *N*-oxidopyridineselenic anhydride.[16] The latter reagent is the more active but is unstable and must be prepared *in situ*. Both can be used catalytically in conjugation with a co-oxidant, TBHP or $PhI(OAc)_2$ respectively, and in this respect provide a convenient alternative to the use of SeO_2. Alkane and allylic hydrocarbon oxidation remains an area of much activity.[17] Many of these procedures suffer

from both modest selectivities and/or low conversions. Further evidence for heteroatom mediated regiocontrol in the Wacker oxidation has been forthcoming[18] whilst methyl ketones may be selectively prepared without contamination by chlorinated by-products in a modified version of the electrochemically mediated Wacker process.[19]

α-Chiral aldehydes, derived from amino-acids, can be prepared in high yields with minimal racemization through the lithium tri-t-butoxyaluminium hydride reduction of the mixed anhydride prepared *in situ* from pivaloyl chloride.[20] In certain cases e.g. arginal, the use of the analogous phenyl ester can provide some advantages. Although less soluble, in other solvents, the use of the corresponding sodium reagent in diglyme results in superior yields of aldehydes with a wider range of substrates.[21] Thionaphthol esters may be efficiently reduced to the aldehyde in a free-radical process using cyclohexa-1,4-diene as the hydrogen atom source.[22]

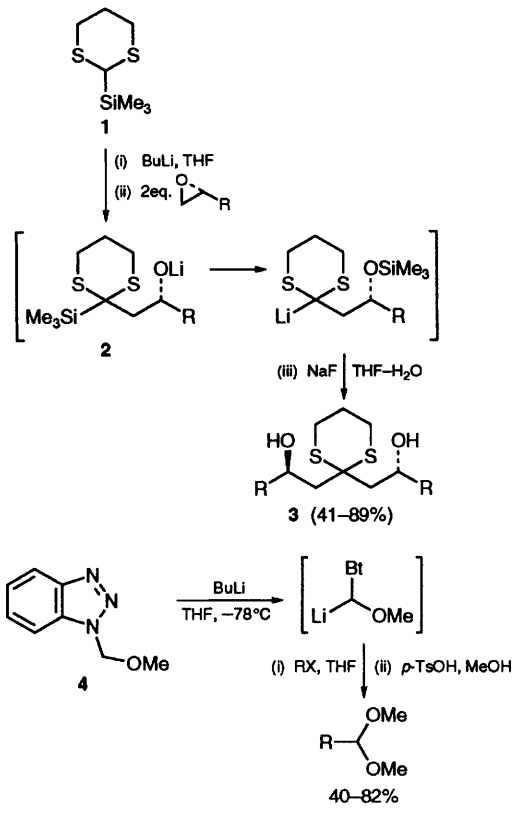
Transfer hydrogenation provides a facile method for the conjugate reduction of enones. Both limonene[23] and ammonium formate[24] prove to be acceptable hydrogen atom sources. Similar high selectivity can be achieved on hydrosilylation and recent developments in this area allow for the formation of bulky silyl enol ethers, *e.g.* triphenylsilyl or triisopropylsilyl.[25] Sodium hydrogen telluride[26] and purified nickel boride[27] also show chemoselectivity for the carbon–carbon double bond, although with the latter reagent isolated alkenes may be competitively reduced.

1.2 Umpolung methods

Protected cyanohydrins continue to find application as umpolung reagents in synthesis. Van Rozendaal *et al.* have shown that saturated aldehydes may be activated in this manner with the resulting lithioanion adding efficiently, in a 1,2 fashion, to a range of vinyl and aryl ketones.[28] Functionality may also be incorporated, providing routes to α-ketoesters.[29]

Upon metallation, 2-trimethylsilyldithiane (**1**) adds efficiently, in a one-pot process, to two equivalents of a variety of terminal epoxides, affording the symmetrical ketone masked as the dithiane **3**, **Scheme 1**.[30] The key step is this process is the [1,4] Brook rearrangement of the initially formed alkoxide **2**.

The anion obtained from treatment of benzotriazol-1-ylmethoxymethane (**4**) with butyl lithium behaves as a classical acylanion equivalent undergoing alkylation and acylation to afford, after acidic methanolysis, the protected aldehyde or α-ketoaldehyde respectively.[31] α,β-Unsaturated acylanion equivalents are obtained by treatment of acrolein and crotonaldehyde acetals with the Schlosser base (LICKOR).[32] The direct formation of acyl-lithiums from carbon monoxide has been extended to allow the preparation of aryl ketones. However, unlike their aliphatic counterparts, the yields obtained render this of little preparative



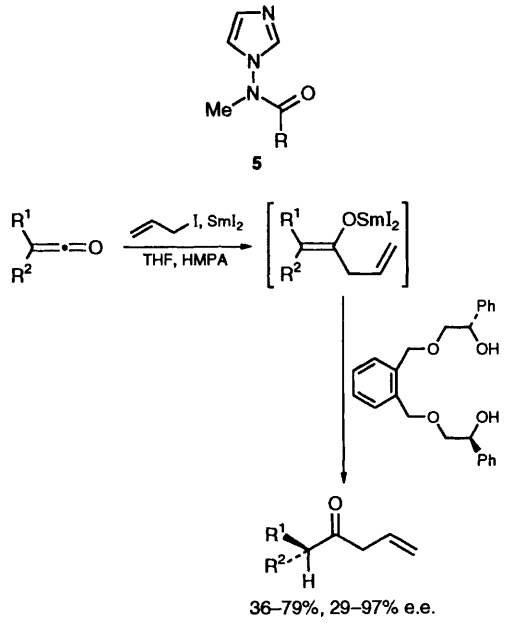
Scheme 1

utility.[33] Acyl samarium[34] and titanium[35] species have been implicated in the coupling of acid chlorides with carbonyl compounds mediated by SmI_2 and $TiCl_3$ respectively. Finally, acyl units may be added in a conjugate fashion to enones in a free radical process initiated by treatment of aldehydes with di-t-butylhyponitrite.[36]

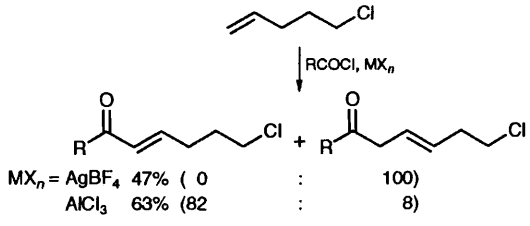
1.3 General methods

Although addition of an organometal to lithium carboxylates provides a simple entry to ketones, over-reaction is frequently a problem. This can be circumvented through the use of the corresponding organocerium reagent.[37] In this case improvements are observed in both the yield and rate of reaction. The synthesis of lactols from lactones is similarly enhanced. A high yield for the ketone has also been obtained in the sonochemical Barbier reaction of lithium benzoate.[38] In this process alkylchlorides are the most efficient substrates with the less reactive bromo and iodoalkanes affording significant amounts of the diketone, presumably via a Wurtz-type coupling mechanism. Similar selectivity has been obtained using other activated carboxylic acid units, including *N*-(*N*-acyl-*N*-methylamino)cycloimminium salts **5**[39] and β-lactams.[40] Upon treatment with SmI_2 and an Fe^{III} catalyst, iodopropyl esters undergo an intramolecular nucleophilic acylation reaction to produce δ-hydroxyketones with almost complete retention of configuration. Similarly, the corresponding ω-iodoesters afford cyclic ketones.[41]

Samarium iodide also promotes the combination of ketenes with allylic halides. Recent reports have delineated the scope and limitations of this strategy in which significant asymmetry can be observed in the final protonation step, **Scheme 2** (see also Section 6.1).[42] Acid chlorides may also be employed in nucleophilic acylation although more recent developments have employed Friedel–Crafts type conditions.[43] In this latter process, using substituted alkenes, some regioselectivity can be observed which depends upon the nature of the Lewis acid employed, **Scheme 3**.[43(c)]



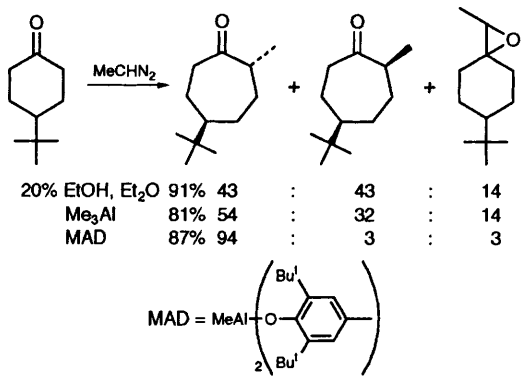
Scheme 2



Scheme 3

Ketones may be converted in moderate to good yield into the branched homologous aldehyde on reaction with lithiotrimethylsilyldiazomethane.[44] Diazoalkanes also undergo Lewis acid catalysed insertion reactions with aldehydes and ketones.[45] These reactions can occur with high regio- and chemo-selectivity to afford the substituted ketones in good yield, **Scheme 4**. Carbene insertion has also been postulated in an efficient chromium-mediated homologation of aldehydes to methylketones.[46]

Alkenes are converted into the homologous aldehyde in the hydroformylation process. This important area has continued to receive much attention. The principal areas of concern have been



Scheme 4

regiochemistry and enantioselectivity. High ratios of branched to linear aldehydes have been achieved with ligands based on aminophosphine oxides,[47] diphosphinites,[48] diphosphites,[49] and phosphinephosphinates.[50] These last ligands, based on the binaphthyl system, have also afforded good levels of asymmetry for both 1,2-disubstituted and monosubstituted alkenes. The regiochemistry of hydroformylation of substituted alkenes appears less dependent on the presence or nature of added ligands and excellent regioselectivities for both linear and branched aldehydes have been reported.[51] Epoxides may replace alkenes as substrates, producing β-silyloxyaldehydes.[52] Further reactions of this product can contaminate this process but are inhibited through the use of Rh-amine catalysts. Finally, utilizing triethylorthoformate as the hydroformylation solvent together with a catalytic amount of *p*-TsOH leads directly to the diethylacetal in good yield.[53]

In a related process t-butylstyrene may be polymerized under an atmosphere of CO in the presence of a bis(oxazoline) palladium catalyst to form a polyketone of high isotacticity and high optical rotation.[54] This represents the first example of good asymmetric induction in such a process. Similar polyketones may also be accessed through the use of free radical polymerization of α-cyclopropyltrimethylsilylenol ethers.[55]

Palladium-mediated catalysis is also involved in the synthesis of β-arylketones from allylic alcohols via the Heck reaction.[56] The presence of a base is essential and although triphenylphosphine affords the best yields the rate is adversely affected. Consequently, the use of potassium acetate is advocated to provide optimum results. In contrast, the related ruthenium-catalysed rearrangement of allylic alcohols to saturated ketones occurs at a much faster rate in the absence of added base when the dimeric ruthenium complex **6** (Figure 1) is employed.[57] The isomeric enol ethers undergo regioselective substitution to afford α-arylated ketones, albeit in moderate yields. The regiochemistry can also be affected by other factors. For example, in the presence of Cp(COD)RuCl, alkynes react with allylic alcohols to afford γ,δ-unsaturated ketones whereas the corresponding

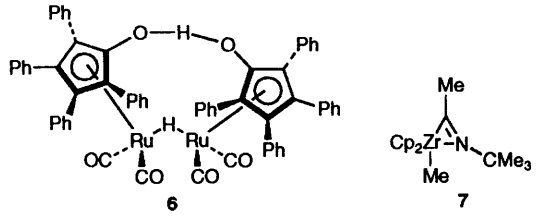


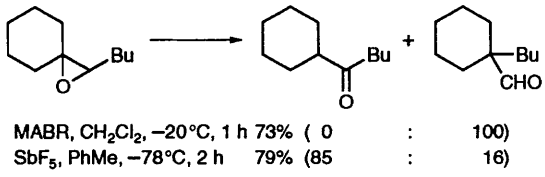
Figure 1

diphosphine complex $(Ph_3P)_2CpRuCl$ leads to the β,γ-unsaturated product. In this process, with the exception of propargylic alcohols which exclusively result in linear product, isomeric mixtures of linear and branched enones arise.[58]

Alkenes and alkynes react with the cationic zirconium η^2-(iminoacyl)complex **7** to form, after hydrolysis, ketones and (*E*)-enones respectively.[59] Hydroboration of alkynyl halides offers entry to β,γ-unsaturated ketones[60] whilst terminal alkynes may be converted into the homologous aldehyde in moderate overall yield via the corresponding propargylic thioether.[61] Developments in aldehyde synthesis have resulted in enhanced procedures being reported for the Vilsmeyer–Haack formylation of organomercurials[62] and the α-oxidation of sulfones utilizing $Me_3SiOOBu^t$ as the oxidant.[63]

Aldehydes may be converted into ketones directly through classical dithiane chemistry; naphthalene-1,8-dithiol has been introduced for this purpose. Photochemical regeneration of the carbonyl compound occurs very efficiently after oxidation to the monosulfoxide.[64] Similar overall transformations can be achieved for aliphatic aldehydes on treatment with a boron ylid.[65]

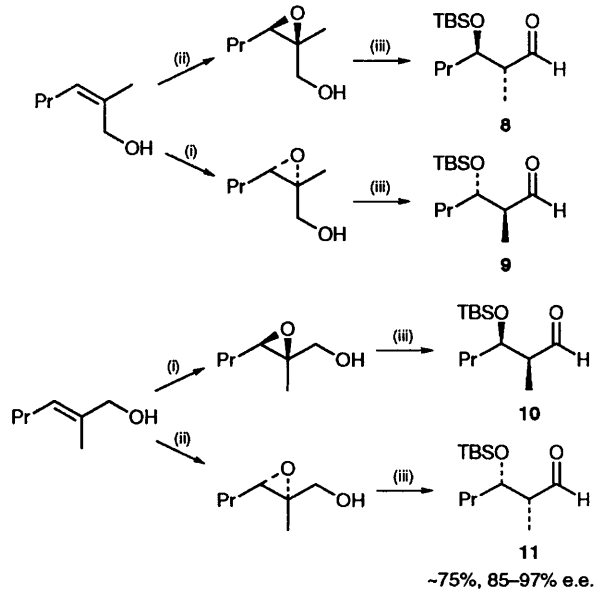
Catalysis of the oxy-Cope rearrangement has been achieved using a designed antibody.[66] The anionic version of this rearrangement is known to proceed at a much higher rate and this has been carried out in tandem with the [2,3] Wittig rearrangement. Since the anionic oxy-Cope rearrangement is stereoconvergent, favouring the (*E*)-olefin, isomer purification after the [2,3] Wittig rearrangement is not required.[67] Tandem rearrangements are also involved in the synthesis of γ,δ-unsaturated aldehydes from allylmethallyl ammonium salts via a base-induced isomerization–aza-Claisen rearrangement sequence.[68] The rearrangement of epoxides continue to provide good routes to carbonyl compounds. Treatment of aliphatic terminal epoxides with the complex iron reagent, Me_4FeLi_2, or an alkyl lithium in the presence of catalytic $FeCl_3$ affords the methyl ketone, presumably by way of the enolate.[69] In contrast, treatment of all terminal epoxides with 2.5 equivalents of lithium tetramethylpiperidide leads to exclusive formation of the aldehyde.[70] Alkenylepoxysilanes undergo radical-induced rearrangements to afford, initially, the α-silylaldehyde which on heating tautomerizes to the isomeric silylenol ether.[71] Under acid-catalysed conditions the regiochemistry of the epoxide rearrangement is similarly dependent on the nature of the initiator.[72] For example, trisubstituted epoxides are converted into aldehydes on treatment with methyl-bis(4-bromo-2,6-di-t-butylphenoxide)aluminium (MABR) whilst the use of antimonylpentafluoride affords ketones, **Scheme 5**.[72(c)]



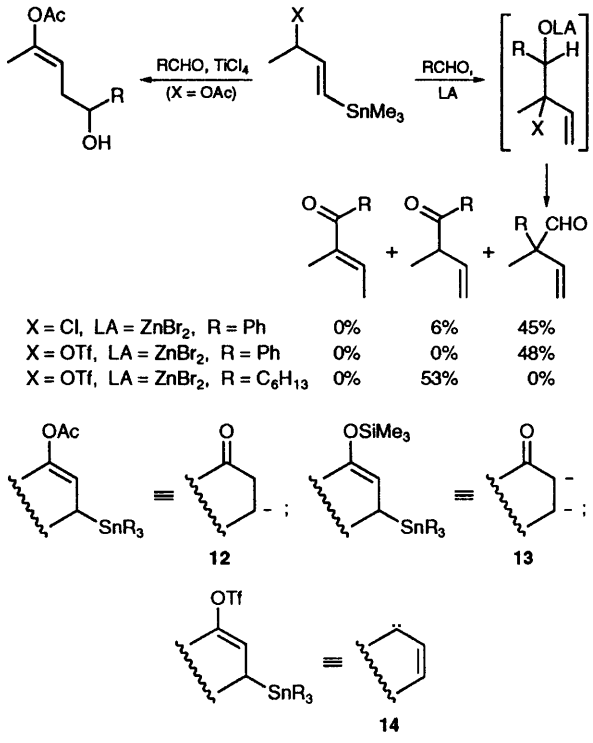
Scheme 5

α,β-Epoxyalcohols undergo pinacol-type migration with high selectivity.[73] Since the starting materials are accessible in enantiomerically pure form through the Sharpless epoxidation this can provide an entry to all four possible aldol isomers **8–11**, **Scheme 6**.[74] Similar rearrangements are also observed in the reaction of γ-functionalized allylstannanes with aldehydes.[75] The regiochemistry is controlled by the alkene substituent with the particular pathway followed being very aldehyde dependent. In general these reagents function as either homoenolate **12**, α,β-dianionic ketone **13**, or vinyl carbene **14** equivalents, **Scheme 7**. True pinacol–pinacolone rearrangements can be efficiently catalysed by aminium salts.[76]

Alkoxycyclopropanes continue to find application as homoenolate equivalents.[77] The synthesis of substituted ketones by oxidative free radical



Scheme 6



Scheme 7

alkylation of silyl enol ethers remains an active area with a variety of electrophiles being employed, including idoesters,[78] organostannanes,[79] selenides,[80] chromium complexes,[81] and allylsilanes.[82]

2 Synthesis of aromatic aldehydes and ketones

The principal development in aromatic acylation chemistry has involved the use of lanthanide triflates as recyclable catalysts for activated aromatic species. Further studies in this area have revealed that the equivalent scandium complexes are more effective catalysts.[83] An alternative to the traditional Lewis acid catalysed procedures utilizes zeolites and this, being heterogeneous, provides further simplifications in the work-up steps.[84] With substituted aromatics, regioselectivity remains a challenge. In a study of the acylation of 2-methoxynaphthalene, Nomura and co-workers have demonstrated that a degree of control can be achieved by varying the strength and stoichiometry of the Lewis acid.[85] Site selective *ortho* formylation of phenol can be achieved via the magnesium phenoxide. Traditionally this has required the use of stoichiometric HMPA although recent reports have suggested that either triethylamine or methanol are equally effective.[86] A method for the synthesis of *meta* acylated phenols has been outlined.[87]

Treatment of pyridylhalides with activated zinc and an acid chloride provide a very direct method for acylation of aromatic species resistant to Friedel–Crafts methodology.[88] Alternatively, although limited in regiochemistry, 4-pyridyldiethylacetals may be directly metallated and the resultant anion alkylated. After hydrolysis this provides the corresponding 4-acylpyridine in excellent overall yield.[89]

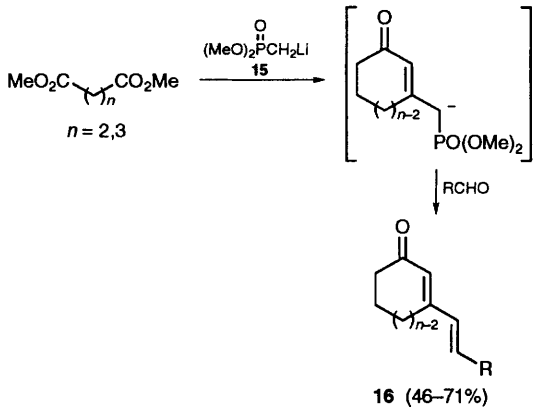
The alternative acylation strategy employing an aryl acyl electrophile has also been explored. Thioesters have found significant use and a survey of the optimum conditions for coupling with a range of cuprates has been reported.[90] Acylsilanes react with the radical anion generated from reaction of diarylketones with ytterbium to afford diarylmethyl ketones in good to moderate yields.[91] Symmetrical diarylketones can be obtained through the electrochemical reduction of aroyl chlorides,[92] whilst unsymmetrical products are accessed through the palladium-catalysed carbonylative coupling of an aryl boronic acid and an aryl halide.[93] Although complete chemoselectivity cannot be obtained, the highest ratios of ketone to biaryl products are gained using potassium carbonate/anisole as the base/solvent combination. Replacing the boronic acid with sodium formate leads to good yields of the aryl aldehyde whereas the use of other formate salts promote reduction.[94] Transmetallation of an aryl lithium with triethylboron generates a tetravalent borate complex which can efficiently undergo palladium-catalysed carbonylation with a variety of alkyl halides.[95]

Oxidation remains a valuable method for the preparation of arylketones. Selective oxidation of polyhydroxymethylphenols can be achieved with MnO_2 through careful control of the reaction conditions.[96] A simplified procedure for benzylic alcohol oxidation is obtained when the reagent is supported on clay in the absence of solvent.[97] Activated benzylic alcohols, ethers, and amines are oxidized to the corresponding aldehyde on treatment with CAN[98] whilst α-hydroxyesters are converted into the corresponding ketone in an electrochemically mediated oxidation.[99] The presence of arylalkyl substituents complicates the process through competing bromination. Diketones can similarly be prepared. Further developments in the Cr^{VI}-catalysed TBHP oxidations of benzylic alcohols have been reported.[100] Although not synthetically viable the same catalytic system also causes oxidation of stilbenes to a complex mixture of ketones, diketones, epoxides, and acids. Interest in other benzylic hydrocarbon oxidations continues with methods utilizing potassium permanganate in conjunction with alumina,[101] calixerenes or 18-crown-6[102] being noted. Diarylmethanes can be converted into the corresponding ketone in good yield using NBS although alkyl substituents are prone to suffer competing (poly)bromination.[103] Arylmethyl groups may be efficiently converted into the aldehyde, under mild conditions, through a sequence involving oxidative cleavage of the corresponding enamine.[104] Oxidative photochemical cleavage of alkenes can be achieved in the presence of 1,4-dimethoxybenzene.[105] Finally, an unusual carbon–carbon bond cleavage, to give indanones, occurs on reaction of 1-hydroxymethylindanes with either PDC or PCC.[106] Similar conversions of

1-hydroxymethyltetralins to tetralones also occur and both are believed to proceed via oxidation of the intermediate enol.

3 Synthesis of cyclic ketones

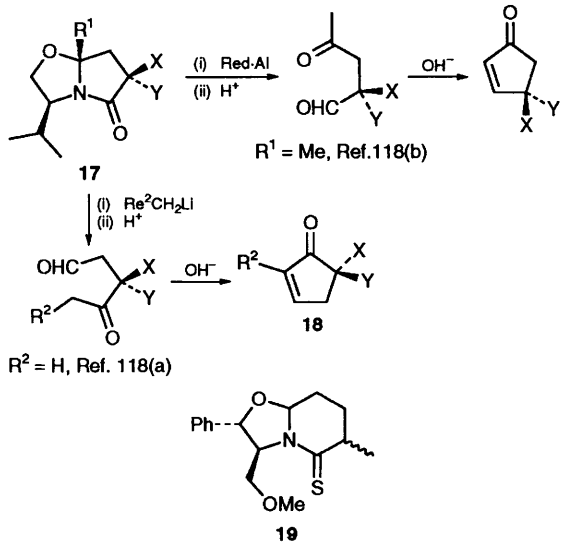
Intramolecular enolate condensations provide the simplest entry to cyclic ketones and enhancements in the synthetic efficiency of these processes continues to attract attention. The 'one-pot' synthesis of 3-alkenyl-2-cyclohexenones **16** and, to a lesser extent, cyclopentenones can be achieved via the cyclocondensation of dimethyl(lithiomethyl)phosphonate **15** with either dimethylglutarate or dimethylsuccinate, respectively, followed by trapping with an appropriate aldehyde, **Scheme 8**.[107] Similar multiple carbon–carbon bond-forming synthesis of cyclic ketones can be achieved through the tandem double Michael addition/ Dieckmann cyclization of active methylene compounds with methylacrylate promoted by disodium iron-tetracarbonyl.[108] The 'one-pot' tandem Robinson annulation–decarboxylation of cyclic β-ketoesters may be achieved under neutral conditions although both high temperatures and the use of HMPA are required.[109] Tandem Cope rearrangements can be utilized to generate a variety of polycyclic ketones and full details of this approach have appeared.[110] Spirocyclic methylenecyclopentanones are accessed in a single step from bis acetylenic alcohols in a tandem oxy-Cope catalysed by t-butylcatechol under conditions of photo-assisted single-electron transfer.[111] Similar methylenecyclopentanones are available through the rearrangements of alkoxyallenes,[112] arylallenylketones,[113] alkynylcyclobutanols,[114] and chromium carbene complexes.[115]



Scheme 8

Cyclopentenones can be efficiently accessed from bulky silylenol ethers and terminal alkynes under the influence of a $SnCl_4$-Bu_3N promoter.[116] A greater variety of alkynes may be employed with this procedure than with the related oxyallylcation [3 + 2] cycloaddition.

Similar products can also be obtained with high diastereoselectivity through the reaction of β-thioenoylsilanes with ketone enolates.[117] The corresponding β-trialkylsilylenoylsilanes do not cyclize efficiently. Enantiomerically pure 5,5-disubstituted cyclopentenones **18** can be prepared from the bicyclic lactam **17**, **Scheme 9**,[118] whilst the related thiolactams **19** can provide access to homochiral 4,4-disubstituted cyclohexenones.[119] Similar products have been prepared using chiral sulfoxides as the initial source of asymmetry[120] whilst Takano *et al.* have outlines methods for the production of 2,5-cyclohexadienone synthons in either enantiomeric form.[121]

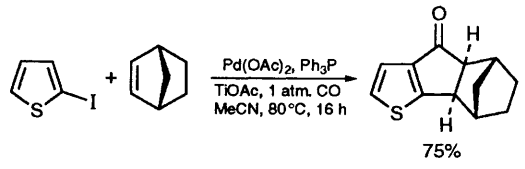


Scheme 9

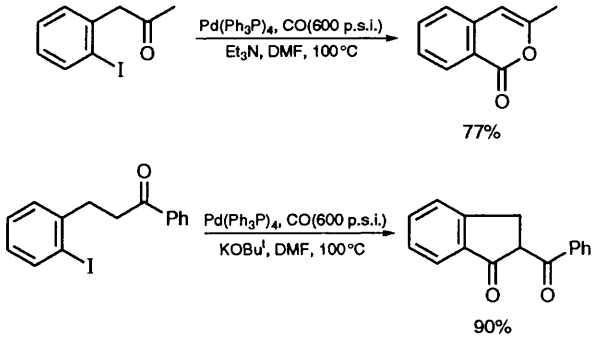
Cyclopentenones may also be accessed through the Pauson–Khand reaction and this remains an active area of study. A simplified procedure which enables the *in situ* preparation of the alkyne-dicobalthexacarbonyl complex has been published.[122] New catalysts and ligands which enable both faster reactions and higher substrate loadings continue to be developed.[123] Similar accelerations are found when employing methylenecyclopropanes.[124] Substrate induced stereoselectivity is also a topic of interest[125] and, in this respect, a range of chiral auxiliaries[126] have been employed with the major advance being asymmetric induction in the intermolecular Pauson–Khand reaction.[127]

Iron carbonyls have been known to promote similar alkyne–alkene couplings, albeit requiring high CO pressures and/or high temperatures. In contrast the related alkyne–allene process proceeds under ambient conditions.[128] Cyclopentenones can also be prepared through the cobalt octacarbonyl induced rearrangement of alkynylcyclopropanols.[129] This conversion can now be achieved catalytically, with good regioselectivity being observed with substituted cyclopropanes. Cyclopentenones may also be realised on photolysis of cyclopropylcarbyne

molybdenum complexes although the yields are only moderate.[130] A number of other cyclocarbonylative routes to cyclic ketones have been reported.[131] In this respect carbon monoxide has found use as a one-carbon component in the Heck reaction, **Scheme 10**.[132] Intramolecular trapping of the intermediate acylpalladium species with enolates can now occur through either oxygen or carbon to yield lactones or ketones respectively. Selectivity is usually controlled by ring size with five- and six-membered ring formation being favoured, **Scheme 11**. When all other factors are equal oxygen-trapping is favoured.[133]



Scheme 10



Scheme 11

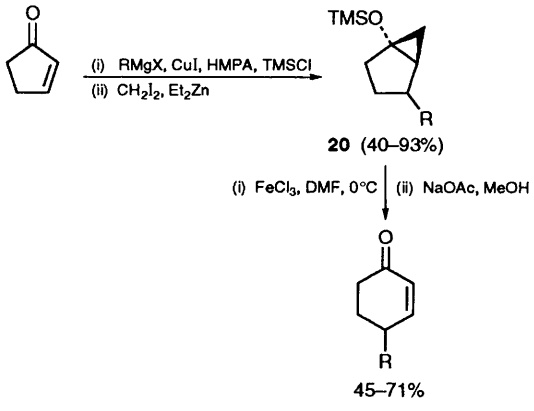
The concurrent generation of two chiral centres can now be achieved with both high diastereoselectivity and high enantioselectivity in rhodium-catalysed intramolecular hydroacylation reactions.[134] A full report on the scope and limitations of such an approach to 3-substituted cyclopentanones has been published.[135] Cyclopentanones are frequently the major product from the rhodium-catalysed decomposition of diazoketones. Much work has been reported on the effect of both substrate and ligand structure on the selectivity and stereochemistry of this process.[136] The carbene need not arise from a diazoalkane. For example, cyclopentenones are obtained by C–H insertion of the alkylidene carbene generated by Michael addition to β-ketoethynyl(phenyl)iodonium triflates[137] whilst β-ketosulfoxonium ylids may be employed in the synthesis of cyclic azaketones.[138]

Similar cyclic azaketones have also been prepared through dioxirane oxidation of allenyltosylamides[139] and the electrochemical oxidation of *N*-carbamoyl piperidines.[140] Related oxygen heterocycles can be prepared in moderate to good overall yields via the Claisen rearrangement of 2-vinyl-4-methylene dioxolanes.[141]

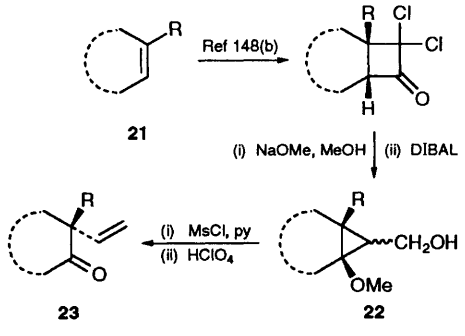
Radical mediated synthesis of cyclic ketones continues to be a fertile area. Dowd and co-workers have illustrated the use of α-chlorocyclobutanones as precursors to ring-enlarged ketones via tandem intramolecular radical acylation/ring expansion sequences.[142] Polycyclic ketones are also accessible through tandem radical macrocyclization–transannular ring closure protocols and further reports have appeared to this effect.[143] Acyl radicals may be directly employed in similar radical macrocyclizations through the treatment of (ω-iodoalkyl)acrylates with tris(tritrimethylsilyl)silane under an atmosphere of carbon monoxide.[144] Radical mediated fragmentations of tertiary alkoxides have also been utilized in the synthesis of macrocyclic ketones.[145]

Fragmentation and ring expansion strategies continue to provide a large number of routes to functionalized cyclic ketones.[146] For example, treatment of the silyloxycyclopropane **20**, readily accessible from cyclopentenone by conjugate addition/enol cyclopropanation, provides a general route to ring-expanded, 4-substituted cyclohexenones,[147] **Scheme 12**; whilst α-vinyl cyclic ketones **23** are readily accessed from the cyclic alkene (**21**) via fragmentation of the alkoxycyclopropane **22** in a cyclopropylcarbinyl/homoallylic ketone rearrangement, **Scheme 13**.[148]

Finally, direct cyclization can provide entry to cyclic ketones. The intramolecular McMurry

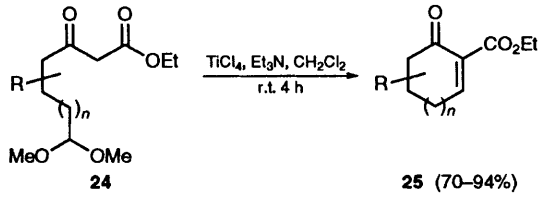


Scheme 12



Scheme 13

olefination may be achieved using α,β-unsaturated esters to provide entry to macrocyclic enones.[149] Silylenol ethers may be trapped by a suitably positioned cobalt-stabilized propargylic cation[150] whilst β-ketoesters provide an excellent terminating group for the Lewis acid mediated cyclization of acetals **24** to afford 2-carboxyalkylcyclohexenones **25** in good yield, **Scheme 14**.[151]



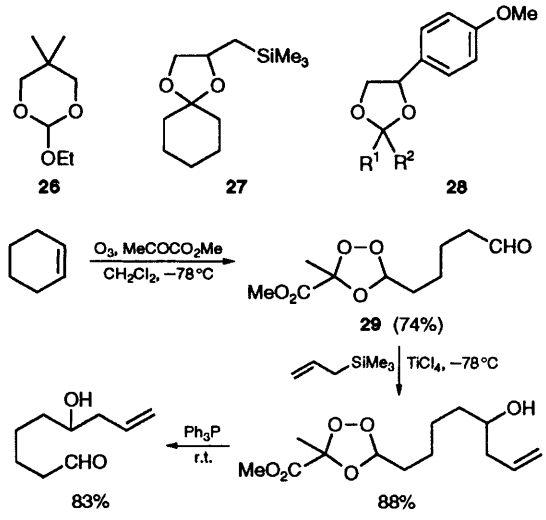
Scheme 14

4 Protection and deprotection strategies

Conditions have been sought that enable the formation of cyclic acetals under milder conditions. In this respect the known reaction of ketones with ethylene epoxide has been re-examined and conditions optimized (0.1 equivalents $F_3B.OEt_2$, $-78°C$) for a range of substrates.[152] A mild, high yielding, room temperature method for the synthesis of dioxanes proceeds from the cyclic orthoester **26**.[153] Selectivity is another ongoing issue and the functionalized dioxolanes **27,28** have been advocated as protecting groups which may be selectively cleaved under conditions in which 'normal' cyclic acetals are stable.[154] However, the non-specific creation of an additional chiral centre during formation can result in analytical or synthetic complications. Selective protection of one of the carbonyl groups derived from alkene ozonolysis can be achieved as the ozonide **29** by *in situ* reaction with methyl pyruvate. Regeneration of the aldehyde is achieved under mild, reductive conditions whilst conversion into the corresponding carboxylic acid occurs on treatment with triethylamine, **Scheme 15**.[155]

Similar to the related rhodium species,[156] the ruthenium catalyst $[Ru(MeCN)_3(triphos)](OTf)_2$ is reported to be an effective promoter for selective acetalizations and transacetalizations.[157] Notably, acyclic acetals are cleaved more rapidly than their cyclic counterparts. Similar observations have been recorded using a $SmCl_3$–AcCl combination which is an enhanced modification of the previously noted $SmCl_3$–TMSCl reagent system.[158] The $SnCl_2$ mediated acetal cleavage process can be accelerated by the addition of certain aromatic hydrocarbons, including naphthalene and C_{60}.[159] π-Acceptors such as DDQ have long been known to promote the hydrolysis of acetals and dithioacetals and additional reports to this effect continue to appear.[160] A survey of a number of these species has indicated that whilst DDQ, $TCNQF_4$, and TCNE are effective promoters both TCNQ and chloranil are not.[161]

Dithioacetals are readily formed on acid-mediated treatment of carbonyl compounds with a dithiol.



Scheme 15

Protic conditions can be avoided through the use of 5M $LiClO_4$ in ether[162] or by the use of various anhydrous heterogeneous catalysts.[163] The latter group of reagents have been shown to be particularly effective for relatively unreactive carbonyl compounds such as diaryl ketones.

Vinyl oxathioacetals, difficult to prepare directly, can be prepared from the corresponding dimethylacetal by sequential treatment with Me_2S–TMSOTf followed by a lithium thiolate.[164] The cyclic counterparts, oxathiolanes, have synthetic utility since it is possible to achieve the selective deprotection of ketones in the presence of aldehydes under conditions in which dithiolanes are stable.[165] In contrast to the acetal, *gem*-diacetates can be employed as acid-stable carbonyl protecting groups. However, the reported methods for cleavage provide only moderate yields. A recent report suggests the use of aromatic alkoxides for this purpose which enables the unmasked aldehyde to be realized in near quantitative yields.[166]

Ketones and aldehydes can also be masked as oximes, hydrazones, and related species. Considerable effort has been applied to developing methods for revealing the parent carbonyl group. Many of these are oxidative in nature and include hydrogen peroxide/TS-1 zeolite,[167] sodium hypochlorite,[168] dimethylsulfoxide–TMSCl,[169] zinc bismuthate,[170] cupric chloride,[171] dioxirane,[172] iodosylbenzenediacetate,[173] and tetrabutylammonium peroxydisulfate.[174] The principal advantage of most of these 'new' methods is that they proceed under neutral or near neutral conditions which enable other functional groups to be tolerated.

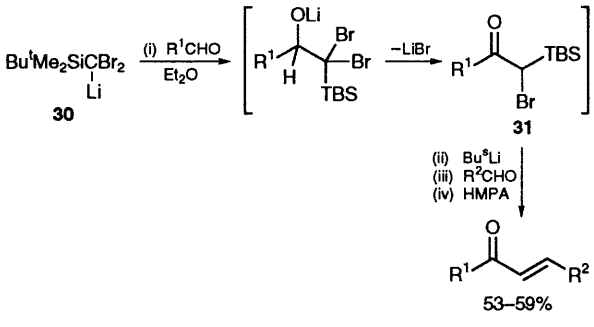
5 Synthesis of functionalized aldehydes and ketones

5.1 Unsaturated aldehydes and ketones

Variations on the selective oxidation of allylic alcohols achieved using palladium catalysts continue to appear.[175] Competing epoxidation can complicate

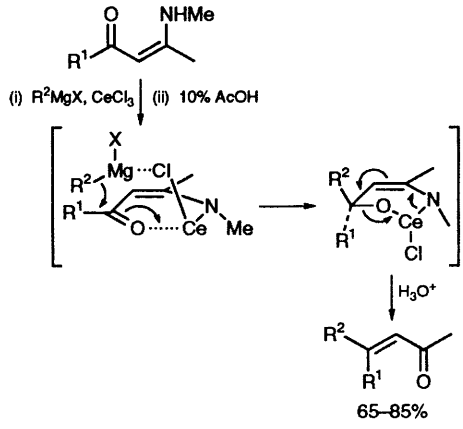
the use of dioxiranes for this purpose and the factors which control the selectivity have been delineated.[176] When the alcohol is subject to steric crowding good selectivity may be attained with a TBHP–$VO(acac)_2$ combination.[177] In the presence of acetic anhydride and pyridine photo-oxygenation of vinyl silanes affords α-trimethylsilylenones in moderate to good yields. Similar products may be obtained from the equivalent vinyl stannane although in this case isolation of the intermediate peroxide is required.[178] Both protocols appear to be prone to producing regioisomeric mixtures.

Treatment of ozonides with a preheated solution of diiodomethane and diethylamine affords the corresponding α-methylene aldehyde in good yields.[179] The parent aldehyde also reacts under the same conditions. Aldol–dehydration strategies continue to provide efficient routes to unsaturated carbonyl compounds.[180] Aldehydes combine with bromomethylketones in a samarium triodide mediated reaction,[181] and enol formates in the presence of various transition metal complexes, to afford enones in a high yielding one-pot processes.[182] Similarly, β-(trimethylsilyl)silylenol ethers react with aldehydes but not ketones in a mild non-basic reaction to afford predominantly the (*E*)-enol in good yield.[183] In an interesting sequence, aldehydes react with t-butyldimethylsilyl dibromomethyl lithium (**30**) to afford α-bromo-α-silyketones **31**. Without isolation, treatment with butyl-lithium affords the silylenolate which combines, in a Peterson-type reaction, with a second aldehyde to provide the desired enone, **Scheme 16**.[184] The nature of the solvent is critical since if THF is employed 1,3 diols result whilst without HMPA the final elimination can be inefficient.



Scheme 16

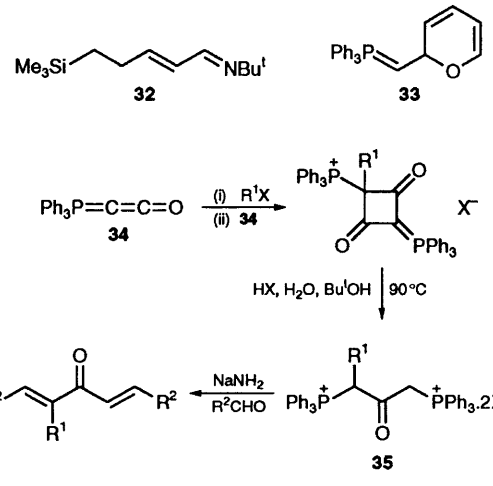
Ketones may be converted into enones with transposition of the carbonyl group through the cerium-mediated addition of Grignard reagents to enaminoketones. Although similar conversions have been recorded using alkyl-lithiums these do not show the selectivity observed in this modification which results in the incoming nucleophile being predominantly *trans* to the new carbonyl group. This is attributed to cerium chelation with addition then occurring *anti* to the *N*-methyl group, **Scheme 17**.[185] Related carbonyl transpositions have been observed in the reaction of β-acyldithioacetals,[186] the Vilsmeyer formylation of dithioacetals,[187] and the



Scheme 17

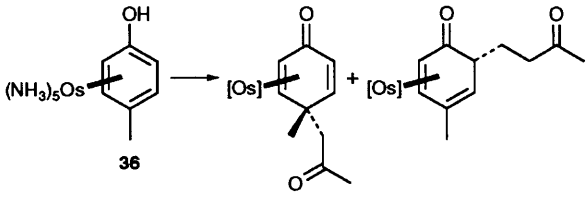
Rupe reaction of cyclic-1-alkynols.[188] Lewis acid mediated rearrangements of silylated alkynyl-1,4-diols provide an efficient entry to α-silylallenones[189] whilst the related epoxyalkynols afford mixtures of allenals and [3]-cummulenals.[190]

In extensions to previously reported strategies, aldehydes may be homologated to the dienals through condensation with the silylated unsaturated imine **32**[191] whilst aromatic aldehydes are converted into the trienone on reaction with the pyrylium-derived Wittig reagent **33**.[192] Trienones have also been prepared through the Heck reaction of β-iodovinylacetals with tertiary allylic alcohols,[193] the Lewis acid promoted reaction of dienylalcohols with β-bromosilylenol ethers,[194] and by dimethyldioxirane oxidation of furans with *in situ* trapping of the dicarbonyl compound with a Wittig reagent.[195] Dienones may be accessed through the Claisen rearrangement of propargylic β-ketothioenol ethers[196] or through the triphenylphosphine-mediated rearrangement of acetylenic ketones.[197] Cross-conjugated dienones are obtained by the reaction of bis-ylids **35**, readily accessible, in good yield, through sequential alkylation and decarboxylation of (triphenyl-phosphoranylidene)ethenone **34**, **Scheme 18**.[198]



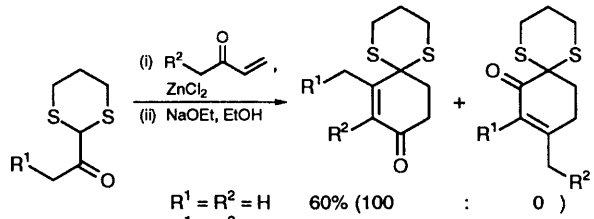
Scheme 18

Both 2,4- and 2,5-cyclohexadienones can be prepared through the reactions of the η^2-phenol-osmium complex **36 Scheme 19**. Whilst selectivity is observed it appears to be highly dependent on the particular combination of substrate, reagents, and conditions employed. Although attractive, this strategy is limited by the moderate yields obtained and also by scale since it currently requires the use of stoichiometric quantities of osmium.[199] Enantiomerically enriched cyclic enones and dienones can be efficiently obtained through the catalytic asymmetric Heck reaction and this conversion has been discussed in some detail.[200] Substituted cyclic enones are produced in the tandem Michael reaction/aldol condensation between 2-acyldithianes and a second enone. Although mixtures of products can arise, some selectivity is observed depending upon the nature of the alkyl substituents, **Scheme 20**.[201]



Pr^i_2NEt, $Zn(OTf)_2$, MeCN, 25°C (5 : 85)
Pr^i_2NEt, $Zn(OTf)_2$, MeOH, −25°C (100 : 0)

Scheme 19

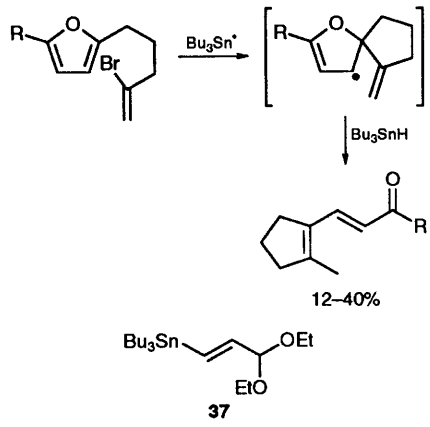


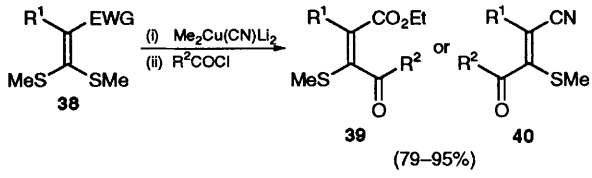
$R^1 = R^2 = H$ 60% (100 : 0)
$R^1 = R^2 = Me$ 78% (5·8 : 1)
$R^1 = R^2 = C_2H_5$ 96% (1 : 7·7)

Scheme 20

A strategy for the synthesis of α-*H*-β,β-disubstituted cyclic enones, which complements earlier routes to α,β disubstituted analogues, has been outlined although this modified procedure is not viable for cyclopentenones.[202] These can be obtained via the oxidation of fulvenes[203] and furans and this latter subject has been comprehensively reviewed.[204] Furans have also been employed as end groups in a tandem radical cyclization-fragmentation approach to β-(cyclopentenyl)-alkenones, **Scheme 21**.[205]

Acylation of vinylanions provides a valuable method for the synthesis of enones. Full details of the palladium-catalysed acylations of bis stannyl ethenes have been reported.[206] In a variation on this theme the vinylstannane acetal **37** has been

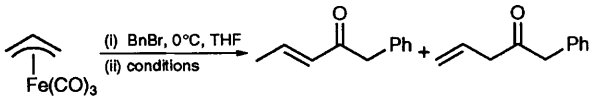




Scheme 21

introduced as a β-formylvinyl anion equivalent.[207] Acylation of the vinyl copper species generated by transmetallation of the ketene dithioacetal **38** affords the functionalized enones **39** and **40**.[208] The stereochemistry of this process is controlled by the bulk of the activating electron-withdrawing group in the β-position.

Iron tricarbonyl diene complexes are well known to produce the (*Z*)-dienone on Friedel–Crafts acyclation. Unusually the (*E*)-isomer results when monoethyl oxalylchloride is employed as the electrophile.[209] η^3-Allyl iron tricarbonyl complexes undergo carbonylative insertion reactions to afford, in good yields, either αβ- or βγ-enones depending on the reaction conditions, **Scheme 22**.[210]



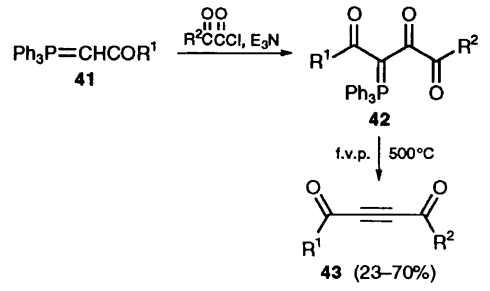
MeCN, 25°C, 12 h, 78% (7 : 2)
MeCN, *hν*, 0°C, 80% (1 : 9)

Scheme 22

Finally, β-oxophosphorus ylids **41**, readily available through simple ylid acylation,[211] couple with α-ketoacids to generate β,γ,β′-trioxo-ylids **42** which on flash vacuum pyrolysis provide 1,4 diketoacetylenes **43** in modest to excellent yields (**Scheme 23**).[212]

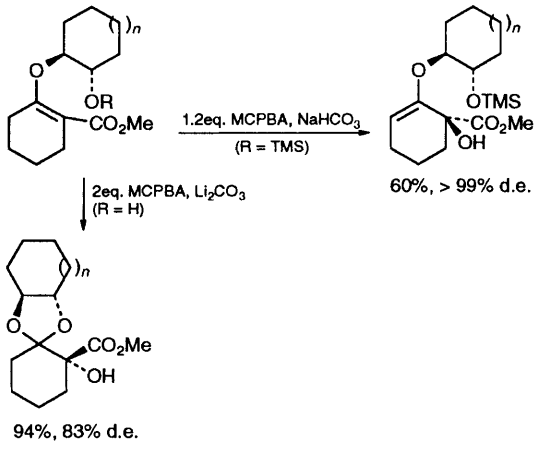
5.2 α-Heteroatom substituted aldehydes and ketones

Enolate oxidation remains the simplest method for the preparation of α-oxycarbonyl compounds. Recent developments have included the use of



Scheme 23

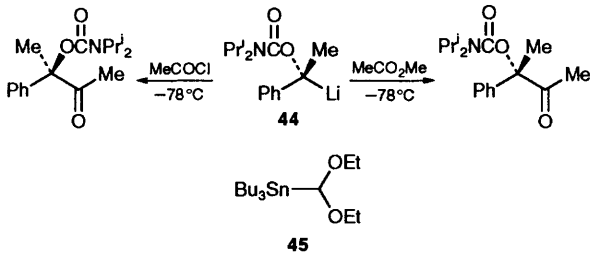
cobalt-catalysed procedures for the mild non-acidic oxidation of enol acetates and silyl enol ethers.[213] Employing MCPBA as the oxidant, good diastereoselectivities are obtained with enol ethers derived from *trans*-cycloalkanediols. Interestingly, the opposite stereochemical outcome is obtained depending on the nature of the second alcohol group of the chiral auxiliary, **Scheme 24**.[214]



Scheme 24

Titanium affords advantages over other counter-ions (rates, yields, and diastereoselectivities) in the dimethyldioxirane-mediated enolate oxidation. Furthermore, significant asymmetry ($\leq$63% e.e.) can be obtained through the use of chiral titanium ligands.[215] The same oxidant can also convert 1,2-diols into α-ketols with chiral starting materials reacting with little degradation of stereochemical purity. No overoxidation or bond cleavage is observed although with unsymmetrical s, s-diols regiochemical mixtures arise.[216] Allenes may be directly converted into ketols through the use of peracetic acid/catalytic $OsCl_3$[217] or TBHP/catalytic OsO_4.[218] High regiochemical control is observed. For example, terminal allenes are converted into hydroxymethyl ketones with no evidence for the alternative α-hydroxyaldehyde. Although asymmetry can be obtained with chiral additives the level of induction is low. High enantiomeric excesses are obtained in the dihydroxylation of enones.[219]

Acylation of α-carbamoyloxylithium **44** proceeds with complete conservation of asymmetry and either retention or inversion of stereochemistry depending upon the electrophile employed, **Scheme 25**.[220] The corresponding alkoxystannane undergoes palladium-mediated acylations with retention of configuration and similar conversions are possible with the corresponding α-aminostannanes.[221] Optimum yields are obtained with arylchlorides. The α-stannylacetal **45** is readily transmetallated to the organolithium derivative and as such reacts as a formyl anion equivalent with a wide range of electrophiles, including aldehydes and ketones.[222]



Scheme 25

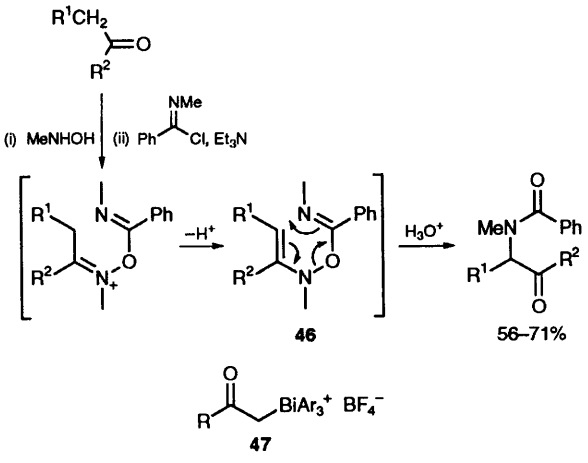
α-Hydroxyacetals can be obtained on oxidation of aldehydes with thianthrenium tetrafluoroborate.[223] These masked α-hydroxyaldehydes may be converted into the isomeric alkoxyketone through an acid-mediated pinacol–pinacolone rearrangement pathway.[224] The two-step conversion of aldehydes and ketones into the homologous trialkylsilyloxyaldehyde can be achieved in excellent yield via cyanohydrin formation.[225] The nitrile to aldehyde reduction can be achieved with no loss of stereochemical purity, although vinylic aldehydes undergo a double bond migration to afford masked dicarbonyl compounds. The samarium iodide promoted synthesis of ketols from isonitriles and carbonyl compounds has been reviewed.[226] This reagent also moderates the formation of α,β-dihydroxy ketones from α-dicarbonyl compounds and aldehydes in what is effectively a crossed aldol reaction. Carbonyl hydrates are equally effective substrates and the reaction may be carried out in aqueous media although in this case the diastereoselectivity is minimal.[227]

α-Thioaldehydes have been prepared in enantiomerically pure form through the use of chiral oxazolines,[228] oxazolidinones,[229] and hydrazones.[230] The latter methodology has also been employed to synthesize quaternary thiocarbonyl compounds as single enantiomers. Homochiral α-silylketones may similarly be prepared.[231] These latter species are also accessible via the inverse Brook rearrangement of β-lithiosilylenol ethers[232] and the condensation of acyl silanes with sulfur ylids.[233]

Thiomethyl sulfonium ylids react with aromatic aldehydes to afford the homologous α-alkylthioaldehydes.[234] This conversion presumably proceeds via the corresponding thioalkyl epoxide. The corresponding sulfoxy-epoxide may be selectively converted into either the α-thioketone or thioenone.[235] Dithiane oxides are efficiently acylated

by acylimidazoles although two equivalents of base are required since the product 2-acyldithiane is considerably more acidic than the starting material. Addition of an alkylhalide can provide a 'one-pot' route to quaternary acyldithaine oxides of high diastereomeric purity.[236] Similarly good diastereoselectivities are obtained in the further reaction of these species with diazodicarboxylates to afford masked β-amino-α-diketones.[237]

α-Aminoketones, but not aldehydes, can be synthesized by the *in situ* Claisen rearrangement of the *N*-vinyl-*O*-imminylhydroxylamines **46**, generated by *O*-alkylation of nitrones with imidoylhalides, **Scheme 26**.[238] Similarly, coupling of diazocarbonyl compounds with tertiary amines affords a transient ammonium ylid which undergoes an *in situ* Stevens rearrangement to give *N,N*-dialkylated α-aminoketones and esters in moderate to good yield.[239] Imidoylhalides may also be metallated and combined with aldehyde to afford hydoxyimines. These tautomerize on heating to generate α-aminoketones in moderate to good overall yield.[240] Finally, nitrogen nucleophiles have continued to find applications with a variety of electrophiles, including α-chloroepoxides, α-nosyloxyketones,[241] and alkyl bismuthonium salts (**47**).[242]



Scheme 26

These last reagents also combine with a multitude of other nucleophiles. With halide salts this can provide a simple, efficient entry to α-halomethylketones. The same products can also be obtained from the reaction of vinyl chlorides with NXS (X = Cl, Br, I) and these substrates have been proposed as being more convenient to handle then the corresponding enol ether as well as providing a cleaner reaction with little competing polyhalogenation.[243] Polybromination of silyldienol ethers can be avoided through the use of phenyltrimethylammonium tribromide as the bromide source.[244] The photo-oxygenation of alkenes to α-chloroketones occurs in enhanced yields using $CuCl_2$ rather than $FeCl_3$. Terminal alkenes afford α-chloromethylketones selectively although regioisomeric mixtures arise from internal olefins unless an additional controlling element, *e.g.* allylic alcohol, is present.[245] Ketones, on reaction with an I_2–CAN combination, afford α,α′-diiodoketones[246] whilst the same reagent system converts enones into β-alkoxy-α-iodo-ketones.[247] α-Iodoenones are obtained from 1-alkynols[248] whilst α-chloroenones can be prepared, in a 'one-pot' procedure, through the reaction of silylenol ethers with an *in situ* generated dichlorocarbene.[249] The corresponding α-chloro- and α-fluoro-enals are simply accessed via formylation of the corresponding α-halosulfoxide followed by thermolysis.[250]

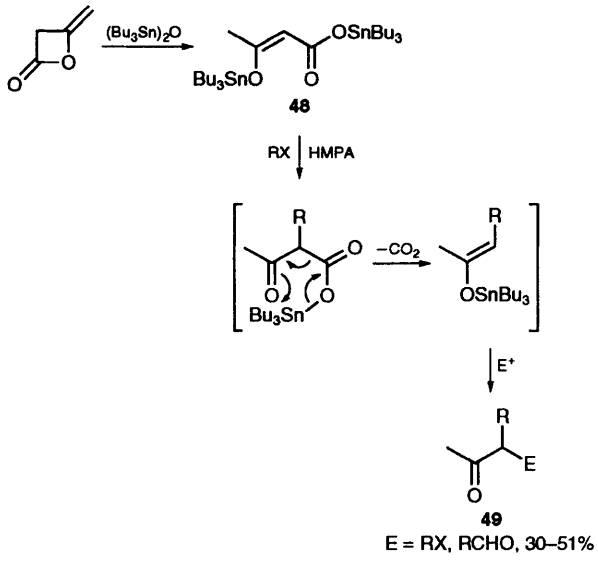
The introduction of fluorine into organic molecules has become an area of much activity. Electrophilic fluorination of β-dicarbonyl compounds remains the most direct entry methods and can provide strategies for the synthesis of secondary and tertiary α-fluoro, α,α-difluoro, and α-fluoro-α,β-unsaturated ketones.[251] Enantiomerically pure α-fluoroketones may be generated through the fluoride ion opening of α-silyl-αβ-epoxymesylates prepared through the Sharpless epoxidation procedure.[252] Similarly nucleophilic-opening of perfluoroalkylenol ether epoxides leads to α-substituted alkyl perfluoroalkyl ketones.[253] Perfluoroalkyl ketones are important synthetic intermediates and a number of strategies for their preparation have been reported,[254] including the Friedel–Crafts perfluoroacetylation of alkenes[255] and the Claisen rearrangement of perfluoroalkylvinyl ethers.[256]

5.3 Dicarbonyl compounds

Polycarbonyl compounds are simply accessed through the C-acylation of enolates. Both *N*-acylaziridines[257] and the bismuthonium salt **47**[258] have proved to be particularly useful for this task. Although Darzens condensations can complicate the direct alkylation of α-haloketones, these difficulties can be circumvented through the use of the corresponding tin enolate and employing α-halo-imines as the electrophile.[259] Branched triketones are efficiently generated through the reaction of β-diketone copper chelates with ketene.[260] The initial diketones can be accessed through the reaction of αβ-acetylenic ketones with benzaldoximate.[261] Imidoyl stannanes have previously been acylated in low yields and a recent report suggests that improved efficiency is obtained with bulkier nitrogen substituents, *e.g.* the *N*-2,6-xylyl species.[262] The α-hydroxyalkylimine generated by reaction of α-iminoalkylsamariumdiiodide with carbonyl compounds may be directly oxidized to the α-diketone.[263] This and other oxidations of α-heterosubstituted ketones provide a relatively facile entry to functionalized dicarbonyl compounds. α-Chloroketones can be converted into the monoprotected diketone via oxidation with NBS followed by silver-promoted methanolysis. The

intermediate α-chloro-α-bromo-ketones are also useful precursors to α-aminoacetals.[264]

α,β-Dihydroxyketones are efficiently converted into the α-diketone on treatment with carbonyldiimidazole[265] or into the triketone by oxidation with various TEMPO derivatives.[266] Triketones can also be prepared through the known oxidation of diazoalkanes with dimethyldioxirane.[267] Copper-catalysed oxidative cleavage of α-alkylated cyclic β-diketones provides routes to unsymmetrical α-diketones[268] whilst symmetrical products are obtained in the cobalt-mediated coupling of aldehydes.[269] Both symmetric and unsymmetric benzils are prepared via the palladium chloride mediated oxidation of diphenylethynes.[270] This affords several advantages over existing oxidative protocols, notably the toleration of aqueous conditions and increased chemoselectivity in relation to competing alkene oxidation.



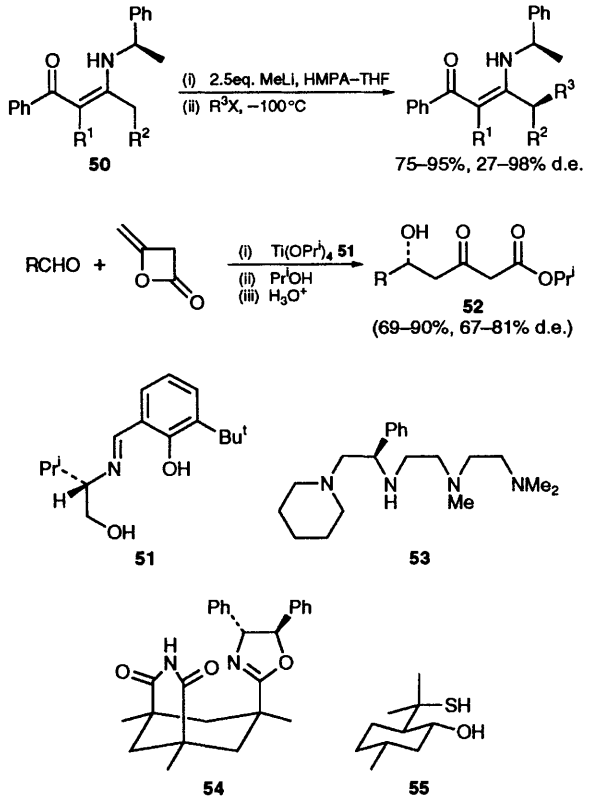
Scheme 27

6 Reactions of aldehydes and ketones

6.1 The aldol reaction and other enolate additions

The α-alkylation of ketones remains an area of intense activity. Normally achieved through the use of lithium enolates the process can suffer from polyalkylation and with unsymmetrical ketones from poor regioselectivity. Improvements in both these areas, notably selective monoalkylation, have been realized through the use of the corresponding manganese reagents.[271] Alternatively, good regiocontrol in the alkylation step can be obtained through the use of the silylenol ether. Alkylation of these is limited to S_N1 active electrophiles although Jefford and co-workers have previously demonstrated that the use of silver trifluoroacetate enables primary halides to be alkylated. Recent reports have indicated that steric bulk in the β-position is no hindrance to this process and that good yields can be achieved with stoichiometric amounts of a primary alkyl halide.[272] The α,α-dialkylatedketones **49** can be obtained in a one-pot process through the use of the tin enolate **48** derived from diketone and bis(tributyltin)oxide, **Scheme 27**. Both α-halo-aldehydes and -ketones are efficiently alkylated by this species with no competing aldol reaction, although simple aldehydes do undergo a tandem aldol dehydration process to afford enones in respectable yields.[273] Increased efficiency in alkylations using acyclic epoxides is observed on addition of yttrium triflate to the reaction mixture. The use of related chiral ytterbium complexes afforded low but measurable levels of asymmetry.[274]

Asymmetric alkylation has been achieved with a number of chiral auxiliaries with varying degrees of success. Most of these reports have focused on cyclic ketones[275] although acyclic chiral 1,3-diketones have been prepared by asymmetric γ-alkylation of the corresponding enaminone **50**, **Scheme 28**.[276] Related aldol products **52** can be obtained from diketene in the presence of the non-covalently bound chiral Schiff base additive **51**.[277]



Scheme 28

The use of such chiral additives was pioneered by the Seebach group and an account of the early work in this area has been published.[278] More recently this has been extended to a catalytic asymmetric process utilizing the polyamine **53** as the source of chirality.[279]

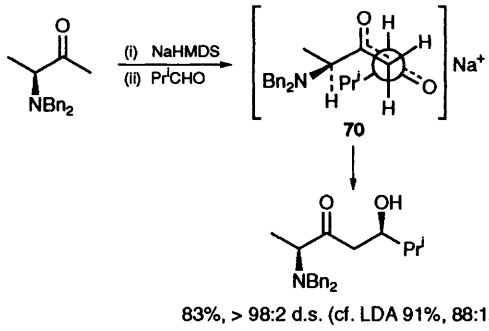
Related to this subject is that of enantioselective deprotonation of ketones and protonation of

enolates and work in this area continues to appear.[280] Most of the proton sources are based on amino alcohols although the use of the chiral imide **54** derived from Kemp's triacid results in ketones of >97% e.e.[281] Enantiopure ketones can also be obtained by resolution through enzymic processes[282] or by formation of a chiral acetal. Eliel's hydroxythiol reagent **55** has been shown to be singularly effective in this latter approach.[283] Determination of enantiopurity of the product ketone can be rapidly and efficiently achieved through the use of (*R,R*)- or (*S,S*)-1,2-diphenylethane diamine.[284]

The aldol reaction continues to see developments. A particularly active area is the design of new promoters for the Mukaiyama aldol reaction. In this respect an *in situ* preparation of trimethylsilylfluorosulfonate, a cheaper alternative to the commonly employed TMSOTf, has been reported.[285] Bismuth trichloride has been used in a 'one-pot' tandem aldol–halogenation reaction although isolation of the intermediate aldol is possible and provides higher overall yields.[286] Tris(perfluorophenyl)boron[287] has been developed as an air-stable water tolerant Lewis acid although this has been superseded by the lanthanide triflates.[288] Recent results in this area indicate that recycling of the catalyst is more efficient if a mixed solvent system (water–ethanol–toluene) is employed.[289] As with Friedel–Crafts acylations (Section 2),[83] the corresponding scandium reagents are not only considerably more effective promoters but are also capable of selectively activating aldehydes in preference to acetals.[290] In the presence of an amine base these lanthanide triflates can efficiently promote the crossed aldol reaction[291] although the scope of these condensations are limited by the low basicity of the catalyst. Enhanced reactivities are possible using the corresponding tris(hexamethyldisilazide).[292]

An alternative ene-type mode of reactivity of silylenol ethers has been developed. This mechanistic pathway is favoured by bulky silyl groups and non-polar solvents. As a consequence of the ene mechanism high *syn* diastereoselectivity is observed regardless of the enol ether geometry whilst through the use of a BINOL–$TiCl_2$ complex very high enantioselectivities may be obtained.[293] Asymmetry may also be incorporated into the aldol reaction through the use of chiral enolates, notably those based on boron, and results in this area continue to appear.[294] Chelation is frequently invoked to account for high stereoselectivity.[295] However, the reaction of sodium enolates of α-amino ketones proceeds with a much higher kinetic diastereoselectivity than the equivalent lithium species. The open transition state **56**, based on electrostatic control, is postulated (**Scheme 29**) to account for this observation.[296]

Finally, a titanium-mediated aldol reaction has been employed, as the key step, in a total synthesis of rapamycin to generate the 31-membered macrocyclic ring, albeit with low diastereoselectivity.[297]

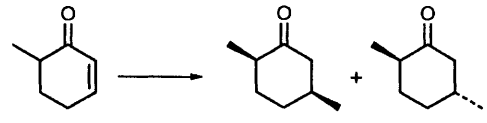


83%, > 98:2 d.s. (cf. LDA 91%, 88:12)

Scheme 29

6.2 Conjugate addition reactions

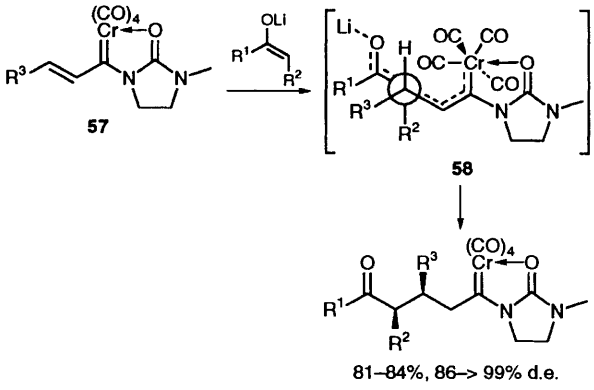
Conjugate addition reactions to enones and enols can suffer from competitive 1,2-addition. Complexation with bulky aluminium Lewis acids can inhibit this unwanted pathway and with substituted enones the addition of organolithiums results in the complementary stereochemical outcome to that obtained using copper reagents, **Scheme 30**.[298] Allylbarium reagents show exclusive 1,4 reactivity with, unusually, a preference for α-attack of the allyl unit.[299] This is an attractive option since allyl cuprates are unstable and tandem alkylation is not feasible with most soft allyl metal units. High levels of 1,4-addition is also obtained with alkyl alanes and titanates in the presence of nickel or copper catalysts.[300] The reaction of alanes with α,β-unsaturated acetals to afford the β-substituted aldehyde is well documented and a similar transformation has how been achieved employing a zirconene catalyst. In this recent development the aldehyde is obtained masked as the corresponding enol ether.[301]



Me_2CuLi 86% (42 : 58)
MeLi/(2,6-$Ph_2C_6H_3O)_3Al$ 73% (94 : 6)

Scheme 30

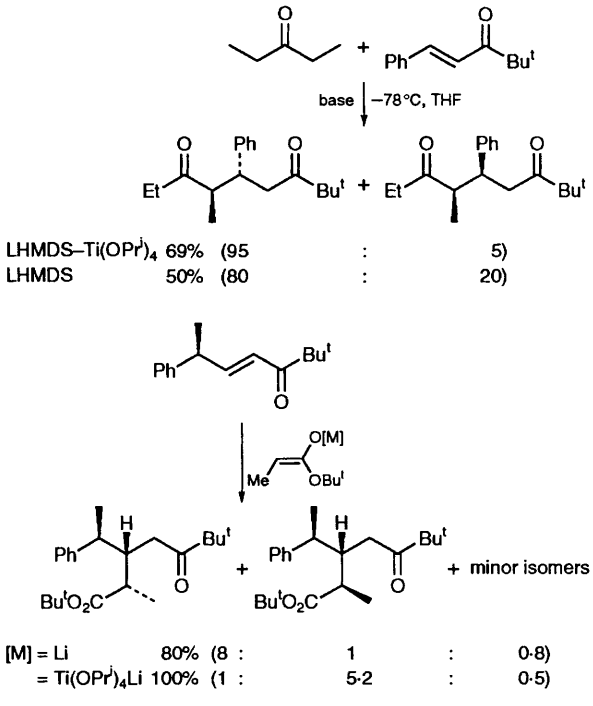
The Mukaiyama–Michael reaction proceeds with high 1,4-selectivity and may be promoted by both P_4O_{10}[302] and also photochemically in the presence of copper(I) salts.[303] A variety of other reagents undergo selective conjugate addition including aryl stibines,[304] silanes,[305] and tellurides,[306] both of these last two can be achieved with moderate to good enantioselectivity and it is in this area of stereocontrolled Michael additions that there has been the greatest activity. As synthons for acrylaldehydes Fischer carbene complexes are exceptionally active Michael acceptors for reactions with ketone enolates but not silyl enol ethers. An extended transition state **58** is proposed to account for the high *syn* selectivity observed (**Scheme 31**). This can be optimized through the use of the



Scheme 31

imidazolidone complex **57**[307] whereas the use of the phenylmenthol as a chiral auxiliary provides very high levels of asymmetric induction.[308]

Differences have emerged in the use of lithium and titanium enolates in conjugate additions to chiral enones. With ketone enolates the use of titanium species affords advantages in terms of yields and selectivities. However, with ester enolates, although both are equally effective, different stereochemical outcomes are obtained, **Scheme 32**, and this has been rationalized in terms



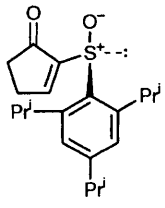
Scheme 32

of a chelated conjugate addition and a cycloaddition mechanism respectively.[309]

The major aspect of this chemistry has focused on chiral reagent mediated strategies with a further emphasis on the development of methods for the catalytic asymmetric conjugate addition. Copper-based reagents remain the most common with the highest enantioselectivities being recorded with sulfur–nitrogen based ligands.[310] Similar levels of asymmetric induction can be achieved in the nickel amine catalysed conjugate addition of dialkylzincs.[311] However, despite these successes it does appear that all these reagents are very substrate specific and that a truly general method remains to be discovered.[312]

A variety of β-ketoester derivatives undergo highly enantioselective selective conjugate additions catalysed by a variety of species, including rhodium ferrocenyl phosphine complexes and lanthanide alkoxides.[313] Using a chiral titanium oxide catalyst the Mukaiyama–Michael reaction has now been rendered both catalytic and asymmetric although with only moderate selectivities when acyclic enones are employed.[314]

Lastly, asymmetric intermolecular radical mediated Michael additions are possible using the sterically hindered chiral β-ketosulfoxide **59** as a chiral auxiliary.[315]



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