# Aldehydes and ketones

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REVIEW PERKIN 1

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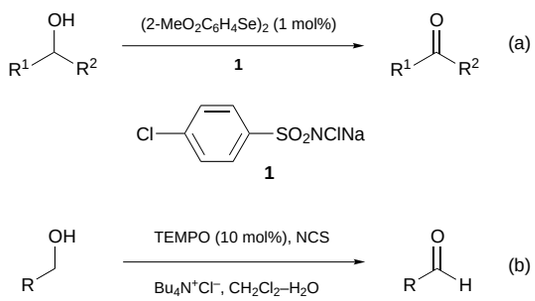
## 1 Oxidation of alcohols

By far the most commonly used method for the synthesis of aldehydes and ketones is the oxidation of alcohols. Many new oxidative methods have been described over the period covered in this review. Several are variants of well studied oxidising agents. For example, Varma and Dahiya describe the microwave-assisted oxidation of alcohols with iron(III) nitrate, under solvent-free conditions using clayfen as the solid support.[1] This rapid, selective and environmentally benign method conserves the use of excess solvents and toxic oxidants usually employed. Alcohols are also oxidised to the corresponding carbonyl compounds by silica supported active manganese dioxide[2] or [bis(acetoxy)iodo]benzene on alumina[3] under microwave radiation.

Whilst there are many catalytic methods for the oxidation of alcohols, most of these reactions are catalysed by transition metal elements. The catalytic oxidation of alcohols to carbonyl compounds mediated by a catalyst [*N*-(arylseleno)-4-chlorobenzenesulfonamide] based on a main group element has been described by Onami *et al.*[4] A wide variety of secondary alcohols and β,γ-unsaturated primary alcohols has been catalytically oxidised to the corresponding carbonyl compounds in good to excellent yields with *N*-chloro-4-chlorobenzenesulfonamide sodium salt **1** by the addition of dimethyl 2,2′-diselenodibenzoate (1–3 mol%) (**Scheme 1a**). Einhorn *et al.* have developed another potentially convenient and high yielding method for the oxidation of primary alcohols to aldehydes with no over-oxidation to carboxylic acids.[5] The reaction is performed in a biphasic dichloromethane–aqueous pH 8.6 buffer system, in the presence of tetrabutylammonium chloride with 2,2,6,6-tetramethylpiperidin-1-yloxyl (TEMPO) as a catalyst and *N*-chlorosuccinimide as the terminal oxidant (**Scheme 1b**). An interesting feature of this process is the high degree of chemoselectivity for the oxidation of primary hydroxy groups in the presence of secondary alcohols. [Bis(acetoxy)iodo]-benzene (BAIB) can be used in a similar oxidising system in which TEMPO is used as a catalyst for the conversion of primary and secondary alcohols to carbonyl compounds.[6] The procedure works efficiently at room temperature, in most common solvents and without solvent in some cases. The process

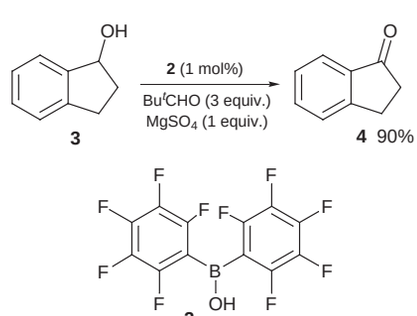



**Scheme 1**

exhibits a very high degree of selectivity for the oxidation of primary alcohols to aldehydes, without any noticeable over-oxidation to carboxy compounds, and a high chemoselectivity in the presence of either secondary alcohols or of other oxidisable moieties.

Yamamoto and co-workers have found that the strongly Lewis acidic bis(pentafluorophenyl)borinic acid **2** is an excellent Oppenauer oxidation catalyst.[7] In the presence of magnesium sulfate and pivalaldehyde (the hydride acceptor), allylic and benzylic alcohols are converted to their corresponding carbonyl compounds (*e.g.* **3**→**4**) (**Scheme 2**). The combination of diisopropoxyaluminium trifluoroacetate and *p*-nitrobenzaldehyde also serves as an excellent Oppenauer oxidant.[8] Catalytic oxidations, using tetra-*n*-propylammonium perruthenate (TPAP), of primary, benzylic and secondary alcohols to aldehydes and ketones bound to resin supports were carried out for the first time.[9] Hinzen and Ley have developed a polymer supported perruthenate reagent that can be used in the same way as TPAP for the oxidation of alcohols.[10] The new reagent offers the usual advantages of a polymer supported reagent; recycling of the reagent is particularly easy. The oxidative properties of trifluoromethanesulfonic anhydride have been studied by Balenkova and co-workers.[11] In a modified Moffat-type process the reaction of dimethyl sulfide with trifluoromethanesulfonic anhydride leads to the formation of the corresponding dimethyl-(trifluoromethanesulfonyl)sulfonium salt. The latter can be used in the mild oxidation of primary and secondary alcohols, including unsaturated ones, to the corresponding carbonyl compounds in 34–75% yield.

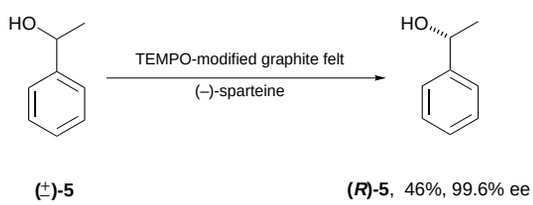
Several other new reagents for the oxidation of alcohols




**Scheme 2**

to the corresponding alcohols include ammonium chlorochromate adsorbed on alumina[12] or silica;[13] trimethylammonium chlorochromate adsorbed on alumina;[14] quinolinium chlorochromate;[15,16] potassium dichromate in benzene–water[17] or in *N*,*N*-dimethylformamide,[18,19] or adsorbed onto Kieselguhr;[20] isoquinolinium fluorochromate;[21] polymeric analogues of *N*,*N*-dichlorotoluene-*p*-sulfonamide;[22] 4 Å molecular sieves and *tert*-butyl hydroperoxide;[23] hydrogen peroxide and a complex dinuclear manganese(IV) complex;[24] and hydrogen peroxide in the presence of a peroxoniobium(V) species.[25] 3-Carboxypyridinium chlorochromate has been used to effect the oxidative deprotection of THP and silyl ethers to give ketones in high yield.[26] Many studies of the kinetics and mechanisms of oxidation reactions employing established oxidising reagents have been carried out over the period covered by this review. These include the study of *N*-chlorosaccharin,[27] quinolinium fluorochromate,[28] *o*-iodoxybenzoic acid and the Dess–Martin periodinane;[29] caesium fluoroxysulfate;[30] and the Swern oxidation of β-amino alcohols.[31]

Osa and co-workers describe an interesting electrochemical method for the kinetic resolution of secondary alcohols.[32] For example the (*S*)-isomer of the alcohol **5** was oxidised to the corresponding ketone whereas the (*R*)-isomer remained unreacted on a TEMPO-modified graphite felt electrode in the presence of (−)-sparteine. The enantiopurity of the remaining (*R*)-alcohol was >99% (**Scheme 3**). Stigter *et al*. have also developed a procedure that involves the enantioselective oxidation of secondary alcohols. The process is effected by purified and reconstituted quinohaemoprotein alcohol dehydrogenase (QH-EDH) from *Comamonas testosteroni*.[33] The (*S*)-enantiomer of chiral secondary *n*-alkyl alcohols is oxidised preferentially by the enzyme.




**(±)-5** **(*R*)-5**, 46%, 99.6% ee

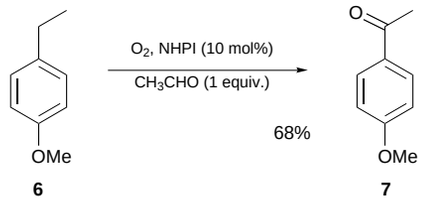
**Scheme 3**

## 2 Oxidation of alkanes

Oxidising systems that do not contain transition metals are particularly attractive for large scale applications. Einhorn *et al*. have developed one such method for the oxidation of benzylic alkanes, which has the additional benefit of having molecular oxygen as the terminal oxidant.[34] They found that hydrocarbons are oxidised efficiently to the corresponding ketone (*e.g*. **6**→**7**) by the action of a catalytic amount of *N*-hydroxyphthalimide (NHPI), molecular oxygen and acetaldehyde (**Scheme 4**). Secondary benzylic alcohols are also oxidised to the corresponding ketones in high yield when the same combination of reagents is used. Benzylic alkanes are oxidised to ketones within 10–30 minutes using $KMnO_4$ impregnated on alumina under microwave activation in dry media.[35] Allylic methyl groups have also been oxidised using a procedure that involves microwave activation.[36] Selenium dioxide and Bu′OOH adsorbed on silica generate α,β-unsaturated aldehydes from allylic methyl groups.

## 3 Oxidation of alkenes

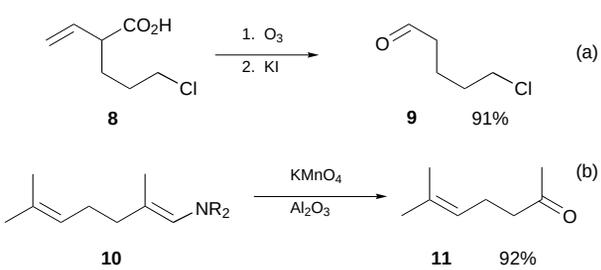
Whilst the ozonolysis of alkenes provides a useful method for the preparation of aldehydes and ketones, it is a procedure that has many disadvantages. One major difficulty, which is particularly problematic for large scale applications, is the low reaction temperature (*ca*. −78→−30 °C). However, Tsuji and Ishikawa




**6** **7**

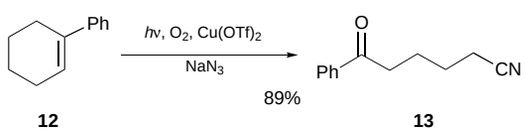
**Scheme 4**

have shown that the efficiency of the ozonolysis of alkenes at higher temperatures (−10→−3 °C) is equal to that of the equivalent reactions at lower temperatures when metal chlorides (*e.g*. $MgCl_2$, $AlCl_3$, $ZnCl_2$, $TiCl_4$) are present in the reaction mixture.[37] Mestres and co-workers have shown that ozonolysis of the carbon–carbon double bond of β,γ-unsaturated α-alkyl carboxylic acids (prepared *via* the alkylation of the corresponding dienediolates) represents a potentially useful synthesis of aldehydes and ketones (*e.g*. **8**→**9**) (**Scheme 5a**).[38] The selective oxidation of β,β-disubstituted enamines can be achieved using alumina-supported potassium permanganate, in a process that represents a one-carbon dehomologation (*e.g*. **10**→**11**) (**Scheme 5b**).[39] The procedure utilises inexpensive reagents, is easily carried out and involves a simple work-up.




**Scheme 5**

Shimizu *et al*. have described an intriguing and potentially useful process for the synthesis of keto nitriles *via* copper(II)-promoted photooxidative cleavage of cyclic alkenes.[40] They found that trisubstituted cyclic alkenes react with sodium azide in the presence of copper(II) triflate upon irradiation under oxygen to give keto nitriles in good yield (*e.g*. **12**→**13**) (**Scheme 6**). The reaction is thought to proceed *via* fragmentation of a cyclic 1,2-(hydroperoxy)azide.



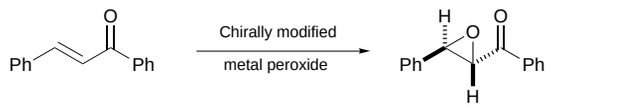

**12** **13**

**Scheme 6**

Whilst the hydration of an alkene *via* hydroboration–oxidation is not an oxidation process overall, it is considered here because of the oxidative process involved in the conversion of the organoborane to the alcohol. Pyridinium fluorochromate (PFC)[41] and NMO–TPAP[42] have both been found to be effective and convenient reagents for the oxidation of organoboranes to the corresponding ketones in good yield.

Two methods for the catalytic asymmetric epoxidation of α,β-unsaturated ketones using chirally modified metal peroxides have recently been developed. Shibasaki and co-workers have developed a procedure which incorporates a chiral lanthanoid complex.[43] The catalyst La–BINOL used in the process is a complex prepared from $La(OPr^i)_3$ and BINOL. It seems that the catalyst functions both as a Brønsted base, thereby activating the peroxide, and as a Lewis acid, thereby activating the ketone to nucleophilic attack. Several features of this process are noteworthy; the reaction is carried out at room

temperature; the catalyst loading is low (1–8 mol%); good enantiomeric excesses are obtained (*e.g.* **14→15**) (method A, **Scheme 7**). Somewhat better enantioselectivity for the same transformation **14→15** was obtained by Jackson and co-workers using a chirally modified magnesium *tert*-butyl peroxide (method B, Scheme 7).[44] The catalyst for the process is prepared simply from (+)-diethyl tartrate (DET) and dibutylmagnesium. The reaction is performed at room temperature in toluene and exhibits excellent enantioselectivity for the epoxidation of a variety of substituted chalcone derivatives. The low cost of the DET makes the method particularly attractive. α,β-Unsaturated ketones also react with tetra-*n*-butylammonium peroxydisulfate in the presence of hydrogen peroxide and base in acetonitrile at 25 °C to give the corresponding epoxides in excellent yields.[45]



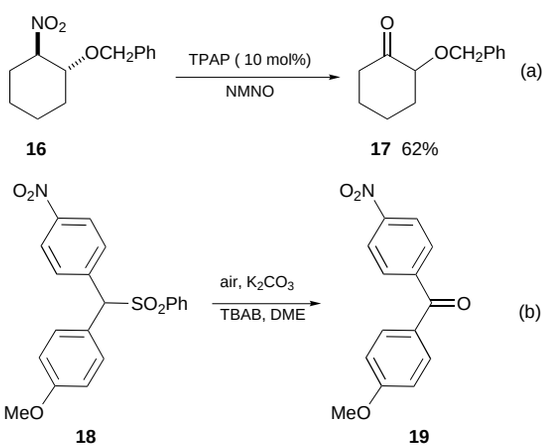

**14** **15** (method A: 93%, 83% ee) (method B: 61%, 94% ee)

**Scheme 7** *Reagents and conditions*: method A (ref. 43): La-(*R*)-BINOL cat. (5 mol%), cumene hydroperoxide; method B (ref. 44): $Bu_2Mg$ (10 mol%), (+)-DET (11 mol%), (11 mol%), $Bu^tOOH$

## 4 Other oxidative methods

A mild method for the oxidative transformation of nitro compounds into ketones by tetrapropylammonium perruthenate (TPAP) has been developed by Ihara and co-workers.[46] The reaction of secondary nitro compounds with a catalytic amount of TPAP in the presence of *N*-methylmorpholine *N*-oxide, silver(I) acetate, potassium carbonate and 4 Å molecular sieves provides the corresponding ketones in moderate to good yields (*e.g.* **16→17**) (**Scheme 8a**).

Wojciechowski has described a new method for the synthesis of nitro-substituted benzophenones, *via* the oxidation of benzylic sulfones, which are easily prepared using the vicarious nucleophilic substitution reaction.[47] For example the sulfone **18** gives the benzophenone **19** *via* autoxidation in the presence of potassium carbonate and tetrabutylammonium bromide (**Scheme 8b**).

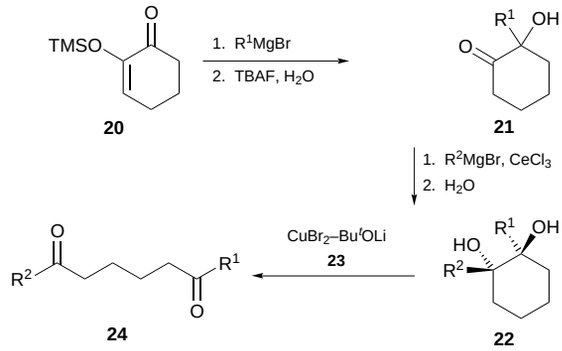



**16** **17** 62%

**18** **19**

**Scheme 8**

An efficient procedure for the oxidative fragmentation of 1,2-diols has been described by Takeda and co-workers (**Scheme 9**).[48] The diols **22** were easily prepared by the addition of Grignard reagents to 2-trimethylsiloxycyclohex-2-enone **20**, followed by hydrolysis and treatment of the resulting 2-hydroxycyclohexanones **21** with a second Grignard reagent [in combination with cerium(III) chloride]. Treatment of the diols **22** with

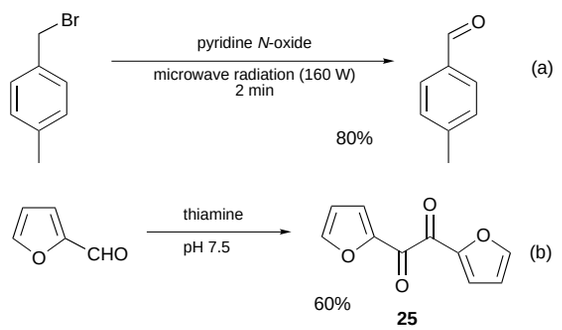



**20** **21** **24** **22**

**Scheme 9**

copper(II) bromide–lithium *tert*-butoxide **23** gives the diones **24** in good yield, probably *via* a bis(bromocopper) derivative. Unlike lead tetraacetate and periodate reagents which are commonly used to oxidatively cleave 1,2-diols, the copper reagent **23** effects the cleavage of both *cis* and *trans* 1,2-diols. 1,5-Diketones can be prepared in a similar fashion from 2-trimethylsiloxy-2-cyclopentenone.

Barbry and Champagne report another example of a reaction conducted under microwave irradiation.[49] They found that pyridine *N*-oxide reacts in a single step with benzylic bromides under microwave irradiation to afford high yields of aromatic aldehydes in a process that resembles the Kornblum oxidation (**Scheme 10a**). A thiamine (vitamin $B_1$)-catalysed preparation of furil **25** from furaldehyde has been described by Kascheres and co-workers (**Scheme 10b**).[50] The procedure avoids the use of sodium cyanide and gives good yields of this and other diketones. However, one significant drawback is the rather long reaction time (30 days).



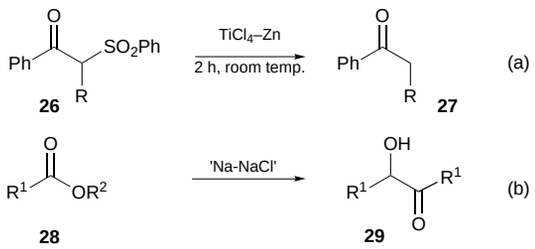

**25**

**Scheme 10**

## 5 Reductive methods

A variety of methods for the synthesis of ketones based on a reduction reaction have been developed this year. For example, β-keto sulfones are readily reduced by $TiCl_4$–Zn to give the corresponding ketones under mild conditions (*e.g.* **26→27**) (**Scheme 11a**).[51] *N*,*N*-Dialkylamides are cleanly reduced to aldehydes by reaction with disiamylborane in THF at room temperature.[52] Aromatic α-bromo or α-iodo ketones are reduced to their parent ketones by activated bismuth prepared from sodium borohydride and bismuth(III) chloride in water.[53] The corresponding α-chloro ketones are only reduced if sodium iodide is added to the reaction mixture.

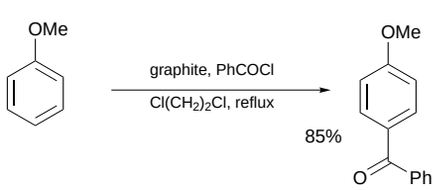
Makosza and Grela have used a form of 'high surface sodium' to effect the acyloin condensation of carboxylic esters.[54] The highly dispersed form of sodium is made by deposition of sodium onto powdered sodium chloride from its solution in liquid ammonia. The non-pyrophoric material is ideal for the synthesis of α-hydroxy ketones from esters (*e.g.* **28→29**) (**Scheme 11b**).




**Scheme 11**

## 6 Synthesis *via* acylation

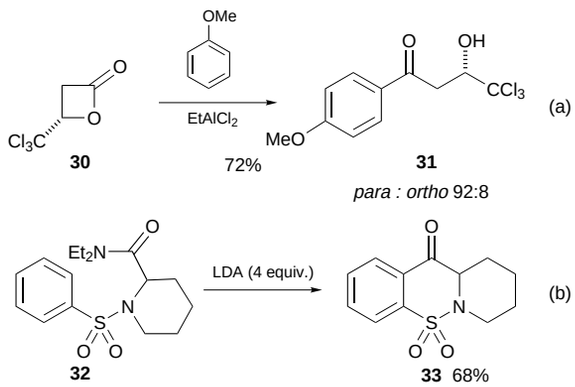
By far the most important method for the synthesis of aromatic ketones is the Friedel–Crafts acylation reaction. Several new procedures for effecting this reaction have been described this year. For example, Kodomari *et al*. report the intriguing finding that graphite is an effective catalyst for the Friedel–Crafts acylation of electron-rich arenes (**Scheme 12**).[55] Of several inorganic catalysts investigated, graphite was by far the best for the synthesis of a variety of aryl ketones in high yield from the corresponding acyl halide. At present the reaction is only useful when the arene possesses activating alkyl or alkoxy substituents. The graphite, of standard commercial grade, is an inexpensive and environmentally benign catalyst. However, since the preferred solvents are 1,2-dichloroethane and benzene the process overall is far from environmentally benign. Nevertheless, the process is undoubtedly a potentially useful one. Several other solid catalysts have been used in the Friedel–Crafts reaction. For example, a variety of aromatic compounds including benzene and toluene are acetylated by acetic acid or acetyl chloride over H-ZSM5 or H-beta zeolite catalysts.[56] Sreekumar and Padmakumar have also found that zeolites HY-zeolite and HZSM-5 are excellent heterogeneous catalysts for the Friedel–Crafts acylation of benzene and toluene with a variety of aliphatic carboxylic anhydrides.[57] Khadilkar and Borkar have found that iron(III) chloride supported on silica gel is an excellent catalyst for the Friedel–Crafts acylation of substituted arenes by benzotrichloride.[58] The acylation of activated aromatic compounds with acyl chlorides can also be achieved using hydrated zirconia as a catalyst.[59] Ranu *et al*. have developed an excellent synthesis of aryl ketones *via* the alumina-promoted Friedel–Crafts acylation of activated arenes with carboxylic acids in the presence of trifluoroacetic anhydride (**Scheme 13**).[60] The advantages of note are the direct use of a carboxylic acid as the acylating reagent, the mild reaction conditions (room temperature), fast reaction times and high yields.




**Scheme 12**

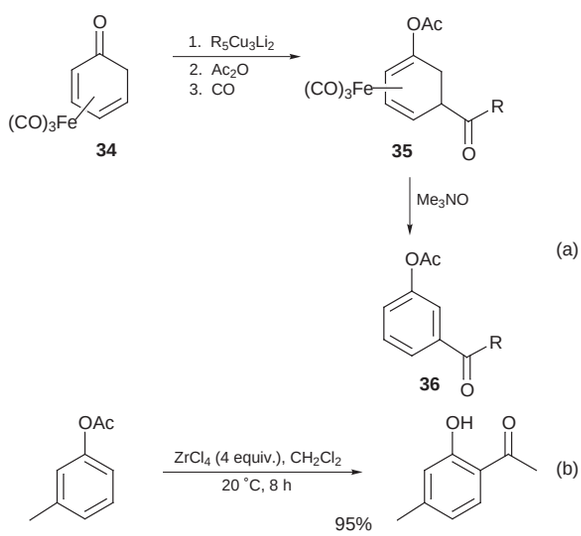

**Scheme 13**

Fujisawa *et al*. have developed an efficient route to enantiomerically pure β-hydroxy-β-trichloromethylated aromatic ketones **31** *via* Friedel–Crafts acylation of arenes with the readily available enantiomerically pure β-lactone **30** (**Scheme 14a**).[61] Snieckus and co-workers have developed a useful route to substituted 4*H*-1,2-benzothiazin-4-one derivatives *via* intramolecular anionic Friedel–Crafts reactions. Treatment of the arenesulfonamides, such as **32** (which are readily available from α-amino acids), with excess LDA gives the desired aryl ketones **33** in good yields (**Scheme 14b**).[62]




**Scheme 14**

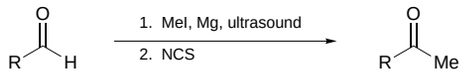
The direct acylation of phenol to give *m*-keto phenols has proven very difficult. Narasaka and co-workers have developed a route to these very same products using tricarbonyl(cyclohexadienone)iron as the phenol equivalent (**Scheme 15a**).[63] Addition of higher order cuprates to this complex followed by treatment with acetic anhydride and carbon monoxide generates the new complex **35**. The *m*-acylphenol derivatives are finally obtained after oxidation of **36** with trimethylamine *N*-oxide. The Fries reaction provides a more conventional method for the synthesis of *o*- and *p*-acylphenols. Harrowven and Dainty have found that zirconium tetrachloride is an effective mediator of *ortho*-Fries rearrangements (**Scheme 15b**).[64] The rearrangement proceeds at ambient temperature with preferential migration toward the least sterically encumbered adjacent carbon atom.




**Scheme 15**

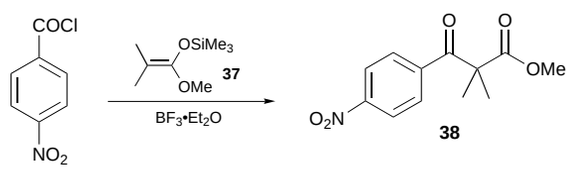
Lee and Kung report a process for the conversion of an aldehyde into a methyl ketone that overall represents an acylation reaction in which the aldehyde serves as the acylating reagent (**Scheme 16**).[65] They found that methyl ketones are produced in a one-pot process that first involves a sonochemical Barbier reaction of methyl iodide, magnesium powder and the aldehyde in a commercial ultrasonic cleaning bath followed by the addition of *N*-chlorosuccinimide (NCS).

The acylation of substituted silylketene acetals **37** with

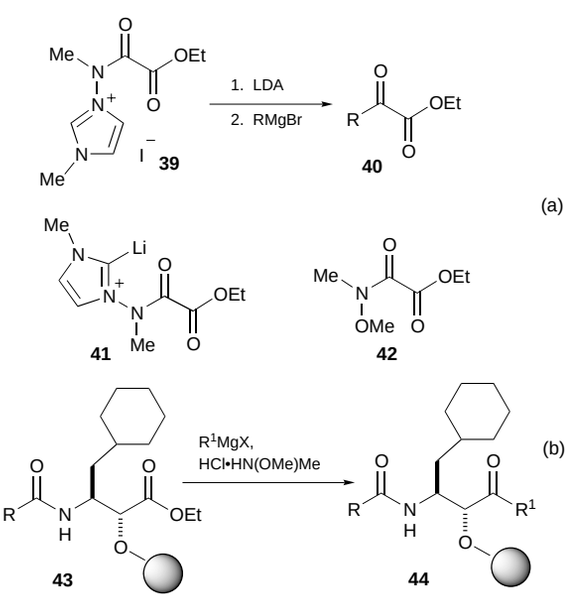



**Scheme 16**

benzoyl chlorides provides a useful route to α,α-disubstituted aryl β-keto esters **38** (**Scheme 17**).[66] The reaction does not require a Lewis acid catalyst when the aryl group bears a strongly electron withdrawing group, such as a nitro or cyano group. In other cases acceptable yields of the keto ester can be obtained by the addition of boron trifluoride–diethyl ether. A general route to another type of keto ester has been developed by Alvarez-Builla and co-workers.[67] They found that organomagnesium reagents add cleanly to the imidazolium salt **39** (after reaction with LDA) to give the α-keto ester **40** in good yield (**Scheme 18a**). The reaction is thought to proceed *via* the lithium derivative **41**. The process is in contrast to the reaction of the corresponding Weinreb amide **42** with an alkyllithium reagent, which results in acylation *via* the ester carbonyl group to give an α-keto amide as the major product. The method has also been applied to the synthesis of other keto esters.[68] A one-pot procedure for the solid phase synthesis of ketones from the corresponding esters, *via in situ* formation of the Weinreb *N*-methoxy-*N*-methylamide, has been described by Wallace (**Scheme 18b**).[69] For example esters of type **43** when treated with a Grignard reagent in the presence of *N*,*O*-dimethylhydroxylamine hydrochloride give the ketones of type **44** in good yield.

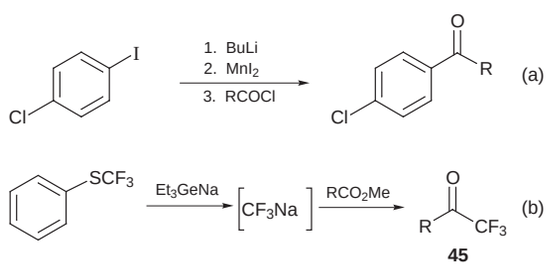



**Scheme 17**

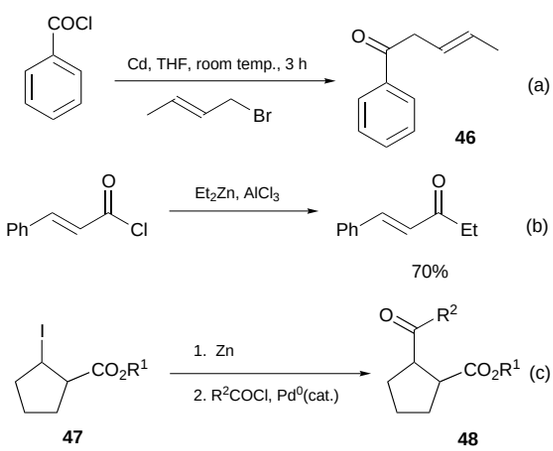



**Scheme 18**

A variety of ketones have been made *via* the acylation of arylmanganese reagents with acyl chlorides. The organomanganese reagents are prepared *via* reaction of the corresponding aryllithium reagent with manganese(II) iodide (**Scheme 19a**).[70] α,β-Unsaturated ketones can be prepared in a similar manner from alkenylmanganese reagents. Yokoyama and Mochida have developed a useful procedure for the synthesis of trifluoromethyl ketones **45** (**Scheme 19b**). The key step is the formation of the trifluoromethyl anion from phenyl trifluoromethyl sulfide by the use of $Et_3GeNa$. They found that the anion made in this way can be used to effect the nucleophilic trifluoromethylation of methyl esters (*e.g.* $RCO_2Me \rightarrow$ **45**).[71] Sandhu and co-workers report a new synthesis of β,γ-unsaturated ketones involving the cadmium promoted allylation of acid chlorides (**Scheme 20a**).[72] For example, the (*E*)-β,γ-unsaturated ketone **46** is the exclusive product of the reaction between (*E*)-crotyl bromide, benzoyl chloride and cadmium powder. The Lewis acid promoted coupling of acid chlorides with organoaluminium and organozinc reagents has been reported by Nakagawa and co-workers, and provides a good method for the synthesis of α,β-unsaturated ketones.[73] For example, diethylzinc readily reacts with cinnamoyl chloride in the presence of an equimolar amount of aluminium(III) chloride to generate the corresponding ketone in high yield (**Scheme 20b**). *cis*-Substituted keto cyclopentanes **48** can be obtained by the palladium(0) catalysed acylation of zinc intermediates, derived from alkyl iodides **47**, with acyl chlorides.[74] The *cis*-selectivity is derived from chelation of the alkoxycarbonyl group to the zinc intermediate (**Scheme 20c**).



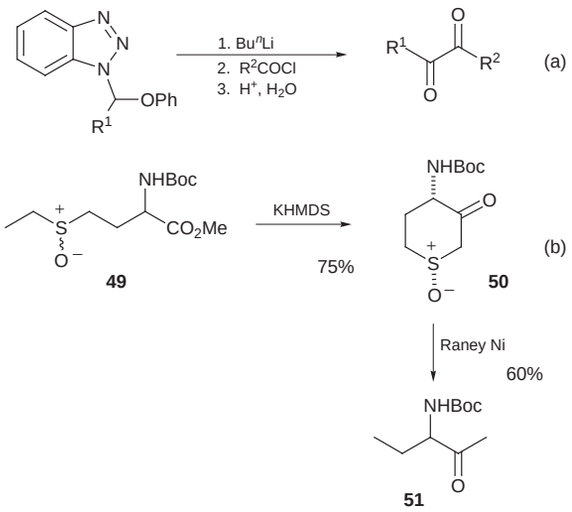

**Scheme 19**




**Scheme 20**

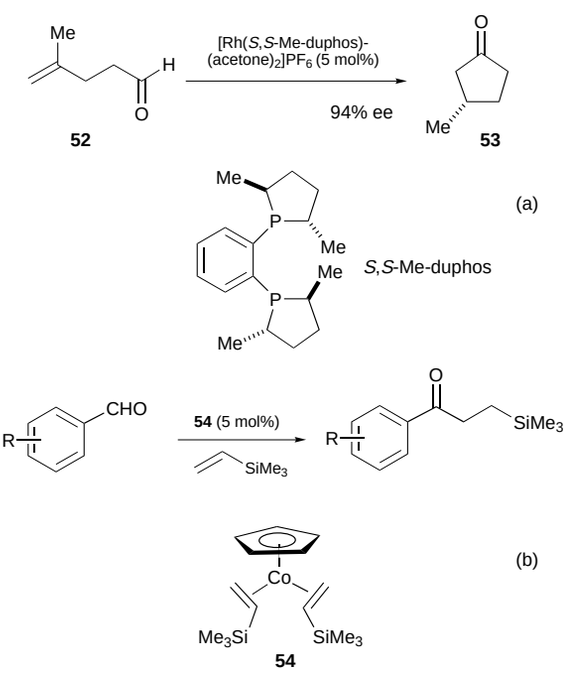
Katritzky *et al*. have found that 1,2-diketones can be prepared by the acylation of phenoxy-substituted benzotriazole derivatives (**Scheme 21a**).[75] A variety of alkyl-, alkenyl-, alkynyl- and aryl-substituted 1,2-diketones were made in this manner. The methionine derived sulfone **49** gives the cyclic ketone **50** upon treatment with base, *via* an intramolecular acylation process (**Scheme 21b**). Taylor and co-workers also found that acylic α-amino ketones **51** can be derived from the cyclic ketones **50** by Raney nickel reduction.[76] As reported, the method is only suitable for the synthesis of racemic α-amino ketones, as the chiral centre bearing the NHBoc group is configurationally unstable.

A very efficient enantioselective method for the synthesis of β-substituted cyclopentanones has been developed by Bosnich and co-workers.[77] The method involves the asymmetric catalytic intramolecular hydroacylation of 4-substituted pent-4-enals (**52**→**53**) (**Scheme 22a**). The catalyst, [Rh(*S*,*S*-Me-duphos)(acetone)$_2$]$PF_6$ is the best for the enantioselective synthesis of




**Scheme 21**

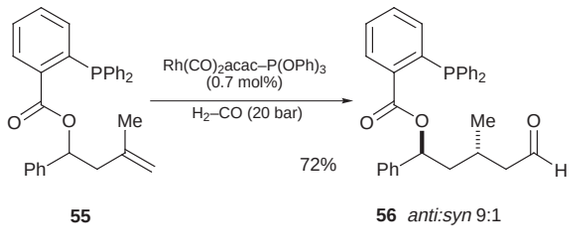
cyclopentanones bearing primary and secondary groups. A similar reaction has been reported by Lenges and Brookhart.[78] They used the cobalt complex **54** to catalyse the hydroacylation of vinyltrimethylsilane with aromatic aldehydes (**Scheme 22b**).




**Scheme 22**

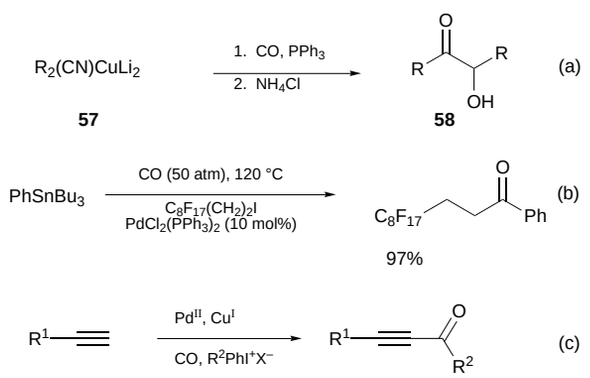
Breit has reported a useful example of substrate controlled diastereoselective hydroformylation of homomethallylic alcohols (**Scheme 23**).[79] The rhodium catalysed hydroformylation reaction is highly 1,3-diastereoselective when the *o*-diphenylphosphinobenzoate moiety is used as a directing group. For example the *anti*-aldehyde **56** is the major product of the hydroformylation reaction of the ester **55**. Work from the same research group has shown that bulky phosphabenzene ligands can be used to great effect in the rhodium catalysed hydroformylation reaction.[80]

Kabalka *et al*. have found that dialkylcyanocuprates, prepared from copper(I) cyanide and the corresponding Grignard reagent, react readily with carbon monoxide in the presence of tributylphosphine to give α-hydroxy ketones in high yield (*e.g*. **57**→**58**) (**Scheme 24a**).[81] Fuchikami and Shimizu have developed an efficient method for the synthesis of β-perfluoroalkyl substituted ketones (**Scheme 24b**).[82] Their method




**Scheme 23**

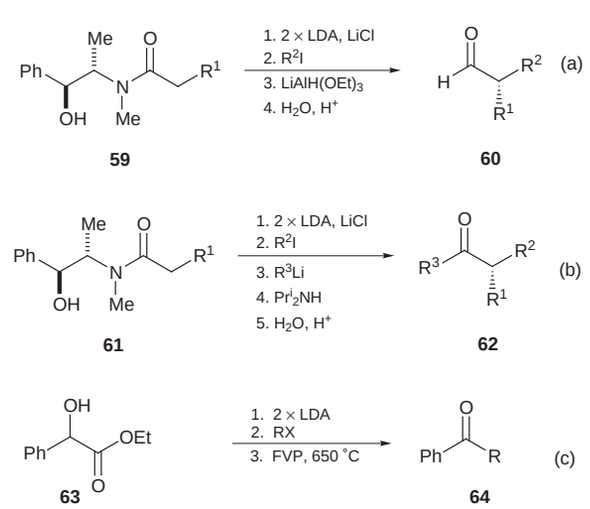
involves the palladium catalysed carbonylative coupling of a β-perfluoroalkyl substituted alkyl halide and an organostannane. Kang *et al*. have found that iodonium salts can be used in the palladium- and copper-catalysed carbonylative cross-coupling reaction with alk-1-ynes, to give alkynyl ketones (**Scheme 24c**).[83] The reaction proceeds rapidly and under mild aqueous conditions at room temperature and only an atmospheric pressure of carbon monoxide is required.




**Scheme 24**

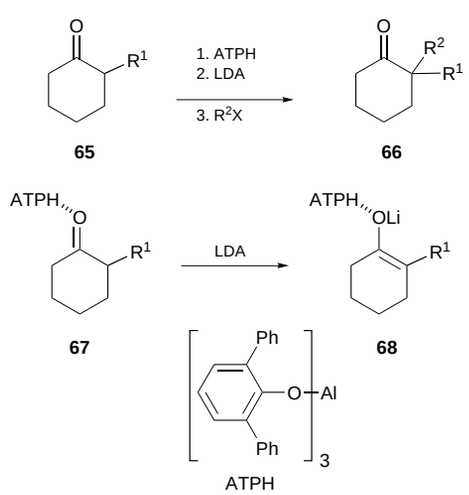
## 7 Functionalisation of the α-position of ketones and aldehydes

Full details of the use of pseudoephedrine as a practical chiral auxiliary for the synthesis of highly enantiomerically enriched aldehydes (**59**→**60**) (**Scheme 25a**) *via* reduction of a pseudoephedrine amide, and ketones (**61**→**62**) (**Scheme 25b**) *via* reaction of the pseudoephedrine amide with an organolithium reagent, have been disclosed by Myers *et al*.[84] The methods will undoubtedly become important ones for the synthesis of chiral ketones and aldehydes. Aitken and Thomas have shown that ethyl mandelate can be regarded as a benzoyl anion equivalent.[85] The products of *C*-alkylation of ethyl mandelate **63** upon flash vacuum pyrolysis (FVP) give the aryl ketones **64** (**Scheme 25c**).

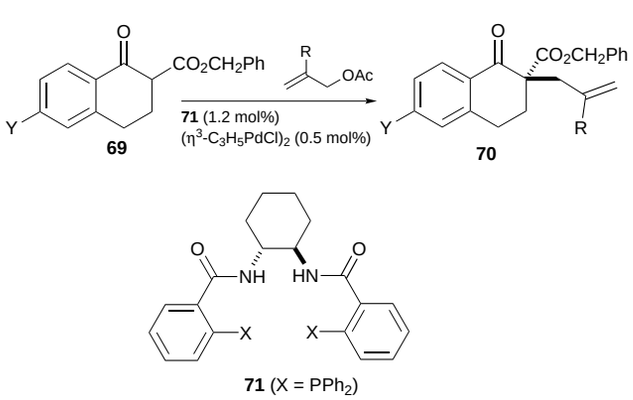



**Scheme 25**

The regioselective alkylation of an unsymmetrical dialkyl ketone has always been a challenging problem in synthetic chemistry. Whilst the formation of the less-substituted enolate is, more or less, reliably achieved using LDA under kinetic control, there are few methods that generate the more substituted enolate with good regioselectivity. Yamamoto and co-workers have reported an excellent method for the kinetically controlled generation of the more substituted enolate by the combined use of aluminium tris(2,6-diphenylphenoxide) (ATPH) and LDA (**Scheme 26**).[86] The ketone **65** is first treated with ATPH and then with LDA, and finally with a reactive alkylating agent (*e.g.* **65→66**). It is suggested that the bulky aluminium reagent co-ordinates to the carbonyl oxygen lone pair *anti* to the most substituted side, thereby preventing the LDA from deprotonating on the least hindered side (*i.e.* **67→68**). Hosomi and co-workers have found that enolates can be generated regiospecifically if they are generated by the reduction of α-acetoxy ketones with manganese-ate complexes.[87] The manganese enolates generated in this way can be reacted with a wide variety of electrophiles. The alkylation of ketones can also be controlled by the use of a phosphonate group. Oh and co-workers have found that α,α-dialkyl-β-keto phosphonates are dephosphonylated by treatment of the lithium enolate with lithium aluminium hydride.[88] The asymmetric alkylation of β-keto esters has been investigated by Trost *et al*. In their study they used π-allylpalladium species as the electrophiles.[89] For example, tetralones such as **69** can be alkylated with very high enantioselectivity when the ligand **71** is used (*e.g.* **69→70**) (**Scheme 27**).

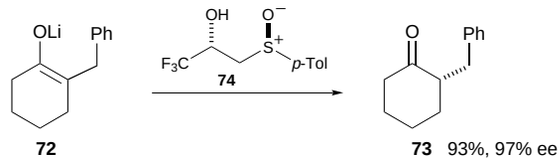



**Scheme 26**



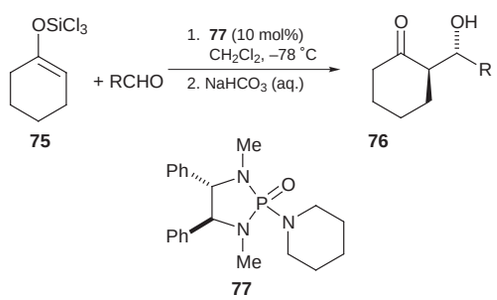

**Scheme 27**

A method for the asymmetric synthesis of ketones bearing an α-chiral centre that has attracted great attention recently involves the enantioselective protonation of a lithium enolate, a process which has been reviewed this year.[90] Kosugi *et al*. report one such highly enantioselective method.[91] The hydroxy sulfoxide **74** was used as the chiral proton source in the conversion of the enolate **72** into the ketone **73** (**Scheme 28**).



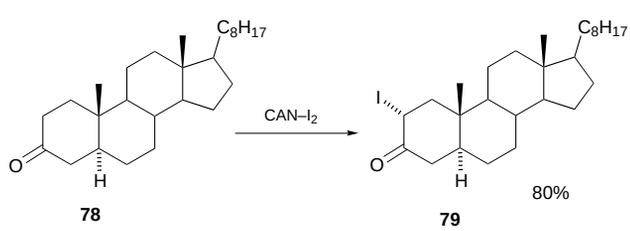

**Scheme 28**

Denmark *et al*. report more details of an excellent system for effecting catalytic asymmetric aldol reactions. They have found that trichlorosilyl enolates (derived from tributylstannyl enolates and silicon tetrachloride) are highly reactive in the chiral phosphoramide catalysed asymmetric aldol reaction (**Scheme 29**).[92] For example, the trichlorosilyl enolate **75** derived from cyclohexanone reacts, in the presence of the phosphoramide **77**, with a variety of aldehydes to give the *anti* aldol product **76** with excellent diastereoselectivity and high enantioselectivity. Mahrwald *et al*. report a rare example of the diastereoselective aldol addition of aldehyde enolates to aldehydes.[93] The reaction is *syn*-selective and occurs in the presence of titanium(IV) chloride and a base.



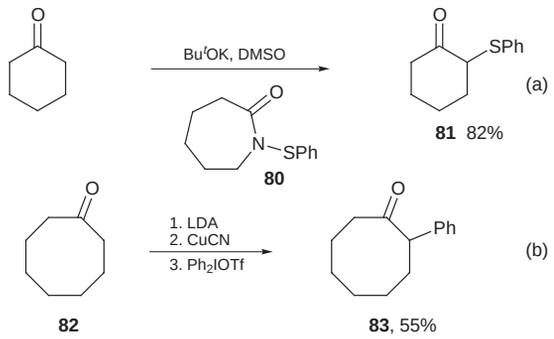

**Scheme 29**

A convenient and direct procedure for the α-iodination of various ketones using iodine–ammonium cerium(IV) nitrate in acetic acid or alcohol has been developed by Horiuchi and Kiji.[94] The α-iodo ketones are obtained in high yields (*e.g.* **78→79**) (**Scheme 30**). α-Chloro ketones have been prepared by the use of polymer supported reagents containing pendant quaternary ammonium species with a dichloroiodate counterion.[95]




**Scheme 30**

*N*-Phenylthiocaprolactam **80** has been used as a source of an electrophilic thiophenyl group (**Scheme 31a**). This reagent reacts with the enolates of aliphatic, aromatic or cyclic ketones to give the corresponding α-phenylthio ketones (*e.g.* cyclohexanone→**81**) in good yield.[96] The reaction gives only the product of monosulfenylation (80–97%) and is performed in DMSO under mild conditions (potassium *tert*-butoxide, 25 °C, 10 min). The corresponding α-phenylselanyl aldehydes and ketones have been prepared using $PhSeCl_3$.[97] Ryan and Stang have developed a novel method for the direct α-arylation of ketones. The reaction of cyclic ketone copper(I) enolates with

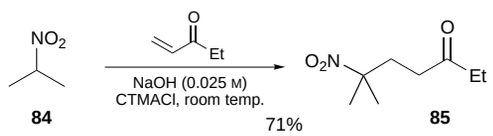



**Scheme 31**

diphenyliodonium triflate gives the α-phenyl ketone in moderate to reasonable yield (*e.g.* **82→83**) (**Scheme 31b**).[98]

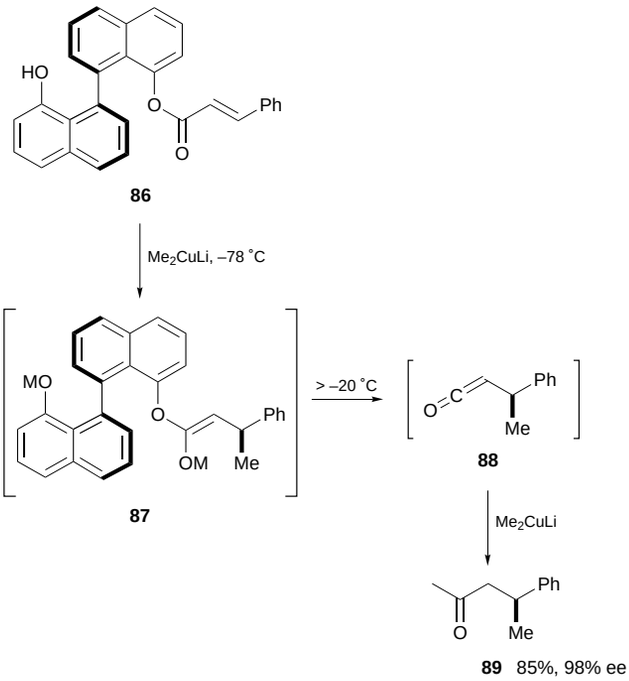
## 8 Ketones and aldehydes *via* Michael reactions

The conjugate addition of a nucleophile to the β-carbon of an α,β-unsaturated ketone represents an important method for the synthesis of functionalised ketones. Many studies of this type of reaction have been reported this year. A good example of the benefits to be gained from using water as a reaction solvent is described by Ballini and Bosica.[99] They have shown that Michael addition of nitroalkanes to α,β-unsaturated ketones occurs in water in the presence of sodium hydroxide and cetyltrimethylammonium chloride (CTMACl), which serves as a cationic surfactant. The reaction proceeds with several nitroalkanes, including branched ones (*e.g.* **84→85**) (**Scheme 32**). In principle, this method should produce very little waste as the process is an addition reaction and both the base and CTMACl are catalysts (6 mol% and 10 mol% respectively). However, a 50 mol% excess of nitroalkane is used. Nevertheless, the procedure which only involves the use of an organic solvent in the work-up offers clear economic and environmental advantages, particularly for large scale applications. Other reports of the synthesis of aldehydes and ketones *via* a Michael reaction include the addition of allylcerium reagents[100] or butyllithium[101] to α,β-unsaturated ketones in the presence of ATPH derivatives; the addition of 2-phenylcyclohexanone to α,β-unsaturated ketones;[102] addition of organolithium reagents to α,β-unsaturated ketones in the presence of beryllium(II) chloride;[103] addition of 1,3-dicarbonyl compounds to α,β-unsaturated ketones in the presence of zeolites.[104]

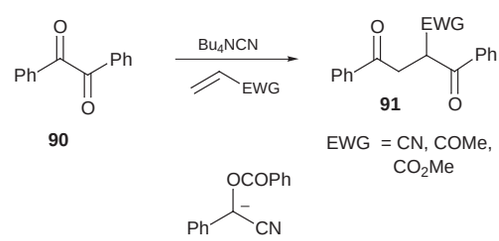



**Scheme 32**

Fuji *et al*. have developed an efficient route to chiral ketones that involves the Michael addition of lithium dialkylcuprates to half esters of 1,1′-binaphthalene-8,8′-diol.[105] For example, treatment of the α,β-unsaturated ester **86** with lithium dimethylcuprate gives the ketone **89** (**Scheme 33**). The reaction is thought to proceed *via* initial 1,4-addition of the cuprate to the enoate to give an enolate **87** which is unstable above −20 °C, giving the ketene **88**, by loss of the auxiliary. Further addition of the cuprate to the ketene finally gives the ketone **89**. Miyashita *et al*. have developed a useful synthesis of 1,4-diketones from 1,2-diketones using a reaction that involves the insertion of an alkene between the two carbonyl groups.[106] Benzils react with Michael acceptors in the presence of a soluble cyanide ion as a catalyst to give the substituted 1,4-diketones (**90→91**) (**Scheme 34**). The reaction proceeds *via* initial formation of




**Scheme 33**

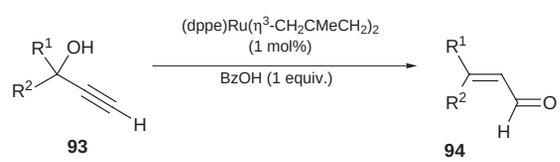



**Scheme 34**

the *O*-aroylmandelonitrile anion **92**, Michael reaction and rearrangement of the aroyl group with loss of cyanide.

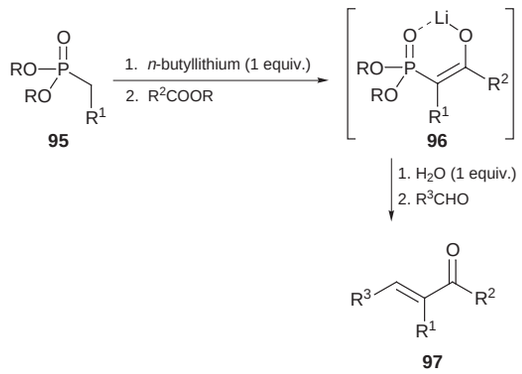
## 9 Synthesis of α,β-unsaturated ketones and aldehydes

Dixneuf and co-workers report a new efficient method for the transformation of prop-2-ynyl alcohols into α,β-unsaturated aldehydes catalysed by a (diphosphine)ruthenium(II) complex in the presence of benzoic acid (**93→94**) (**Scheme 35**).[107] The yields are good, but when $R^1 \neq R^2$ a mixture of *Z*- and *E*-α,β-unsaturated aldehydes is produced.




**Scheme 35**

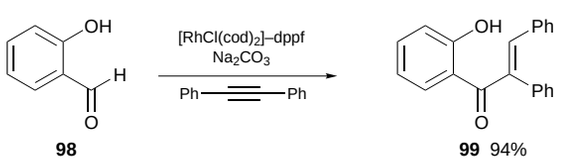
Mulzer *et al*. have developed a potentially useful one-pot three-component synthesis of α,β-unsaturated ketones, based on the well known Horner–Wadsworth–Emmons (HWE) olefination reaction (**Scheme 36**).[108] Reaction of the alkylphosphonate **95**, first with *n*-butyllithium and then an ester gives the intermediate keto phosphonate anion **96**. Although this anion was found not to react directly with aldehydes, it does indeed produce α,β-unsaturated ketones **97** in good yield by reaction first with one equivalent of water and then the appropriate aldehyde. It is thought that the lithium hydroxide produced in the reaction of the anion **96** with the water is the base that




**Scheme 36**

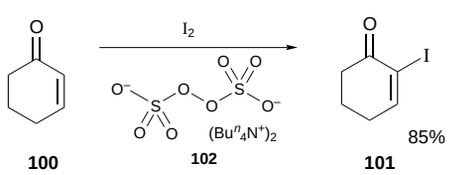
promotes the HWE reaction. For the examples described the reaction is highly selective ($E:Z > 95:5$) when $R^1$ is either a hydrogen atom or a methyl group.

A useful route to functionalised α,β-unsaturated ketones, involving the hydroacylation of alkynes, has been developed by Miura and co-workers (**Scheme 37**).[109] They found that substituted salicylaldehydes can effectively act as the source of the acyl group and couple to alkynes by the action of a suitable rhodium catalyst in the presence of sodium carbonate (*e.g.* **98**→**99**). Unfortunately, the regioselectivity in the reaction of terminal alkynes is not high.




**Scheme 37**

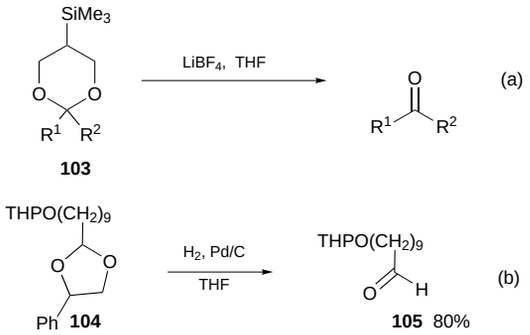
A novel procedure for the α-iodination of α,β-unsaturated ketones **100**, using a combination of iodine and bis(tetra-*n*-butylammonium) peroxydisulfate **102**, has been described by Kim and co-workers (**Scheme 38**).[110] α,β-Unsaturated ketones react with iodine in the presence of the disulfate **102** in acetonitrile at 25 °C to give the corresponding α-iodinated ketone **101** in good yield. The reaction is thought to occur *via* addition of the iodine radical cation (produced *via* single electron transfer to **102**) to the carbon–carbon double bond to give an epi-iodonium ion, which in the presence of sulfate ion rearranges to the product.




**Scheme 38**

## 10 Deprotection of protected aldehydes and ketones

Lipshutz *et al*. have developed a new acetal-type protecting group (the cyclo-SEM group), which is removed by treatment with lithium tetrafluoroborate (**103**→carbonyl compound) (**Scheme 39a**).[111] A mild, convenient and pH-neutral method for deprotection of 4-phenyl 1,3-dioxolane derivatives by the use of catalytic hydrogenation has been described by Chandrasekhar *et al*. (*e.g.* **104**→**105**) (**Scheme 39b**).[112] Cerium(III) chloride·$H_2O$–sodium iodide has been used to convert dioxolanes to their carbonyl compounds.[113] The cleavage of acetals to their carbonyl compounds has been found to be effected by




**Scheme 39**

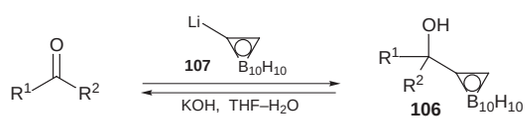
Montmorillonite K 10.[114–116] Montmorillonite clay has also been used to regenerate aldehydes from 1,1-diacetates.[117]

Layered zirconium sulfophenyl phosphonate is an efficient heterogeneous catalyst for the mild hydrolysis of 1,2-dithiolanes and 1,3-dithianes to their corresponding carbonyl compounds.[118] The same transformation, under heterogeneous conditions, is effected by ferric nitrate[119] or by a silver salt and iodine.[120] Thioketals are also deprotected photochemically when benzene-1,2,4,5-tetracarbonitrile is used as a photosensitiser.[121]

Ballini *et al*. have found that Envirocat EPZG is an excellent heterogeneous catalyst for the efficient regeneration of ketones from their corresponding tosylhydrazones.[122] The reactions are mild; the tosylhydrazone is generally heated in acetone–water at 80 °C for 3–4 h. Tosylhydrazone derivatives of aldehydes were much less reactive under these conditions. Thallium trinitrate has also been used to regenerate carbonyl compounds from their tosylhydrazones.[123]

The use of $Mo(CO)_6$ for the regeneration of aldehydes and ketones from their corresponding oximes has been described by Moradpour and co-workers.[124] Even though the catalyst is present in substoichiometric quantities (35 mol%), its toxicity will probably ensure that the method remains obscure. Oximes (and tosylhydrazones) can be cleaved to their parent carbonyl compounds by the action of *tert*-butyl hydroperoxide in refluxing acetone or carbon tetrachloride.[125] Ammonium persulfate on silica gel rapidly regenerates the parent carbonyl compound from oximes using microwaves under solventless 'dry' conditions.[126] Bismuth(III) chloride in THF under microwave radiation effects the same transformation.[127]

*o*-Carborane has been used as a novel protective group for aldehydes and ketones by Yamamoto and co-workers.[128] The *o*-carboranylmethanol derivatives **106** (prepared readily from reaction of the carbonyl compound and lithiocarborane **107**) are very stable under both aqueous protic and Lewis acid conditions. The carbonyl compound can be regenerated from **106** by treatment with aqueous potassium hydroxide (**Scheme 40**).

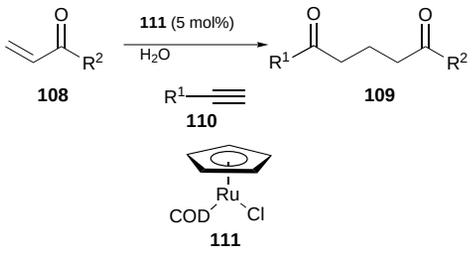



**Scheme 40**

## 11 Miscellaneous methods

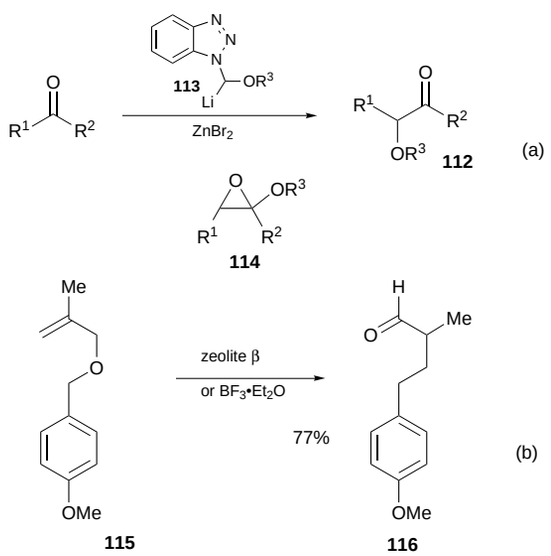
Trost *et al*. have developed a ruthenium-catalysed three component addition reaction which forms 1,5-diketones **109** (**Scheme 41**).[129] The ruthenium complex **111** is an excellent catalyst for the coupling of water, an alkyne **110** and an α,β-unsaturated ketone **108**.

A novel method for the synthesis of α-alkoxyalkyl ketones **112** has been described by Katritzky *et al*. (**Scheme 42a**).[130] Treatment of a ketone with benzotriazoyl-stabilised anions **113**,




**Scheme 41**

in the presence of zinc bromide, gives the homologated ketone **112** in good yield. In some cases the intermediate epoxide **114** can be isolated. When the alkoxy group is replaced by a substituted phenyl (or heteroaromatic) group the method provides an excellent route to α-aryl ketones.[131] A new route to aldehydes involving the acid catalysed rearrangement of *p*-methoxybenzyl protected allylic alcohols has been investigated by Frejd and co-workers.[132] Allyl *p*-methoxybenzyl ethers **115** undergo acid catalysed 1,4-rearrangement to give *p*-methoxyphenylbutyraldehydes (**115**→**116**) (**Scheme 42b**). The reaction is efficient when the acid catalyst is either zeolite β or $BF_3{\cdot}Et_2O$; the rearrangement does not occur when an unsubstituted benzyl group is used.




**Scheme 42**

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