Aldehydes and ketones

PATRICK G. STEEL

Department of Chemistry, Science Laboratories, South Road, Durham, DH1 3LE

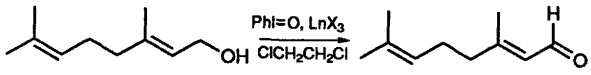
Reviewing the literature published between July 1992 and June 1993

1 Synthesis of saturated aldehydes and ketones

1.1 Redox methods

The principal route to aldehydes and ketones is *via* the oxidation of the appropriate alcohol, and there have been a number of important developments in this area. Methods based on oxidation with supported reagents continue to expand. The use of V_2O_5/ZrO_2, prepared by the calcination, in air at 500 °C, of a mixture of $Zr(OH)_2$ and HN_4VO_3, oxidizes a range of saturated and unsaturated alcohols to the corresponding aldehyde or ketone in moderate to good yield (37–100%). On completion of the reaction, the reagent is simply separated from the product by filtration and reactivated by heating in air.[1] A frequent problem with this reagent, and also with the related chromium and manganese oxide based oxidizing agents, is the associated acidity of the reaction medium. Zinc chlorochromate nonahydrate has been introduced as a cheap, readily accessible, and mild oxidizing agent. It efficiently converts a variety of hydroxy compounds, as well as unsaturated and benzylic hydrocarbons, into the corresponding aldehyde or ketone.[2] At 2.3, the pH of this reagent is somewhat higher than that reported for PCC although pyridinium fluorochromate is still less acidic (pH = 2.45).[3]

Apart from their acidity many chromium reagents exhibit considerable toxicity and thus alternatives have been sought. A combination of copper(II) bromide and lithium t-butoxide has been employed for the oxidation of secondary, allylic, and benzylic alcohols. Primary alcohols are resistant to this reagent combination.[4] In contrast, iodosylbenzene in the presence of a catalytic amount of ytterbium(III) nitrate selectively oxidizes all primary alcohols in preference to secondary alcohols.[5] Other lanthanide(III) nitrates were found to be similarly effective. For allylic alcohol substrates the corresponding lanthanide(III) acetates offer significantly improved yields, albeit at a much slower rate (**Scheme 1**).

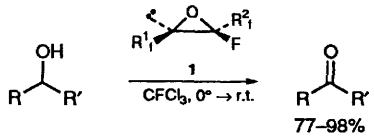


X = NO_3 35% 4h
= OAc 60% 12h

Scheme 1

The advantages afforded by the combination of t-butylhydroperoxide and catalytic $RuCl_2(Ph_3P)_3$ over a variety of similar systems continue to be emphasized.[6] Recyclable NAD-type catalysts afford a method for the oxidation of various secondary and benzylic alcohols with good catalyst turnovers and moderate yields.[7]

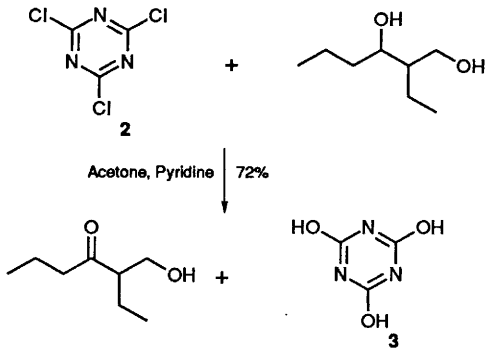
Recent developments not using transition metals include the use of triphosgene as an activator for DMSO oxidations of a range of alcohols in good to excellent yields.[8] High yields of ketones can also be obtained by the oxidation of secondary alcohols with the perfluorinated *cis*-2,3-dialkyloxaziridine reagent **1** (**Scheme 2**).[9] As well as simple acyclic alcohols, more complex species such as α-hydroxyesters, borneols, and sterols are also acceptable substrates.



$R^1_f = C_4F_9$, $R^2_f = C_3F_7$ *or* $R^1_f = C_6F_{13}$, $R^2_f = C_5H_{11}$

Scheme 2

Trichloroisocyanuric acid **2** allows the selective oxidation of secondary alcohols in the presence of primary alcohols (**Scheme 3**).[10] Since this reagent is

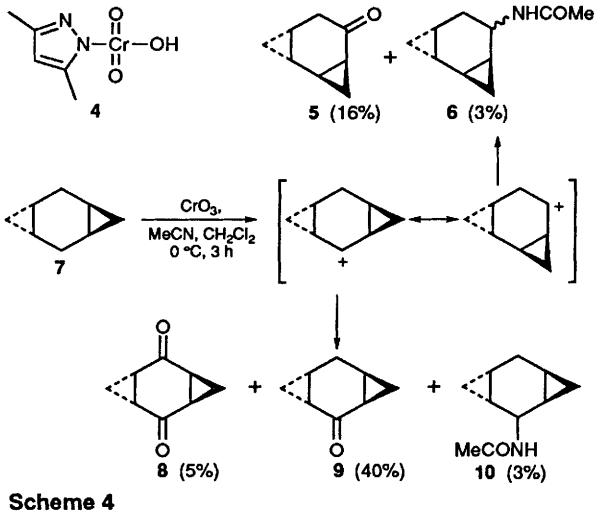


Scheme 3

also capable of the α-chlorination of ketones[11] the reaction is carried out in acetone which minimizes the effect of any side-reaction. Oxidations are extremely rapid ($\leq$20 min.) and practically very simple; in addition the cyanuric acid by-product **3** is insoluble in ether and may be separated by filtration.

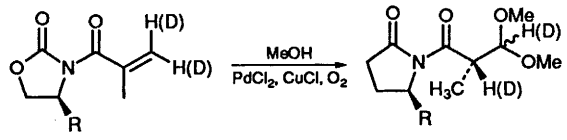
In many synthetic pathways alcohols are frequently protected as their silyl ethers and methods for the direct oxidation of these compounds to the corresponding carbonyl species have been reviewed.[12]

Aldehydes and ketones can be procured from alkanes by oxidation with molecular oxygen in the presence of acetaldehyde and a catalytic amount of a copper salt, such as $Cu(OH)_2$.[13] Although the reported yields are good, the process is inefficient in terms of starting material conversion. Furthermore, acyclic aliphatic substrates exhibit poor regioselectivity. In contrast, cyclopropyl alkanes undergo a highly selective oxidation to α-cyclopropylketones on treatment with chromium trioxide-3,5-dimethylpyrazole **4**.[14] This reaction is believed to proceed *via* the cyclopropyl methyl cation as shown by the isolation of side-products **5**, **6**, and **8–10** when the dicyclopropylcyclohexane **7** was treated with chromium trioxide in acetonitrile and dichloromethane (**Scheme 4**).



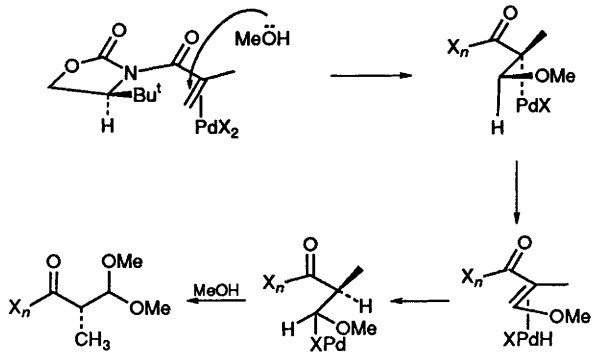
Scheme 4

Enhanced selectivity for aldehyde formation in Wacker type oxidations of terminal olefins can be obtained in t-butanol using a catalyst derived from bis(acetonitrile)-palladium dichloride, copper(II)chloride, and a chloride salt.[15] Complete regioselectivity and, depending on the chiral auxiliary, very high diastereoselectivity is observed in the palladium catalysed oxidation of chiral methacrylamides (**Scheme 5**).[16] These results are consistent with a mechanism that involves coordination of the palladium catalyst to the less hindered face of the *s-trans* conformation of the acrylamide followed by *anti* addition of methanol. A stereoselective palladium controlled 1,2-hydride shift then occurs to create the new chiral centre (**Scheme 6**).



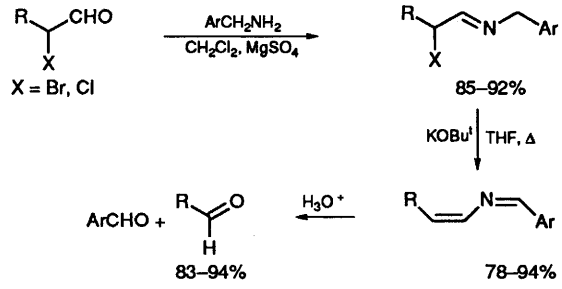
R = Bu^t 89%, 95% d.e.
R = Pr^i 66%, 61% d.e.

Scheme 5



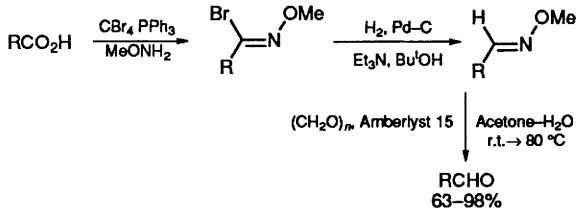
Scheme 6

Oxidative cleavage of various alkenes into two equivalents of aldehydes can be readily achieved using potassium permanganate adsorbed onto moist alumina.[17] Carbonyl compounds can also be generated by oxidative scission of tosyl hydrazones, using DMSO activated by trimethylsilyl chloride,[18] and oximes on treatment with ozone,[19] dioxirane,[20] or bis(trimethylsilyl)chromate.[21] Over-oxidation to the carboxylic acid can be a problem, and consequently only this last reagent is suitable for the cleavage of aldoximes. However, certain aliphatic aldoximes undergo an alternative oxidation to yield the corresponding nitrile. The copper bromide/lithium t-butoxide system alluded to earlier also provides a simple route to aldehydes from secondary amines. This is a two-step process proceeding *via* the imine and occurs in high overall yield.[22] Primary amines are not suitable substrates since they are readily converted into the corresponding nitrile. Imines are also intermediates in a multistep route for the dehalogenation of α-haloaldehydes (**Scheme 7**).[23] Unlike many of the existing methods for the dehalogenation of α-halocarbonyl compounds,[24] this procedure uses simple, readily available reagents compatible with the aldehyde function. However, it does require the separation of the desired product from the aryl aldehyde by-product.



Scheme 7

Aldehydes can also be synthesized from the appropriate carboxylic acid in a sequence involving conversion to the α-bromo-*O*-methyloxime, reductive dehalogenation by catalytic hydrogenation, and mild acid hydrolysis (**Scheme 8**).[25] The latter step is also amenable to the regeneration of ketones from *O*-methylketoximes.



Scheme 8

Improvements in the conjugate reduction of enones have been reported. The efficiency of conjugate reduction under the conditions of the water-gas shift reaction rises with increasing quantities of water and triethylamine to a limit when the reaction mixture becomes heterogeneous.[26] New catalytic species have been developed. For example, hydrogenation of all types of enone in the presence of a catalyst, derived by air oxidation of the binuclear palladium diphosphine complex $[(Bu^t_2PH)_2Pd(PBu^t_2)]_2$, produces the saturated carbonyl compound in good to excellent yields (80–98%).[27] Similar enhancements in catalyst technology have been applied to the hydrosilylation of α,β-unsaturated carbonyl compounds to give the desired aldehyde or ketone masked as its silylenol ether.[28] Ketones protected as the corresponding dialkylacetals are also formed on catalytic hydrogenation of enones in alcohol solvents.[29]

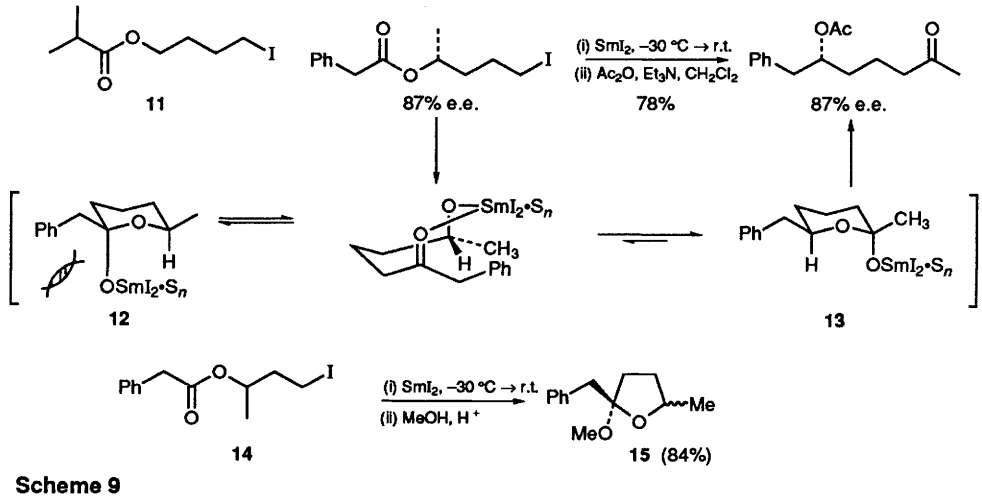
Finally, δ-hydroxyketones can be prepared from the appropriate δ-iodoacetates in a highly stereospecific fashion through a samarium iodide mediated tandem intramolecular nucleophilic acylation—Meerwein–Ponndorf–Verley/Oppenauer redox process.[30] The stereospecificity and, in the case of iodobutyrate **11**, reversal of the normal MPV/Oppenauer selectivity observed can be accounted for by consideration of the two possible samarium acetal intermediates **12** and **13** (**Scheme 9**). Consistent with this hypothesis is the observation that the γ-lactol **15**, the product of simple nucleophilic acylation, is produced when the γ-hydroxyacetate **14** is submitted to the reaction conditions.

1.2 Umpolung methods

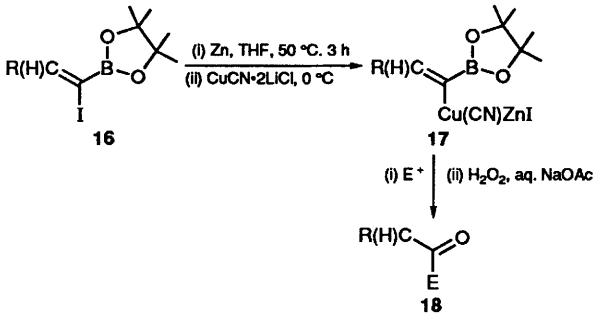
Acyl anions can be generated by the direct addition of organolithium compounds to carbon monoxide at very low temperatures, -110 to -135°C. Using this procedure, Seyferth *et al.* have prepared and trapped this species with various electrophiles.[31] An alternative, and practically simpler, procedure is to lithiate the equivalent thioester at -78°C.[32] Quenching the resulting anion with an electrophile then affords the corresponding ketone or aldehyde. The latter may also be obtained from the starting thioester by treatment with Bu_3SnH and a Pd^0 catalyst.[33]

1-Boron-1-copper alkenylbimetallic reagents **17**, which are prepared by treatment of the equivalent α-iodoallenylboronic ester **16** with zinc dust followed by transmetallation, react with numerous electrophiles to afford substituted boronic esters. On alkaline hydrogen peroxide oxidation, these provide a variety of functionalized ketones (**Scheme 10**).[34]

4-Alkyl-2-oxazolindinone anions are readily generated on treatment with triethylamine, and combine with a variety of electrophiles to afford the α-substituted analogues. Subsequent mild acid hydrolysis smoothly reveals the substituted aldehyde,



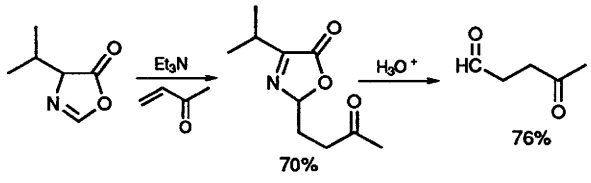
Scheme 9



16 17 18

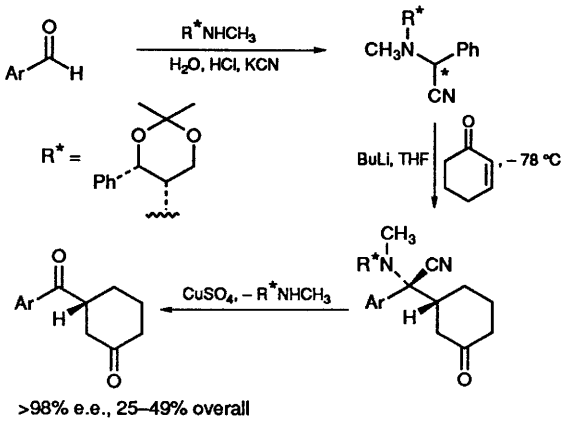
Scheme 10

(**Scheme 11**).[35] Although simple aldehydes react efficiently, dimeric products are formed upon cleavage of the oxazolidinone.



Scheme 11

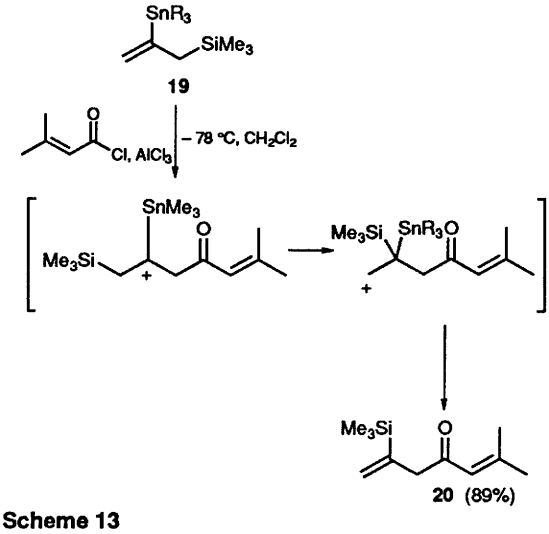
Cyanohydrins continue to see use as acyl anion equivalents. Allyl cyanohydrins undergo selective α-alkylation to produce, on deprotonation, the α'-substituted enone.[36] The related α-aminonitriles yield very high enantioselectivities in the synthesis of 1,4-diketones *via* asymmetric Michael addition (**Scheme 12**).[37]



Scheme 12

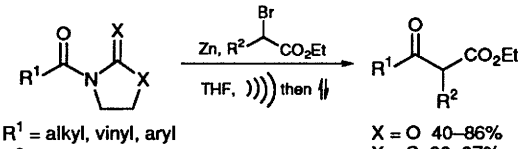
1.3 General methods

Nucleophilic acylation reactions remain one of the most commonly used options for the synthesis of aldehydes and ketones. The alkyliron reagents R_3FeLi and R_2Fe, which are generated *in situ*, are useful for the conversion of acyl chlorides into ketones. The procedure can also be carried out using a catalytic amount of $FeCl_3$ and the appropriate Grignard reagent.[38] Other developments in this area allow for the introduction of functionality into either the acid chloride, using manganese catalysed Grignard techniques,[39] or into the nucleophile through the use of organomercurials.[40] Allyl silanes continue to be used for this purpose and an unusual result is obtained when 2-trialkylstannylprop-2-enyl trimethylsilane **19** is coupled with an acid chloride (**Scheme 13**). Instead of the expected vinylstannyl ketone the corresponding silylated species **20** is obtained.[41] This is rationalized by a cationic 1,2-silyl migration followed by selective destannylation.



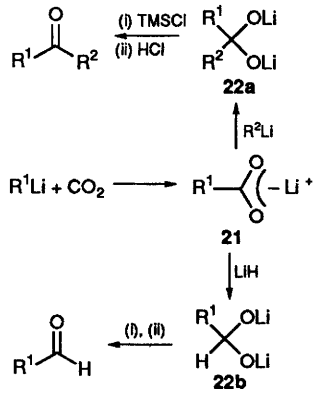
Scheme 13

Acid chlorides and esters are suitable substrates for a McMurray type coupling with aromatic ketones. The intermediate vinylic species are not isolated as the reaction proceeds directly to the desired ketones in moderate to excellent yield (52–96%).[42] The use of diesters or diacyl chlorides leads to the synthesis of diketones. Using anhydrous magnesium chloride/triethylamine[43] as a base to metallate potassium ethylmalonate affords a one-pot synthesis of β-ketoesters from all types of acid chloride.[44] This procedure is more efficient and amenable to larger scales than related processes using other malonate ester equivalents which either require the use of more hazardous reagents, *e.g.* butyl lithium, or lead to significant amounts of methyl ketone by-products. Substituted β-ketoesters are produced in the ultrasound promoted reaction of zinc Reformatsky reagents with acyl oxazolidinones or their thio analogues (**Scheme 14**).[45]



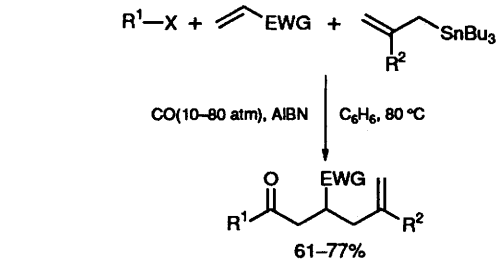
Scheme 14

Addition of organolithium compounds to carbon dioxide generates the acyl lithium **21**. After removal of excess carbon dioxide these acyl lithiums can be coupled with another alkyllithium or lithium hydride to provide routes to symmetrical and unsymmetrical ketones and aldehydes respectively.[46] The formation of alcohol by-products can be suppressed if the intermediate dilithioacetals **22** are trapped with trimethylsilyl chloride (**Scheme 15**).



Scheme 15

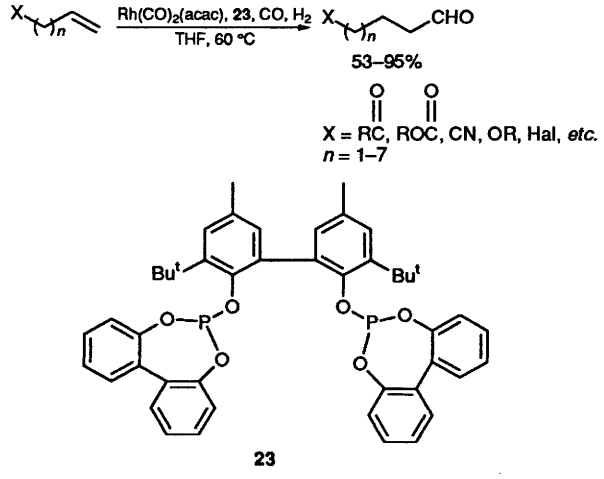
Carbon monoxide can be used as a source of the carbonyl group. Generation of alkyl radicals in the presence of an appropriate radical trap under an atmosphere of carbon monoxide provides efficient routes to a range of aldehydes and substituted ketones. Due to its lower reactivity with the initial alkyl radical, the use of tris(trimethylsilyl)silane, as opposed to tributyltinhydride, provides enhanced yields at lower CO pressures.[47] Other radical traps, such as allyl stannanes, furnish ketones of increased functionalization (**Scheme 16**).[48]



X = Br, I; EWG = CN, CHO, $COCH_3$, CO_2R^3; R^2 = H, CH_3

Scheme 16

Functionalized aldehydes are obtainable through the rhodium-catalysed hydroformylation reaction of substituted olefins using the bidentate phosphite ligand **23**, (**Scheme 17**).[49] This catalyst had previously been shown to produce a high ratio of linear to branched aldehydes.[50] Indium-catalysed hydroformylation, using

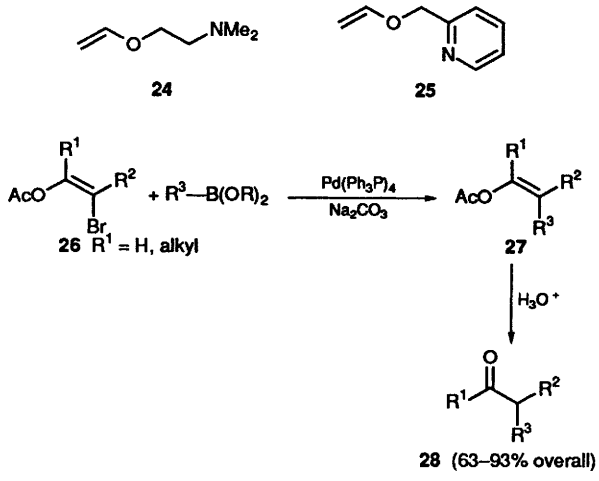


Scheme 17

trialkylsilanes instead of hydrogen, affords an efficient synthesis of acyl silanes.[51]

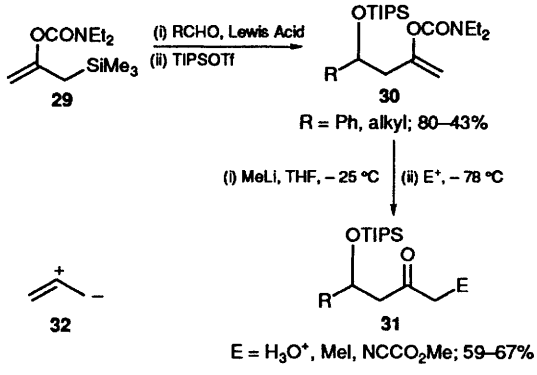
Palladium-catalysed coupling of vinyl ethers with aryl halides and triflates can provide routes to both aryl ketones or the homologous aldehydes. Normally, mixtures are obtained. Ketones are formed by α-arylation and this is achieved selectively through the use of bidentate phosphine ligands.[52] In order to prepare aldehydes it is necessary to incorporate a second metal binding site into the vinyl ether component, and in this respect the ethanolamine **24** and 2-pyridyl **25** derivatives have proved highly effective.[53]

An alternative approach to achieve regioselectivity is to use a β-haloenol acetate **26**. Suzuki coupling of these acetates with organoboranes stereospecifically affords substituted enol acetates **27**. Subsequent hydrolysis yields either the aldehyde or ketone, depending on the starting enol acetate (**Scheme 18**).[54]



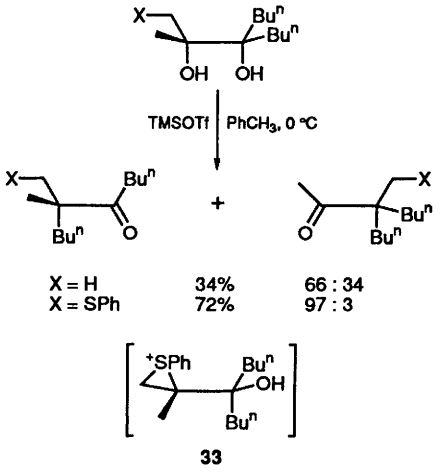
Scheme 18

2-(*N*,*N*-Diethylcarbamoyloxy)-allylsilane **29** behaves as a masked acetone α,α'-acetone dianion (**Scheme 19**), or as an allene-1,2-dipole **32** equivalent.[55] This strategy of carbonyl group generation in masked form has also found use in the synthesis of perfluoroalkyl ketones from the corresponding fluorinated esters, anhydrides, and dialkylamides with phosphorus ylids.[56] Interestingly, (*Z*)-enol ethers are formed exclusively when esters are the substrates whereas reactions with amides are not selective.



Scheme 19

The pinacol-pinacolone rearrangement of tetraalkylsubstituted diols produces mixtures of isomeric ketones. Selectivity may be imparted to this rearrangement by the presence of a sulfenylmethyl group.[57] Control is achieved through formation of an episulfonium ion intermediate **33** (**Scheme 20**). This modification not only imparts higher selectivity, it also increases both the rate and yield of the reaction. The thiophenol group is easily removed from the product by Raney-Nickel hydrogenolysis.



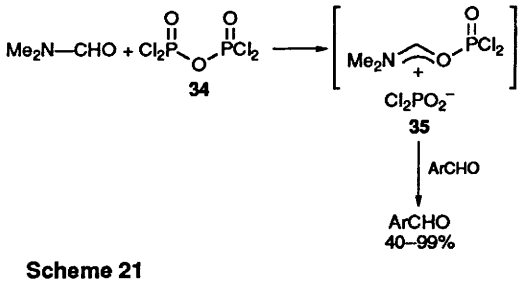
Scheme 20

The rearrangement of epoxides to carbonyl compounds has been simplified by the introduction of aluminium alkoxide reagents supported on a silica gel column. This modification permits the reaction to be run as a continuous flow method.[58]

2 Synthesis of aromatic aldehydes and ketones

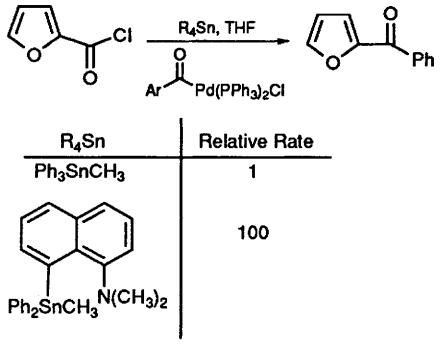
The Friedel–Crafts reaction between aromatic compounds and mixed anhydrides, formed *in situ* from the free carboxylic acid and *p*-trifluoromethylbenzoic acid, proceeds under mild conditions in the presence of an active catalyst generated from $SiCl_4$ and $AgClO_4$.[59] Although aromatic ketones have previously been synthesized from free acids, using catalytic amounts of initiators, the conditions required are rather drastic.

Replacing phosphoryl chloride with pyrophosphoryl chloride **34** in the Vilsmeier formylation generates a more reactive and more sterically demanding formylating agent **35**, (**Scheme 21**).[60]



Scheme 21

Simple phenyl ketones can be obtained by the palladium-catalysed reaction of sodium tetraphenylborate ($NaBPh_4$) with acid chlorides.[61] The cross-coupling reaction between 9-alkyl-9BBN derivatives, t-butylisocyanide, and haloarenes occurs on treatment with catalytic tetrakistriphenylphosphinepalladium (0) and a weak base, *e.g.* K_3PO_4, in dioxane at 50°C. The resulting ketimines are hydrolysed readily to give aryl alky ketones in high yield.[62] The palladium-catalysed arylation of furanoyl chlorides is accelerated by the presence of a neighbouring t-amino group in the organostannane co-promoter (**Scheme 22**).[63]



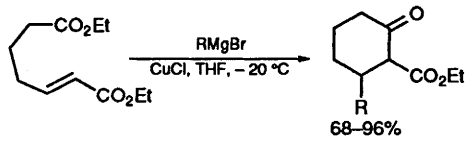
Scheme 22

Direct selective oxidation of aryl methyl groups to aldehydes can be achieved either photochemically, in the presence of TiO_2–Ag_2SO_4,[64] or in the vapour phase over a V_2O_5–Tl_2O catalyst.[65] Neither method is tremendously efficient, although yields do increase with increasing electron donating ability of the aromatic nucleus. Far more efficient are the ruthenium-catalysed benzylic oxidations developed by Murahashi *et al.*[66] Aliphatic alkanes are also oxidized but, with the exception of simple cyclic species, show little regioselectivity. Benzylic olefins are converted into the aryl ketone on treatment with zinc chlorochromate-nonahydrate,[2] *vide supra*, whilst aryl allenes afford arylenones on reaction with Koser's reagent, tosyloxy(hydroxy)iodobenzene.[67]

Aryl ketones are also obtained in moderate to excellent yield from the appropriate acyl telluride *via* trapping of the photochemically generated acyl radical. Much higher yields (80–96%) are obtained in intramolecular reactions. In contrast to the well established reactions of alkyl acyl cobalt radicals, this method only proceeds with aryl acyl tellurides.[68]

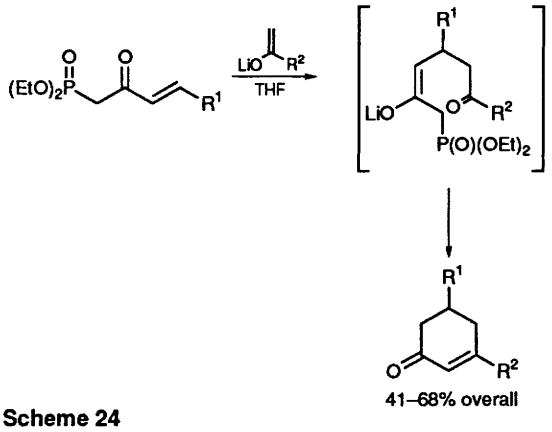
3 Synthesis of cyclic ketones

Tandem reaction sequences have provided a number of synthetic pathways to cyclic ketones. A conjugate addition/Dieckmann condensation sequence (**Scheme 23**), affords an efficient route to substituted six-membered cyclic β-ketoesters.[69] Substitution cannot be tolerated on either carbon of the acrylate moiety, which is consistent with earlier, related approaches to other cycloalkanones.[70]



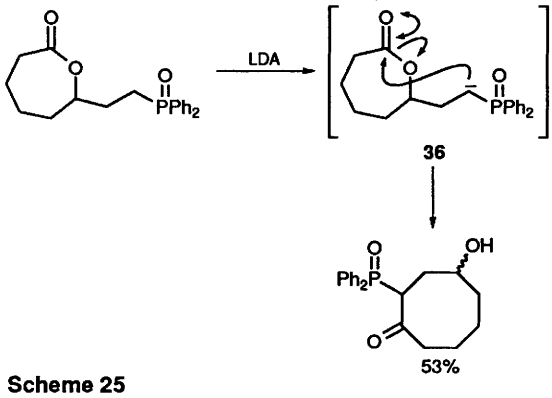
Scheme 23

A similar strategy, involving the condensation of ketone enolates and β-enone-phosphonates to provide substituted cyclohexenones, has been outlined by Wada *et al.*, (**Scheme 24**).[71]



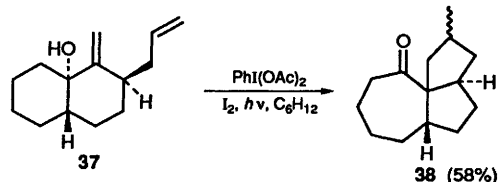
Scheme 24

Medium-ring ketones have been prepared by a number of ring expansion sequences. For example, generation of the phosphorus stabilized anion **36** smoothly leads, *via* an intramolecular acylation step, to the cyclooctanone, (**Scheme 25**).[72]

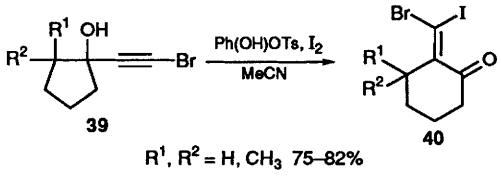


Scheme 25

Radical-initiated ring expansion routes to cyclic ketones have also been reported. Thus, generation of an alkoxy radical by oxidation of the *trans*-decalinol **37** with iodosylbenzene diacetate affords the tricyclic ketone **38** in 58% yield (**Scheme 26**).[73] This reaction is found to be very dependent upon the relative stereochemistry of the starting alcohol. The related reagent [tosyloxy(hydroxy)iodo]benzene, in the presence of iodine, promotes the cationic ring expansion of 1-bromoalkynylcyclopentanols **39** to alkylidene cyclohexanes **40** (**Scheme 27**).[74] Other polyvalent iodine species, including iodosylbenzene diacetate, prove ineffective for this conversion.



Scheme 26



R^1, R^2 = H, CH_3 75–82%

Scheme 27

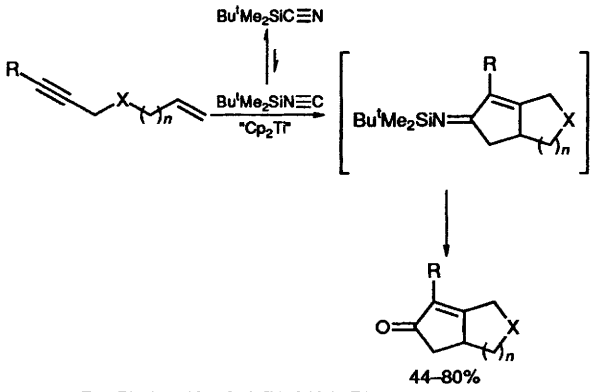
Radicals have also been implicated in the cleavage of cyclopropanols, to give β-ketoradicals, with ferric chloride[75] or manganese (III) 2-pyridinecarboxylate.[76] If fused to a pre-existing ring, this affords a general route to ring expanded ketones. The resulting radical can be trapped with various species, providing access to bicyclic ketones[77] and dicarbonyl compounds.[71] Alkyl radicals generated from the appropriate ω-alkenyliodoacylgermane cyclize smoothly and rapidly to form the corresponding cyclic ketone. However, difficulties in the preparation of the radical precursor limit this method to simple substrates.[78]

Enhanced enantioselectivities (70–99% e.e.) can be realized in the rhodium-catalysed cyclization of substituted 4-pentenals to cyclopentanones using a binaphthylphosphine ligand.[79] The 1,1,3-trialkylbutadiene iron tricarbonyl complex is converted efficiently into the conjugated cyclopentenone on treatment with aluminium trichloride at room temperature. The reaction is very substrate specific, producing only low yields of cyclic ketones with other substituted butadienes. Slightly improved yields, however, can be produced under more forcing conditions (100 atm. CO, 100°C).[80]

The Pauson–Khand synthesis of cyclopentenones continues to receive attention. Using DMSO as a promoter, molybdenum hexacarbonyl provides a very simple and efficient alternative to the well established dicobalt octacarbonyl mediated process.[81] Buchwald and co-workers have developed a titanium version of this reaction which is tolerant of a wide range of polar functionality.[82] More recently, the same research group has reported a catalytic version of the Pauson–Khand reaction based on the (trialkylsilyl)cyanide–(trialkylsilyl)isocyanide equilibrium (**Scheme 28**).[83] This limits the amount of reactive isocyanide present in the reaction mixture and prevents deactivation of the nascent catalyst through trapping with excess isocyanide. Using this system a variety of enynes can be converted into bicyclic cyclopentenones in moderate to good yield by using substoichiometric amounts (10 mol%) of $Cp_2Ti(PMe_3)_2$.

Cyclopentenones can also be prepared through the combination of chromium carbene complexes with allenes. Both alkyl[84] and cyclopropylalkyl[85] complexes give the same products, albeit by very different

mechanistic pathways. With the exception of deactivated acetylenes, moderate to good yields (≤78%) are obtained with both reagents.



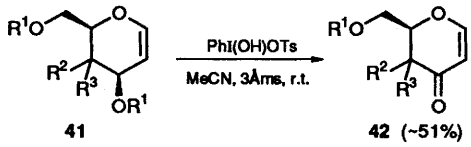
R = Ph, Me; X = O, NR', C(CO$_2$R')$_2$; n = 1, 2

Scheme 28

4 Synthesis of functionalized aldehydes and ketones

4.1 Unsaturated aldehydes and ketones

The direct oxidative conversion of allylic *O*-acyl and *O*-benzyl goups of peracylated and perbenzylated glycols **41** into the corresponding hex-1-enopyran-3-uloses **42** is achieved by reaction with [tosyloxy(hydroxy)iodo]benzene (**Scheme 29**).[86] Unlike the analogous oxidation (R = H) with manganese dioxide,[87] both epimers of the allylic alcohol derivative are suitable substrates.

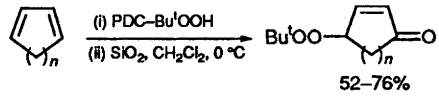


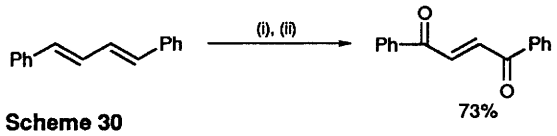
41 **42** (~51%)

R^1 = Ac, Bn R^2 = H, R^3 = OR^1; R^2 = OR^1, R^3 = H

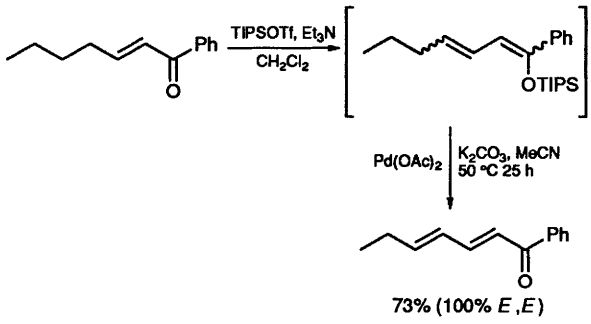
Scheme 29

Dienes may be oxidized to 4-dioxy-2-enones using the pyridinium dichromate-t-butylhydroperoxide reagent system.[88] The reaction proceeds in moderate to good yield even with sub-stoichiometric amounts of PDC. Under the same conditions diaryl dienes afford enediones (**Scheme 30**). Similarly, treatment of conjugated olefins with oxygen and triethylsilane in the presence of a cobalt(II)porphyrin complex yields the corresponding ketone. Acylation of the amide reaction mixture alleviates problems associated with hydroperoxide formation.[89] The Saegusa synthesis of enones, *via* oxidation of silyl enol ethers, may be extended to dienones through the intermediacy of triisopropylsilyl dienol ethers (**Scheme 31**). The resulting diene geometry was found to depend on the degree of substitution of the starting enone. Substrates with no additional β-substituent were the most selective, producing mainly, or exclusively, the (*E*,*E*) isomers in good to moderate yield.[90]



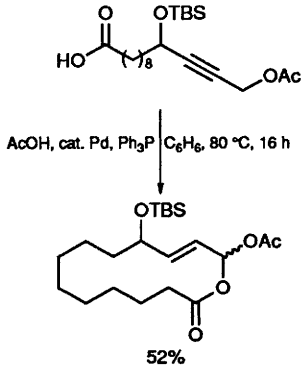


Scheme 30



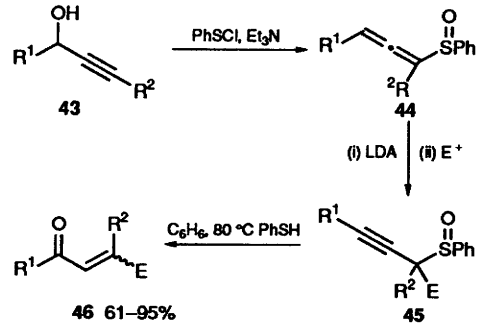
Scheme 31

Dienones can also be prepared from ynones in an internal redox process catalysed by triphenylphosphine.[91] Allenones undergo a similar transformation even more rapidly and may be intermediates on the reaction pathway. Although the mechanism of this process is not clear, the compatibility of a range of functionalized substrates with the reaction conditions makes it a valuable addition to the synthetic armoury. A similar intramolecular redox process is observed on treatment of terminal propargylic acetates with acetic acid and a catalytic amount of a palladium complex, derived from [(dba)$_3$Pd$_2$·CHCl$_3$] and triphenylphosphine, to produce exclusively (*E*)-enones masked as the geminal diacetates.[92] Furthermore, this reaction may be carried out in an intramolecular fashion to provide a synthesis of macrolides (**Scheme 32**).

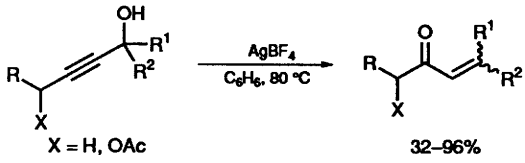


Scheme 32

Internal propargylic alcohols **43** can be converted into substituted enones **46** *via* the allenic sulfoxide **44**. Alkylation followed by sulfoxide–sulfenate rearrangement yields the desired carbonyl compound (**Scheme 33**).[93] Transposition of the alcohol function is achieved by treatment of the propargylic alcohol with silver tetrafluoroborate in refluxing benzene (**Scheme 34**). Milder reaction conditions can be used through the introduction of trimethylsilyl chloride.[94]

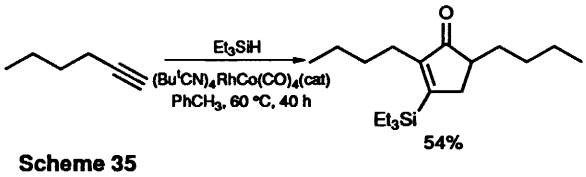


Scheme 33



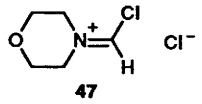
Scheme 34

Ojima *et al.* have reported enhanced efficiency in the silaformylation of alkynes using mixed Rh–Co bimetallic catalysts at ambient temperature and atmospheric pressure of carbon monoxide.[95] This report claims higher yields and greater selectivity than the analogous method using $Rh_4(CO)_{12}$.[96] In addition, the products are exclusively (*Z*)-1-silyl-2-formyl substituted olefins. The use of a trialkylsilane and excess alkyne can lead to moderate yields of cyclopentenones *via* a silacarbocyclization pathway (**Scheme 35**).



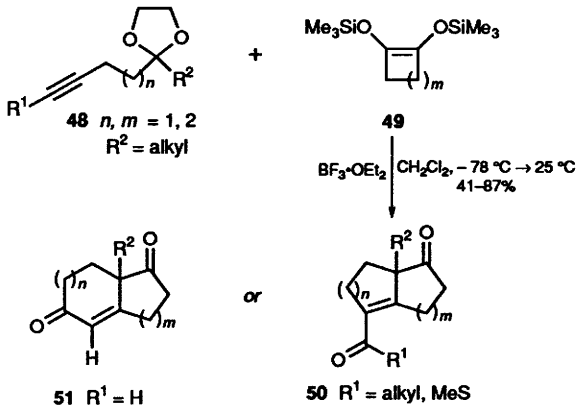
Scheme 35

Although silaformylations of allenes produce complex mixtures of products the expected enals can be obtained by analogous treatment of tertiary propargylic amines.[97] Simple formylation of unactivated olefins has been achieved in good yields with the morpholine derived Vilsmeier reagent **47**.[98] The corresponding ketones can be obtained by the copper-catalysed acylation of an alkenylzirconocene chloride, prepared *in situ* by hydrozirconation of the appropriate acetylene. This methodology is also suitable for the synthesis of saturated ketones from alkenes in an entirely analogous fashion.[99] The same components may also be coupled using organoboron technology and this particular strategy is amenable to the synthesis of α-chiral enones.[100]



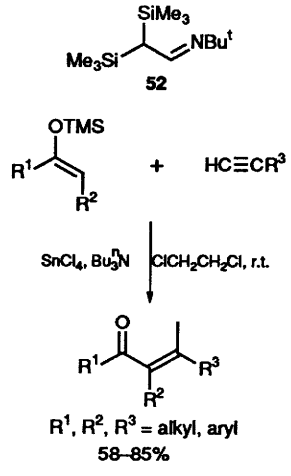
47

Unsaturated, polycyclic ketones are obtained from the Lewis acid mediated treatment of alkynyl acetals **48** with *bis*-silyloxycycloalkenes **49**. Depending on the substitution pattern of the alkyne, terminal or internal, either *exo*-**50** or *endo*-cyclic **51** enones are formed (**Scheme 36**).[101]

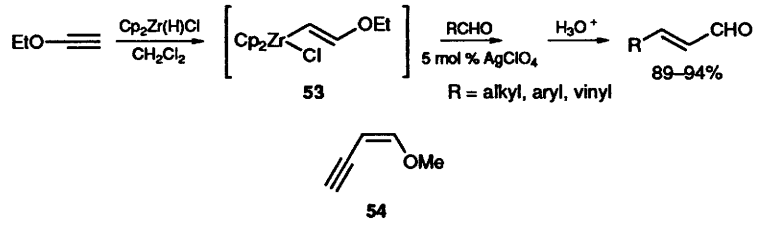


Scheme 36

The classic route to α,β-unsaturated carbonyl compounds is *via* the aldol reaction and a number of alternative or refined strategies have been reported. A one-pot Mukaiyama aldol-dehydration sequence can be simply executed through the stepwise addition of trifluoroacetic anhydride and triethylamine to the reaction mixture.[102] Allylic acetates couple efficiently with aromatic aldehydes, in neutral conditions, using a $PdCl_2(PhCN)_2$–$SnCl_2$ catalyst combination.[103] Tin enolates are also intermediates in the condensation of phenacylketones and aldehydes in the presence of tin(II) chloride and sodium sulfite.[104] Exclusive (*E*)-olefin formation is observed in the zinc bromide catalysed tandem aldol coupling/Peterson reaction of α,α-bis(trimethylsilyl) t-butylacetalaldimine **52** with aldehydes.[105] The tin tetrachloride/tributylamine promoted reaction of silylenol ethers with terminal alkynes afford (*E*)-enones stereoselectively ($E:Z \geq 18:1$) in good yield (**Scheme 37**).[106]



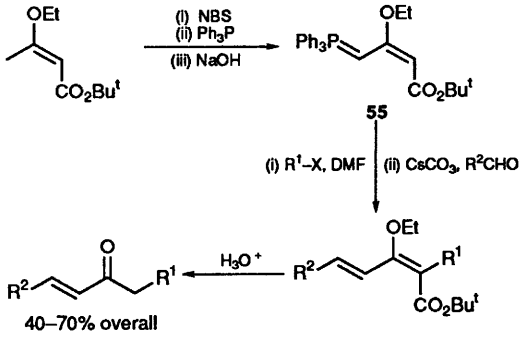
Scheme 37



Scheme 38

Hydrozirconation of ethoxyethyne generates the β-alkoxyalkenylzirconocene chloride **53** which, in the presence of silver perchlorate, condense with aldehydes to produce dienol ethers. These, on acid hydrolysis, lead exclusively to (*E*)-enals in excellent yields (89–94%) (**Scheme 38**). Commencing from the vinylogous enol ether **54** this procedure provides a similarly efficient route to (*E*,*E*)-dienols.[107]

Unlike their reactions with aldehydes, which produce alkenes, the coupling, in the presence of potassium carbonate/dibenzo-18-crown-6, of benzyl sulfonyl fluorides with α-haloketones yields a variety of aryl enones.[108] The reaction proceeds *via* initial nucleophilic substitution of the halogen followed by an E_1cB elimination to produce exclusively the (*E*)-olefin. Wittig chemistry can furnish routes to functionalized olefins either through the reaction of the methoxymethylphosphonium ylid with α-epoxyaldehydes,[109] or *via* the β-ketoester derived ylid **55** (**Scheme 39**).[110]



Scheme 39

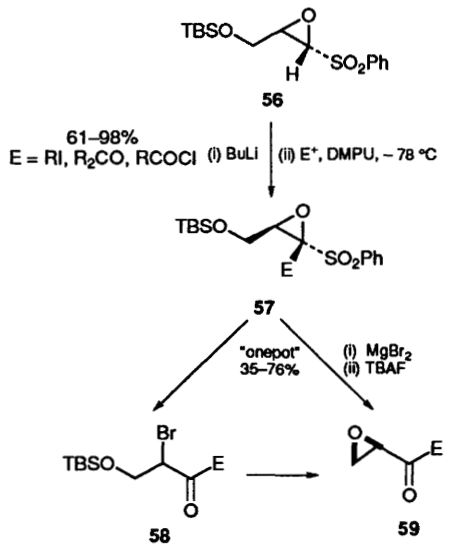
(*Z*)-α-Fluorinated enones are accessible in good yield through the reaction of α-diazoketones with phenylselenyl fluoride followed by oxidation and selenoxide elimination.[111] The corresponding α-chloroenones are procured from the parent enone by oxidative chlorination using MCPBA and hydrogen chloride in DMF.[112] β,β-Difluoroenones undergo facile substitution with various carbon nucleophiles in a conjugate addition–elimination process.[113] Since the starting ketones are readily prepared in a multicomponent procedure[114] this method provides routes to the fully substituted enone, albeit with little control of olefin stereochemistry.

4.2 α-Heteroatom substituted aldehydes and ketones

Rhodium-catalysed silaformylation of aldehydes provides a rapid entry to α-silyloxyaldehydes.[115] The reaction is quite sensitive to steric effects and consequently secondary reactions are not a problem. Ketones are not substrates, and yield silyl enol ethers as the sole product. This indicates that β-hydride elimination from a sterically hindered silyloxyalkyl rhodium complex is faster than insertion of carbon monoxide. Reduction of symmetrical α-diketones with sodium hydrogen selenide[116] is easier than the equivalent process using the analogous tellurium reagent.[117] The oxidation of optically active α-amino and α-alkoxy alcohols to the corresponding aldehydes and ketones with TEMPO occurs without racemization.[118] A multiplicity of functionalized alkenes can be converted into α-ketols on exposure to aqueous peracetic acid in the presence of a ruthenium trichloride catalyst.[119] Similar products may be obtained in enantiomerically enriched form (77–98% e.e.) through the asymmetric dihydroxylation of enol ethers.[120] Enantiomerically pure ketols can also be obtained from the appropriate epoxy alcohols prepared by the Sharpless epoxidation. Nucleophilic opening of fluoro epoxy alcohols prepared in this fashion give access to a range of enantiomerically pure α'-substituted α-ketols in good yield.[121]

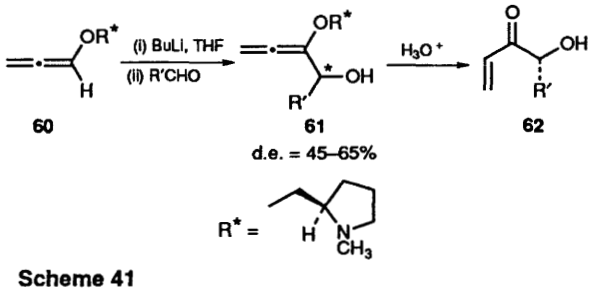
Epoxide ring opening reactions of α-alkoxyepoxysulfones **57** provide a synthesis of terminal epoxy ketones, **59** *via* the α-bromoketones **58** which can also be isolated in good yield (63–100%) (**Scheme 40**).[122] When the epoxide **56** is acylated, with an acid chloride, magnesium bromide promoted ring opening affords the corresponding α-bromoaldehyde. This is effectively an umpolung route to these functionalized ketones, and a number of other related processes have been reported. Most of these processes are designed in the alternative sense, relying upon the addition of an aldehyde to the acyl anion, and they include acyl anions derived from carbon monoxide/alkyl lithiums,[31] benzoyl cyanide/titanium trichloride,[123] and xylyl isocyanide/samarium diiodide/alkyl iodide.[124] If, in this last procedure, the alkyl halide is omitted then α-hydroxyaldehydes are obtained. The preparation of α-ketols may also be achieved enzymatically. Purified yeast pyruvate decarboxylase catalyses the condensation between aromatic aldehydes and pyruvate, providing acylations of high enantiomeric purity in good to moderate yields.[125]

Homochiral alkoxyallenes **60** can be α-metallated and condensed with an aldehyde to provide α-hydroxyallenic ethers **61**. The diastereoselection observed is variable and depends upon both the chiral auxiliary and the aldehyde. However, on mild acid



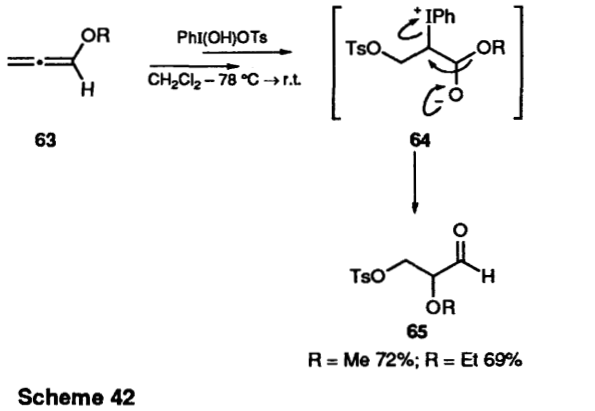
Scheme 40

hydrolysis the enol ethers are smoothly converted into α-hydroxyenones **62** without further erosion of optical purity (**Scheme 41**).[126]



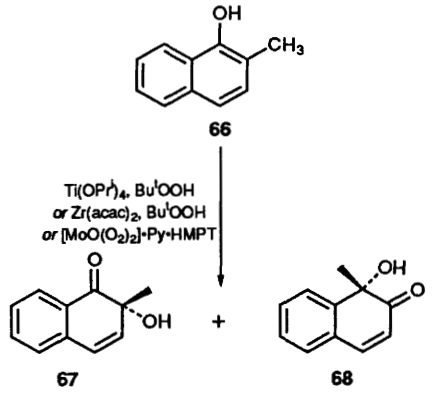
Scheme 41

Alkoxyallenes can also be converted into carbonyl compounds on oxidation with hypervalent iodine reagents. Whereas treatment with (iodosylbenzene)diacetate leads to mixed alkynylacetals, the low temperature reaction with [tosyloxy(hydroxy)iodo]benzene affords α-alkoxy-β-tosyloxyaldehydes **65** and is postulated to form *via* a pinacol type rearrangement of the mixed hemiacetal **64** (**Scheme 42**).[67] Treatment of ketones with this latter reagent provides a direct means of α-tosyloxylation.[127] This process is greatly enhanced by ultrasound.[128] Direct α-hydroxylation can be carried out in acidic media using [bis(trifluoroacetoxy)iodo]benzene.[129]



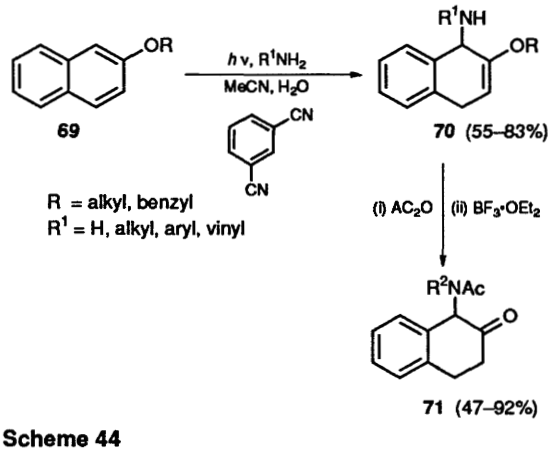
Scheme 42

Enolate oxidations are a well established route to α-hydroxycarbonyl compounds, although methoxylation traditionally requires a multi-step sequence. Rozen *et al.* have introduced methylhypofluorite as a source of the methoxylium ion, 'MeO^+'.[130] This reacts most efficiently with methyl enol ethers; other types of enols such as silylenol ethers and enol acetates offer limited success. α-Alkylated naphthols **66**, effectively aromatic enols, may be oxidized to the corresponding α-ketols **67** and **68**, with concomitant dearomatization and partial shift of the alkyl group on reaction with either the molybdenum oxodiperoxo complex ($MoO(O_2)_2$·Py-HMPT) or t-butylhydroperoxide and a transition metal catalyst (**Scheme 43**).[131] The amount of rearranged product varies with the nature of the starting naphthol, although the zirconium and molybdenum reagents tend to suppress this pathway.



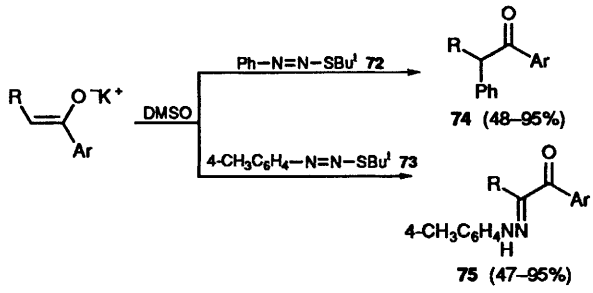
Scheme 43

Photo-oxidative aminations of β-alkoxy-naphthalenes **69** are achieved on irradiation in the presence of 3-dicyanobenzene and a primary amine. Acylation of the intermediate aminodihydronaphthalenes **70** followed by treatment with BF_3–OEt_2 then yields substituted α-amino-2-tetralones **71** (**Scheme 44**).[132] α-Nitrogen functionality may also be introduced *via* enolate 'alkylation' with tetranitromethane[133] or arylazo-t-butylsulfides.[134] This latter reagent can furnish routes to either the α-ketotolylhydrazone **75** or the benzyl ketone **74** simply by switching between tolylazosulfide **73** and phenylazosulfide **72**, respectively (**Scheme 45**).

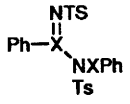


Scheme 44

Treatment of trimethysilylenol ethers with the reagent **76**, derived from diphenyldisulfide and chloramine T, provides a mild and efficient route to α-thioketones.[135] The corresponding selenium containing reagent **77** behaves in an entirely analogous fashion.



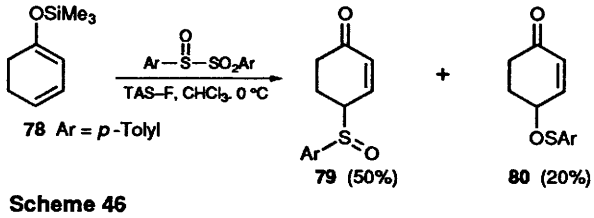
Scheme 45



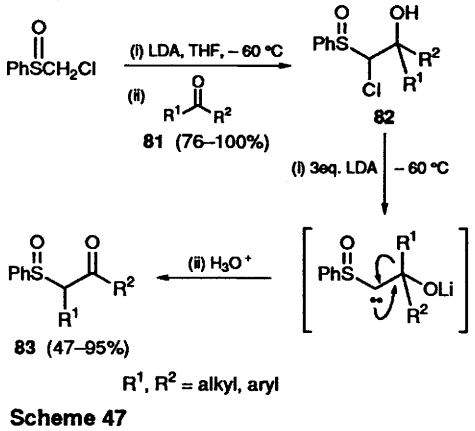
76 X = S
77 X = Se

Direct conversion of a silylenol ether into the corresponding ketosulfoxide is achieved on reaction with 4-toluenesulfenyl-1,4-tolylsulfone in the presence of tris(dimethylamino)sulfur-trimethylsilyldifluoride (TAS-F) in anhydrous chloroform.[136] Interestingly, treatment of dienol silyl ethers with this reagent lead predominantly to the γ-substituted products (**Scheme 46**). The allylic sulfenic ester **80** presumably arises through a 2,3-shift of the initially formed α-sulfoxide.

Ketones are converted into the homologous ketosulfoxides by addition of lithio-α-chloromethylphenylsulfoxide and treatment of the resulting adduct **82** with three equivalents of LDA (**Scheme 47**).[137]



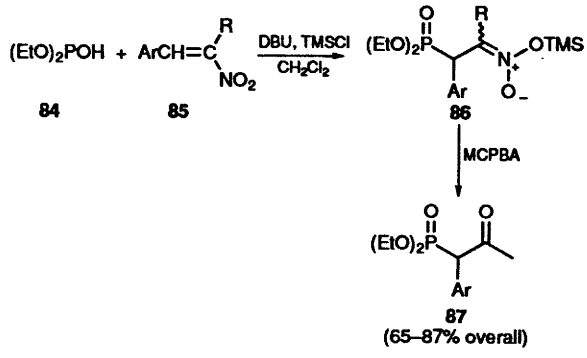
Scheme 46



Scheme 47

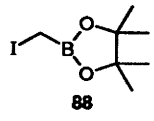
α-Alkenylsilanes, which are effectively masked carbonyl compounds, may be converted directly into the analogous α-thiocarbonyl species by electrolysis in the presence of thiophenol and molecular oxygen.[138] Good yields of phenylthiomethylketones are obtained with α-alkylvinylsilanes. However, more heavily substituted substrates give significantly lower yields. Although aldehydes can be prepared by this method the yields are variable.

β-Ketophosphonates **87** are synthesized efficiently in a two step procedure involving Michael addition of diethyl phosphite **84** to the vinyl nitrate **85**, followed by oxidation of the resulting silylnitronate ether **87** (**Scheme 48**).[139] The mild nature of this conversion contrasts with traditional methods for the synthesis of this functional group.



Scheme 48

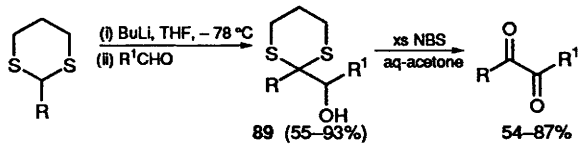
The analogous β-ketoboronates are accessible, in good yield, *via* enolate alkylation with the iodomethylboronic ester **88**.[140] These compounds show moderate to excellent stereoselectivity in a range of aldol reactions.[141] Finally, α-chloroketones are the products when epoxides are treated with oxalyl chloride and DMSO at -60°C in the presence of triethylamine and 5–10 mol% of methanol.[142]



88

4.3 Dicarbonyl compounds

N-Bromosuccinimide oxidation of 2-(α-hydroxyalkyl)-1,3-dithianes **89**, prepared by addition of the dithianyl anion to the corresponding aldehyde, provides a simple route to both symmetrical and unsymmetrical 1,2-dicarbonyl compounds (**Scheme 49**).[143]

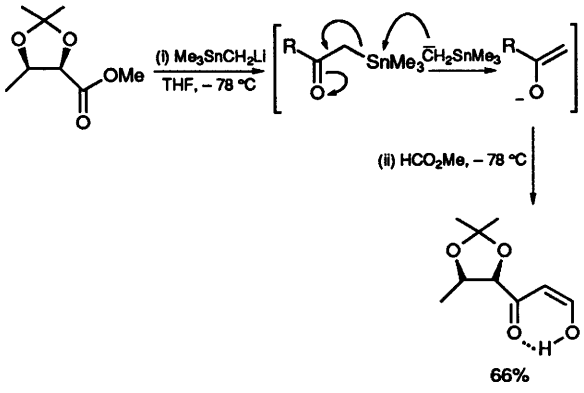


R = aryl; R^1 = aryl, alkyl

Scheme 49

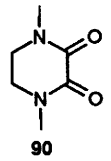
α,α'-Diarylacetaldehydes can be converted into the corresponding diaryl-α-diketones by oxidation with tris(2,4-dibromophenyl)ammoniumylhexachloroantimonate, $[(2,4\text{-}Br_2C_6H_3)_3N^+SbCl_6^-]$.[144] Propionaldehyde and higher homologues give much poorer yields, as competing α-chlorination occurs. Symmetrical diaryl α-diketones are obtained in good yield through the electrolysis of the appropriate carboxylic esters.[145]

Mild acid catalysed rearrangements of $\alpha\beta$-epoxyarylketones to α-diketones occur on adsorption onto general purpose silica gel.[146] Masked β-heteroaldehydes result from the alumina mediated addition of propanedithiol to acetylenic ketones,[147] whilst in a similar process trimethylsilylethynyl ketones are easily converted into β-ketoacetals, vinylogous amides, or esters.[148] Free β-ketoaldehydes can be isolated in a one-pot sequence involving the treatment of esters with two equivalents of (trimethylstannyl)methyllithium and quenching the resulting anion with methyl formate (**Scheme 50**).[149]



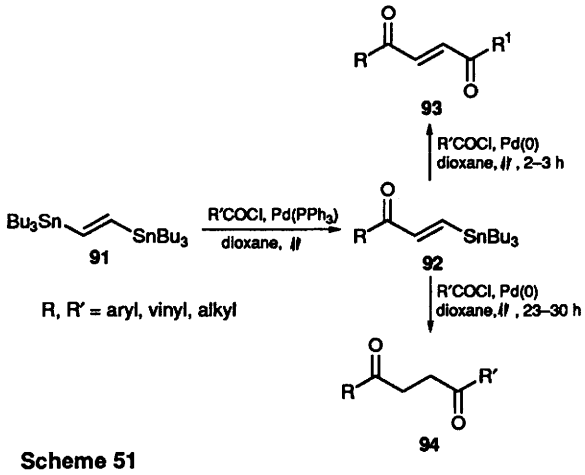
Scheme 50

Although reactions of organolithium compounds with oxalyl dipiperidide fail to yield any diketone the cyclic *cis*-fused oxamide **90** proves to be an excellent substrate for a variety of organolithium and Grignard reagents.[150] Similarly, the use of 1,1′-oxalylimidazole provides a convenient entry to sterically hindered symmetrical diaryl α-diketones.[151]



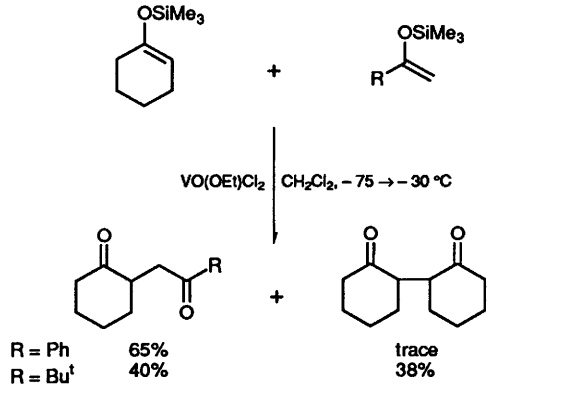
90

Refluxing the stannane **91** with two equivalents of an acid chloride in dioxane for 2–3 h in the presence of catalytic tetrakis(triphenylphosphine)palladium(0) afforded the expected ene-dione **93**. However, prolonged reaction times produced the saturated 1,4-dione **94**.[152] This, *in situ*, reduction is believed to occur through the participation of a palladium hydride species formed by β-hydride elimination from an intermediate n-butylpalladium complex. The latter is formed from the reaction of the catalyst with the tributyltin chloride generated in the reaction. The inhibition of the reduction step through the use of trimethyltin chloride is consistent with this proposal. Since selective monoacylation of the parent stannane **91** is possible,[153] this chemistry provides routes to both symmetrical and unsymmetrical diones (**Scheme 51**).



Scheme 51

Oxidative couplings of silylenol ethers are achieved efficiently using the one-electron oxidant $VO(OR)Cl_2$.[154] Whereas cyclic enol ethers react efficiently to give the homocoupled compounds, only small amounts of symmetrical diketones are produced with acyclic silylenol ethers. This difference in reactivity can be harnessed to furnish a route to unsymmetrical ketones (**Scheme 52**). The selectivity of this process is very sensitive to the degree of substitution. Similarly, reaction of silyldienol ethers with silyl enol ethers initiated by ceric ammonium nitrate (CAN) provides 6-oxo-α,β-unsaturated carbonyl compounds in good yield.[155] In a series of reports, Narasaka and co-workers[156] have generated various radical cations by oxidative methods, and added these species to a number of olefinic substrates.

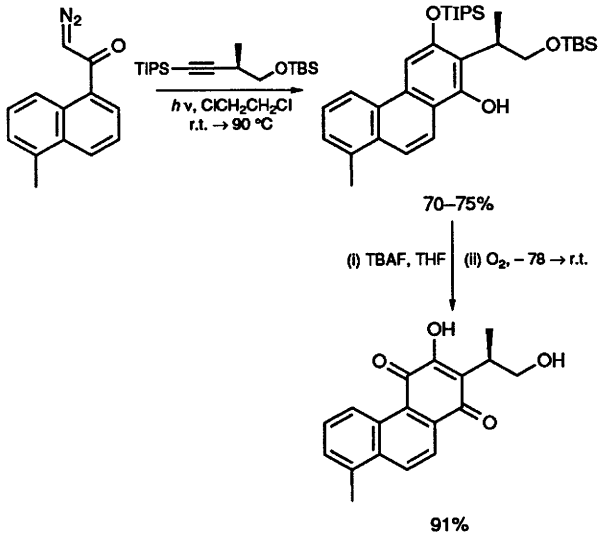


Scheme 52

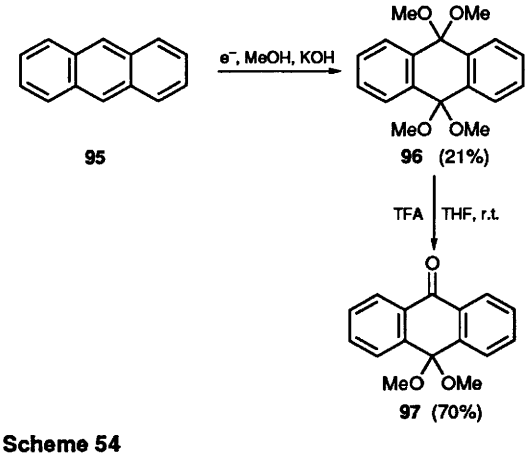
Using 2-tributylstannyl-1,3-dithianes[156a] or enamines[156b] as the radical source, and silyl enol ethers as the acceptor, leads to the synthesis of masked 1,3- and 1,4-dicarbonyl compounds respectively. Radicals have also been implicated in the coupling reactions of α-bromoketones on treatment with bis(trimethylsilyl)-or bis(trimethylgermyl)mercury.[157]

Although the reactions proceed efficiently (75–91%) they have the experimental drawback that elemental mercury is a by-product.

Oxidations of hydroquinones to quinones can be achieved in the solid state using a mixture of potassium bromate and catalytic CAN.[158] Quinones can also be obtained from phenols by treatment with either iodosylbenzene diacetate[159] or molecular oxygen in the presence of a copper (II) chloride/amine hydrochloride catalyst.[160] A similar oxidation forms the last step in the Danheiser synthesis of quinones through the addition of vinylketenes to acetylenes. This annulation procedure can be extended to include the synthesis of polycyclic benzoquinones (**Scheme 53**).[161] The direct electrochemical oxidation of anthracene in methanolic potassium hydroxide affords the quinone bisketal **96** which can be mono deprotected selectively to give 10,10-dimethoxyanthracen-9-one **97** on brief exposure to trifluoroacetic acid, (**Scheme 54**).[162]



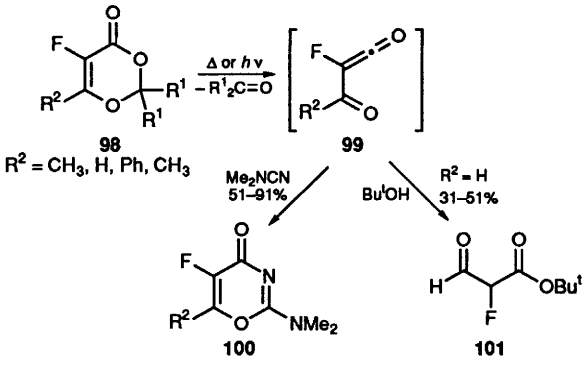
Scheme 53



Scheme 54

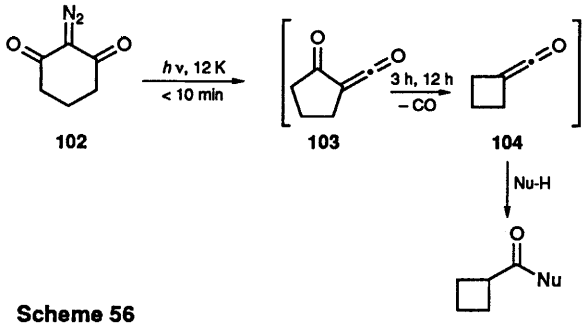
5 Synthesis of ketenes and cumulenes

Earlier work on the chemistry of ketenes and cumulenes has been reviewed.[163] More recent work has focused on the synthesis and chemistry of functionalized and/or more stable, observable, species. For example, α-fluoro-α′-oxoketenes **99** are generated either thermally or photochemically from the α-fluorodioxinones **98**.[164] These species can then be trapped to provide a variety of useful fluorinated heterocycles and β-keto- or β-formylesters, (**Scheme 55**).

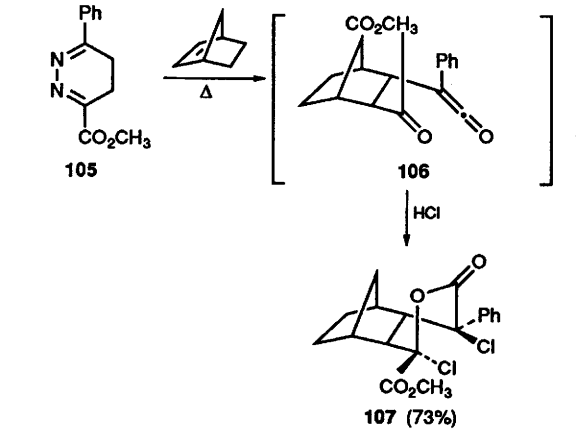


Scheme 55

α-Oxoketenes can be prepared routinely by either flash vacuum pyrolysis of β-ketoesters[165] or by photolysis of diazo-β-diketones.[166] Thus, commencing with 2-diazacyclohexa-1,3-dione, the latter provides the cyclopentyloxoketene **103** which on standing at 12K extrudes carbon monoxide to afford cyclobutylketene **104** and hence a variety of cyclobutylcarbonyl compounds (**Scheme 56**). γ-Oxoketenes can be accessed through the tandem Diels–Alder retro-Diels–Alder reaction of the 1,3,4-oxadiazinone **105** with cyclic olefins. Treatment of the γ-oxoketenes with hydrogen chloride then affords the stable δ-chloro-δ-lactone **107** (**Scheme 57**).[167]

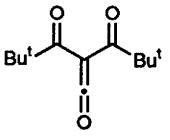


Scheme 56

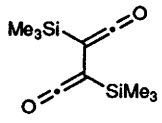


Scheme 57

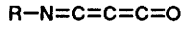
The dioxoketene **108** is relatively stable at room temperature dimerizing only slowly in an unusual $[4\pi + 2\pi]$ process.[168] Silyl substitution is known to stabilize ketenes. This feature has permitted their chemistry to be more fully explored,[169] and led to the isolation of the stable bisketene **109**.[170] Synthetic routes to isocyanocumulenes **110** using FVP have also been reported.[171]



108



109

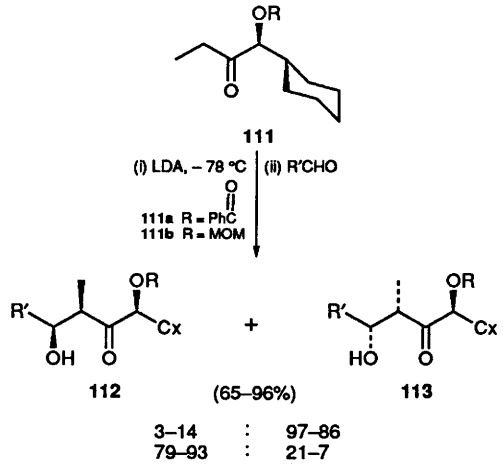


110

6 Reactions of aldehydes and ketones

6.1 The aldol reaction and other enolate additions

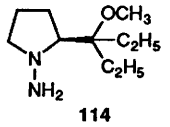
Reactions of ketone enolates are dominated by the aldol reaction and recent developments in this area are, principally, concerned with the stereochemical outcome. A number of chiral auxiliaries have been examined. Boron enolates of homochiral *o*-methoxyacetophenone chromium tricarbonyl complex give good diastereoselectivities in the aldol reaction with a range of aldehydes.[172] Thornton has developed methodology for the synthesis of either *syn*-aldol diastereoisomer using the lithium enolate of the α-cyclohexyl-α-ketol **111**.[173] The high *syn-anti* selectivity observed (**Scheme 58**) with the 'apparently non-chelated enolate', derived from **111a**, is attributed to an extended chelate cycle involving the benzoyl carbonyl oxygen atom.[173a] Enhanced selectivity ($\geq 32:1$) for the *syn-syn* aldol product **112** is observed with the triisopropoxytitanium enolate.[173b]



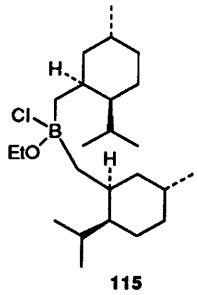
Scheme 58

The sterically demanding hydrazine SAEP, **114**, is required to obtain both high yields and diastereoselectivities in the aldol reactions of the related hydrazones derived from arylpyruvates.[174]

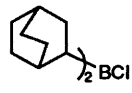
Reagent based control of aldol diastereoselectivity has also been examined, both theoretically[175] and experimentally. Highly selective (*E*)-boron enolate generation, and hence *anti*-aldol synthesis, can be realized using the dialkylchloroboranes **115** and **116** derived from menthone[176] and [2.2.2]-bicyclooctene,[177] respectively. The former reagent provides aldol products of reasonable enantioselectivities (56–88%). Brown *et al.* have also reported on a systematic study on the effect of the ketone enolate geometry of the leaving group (X) in R_2BX.[178] In general, poorer leaving groups favour *E*-enol borinates, a feature enhanced by more sterically bulky alkyl groups.



114

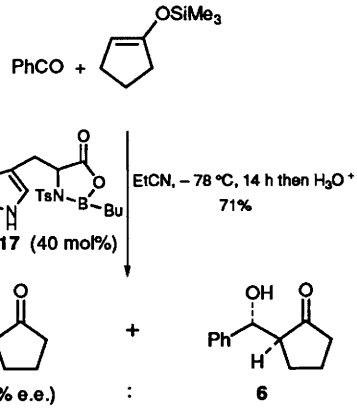


115



116

Very high enantioselectivities are obtained in the Mukaiyama aldol reaction catalysed by the tryptophan derived oxazaborolidine **117**.[179] Terminal enol ethers prove to be the best substrates, although more substituted species still give reasonable results (**Scheme 59**). Interestingly, unlike many of the pre-existing catalysts, silyl ketene acetals do not react with pronounced enantioselectivity.

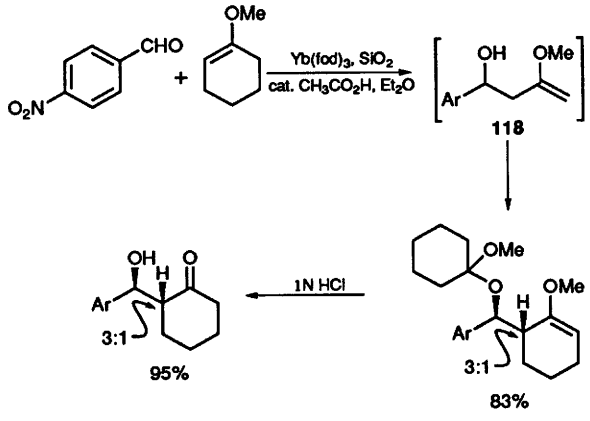


Scheme 59

Catalytic enantioselective addition in the Bayliss–Hillman reaction has also been recorded, using chiral rhodium phosphine complexes.[180] Although only low enantioselection was observed this represents the first application of chiral rhodium catalysis to the 'aldol' reaction. Other developments in catalyst technology have led to the introduction of the catalysts $[MCl_2(CF_3SO_3)_2 \cdot Sn]$ (M = Ti, $n = 0$; M = Zr, $n = 1$) which efficiently promote the coupling of silyenol ethers with *both* aldehydes *and* ketones.[181]

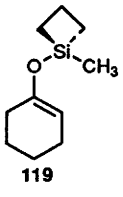
Lanthanide triflates provide a reusable catalyst for the Mukaiyama aldol reaction of silyl enol ethers with aldehydes and acetals in either aqueous[182] or organic[183] solvents. After workup the catalyst may be recycled from the aqueous extracts by concentration and drying *in vacuo* without any loss of activity. The

use of organic solvents allows this chemistry to be extended to the more hydrolytically labile silyl ketene acetals. Lanthanide catalysis of the bimolecular ene reaction between enol ethers and aldehydes provides differently masked aldol products in good yields, albeit with only moderate selectivity, (**Scheme 60**).[184] The intermediate hydroxy enol ether[118] can be isolated when the reaction is carried out in the presence of a trace amount of potassium carbonate.

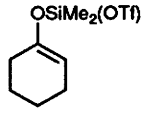


Scheme 60

The use of Lewis acids may be avoided by the adoption of more reactive silyl enol ethers. Both cyclobutyldimethylsilyl **119**[185] and dimethylsilyltriflate enol ethers **120**[186] couple smoothly with aldehydes in the absence of Lewis acids, even at −78°C.



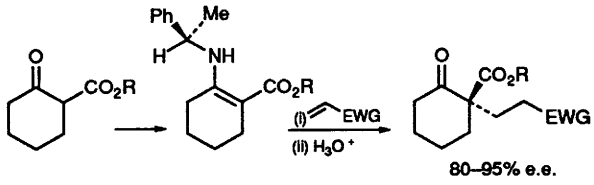
119



120

A NCS/tin(II) chloride combination permits the use of the more stable, easier to handle, enol esters in aldol type reactions.[187] In contrast, organotin(IV) enolates are more reactive than the corresponding silyl enol ether although, to date, the associated preparative difficulties has limited their use. In response to this, several methods have been reported for their *in situ* generation. These include the treatment of α-iodoketones with hexabutylditin in the presence of a co-promoter, usually Bu_3SnI_2. HMPA,[188] and the fragmentation of α-epoxyketones with tributyltin hydride.[189] The latter process also provides access to a range of annulated cyclic ketones (**Scheme 61**).[190] Ring opening of epoxy alcohols can be an efficient, indirect route to aldols[191] and homoaldols.[192] The latter products can also be obtained through the ozonolysis of glucals,[193] whilst vinylogous aldols are accessible through the addition of α-chlorosulfoxides to enones.[194]

The conjugate addition reactions of enolates can be enhanced by a switch in the counter-ion from lithium to titanium.[195] The addition of ketone enolates to α,β-unsaturated esters, normally a contrathermodynamic process, can be achieved by the introduction of an activating group into the α-position of the crotonate. The ratio of *anti* to *syn* products can be controlled by varying the counter-ion, the solvent, and the reaction temperature.[196] Excellent disastereoselection is observed in the reaction of chiral enaminoesters with a variety of Michael acceptors (**Scheme 62**). This subject has been comprehensively reviewed.[197]



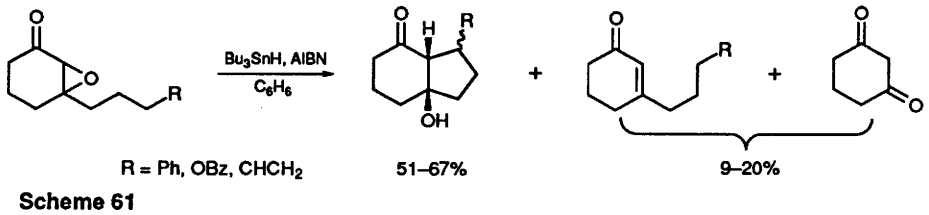
Scheme 62

Lithiated chiral enamines **123** derived from α-alkyl-β-ketoesters **121** and (*S*)-valine t-butylester **122** can be alkylated to give either enantiomeric product depending upon the solvent (**Scheme 63**).[198]

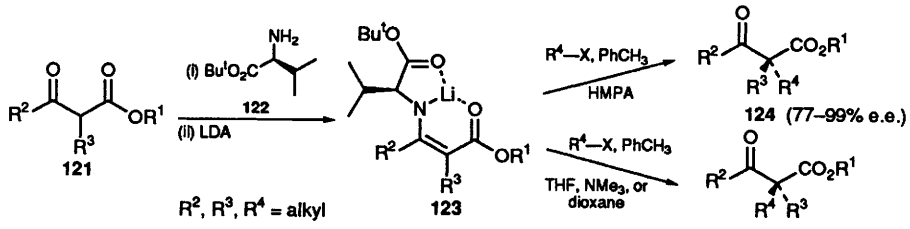
Protonation of a ketone enolate may also occur in an enantioselective fashion using the piperazine **126**[199] or the chiral amine **127**[200] as the proton source. The sense of asymmetric induction obtained on protonation with the amine **127** is opposite to that observed on alkylation with alkyl halides under otherwise identical conditions (**Scheme 64**). Finally, asymmetric deprotonations continue to be a viable route to enantiomerically enriched ketones.[201]

6.2 Conjugate addition reactions

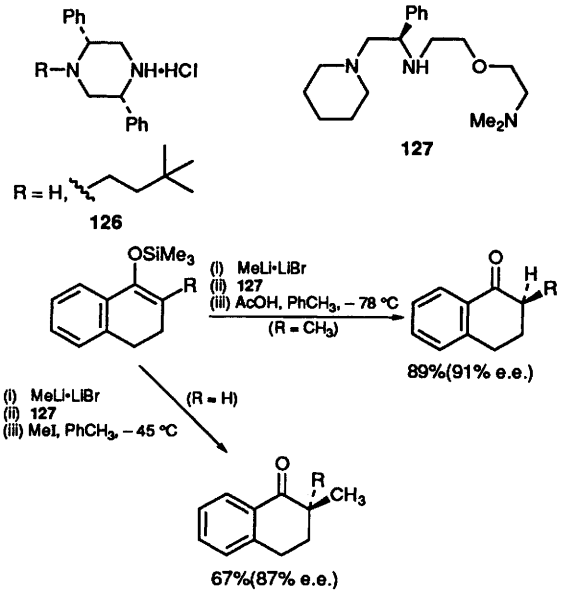
Studies of enantioselective conjugate addition reactions continue to be an area of considerable activity. The classical method of addition of an organometallic unit can be rendered enantioselective by the use of either internal (non-transferable) or external chiral modifiers. The use of *N*-methyl-1-phenyl-2-(1-piperidinyl)ethanamine **128**[202] as a non-transferable ligand for heterocuprates affords good



Scheme 61

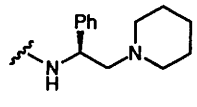


Scheme 63

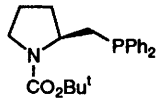


Scheme 64

yields of the conjugate addition product in greater than 97% e.e. Similarly good enantioselectivities are obtained using the amidophosphine ligand **129** with homocuprates.[203] This external ligand works on the principal of metal differentiating coordination, in which the phosphorus and amido carbonyl oxygen coordinate selectively to the copper and lithium atoms of the cuprate aggregate respectively. Catalytic chiral controllers are much rarer.

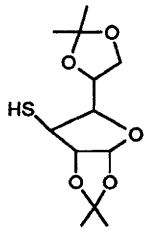


128

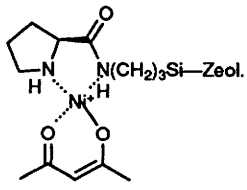


129

One recent report details the use of 1,2:5,6-di-*O*-isopropylidene-3-α-D-thioglucofuranose **130** in the copper-catalysed addition of Grignard reagents to enones.[204] The observed enantioselectivities vary strongly with the reaction conditions, reaching a maximum of 60% e.e. Coupling of the catalyst to a solid support allows for recycling. Using this strategy Sanchez and co-workers have been able to add, conjugatively, diethylzinc to a variety of enones in the presence of a zeolite bound nickel complex **131** with high enantioselection, 38–95%.[205]

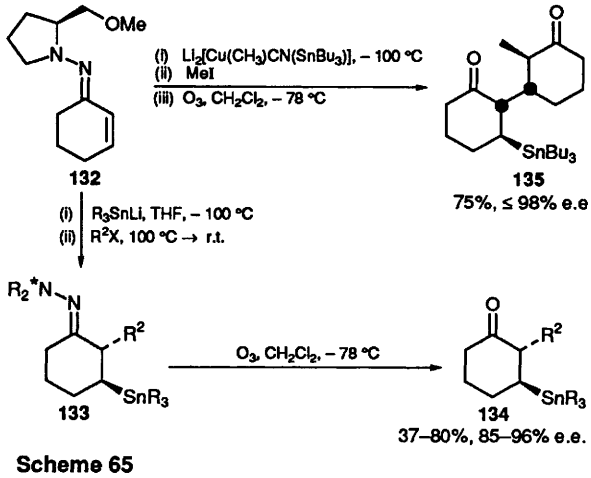


130



131

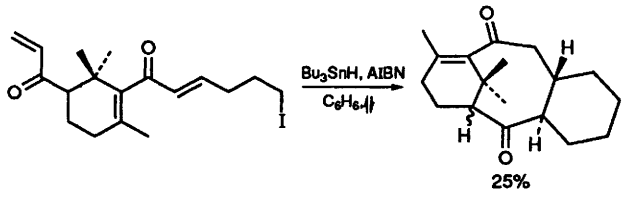
Highly enantioselective conjugate addition-enolate alkylation sequences can be realized through the addition of trialkylstannyllithium to the cyclohexanone SAMP hydrazone **132** (**Scheme 65**). When the organotributylstannylcuprate,



Scheme 65

$Li_2[Cu(CH_3)CN(SnBu_3)]$, is used as the nucleophile, a tandem double Michael addition–alkylation reaction occurs to give the bis-cyclohexanone **135** in 75% yield and ≥ 98% d.e.[206]

Lastly, tandem radical Michael additions to enones have been elegantly utilized in a synthetic approach to the taxane carbon skeleton (**Scheme 66**).[207]



Scheme 66

7 References

1 H. Nakamura, H. Matsuhashi, and K. Arata, *Chem. Lett.*, 1993, 749.
2 H. Firouzabadi and A. Sharifi, *Synthesis*, 1992, 999.
3 M.N. Bhattacharjee, M.K. Chaudhuri, H.S. Dagupta, N. Roy, and D.T. Khathing, *Synthesis*, 1982, 588.
4 J.-I. Yamaguchi, S. Yamamoto, and T. Takeda, *Chem. Lett.*, 1992, 1185.
5 T. Yokoo, K. Matsumoto, K. Oshima, and K. Utimoto, *Chem. Lett.*, 1993, 571.
6 S.-I. Murahashi and T. Naota, *Synthesis*, 1993, 433.
7 T. Nagamatsu, H. Yamato, M. Ono, S. Takarada, and F. Yoneda, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2101.
8 I.A. Rivero, R. Somanathan, and L.H. Hellberg, *Org. Prep. Proced. Int.*, 1992, **24**, 363.
9 D.D. DesMarteau, V.A. Petrov, V. Montanari, M. Pregnolato, and G. Resnati, *Tetrahedron Lett.*, 1992, **33**, 7245.
10 G.A. Heigel and M. Nalbandy, *Synth. Commun.*, 1992, **22**, 1589.
11 P.S. Radhakrishnamurti and N.K. Rath, *Indian J. Chem. A*, 1985, **24**, 300.
12 J. Muzart, *Synthesis*, 1993, 11.
13 S.-I. Murahashi, Y. Oda, T. Naota, and N. Komiya, *J. Chem. Soc., Chem. Commun.*, 1993, 139.
14 M.G. Banwell, N. Haddad, J.A. Huglin, M.F. Mackay, M.E. Reum, J.H. Ryan, and K.A. Turner, *J. Chem. Soc., Chem. Commun.*, 1993, 954.
15 T.T. Wenzel, *J. Chem. Soc., Chem. Commun.*, 1993, 862.
16 T. Hosokawa, T. Yamanaka, and S.-I. Murahashi, *J. Chem. Soc., Chem. Commun.*, 1993, 117.
17 D.G. Lee, T. Chen, and Z. Wang, *J. Org. Chem.*, 1993, **58**, 2918.
18 F. Ghelfi, R. Grandi, and U.M. Pagnoni, *Synth. Commun.*, 1992, **22**, 1845.
19 Y. Yang, Y. Li, and Y. Lin, *Synth. Commun.*, 1993, **23**, 1121.
20 J.C. Jung, K.S. Kim, and Y.H. Kim, *Synth. Commun.*, 1992, **22**, 1583; G. Olah, Q. Liao, C.-S. Lee, and G.K.S. Prakash, *Synlett.*, 1993, 427.
21 J.G. Lee, K.H. Kwak, and J.P. Hwang, *Synth. Commun.*, 1992, **22**, 2425.
22 J.-i. Yamaguchi and T. Takeda, *Chem. Lett.*, 1992, 1933.
23 N. DeKimpe, M. Nagy, M. Boeykens, and D. Van der Schueren, *J. Org. Chem.*, 1992, **57**, 5761.
24 One notable exception is 1,3-dimethyl-2-phenylbenzimidazoline; see H. Chikashita, H. Ide, and K. Itoh, *J. Org. Chem.*, 1986, **51**, 5400.
25 T. Sakamoto and Y. Kikugawa, *Synthesis*, 1993, 563.
26 T. Joh, K. Fujiwara, and S. Takahashi, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 978.
27 M. Sommovigo and H. Alper, *Tetrahedron Lett.*, 1993, **34**, 59.
28 T.H. Chan and G.Z. Zheng, *Tetrahedron Lett.*, 1993, **34**, 3095.
29 P. Hudson and P.J. Parsons, *Synlett*, 1992, 867.
30 G.A. Molander and J.A. McKie, *J. Am. Chem. Soc.*, 1993, **115**, 5821.
31 D. Seyferth, R.M. Weinstein, R.C. Hui, W.-L. Wang, and C.M. Archer, *J. Org. Chem.*, 1992, **57**, 5620.
32 J.H. Penn and W.H. Owens, *Tetrahedron Lett.*, 1992, **33**, 3737.
33 H. Kuniyasu, A. Ogawa, and N. Sonoda, *Tetrahedron Lett.*, 1993, **34**, 2491.
34 J.R. Waas, A.R. Sidduri, and P. Knochel, *Tetrahedron Lett.*, 1992, **33**, 3717.
35 A. Barco, S. Benetti, C. De Risi, G.P. Pollini, G. Spalluto, and V. Zanirato, *Tetrahedron Lett.*, 1993, **34**, 3907.
36 S. Hunig and M. Koch, *Chem. Ber.*, 1992, **125**, 1635.
37 D. Enders, D. Mannes, and G. Raabe, *Synlett*, 1992, 837.
38 T. Kauffmann, K.-U. Voss, and G. Neiteler, *Chem. Ber.*, 1993, **126**, 1453.
39 G. Cahiez and B. Laboue, *Tetrahedron Lett.*, 1992, **33**, 4439.
40 R.C. Larock and Y. Lu, *J. Org. Chem.*, 1993, **58**, 2846.
41 K.T. Kang, J.C. Lee, and J. S. U, *Tetrahedron Lett.*, 1992, **33**, 4953.
42 D. Shi, J. Chen, W. Chai, W. Chen, and T. Kao, *Tetrahedron Lett.*, 1993, **34**, 2963.
43 This reagent combination is known to efficiently deprotonate ethylmalonate. M.W. Rathke and P.J. Cowan, *J. Org. Chem.*, 1985, **50**, 2622.
44 R.J. Clay, T.A. Collom, G.L. Karrick, and J. Wemple, *Synthesis*, 1993, 290.
45 C. Kashima, X.C. Huang, Y. Harada, and A. Hosomi, *J. Org. Chem.*, 1993, **58**, 793.
46 G. Zadel and E. Breitmaier, *Angew. Chem. Int. Ed. Engl.*, 1992, **31**, 1035.
47 I. Ryu, M. Hasegawa, A. Kurihara, A. Ogawa, S. Tsunoi, and N. Sonoda, *Synlett*, 1993, 143.
48 I. Ryu, H. Yamazaki, A. Ogawa, N. Kambe, and N. Sonoda, *J. Am. Chem. Soc.*, 1993, **115**, 1187.
49 G.D. Cuny and S.L. Buchwald, *J. Am. Chem. Soc.*, 1993, **115**, 2066.
50 E. Billig, A.G. Abatjoglou, and D.R. Bryant, *U.S. Patents*, 1987, 4688651; 1988, 4769498.
51 N. Chatani, S. Ikeda, K. Ohe, and S. Murai, *J. Am. Chem. Soc.*, 1992, **114**, 9710.
52 W. Cabri, H. Candiani, A. Bedeschi, and S. Penco, *J. Org. Chem.*, 1992, **57**, 1481.
53 M. Larhed, C.M. Andersson, and A. Hallberg, *Acta Chem. Scand.*, 1993, **47**, 213.
54 S. Abe, N. Miyaura, and A. Suzuki, *Bull. Chem. Soc. Jpn*, 1992, **65**, 2863.
55 M. Tsukazaki and V. Snieckus, *Tetrahedron Lett.*, 1993, **34**, 411.
56 J.P. Bégué, D. Bonnet-Delpon, D. Mesureur, G. Née, and S.-W. Wu, *J. Org. Chem.*, 1992, **57**, 3807.
57 K. Kudo, K. Saigo, Y. Hashimoto, K. Saito, and M. Hasegawa, *Chem. Lett.*, 1992, 1449.
58 S. Nagahara, K. Maruoka, and H. Yamamoto, *Chem. Lett.*, 1992, 1193.
59 T. Mukaiyama and K. Suzuki, *Chem. Lett.*, 1992, 1751.
60 I.M. Downie, M.J. Earle, H. Heaney, and K.F. Shuhaibar, *Tetrahedron*, 1993, **49**, 4015.
61 C.S. Cho, K. Itotani, and S. Uemura, *J. Orgmet. Chem.*, 1993, **443**, 253.
62 T. Ishiyama, T. Oh-e, N. Miyaura, and A. Suzuki, *Tetrahedron Lett.*, 1992, **33**, 4465.
63 J.M. Brown, M. Pearson, J.T.B.H. Jastrzebski, and G. van Koten, *J. Chem. Soc., Chem. Commun.*, 1992, 1440.
64 E. Baciocchi, G.C. Rosato, C. Rol, and G.V. Sebastiani, *Tetrahedron Lett.*, 1992, **33**, 5437.
65 M. Ueshima and N. Saito, *Chem. Lett.*, 1992, 1341.
66 (*a*) S.-I. Murahashi, Y. Oda, T. Naota, and T. Kuwabara, *Tetrahedron Lett.*, 1993, **34**, 1299; (*b*) S.-I. Murahashi, Y. Oda, and T. Naota, *J. Am. Chem. Soc.*, 1992, **114**, 7913.
67 R.M. Moriarty, T.E. Hopkins, R.K. Vaid, B.K. Vaid, and S.G. Levy, *Synthesis*, 1992, 847.

68 C. Chen, D. Crich, and A. Papadatos, *J. Am. Chem. Soc.*, 1992, **114**, 8313.
69 R.A. Bunce and C.R. Harris, *J. Org. Chem.*, 1992, **57**, 6981.
70 W.A. Nugent and F.W. Hobbs Jr., *J. Org. Chem.*, 1986, **51**, 3376 and references therein.
71 E. Wada, J. Funakoshi, and S. Kanemasa, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 2456.
72 P. Wallace and S. Warren, *J. Chem. Soc., Perkin Trans. 1*, 1992, 3169.
73 C.E. Mowbray and G. Pattenden, *Tetrahedron Lett.*, 1993, **34**, 127.
74 P. Bovonsombat and E. McNelis, *Tetrahedron*, 1993, **49**, 1525.
75 Y. Itoh, S. Fujii, M. Nakatsuka, F. Kawamoto, and T. Saegusa, *Org. Synth. Coll. Vol. 6*, 1988, 327.
76 N. Iwasawa, S. Hayakawa, M. Funahashi, K. Isobe, and K. Narasaka, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 819.
77 K.I. Booker-Milburn, *Synlett*, 1992, 809.
78 D.P. Curran and M. Palovich, *Synlett*, 1992, 631.
79 X.-M. Wu, K. Funakoshi, and K. Sakai, *Tetrahedron Lett.*, 1992, **33**, 6331.
80 M. Franck-Neumann, E.L. Michelotti, R. Simler, and J.M. Vernier, *Tetrahedron Lett.*, 1992, **33**, 7361.
81 N. Jeong, S.J. Lee, B.Y. Lee, and Y.K. Chung, *Tetrahedron Lett.*, 1993, **34**, 4027.
82 R.B. Grossman, and S.L. Buchwald, *J. Org. Chem.*, 1992, **57**, 5803.
83 S.C. Berk, R.B. Grossman, and S.L. Buchwald, *J. Am. Chem. Soc.*, 1993, **115**, 4912.
84 C.A. Challener, W.D. Wulff, B.A. Anderson, S. Chamberlin, K.L. Faron, O.K. Kim, C.K. Murray, Y.-C. Xu, D.C. Yang, and S.D. Darling, *J. Am. Chem. Soc.*, 1993, **115**, 1359.
85 S.U. Tumer, J.W. Herndon, and L.A. McMullen, *J. Am. Chem. Soc.*, 1992, **114**, 8394.
86 A. Kirschning, G. Dräger, and J. Harders, *Synlett*, 1993, 289.
87 B. Fraser-Reid, B.J. Carthy, N.L. Holder, and M. Yunker, *Can. J. Chem.*, 1971, **49**, 3038.
88 S. Bhat, N. Chidambaram, and S. Chandrasekaran, *J. Chem. Soc., Chem. Commun.*, 1993, 651.
89 (*a*) Y. Matsushita, T. Matsui, and K. Sugamoto, *Chem. Lett.*, 1992, 1381; (*b*) Y. Matsushita, K. Sugamoto, and T. Matsui, *ibid.*, 1992, 2165.
90 M. Ihara, S. Suzuki, N. Taniguchi, and K. Fukumoto, *Synlett*, 1993, 435.
91 B.M. Trost and U. Kazmaier, *J. Am. Chem. Soc.*, 1992, **114**, 7933.
92 B.M. Trost, W. Brieden, and K.H. Baringhaus, *Angew. Chem. Int. Ed. Engl.*, 1992, **31**, 1335.
93 J.B. Baudin, S.A. Julia, and R. Lorne, *Bull. Soc. Chim. Fr.*, 1992, **129**, 440.
94 Y. Shigemasa, H. Oikawa, S.-I. Ohrai, H. Sashiwa, and H. Saimoto, *Bull. Chem. Soc. Jpn*, 1992, **65**, 2594.
95 I. Ojima, R.J. Donovan, M. Eguchi, W.R. Shay, P. Ingallina, A. Korda, and Q. Zheng, *Tetrahedron*, 1993, **49**, 5431.
96 I. Matsuda, A. Ogiso, S. Sato, and Y. Izumi, *J. Am. Chem. Soc.*, 1989, **111**, 2332.
97 I. Matsuda, J. Sakakibara, H. Inoue, and H. Nagashima, *Tetrahedron Lett.*, 1992, **33**, 5799.
98 A.R. Katritzky, I.V. Shcherbakova, R.D. Tack, and P.J. Steel, *Can. J. Chem.*, 1992, **70**, 2040.
99 P. Wipf and W. Xu, *Synlett*, 1992, 718.
100 H.C. Brown and V.K. Mahindroo, *Synlett*, 1992, 626; *Tetrahedron Asymm.*, 1993, **4**, 59.
101 J. Sisko, A. Balog, and D.P. Curran, *J. Org. Chem.*, 1992, **57**, 4341.
102 E. Bouhlel and B.B. Hassine, *Synth. Commun.*, 1992, **22**, 2183.
103 Y. Masuyama, T. Sakai, and Y. Kurusu, *Tetrahedron Lett.*, 1993, **34**, 653.
104 R. Lin, Y. Yu, and Y. Zhang, *Synth. Commun.*, 1993, **23**, 271.
105 M. Bellassoued and A. Majidi, *J. Org. Chem.*, 1993, **58**, 2517.
106 M. Yamaguchi, A. Hayashi, and M. Hirama, *J. Am. Chem. Soc.*, 1993, **115**, 3362.
107 H. Maeta and K. Suzuki, *Tetrahedron Lett.*, 1993, **34**, 341.
108 S. Kagabu, C. Shimizu, J. Takahashi, K. Hara, M. Koketsu, and M. Ishida, *Bull. Soc. Chim. Fr.*, 1992, **129**, 435.
109 L. Yu and Z. Wang, *J. Chem. Soc., Chem. Commun.*, 1993, 232.
110 M. Hatanaka, R. Imashiro, and I. Ueda, *Chem. Lett.*, 1992, 2253.
111 Y. Usuki, M. Iwaoka, and S. Tomoda, *J. Chem. Soc., Chem. Commun.*, 1992, 1149.
112 K.M. Kim, K.H. Chung, J.N. Kim, and E.K. Ryu, *Synthesis*, 1993, 283.
113 J. Ichikawa, N. Yokata, M. Kobayashi, and T. Minami, *Synlett*, 1993, 186.
114 J. Ichikawa, S. Hamada, T. Sonoda, and M. Kobayashi, *Tetrahedron Lett.*, 1992, **33**, 337.
115 M.E. Wright and B.B. Cochran, *J. Am. Chem. Soc.*, 1993, **115**, 2058.
116 M. Qui, C. Chen, A. Zhang, and X.J. Zhou, *Synth. Commun.*, 1992, **22**, 1529.
117 J. Chen, P. Lue, and X.J. Zhou, *Chin. J. Org. Chem.*, 1987, 459.
118 M.R. Leanna, T.J. Sowin, and H.E. Morton, *Tetrahedron Lett.*, 1992, **33**, 5029.
119 S.-I. Murahashi, T. Saito, H. Hanaoka, Y. Murakami, T. Naoto, H. Kumobayashi and S. Akutagawa, *J. Org. Chem.*, 1993, **58**, 2929.
120 See for example, T. Hashiyama, K. Morikawa, and K.B. Sharpless, *J. Org. Chem.*, 1992, **57**, 5067.
121 C. Gosmini, R. Sauvêtre, and J.F. Normant, *Bull. Soc. Chim. Fr.*, 1993, **130**, 236.
122 S.F.C. Dunn and R.F.W. Jackson, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2863.
123 A. Clerici and O. Porta, *J. Org. Chem.*, 1993, **58**, 2889.
124 M. Murakami, T. Kawano, H. Ito, and Y. Ito, *J. Org. Chem.*, 1993, **58**, 1458.
125 V. Kren, D.H.G. Crout, H. Dalton, D.W. Hutchinson, W. König, M.M. Turner, G. Dean, and N. Thomson, *J. Chem. Soc., Chem. Commun.*, 1993, 341.
126 P. Rochet, J.-M. Vatèle, and J. Gore, *Synlett.*, 1993, 105.
127 G.F. Koser, A.G. Releyni, A.N. Kalos, L. Rebrovic, and R.H. Wettach, *J. Org. Chem.*, 1982, **47**, 2487.
128 A. Tuncay, J.A. Dustman, G. Fisher, C.I. Tuncay, and K.S. Suslick, *Tetrahedron Lett.*, 1992, **33**, 7647.
129 R.M. Moriarty, B.A. Berguland, and R. Penmasta, *Tetrahedron Lett.*, 1992, **33**, 6065.
130 S. Rozen, E. Mishani, and M. Kol, *J. Am. Chem. Soc.*, 1992, **114**, 7643.
131 K. Krohn, K. Brüggmann, D. Döring, and P.G. Jones, *Chem. Ber.*, 1992, **125**, 2439.
132 T. Yamashita, K. Yamano, M. Yasuda, and K. Shima, *Chem. Lett.*, 1993, 627.
133 R. Rathore, Z. Lin, and J.K. Kochi, *Tetrahedron Lett.*, 1993, **34**, 1859.
134 C. Dell'Erba, M. Novi, G. Petrillo, and C. Tavani, *Tetrahedron*, 1993, **49**, 235.
135 P. Magnus and P. Rigollier, *Tetrahedron Lett.*, 1992, **33**, 6111.

136 R. Caputo, C. Ferreri, L. Longobardo, G. Palumbo, and S. Pedatella, *Synth. Commun.*, 1993, **23**, 1515.
137 T. Satoh, Y. Hayashi, Y. Mizu, and K. Yamakawa, *Tetrahedron Lett.*, 1992, **33**, 7181.
138 S. Nakatani, J.-I. Yoshida, and S. Isoe, *Tetrahedron*, 1993, **49**, 2011.
139 D.Y. Kim, K. Lee, and D.Y. Oh, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2451.
140 R.J. Mears and A. Whiting, *Tetrahedron*, 1993, **49**, 177.
141 A.D.M. Curtis, R.J. Mears, and A. Whiting, *Tetrahedron*, 1993, **49**, 187.
142 S. Raina, D. Bhuniya, and V.K. Singh, *Tetrahedron Lett.*, 1992, **33**, 6021.
143 P.C. Bulman-Page, A.E. Graham, and B.K. Park, *Tetrahedron*, 1992, **48**, 7265.
144 L. Lopez, G. Mele, A. Nacci, and L. Troisi, *Tetrahedron Lett.*, 1993, **34**, 3897.
145 M. Heintz, M. Devaud, H. Hébri, E. Duñach, and M. Troupel, *Tetrahedron*, 1993, **49**, 2249.
146 T.B. Rao and J.M. Rao, *Synth. Commun.*, 1993, **23**, 1527.
147 B.C. Ranu, S. Bhar, and R. Chakraborti, *J. Org. Chem.*, 1992, **57**, 7349.
148 S.M. Bromidge, D.A. Entwhistle, J. Goldstein, and B.S. Orleck, *Synth. Commun.*, 1993, **23**, 487.
149 T. Sato and S. Ariura, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 105.
150 U.T. Mueller-Westerhoff and M. Zhou, *Tetrahedron Lett.*, 1993, **34**, 571.
151 R.H. Mitchell and V.S. Iyer, *Tetrahedron Lett.*, 1993, **34**, 3683.
152 M. Pérez, A.M. Castaño, and A.M. Echavarren, *J. Org. Chem.*, 1992, **57**, 5047.
153 R.A. Haack, T.D. Penning, S.W. Djuric, and J.A. Dziuba, *Tetrahedron Lett.*. 1988, **29**, 2783.
154 T. Fujii, T. Hirao, and Y. Ohshiro, *Tetrahedron Lett.*, 1992, **33**, 5823.
155 A.B. Paolobelli, D. Latini, and R. Ruzziconi, *Tetrahedron Lett.*. 1993, **34**, 721.
156 (*a*) K. Narasaka, Y. Kohno, and S. Shimada, *Chem. Lett.*, 1993, 125; (*b*) K. Narasaka, T. Okauchi, and N. Arai, *ibid.*, 1992, 1229; (*c*) K. Narasaka, T. Okauchi, K. Tanaka, and M. Murakami, *ibid.*, 1992, 2099.
157 D.V. Gendin, P.A. Petrov, A.S. Mokov, and M.G. Voronkov, *Zh. Obsch. Khim.*, 1992, **62**, 2095.
158 J. Morey and J.M. Saá, *Tetrahedron*, 1993, **49**, 105.
159 A.S. Mitchell and R.A. Russell, *Tetrahedron Lett.*, 1993, **34**, 545.
160 M. Shimizu, Y. Watanabe, H. Orita, T. Hayakawa, and K. Takehira, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 1522.
161 R.L. Danheiser, D.S. Casebier, and J.L. Loebach, *Tetrahedron Lett.*, 1992, **33**, 1149.
162 Z. Yang, Y.X. Cui, H.N.C. Wong, R.J. Wang, T.C.W. Mak, H.M. Chang, and C.M. Lee, *Tetrahedron*, 1992, **48**, 3293.
163 R.F.C. Brown and F.W. Eastwood, *Synlett*, 1993, 9.
164 T. Iwaoka, T. Murahashi, M. Sato, and C. Kaneko, *Synthesis*, 1992, 977.
165 R. Leung-Toung and C. Wentrup, *Tetrahedron*, 1992, **48**, 7641.
166 R. Leung-Toung and C. Wentrup, *J. Org. Chem.*, 1992, **57**, 4850.
167 J. Hegmann, E. Ditterich, G. Huttner, M. Christl, E.M. Peters, K. Peters, and H.G. Von Schnering, *Chem. Ber.*, 1992, **125**, 1913.
168 C.O. Kappe, G. Färber, C. Wentrup, and G. Kollenz, *J. Org. Chem.*, 1992, **57**, 7078.
169 S. Akai, Y. Tsuzuki, S. Matsuda, S. Kitagaki, and Y. Kita, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2813.
170 D. Zhao and T.T. Tidwell, *J. Am. Chem. Soc.*, 1992, **114**, 10980.
171 T. Mosandl, C.O. Kappe, R. Flammang, and C. Wentrup, *J. Chem. Soc., Chem. Commun.*, 1992, 1571.
172 M. Uemura, T. Minami, M. Shiro, and Y. Hayashi, *J. Org. Chem.*, 1992, **57**, 5590.
173 (*a*) A. Choudhury and E.R. Thornton, *Tetrahedron Lett.*, 1993, **34**, 2221; (*b*) *idem., Tetrahedron*, 1992, **48**, 5701.
174 D. Enders, H. Dyker, and G. Raabe, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 421.
175 A. Vulpetti, A. Bernardi, C. Gennari, J.M. Goodman, and I. Paterson, *Tetrahedron*, 1993, **49**, 685.
176 C. Gennari, C.T. Hewkin, F. Molinari, A. Bernardi, A. Comotti, J.M. Goodman, and I. Paterson, *J. Org. Chem.*, 1992, **57**, 5173.
177 H.C. Brown, K. Ganesan, and R.K. Dhar, *J. Org. Chem.*, 1992, **57**, 3767.
178 H.C. Brown, K. Ganesan, and R.K. Dhar, *J. Org. Chem.*, 1993, **58**, 147.
179 E.J. Corey, C.L. Cywin, and T.D. Roper, *Tetrahedron Lett.*, 1992, **33**, 6907.
180 G.H.P. Roos, R.J. Haines, and C.E. Raab, *Synth. Commun.*, 1993, **23**, 1251.
181 T.K. Hollis, N.P. Robinson, and B. Bosnich, *Tetrahedron Lett.*, 1992, **33**, 6423.
182 S. Kobayashi, I. Hachiya, and T. Takahori, *Synthesis*, 1993, 371.
183 S. Kobayashi and I. Hachiya, *Tetrahedron Lett.*, 1992, **33**, 1625.
184 M.V. Deaton and M.A. Ciufolini, *Tetrahedron Lett.*, 1993, **34**, 2409.
185 (*a*) A.G. Myers, S.E. Kephart, and H. Chen, *J. Am. Chem. Soc.*, 1992, **114**, 7922; (*b*) S.E. Denmark, B.D. Griedel, and D.M. Coe, *J. Org. Chem.*, 1993, **58**, 988.
186 S. Kobayashi and K. Nishio, *J. Org. Chem.*, 1993, **58**, 2647.
187 Y. Masuyama, Y. Kobayashi, R. Yanagi, and Y. Kurusu, *Chem. Lett.*, 1992, 2039.
188 I. Shibata, T. Yamaguchi, A. Baba, and H. Matsuda, *Chem. Lett.*, 1993, 97.
189 E. Hasegawa, K.M. Ishiyama, T. Kato, T. Horaguchi, T. Shimizu, S. Tanaka, and Y. Yamashita, *J. Org. Chem.*, 1992, **57**, 5353.
190 S. Kim and J.S. Kol, *J. Chem. Soc., Chem. Commun.*, 1992, 1377. For a related sequence using the corresponding enol acetates, see V.H. Rawal and V. Krishnamurthy, *Tetrahedron Lett.*, 1992, **33**, 3439.
191 A. Degl'Innocenti, A. Mordini, S. Pecchi, D. Pinzani, G. Reginato, and A. Ricci, *Synlett*, 1992, 753.
192 Y. Masaki, T. Miura, and M. Ochiai, *Chem. Lett.*, 1993, 17.
193 S. Hillers, A. Niklaus, and O. Reiser, *J. Org. Chem.*, 1993, **58**, 3169.
194 T. Satoh, S. Motohashi, N. Tokutake, and Y. Yamakawa, *Bull. Chem. Soc. Jpn*, 1992, **65**, 2966.
195 A. Bernardi, P. Dotti, G. Poli, and C. Scolastico, *Tetrahedron*, 1992, **48**, 5597.
196 E.J. Corey and I. N. Houpis, *Tetrahedron Lett.*, 1993, **34**, 2421.
197 J. d'Angelo, D. Desmaële, F. Dumas, and A. Guingant, *Tetrahedron Asymm.*, 1992, **3**, 459.
198 K. Ando, Y. Takemasa, K. Tomioka, and K. Koga, *Tetrahedron*, 1993, **49**, 1579.
199 N. Fuji, K. Tanaka, and H. Miyamoto, *Tetrahedron Asymm.*, 1993, **4**, 247.
200 T. Yasukata and K. Koga, *Tetrahedron Asymm.*, 1993, **4**, 35.

201 B.J. Bunn, P.J. Cox, and N.S. Simpkins, *Tetrahedron.*, 1993, **49**, 207.
202 B.E. Rossiter, M. Eguchi, G. Miao, N.M. Swingle, A.E. Hernández, D. Vickers, A. Fluckiger, R.G. Patterson, and K.V. Reddy, *Tetrahedron*, 1993, **49**, 965.
203 M. Kanai, M. Koga, and K. Tomioka, *Tetrahedron Lett.*, 1992, **33**, 7193.
204 M. Spescha and G. Rihs, *Helv. Chim. Acta*, 1993, **76**, 1219.
205 A. Corma, M. Iglesias, M.V. Martin, J. Rubio, and F. Sánchez, *Tetrahedron Asymm.*, 1992, **3**, 845.
206 D. Enders, K.-J. Heider, and G. Raabe, *Angew. Chem. Int. Ed. Engl.*, 1993, **32**, 598.
207 S.A. Hitchcock and G. Pattenden, *Tetrahedron Lett.*, 1992, **33**, 4843.