Aldehydes and ketones

PATRICK G. STEEL

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

Reviewing the literature published between October 1994 and September 1995
Continuing the coverage in *Contemporary Organic Synthesis*, 1995, **2**, 151

1 Synthesis of saturated aldehydes and ketones
1.1 Redox methods
1.2 Umpolung methods
1.3 General methods
2 Synthesis of aromatic aldehydes and ketones
3 Synthesis of cyclic ketones
4 Protection and deprotection strategies
5 Synthesis of functionalised aldehydes and ketones
5.1 Unsaturated aldehydes and ketones
5.2 α-Heteroatom substituted aldehydes and ketones
5.3 Dicarbonyl compounds
6 Reactions of aldehydes and ketones
6.1 The aldol reaction and other enolate additions
6.2 Conjugate addition reactions
7 References

1 Synthesis of saturated aldehydes and ketones

1.1 Redox methods

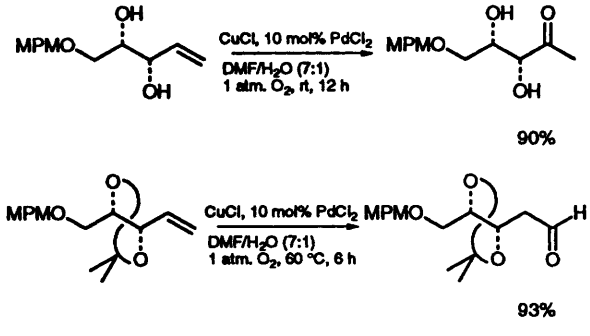
The Oppenauer oxidation forms a classical method for the conversion of alcohols to carbonyl compounds. Recent developments in the general area of Oppenauer–Meerwein–Ponndorf–Verley redox processes have been reviewed.[1] Oppenauer type oxidations can also be achieved through the mediation of zirconocene derived catalysts although this latter route does require the use of one equivalent of a sacrificial aldehyde.[2]

Chromium reagents retain a predominant role in this oxidation, although there is still demand for more convenient procedures. In this respect, the use of polychromates have been advocated as the reagents of choice.[3] These not only provide equivalent yields and selectivities, as do PCC and PDC, but are much cheaper. Similarly 18-crown-6 complexes of various chromate salts have been developed as more soluble, non-hygroscopic alternatives to PCC.[4] Other enhancements in this area have focused on the use of sub-stoichiometric quantities of chromium salts in the presence of co-oxidants such as sodium percarbonate.[5,6] In the second of these reports it has been found that the use of phase transfer catalysis provides enhanced efficiency although simple primary aliphatic alcohols are prone to over-oxidation. This proviso also applies to many of the reported alternatives to chromium catalysts which have included complexes based on palladium,[7] cobalt,[8] rhenium[9] and ruthenium.[10] However, ruthenium porphyrin catalysts are suitable for the $^1O_2$ mediated oxidation of the complete spectrum of alcohols.[11]

C–H bond activation can be competitive with such ruthenium catalysts and this aspect has been exploited in the direct synthesis of carbonyl compounds from hydrocarbons. The use of peracids as the co-oxidant has been shown to provide much better conversions and ketone: alcohol selectivity than the previously favoured TBHP.[12] Similar transformations, albeit with lower efficiencies, have been reported for a variety of other systems[13] and in general, at present, the transformation is only synthetically viable for benzylic methylene units.[14]

Modifications to the direct oxidation of alkenes to carbonyl groups – the Wacker reaction – have been reported. In particular, the use of β-cyclodextrins has been advocated for the oxidation of higher α-olefins. Whilst, as phase transfer catalysis, there is some precedent for this observation, this latest report utilises partially methylated cyclodextrins to provide optimal yields, rates and selectivities.[15] Interestingly, it has been shown that the regiochemistry of the Wacker oxidation can be controlled by simple variations in substrate structure (**Scheme 1**).[16]

Amongst the more popular oxidants employed today is the Dess–Martin periodinane. Recent reports have suggested that the addition of a stoichiometric amount of water can provide a more



Scheme 1

effective oxidant.[17] The authors' comment on the effect of prevailing humidity illustrate the difficulties that can arise. In this respect it has been noted that the use of *o*-iodoxybenzoic acid, which is the precursor to the Dess–Martin reagent, is not only an effective and selective oxidant but is less sensitive to moisture. The only drawback to this reagent is the requirement for DMSO as the solvent.[18]

Perfluoroalkyl oxaziridines have been employed in the conversion of *sec*-alkyl ethers into the corresponding ketones in good yield. Similar transformations have previously been reported with dimethyl dioxirane although this new modification appears more facile.[19] The latter reagent has been advocated as the reagent of choice for the selective oxidation of the secondary alcohol of cyclic and α- and β-linear diols. For saturated linear diols hydrogen peroxide in the presence of TS-1 zeolite proves more effective.[20] This combination is also effective for the oxidation of secondary benzylic amines although oxime formation is competitive.[21] Oximes may be converted to the corresponding carbonyl compound on treatment with manganese dioxide; under these mild conditions α,β-unsaturated carbonyl groups do not suffer from olefin isomerisation.[22] Similar conversions are also possible using copper nitrate or silver carbonate supported on silica or bentonite clay respectively[23] (see also Section 4). Enamines undergo oxidative cleavage to the homologous ketone upon treatment with a variety of reagents. A systematic survey on the use of potassium dichromate has shown that a biphasic solvent mixture can help inhibit over-oxidation which is a problem for substrates lacking β-substituents.[24]

Approaches that minimise side products are of interest and in this respect the electrochemically mediated oxidation of primary and secondary alcohols has been reported.[25] In general these procedures appear to be more effective with benzylic alcohol substrates.[26] In a similar vein, Pirrung has reported that the photolysis of substituted benzoylformate esters affords the corresponding ketones in good yield.[27] The relatively long wavelength employed means that most common chromophores are unaffected by this transformation. Minimisation of the problems associated with heavy metal oxidants can also be achieved through the use of supported reagents: reviews on the use of silicates[28] and zirconia[29] have appeared. Enzymatic oxidation is also another possibility which can result in a kinetic resolution of suitably structured alcohols.[30] Procedures for the efficient, mild oxidative cleavage of 5-substituted furfurals to γ-ketoesters[31] and nitroalkenes to the corresponding ketone[32] have been published.

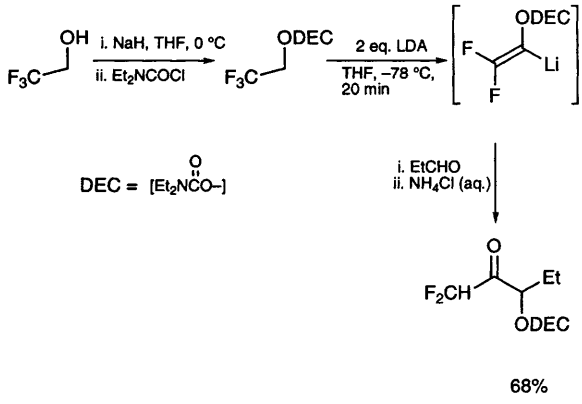
Selective reduction of acid chlorides has been recognised as an efficient method for aldehyde synthesis. Excellent yields are obtained in the zinc–copper couple mediated reduction of an *in situ* generated acyl phosphonium salt.[33] Transfer hydrogenation remains a favourite method for the conjugate reduction of enones. Aqueous phase reductions are possible using the water soluble complex, $Rh[(ptah)(pta)_2Cl]Cl$ {where pta is 1,3,5 triaza-7-phosphaadamantane}.[34] Further reports have appeared on the use of the ammonium formate/Pd–C system which may be employed in the presence of both non-conjugated olefins and carbonyl groups.[35] Similar claims have been made for the use of sodium dithionate in water–dioxane solvent systems. Contrary to previous reports it is suggested that the use of phase transfer catalysis is detrimental to the chemoselectivity.[36]

1.2 Umpolung methods

Nucleophilic acyl radicals can be considered as umpolung reagents and this area remains one of some considerable activity. Aryl selenides[37] and chromium carbene complexes[38] are both suitable precursors. The latter combine with most electrophilic acceptor olefins although efficient yields are only obtained with aromatic carbene complexes which lack *ortho* substituents. Electrochemical reduction of an acyl chloride provides an alternative entry point and the resultant radical combines with carbon dioxide to produce α-keto-acids in moderate yields.[39] Similar products can be more efficiently accessed through the use of lithiated ethoxyacetylene. Treatment of the initial adduct with neutral $KMnO_4$ affords the β-hydroxy α-keto ester. If aldehydes are used as the substrate this can provide a very rapid access to 1,2,3-tricarbonyl species.[40]

Collman's reagent, $Na_2[Fe(CO)_4]$, provides a number of routes to ketones. However, it is an extremely pyrophoric compound and this has restricted its use. The corresponding potassium salt, introduced by Yamashita, is much more stable and a simplified preparation has recently been published.[41]

In an elegant series of papers, Percy and co-workers have illustrated the use of protected 1,1,1-trifluoroethanol as a precursor to a variety of α,α-difluoro ketones (**Scheme 2**).[42] α-Pefluoroalkyl aldehydes can be accessed from the treatment of perfluoroalkyl ketones with trimethylsilylthiazole.[43] This represents the first reported addition of this



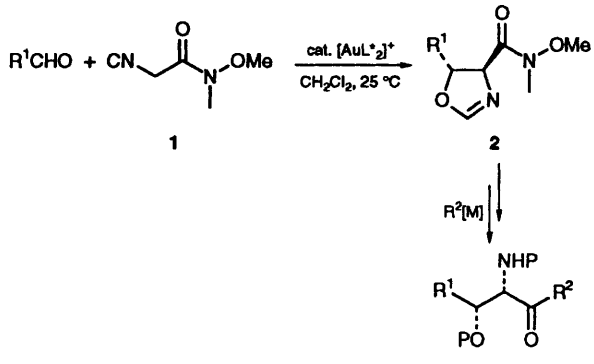
Scheme 2

umpolung reagent to ketones and reflects the increased reactivity due to the perfluoroalkyl group.

β-Chlorovinyl acetals undergo facile lithium–halogen exchange and as such represent a β-acyl vinyl anion equivalent.[44] The generation of α-alkoxyvinyllithium is enhanced if tetrahydropyran is used as the solvent since this avoids contamination with acetaldehyde enolate which can be a problem in THF.[45] Similarly δ-thio ketals can function as bis-homoenolate equivalents.[46] Finally, cyanophosphonates may be employed as asymmetric cyanohydrin equivalents, undergoing alkylation with high diastereoselectivity.[47]

1.3 General methods

Predominant in the modern repertoire for the preparation of ketones (and aldehydes) from a carboxylate function is the Weinreb amide, RC(=O)N(OMe)Me, and these can be efficiently prepared from the free acid using bromomethyl pyridinium iodide as a relatively inexpensive coupling agent.[48] Alternatively, esters may be directly converted to the corresponding ketone through consecutive treatment with the amine hydrochloride followed by 2 equiv. of the appropriate organometallic.[49] The amide is sufficiently stable to be compatible with a number of other synthetic transformations. For example, the asymmetric aldol reaction of *N*-methoxy-*N*-methyl-α-isocyanoacetamide **1** affords the corresponding oxazoline **2** which may subsequently be combined with a range of organometallic reagents to provide access to both amino and hydroxy substituted ketones and aldehydes (**Scheme 3**).[50]



Scheme 3

A number of alternative leaving groups have been developed including piperidino carbamates which couple with the complete gamut of unhindered organolithiums to provide symmetrical ketones in excellent yield.[51] Unsymmetrical ketones are accessible through the use of acyl-1,2-diazoles[52] or imidazole based hydrazines.[53] The former also react with Reformatsky reagents to afford β-keto esters in moderate to good yield, whilst the latter, on reduction with DIBALH, provide aldehydes in excellent yield. Although acyl chlorides are normally too reactive to be used in this context it has been reported that *in situ* generated lithium tetra-alkylgallates do not add to ketones and can be employed in this respect. However, the difference in the migratory aptitude of the gallate substituents [Br > Ph > PhC≡C > primary alkyl > secondary alkyl] is not always large and mixtures of products can result. In general, alkynyl transfer can be more effectively achieved using thallium reagents.[54]

Full details on the scope and limitations of the sonochemical Barbier reaction have been published.[55] Trifluoromethyl ketones can be obtained through the *in situ* lithium–halogen exchange reaction between alkyl iodides and one equivalent of *tert*-butyllithium in the presence of a fluoroacyl cation equivalent.[56] The stoichiometry of this process is crucial for good yields to be obtained. The same products are produced in the reaction of acid chlorides with trifluoroacetic anhydride.[57]

A similar synthesis of aliphatic β-keto esters can be achieved from the half ester of malonic acid.[58] Alternatively, α-bromo esters undergo a Claisen type condensation with concomitant reduction of the C–Br bond on treatment with samarium iodide (see also Section 6.1).[59] These and other syntheses of β-keto esters have been reviewed.[60]

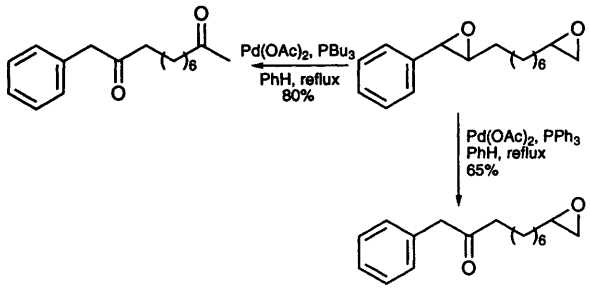
A trifluoromethoxy group is essential in the free radical mediated synthesis of α-keto esters from α-alkoxyacrylates.[61] α-Epoxy esters undergo low temperature addition of organometallics to afford the corresponding ketone in good yield.[62] The presence of trimethylsilyl chloride is beneficial and becomes essential if Grignard reagents are used. 2-Tetrahydrofuranyl carboxylate is converted to the corresponding ketone on reaction with 2 equiv. of an organometallic nucleophile; the various options for this particular conversion have been surveyed.[63] The resultant tetrahydrofuranyl ketones are readily cleaved to the corresponding ω-hydroxy ketone on reaction with SmI_2. This transformation proceeds via the samarium enolate which may be efficiently trapped with a range of electrophiles.[64] Homologous β-tetrahydrofuryl ketones can be accessed through a palladium mediated tandem radical cyclisation–carbonylation of alkyl 9-BBN derivatives. This report confirms the radical mediated nature of this previously reported route to acyclic ketones.[65]

β-Keto amides are produced in the lanthanide mediated coupling of azaketones and aldehydes.[66] The intermediate α-imino-oxetanes can also be used to produce β-lactams. A β-keto acylsilane is produced in the unusual aldol coupling of an acylsilane with excess benzaldehyde. However, the yield is only moderate and the generality was not stated.[67]

On treatment with lead tetraacetate and carbon monoxide, tertiary cyclobutanols undergo ring opening acylation to afford substituted δ-keto esters in moderate yields.[68] Isomeric oxetanes undergo rhodium mediated carbonylative ring opening to produce the δ-silyloxy aldehyde.[69] Unlike earlier

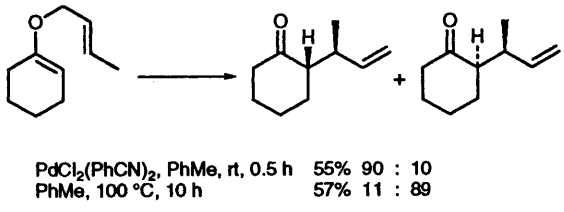
reports, this modification only requires stoichiometric quantities of the starting oxetane.

Epoxides undergo rearrangement to carbonyl compounds on treatment with Lewis acids; there have been a number of reports in this area focusing on the aldehyde:ketone selectivity obtainable.[70] With styrene oxides, the use of strong Lewis acids may be avoided through the simple use of silica gel.[71] Very high chemoselectivity is obtained via the utilisation of different phosphine ligands in the palladium acetate mediated version of this reaction (**Scheme 4**).[72]



Scheme 4

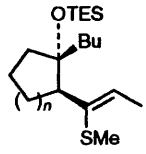
Palladium catalysis is also effective in promoting the Claisen rearrangement and this can produce different stereochemical outcomes to that observed in the thermal modification (**Scheme 5**).[73] In the presence of rhodium salts the Cope rearrangement can also be catalysed although under these conditions the product aldehyde is prone to undergo an intramolecular hydroacylation.[74]



Scheme 5

In the presence of $TiCl_4$, allylsilanes add to α-diketone ketals to afford a variety of ketonic products via simple acetal substitution followed by pinacol type rearrangements.[75] Treatment of MEM ethers of δ-hydroxy-(*E*)-vinylsilanes with the same Lewis acid results in C—C bond cleavage and the production of ketones.[76] The corresponding (*Z*)-vinylsilane leads preferentially to dihydropyran products. Reactions of alkenyl sulfides **3** also occur with C—C bond cleavage and the Lewis acid mediated reactions of this nucleophile have been extended to include conjugate addition, which proceeds with excellent stereoselectivity.[77]

Full details have appeared on the *trialkyl*-aluminium promoted homologation of aldehydes and ketones with diazoalkanes,[78] the aluminium



3

trichloride induced rearrangement of aryl *tert* butyl ketones[79] and the palladium mediated addition of alcohols to chiral methacrylates to afford α-chiral aldehydes masked as the corresponding acetal.[80] Aldehydes and ketones masked as the enol ether are accessed through the coupling of an α-methoxy sulfone with a second lithiated sulfone.[81]

Mixed acetals are produced from the reaction of alcoholic solutions of allylic ethers with CO in the presence of dicobalt octacarbonyl.[82] The free aldehyde is the product when water is used as the solvent. Alkynols are converted to ketones in a tandem hydrosilylation–isomerisation process catalysed by cationic rhodium(I) complexes.[83] Although the reaction can be carried out in a single pot the yields are better if each step is achieved separately.

Developments in hydroformylation continue to appear with a particular focus on the stereoselectivity of the process.[84] Reports on the regioselectivity of dienes,[85] acrylate[86] and vinyl heterocycles[87] have been published. However, the main body of work in this area has been concerned with control of the absolute stereochemistry and in this respect a number of new chiral ligands have been identified.[88] Labile aldehydes can be masked as the acetal *in situ* through the use of triethyl orthoformate; further developments in this strategy allow this to be achieved at lower pressures and higher rates than had previously been reported.[89] Other enhancements to the efficiency of the hydroformylation process have included heterogenisation or biphasic/supported aqueous phase media.[90]

2 Synthesis of aromatic aldehydes and ketones

Aryl carbonyl compounds can be accessed through benzylic hydrocarbon oxidation; a number of procedures in this area have been published.[91] Whilst many of these suffer from competitive over-oxidation this is not the case for the enzymatic process utilising laccase.[92] In an interesting variant, trichloromethyl aryl groups can be converted to the corresponding aldehyde on reaction with pyridine; a mechanism for this transformation has been proposed.[93] Oxidation of the corresponding benzyl alcohol is facile and new protocols and reagents for this conversion have been reported.[94]

Calcium borohydride–cyclooctadiene affords a reagent for the efficient reduction of aryl and other non-enolisable esters to the corresponding aldehyde.[95]

Friedel–Crafts methods remain one of the most popular options for the synthesis of aryl carbonyl

units. Whereas most arenes undergo alkylation with lactones, *N*-methylpyrrole affords the acylated product in good yield.[96] The regiochemistry of substitution of *N*-sulfonyl pyrroles can be controlled by the nature of the reaction solvent.[97] For example, nitromethane favours a strongly dissociated acylium ion which leads to exclusive 3-substitution. Simple acylation can be achieved under very mild conditions using a combination of anhydride, dimethyl sulfide and boron trifluoride.[98] This combination is equivalent in reactivity to acetyl triflate but is much cheaper and simpler in operation. Reports on the efficacy of a number of alternative Lewis acids have been published including rhenium pentacarbonyl bromide,[99] hafnium triflate[100] and lanthanide salts of superacids.[101] The latter are claimed to be even more effective than the previously reported triflates.[102]

In addition to promoting the Friedel–Crafts reaction, scandium triflate is also an effective catalyst for the Fries rearrangement.[103] This transformation can also be initiated photochemically; although this produces isomeric mixtures the product ratios can be enhanced through the appropriate choice of solvent.[104] Similar problems befall the synthesis of *o*-hydroxyphenyl acetones via the Carroll rearrangement of aryl acetoacetates derived from the reaction of *p*-quinols and diketene.[105]

Enhanced reactivity with acylating agents can be obtained through the generation of an aryl organometallic reagent which also overcomes problem or regiocontrol. Direct generation of halo aryl copper species is possible from haloiodoarenes and activated copper.[106] Similar iodoarenes can be converted to the corresponding trifluoromethyl ketone via conversion to the arylstannane.[107] This latter transformation is catalysed by palladium complexes and a variety of carbonylation processes are similarly promoted.[108] A general review of the synthesis of diaryl ketones by such a strategy has been published.[109] In related processes triarylbismuth may be employed as the arene source in a rhodium(I) catalysed coupling reaction,[110] whilst iron pentacarbonyl can be used in an aqueous phase version of this synthesis.[111] Directed metallation of the arene provides an alternative option for regiocontrol.[112] Such a process may then be combined with a transition metal catalysed acylation sequence.[113] In an interesting variant on this strategy activation of the *ortho* hydrogen of an aromatic ketone is possible on treatment with the ruthenium dihydro complex $[Rh(H)_2CO(PPh_3)_3]$, and a full account of this work has been published.[114]

Benzyne combines with ketene silylacetals with high selectivity to provide access to benzocyclobutanones with the regiochemistry controlled by the nature of the aryne substituents.[115] The Lewis acid promoted rearrangement of 3-aryl-β-sultams provides aryl ketones or substituted arylethanals in good overall yield.[116] Aryl methyl ketones are obtained through the reaction of Fischer carbene complexes with chloromethyllithium.[117] Finally, two unusual transformations which produce aryl carbonyl units have appeared. Flash vacuum pyrolysis of 1,2-dialkoxybenzene affords mixtures of *o*-hydroxybenzaldehyde[118] whilst treatment of α,β-epoxy ketones with the Vilsmeier reagent leads to moderate yields of 2,3-dichlorobenzaldehydes.[119]

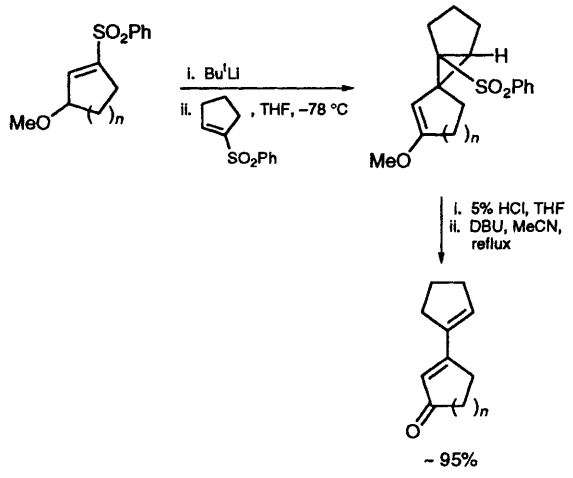
3 Synthesis of cyclic ketones

Cyclopropanone ketals are routinely accessed from ethyl β-halopropionate by treatment with sodium metal and trimethylchlorosilane. However, these conditions can cause difficulties with more complex substrates and the use of highly activated zinc has been advocated.[120] The ring strain associated with cyclopropanes also aids the oxidation of bicyclo[3.1.0]hexanols to the corresponding 3-bromomethyl ketone.[121] Fully protected glycols may be oxidised to 2,3-dihydropyranones by hypervalent iodine reagents.[122] The same class of products are also accessible through the asymmetric heteroatom Diels–Alder reaction.[123]

Oxidation of allylic, benzylic or cyclic alcohols can be achieved by conversion to the diazoacetate followed by rhodium mediated diazoalkane decomposition.[124] Although the yields are only moderate this represents the first reported examples of this particular pathway. The normal pathway for transition metal catalysed decomposition of diazocarbonyl compounds is via C–H insertion and this has been exploited in a number of cyclic ketone syntheses.[125] Cyclic α-diazo β-diketones undergo a photochemically induced ring contraction to the corresponding α-amido cyclic ketone.[126] Full details have appeared on the thermolysis of bis(diazomethyl ketones) to afford cyclic enones.[127] Both five- and six-membered rings can be generated with, notably, *trans*-hydroindenones being accessible in excellent yield, albeit with the proviso that non-symmetrical substrates produce isomeric mixtures. Owing to difficulties in the preparation of the corresponding bis(diazomethylketones), synthesis of *cis*-hydroindenones is limited in efficiency. However, these are routinely accessible by classical methods and consequently this represents a complementary study.

The synthesis of cyclopentenones is dominated by the Pauson–Khand reaction and variants thereof.[128] Developments have included the extension to different substrates including allene,[129] electron deficient alkenes[130] and terminal alkynes.[131] The latter also appear in a catalytic rhodium mediated cyclisation of diynes.[132] Alkynes combine with β-amino Fischer chromium carbene complexes to form enaminocyclopentenones.[133] Different isomeric products are obtained depending on the solvent used. Whereas the vinylcyclopropane–cyclopentene rearrangement proceeds with loss of stereochemical integrity, the corresponding rearrangement of cyclopropylchromium carbene complexes occur with retention of configuration.[134]

Cyclopropyl intermediates are also involved in the condensation of γ-methoxy vinyl sulfones with a second vinyl sulfone to afford, after hydrolysis, β-cyclopentyl dienones (**Scheme 6**).[135] This is a further modification of previously reported methodology for the synthesis of β-alkylated cyclic enones.[136] Developments to this strategy have now extended this approach to the synthesis of cyclopentenone derivatives which previously underwent preferential self condensation.[137] Sulfone stabilised anions are also employed in the annulation of a cyclopentanone ring to a pre-existing cyclic α-sulfonium enone.[138]

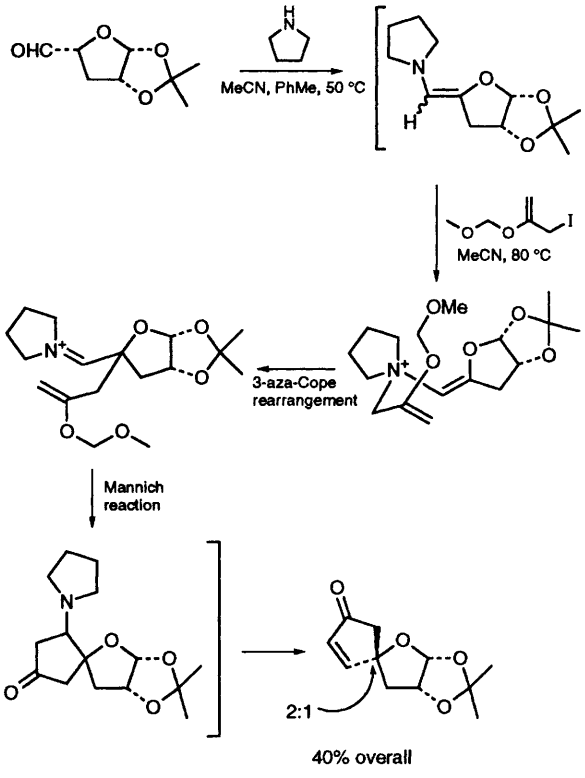


Scheme 6

Nazarov cyclisations frequently produce complex mixtures of isomeric cyclopentenones. However, substrates containing a difluoromethylene unit react rapidly at room temperature to afford a single isomer in excellent yield, and this result is attributed to the β-cation destabilising effect of fluorine. However, for optimal yields the use of highly solvating 1,1,1,3,3,3-hexafluoropropanol is required as a cosolvent.[139] 2,4-Diene-1,6-diones undergo intramolecular Michael reactions to afford cyclopentenones in moderate yields although the substituent requirements for this pathway are high.[140]

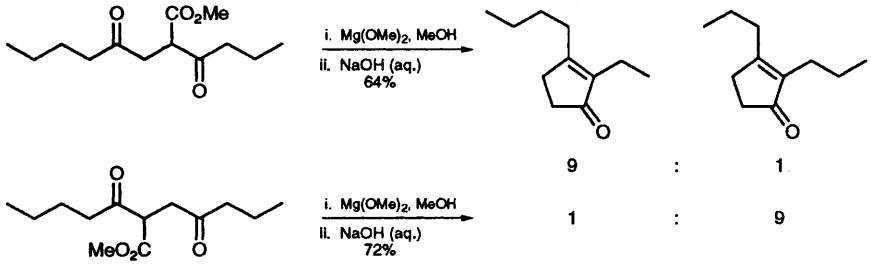
The nature of the substitution pattern in 1,4-diketones can markedly effect the chemoselectivity of the aldol cyclisation (**Scheme 7**).[141] The basic nature of many of these cyclisations frequently results in isomerisation of the olefin. This can be avoided in a 'Robinson type annulation' of cyclopentenones through a strategy involving alkylation with (*Z*)-3-bromo-1-iodopropene.[142]

One pot, five step (imine–enamine tautomerisation, alkylation, aza-Cope rearrangement, Mannich cyclisation, elimination) strategy has been developed for the synthesis of cyclopentenones from aldehydes (**Scheme 8**). However, in the single example given the level of diastereoselection obtained at the newly formed chiral centre was small.[143]



Scheme 8

A number of Wittig based strategies have been developed for the synthesis of cyclopentenones.[144] Notably, stabilised Wittig reagents (*e.g.* $Ph_3P{=}CHCO_2Bu^t$) couple with vinyl vicinal tricarbonyl units to produce a cyclic enone in good yield. In a similar fashion a variety of stabilised carbon nucleophiles react to produce cyclopentanediones.[145] Such stabilised Wittig reagents



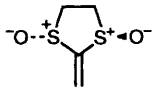
Scheme 7

combine with cyclopropanones in a general ring expansion sequence to substituted cyclobutanones from cyclobuta-1,3-diones[148] whilst an efficient ultrasound promoted route to the 1,2-dione has been published.[149] Ring expansion of cyclobutanones to cyclopentanones is simply and efficiently achieved upon treatment with samarium iodide–diiodomethane, although mixtures of regioisomers occur with non-symmetrical substrates.[150] Reaction of carbenoids with an alkyne affords 2-ynones in addition to the expected cyclopropenone. A recent report has developed this observation into a general method for the ring expansion of cyclic alkynes to the homologous 2-ynones.[151] A large number of other reports have appeared, detailing ring expansion routes to cyclic ketones promoted by – amongst others[152] – Lewis acids,[153] oxidising agents[154] and free radical initiators.[155] However, many of these involve multiple steps and/or are substrate specific, and although efficient, the overall yields are only moderate.

Medium to large ring-fused tricyclic ketones can be prepared by a sequential Type 2 intramolecular Diels–Alder cycloaddition – ozonolysis – aldol condensation strategy.[156] Polycyclic ketones are obtained with excellent control via tandem Diels–Alder reactions.[157] Similar products have also been prepared through a tandem radical cyclisation–Diels–Alder cycloaddition approach.

Seven-membered ring ketones are approachable through the $TiCl_4$-promoted intramolecular [4+3] cycloaddition reaction of oxyallyl cations. Harmata has examined the diastereoselectivity of this process.[158] Oxyallyl cations also combine with olefins in a [3+2] cycloaddition to produce cyclopentenones. In contrast to most earlier reports, an excess of the olefin trap is not required when bis-sulfenyl ketones are used as the oxyallyl cation precursor.[159] [6+2] Cycloadditions of chromium cycloheptatriene complexes with heterocumulenes are precedented.[160] A recent report has demonstrated that chromium carbenes are also suitable 2π components in this process although the present yields are low.

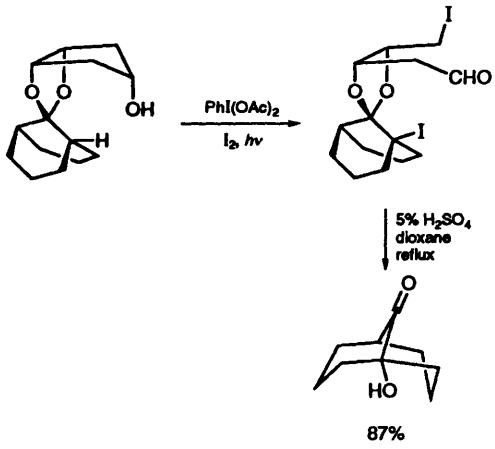
The development of efficient asymmetric ketene equivalents continues. The dithiolane dioxide **4** proves to be both accessible and selective.[161] An alternative strategy is to use a chiral vinyl sulfate in an intramolecular cycloaddition.[162]



4

Bicyclic ketones have also been accessed from substituted cyclic ketones with the crucial bond formation achieved either by anionic[163] or free radical cyclisation.[164] The latter, mediated by $Mn(OAc)_3$, provides a method for free radical alkylation with alkenes, albeit one limited to products which cannot undergo enolisation.

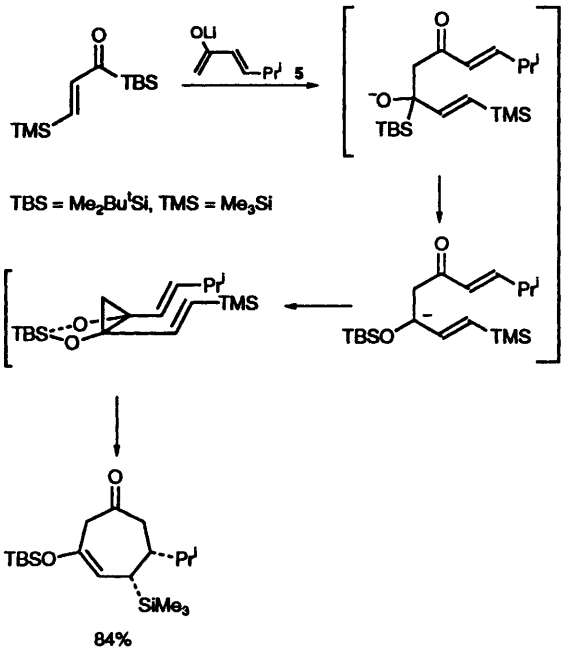
Bridgehead functionalisation of bicyclic ketones is normally difficult and Eaton has introduced the 1,2,4-trihydroxycyclopentane ketal as a controlling group for this operation (**Scheme 9**).[165]



87%

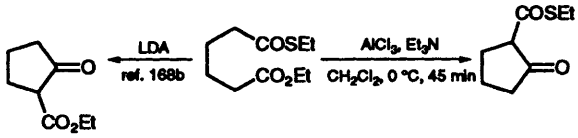
Scheme 9

Free radical cyclisation of δ-bromo-δ-stannylacylsilanes provides moderate to excellent yields of the cyclopentanone derived silyl enol ether via a Brook type rearrangement of an α-silyloxyl radical.[166] The anionic Brook rearrangement forms an integral part of the condensation of β-silyl α,β-unsaturated acylsilanes with the conjugated dienolate **5** (**Scheme 10**).[167]



Scheme 10

Cyclohexanes are classically prepared by the Dieckman cyclisation. This can theoretically proceed to give two products. Control of the regiochemistry is possible through either base or Lewis acid

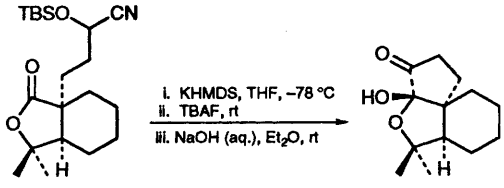


Scheme 11

promotion (**Scheme 11**).[168] Attempts to achieve chemoselectivity through the use of Weinreb amides is not always successful with the product ratio depending on the precise conditions employed.[169] Although not intended, the Dieckman cyclisation of chiral bis-oxazolidinones can proceed with high diastereoselectivity and this can provide an efficient entry to enantiopure cyclohexanones.[170]

In a homologation of earlier reports cyclohexenones are prepared through the copper-catalysed addition of ω-ester functionalised organozinc reagents to ynoates.[171] Similar products are obtained in good yield from the ruthenium catalysed condensation of 2 equiv. of a β-ketoester with an allylic alcohol or amine.[172]

Finally, intramolecular umpolung strategies have been employed in the synthesis of cyclic ketones. Electrolytic reduction of α,ω-ketoacids in the presence of tributylphosphine affords the corresponding α-hydroxycyclic ketone in moderate yields.[173] The reaction is believed to proceed via reduction of an acyl phosphonium salt. Treatment of the cyanohydrin **6** with KHMDS leads after hydrolytic workup to the keto lactol **7** (**Scheme 12**), and this represents the first example of the reaction of a cyanohydrin anion with a lactone electrophile.[174]



Scheme 12

4 Protection and deprotection strategies

In the search for milder conditions for protection and deprotection, the use of diallyl acetals has been advocated. Selective deprotection is promoted by rhodium(I) catalysis whilst formation is routinely achieved following the Noyori protocol.[175] A modified version of this process has been developed for the mild introduction of the dioxolane acetal.[176]

α,β-Unsaturated aldehydes are efficiently protected as the dioxolane in the presence of $MgSO_4$.[177] A significant rate enhancement is observed in the formation of all dioxolanes through the use of microwave irradiation[178] whilst substrate selectivity is obtained in the presence of montmorillonite clays.[179] Methods for the selective protection of either component of α-keto aldehydes have been published.[180] Geminal diacetates have been advocated as acid-stable, base-labile protecting groups; their efficient synthesis can be achieved in the presence of a β-zeolite.[181]

Acetals may be converted to mixed acetals on treatment with appropriate nucleophiles (*e.g.* thiols, *etc.*) in the presence of a dicyano ketene acetal as a novel π acid catalyst.[182] Oxathiolanes can similarly be prepared through the use of TMSOTf or bismuth(III) salts as strong catalysts.[183] These also promote the formation of dithioacetals. Selectivity in the preparation of the latter is observed through the use of catalytic amounts of CAN (ceric ammonium nitrate) as the promoter. Aldehydes react with ketones and cyclic ketones in preference to acyclic and aromatic ketones.[184]

Selenium dioxide has been suggested as an efficient reagent for the deprotection of dithioacetals. However, an excess is required and the use of acetic acid as the solvent is essential.[185] Oxathiolanes are much more labile and these can readily be exchanged with a polymer bound nitrobenzaldehyde residue. The same reagent is also effective for the conversion of thioketones to ketones.[186]

Molybdenyl(VI) acetylacetonate proves to be a mild and efficient catalyst for the deprotection of a range of acetals and ketals.[187] The latter are efficiently cleaved by NO_2 but acetals undergo oxidation to α-hydroxy esters.[188] α-Chloro acetals are converted to the corresponding α-chloro aldehyde upon treatment with a combination of acetic anhydride and acetyl chloride. Although α-bromo acetals are substrates, halogen exchange also occurs.[189] Enol ethers represent an alternative mode of protection; an efficient mild synthesis of this functionality from chiral alcohols has been reported.[190]

Protection/deprotection strategies reduce synthetic efficiency; methodology which avoids this has been reported. Commins has previously reported that aldehydes could be masked *in situ* through the formation of amide base adducts. Higher stabilities in this process can be obtained through the use of Weinreb amide.[191] In a similar vein Yamamoto has extended his work on the protection of carbonyl groups through the use of bulky aluminium Lewis acids. In these latest reports the promotion of 1,4 (conjugate) addition to enones in preference to 1,2-addition at alkyllithium reagents is outlined.[192]

5 Synthesis of functionalised aldehydes and ketones

5.1 Unsaturated aldehydes and ketones

Oxidation of enol silanes (silyl enol ethers) to the corresponding enone using stoichiometric palladium

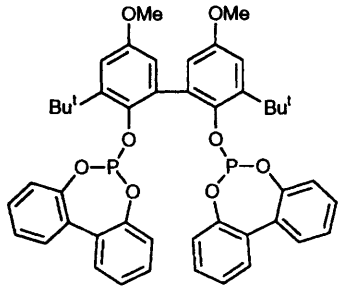
reagents is well established. Larock has developed a procedure in which this conversion can be achieved using catalytic quantities of the palladium salt.[193] Alternatively, this conversion can be efficiently realised using CAN in DMF.[194] Electrochemical oxidation of the corresponding enol acetate also provides the enone. However, this process is only efficient if a β-trimethylsilyl group is present.[195]

More traditionally, unsaturation is introduced in a two step procedure involving activation and elimination. This can be achieved in a one pot process using potassium enolates and methoxyphenyl sulfoxide as the electrophile.[196] Similarly the nitro group can function as the leaving group; this forms part of a multistep elongation of aldehydes to enediones.[197] Similar products can be obtained from the photochemical addition of $^3O_2$ to furans.[198] In this latter case the olefin is exclusively of *cis* geometry. Steroidal enediones are accessed through the PCC oxidation of the corresponding allylic alcohol.[199] α,β-Unsaturated aldehydes are formed on treatment of isoxazolines with methyl iodide. The yields are only moderate unless a second oxidation step follows.[200]

Oxidative cyclisation of anisole containing oximes promoted by Bu_4NReO_4 affords good yields of spirocyclic dienones.[201] Similar products are also obtained in the radical cyclisation of a functionalised quinol.[202] Linear dienones are formed in the palladium catalysed rearrangement of 2-acyl-3-vinyl aziridines.[203]

Aliphatic Friedel–Crafts type acylations have been explored as routes to unsaturated ketones using acyl fluoroborate salts or electrolytic reduction of acid chlorides to provide the electrophile.[204] Lewis acid catalysed addition of acid chlorides to enynes affords mixtures resulting from both 1,2- and 1,4-addition, with the allenyl ketone predominating as the degree of substitution of the enyne increases.[205] Alkynes also couple directly with aldehydes or ketones in the presence of tin halide–tertiary amine catalyst mixtures. Good *E/Z* selectivity is obtained whilst the use of trimethylsilyl chloride with ketone substrates affords the β,γ-unsaturated product.[206] Other β,γ-unsaturated ketones are available through the condensation of dienylmagnesium complexes with esters and lactones,[207] the trimethylsilyl chloride promoted deconjugation of β-bromo or β-iodo enones,[208] or the palladium mediated carbonylative coupling of organozinc reagents with various alkylating agents.[209]

γ,δ-Unsaturated aldehydes arise from the ruthenium catalysed coupling of alkynes with allylic alcohols.[210] Dienol derivatives undergo palladium catalysed condensation with propargyl carbonates in both inter- and intra-molecular fashion to produce mixtures of isomeric enals in moderate to good yield.[211] Similar results are obtained using vinylic diol carbonates.[212] Isomerisation of secondary prop-2-ynylic alcohols is possible on treatment with Wilkinson's catalyst in the presence of tributylphosphine. The nature of the phosphine is important as triisopropylphosphine affords allylic alcohols.[213] Rhodium catalysts are also important in the silaformylation of alkynes. A number of reports in this area have been forthcoming.[214] In related work the first example of germaformylation has been noted.[215] Hydroformylation of alkynes is frequently complicated by concomitant reduction to the saturated aldehyde. However, good yields of the desired enal can be obtained using the bisphosphite ligand **8** developed for alkene hydroformylation.[216] However, with non-symmetrical alkenes the regiochemistry is at best moderate.

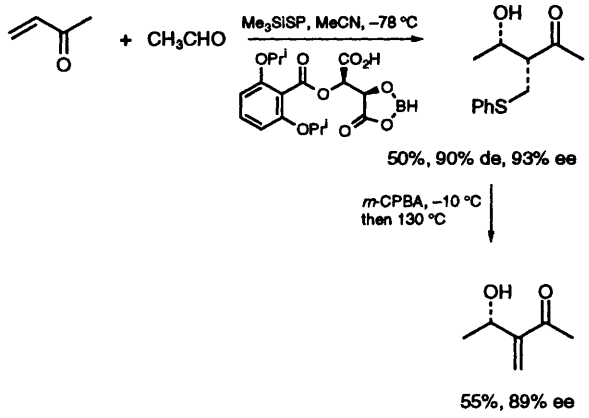


8

Full details have been published on the use of dioxolanyl salts as acyl equivalents for coupling with alkynyl borates.[217] There have been a particularly large number of reports for the elaboration of unsaturated trifluoromethyl ketones: these have involved reagents based on boron,[219] tellurium[220] and phosphorus.[221] Fluorine aids an efficient homologation of ketones to the corresponding enal through treatment with difluoromethyllithium.[222]

One of the most common methods for the generation of unsaturated ketones is via the Wittig reaction. The direct reaction of a stabilised Wittig reagent with the ozonide derived from a terminal alkene is possible but slow. This reaction is markedly accelerated by the addition of triethylamine.[223] Non-stabilised Wittig reagents afford mixtures of stereoisomers. *Cis* enals can be isomerised to the corresponding *trans* isomer on treatment with catalytic potassium carbonate and thioacetamide in DMF.[224] Conversion of unsymmetrical 1,3-diketones to the corresponding β-haloenone was first reported by Piers; this method affords the more sterically hindered ketone.[225] The alternative regiochemistry can now be attained in moderate yields by one of the three methods.[226]

α-Functionalisation of enones is readily achieved via the Bayliss–Hillman reaction. The first enantioselective strategy for this conversion has recently been developed (**Scheme 13**).[227] Related α-methylene ketones can be obtained through the iodine mediated oxidation of tertiary allylic alcohols[228] or through the palladium mediated carbonylative alkylation of bis-homoallenic alcohols.[229] A similar transformation is possible through the reaction with acyl tetracarbonyl cobalt.[230]



Scheme 13

5.2 α-Heteroatom substituted aldehydes and ketones

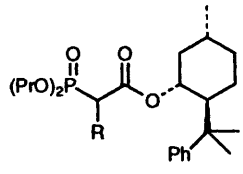
The most common strategy for the construction of α-hydroxy ketones is via enolate oxidation.[231] Improved conditions for the Rubottom oxidation of bicyclic silyl enol ethers have been claimed.[232] Oxidation of titanium enolates with *tert*-butylhydroperoxide (TBHP) is possible: this represents the first recorded use of this particular oxidant for this transformation.[233] Interestingly, with chiral ketones, modest to excellent diastereoselectivities are obtained. Fluoroalkyl analogues of Koser's reagent, $PhI(OTs)_2$ provide a stable convenient oxidant for the conversion of enol ethers to α-tosyloxy ketones.[234] Allenes are oxidised to α-ketols by hydrogen peroxide in the presence of catalytic peroxytungstophosphates,[235] whilst in the presence of a ruthenium catalyst and an oxygen atmosphere TEMPO selectively converts primary alcohols to the corresponding α-aldol.[236]

Dioxirane oxidation of symmetrical diols affords the corresponding ketol.[237] Homologation of an aldehyde to an α-ketol can be achieved under non-oxidising conditions through the reaction with benzotriazolylphenoxymethane.[238] Katritzky has also introduced other substituents into these benzotriazole based acylanion equivalents.[239] In addition to the reaction with carbonyl groups to afford functionalised ketols they also function as nucleophiles with a range of other electrophiles, *e.g.* enones. The use of functionalised methoxymethane derivatives is a development of the original procedure of Trost who introduced the phenylsulfenylmethoxymethane reagent for α-methoxy ketone synthesis. Improvements in this latter strategy are obtained thorugh the use of zirconium or hafnium tetrachloride to catalyse the pinacol type rearrangement.[240] In a similar vein, α-chloro carbonyl compounds may be accessed via treatment of the homologous carbonyl compound with lithiodichloromethylphenyl sulfoxide.[241] Sterically hindered ketones may be directly converted to the α-methoxyketone on treatment with a MeI–CCl_4–KOH combination under phase transfer conditions.[242]

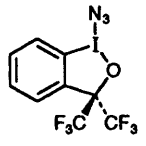
Conversion of an aryl epoxide to the corresponding α-silyloxyarylketones occurs with no loss of stereochemical integrity on treatment with trimethylsilyl triflate in DMSO.[243] In an approach to the bryostatins, an α-silyloxy epoxide is selectively converted to the corresponding α-keto diol in the presence of silver tetrafluoroborate,[244] whilst on treatment with $BF_3{\cdot}OEt_2$ bicyclo-α,β-epoxyacrylates undergo a regioselective rearrangement to α-acyloxy spirocycloalkanones.[245]

α-Hydroxy-acids, on treatment with a perfluoro acid anhydride, regioselectively afford the acyl perfluoroalkyl carbinol.[246] Although the mechanism of this process has not been elucidated it parallels that of the Dakin–West reaction of *N*-alkyl *N*-acyl amino acids.[247] The rearrangement of a ketose to the hydroxymethylene aldose is catalysed by nickel ethylenediamine complexes.[248] The Wittig rearrangement of chiral allyloxyhydrazones provides efficient routes to enantiomerically enriched (63–90% ee) α-hydroxycarbonyl compounds.[249] Hydrazones also prove to be effective chiral auxiliaries for the alkylation of protected hydroxyacetaldehydes.[250] A variety of other chiral auxiliary mediated strategies for the production of α-hydroxy or α-amino aldehydes and ketones have been delineated.[251] Both protected α-hydroxy and α-amino carboxylates may be selectively converted to the aldehyde or ketone.[252] In this respect the reaction of α-acetoxy acyl chlorides with organomanganese reagents to afford the α-acetoxy ketone with complete chemoselectivity and minimal stereochemical degradation is particularly noteworthy.[253]

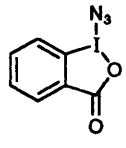
The generation of quarternary α-amino ketones through the rearrangement of β-hydroxy imines has been rendered enantioselective.[254] Enantiomeric α-amino aldehydes are produced *in situ* on reaction with the phenylmenthol containing phosphonate **9**.[255] Similar dynamic kinetic resolution strategies have also been employed with other aldehydes.[256] The direct conversion of an alkene to an α-keto azide is possible through the use of hypervalent iodine reagents in combination with trimethylsilylazide. The stable azido iodinananes **10–12** have been introduced as more convenient



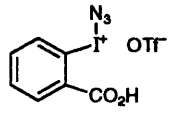
9



10



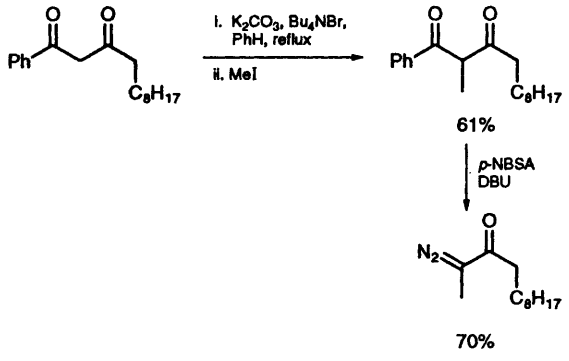
11



12

reagents for this transformation.[257] However, some of these compounds have explosive tendencies and the use of chromyl azide which can be prepared *in situ* has been advocated.[258] The same authors have also reported the analogous preparation of chromyl nitrate for the synthesis of α-nitro ketone from alkenes.[259] α-Nitro ketones are also accessed through the tin(II) chloride mediated reaction of trichloronitromethane with acid chlorides.[260]

Regiospecific diazo transfer to non-symmetrical ketones can be achieved from the corresponding α-phenacyl ketones (**Scheme 14**).[261] Such decarbonylative procedures are also found in the regioselective bromination of tertiary β-keto esters.[262] Perfect regiocontrol is exhibited in the bromination of enol borinates prepared via the hydrozirconation–acylation of vinyl borinates.[263] Asymmetric bromination is possible using an acyl dithiane oxide chiral auxiliary. The product may be converted to the corresponding α-aminoketone, albeit with some loss of optical purity.[264]



Scheme 14

Although the initial addition is not particularly selective, electrolytic fluorination of camphanyl enol ethers affords routes to enantiomeric α-fluoro ketones.[265] *N*-Fluoro *o*-benzenedisulfonimide has been introduced as a selective electrophilic fluorinating agent. Comparisons with similar existing reagents indicate that this provides a more effective method for enolate fluorination.[266] β-Dicarbonyl compounds undergo a very facile enol fluorination on reaction with diluted fluorine.[267] The same reagent system is useful for the synthesis of α- and α,β-difluoro enones.[268] The corresponding α-iodo enones can be obtained through the reaction of an enone with trimethylsilyl azide and iodine.[269] α,α-Difluoro ketones are produced in the reaction of acetylenes with Bank's fluorinating reagent, through the palladium(0)-mediated addition of iododifluoromethyl ketones to allenes and via the treatment of α-hydroxy orthodithioesters with $Bu_4NH_2F_3$ and 1,3 dibromodimethylhydantoin.[270]

Reaction of an α-dibromo ketones with ethylthiolate efficiently leads to an α-keto thioether, probably via an SET (single electron transfer) process.[271] The latter can also be prepared through the use of the hydrazone methodology developed by de Kimpe; full details of these procedures which provide access to a range of α-substituted carbonyl compounds have been published.[272] Equally good yields of α-keto dithianes result from the reaction of tris(thiomethyl)methyllithium with esters.[273] In addition, several routes to the seleno analogues have been reported.[274] Strategies for the synthesis of other α-sulfur containing carbonyl groups have appeared including α-keto sulfones and thiocyanates.[275]

The stereochemistry of the acylation of chiral phosphine oxides has been elucidated,[276] whilst the use of chiral auxiliaries in the rearrangement of vinyl phosphonates to β-keto phosphonates results in a small but measurable asymmetric induction.[277]

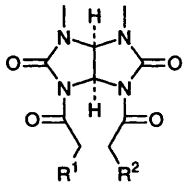
5.3 Dicarbonyl compounds

The oxidation of acyclic 1,2-diols to diketones can efficiently be achieved through the action of hydrogen peroxide in the presence of a peroxytungstophosphate catalyst.[278] Cyclic substrates are more resistent to oxidation. The reaction proceeds via the intermediacy of the corresponding α-ketol and these are also suitable substrates. TEMPO derivatives have previously been used for simple alcohol oxidation and a recent report extends the scope of this reaction to include the diol to diketone conversion. In this respect the yields obtained are better than those found using the Swern protocol.[279] However, the latter is an effective reagent system for the production of aromatic 1,2-carboxaldehydes.[280]

The double acylation of oxalic acid units provides a number of opportunities for 1,2-diketone synthesis. Full accounts have been published on the use of bis-Weinreb amides[281] and cyclic oxamides.[282] Oxalyl chloride is a suitable substrate for condensation with two equivalents of a magnesiocuprate provided additional lithium bromide is added.[283] The electrochemical acyloin reaction proceeds directly to afford the symmetrical diketone with no requirement for an additional oxidation step. If trimethylsilylchloride is added then the α-ketol may be isolated.[284]

Monoprotected 1,2-dicarbonyl compounds are produced in a multistep α-oxidation of α,β-unsaturated ketones,[285] the dioxirane oxidation of 1,4-dioxenes to α-ketal aldehydes,[286] and in the rhodium mediated decomposition of α,α′-diazo ketones in the presence of a primary alcohol. However, the latter is only an efficient process for the synthesis of indanediones.[287]

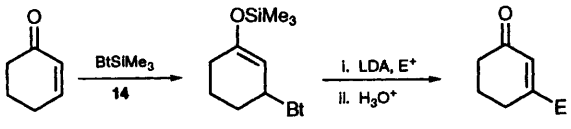
2,2-Dialkylindane-1,3-diones are accessed via the Wittig–Horner reaction of phthalide phosphonates.[288] 1,3-Diketones are generally prepared through a Claisen type strategy as evidenced in a biomimetic polyketide synthesis using a tetramethylglycoluril template **13**.[289] Unsaturated acyl electrophiles are not always efficient although the use of the Weinreb amide analogue may help.[290]



13

Difficulties in the condensation of ketones with perfluoroalkyl acyl chlorides can be avoided through the use of the morpholino enamine.[291] Cyclobutanes are a suitable electrophilic component in the vanadium(v) mediated reaction with silyl enol ethers although tetrahydrofuran formation can compete.[292] Alkylation using β-lactams as substrates provides modest diastereoselectivity at C-3.[293] A general approach to 3-unsubstituted diaryl pentane-1,3-diones is available via isoxazolines derived from nitryloxide–alkene cycloadditions.[294]

Hexane-2,5-dione is efficiently generated via the dioxirane oxidation of *cis*-diamino-1,2-dimethylcyclobutane. Whether this is a general transformation remains to be seen.[295] The conjugate addition/trapping of trimethylsilylbenzotriazole **14** provides a novel acyl anion for the synthesis of 2-ene-1,4-diones (**Scheme 15**). This sequence is general for the β-enone functionalisation.[296] 1,4-Diketones are produced when enones are combined with (i) aldehydes in a photochemical reaction,[297] (ii) furans in the presence of Lewis acids[298] and (iii) nickel acylate complexes.[299] The last of these also couple with a variety of alternative Michael acceptors such as nitro alkenes to afford other 1,*n*-diketones. Enhancements have been developed for the synthesis of bis-enones from cycloalkenones via a tandem ozonolysis–Wittig reaction.[300]



Bt = benzotriazole
E = RCOCl, RCHO, RX, *etc.*

Scheme 15

Finally there have been a number of developments in the search for high activity and stereoregularity in the olefin–carbon monoxide copolymerisation.[301] In a related study polycarbonyl compounds are produced in the lanthanide promoted polymerisation of cycloalkenones.[302]

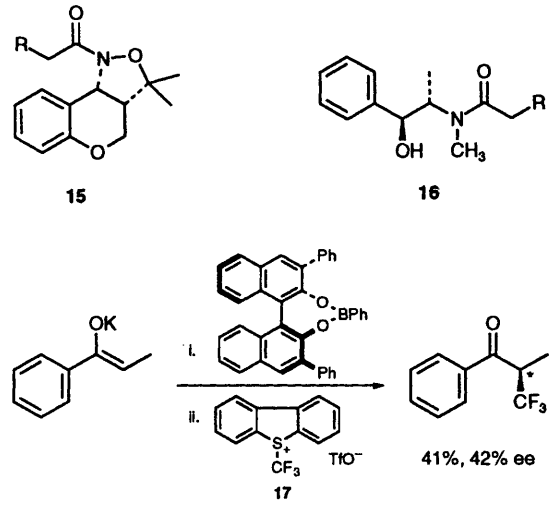
6 Reactions of aldehydes and ketones

6.1 The aldol reaction and other enolate additions

The advantages associated with the use of Mn enolates, *e.g.* regioselective monoalkylation, *etc.*, have been recorded. These compounds can now be generated using phenylmanganese chloride and a catalytic amount of amine base.[303] In the enantioselective deprotonation of ketones with chiral amide bases the effect of added lithium chloride is normally to raise the enantioselectivity and allows for an efficient 'external quench'. Whilst this effect has been probed, the use of ~0.4 mole equivalents of zinc chloride is found to produce enhanced levels of asymmetric induction.[304]

Koga's work on the enantioselective alkylation of tetralone enolates has been reviewed.[305] This substrate is also a favourite for studies on asymmetric enolate protonation for which excellent selectivities (>94% ee) can now be observed.[306] It remains to be seen how general these procedures are. α-Substituted ketones may also be resolved through enzyme mediated hydrolysis of the corresponding oxime acetates.[307] Antibodies have been raised for the hydrolysis of enol ethers and the origin and extent of the enantioselectivities obtained have been discussed in some detail.[308] The same authors have also recorded the first antibody catalysed aldol reaction albeit with fairly modest levels of asymmetric induction.[309]

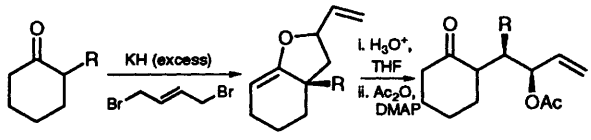
There have been a number of developments in auxiliary mediated asymmetric alkylation. This can be achieved electrochemically via the concomitant decarboxylation of a malonic ester derivatives an an allyl carboxylic acid.[310] Two auxiliaries **15** and **16**, suitable for the direct conversion into the free chiral aldehyde or ketone with minimal racemisation, have been introduced.[311] Enantioselective trifluoromethylation of an achiral ketone enolates is now a possibility using the CF_3^+ equivalent **17** developed by Umemoto (**Scheme 16**).[312]



Scheme 16

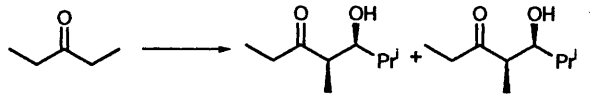
Both alkenes and dienes can function as electrophiles in the presence of manganese acetate or CAN respectively.[313] The latter is also suitable for the allylation of β-diketones with allyltrimethylsilane under neutral conditions,[314] whilst in the presence of

cobalt salts a number of compounds such as allylic alcohols function as alkylating agents.[315] The various methods for alkylation of these dicarbonyl substrates have been surveyed.[316] A problem with many of these enolate alkylation sequences is the competition between *C*- and *O*-alkylation; now conditions have been refined for selective *C*-alkylation of β-diketones.[317] Related to this, Zhao has reported an unusual sequence for the synthesis of homologous aldols in high diastereoselectivity through the tandem *C*- and *O*-alkylation of cyclohexanone enolates (**Scheme 17**).[318] β-Keto ester dianions can effectively formed *in situ* through the samarium iodide treatment of bromo esters.[319] Such metal–halogen exchange provides an alternative route for enolate generation and whilst samarium seems to be the reagent of choice a number of alternatives have also been employed.[320]



Scheme 17

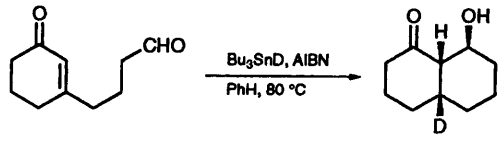
Syn aldols, and therefore (*Z*)-enolates, are efficiently produced in the absence of base when ketones are treated with 5 mol% titanium tetrafluoride in the presence of an acceptor aldehyde. The alternative *anti* diastereoisomer is obtained thorugh the use of $PhTi(OR)_4MgBr$ in a thermodynamically controlled process (**Scheme 18**).[321]



$PhTi(OPr^i)_4MgBr$	72%	2 :	98
5 mol% TiF_4	63%	68 :	32

Scheme 18

Similar control of diastereoselectivity can be observed in the use of antimony salts in the addition of tin enolates to 2-chlorocyclohexanone.[322] Tin enolates are also generated in a neutral free radical mediated aldol type process reported by Enholm (**Scheme 19**).[323] The diastereoselectivity observed in aldol processes involving various other enolates,



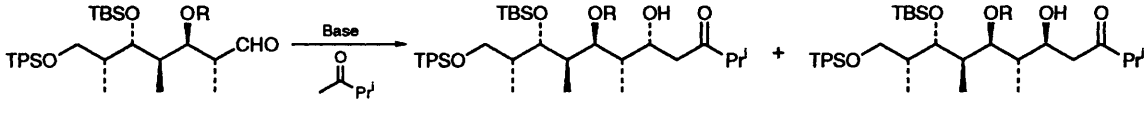
Scheme 19

including those from α-azido ketones,[324] enones (both free[325] and manganese complexed[326]) and β-hydroxy ketones (aldols),[327] has been studied.

Various factors which affect the diastereoselectivity of the double asymmetric aldol reaction have explored including the stereochemistry of the chiral aldehyde, the metal enolate utilised and the nature of the β-substituent, including the particular protecting group employed. Through careful choice of the reaction conditions it is relatively easy to produce the opposite sense of diastereoselection commencing from the same starting material (**Scheme 20**).[328] To help account for these factors, particularly 1,3-asymmetric induction, Evans has described modified aldol transition states.[329] Similar control can be realised through the appropriate choice of ligand in the chiral Lewis acid mediated aldol reaction.[330] An ene type mechanism is presumably involved in the titanium mediated asymmetric aldol reaction utilising the cheap commodity chemical, 2-methoxypropene.[331] The chiral ligand is that previously employed by the same group in the asymmetric aldol reaction of ketene silyl acetals. Palladium catalysis is also effective for the asymmetric aldol reaction which proceeds via an oxygen bound enolate rather than the traditional Lewis acid catalysed mechanism.[332]

Multistep strategies for the synthesis of enantiomeric aldol products have been reported using chiral sulfoxides[333] and nitrile oxide cycloadducts.[334] Similarly homochiral β-amino ketones are obtained via the asymmetric Michael addition to α,β-unsaturated Weinreb amides.[335] These products are also accessible through a nickel catalysed ketone–imine condensation[336] and the lanthanide mediated addition of enol ethers to *in situ* generated imines.[337] These reactions may be carried out in aqueous THF. Other water tolerant or water stable Lewis acids have been noted.[338] The aldol reactions of unprotected sugars in aqueous methanol using calcium hydroxide as a base have also been reported.[339]

Not surprisingly, in view of these developments, the stereocontrolled aldol reaction retains a pivotal



R = MOM	LHMDS, THF	95%	97	:	3
R = Me_3Si	Bu_2BOTf, Et_3N, CH_2Cl_2	74%	≤5	:	≥95

Scheme 20

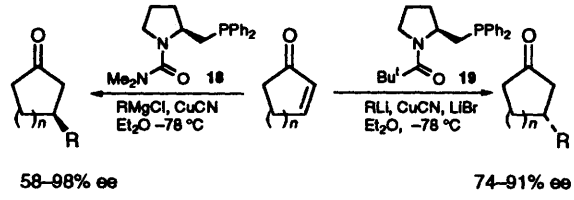
role in natural product synthesis. As examples, the reader is directed to the synthesis of oleandolide reported by Paterson and an approach to taxol® from the Mukaiyama group.[340]

6.2 Conjugate addition reactions

Organocopper species retain a pivotal role in conjugate addition reactions. The complex mixed salts Li_2CuX_3 are excellent sources of copper(I) for use in the catalysed addition of Grignard reagents to enones.[341] As with many of these procedures the use of trimethylsilylchloride is recommended for optimal yields. Alternatively, novel mixed thio–alkoxy ligands have been introduced as joint lithium–copper chelators to enhance the reactivity of these reagents.[342] This can also be achieved through the use of Lewis acid activators of the enone system; a rhenium complex proves to be effective both chemically and stereochemically.[343] An asymmetric Lewis acid catalysed Michael addition of silyl enol ethers is also possible which exhibits high diastereoselectivity if not particularly high enantioselectivity.[344]

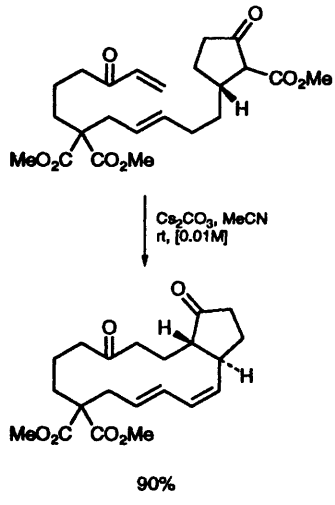
Copper also acts as an effective catalyst for the conjugate addition of alkylaluminium reagents including the higher organoalanes to enones. Enals, however, only couple efficiently with trimethylaluminium.[345] Nickel acetylacetonate is also an effective promotor, being particularly suitable for sterically hindered enones.[346] As with many transition metal catalysed processes, the use of alkyl groups containing β-hydrogens is not possible. Since only one group is transferred from the aluminium, studies of the effect of the additional ligands have been undertaken which show that the use of dialkylethoxyaluminium does not require any promoter. The use of trimethylsilyl chloride minimises the amount of copper catalyst required, although trimethylsilyl bromide completely suppresses the conjugate addition.[347] Addition of a silyl triflate promotes the conjugate addition of organoaluminates. Whilst 1,2-addition can compete when alkyl group transfer is attempted, both alkenyl and alkynyl delivery is very efficient.[348] The latter is not normally possible using classical cuprate methodology. 1,4-Addition of aromatic units to enones may be achieved via the palladium catalysed coupling of amino boronic acids with enones in the presence of antimony trichloride.[349]

The principal focus of much of the work in this area remains absolute stereoselectivity. Chiral auxiliaries have been employed in both substrate[350] and nucleophile[351] with moderate to excellent diastereoselectivity being obtained. Greater emphasis is currently placed on catalytic asymmetric synthesis; this is also true of conjugate addition. With one exception the successful examples of such a strategy have employed stabilised anions.[352] The exception is a report by Tomioka who employed the proline based phosphines **18** and **19** to catalyse the conjugate addition of Grignard derived cycanocuprates.[353] Interestingly these afford the enantiomeric products to those obtained from the corresponding lithium reagents (**Scheme 21**). New inexpensive accessible chiral ligand systems have also been identified for the nickel catalysed conjugate addition of dialkylzincs to enones.[354]



Scheme 21

Finally, macrocyclisation via the caesium carbonate mediated Michael reaction of enones and ynones affords good yields of the 14-membered ring ketone without the need for slow addition or exceptionally high dilution (0.01 M), as shown in **Scheme 22**. Whilst an attractive strategy, there is some evidence that the process can be substrate specific, particularly in relation to enone geometry.[355]



Scheme 22

7 References

1 C. F. de Graauw, J. A. Peters, H. van Bekkum and J. Huskens, *Synthesis*, 1994, 1007.
2 B. Zheng and M. Srebnik, *J. Org. Chem.*, 1995, **60**, 3278.
3 P. H. J. Carlsen, C. Kjaerstad and K. Aasbø, *Acta Chem. Scand.*, 1995, **49**, 152.
4 H. S. Kasmai, S. G. Mischke and T. J. Blake, *J. Org. Chem.*, 1995, **60**, 2267.
5 J. Muzart and S. Aït-Mohand, *New J. Chem.*, 1995, **19**, 207.
6 S. Aït-Mohand and J. Muzart, *Synth. Commun.*, 1995, **25**, 2373.
7 S. Aït-Mohand, F. Hénin and J. Muzart, *Tetrahedron Lett.*, 1995, 2473.

8 T. Iwahama, S. Sakaguchi, Y. Nishiyama and Y. Ishii, *Tetrahedron Lett.*, 1995, 6923; S. Iyer and J. P. Varghese, *Synth. Commun.*, 1995, **25**, 2261.
9 R. W. Murray, K. Iyanar, J. Chen and J. T. Wearing, *Tetrahedron Lett.*, 1995, 6415.
10 S.-I. Murahashi, T. Naota, Y. Oda and N. Hirai, *Synlett*, 1995, 733.
11 H. Ohtake, T. Higuchi and M. Hirobe, *Heterocycles*, 1995, **40**, 867.
12 S.-I. Murahashi, Y. Oda, N. Komiya and T. Naota, *Tetrahedron Lett.*, 1994, 7953.
13 J. Tateiwa, H. Horiuchi and S. Uemura, *J. Chem. Soc., Chem. Commun.*, 1994, 2567; G. Lu, H. Gao, J. Suo and S. Li, *J. Chem. Soc., Chem. Commun.*, 1994, 2423; D. H. R. Barton, A. H. Beck and D. K. Taylor, *Tetrahedron*, 1995, **51**, 5245.
14 Y. Ishii, K. Nakayama, M. Takeno, S. Sakaguchi, T. Iwahama and Y. Nishiyama, *J. Org. Chem.*, 1995, **60**, 3934.
15 E. Monflier, S. Tilloy, G. Fremy, Y. Barbaux and A. Mortreux, *Tetrahedron Lett.*, 1995, 387; E. Monflier, E. Blouet, Y. Barbaux and A. Mortreux, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 2100.
16 S.-K. Kang, K.-Y. Jung, J.-U. Chung, E.-Y. Namkoong and T.-H. Kim, *J. Org. Chem.*, 1995, **60**, 4678.
17 S. D. Meyer and S. L. Schreiber, *J. Org. Chem.*, 1994, **59**, 7549.
18 M. Frigerio and M. Santagostino, *Tetrahedron Lett.*, 1994, 8019.
19 A. Arnone, R. Bernardi, M. Cavicchioli and G. Resnati, *J. Org. Chem.*, 1995, **60**, 2314.
20 P. Bovicello, P. Lupattelli, A. Sanetti and E. Mincione, *Tetrahedron Lett.*, 1994, 8477.
21 R. Joseph, T. Ravindranathan and A. Sudalai, *Tetrahedron Lett.*, 1995, 1903.
22 T. Shinada and K. Yoshihara, *Tetrahedron Lett.*, 1995, 6701.
23 J. G. Lee and J. P. Hwang, *Chem. Lett.*, 1995, 507; R. Sanabria, R. Miranda, V. Lara and F. Delgado, *Synth. Commun.*, 1994, **24**, 2805.
24 C. E. Harris, L. Y. Lee, H. Dorr and B. Singaram, *Tetrahedron Lett.*, 1995, 2921.
25 Y. Matsumara, M. Yamada, N. Kise and M. Fujiwara, *Tetrahedron*, 1995, **51**, 6411.
26 S. Torii and A. Yoshida, *Chem. Lett.*, 1995, 369.
27 M. C. Pirrung and R. J. Tepper, *J. Org. Chem.*, 1995, **60**, 2461.
28 P. Kumar, R. Kumar and B. Pandey, *Synlett*, 1995, 289.
29 H. Nakamura and H. Matsuhashi, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 997.
30 See for example G. Fantin, M. Fogagnolo, P. P. Giovannini, A. Medici, P. Pedrini and S. Poli, *Tetrahedron Lett.*, 1995, 441.
31 L. Cottier, G. Descotes, L. Eymard and K. Rapp, *Synthesis*, 1995, 303.
32 R. Ballini and G. Bosica, *Synthesis*, 1994, 723.
33 H. Maeda, T. Maki and H. Ohmori, *Tetrahedron Lett.*, 1995, 2247.
34 D. J. Darensbourg, N. W. Stafford, F. Joó and J. H. Reibenspies, *J. Organomet. Chem.*, 1995, **488**, 99.
35 B. C. Ranu and A. Sarkar, *Tetrahedron Lett.*, 1994, 8649.
36 R. S. Dhillon, R. P. Singh and D. Kaur, *Tetrahedron Lett.*, 1995, 1107.
37 P. A. Evans and J. D. Roseman, *Tetrahedron Lett.*, 1995, 31.
38 H. Sakurai and K. Narasaka, *Chem. Lett.*, 1994, 2017.
39 V. D. Pokhodenko, V. G. Koshechko, V. E. Titov and V. A. Lopushanskaja, *Tetrahedron Lett.*, 1995, 3277.
40 J. H. Tatlock, *J. Org. Chem.*, 1995, **60**, 6221.
41 A. Baby, J.-J. Brunet, F. B. Kindela and D. Neibecker, *Synth. Commun.*, 1994, **24**, 2827.
42 J. A. Howarth, W. M. Owton and J. M. Percy, *J. Chem. Soc., Chem. Commun.*, 1995, 757; S. T. Patel, J. M. Percy and R. D. Wilkes, *Tetrahedron*, 1995, **51**, 9201; J. A. Howarth, W. M. Owton, J. M. Percy and M. H. Rock, *Tetrahedron*, 1995, **51**, 10289.
43 A. Dondoni, A. Boscarato, P. Formaglio, J.-P. Bégué and F. Benayoud, *Synthesis*, 1995, 654.
44 A. Bachki, F. Foubelo and M. Yus, *Tetrahedron Lett.*, 1994, 7643.
45 M. Shimano and A. I. Meyers, *Tetrahedron Lett.*, 1994, 7727.
46 T. Cohen, B. Zhang and J. P. Cherkauskas, *Tetrahedron*, 1994, **50**, 11569.
47 T. Schrader, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 917.
48 M. P. Sibi, C. C. Stessman, J. A. Schultz, J. W. Christensen, J. Lu and M. Marvin, *Synth. Commun.*, 1995, **25**, 1255.
49 J. M. Williams, R. B. Jobson, N. Yasuda, G. Marchesini, U.-H. Dolling and E. J. J. Grabowski, *Tetrahedron Lett.*, 1995, 5461.
50 M. Sawamura, T. Nakayama, T. Kato and Y. Ito, *J. Org. Chem.*, 1995, **60**, 1727.
51 G. K. Surya Prakash, C. York, Q. Liao, K. Kotian and G. A. Olah, *Heterocycles*, 1995, **40**, 79.
52 C. Kashima, I. Kita, K. Takahashi and A. Hosomi, *J. Heterocycl. Chem.*, 1995, **32**, 723.
53 M. A. de las Heras, J. J. Vaquero, J. L. García-Navio and J. Alvarez-Builla, *Tetrahedron Lett.*, 1995, 455.
54 Y. Han, L. Fang, W.-T. Tao and Y.-Z. Huang, *Tetrahedron Lett.*, 1995, 1287.
55 M. J. Aurell, Y. Danhui, J. Einhorn, C. Einhorn and J. L. Luche, *Synlett*, 1995, 459.
56 I. Villuendas, A. Parrilla and A. Guerrero, *Tetrahedron*, 1994, **50**, 12673.
57 J. Boivin, L. El Kaim and S. Z. Zard, *Tetrahedron*, 1995, **51**, 2573.
58 X. Wang, W. T. Monte, J. J. Napier and A. Ghannam, *Tetrahedron Lett.*, 1994, 9323.
59 H. S. Park, I. S. Lee and Y. H. Kim, *Tetrahedron Lett.*, 1995, 1673.
60 S. Benetti, R. Romagnoli, C. De Risi, G. Spalluto and V. Zanirato, *Chem. Rev.*, 1995, **95**, 1065.
61 D. H. R. Barton, C.-Y. Chen and J. Cs. Jaszberenyi, *Tetrahedron*, 1995, **51**, 1867.
62 L. Pégorier, Y. Petit, A. Mambu and M. Larchevêque, *Synthesis*, 1994, 1403.
63 E. J. Enholm and J. A. Schreier, *J. Heterocycl. Chem.*, 1995, **32**, 109.
64 E. J. Enholm and J. A. Schreier, *J. Org. Chem.*, 1995, **60**, 1110.
65 T. Ishiyama, M. Murata, A. Suzuki and N. Miyaura, *J. Chem. Soc., Chem. Commun.*, 1995, 295.
66 G. Barbaro, A. Battaglia and P. Giorgianni, *J. Org. Chem.*, 1995, **60**, 1020.
67 P. Huber, V. Enev, A. Linden and S. Bienz, *Tetrahedron*, 1995, **51**, 3749.
68 S. Tsunoi, I. Ryu, Y. Tamura, S. Yamasaki and N. Sonoda, *Synlett*, 1994, 1009.
69 Y. Fukumoto, S. Yamaguchi, N. Chatani and S. Murai, *J. Organomet. Chem.*, 1995, **489**, 215.
70 K. Ishihara, N. Hanaki and H. Yamamoto, *Synlett*, 1995, 721; M. E. Jung and D. C. D'Amico, *J. Am. Chem. Soc.*, 1995, **117**, 7379.

71 C. Lemini, M. Ordonez, J. Pérez-Flores and R. Cruz-Almanza, *Synth. Commun.*, 1995, **25**, 2695.
72 S. Kulasegaram and R. J. Kulawiec, *J. Org. Chem.*, 1994, **59**, 7195.
73 M. Sugiura and T. Nakai, *Chem. Lett.*, 1995, 697; M. Sugiura, M. Yanagisawa and T. Nakai, *Synlett*, 1995, 447.
74 P. Eilbracht, A. Gersmeier, D. Lennartz and T. Huber, *Synthesis*, 1995, 330.
75 H. Pellissier, R. Faure and M. Santelli, *J. Chem. Soc., Chem. Commun.*, 1995, 1847; H. Pellissier and M. Santelli, *J. Chem. Soc., Chem. Commun.*, 1995, 607.
76 Y. Horiuchi, M. Taniguchi, K. Oshima and K. Utimoto, *Tetrahedron Lett.*, 1994, 7977.
77 M. Takayanagi, K. Tanino and I. Kuwajima, *Synlett*, 1995, 173.
78 K. Muruoka, A. B. Concepcion and H. Yamamoto, *Synthesis*, 1994, 1283.
79 G. Gopalakrishnan and S. Anandhi, *Synth. Commun.*, 1995, **25**, 2521.
80 T. Hosokawa, T. Yamanaka, M. Itotani and S.-I. Murahashi, *J. Org. Chem.*, 1995, **60**, 6159.
81 A.-K. Habermann, M. Julia, J.-N. Verpeaux and D. Zhang, *Bull. Soc. Chim. Fr.*, 1994, **131**, 965.
82 B.-H. Chong, *J. Organomet. Chem.*, 1995, **492**, 31.
83 R. Takeuchi, S. Nitta and D. Watanabe, *J. Org. Chem.*, 1995, **60**, 3045.
84 S. Gladiali, J. C. Báyon and C. Claver, *Tetrahedron: Asymmetry*, 1995, **6**, 1453.
85 S. Bertozzi, N. Campigli, G. Vitulli, R. Lazzaroni and P. Salvadori, *J. Organomet. Chem.*, 1995, **487**, 41.
86 C. W. Lee and H. Alper, *J. Org. Chem.*, 1995, **60**, 499.
87 M. R. Detty and D. S. Hays, *Heterocycles*, 1995, **40**, 925; R. Settambolo, S. Pucci, S. Bertozzi and R. Lazzaroni, *J. Organomet. Chem.*, 1995, **489**, C50.
88 C. G. Arena, F. Nicolò, D. Drommi, G. Bruno and F. Faraone, *J. Chem. Soc., Chem. Commun.*, 1994, 2251; A. M. Masdeu-Bultó, A. Orejón, S. Castillón and C. Claver, *Tetrahedron: Asymmetry*, 1995, **6**, 1885; S. Gladiali, D. Fabbri and L. Kollàr, *J. Organomet. Chem.*, 1995, **491**, 91; C. Basoli, C. Botteghi, M. A. Cabras, G. Chelucci and M. Marchetti, *J. Organomet. Chem.*, 1995, **488**, C20.
89 K. Soulantica, S. Sirol, S. Koïnis, G. Pneumatikakis and Ph. Kalck, *J. Organomet. Chem.*, 1995, **498**, C10.
90 G. Fremy, E. Monflier, J.-F. Carpentier, Y. Castanet and A. Mortreux, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1474; D. Cauzzi, M. Lanfranchi, G. Marzolini, G. Predieri, A. Tiripicchio, M. Costa and R. Zanoni, *J. Organomet. Chem.*, 1995, **488**, 115.
91 T. Thyrann and D. A. Lighner, *Tetrahedron Lett.*, 1995, 4345; J. Muzart and S. Aït-Mohand, *Tetrahedron Lett.*, 1995, 5735; G. C. Maikap, D. Guhathakurta and J. Iqbal, *Synlett*, 1995, 189; D. Worsley, A. Mills, K. Smith and M. G. Hutchings, *J. Chem. Soc., Chem. Commun.*, 1995, 1119.
92 A. Potthast, T. Rosenau, C.-L. Chen and J. S. Gratzl, *J. Org. Chem.*, 1995, **60**, 4320.
93 L. I. Belen'kii, I. S. Poddubnyi and M. M. Krayushkin, *Tetrahedron Lett.*, 1995, 5075.
94 R. E. Banks, N. J. Lawrence and A. L. Popplewell, *Synlett*, 1994, 831; F. Kovac and A. L. Baumstark, *Tetrahedron Lett.*, 1994, 8751; S. Rajendran and D. C. Trivedi, *Synthesis*, 1995, 153.
95 S. Narasimhan, K. Ganeshwar Prasad and S. Madhavan, *Synth. Commun.*, 1995, **25**, 1689.
96 D. C. Harrowven and R. F. Dainty, *Tetrahedron Lett.*, 1995, 6739.
97 J. A. H. Lainton, J. W. Huffman, B. R. Martin and D. R. Compton, *Tetrahedron Lett.*, 1995, 1401.
98 A. S. Kiselyov and R. G. Harvey, *Tetrahedron Lett.*, 1995, 4005.
99 H. Kusama and K. Narasaka, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 2379.
100 I. Hachiya, M. Moriwaki and S. Kobayashi, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 2053; *Tetrahedron Lett.*, 1995, 409.
101 J. Inanaga, Y. Sugimoto and T. Hanamoto, *New J. Chem.*, 1995, **19**, 707.
102 I. Shiina, M. Miyashita, M. Nagai and T. Mukaiyama, *Heterocycles*, 1995, **40**, 141.
103 S. Kobayashi, M. Moriwaki and I. Hachiya, *J. Chem. Soc., Chem. Commun.*, 1995, 1527.
104 R. Suau, G. Torres and M. Valpuesta, *Tetrahedron Lett.*, 1995, 1311.
105 K. L. Sorgi, L. Scott and C. A. Maryanoff, *Tetrahedron Lett.*, 1995, 3597.
106 G. W. Ebert, D. R. Pfennig, S. D. Suchan, T. A. Donovan Jr., E. Aouad, S. S. Tehrani, J. N. Gunnersen and L. Dong, *J. Org. Chem.*, 1995, **60**, 2361.
107 J. W. Guiles, *Synlett*, 1995, 165.
108 S. Brown, S. Clarkson, R. Grigg and V. Sridharan, *J. Chem. Soc., Chem. Commun.*, 1995, 1135; C. S. Cho, T. Ohe and S. Uemura, *J. Organomet. Chem.*, 1995, **496**, 221; L. Delaude, A. M. Masdeu and H. Alper, *Synthesis*, 1994, 1149.
109 J.-J. Brunet and R. Chauvin, *Chem. Soc. Rev.*, 1995, **24**, 89.
110 C. S. Cho, Y. Yoshimori and S. Uemura, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 950.
111 J.-J. Brunet and A. El Zaizi, *J. Organomet. Chem.*, 1995, **486**, 275.
112 P. Haewawasam and N. A. Meanwell, *Tetrahedron Lett.*, 1994, 7303.
113 P. A. Evans, J. D. Nelson and A. L. Stanley, *J. Org. Chem.*, 1995, **60**, 2298.
114 F. Kakiuchi, S. Sekine, T. Tanaka, A. Kamatani, M. Sonoda, N. Chatani and S. Murai, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 62.
115 T. Hosoya, T. Hasegawa, Y. Kuriyama and K. Susuki, *Tetrahedron Lett.*, 1995, 3377; T. Hosoya, T. Hasegawa, Y. Kuriyama, T. Matsumoto and K. Suzuki, *Synlett*, 1995, 177.
116 T. Kataoka and T. Iwama, *Tetrahedron Lett.*, 1995, 245.
117 J. Barluenga, P. L. Bernard Jr. and J. M. Concellón, *Tetrahedron Lett.*, 1994, 9471.
118 D. Gröschl and H. Meier, *Liebigs Ann. Chem.*, 1995, 441.
119 S. Megati and K. G. S. Rao, *Tetrahedron Lett.*, 1995, 5819.
120 K. Yasui, S. Tanaka and Y. Tamaru, *Tetrahedron*, 1995, **51**, 6881.
121 J. Cossy and N. Furet, *Tetrahedron Lett.*, 1995, 3691.
122 A. Kirschning, *J. Org. Chem.*, 1995, **60**, 1228.
123 G. E. Keck, X.-Y. Li and D. Krishnamurthy, *J. Org. Chem.*, 1995, **60**, 5998.
124 M. P. Doyle, A. B. Dyatkin and C. L. Autry, *J. Chem. Soc., Perkin Trans. 1*, 1995, 619.
125 T. Ye, C. Fernández García and M. A. McKervey, *J. Chem. Soc., Perkin Trans. 1*, 1995, 1373; F. Kido, K. Yamaji, S. C. Sinha, T. Abiko and M. Kato, *Tetrahedron*, 1995, **51**, 7697.
126 J. Cossy, D. Belotti, A. Bouzide and A. Thellend, *Bull. Soc. Chim. Fr.*, 1994, **131**, 723.

127 K. Nakatini, T. Takada and S. Isoe, *J. Org. Chem.*, 1995, **60**, 2466.
128 M. E. Krafft, R. H. Romero and I. L. Scott, *Synlett*, 1995, 577; C. Mukai, M. Uchiyama, S. Sakamoto and M. Hanaoka, *Tetrahedron Lett.*, 1995, 5761; S. Fonquerna, A. Moyano, M. A. Pericàs and A. Riera, *Tetrahedron*, 1995, **51**, 4239.
129 J. L. Kent, H. Wan and K. M. Brummond, *Tetrahedron Lett.*, 1995, 2407; M. Ahmar, F. Antras and B. Cazes, *Tetrahedron Lett.*, 1995, 4417.
130 M. Costa and A. Mor, *Tetrahedron Lett.*, 1995, 2867.
131 J. Barluenga, R. Sanz and F. J. Fananás, *J. Chem. Soc., Chem. Commun.*, 1995, 1009.
132 I. Ojima, D. A. Fracchiolla, R. J. Donovan and P. Banerji, *J. Org. Chem.*, 1994, **59**, 7594.
133 B. L. Flynn, C. C. Silveira and A. de Meijere, *Synlett*, 1995, 812.
134 J. W. Herndon, D. K. Hill and L. A. McMullen, *Tetrahedron Lett.*, 1995, 5687; see also J. W. Herndon and L. A. McMullen, *J. Am. Chem. Soc.*, 1989, **111**, 6854.
135 Z. Jin and P. L. Fuchs, *J. Am. Chem. Soc.*, 1995, **117**, 3022.
136 Z. Jin and P. L. Fuchs, *J. Am. Chem. Soc.*, 1994, **116**, 5995.
137 S. H. Kim, Z. Jin and P. L. Fuchs, *Tetrahedron Lett.*, 1995, 4537.
138 T. Yechezkel, E. Ghera, D. Ostercamp and A. Hassner, *J. Org. Chem.*, 1995, **60**, 5135.
139 J. Ichikawa, S. Miyazaki, M. Fujiwara and T. Minami, *J. Org. Chem.*, 1995, **60**, 2320.
140 C. W. Ong, C. M. Chen and S. S. Juang, *J. Org. Chem.*, 1994, **59**, 7915.
141 M. L. F. Cadman, L. Crombie, S. Freeman and J. Mistry, *J. Chem. Soc., Perkin Trans. 1*, 1995, 1397.
142 E. Piers, K. L. Cook and C. Rogers, *Tetrahedron Lett.*, 1994, 8573.
143 G. Kuhn, G. Le Gouadec, A. L. Skaltsounis and J.-C. Florent, *Tetrahedron Lett.*, 1995, 3137.
144 M. Mikolajczyk and M. Mikina, *J. Org. Chem.*, 1994, **59**, 6760; M. Hatanaka, Y. Tanaka and I. Ueda, *Tetrahedron Lett.*, 1995, 3719; M. Hatanaka, Y. Himeda, Y. Tanaka and I. Ueda, *Tetrahedron Lett.*, 1995, 3211.
145 H. H. Wasserman, M. Shiraishi, S. J. Coats and J. D. Cook, *Tetrahedron Lett.*, 1995, 6785.
146 I. Kortmann and B. Westermann, *Synthesis*, 1995, 931.
147 T. Nakajima, M. Segi, T. Mituoka, Y. Fukute, M. Honda and K. Naitou, *Tetrahedron Lett.*, 1995, 1667.
148 L. S. Liebeskind, G. B. Stone and S. Zhang, *J. Org. Chem.*, 1994, **59**, 7917.
149 M. S. A. Parker and C. J. Rizzo, *Synth. Commun.*, 1995, **25**, 2781.
150 S. Fukuzawa and T. Tsuchimoto, *Tetrahedron Lett.*, 1995, 5937.
151 R. Gleiter and M. Merger, *Synthesis*, 1995, 969.
152 G. Liu, T. C. Smith and H. Pfander, *Tetrahedron Lett.*, 1995, 5979; N. Brosse, B. Jamart-Grégoire and P. Caubère, *Chem. Lett.*, 1995, 193; D. Patra and S. Ghosh, *J. Org. Chem.*, 1995, **60**, 2526; M. Sato, S. Sunami, T. Kogawa and C. Kaneko, *Chem. Lett.*, 1994, 2191; R. A. Bunce and C. L. Schilling, III, *J. Org. Chem.*, 1995, **60**, 2748; S. M. Ruder and V. R. Kulkarni, *J. Org. Chem.*, 1995, **60**, 3084.
153 J. Fujiwara, J. Tokuyasu and T. Sato, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 289; L. Fitjer, M. Schlotmann and M. Noltemeyer, *Tetrahedron Lett.*, 1995, 4985; A. Balog and D. P. Curran, *J. Org. Chem.*, 1995, **60**, 337; A. Balog, S. J. Geib and D. P. Curran, *J. Org. Chem.*, 1995, **60**, 345.
154 H. Suginome, T. Takeda, M. Itoh, Y. Nakayama and K. Kobayashi, *J. Chem. Soc., Perkin Trans. 1*, 1995, 49; H. Suginome, T. Kondoh, C. Gogonea, V. Singh, G. Gotó and E. Osawa, *J. Chem. Soc., Perkin Trans. 1*, 1995, 69.
155 A. Nishida, Y. Ogasawara, N. Kawahara and M. Nishida, *Tetrahedron Lett.*, 1995, 3015; K. I. Booker-Milburn and D. F. Thompson, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2315; P. Dowd, W. Zhang and K. Mahmood, *Tetrahedron*, 1995, **51**, 39; W. Zhang, M. R. Collins, K. Mahmood and P. Dowd, *Tetrahedron Lett.*, 1995, 2729.
156 S. L. Gwaltney II, S. T. Sakata and K. J. Shea, *Tetrahedron Lett.*, 1995, 7177.
157 J. D. Winkler, S. Kim, K. R. Condrosoki, A. Asensio and K. N. Houk, *J. Org. Chem.*, 1994, **59**, 6879.
158 M. Harmata, S. Elahmad and C. L. Barnes, *Tetrahedron Lett.*, 1995, 1397; M. Harmata, C. B. Gamlath, C. L. Barnes and D. E. Jones, *J. Org. Chem.*, 1995, **60**, 5077.
159 S. A. Hardinger, C. Bayne, E. Kantorowski, R. McClellan, L. Larres and M.-A. Nuesse, *J. Org. Chem.*, 1995, **60**, 1104.
160 J. H. Rigby, F. C. Pigge and M. D. Ferguson, *Tetrahedron Lett.*, 1994, 8131.
161 V. K. Aggarwal, J. Drabowicz, R. S. Grainger, Z. Gültekin, M. Lightowler and P. L. Spargo, *J. Org. Chem.*, 1995, **60**, 4962.
162 P. Metz, M. Fleischer and R. Frölich, *Tetrahedron*, 1995, **51**, 711.
163 E. Ghera, N. G. Ramesh, A. Laxer and A. Hassner, *Tetrahedron Lett.*, 1995, 1333.
164 B. B. Snider and B. M. Cole, *J. Org. Chem.*, 1995, **60**, 5376.
165 U. P. Spitz and P. E. Eaton, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 2220.
166 Y.-M. Tsai and S.-Y. Chang, *J. Chem. Soc., Chem. Commun.*, 1995, 981.
167 K. Takeda, M. Takeda, A. Nakajima and E. Yoshii, *J. Am. Chem. Soc.*, 1995, **117**, 6400.
168 (a) S. Tamai, H. Ushirogochi, S. Sano and Y. Nagao, *Chem. Lett.*, 1995, 295; (b) Y. Yamada, T. Ishii, M. Kimura and K. Hosaka, *Tetrahedron Lett.*, 1981, 1353.
169 M. P. Sibi, J. W. Christensen, S.-G. Kim, M. Eggen, C. Stessman and L. Oien, *Tetrahedron Lett.*, 1995, 6209.
170 S. M. Sieburth and C.-A. Chen, *Synlett*, 1995, 928.
171 M. T. Crimmins, S. Huang, L. E. Guise and D. B. Lacy, *Tetrahedron Lett.*, 1995, 7061.
172 S.-W. Zhang, T. Mitsudo, T. Kondo and Y. Watanabe, *J. Organomet. Chem.*, 1995, **485**, 55.
173 H. Maeda, T. Maki, H. Ashie and H. Ohmori, *J. Chem. Soc., Chem. Commun.*, 1995, 871.
174 F. T. Hong and L. A. Paquette, *Tetrahedron Lett.*, 1994, 9153.
175 J. B. Brogan, J. E. Richard and C. K. Zercher, *Synth. Commun.*, 1995, **85**, 587.
176 M. Kurihara and N. Miyata, *Chem. Lett.*, 1995, 263.
177 T.-J. Lu, J.-F. Yang and L.-J. Sheu, *J. Org. Chem.*, 1995, **60**, 2931.
178 F. Matloubi Moghaddam and A. Sharifi, *Synth. Commun.*, 1995, **25**, 2457.
179 J. Tateiwa, H. Horiuchi and S. Uemura, *J. Org. Chem.*, 1995, **60**, 4039.
180 L. Khamliche, S. Bakkas and A. Robert, *Synthesis*, 1994, 1129.

181 P. Kumar, V. R. Hegde and T. P. Kumar, *Tetrahedron Lett.*, 1995, 601; C. Pereira, B. Gigante, M. J. Marcelo-Curto, H. Carreyre, G. Pérot and M. Guisnet, *Synthesis*, 1995, 1077.
182 T. Miura and Y. Masaki, *Tetrahedron*, 1995, **51**, 10477; *Tetrahedron Lett.*, 1994, 7961.
183 N. Komatsu, M. Uda and H. Suzuki, *Synlett*, 1995, 984: T. Ravindranathan, S. P. Chavan and S. W. Dantale, *Tetrahedron Lett.*, 1995, 2285.
184 P. K. Mandal and S. C. Roy, *Tetrahedron*, 1995, **51**, 7823.
185 S. A. Haroutounian, *Synthesis*, 1995, 39.
186 T. Ravindranathan, S. P. Chavan and M. M. Awachat, *Tetrahedron Lett.*, 1995, 2285; T. Ravindranathan, S. P. Chavan, M. M. Awachat and S. V. Keikar, *Tetrahedron Lett.*, 1995, 2277.
187 M. Lakshmi Kantam, V. Swapna and P. Lakshmi Santhi, *Synth. Commun.*, 1995, **25**, 2529.
188 T. Nishiguchi, T. Ohosima, A. Nishida and S. Fujisaki, *J. Chem. Soc., Chem. Commun.*, 1995, 1121.
189 M. Benincasa, M. Boni, F. Ghelfi and U. M. Pagnoni, *Synth. Commun.*, 1995, **25**, 1843.
190 G. Dujardin, S. Rossignol and E. Brown, *Tetrahedron Lett.*, 1995, 1653.
191 R. W. Hoffmann and I. Münster, *Tetrahedron Lett.*, 1995, 1431.
192 K. Maruoka, H. Imoto and H. Yamamoto, *Synlett*, 1995, 719; K. Maruoka, I. Shimida, M. Akakura and H. Yamamoto, *Synlett*, 1994, 847.
193 R. C. Larock, T. R. Hightower, G. A. Kraus, P. Helm and D. Zheng, *Tetrahedron Lett.*, 1995, 2423.
194 P. A. Evans, J. M. Longmire and D. P. Modi, *Tetrahedron Lett.*, 1995, 3985.
195 L. C. Lin, L. L. Chueh, S.-W. Tsay and J. R. Hwu, *Tetrahedron Lett.*, 1995, 4093.
196 J. E. Resek and A. I. Meyers, *Tetrahedron Lett.*, 1995, 7051.
197 R. Ballini and G. Bosica, *J. Org. Chem.*, 1994, **59**, 5466.
198 M. R. Iesce, F. Cermola, A. Piazza, R. Scarpati and M. L. Graziano, *Synthesis*, 1995, 439.
199 K. Blaszczyk and Z. Paryzek, *Synth. Commun.*, 1994, **24**, 3255.
200 M. P. van Boggelen, B. F. G. A. van Dommelen, S. Jiang and G. Singh, *Tetrahedron Lett.*, 1995, 1899.
201 H. Kusama, K. Uchiyama, Y. Yamashita and K. Narasaka, *Chem. Lett.*, 1995, 715.
202 S. P. Green and D. A. Whiting, *J. Chem. Soc., Chem. Commun.*, 1994, 2441.
203 Y. Matano, M. Yoshimune and H. Suzuki, *J. Org. Chem.*, 1995, **60**, 4663.
204 V. G. Nenajdenko, M. V. Lebedev and E. S. Balenkova, *Tetrahedron Lett.*, 1995, 6317; R. Vukicevic, S. Konstantinovic, L. Juksovic, G. Ponticelli and M. L. Mihailovic, *Chem. Lett.*, 1995, 275.
205 C. Santelli-Rouvier, S. Lefrère, M. Mamai and M. Santelli, *Tetrahedron Lett.*, 1995, 2459.
206 A. Hayashi, M. Yamaguchi and M. Hirama, *Synlett*, 1995, 195.
207 R. D. Rieke, M. S. Sell and H. Xiong, *J. Am. Chem. Soc.*, 1995, **117**, 5429.
208 F.-T. Luo and L.-C. Hsieh, *Tetrahedron Lett.*, 1994, 9585.
209 K. Yasui, K. Fugami, S. Tanaka and Y. Tamura, *J. Org. Chem.*, 1995, **60**, 1365.
210 S. Dérien and P. H. Dixneuf, *J. Chem. Soc., Chem. Commun.*, 1994, 2551.
211 H. Bienaymé, *Bull. Soc. Chim. Fr.*, 1995, **132**, 696; *Tetrahedron Lett.*, 1994, 7383, 7387.
212 T. Minami and M. Hanaoka, *Tetrahedron Lett.*, 1994, 9425.
213 M. K. E. Saïah and R. Pellicciari, *Tetrahedron Lett.*, 1995, 4497.
214 F. Monteil, I. Matsuda and H. Alper, *J. Am. Chem. Soc.*, 1995, **117**, 4419; I. Ojima, E. Vidal, M. Tzamarioudaki and I. Matsuda, *J. Am. Chem. Soc.*, 1995, **117**, 6797; I. Matsuda, H. Ishibashi and N. Ii, *Tetrahedron Lett.*, 1995, 241.
215 F. Monteil and H. Alper, *J. Chem. Soc., Chem. Commun.*, 1995, 1601.
216 J. R. Johnson, G. D. Cuny and S. L. Buchwald, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1760.
217 A. Pelter and M. E. Colclough, *Tetrahedron*, 1995, **51**, 811.
218 E. Jehanno and M. Vaultier, *Tetrahedron Lett.*, 1995, 4439; H. Al-Badri, E. About-Jaudet and N. Collignon, *Tetrahedron Lett.*, 1995, 393; J. A. Cabezas and A. C. Oehlschlager, *Tetrahedron Lett.*, 1995, 5127; T. Takeda, Y. Kabasawa and T. Fujiwara, *Tetrahedron*, 1995, **51**, 2515; P. Bonete and C. Nájera, *Tetrahedron*, 1995, **51**, 2763.
219 S. Hara, N. Kato, E. Takeda and A. Suzuki, *Synlett*, 1994, 961.
220 X.-S. Mo and Y.-Z. Huang, *Synlett*, 1995, 181; *Tetrahedron Lett.*, 1995, 3539.
221 W. S. Huang and C. Y. Yuan, *J. Chem. Soc., Perkin Trans. 1*, 1995, 741.
222 F. Tellier and R. Sauvêtre, *Tetrahedron Lett.*, 1995, 4223.
223 Y.-S. Hon and L. Lu, *Tetrahedron*, 1995, **51**, 7937.
224 O. A. Phillips, P. Eby and S. N. Maiti, *Synth. Commun.*, 1995, **25**, 87.
225 E. Piers, J. Grierson, C. K. Lau and I. Nagakura, *Can. J. Chem.*, 1982, **60**, 210.
226 M. H. Kress and Y. Kishi, *Tetrahedron Lett.*, 1995, 4583.
227 A. G. M. Barrett and A. Kamimura, *J. Chem. Soc., Chem. Commun.*, 1995, 1755.
228 E. Ciganek and J. C. Calabrese, *J. Org. Chem.*, 1995, **60**, 4439.
229 R. D. Walkup, L. Guan, Y. S. Kim and S. W. Kim, *Tetrahedron Lett.*, 1995, 3805.
230 R. W. Bates and T. Rama Devi, *Tetrahedron Lett.*, 1995, 509.
231 M. Schmittel and M. Levis, *Chem. Lett.*, 1994, 1935, 1939.
232 J. Jauch, *Tetrahedron*, 1994, **50**, 12903.
233 M. Schultz, R. Kluge, M. Schüssler and G. Hoffmann, *Tetrahedron*, 1995, **51**, 3175.
234 V. V. Zhdankin, C. J. Kuehl and A. J. Simonsen, *Tetrahedron Lett.*, 1995, 2203.
235 S. Sakaguchi, S. Watase, Y. Katayama, Y. Sakata, Y. Nishiyama and Y. Ishii, *J. Org. Chem.*, 1994, **59**, 5681.
236 T. Inokuchi, K. Nakagawa and S. Torii, *Tetrahedron Lett.*, 1995, 3223.
237 P. Bovicelli, P. Lupattelli, A. Sanetti and E. Mincione, *Tetrahedron Lett.*, 1995, 3031.
238 A. R. Katritzky, Z. Yang and J.-L. Moutou, *Tetrahedron Lett.*, 1995, 841.
239 A. R. Katritzky and J. Jiang, *J. Org. Chem.*, 1995, **60**, 6.
240 J. G. Montana, N. Phillipson and R. J. K. Taylor, *J. Chem. Soc., Chem. Commun.*, 1994, 2289.
241 T. Satoh, Y. Mizu, T. Kawashima and K. Yamakawa, *Tetrahedron*, 1995, **51**, 703.
242 E. Abele, K. Rubina, M. Shymanska and E. Lukevics, *Synth. Commun.*, 1995, **25**, 1371.

243 D. Gala and D. J. Di Benedetto, *Tetrahedron Lett.*, 1994, 8299.
244 K. Ohmori, S. Nishiyama and S. Yamamura, *Tetrahedron Lett.*, 1995, 6519.
245 H. Fujioka, S. Kitagaki, R. Imai, M. Kondo, S. Okamoto, Y. Yoshida, S. Akai and Y. Kita, *Tetrahedron Lett.*, 1995, 3219.
246 M. Kawase and T. Kurihara, *Tetrahedron Lett.*, 1994, 8209.
247 M. Kawase, *Tetrahedron Lett.*, 1994, 149.
248 R. Yanagihara, J. Egashira, S. Yoskikawa and S. Osanai, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 237.
249 D. Enders and D. Bakhaus, *Synlett*, 1995, 631; D. Enders, D. Backhaus and J. Runsink, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 2098.
250 D. Enders and U. Reinhold, *Synlett*, 1994, 792.
251 K. R. Muralidharan, M. K. Mokhallalati and L. N. Pridgen, *Tetrahedron Lett.*, 1994, 7489; T. Harder, T. Löhl, M. Bolte, K. Wagner and D. Hoppe, *Tetrahedron Lett.*, 1994, 7365; P. O'Brien and S. Warren, *Tetrahedron Lett.*, 1995, 2681; A. Alexakis, N. Lensen, J.-P. Tranchier, P. Mangeney, J. Feneau-Dupont and J. P. Declercq, *Synthesis*, 1995, 1038.
252 P. Zlatoidsky, *Tetrahedron Lett.*, 1995, 7281; R. C. Klix, S. A. Chamberlin, A. V. Bhatia, D. A. Davis, T. K. Hayes, F. G. Rojas and R. W. Koops, *Tetrahedron Lett.*, 1995, 1791; see also D. M. Spero, S. Kapadia and V. Farina, *Tetrahedron Lett.*, 1995, 4543.
253 G. Cahiez and E. Metais, *Tetrahedron Lett.*, 1995, 6449.
254 P. Compain, J. Goré and J.-M. Vatèle, *Tetrahedron Lett.*, 1995, 4059.
255 T. Rein, R. Kreuder, P. von Zezschwitz, C. Wulff and O. Rieser, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1023.
256 T. Rein, J. Anvelt, A. Soone, R. Kreuder, C. Wulff and O. Reiser, *Tetrahedron Lett.*, 1995, 2303.
257 V. V. Zhdankin, C. J. Kuehl, A. P. Krasutsky, M. S. Formaneck and J. T. Bolz, *Tetrahedron Lett.*, 1994, 9677.
258 M. V. R. Reddy, R. Kumareswaran and Y. D. Vankar, *Tetrahedron Lett.*, 1995, 6761.
259 M. V. R. Reddy, R. Kumareswaran and Y. D. Vankar, *Tetrahedron Lett.*, 1995, 7149.
260 A. S. Demir, C. Tanyeli, H. Aksoy, V. Gulbeyaz and A. S. Mahasneh, *Synthesis*, 1995, 1071.
261 D. F. Taber, D. M. Gleave, R. J. Herr, K. Moody and M. J. Hennessy, *J. Org. Chem.*, 1995, **60**, 2283.
262 R. E. Boyd, C. R. Rasumussen and J. B. Press, *Synth. Commun.*, 1995, **25**, 1045.
263 B. Zheng and M. Srebnik, *Tetrahedron Lett.*, 1995, 5665.
264 P. C. Bulman-Page, M. J. McKenzie, S. M. Allin, E. W. Collington and R. A. E. Carr, *Tetrahedron*, 1995, **51**, 1285.
265 F. M. Ventalon, R. Faure, E. G. Laurent and B. S. Marquet, *Tetrahedron: Asymmetry*, 1994, **5**, 1909.
266 F. A. Davis, W. Han and C. K. Murphy, *J. Org. Chem.*, 1995, **60**, 4730.
267 R. D. Chambers, M. P. Greenhall and J. Hutchinson, *J. Chem. Soc., Chem. Commun.*, 1995, 21.
268 M. Sato, T. Taniguchi, T. Hirokawa and C. Kaneko, *Tetrahedron Lett.*, 1995, 6705.
269 C.-K. Sha and S.-J. Huang, *Tetrahedron Lett.*, 1995, 6927.
270 M. Zupan, J. Iskra and S. Stavber, *J. Org. Chem.*, 1995, **60**, 259; Z.-M. Qiu and D. J. Burton, *J. Org. Chem.*, 1995, **60**, 5570; M. Kuroboshi, S. Furuta and T. Hiyama, *Tetrahedron Lett.*, 1995, 6121.
271 M. Boeykens and N. De Kimpe, *Tetrahedron*, 1994, **50**, 12349.
272 M. Boeykens, N. De Kimpe and K. A. Tehrani, *J. Org. Chem.*, 1994, **59**, 6973.
273 M. Barbero, S. Cadamuro, I. Degani, S. Dughera and R. Fochi, *J. Org. Chem.*, 1995, **60**, 6017.
274 S. Ponthieux, F. Outurquin and C. Paulmier, *Tetrahedron Lett.*, 1995, 6453.
275 T. Kataoka and T. Iwama, *Synlett*, 1994, 1017; Y. Tanabe, T. Makita and K. Mori, *Chem. Lett*, 1994, 2275.
276 N. Feeder, G. Hutton and S. Warren, *Tetrahedron Lett.*, 1994, 5911.
277 Y.-Z. An, J. G. An and D. F. Wiemer, *J. Org. Chem.*, 1994, **59**, 8197.
278 T. Iwahama, S. Sakaguchi, Y. Nishiyama and Y. Ishii, *Tetrahedron Lett.*, 1995, 1523.
279 M. G. Banwell, V. S. Bridges, J. R. Dupuche, S. L. Richards and J. M. Walter, *J. Org. Chem.*, 1994, **59**, 6338.
280 O. Farooq, *Synthesis*, 1994, 1035.
281 M. P. Sibi, M. Marvin and R. Sharma, *J. Org. Chem.*, 1995, **60**, 5016.
282 U. T. Mueller-Westerhoff and M. Zhou, *Synlett*, 1994, 975.
283 F. Babudri, V. Fiandanese, G. Marchese and A. Punzi, *Tetrahedron Lett.*, 1995, 7305.
284 S. Kashimura, Y. Murai, M. Ishifune, H. Masuda, H. Murase and T. Shono, *Tetrahedron Lett.*, 1995, 4805.
285 A. Feuerer and T. Severin, *J. Org. Chem.*, 1994, **59**, 6026.
286 C. Babylon and I. Hanna, *Tetrahedron Lett.*, 1995, 6475.
287 S. Murata, C. Kongou and H. Tomioka, *Tetrahedron Lett.*, 1995, 1499.
288 M. Watanabe, H. Morimoto, M. Tomoda and U. Iwanaga, *Synthesis*, 1994, 1083.
289 S. Sun and P. Harrison, *J. Chem. Soc., Chem. Commun.*, 1994, 2235.
290 T. Hiyama, G. Bhasker Reddy, T. Minami and T. Hanamoto, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 350.
291 H. Trabelsi and A. Cambon, *Tetrahedron Lett.*, 1995, 3145.
292 T. Hirao, T. Fujii, T. Tanaka and Y. Ohshiro, *Synlett*, 1994, 845.
293 I. Ojima, E. W. Ng and C. M. Sun, *Tetrahedron Lett.*, 1995, 4547.
294 J. Pulkkinen, J. Vepsäläinen and R. Laatikainen, *Tetrahedron Lett.*, 1994, 9749.
295 J. L. Gagnon and W. W. Zajac Jr., *Tetrahedron Lett.*, 1995, 1803.
296 A. R. Katritzky, J. Soloducho, R. P. Musgrave and J. C. Breytenbach, *Tetrahedron Lett.*, 1995, 5491.
297 G. A. Kraus and P. Liu, *Tetrahedron Lett.*, 1994, 7723.
298 G. Dujardin and J.-M. Poirier, *Bull. Soc. Chim. Fr.*, 1994, **131**, 900.
299 J. R. Hermanson, M. L. Gunther, J. L. Belletire and A. R. Pinhas, *J. Org. Chem.*, 1995, **60**, 1900.
300 J. Montgomery, A. V. Savchenko and Y. Zhao, *J. Org. Chem.*, 1995, **60**, 5699.
301 Z. Jiang and A. Sen, *J. Am. Chem. Soc.*, 1995, **117**, 4455; B. A. Markies, D. Kruis, M. H. P. Rietveld, K. A. N. Verkerk, J. Boersma, H. Kooijman, M. T. Lakin, A. L. Spek and G. van Koten, *J. Am. Chem. Soc.*, 1995, **117**, 5263; E. Amevor, R. Bürli and G. Consiglio, *J. Organomet. Chem.*, 1995, **497**, 81; S. Bronco, g. Consiglio, S. Di Benedetto, M. Fehr,

F. Spindler and A. Togni, *Helv. Chim. Acta*, 1995, **78**, 883.
302 B.-J. Deelman, E. A. Bijpost and J. H. Teuben, *J. Chem. Soc., Chem. Commun.*, 1995, 1741.
303 G. Cahiez, M. Kanaan and P. Cléry, *Synlett*, 1995, 191.
304 P. Coggins, S. Gaur and N. S. Simpkins, *Tetrahedron Lett.*, 1995, 1545; M. Majewski, R. Lazny and P. Nowak, *Tetrahedron Lett.*, 1995, 5465.
305 D. J. Berrisford, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 178.
306 K. Fuji, T. Kawabata, A. Kuroda and T. Taga, *J. Org. Chem.*, 1995, **60**, 1914; S. J. Aboulhoda, S. Létinois, J. Wilken, I. Reiners, F. Hénin, J. Martens and J. Muzart, *Tetrahedron: Asymmetry*, 1995, **6**, 1865; C. Fehr and J. Galindo, *Helv. Chim. Acta*, 1995, **78**, 539; E. Vedejs and N. Lee, *J. Am. Chem. Soc.*, 1995, **117**, 891; K. Ishihara, M. Kaneeda and H. Yamamoto, *J. Am. Chem. Soc.*, 1994, **116**, 11179.
307 M. Murakata, M. Imai, M. Tamura and O. Hoshino, *Tetrahedron: Asymmetry*, 1994, **5**, 2019.
308 G. K. Jahangiri and J. L. Reymond, *J. Am. Chem. Soc.*, 1994, **116**, 11264; see also S. C. Sinha and E. Keinan, *J. Am. Chem. Soc.*, 1995, **117**, 3653.
309 J. L. Reymond and Y. Chen, *Tetrahedron Lett.*, 1995, 2575. For a recent survey of the enzyme mediated aldol reaction, see H. J. M. Gijsen and C. H. Wong, *J. Am. Chem. Soc.*, 1994, **116**, 8422.
310 B. Klotz-Berendes, H. J. Schäfer, M. Grehl and R. Fröhlich, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 189.
311 A. Abiko, O. Moriya, S. A. Filla and S. Masamune, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 793; A. G. Myers, B. H. Yang, H. Chen and J. L. Gleason, *J. Am. Chem. Soc.*, 1994, **116**, 9361.
312 T. Umemoto and K. Adachi, *J. Org. Chem.*, 1994, **59**, 5692.
313 U. Linker, B. Kersten and T. Linker, *Tetrahedron Lett.*, 1995, **51**, 9917; A. B. Paolobelli, P. Ceccherelli, F. Pizzo and R. Ruzziconi, *J. Org. Chem.*, 1995, **60**, 4954.
314 J. R. Hwu, C. N. Chen and S.-S. Shiao, *J. Org. Chem.*, 1995, **60**, 856.
315 M. M. Reddy, B. Bhatia and J. Iqbal, *Tetrahedron Lett.*, 1995, 4877; M. Mukhopadhyay and J. Iqbal, *Tetrahedron Lett.*, 1995, 6761.
316 C. Cativiela, J. L. Serrano and M. M. Zurbano, *J. Org. Chem.*, 1995, **60**, 3074.
317 A. V. Bedekar, T. Watanabe, K. Tanaka and K. Fuji, *Synthesis*, 1995, 1069.
318 T. Wang, J. Chen and K. Zhao, *J. Org. Chem.*, 1995, **60**, 2668.
319 K. Utimoto, T. Matsui, T. Takai and S. Matsubara, *Chem. Lett.*, 1995, 197.
320 Y. Aoyagi, M. Yoshimura, M. Tsuda, T. Tsuchibuchi, S. Kawamata, H. Tateno, K. Asano, H. Nakamura, M. Obokata, A. Ohta and Y. Kodama, *J. Chem. Soc., Perkin Trans. 1*, 1995, 689; T. Arime, H. Takahashi, S. Kobayashi, S. Yamaguchi and N. Mori, *Synth. Commun.*, 1995, **25**, 389; Y. Aoki, K. Oshima and K. Utimoto, *Chem. Lett.*, 1995, 463.
321 R. Mahrwald, *Chem. Ber.*, 1995, **128**, 919; *Tetrahedron*, 1995, **51**, 9015.
322 M. Yasuda, T. Oh-hata, I. Shibata, A. Baba, H. Matsuda and N. Sonoda, *Tetrahedron Lett.*, 1994, 8627; *Bull. Chem. Soc. Jpn.*, 1995, **68**, 1180.
323 E. J. Enholm, Y. Xie and K. A. Abboud, *J. Org. Chem.*, 1995, **60**, 1112.
324 T. Patonay and R. V. Hoffman, *J. Org. Chem.*, 1995, **60**, 2368.
325 A. Fernández Mateos, G. Pascual Coca, J. J. Pérez Alonso, R. Rubio González and C. Tapia Hernández, *Tetrahedron Lett.*, 1995, 961.
326 D. Schnizer, T. Blume and M. Woltering, *Synlett*, 1994, 1045.
327 G. P. Luke and J. Morris, *J. Org. Chem.*, 1995, **60**, 3013.
328 D. J. Gustin, M. S. Van Nieuwenhze and W. R. Roush, *Tetrahedron Lett.*, 1995, 3443; D. A. Evans, M. J. Dart, J. L. Duffy and D. L. Rieger, *J. Am. Chem. Soc.*, 1995, **117**, 9073.
329 D. A. Evans, J. L. Duffy and M. J. Dart, *Tetrahedron Lett.*, 1994, 8537.
330 See for example S. Kobayashi and T. Hayashi, *J. Org. Chem.*, 1995, **60**, 1098.
331 E. M. Carriera, W. Lee and R. A. Singer, *J. Am. Chem. Soc.*, 1995, **117**, 3649.
332 M. Sodeoka, K. Ohrai and M. Shibasaki, *J. Org. Chem.*, 1995, **60**, 2648.
333 F. R. Blase and H. Le, *Tetrahedron Lett.*, 1995, 4559.
334 T. Berranger and Y. Langlois, *J. Org. Chem.*, 1995, **60**, 1720.
335 S. G. Davies and T. D. McCarthy, *Synlett*, 1995, 700.
336 N. Shida, Y. Kubota, H. Fukui, N. Asao, I. Kadota and Y. Yamamoto, *Tetrahedron Lett.*, 1995, 5023.
337 S. Kobayashi and H. Ishitani, *J. Chem. Soc., Chem. Commun.*, 1995, 1379; S. Kobayashi, M. Araki and M. Yasuda, *Tetrahedron Lett.*, 1995, 5773.
338 K. Ishihara, N. Hanaki, M. Funahashi, M. Miyata and H. Yamamoto, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 1721; P. T. Buonora, K. G. Rosauer and L. Dai, *Tetrahedron Lett.*, 1995, 4009.
339 H. Saimoto, S. Yatani, H. Sashiwa and Y. Shigemasa, *Tetrahedron Lett.*, 1995, 937.
340 I. Paterson, R. D. Norcross, R. A. Ward, P. Romea and M. A. Lister, *J. Am. Chem. Soc.*, 1994, **116**, 11287; I. Shiina, K. Uoto, N. Mori, T. Kosugi and T. Mukaiyama, *Chem. Lett.*, 1995, 181; T. Mukaiyama, I. Shiina, K. Kimura, Y. Akiyama and H. Iwadare, *Chem. Lett.*, 1995, 229.
341 M. T. Reetz and A. Kindler, *J. Organomet. Chem.*, 1995, **502**, C5.
342 J. Green and S. Woodward, *Synlett*, 1995, 155.
343 Y. Wang and J. A. Gladysz, *J. Org. Chem.*, 1995, **60**, 903.
344 A. Bernardi, K. Karamfilova, G. Boschin and C. Scolastico, *Tetrahedron Lett.*, 1995, 1363; J. Otera, Y. Fujita, S. Fukuzumi, K. Hirai, J.-H. Gu and T. Nakai, *Tetrahedron Lett.*, 1995, 95.
345 J. Kabbara, S. Flemming, K. Nickisch, H. Neh and J. Westermann, *Tetrahedron*, 1995, **51**, 743.
346 J. Kabbara, S. Flemming, K. Nickisch, H. Neh and J. Westermann, *Liebigs Ann. Chem.*, 1995, 401; S. Flemming, J. Kabbara, K. Nickisch, H. Neh and J. Westermann, *Synthesis*, 1995, 317.
347 J. Kabbara, S. Flemming, K. Nickisch, H. Neh and J. Westermann, *Tetrahedron Lett.*, 1994, 8591.
348 S. Kim and J. H. Park, *Synlett*, 1995, 163.
349 C. S. Cho, S. Motofusa, K. Ohe, S. Uemura and S. C. Shim, *J. Org. Chem.*, 1995, **60**, 883.
350 K. Utimoto, T. Kodama and S. Matsubara, *Synlett*, 1995, 501; E. Urban, G. Riehs and G. Knühl, *Tetrahedron Lett.*, 1995, 4773; E. Urban, G. Knühl and G. Helmchen, *Tetrahedron Lett.*, 1995, 7229.
351 D. Enders, J. Kirchhoff, D. Mannes and G. Raabe, *Synthesis*, 1995, 659; T. W. Wallace, I. Wardell, K.-D.

Li, P. Leeming, A. D. Redhouse and S. R. Challand, *J. Chem. Soc., Perkin Trans. 1*, 1995, 2293; C. Baldoli, P. Del Buttero, E. Licandro, S. Maiorana, A. Papagni and A. Zanotti-Gerosa, *J. Organomet. Chem.*, 1995, **486**, 279.

352 A. Kawara and T. Taguchi, *Tetrahedron Lett.*, 1994, 8805; M. Sawamura, H. Hamashima, H. Shinoto and Y. Ito, *Tetrahedron Lett.*, 1995, 6479; H. Sasai, T. Arai, Y. Satow, K. N. Houk and M. Shibasaki, *J. Am. Chem. Soc.*, 1995, **117**, 6194; M. Yamaguchi, T. Shiraishi, Y. Igarashi and M. Hirama, *Tetrahedron Lett.*, 1994, 8233.

353 M. Kanai and K. Tomioka, *Tetrahedron Lett.*, 1995, 4273, 4275.

354 T. Fujisawa, S. Itoh and M. Shimizu, *Chem. Lett.*, 1994, 1777.

355 C. Crévsy, M. Couturier, C. Dugave, Y. L. Dory and P. Deslongchamps, *Bull. Soc. Chim. Fr.*, 1995, **132**, 360; G. Berthiaume and P. Deslongchamps, *Bull. Soc. Chim. Fr.*, 1995, **132**, 371.