Aldehydes and ketones

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Continuing the coverage in *Contemporary Organic Synthesis*, 1996, **3**, 151

1 Synthesis of aldehydes and ketones

1.1 Redox methods

By far the most commonly used method for the synthesis of aldehydes and ketones is the oxidation of alcohols. Many new oxidative methods have been described over the period covered in this review. Several are variants of well studied oxidising agents. For example, Khadilkar and co-workers[1] report the preparation of silica gel-supported chromium trioxide and describe its use in the selective oxidation of alcohols. The reagent oxidises alcohols to their corresponding carbonyl compounds; primary alcohols are not over-oxidised to the carboxylic acids. The oxidation is carried out in 1,2-dichloroethane and is complete after 15 min at room temperature. The product of the reaction is obtained simply by filtration of the reaction mixture. Another chromium-based reagent quinolinium chlorochromate (QCC) has been shown to be an efficient reagent for the selective oxidation of primary and secondary alcohols.[2,3] The related quinolinium bromochromate, reported by Özgün and Degirmenbasi and co-workers,[4] is also a new reagent for the oxidation of alcohols to carbonyl compounds. The reagent also functions as a brominating agent for aromatic compounds.

An improved protocol for the oxidation of secondary alcohols by copper permanganate is described by Craig and Ansari. The reaction is carried out in a homogeneous medium (acetic acid), affording rapid and complete conversion of the alcohols to ketones.[5] Hexadecyl silica-supported cupric nitrate, in carbon tetrachloride, oxidises alcohols to their corresponding carbonyl compounds. It oxidises primary alcohols in the presence of secondary alcohols with absolute chemoselectivity in high yields.[6]

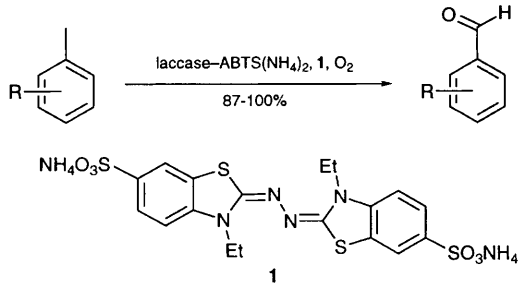
Delaude and Laszlo[7] describe full details of the use of another oxidising reagent, potassium ferrate(VI) and K10 montmorillonite clay.[8,9] The reagent is a strong and environmentally benign oxidant for the oxidation of benzyl alcohol. The development of other clean oxidising systems has seen much activity this year. Systems that use only a catalytic quantity of a metal complex are particularly attractive. A practical procedure for the molybdenum-catalysed oxidation of alcohols by sodium percarbonate is detailed by Muzart and co-workers.[10] The oxidation is carried out at reflux in acetonitrile or 1,2-dichloroethane in the presence of catalytic molybdenyl acetylacetonate and Adogen 464. The process is generally applicable for the synthesis of a wide range of carbonyl compounds.

Processes that have no metal catalyst and use oxygen or air as the terminal oxidant have even greater potential as clean synthetic methods. One such process, a simple and convenient method for the oxidation of secondary alcohols using molecular oxygen, benzaldehyde in 1,2-dichloroethane in the absence of metal catalysts, is described by Choudary and Sudha for the first time.[11] Villemin and Hammadi have found that 1,2-diketones can be efficiently prepared by the Kornblum DMSO oxidation of 1,2-dibromides.[12] The reaction can be effected by heating the dibromides in refluxing DMSO or by heating in a conventional microwave oven (350 W) for 3 minutes.

Rodrigues and co-workers have found that acyl nitrates can be used to oxidise primary and secondary alcohols to aldehydes and ketones.[13] Acetyl nitrate supported on montmorillonite clay gives the best results. The reaction is explained by a mechanism involving the formation of an intermediate alkyl nitrate which decomposes to give the carbonyl compound. Although the authors do not report any problems with this procedure they do not present any safety analysis which would have been welcome considering the known safety hazards

associated with the use of acetyl nitrate. Another new non-metal-based oxidising agent, efficient for the oxidation of alcohols, is the 1:1 complex of *N*-bromosuccinimide and tetrabutylammonium iodide.[14]

Chen and co-workers describe the potentially useful, and environmentally benign, enzyme-mediated molecular oxygen oxidation of substituted benzyl alcohol derivatives to the corresponding aldehydes (**Scheme 1**).[15] The enzyme used, laccase, requires an artificial co-factor, diammonium 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonate) [ABTS-$(NH_4)_2$] **1**. The reaction proceeds under physiological conditions to yield quantitatively the product aldehydes.



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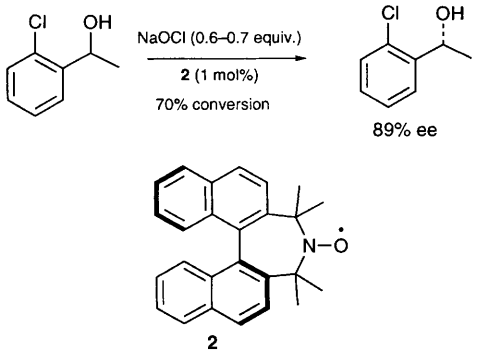
Scheme 1

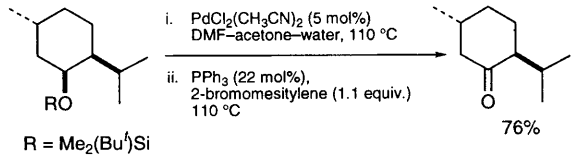
An intriguing and efficient enantioselective protocol for the oxidation of secondary alcohols is reported by Rychnovsky *et al.*[16] They used the optically pure nitroxide catalyst **2**, which is essentially a 'chiral version' of TEMPO (tetramethylpiperidine-*N*-oxyl), a well studied oxidation catalyst. The azepine **2** oxidises activated secondary alcohols in the presence of the terminal oxidant sodium hypochlorite (0.6–0.7 equiv). The resolution of the benzylic alcohol is efficient; the (*S*) isomer is oxidised six times faster than the (*R*) enantiomer (**Scheme 2**).



2

Scheme 2

A procedure for the one-pot desilylation–oxidation of aliphatic *tert*-butyldimethylsilyl ethers using a palladium(II) catalyst is reported by Wilson and Keay.[17] The desilylation involves heating the silyl ether in acetone–DMF containing water (5 equiv.) in the presence of $PdCl_2(CH_3CN)_2$ (5 mol%). Once the desilylation is complete, triphenylphosphine (22 mol%) and 2-bromomesitylene (1.08 equiv.) are added and the mixture heated at 110 °C (**Scheme 3**) to effect the oxidation of the alcohol.

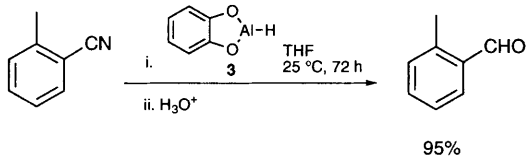


R = $Me_2(Bu^t)Si$

Scheme 3

Finally, 3,3′-thiodipropionic acid and its salts have been found to be effective as reducing agents for the reductive work-up of ozonolysis reactions. The acid is a good replacement for dimethyl sulfide in the reductive quench of the ozonolysis of cyclic alkenes.[18]

Examples of the synthesis of aldehydes and ketones *via* reductive methods are much rarer than those involving the oxidation of alcohols. One example involves the use of catecholalane **3**, prepared by the reaction between catechol and aluminium hydride in THF at 0 °C. It is an excellent reagent for the partial reduction of nitriles to aldehydes (**Scheme 4**).[19]

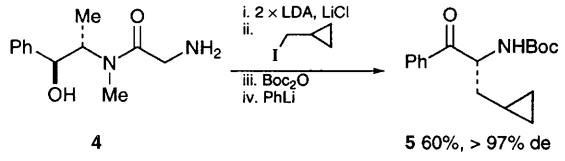


Scheme 4

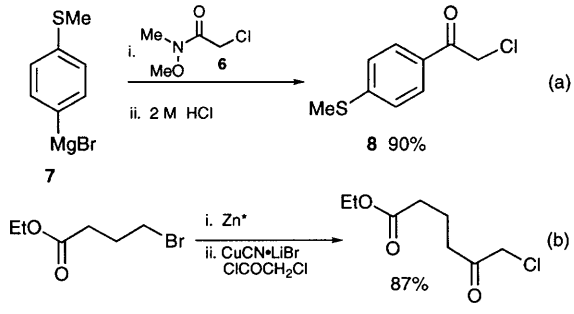
1.2 Acylation and other methods

Another common method for the synthesis of carbonyl compounds involves the acylation of carbon nucleophiles. An example of this process is described by Myers and Yoon who have extended their elegant use of pseudoephedrine as a chiral auxiliary. Treatment of the glycinamide **4** with lithium diisopropylamide followed by alkylation, *N*-Boc protection and treatment with a Grignard or organolithium reagent generates α-amino ketones with exceedingly high enantioselectivity (**4**→**5**) (**Scheme 5**).[20]

Tillyer *et al.* report a simple, high yielding synthesis of α-chloro ketones **8** by the reaction of organometallic reagents with *N*-methoxy-*N*-methylchloroacetamide, a process pioneered by Wienreb. Addition of Grignard and organolithium reagents to *N*-methoxy-*N*-methylchloroacetamide **6**, prepared by Schotten–Baumann reaction of *N*,*O*-dimethylhydroxylamine and chloroacetyl chloride, gives after acidic work-up the corre-



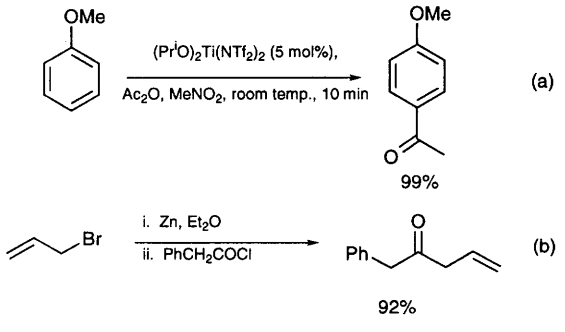
Scheme 5



Scheme 6

sponding chloro ketone (*e.g.* **7**→**8**) (**Scheme 6a**). The efficiency of the procedure was greatly increased by the regeneration of the chloroacetamide directly by chloroacetylation of the aqueous phase using chloroacetyl chloride–K_2CO_3. The procedure is also effective for the synthesis of α-fluoro ketones from *N*-methoxy-*N*-methylfluoroacetamide. Rieke *et al.* also report a method for the synthesis of α-chloromethyl ketones.[22] Copper-catalysed cross-coupling of functionalised organozinc reagents with chloroacetyl chloride generates functionalised α-chloromethyl ketones in excellent yields (**Scheme 6b**). The zinc reagents were prepared by the reaction of Rieke zinc (prepared by the reduction of zinc chloride in THF with lithium naphthalenide) with alkyl or aryl bromides.

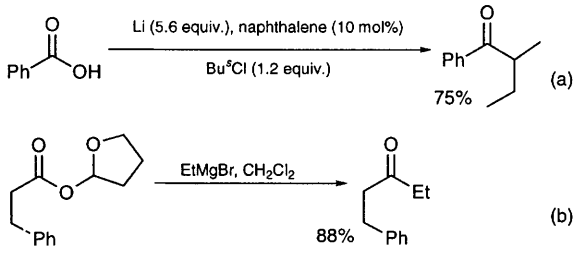
Metal bis(trifluoromethylsulfonyl)amides have been used by Mikami *et al.* as highly efficient Lewis acid catalysts for the Friedel–Crafts acylation of arenes (**Scheme 7a**).[23] Unlike most of the existing catalysts used to accomplish this type of reaction, the bistrifuoromethylsulfonamides of aluminium, titanium and ytterbium can be used in substoichiometric quantities. Fries reactions of phenol and 1-naphthol derivatives with acyl chlorides also proceed smoothly in the presence of a small amount of $Sc(OTf)_3$ (5–20 mol%) to afford the corresponding ketones in high yields as detailed by Kobayashi *et al.*[24] The same research group have also found that lithium perchlorate greatly accelerates the scandium or ytterbium trifluoromethanesulfonate-catalysed Friedel–Crafts reaction. The mixture of rare-earth trifluoromethanesulfonate and lithium perchlorate is easily recovered from the reaction mixture by simple extraction and can be reused without a decrease in its catalytic activity.[25] The reaction of an acid chloride, allyl bromide and commercial zinc dust in diethyl ether conveniently generates β,γ-unsaturated ketones (**Scheme 7b**).[26]



Scheme 7

A description of the synthesis of aryl trifluoromethyl ketones by a Friedel–Crafts acylation reaction has appeared from Simchen and Schmidt.[27] They used 4-dimethylamino-1-trifluoroacetylpyridinium trifluoroacetate as an effective, easy to handle and stable trifluoroacetylation agent. Arenes are converted to their corresponding trifluoromethyl ketones by its action in the presence of aluminium chloride.

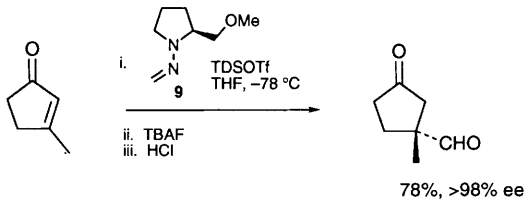
The synthesis of a variety of ketones, in moderate yield, by the lithium-mediated coupling of carboxylic acids and alkyl or aromatic chlorides has been detailed by Yus and co-workers (**Scheme 8a**).[28] Rapoport and Mattson have also devised a method for the conversion of carboxylic acids to ketones.[29] They found that the addition of a Grignard reagent (100 mol%) to an acyl hemiacetal in dichloromethane generates the corresponding ketone with little tertiary alcohol formation (**Scheme 8b**). If desired, the formation of the acyl hemiacetal and Grignard addition can be carried out in the same pot.



Scheme 8

An interesting synthesis of enantio-enriched β-formyl ketones from α,β-unsaturated ketones (**Scheme 9**) has been reported by Lassaletta *et al.*[30] This is achieved by an enantioselective Michael addition of the neutral formyl anion equivalent **9**. The addition of the formaldehyde (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP)-hydrazone **9** is promoted by dimethyl(1,1,2-dimethylpropyl)silyl (TDS) trifluoromethanesulfonate.

Secondary and tertiary alkylzinc bromides have been found to add conjugatively to α,β-unsaturated ketones, in the presence of trimethylsilyl chloride and $BF_3 \cdot OEt_2$, without a copper catalyst.[31]

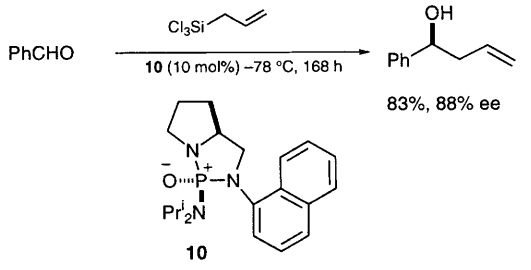


Scheme 9

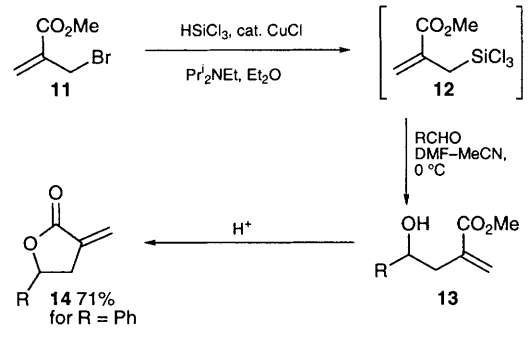
2 Reactions of aldehydes and ketones

2.1 Synthesis of alcohols *via* allylation

Many new methods involving the nucleophilic allylation of aldehydes and ketones have appeared during the period covered by this review. Many of these methods involve asymmetric allylation. For example, Kobayashi and co-workers have developed a very efficient protocol for the asymmetric allylation of aldehydes using phosphoramides as substoichiometric catalysts.[32] The best results were obtained for the reaction of benzaldehyde and allyltrichlorosilane with the catalyst **10** derived from (*S*)-proline (**Scheme 10**). Kobayashi *et al.* have also found that the trichloro(allyl)silane **12** is a useful precursor in the synthesis of α-methylene-γ-lactones **14** (**Scheme 11**).[33] The allylsilane **12** was prepared by the reaction of methyl α-(bromomethyl)acrylate **11** in the presence of copper(I) chloride and diisopropylamine. The intermediate **11** reacts with aldehydes to give the corresponding α-methylene-γ-hydroxy esters **13**, which readily cyclise to the lactones **14** upon treatment with acid.

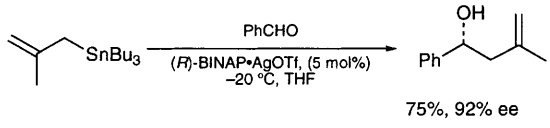


Scheme 10



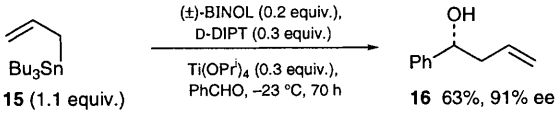
Scheme 11

It is not often that reports appear describing asymmetric catalysis using a silver catalyst. However, a particularly efficient process for the catalytic asymmetric allylation of aldehydes using a chiral silver(I) complex has been described by Yamamoto and co-workers.[34] Having screened a range of metal catalysts and found that the efficiency of the silver trifluoromethanesulfonate-catalysed allylation of benzaldehyde is greatly improved by the presence of triphenylphosphine, the group developed an asymmetric process. The catalyst BINAP•AgOTf, prepared from BINAP and silver(I) trifluoromethansulfonate, gives the highest enantioselectivity in the reaction of methallyltributyltin (**Scheme 12**). Although the catalytic mechanism has not yet been fully elucidated, the BINAP•AgOTf complex is thought to act as a chiral Lewis acid rather than an as a precursor to an allylsilver reagent.



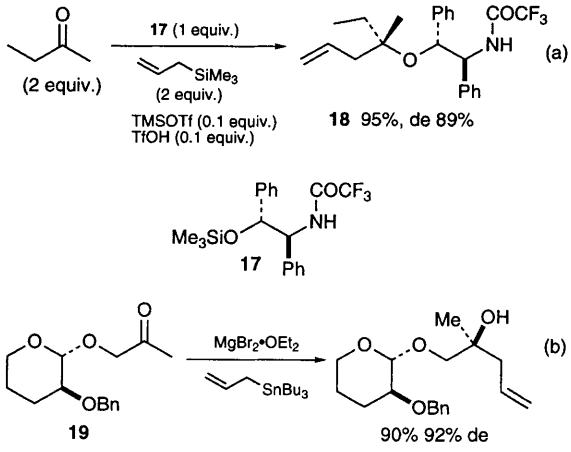
Scheme 12

The enantioselective addition of tributyl(allyl)stannane to aldehydes is known to be effected particularly efficiently with (*R*)- or (*S*)-BINOL [1,1′-bi(2-naphthol)] and $Ti(OPr^i)_4$. Faller *et al.* have developed a cheaper alternative process that avoids the use of very expensive resolved BINOL.[35] They showed that there is a non-linear relationship between the enantiomeric excess of the product and the BINOL catalyst. Exploiting this finding, they found that a catalyst prepared from racemic BINOL–$Ti(OPr^i)_4$ and D-diisopropyl tartrate (DIPT)–$Ti(OPr^i)_4$ (both of which are poor catalysts on their own) was a good one for the process (**15**→**16**)(**Scheme 13**). The addition of the (DIPT)–$Ti(OPr^i)_4$ poison appears to deactivate the (*R*)-BINOL derived catalyst far more effectively than the (*S*)-BINOL derived catalyst.



Scheme 13

The new 1,2-amino alcohol derivative **17** and its application in the stereoselective allylation of ethyl methyl ketone has been described by Tietze *et al.*[36] The allylation of ethyl methyl ketone with allyltrimethylsilane is catalysed by **17**, allowing the synthesis of homoallylic ether **18** with high enantio- and diastereo-selectivity (de 89%)(**Scheme 14a**). Charette *et al.* have shown that the addition of allyltributylstannane to ketones of the type **19**



Scheme 14

(**Scheme 14b**), possessing the 2-benzyloxytetrahydropyranyl group, is also highly diastereoselective in the presence of $MgBr_2 \bullet OEt_2$.[37]

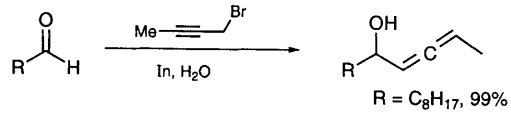
Many non-asymmetric allylation procedures have been developed in the past year. For example, Aggarwal and Vennall[38] have found that scandium trifluoromethanesulfonate (2–10 mol%) is a highly efficient catalyst for the addition of allyltrimethylsilane to both aromatic and aliphatic aldehydes. Kobayashi and Nagayama have shown that scandium(III) chloride supported on Nafion (NR-50) catalyses the allylation of aldehydes with tetraallylstannane in a continuous flow system.[39] Young and co-workers also describe a convenient allylation procedure.[40] They have found that tetraallyltin adds to aldehydes in methanol at 30 °C with no additional catalysts. Tin-mediated additions of allylic bromides to aldehydes lead to adducts with high diastereoselectivity and diastereofacial selectivity in the presence of indium trichloride in water.[41] A similar reaction can be carried out in acetonitrile or dichloromethane.[42] Tin also features in a new reagent system (allylbromide–tin–Me_3SiCl–MeOH) designed for the allylation of aldehydes and ketones.[43] Trehan and co-workers demonstrate that the Brønsted acid bis(fluorosulfuryl)imide catalyses the addition of allyltrimethylsilane to carbonyl compounds.[44]

A mild and simple zinc-promoted Barbier-type allylation of aromatic aldehydes in liquid ammonia has been published by Makosza and Grela.[45] The authors comment that procedures involving liquid ammonia are often considered inconvenient. However, they argue that their procedure is simple and convenient. The ammonia is introduced into a cold reaction flask (dry ice–acetone) and the reaction temperature is kept constant at −33 °C by allowing the ammonia to evaporate slowly. The use of ammonia on a large scale is also convenient since it is cheap, readily available and easily recycled.

Whitesell and Apodaca detail a procedure for the allylation of aldehydes with allyltributyltin in the presence of 10 mol% dibutyltin dichloride and either an acid chloride or trimethylsilyl chloride. Homoallylic esters, carbonates, trimethylsilyl ethers, and alcohols were obtained in up to 99% yield.[46] The use of bis(pentafluorophenyl)tin dibromide as a catalyst for the same reactions has been described by Otera and co-workers.[46]

The Lewis acid-mediated reaction of an aldehyde with allylstannanes and allylsilanes is usually faster than the reaction of the corresponding imine. Yamamoto and co-workers outline a reaction with entirely the opposite chemoselectivity.[47] They found that imines are allylated chemoselectively in the presence of aldehydes using allylstannanes with a π-allylpalladium chloride dimer catalyst. Kang and co-workers report the palladium-catalysed carbonyl allylation of aldehydes with allylic phosphates.[49] The allylation is effected by reaction of the aldehyde with an allylic phosphate and diethylzinc in the presence of catalytic $Pd(PPh_3)_4$. The reaction is thought to proceed *via* addition of a nucleophilic allylzinc species to the aldehyde.

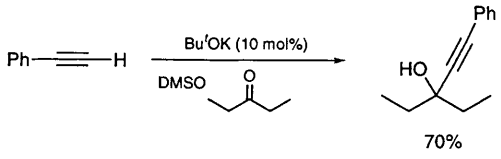
Chan and Isaac describe a useful, and related, protocol for the coupling of aldehydes with prop-2-ynyl bromides in aqueous media mediated by indium to give allenyl alcohols (**Scheme 15**). As with other processes that can be carried out in water this procedure offers the benefits of a cheap, non-toxic, non-flammable solvent; there is no need for a hydroxy protecting group; substrates that show minimal solubility in organic solvents can be used; and selectivity changes often occur.[50] Aldehydes may be coupled with allyl bromides in a similar fashion.[51] A general useful review of synthetic organoindium chemistry[52] has appeared this year.



Scheme 15

2.2 Synthesis of alcohols *via* alkynylation

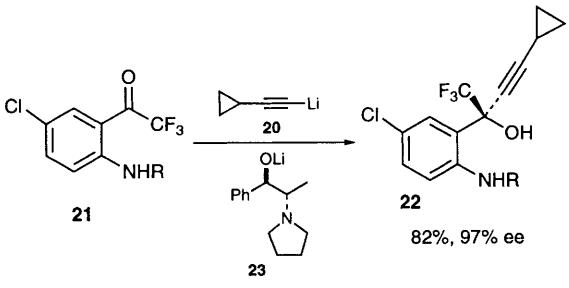
A useful procedure for the addition of terminal alkynes to ketones has been devised by Babler *et al.*[53] Examination of the equilibrium acidities in DMSO of phenylacetylene ($pK_a = 28.7$) and *tert*-butyl alcohol ($pK_a = 32.2$) indicated that potassium *tert*-butoxide would be a good base in the alkynation reaction. This turned out to be true (**Scheme 16**). Indeed, since the product of the addition to the ketone is initially a tertiary alkoxide, the base can be used catalytically. The procedure clearly has



Scheme 16

advantages over the strong bases used traditionally to facilitate this transformation (*e.g.* methylmagnesium bromide, butyllithium and sodium amide). Yoon and co-workers have found that sodium trimethyl(ethynyl)aluminate (STEA), prepared from sodium acetylide and trimethylaluminium, is an excellent chemoselective reagent for the addition of acetylide anion to ketones and aldehydes.[54] The reagent did not react with representative alkyl and benzyl halides, epoxides, amides and nitriles at room temperature and esters at 0 °C. Zwierzak and Tomassy report a procedure for the reaction of alkynylmagnesium bromides with paraformaldehyde, thereby avoiding the use of gaseous formaldehyde.[55]

Examples of the asymmetric catalytic addition of organolithium reagents to carbonyl compounds are rare. However, Thompson *et al.* have shown that the lithium acetylide **20** adds enantioselectively to the trifluoromethyl ketone **21** in the presence of the ephedrine alkoxide **23** to give the alcohol **22**, a key intermediate in the synthesis of the reverse transcriptase inhibitor L-743,726 (**Scheme 17**).[56]



Scheme 17

2.3 Synthesis of alcohols *via* alkylation

An excellent method for the enantioselective synthesis of alcohols involves the asymmetric catalytic addition of an organometallic reagent to an aldehyde. The organometallic reagent is usually an organozinc species. This area of research is proving as popular as ever (**Figure 1**). Some of the new catalysts used to promote the addition of diethylzinc to aldehydes include the diselenide **24**,[57] the proline-derived β-amino disulfide **25**,[58] the oxazolidine derivative **26**,[59] the oxazolidine **27** derived from the natural product abrine[60] and the zinc alkoxide **28**.[61]

The use of alkylzinc chemistry for the highly efficient enantioselective catalytic asymmetric automultiplication of chiral pyrimidinyl alcohol **30** has been impressively described by Soai and co-workers.[62] They describe a rare case of a catalytic reaction that incorporates the product as catalyst. In such reactions separation of the product and catalyst is clearly not an issue. In addition, once the first reaction has been performed the catalyst will be readily available. Soai and his group found that the addition of diisopropylzinc to pyrimidine-5-carbaldehyde is catalysed by the product of the

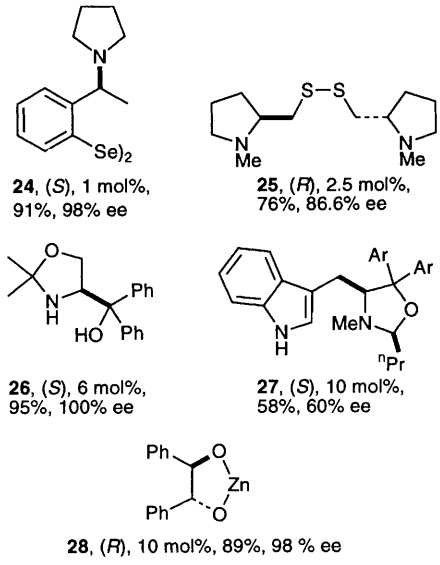
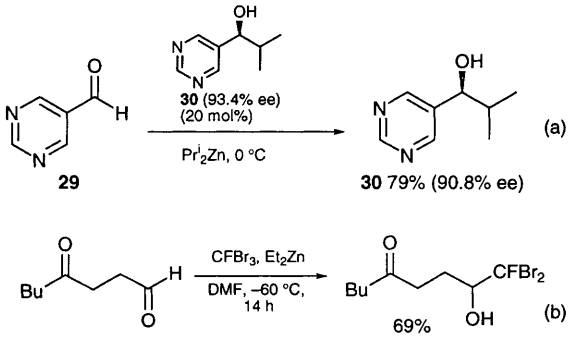


Figure 1 Selectivity in the addition of $ZnEt_2$ to PhCHO [configuration of PhCH(OH)Et, catalyst mol%, yield, ee]

reaction, the alcohol **30**. When the reaction is performed with enantio-enriched **30** (93.4% ee) the stereo-replication is highly efficient giving the product **30** with similar enantiopurity (90.8% ee) (**Scheme 18a**). The process has been described as a paradigm for the origin of the homochirality of natural biomolecules since it was found that when **30** (5% ee) is used as the catalyst the product alkanol has an enantiomeric excess of 39%.[63] The process therefore provides a mechanism by which a small initial imbalance in chirality can become overwhelming. The same principle of asymmetric autocatalysis has been demonstrated in the reaction of diisopropylzinc with quinoline-3-carbaldehyde.[64,65]

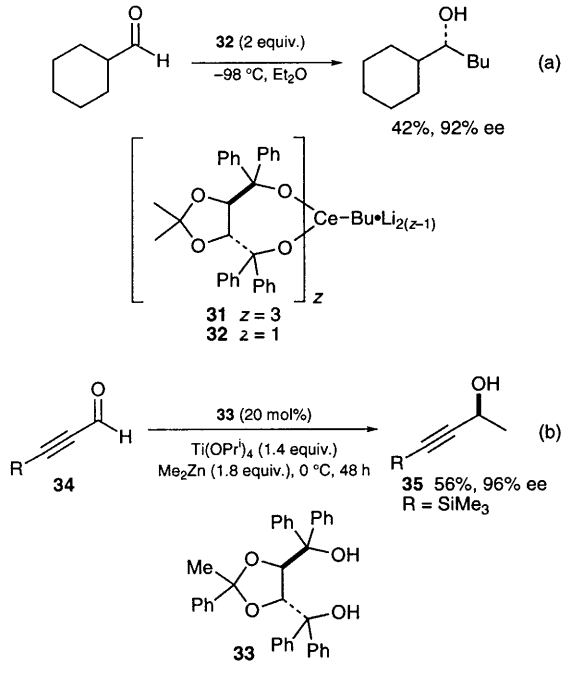
The carbenoid reagent $XZnCFBr_2$, prepared by treatment of tribromofluoromethane with diethylzinc, reacts smoothly and chemoselectively with aldehydes (**Scheme 18b**).[66] The method, described by Shimizu and co-workers, is a good one for the synthesis of α-dibromofluoromethyl alcohols.

Greeves and Pearce have illustrated, in two reports, that novel organocerium reagents incorporating TADDOL (α,α,α,α′-tetraaryl-1,3-dioxolane-



Scheme 18

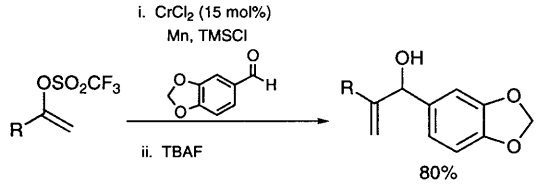
4,5-dimethanol) can be used to generate enantiomerically enriched alcohols from aldehydes. It was found that the tris(TADDOL) derivative **31** can be used to add a butyl group to aldehydes with the highest enantioselectivity (**Scheme 19a**).[67] The enantioselectivity is much higher than when the complex **32**, which only has one TADDOL ligand, is used.[68] Oguni *et al.* have used a related reaction incorporating the TADDOL derivative **33** to make the prop-2-ynyl alcohol **35** (**Scheme 19b**).[69] Of the many catalysts tested the complex **33**–$Ti(OPr^i)_4$ was the best for promoting the addition of dimethylzinc to the aldehyde **34**.



Scheme 19

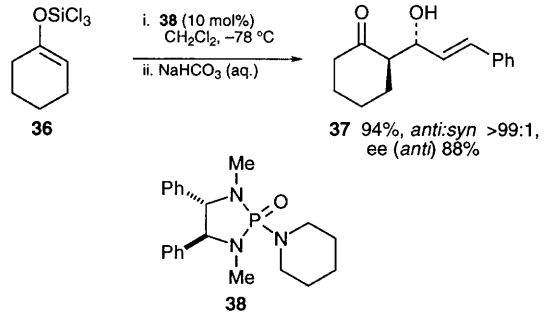
The Nozaki–Hiyama–Kishi coupling of organochromium compounds to aldehydes provides a powerful method for the synthesis of alcohols. However, the toxicity of chromium salts greatly reduces its attractiveness for large-scale applications. Fürstner and Shi have devised a modified process that involves a catalytic amount of chromium chloride [doped with nickel(II) chloride] and stoichiometric manganese (**Scheme 20**).[70]

A well established method for the synthesis of β-keto alcohols from aldehydes involves the aldol reaction. Many important procedures concerning



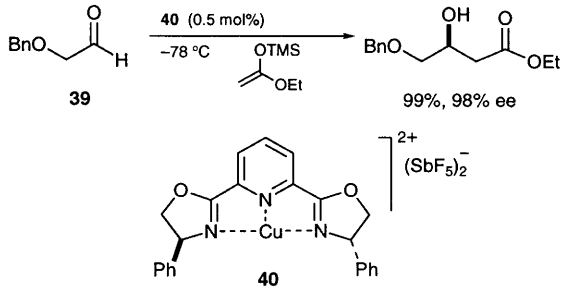
Scheme 20

the aldol reaction have been published in the past year. For example, Denmark *et al.* report a new system for effecting catalytic asymmetric aldol reactions. They have found that trichlorosilyl enolates (derived from tributylstannyl enolates and silicon tetrachloride) are highly reactive in the chiral phosphoramide-catalysed asymmetric aldol reaction (**Scheme 21**).[71] For example, the trichlorosilyl enolate **36** derived from cyclohexanone reacts, in the presence of the phosphoramide **38**, with (*E*)-cinnamaldehyde to give the *anti* aldol product **37** with excellent diastereoselectivity and high enantioselectivity.



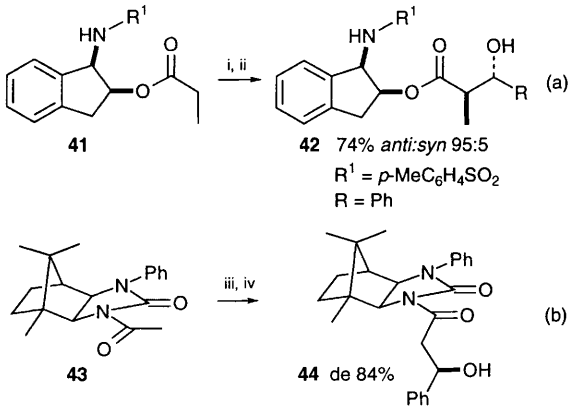
Scheme 21

Evans *et al.* have developed an excellent asymmetric variant of the Mukaiyama aldol reaction of α-benzyloxy aldehydes **39** (**Scheme 22**).[72] These types of aldehyde react with trimethylsilylketene acetals in the presence of the C_2-symmetric copper(II) complex **40** with exceptionally high enantioselectivity. The success of the reaction is due, in part, to the aldehyde's ability to coordinate to the copper atom in a bidentate fashion. The indium trichloride-catalysed Mukaiyama aldol reaction has been reported by Loh *et al.*[73] They found that ketone trimethylsilyl enol ethers react in water with aldehydes in the presence of indium(III) chloride (20 mol%) to afford the corresponding aldol products in good yields. The ever effective Lewis acid scandium trifluoromethanesulfonate catalyses the aldol reaction of polymer-supported silyl enol ethers with aldehydes, providing a convenient method for the preparation of β-hydroxy ester libraries.[74]



Scheme 22

The use of the *cis*-1-amino-2-indanol as an auxiliary for the synthesis of enantiomerically pure *anti* aldol products (**Scheme 23a**) has been described by Ghosh and Onishi. The reaction of the (*Z*)-titanium enolate of **41** with aldehydes is both highly diastereo- and enantio-selective. The methodology provides convenient access to either *anti* aldol enantiomer **42** since both enantiomers of *cis*-1-amino-2-indanol, from which **41** is derived, are commercially available. Palomo *et al.* have shown that enolate of the chiral imide acetate **43** reacts upon lithium and titanium enolate formation with aldehydes in a stereoselective manner (**Scheme 23b**).[76] For example the reaction of the lithium enolate of with benzaldehyde (**43**→**44**) provides a rare example of a stereoselective reaction of a chiral enolate that bears no α-substituents other than hydrogen.

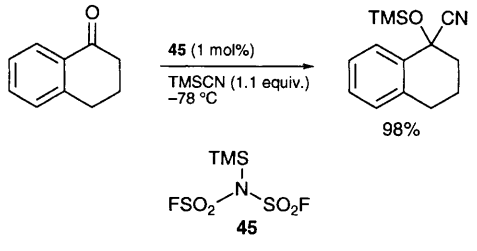


Reagents: i. $TiCl_4$, Pr^i_2NEt, 23 °C; ii. RCHO, $TiCl_4$, CH_2Cl_2, –78 °C; iii. $TiCl_4$, Pr^i_2NEt, 0 °C; iv. PhCHO, –78 °C

Scheme 23

2.4 Synthesis of cyanohydrins

Trehan and co-workers have found that *N*-trimethylsilylbis(fluorosulfonyl)imide **45** is an efficient catalyst for the addition of trimethylsilyl cyanide to ketones and aldehydes (**Scheme 24**).[77] In the presence of **45** (1 mol%), trimethylsilyl cyanide adds efficiently to carbonyl compounds to give the corresponding *O*-trimethylsilyl cyanohydrin. The imide **45** is a more effective catalyst for the reaction than trimethylsilyl trifluoromethanesulfonate. A combination of dibutyltin dichloride and diphenyltin dichloride also functions as an effective catalyst for the trimethylsilylcyanation of aldehydes and ketones.[78] Numbered among the various catalysts that have been used for the asymmetric trimethylsilylcyanation of aldehydes are the salen [bis(salicylidene)ethylenediamine] complexes **46**[79] and **47**[80] and the Schiff base **48** (**Figure 2**), all of which are used in combination with $Ti(OPr^i)_4$.[81]



Scheme 24

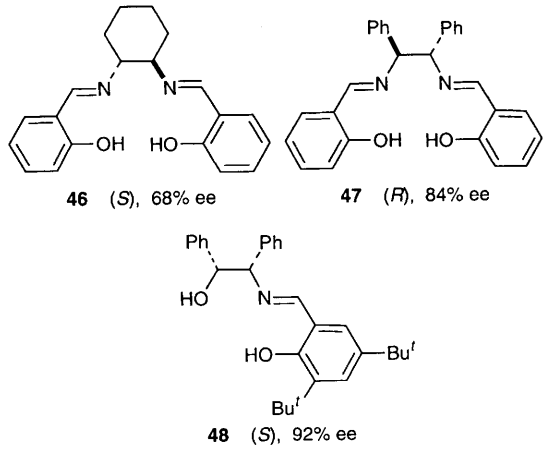
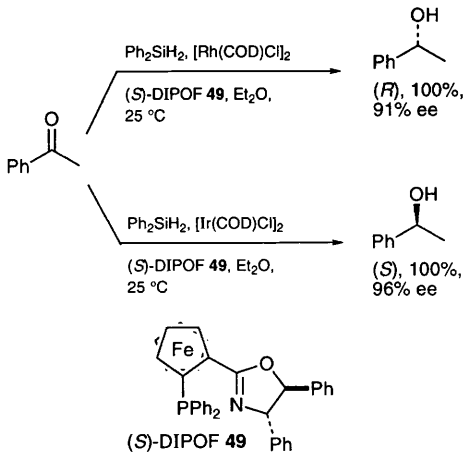


Figure 2 : Enantioselectivities in the addition of TMSCN to PhCHO with $Ti(OPr^i)_4$ (configuration of the product TMS-cyanohydrin, ee)

2.5 Reduction of aldehydes and ketones

The development of new reagents for the efficient reduction of aldehydes and ketones has featured widely this year. For example, Kobayashi *et al.* report that a combination of trichlorosilane and dimethylformamide efficiently reduces aldehydes and imines.[82] The reagent system also effects reductive amination of aldehydes under mild conditions. Hypervalent hydridosilicates, generated by the coordination of DMF to Cl_3SiH, are the active reducing species, which enable efficient and selective reduction under mild conditions. An aryl chloride and aryl nitro group and carbon–carbon double and triple bonds are tolerated by the system. Uemura and co-workers also describe the reduction of ketones using a silane, but in this case the reaction is asymmetric. They found that the chiral oxazolylferrocenylphosphine hybrid ligand (DIPOF) **49** is a very efficient ligand for the iridium(I)-catalysed asymmetric hydrosilylation of simple ketones (**Scheme 25**).[83] After acid hydrolysis, the product secondary alcohols are obtained in very high optical purity (ee up to 96%). Strangely when the iridium complex is replaced by the corresponding rhodium complex, the antipodal alcohol is isolated.[84] Iodotrichlorosilane, prepared *in situ* from $SiCl_4$–NaI, effects the chemoselective reduction of α,β-unsaturated ketones to their saturated counterparts.[85] Similarly, Cu–SiO_2 can be conveniently used for the hydrogenation of conjugated enones to



Scheme 25

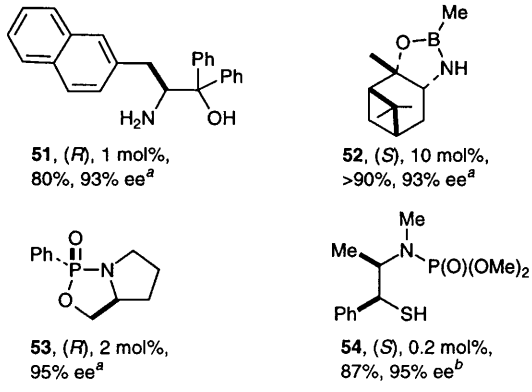
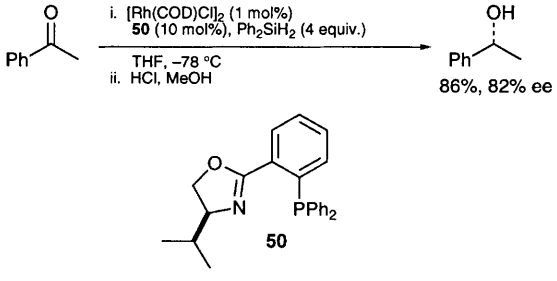


Figure 3 Selectivity in the borane reduction of PhCOMe[a] or PhCOEt[b] (configuration of product, catalyst mol%, yield, ee)

saturated ketones in the presence of isolated alkene functionality present within the same molecule.[86] Molecular hydrogen or propan-2-ol can also be used as the hydrogen source. The H_2–Lindlar catalyst system has been found to be highly effective for the reduction of carbon–carbon double bonds of α,β-unsaturated carbonyl compounds.[87]

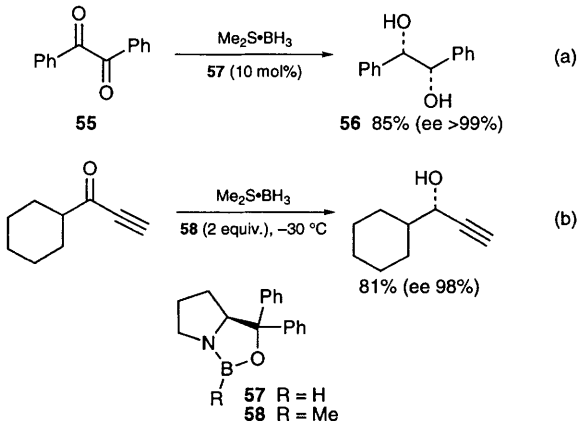
Williams[88] and co-workers describe the rhodium-catalysed asymmetric reduction of ketones using phosphorus-containing oxazoline ligands. The rhodium-catalysed hydrosilylation of acetophenone in the presence of the oxazolinyl phosphine ligand **50** proceeds with good enantioselectivity (**Scheme 26**). The same observation was reported, at the same time, by Helmchen[89] and co-workers.



Scheme 26

Asymmetric protocols using oxazaborolidine catalysts have seen widespread use for the borane reduction of ketones.[90] Among the many new catalysts, introduced over the past year, are the β-amino alcohol **51**,[91] the pinene-derived oxazaborolidine **52**,[92] the oxazaphospholidine oxide **53**[93] and the thiol **54** (**Figure 3**).[94]

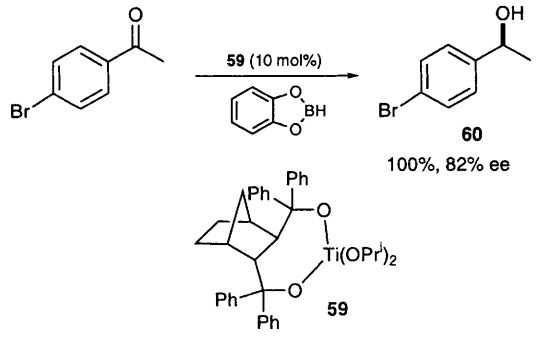
Prasad and Joshi have shown that the oxazaborolidinone catalysed borane reduction of diaryl-1,2-diones leads to the corresponding enantiomerically pure 1,2-diol.[95] For example, benzil **55** gives (1*S*,2*S*)-dihydrobenzoin **56** (ee > 99%) when treated with borane–dimethyl sulfide and the oxazaborolidinone catalyst **57** (**Scheme 27a**). In this case the ratio of *threo* to *erythro* diastereoisomers is 88:12. The procedure provides a useful alternative to the Sharpless asymmetric dihydroxylation protocol. Parker and Ledeboer have revealed that the related oxazaborolidinone **58** is an excellent catalyst for the borane reduction of alkynyl ketones (**Scheme 27b**).[96] The ketones are reduced rapidly with high enantioselectivities. The process was particularly effective where other procedures, {BINAL-H [lithium 1,1′-bi(2-naphthoxy)aluminium hydride] and Alpine-borane[98]} were ineffective, due to the associated long reaction times.



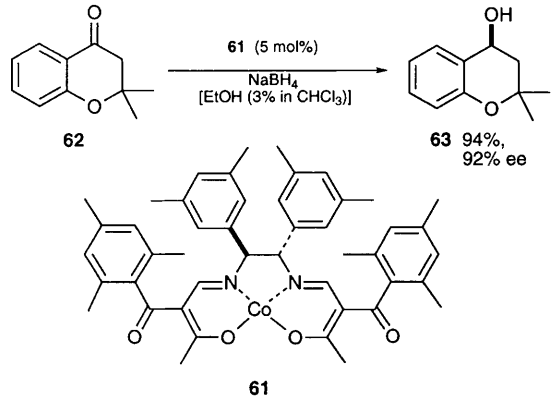
Scheme 27

The use of chiral titanium alkoxides as catalysts for the enantioselective reduction of ketones with boranes (**Scheme 28**) has been disclosed by Wandrey and co-workers.[97] For example, the TADDOL-like ligand **59** catalyses the catechol-borane reduction of *p*-bromoacetophenone with high selectivity to give the alcohol **60**.

A cobalt-based asymmetric reducing system has been designed by Mukaiyama and co-workers. They have shown that the (β-oxoaldiminato)cobalt(II) complex **61** is a highly efficient catalyst for the



Scheme 28

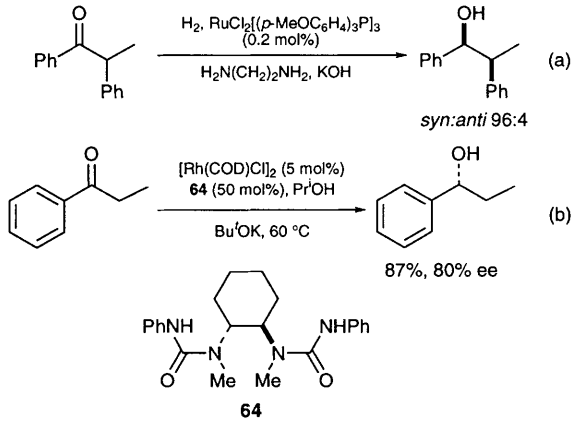


Scheme 29

reduction of prochiral ketones with sodium borohydride *e.g.* (**62→63**)(**Scheme 29**).[98]

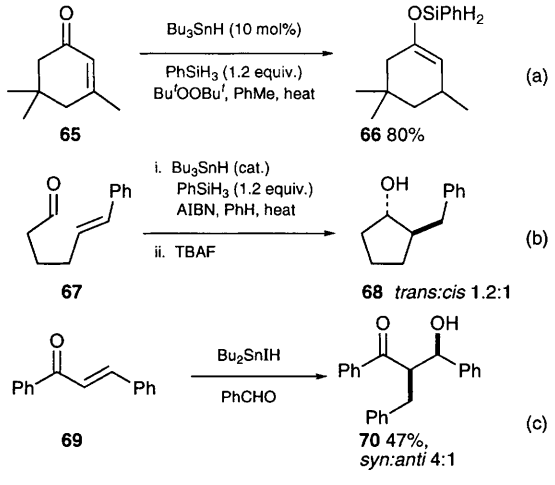
The development of modified borohydride reagents for the non-asymmetric reduction of carbonyl compounds has also been a particularly active area of research this year. For example titanocene borohydride (prepared *in situ* from Cp_2TiCl_2 and $NaBH_4$ in DME) has been shown to effect the efficient reduction of ketones to the corresponding alcohols. The reduction of 4-*tert*-butylcyclohexanone is highly *trans* selective (*trans:cis* = 97:3).[99] Another titanium reagent, diisopropoxytitanium(III) tetrahydroborate, made by Ravikumar and Chandrasekaran is also an excellent reducing agent for the chemoselective reduction of ketones.[100] With this reagent cyclic ketones are reduced with excellent axial hydride delivery. α,β-Unsaturated aldehydes are reduced efficiently to give allylic alcohols. The reagent is prepared *in situ* by the reaction of diisopropoxytitanium dichloride with benzyltriethylammonium borohydride (2 equiv.). Another borohydride reagent, methyltriphenylphosphonium borohydride, reduces aldehydes and ketones in dichloromethane to their corresponding alcohols in high yield; α,β-unsaturated carbonyl compounds undergo 1,2-reduction.[101]

A ruthenium(II) catalyst formed *in situ* from $RuCl_2(PPh_3)_3$, a 1,2-diamine and potassium hydroxide in 1:1:2 molar ratio effects the facile reduction of various ketones in propan-2-ol in 1–8 atm of hydrogen.[102] The process, developed by Noyori and co-workers, presents a good method for the diastereoselective synthesis of alcohols. For example, the reduction of 4-*tert*-butylcyclohexanone occurs with excellent *cis* selectivity (*cis:trans* 4-*tert*-butylcyclohexanol 98.4:1.6). The reducing system shows excellent Cram selectivity when tris(*p*-methoxyphenyl)phosphine is part of the catalyst (**Scheme 30a**). Lemaire and co-workers have found that the ligand **64**, containing two urethane groups, gave the best enantioselectivity in the rhodium-catalysed reduction of propiophenone using propan-2-ol as the hydrogen source (**Scheme 30b**).[103] Rubidium- and strontium-modified L zeolite-supported platinum catalysts are highly selective for the chemoselective hydrogenation of cinnamaldehyde to cinnamyl alcohol.[104]



Scheme 30

Several reductive methods involving substituted tin hydrides as the active reducing species have appeared in the past year. A useful method for the conjugate reduction of α,β-unsaturated ketones using catalytic tributyltin hydride (**Scheme 31a**) has been disclosed by Fu and co-workers.[105] Using a combination of phenylsilane and tributyltin hydride (cat.) in the presence of a radical initiator the enone

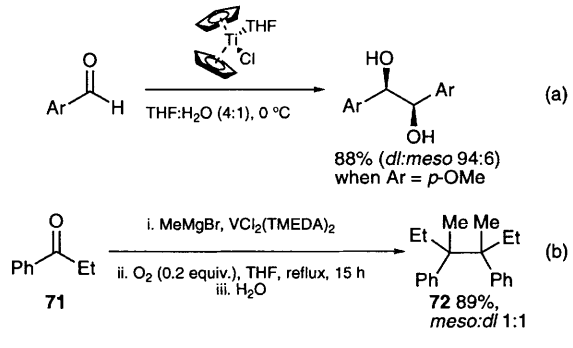


Scheme 31

65 is reduced to the silyl enol ether **66** from which the corresponding ketone can be generated by alkaline hydrolysis. The process has the obvious advantage of involving substoichiometric quantities of the toxic tin hydride. The same workers have also shown that the Bu_3SnH(cat.)–$PhSiH_3$ system can be used to effect the reductive cyclisation of enals and enones (*e.g.* **67→68**)(**Scheme 31b**).[106]

Baba and co-workers describe the use of dibutyliodotin hydride for the reduction of α,β-unsaturated ketones.[107] The reagent reduces aldehydes in poor yield. This chemoselectivity can be exploited to enable aldol reactions to be carried out between α,β-unsaturated ketones and aldehydes (*e.g.* **69→70**)(**Scheme 31c**). The conjugate reduction of α,β-unsaturated ketones and aldehydes is also effected by the combined action of the Lewis acid aluminium tris(2,6-diphenylphenoxide) and the complex DIBAlH–BuLi.[108]

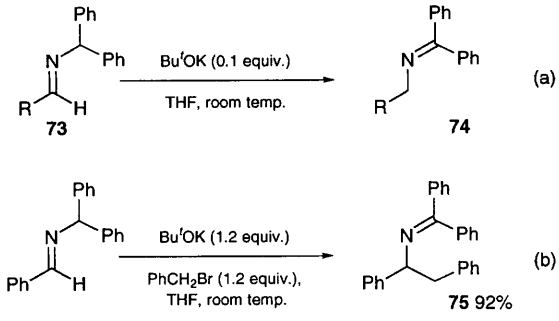
The pinacol coupling of aldehydes and ketones is a particularly useful route to glycols. However, most methods require rigorously dry reaction conditions and are incompatible with protic functionality. A procedure that avoids these restrictions has been developed by Barden and Schwartz.[109] They have found that reaction of titanocene chloride with aromatic aldehydes, in a mixture of THF and brine, yields the corresponding 1,2-diol with very high stereoselectivity (**Scheme 32a**). A simple and rapid procedure for effecting the pinacol reaction of aromatic aldehydes has been devised by Khurana *et al.* The pinacol reaction is effected by the inexpensive combination of aluminium powder and potassium hydroxide in methanol at room temperature.[110] Hindered ketones are reduced to the corresponding alcohols by the same reagent. A reaction related to the pinacol coupling has been reported by Kataoka and Tani and co-workers. They have devised a new C–C single bond-forming reaction by reductive coupling mediated by a system comprised of a Grignard reagent, low-valent vanadium and a catalytic amount of oxygen (**Scheme 32b**).[111] For example, the coupled product **72** is formed by reaction of the ketone **71**, using methylmagnesium bromide in the presence of vanadium(II) dichloride(TMEDA)$_2$. The intermediate alkoxyvanadium species undergoes reductive coupling by the action of oxygen to give **72**.



Scheme 32

Several new methods for the reductive amination of aldehydes and ketones have been reported in the past year. A general, preparatively efficient, simple method for the preparation of *N*,*N*-dialkyl-*N*-(β-phenylethyl)amines, *via* reductive alkylation of benzylaldehyde and benzyl ketones with various dialkylamines, using titanium(IV) isopropoxide and $NaBH_4$ has been reported by Bhattacharyya.[112] DiMare and co-workers have devised a simple and mild protocol for the reductive amination of aldehydes and ketones using methanolic pyridine–borane, an amine and 4 Å molecular sieves.[113]

An efficient transamination protocol under mild conditions has been revealed by Cainelli, Giacomini and co-workers.[114] This is not really a reduction, but is included here since it represents a reaction equivalent to the reductive amination of an aldehyde. The method is ideal for the transformation of aldehydes to amines, *via* their imines **73** derived from aminodiphenylmethane (**Scheme 33a**). Treatment of the imine **73** with a catalytic amount of potassium *tert*-butoxide generates the isomerised product **74** in excellent yield. Subsequent hydrolysis with hydrochloric acid generates the amine. When the aldehyde is benzaldehyde or 2-furaldehyde the intermediate 2-azaallyl anion can be trapped with a variety of electrophiles to generate a secondary amine derivative **75** (**Scheme 33b**). The corresponding reaction of ketones has only been reported for 1,2-diones.



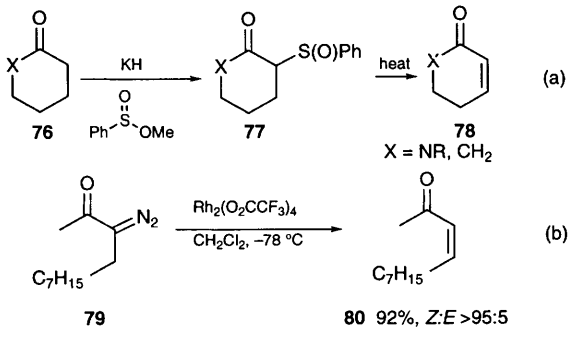
Scheme 33

A modified Clemmensen reduction procedure for conversion of aryl ketones into aryl alkenes is reported by Hiegel and Carney.[115] Aryl alkenes can be prepared from aryl ketones through reduction by treatment with amalgamated zinc in a mixture of formic acid and ethanol.

2.6 Oxidation of aldehydes and ketones

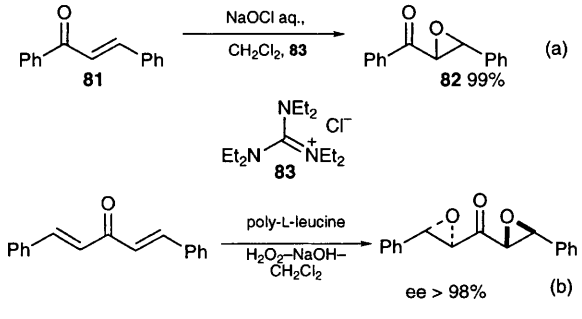
Meyers and Resek report the synthesis of α,β-unsaturated ketones, nitriles and lactams from the saturated carbonyl compound using methyl phenylsulfinate.[116] The sulfinate is prepared by the treatment of diphenyl disulfide with bromine in the presence of methanol. α-Sulfinyl carbonyl compounds **77** are formed upon treatment of a mixture of the methyl phenylsulfinate and the

carbonyl compound **76** with potassium hydride. Thermal elimination of the sulfoxide **77** generates the α,β-unsaturated carbonyl compound **78** (**Scheme 34a**). Although not an oxidation the following synthetic method is related to the previous one. Taber *et al.* have shown that α-diazo ketones undergo β-hydride elimination with rhodium(II) trifluoroacetate to produce (*Z*)-α,β-unsaturated ketones in high yield (**79→80**)(**Scheme 34b**).[117] This contrasts with the rhodium(II) acetate-catalysed reaction which also produces carbocycles from a competing 1,5-insertion process.



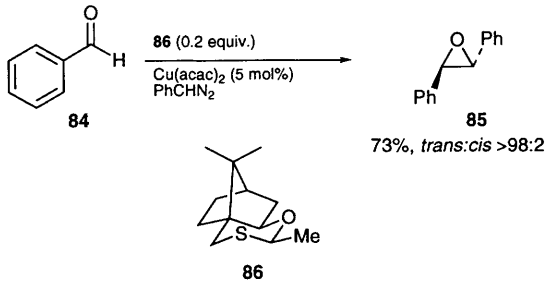
Scheme 34

Several methods for the epoxidation of alkenes have appeared over the past year. For example, Mioskowski and co-workers have found that sodium hypochlorite is a convenient oxidant for the epoxidation of α,β-unsaturated ketones (**81→82**)(**Scheme 35a**).[118] This is possible by employing a two-phase system and hexaethylguanidinium chloride **83** as a phase-transfer agent. An intriguing asymmetric process for the epoxidation of α,β-unsaturated ketones and dienones has been disclosed by Roberts and co-workers (**Scheme 35b**).[119,120] In these reactions poly-L-leucine and poly-D-leucine are used as asymmetric catalysts.



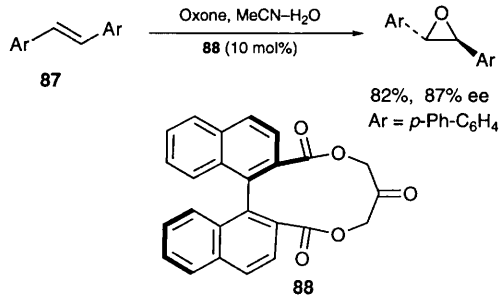
Scheme 35

An optimised process for the direct asymmetric epoxidation of aldehydes using an ingenious reagent system that involves a catalytic sulfide is described by Aggarwal *et al.*[121] A mixture of aldehyde, diazo compound, catalytic enantiopure sulfide **86** and copper(II) acetylacetonate provides an efficient route to epoxides (**84→85**) with *trans* selectivity. The sulfur ylide is generated from the copper-catalysed reaction of the sulfide and diazo compound. The ylide reacts with the aldehyde to provide the epoxide, of exceptionally high enantiopurity, and returns the sulfide to the catalytic cycle (**Scheme 36**).



Scheme 36

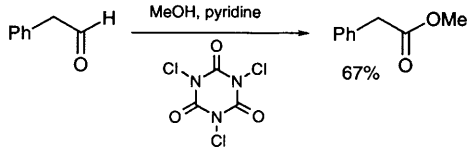
The use of the C_2-symmetric chiral ketone **88** for the asymmetric epoxidation of unfunctionalised olefins (**Scheme 37**) has been described by Yang and co-workers.[122] The axially chiral ketone **88** is particularly effective for the asymmetric epoxidation of the stilbene derivative **87** (ee 87%). The reaction is carried out using Oxone® in an homogeneous acetonitrile–water solvent system. This is the highest enantioselectivity reported for the epoxidation of an alkene *via* a chiral dioxirane.



Scheme 37

α-Halo ketones are oxidatively cleaved to give carboxylic acids with sodium percarbonate, a stable, inexpensive, non-toxic and easily handled source of hydrogen peroxide.[123] For example, α-chlorocyclohexanone furnishes adipic acid. It was found that the reaction is greatly accelerated by ultrasound. The complex, HOF•MeCN made directly by bubbling fluorine through aqueous acetonitrile, reacts quickly and efficiently with enolic forms of ketones to produce α-hydroxy ketones.[124]

Hiegel *et al.* report the potentially useful direct oxidative conversion of an aldehyde to its corresponding methyl ester in the absence of metals (**Scheme 38**).[125] Treatment of the aldehyde with a

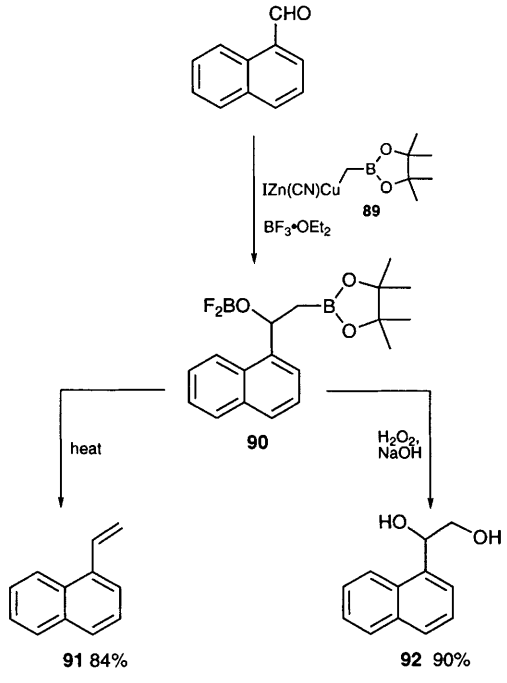


Scheme 38

solution of methanol, pyridine and trichloroisocyanuric acid in acetone, acetonitrile or dichloromethane efficiently gives the methyl ester.

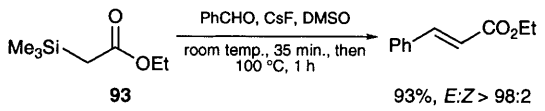
2.7 Alkene synthesis

Miyaura and co-workers[126] have shown that alkenes can be prepared from aldehydes using Knochel-like (dialkoxyboryl)methylcopper reagents (**Scheme 39**). The *in situ* preparation of **90** from Knochel's (dialkoxyboryl)methylzinc reagent **89** and CuCN•2LiCl in THF, followed by its addition to aldehydes in the presence of boron trifluoride–diethyl ether, yielded the rather stable β-hydroxyalkylboronate derivative **90**. The thermally promoted boron Wittig reaction or the alkaline hydrogen peroxide oxidation of **90** gave the corresponding alkenes **91** or 1,2-alkanediols **92** in high yields. The reaction provides a very simple procedure for the olefination or the hydroxymethylation of aldehydes.



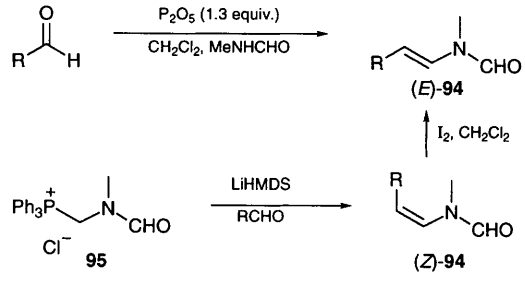
Scheme 39

A potentially useful modification of the Peterson olefination has been introduced by Bellassoued and Ozanne. The coupling of the silyl reagent **93** with an aldehyde and subsequent elimination of 'Me$_3$SiOH' are both catalysed by fluoride ion in DMSO in a one-pot operation (**Scheme 40**).[127]



Scheme 40

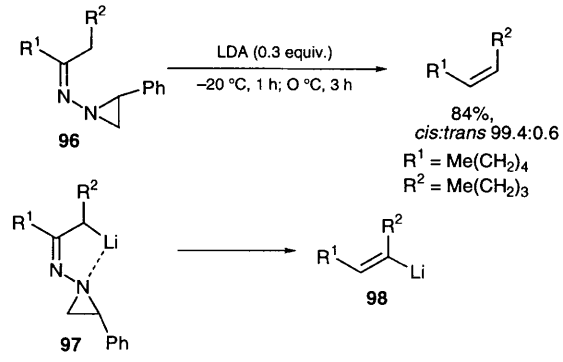
Two complementary methods for the conversion of an aldehyde to its corresponding *N*-alkenyl-*N*-methylformamide derivative **94** (**Scheme 41**) have been disclosed by Paterson *et al.*[128] The first method involves the acid-catalysed condensation of the aldehyde with *N*-methylformamide. Phosphorus pentoxide is the best catalyst, serving both as acid and dehydrating agent. The second method involves a Wittig reaction of the phosphonium salt **95** to produce the (*Z*)-formamide **94** as the major product (*E*:*Z* 1.4 to 1:10). Isomerisation to the (*E*)-alkene is achieved by treating the alkene with molecular iodine (5 mol%, CH_2Cl_2, 20 °C) in the absence of light. Patil and Mävers have found that the Wittig reaction between aldehydes and triphenyl(ethoxycarbonylmethylene)phosphorane can be carried out in hexane in the presence of silica gel. This protocol is a convenient method for the synthesis of (*E*)-α,β-unsaturated esters. The silica gel both accelerates the reaction and absorbs the triphenylphosphine oxide by-product. The product ester can be obtained pure by simply filtering the reaction mixture. An interesting review of asymmetric Wittig-type reactions has appeared this year.[130]



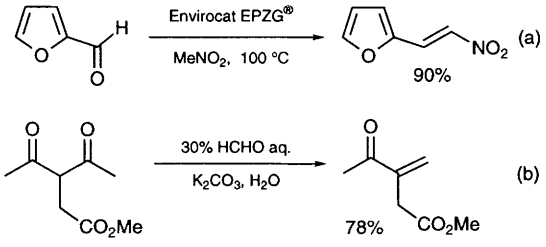
Scheme 41

An intriguing synthesis of alkenes from the *N*-(aziridin-1-yl)imine derivative of ketones is illustrated in **Scheme 42**.[131] This catalytic Shapiro reaction, invented by Yamamoto and co-workers, is effected by a substoichiometric quantity of LDA. The high levels of *cis* stereoselectivity and regioselectivity are explained by α-deprotonation of the hydrazone **96** to give the organolithium derivative **97**, which decomposes to the vinyllithium species **98** with extrusion of styrene and nitrogen. The LDA is regenerated from the diisopropylamine formed in the first step and the vinyllithium **98**.

Bandgar and co-workers have found that the Envirocat EPZG® is also an efficient and environmentally benign catalyst for the synthesis of conjugated nitroolefins *via* the Henry reaction of



Scheme 42

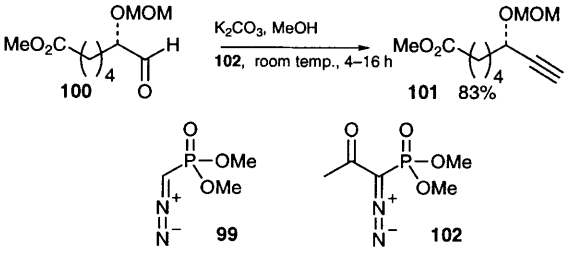


Scheme 43

aldehydes and nitroalkanes (**Scheme 43a**).[132] Ben Ayed and Amri have disclosed a potentially useful synthesis of α-functionalised but-1-en-3-one derivatives.[133] They found that the reaction of pentane-1,3-dione with 30% aqueous formaldehyde in the presence of potassium carbonate generates the corresponding butenone derivative (**Scheme 43b**).

2.8 Alkyne synthesis

It has long been known that the addition of the anion of dimethyl diazomethylphosphonate **99** to aldehydes generates alkynes. Bestmann and co-workers[134] have developed an improved one-pot procedure for the synthesis of terminal alkynes (**100** →**101**) from aldehydes using the phosphonate **102** (**Scheme 44**). The one-pot procedure is high yielding, under very mild conditions, without requiring low temperatures or inert gas techniques and avoids the use of strong bases. The anion of **99**

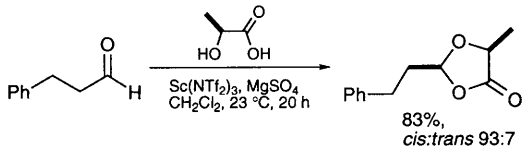


Scheme 44

is generated *in situ* by mild base promoted acyl cleavage of **102**. The procedure is likely to be a valuable alternative to the commonly used Corey–Fuchs dibromomethylation–elimination protocol.

3 Protection of aldehydes and ketones

By far the most common method for the protection of aldehydes and ketones involves the synthesis of acetals and thioacetals. Much research has focused on milder methods for their synthesis and removal. For example, Bandgar and co-workers[135] have found that the Envirocat EPZG® is an excellent homogeneous catalyst for the thioacetalisation of ketones and aldehydes with 1,2-ethanedithiol. The process offers high yields and easy separation of products and catalyst by filtration. The same transformation is catalysed by Fe^{3+}-exchanged montmorillonite,[136] and by kaolinitic clay.[137] Schmittel and Levis[138] describe the use of the one electron oxidant iron(III) tris(phenanthroline hexafluorophosphate) in the deprotection of benzyl-substituted 1,3-dithianes. Scandium trifluoromethanesulfonimide has been shown to be a highly efficient Lewis acid catalyst for the synthesis of ketals from ketones and 1,2 or 1,3-diols.[139] The catalyst can also be used for the diastereoselective preparation of 1,3-dioxolanones from aldehydes (**Scheme 45**).



Scheme 45

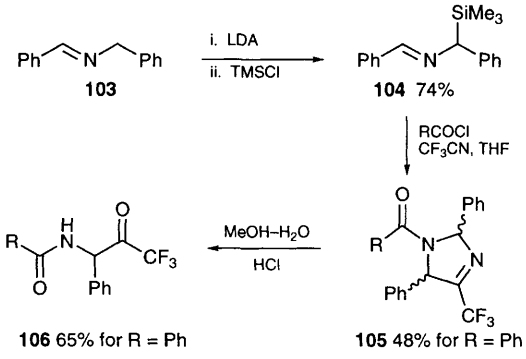
A novel method for the deprotection of *S,S*-acetals using air and catalytic bismuth(III) nitrate has been reported by Komatsu *et al.*[140] Both cyclic and acyclic *S,S*-acetals of ketones and aldehydes are smoothly deprotected to regenerate the parent carbonyl compound and diphenyl disulfide. Curini and co-workers have found that layered zirconium sulfophenyl phosphonate [*e.g.* $Zr(O_3PCH_3)_{1.2}(O_3PC_6H_4SO_3H)_{0.8}$] is an efficient heterogeneous catalyst for mild hydrolysis of oximes, semicarbazones and tosylhydrazones.[141] The same research group have also found that ketones and aldehydes can be regenerated from their corresponding 1,3-dithiolanes and 1,3-dithianes using Oxone® and wet alumina.[142]

A variety of other derivatives of ketones and aldehydes are converted to the parent carbonyl compound by new protocols. For example, enol ethers are converted to aldehydes by Bu_4NF–$BF_3 \cdot OEt_2$-catalysed hydrolysis.[143] Ketones are oxidatively regenerated, under neutral conditions, from tosylhydrazones by treatment with tetrabutylammonium peroxydisulfate.[144] The conversion of oximes, derived from aldehydes, into nitriles can be carried out in the absence of solvent using the

Envirocat EPZG® catalyst.[145] *O*-Acyloximes of aldehydes and ketones are easily reduced, to the corresponding amine, with sodium borohydride–iodine in a few hours.[146]

4 Halogenation of aldehydes and ketones

Katzenellenbogen and co-workers have developed an efficient route to trifluoromethyl ketones **106** using trifluoromethyl-substituted imidazolines (**Scheme 46**).[147] The imidazolines **105** are prepared by the reaction of the silyl *N*-benzylidenebenzylamine **104** (made from **103**) with acid chlorides and trifluoroacetonitrile. The reaction proceeds *via* a 1,3-dipolar cycloaddition between the *N*-acylazomethine ylide generated from the acid chloride and the silyl imine. Mild acid hydrolysis of the imidazoline generates the trifluoromethyl ketone **106**. The process can also be used to generate trifluoromethyl ketones that are incorporated in bioactive peptides.



Scheme 46

A series of *N*-fluoropyridinium-2-sulfonates including **107**, developed by Umemoto and Tomizawa act as highly selective electrophilic[148,149] fluorinating agents. Formal transfer of 'F^+' occurs with a variety of nucleophilic substrates including enol trialkylsilyl and alkyl ethers (**Scheme 47a**).[150]

α,α-Difluoro ketones are prepared from hydroxy-substituted aromatic derivatives by reaction with 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) [Accufluor™ *NFTh*] **108** in methanol or acetonitrile (**Scheme 47b**).[151] The same reagent **108** has also been used for the high-yield direct α-fluorination of ketones.[152] Iodotoluene difluoride can also be used to selectively fluorinate β-keto esters in the α-position.[153]

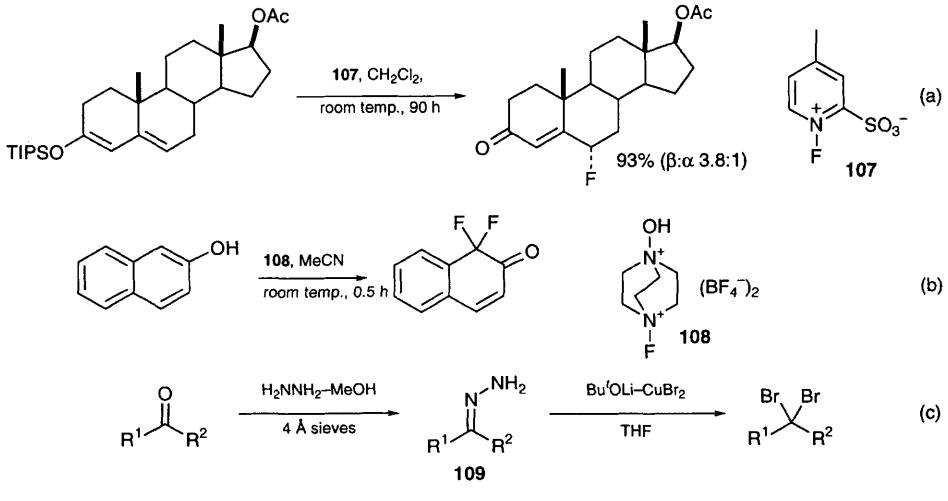
The bromination of 1,3-diketones can be achieved using a mixture of potassium bromate and potassium bromide in the presence of Dowex® 50X2-200 ion-exchange resin.[154]

A useful method for the transformation of ketones and aldehydes to *gem*-dibromides has been developed by Takeda *et al.*[155] The ketone or aldehyde is first converted to its corresponding hydrazone **109** which is then treated with copper(II) bromide–lithium *tert*-butoxide to give the *gem*-dibromide in good yield (**Scheme 47c**).

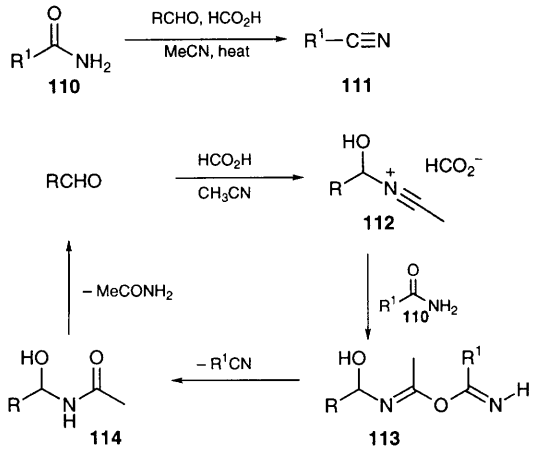
5 Miscellaneous transformations

Mioskowski and co-workers report an interesting procedure for the conversion of primary amides to nitriles (**110**→**111**)(**Scheme 48**).[156] The process involves aldehyde- and acid-catalysed water transfer from the amide to acetonitrile. Whilst various aldehydes are effective as catalysts, only formic acid serves as a successful acid catalyst. The proposed catalytic cycle involves the formation of the nitrilium salt **112** from the aldehyde, formic acid and acetonitrile. Reaction of this salt with the primary amide is thought to give the intermediate **113** which collapses, with release of the nitrile **111**, to the β-hydroxy amide **114**. The aldehyde is regenerated from the β-hydroxy amide **114** and at the same time producing acetamide. The mild reaction conditions should render the process useful.

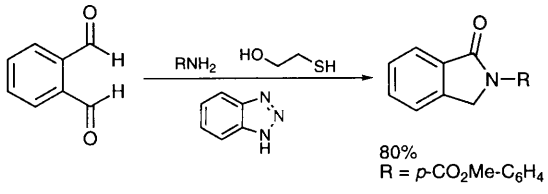
A potentially useful method for the synthesis of phthalimidine derivatives from *o*-phthalaldehyde and an amine has been revealed by Takahashi and co-workers (**Scheme 49**).[157] They found that the



Scheme 47



Scheme 48



Scheme 49

reaction is efficient when 1,2,3-1*H*-benzotriazole and 2-mercaptoethanol are present in the reaction mixture.

Finally, certain aldehydes can be decarbonylated by the action of scandium trifluoromethanesulfonate.[158] For example, 2,4,6-trimethoxybenzaldehyde on heating with scandium trifluoromethanesulfonate (16 mol%) is rapidly converted to 1,3,5-trimethoxybenzene and methyl formate. Aromatic aldehydes less electron rich than 2,4,6-trimethoxybenzaldehyde react very sluggishly.

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