

Second Supplements to the 2nd Edition of

RODD'S CHEMISTRY OF CARBON COMPOUNDS

A modern comprehensive treatise

Edited by

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Second Supplement to

VOLUME I ALIPHATIC COMPOUNDS

**Part C: Monocarbonyl Derivatives of Aliphatic Hydrocarbons,
Their Analogues and Derivatives**



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ALIPHATIC CARBONYL COMPOUNDS: ALIPHATIC ALDEHYDES

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1. Introduction

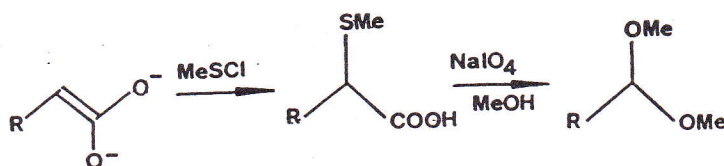
The recent literature reveals numerous improvements of earlier procedures and a prodigious number of new and quite effective methods for the synthesis of aliphatic aldehydes. A variety of monographs deals either comprehensively or with more or less specific areas of preparation of carbonyl compounds ("Aldehyde", Houben-Weyl, Methoden der Organischen Chemie, Vol. E3, J. Falbe, ed., G. Thieme, Stuttgart, New York, 1983; "Chromium Oxidation in Organic Chemistry", C. Cainelli, G. Cardillo, eds., Springer Verlag, Berlin, 1984; E.I. Negishi, "Organometallics in Organic Synthesis", Vol. 1, John Wiley & Sons, New York, 1980; A.I. Meyers, "Heterocycles in Organic Synthesis", John Wiley & Sons, London-New York-Sidney-Toronto, 1974; M. Peyreyre *et al.*, "Tin in Organic Synthesis", Butterworth Ltd., London, 1987; P. Hodge, D.C. Sherrington, "Polymer Supported Reactions in Organic Synthesis", John Wiley & Sons, New York 1980; R.A. Shelton, J.K. Kochi, "Metal Catalyzed Oxidations of Organic Compounds", Academic Press, New York, 1981). In addition there are various review articles partly describing the respective transformations into aldehydes of alcohols, alkyl halides, amino, nitro, and carbonyl compounds, carboxylic acids and derivatives, alkenes, alkynes, epoxides and others by multifarious preparative procedures which will be cited in the corresponding chapters.

Irrespective of the structure of the aldehydes, and of the starting materials, the main sections are distinguished by the respective groups of procedures which either reduce or retain the number of carbon atoms or extend the carbon chains by one, two, three or more carbon atoms in the process of aldehyde formation. In the subsections the transformations into aldehydes of each of the different groups of precursors by various procedures are described.

2. Syntheses with reduction of the number of carbon atoms

Reactions of this type are accomplished as follows:

(i) from carboxylic acids by formation of their α -methylsulfonyl derivatives, followed by sodium periodate oxidation in methanol, which forms the nor-aldehyde dimethyl acetals. (B.M. Trost, *Acc. Chem. Res.*, 1978, **11**, 453).



(ii) by ozonolysis of 1-alkenes, followed by reductive cleavage of the ozonides by thiourea. Cycloalkenes yield dials (D. Gupta, R. Soman, S. Dev, *Tetrahedron*, 1982, **38**, 3013).

(iii) through enantioselective formation of 2-methyl-aldehydes by regioselective ring-opening of homochiral hydroxymethyl epoxides with trimethylaluminum, followed by periodate fission of the resulting 3-methyl-1,2-diols (W.R. Roush *et al.*, *Tetrahedron Lett.*, 1983, 1377). Best results are obtained with this reagent in the presence of wet silica gel (M. Daumas *et al.*, *Synthesis*, 1989, 64).

3. Synthesis with retention of the number of carbon atoms

(a) Oxidation reactions of primary alcohols



(for a review see: F.A. Luzzio, F.S. Guziec, "Recent Applications of Oxochromium (VI) - Amine Reagents", *Org. Prep. Proc. Int.*, 1988, **20**, 533)

Reactions of this type use a plethora of reagents and can be effected by:

(i) pyridinium chlorochromate (PCC, $C_5H_5N^+H(CrO_3Cl)^-$) (E.J. Corey, J. W. Suggs, *Tetrahedron Lett.*, 1975, 2647; review: G. Piancatelli, A. Scettri, M.D. Anria, *Synthesis*, 1982, 245) the acidity of which can be buffered by sodium acetate to save acid sensitive groups and to prevent (Z)-(E) isomerizations. Primary alcohols containing acid sensitive groups, or those requiring anhydrous conditions are converted into their borate esters by borane-dimethylsulfide prior to PCC oxidation (H.C. Brown, S.U. Kulkarni, C.G. Rao, *Synthesis*, 1979, 702). In this context the conversion of the substrates into trimethylsilyl ethers by triphenylmethenium tetrafluoroborate (M.E. Jung, *J. Org. Chem.*, 1976, **41**, 1479), or into tributylstannyl ethers by nitrosonium tetrafluoroborate (G.A. Olah, T.L. Ho, *Synthesis*, 1976, 609), is recommended.

(ii) the more stable and internally buffered 2,2'-bipyridinium chlorochromate, is equally mild and effective for the oxidation of saturated and unsaturated alcohols and allows simpler workup (F.S. Guziec, F.A. Luzzio, *Synthesis*, 1980, 691).

(iii) 4-(dimethylamino)pyridinium chlorochromate (DMAPH⁺ (CrO₃Cl)⁻). This reagent is preferred for the oxidation of primary 2-alkenols. Primary alcohols react very slowly (F.S. Guziec, F.A. Luzzio, *J. Org. Chem.*, 1982, **47**, 1787).

(iv) poly(vinyl(pyridinium chlorochromate)) (PVPCC), preferably in cyclohexane or heptane, oxidizes 2-alkenols faster than primary alkanols and less reagent is needed than in oxidations with PCC. Yields depend on the quality of the poly(vinylpyridine), but work-up of the reaction mixture is simple and the resin may be quantitatively recovered and regenerated (J.M.J. Frechet, J. Warnock, M.J. Farrall, *J. Org. Chem.*, 1978, **43**, 2618; *ibid.* 1981, **46**, 1728). The Amberlyst A-26-chromate reagent (G. Cainelli *et al.*, *J. Am. Chem. Soc.*, 1976, **98**, 6737) is similar to handle, but is less effective than PVPCC.

(v) tetrabutylammonium chlorochromate (TBACC) is a fairly stable, but light sensitive reagent for the selective oxidation of 2-alkenols (E. Santaniello, F. Milani, R. Casati, *Synthesis*, 1983, 749). The homogeneous solutions of methyltrialkylammonium dichromate, formed from Andogen 464 and potassium dichromate in benzene, also only oxidize 2-alkenols (R.O. Hutchins, N.R. Natale, W.J. Cook, *Tetrahedron Lett.*, 1977, 4167) as does bis (benzyltriethylammonium) dichromate, a neutral oxidant (X. Huang, C. Chan, *Synthesis*, 1982, 1091). However, the seemingly similar tetrabutyl-ammonium chromate formed *in situ* in

chloroform and only applicable in chlorohydrocarbon solvents is distinctly less selective (S. Cacchi, F. LaTorre, D. Misti, *Synthesis*, 1979, 356).

(vi) the bulkier quinolinium chlorochromate. This reagent selectively oxidizes unbranched primary alkanols and alkenols (J. Singh *et al.*, *Chem. Ind. (London)*, 1986, 751).

(vii) pyridinium fluorochromate ($C_5H_5N^+H(CrO_3F)^-$) in acetonitrile. It is a less acidic and a more efficient oxidant than PCC (N.N. Bhattacharjee *et al.*, *Synthesis*, 1982, 588).

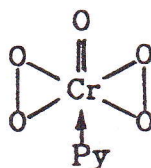
(viii) pyridinium dichromate (PDC, $(PyH^+)_2(Cr_2O_7^{2-})$) (E.J. Corey, G. Schmidt, *Tetrahedron Lett.*, 1979, 399), which needs to be handled with caution (J. Salmon, *Chemistry in Britain*, 1982, 703), exhibits solvent dependent selectivities. In the presence of excess of bis-trimethylsilyl peroxide as reoxidant, PDC can be more safely employed in catalytic amounts (K. Oshima *et al.*, *Tetrahedron Lett.*, 1983, 2185). Although 3- or 4-carboxy-pyridinium dichromates are safer than PDC, they are less effective oxidants (C. Lopez *et al.*, *Synth. Commun.*, 1985, 15, 1197).

(ix) pyridine-chromyl chloride-t-butanol, a remarkably effective oxidant for the large-scale preparation of simple alkanals and 2-alkenals, giving excellent yields (K.B. Sharpless, K. Alashi, *J. Am. Chem. Soc.*, 1975, 97, 5927). The complex formed by slow addition of CrO_3 to hexamethylphosphoric triamide (HMPA) can be applied without additional solvent and is equally effective (G. Cardillo, M. Orena, S. Sandri, *Synthesis*, 1976, 394). This system is similar in action to CrO_3 in HMPA and with crown ethers (*idem*, *Tetrahedron Lett.*, 1976, 3985), and to potassium dichromate in dimethylsulfoxide (DMSO) or in polyethylene glycols. It oxidizes 2-alkenols exclusively (E. Santaniello, P. Ferraboschi, *Synthesis*, 1980, 646).

(x) potassium dichromate/sulfuric acid in water/dichloromethane in the presence of tetrabutylammonium hydrogensulfate. The phase transfer conditions are quite compatible with acid sensitive alcohols and the resulting alkanals and alkenals, but are restricted to lipophilic substrates (D. Landini, F. Montanara, F. Rolla, *Synthesis*, 1979, 134). See also G. Gelbard, T. Brunelet, C. Jouitteau (*Tetrahedron Lett.*, 1980, 4653).

(xi) pyridinechromium peroxide (PCP) ($PyCrO_5$, pyridine-bis(peroxy)-oxochromium (VI)), prepared either from pyridine, CrO_3 and H_2O_2 (G.W.J. Fleet, W. Little, *Tetrahedron Lett.*, 1977, 3749) or in crystalline form as for 2,2'-bipyridylchromium peroxide (BPCP, $2,2'$ -bipy CrO_5) (H. Firouzabadi *et al.*, *Tetrahedron*, 1986, 42, 719). The latter reagent is the more effective, allowing

oxidations of various kinds of primary alcohols under neutral conditions at ambient temperatures. Yields are high. In contrast to most oxochromium (VI) reagents, the oxidation with both of these complexes succeeds with equimolar amounts of substrate and oxidant.



(xii) 3,5-dimethylpyrazole-CrO₃, which is also useful for larger scale oxidations of saturated and unsaturated primary alcohols and affords very good yields (E.J. Corey, G.W.J. Fleet, *Tetrahedron Lett.*, 1973, 4499).

(xiii) diisopropyl sulfide/N-chlorosuccinimide (NCS)/triethylamine (K.S. Kim *et al.*, *J. Chem. Soc., Chem. Commun.*, 1984, 762). Unlike the original reagent combination described by E.J. Corey, C.U. Kim (*Tetrahedron Lett.*, 1974, 287), this reagent distinguishes between saturated and unsaturated primary alcohols and secondary alcohols merely by selection of an appropriate reaction temperature. An analogous procedure employs the dimethylselenide-NCS complex. The intermediate chlorodimethylselenium alkoxides (Me₂Se(Cl)OCH₂R) undergo base-induced elimination with formation of aldehydes (T. Takaki *et al.*, *J. Org. Chem.*, 1983, 48, 54).

Oxochromium (VI) reactants adsorbed on inorganic supports (xiv - xx). They form part of the important group of polymer-bound reagents and are particularly advantageous (reviews: A. McKillop, D.W. Young, *Synthesis*, 1979, 401 and 481).

(xiv) silica gel supported chromic acid, prepared and employed under various conditions (E. Santaniello, F. Ponti, A. Manzocchi, *Synthesis*, 1978, 534; J.D. Lou, Y.Y. Wu, *Chem. Ind. (London)*, 1987, 531).

(xv) chromic acid adsorbed on Kieselguhr, a stable and efficient oxidant (J.D. Lou, *Synth. Commun.*, 1989, 19, 1841).

(xvi) pyridinium chromate on silica gel containing a small amount of acetic acid. This reagent shows solvent dependent oxidation rates (R.P. Singh, H.N. Subbarao, S. Dev, *Tetrahedron*, 1979, 35, 1789).

(xvii) pyridinium chlorochromate/amine with ultrasonication. This renders PCC less acidic, simplifies the workup and gives excellent results. Good compatibility with acid sensitive groups is also noted (L.L. Adams, F.A. Luzzio, *J. Org. Chem.*, 1989, **54**, 5387). PCC on aluminum oxide gives equally good results (Y.S. Cheng, W.L. Liu, S.H. Chen, *Synthesis*, 1980, 223).

(xviii) chromic acid on aluminum silicate in nonpolar solvents (D.D. Lou, Y.Y. Wu, *Synth. Commun.*, 1987, **17**, 1717).

(xix) chromyl chloride (CrO_2Cl_2) on silica gel under neutral, anhydrous conditions. While C-C-double bonds are cleaved, carbon-halogen bonds, esters, ethers and cyano groups are not affected (J.S. Filippo, C.I. Chem, *J. Org. Chem.*, 1977, **42**, 2182). The reagent is more selective than that described by K.B. Sharpless *et al.* (*J. Am. Chem. Soc.*, 1977, **99**, 3120).

(xx) CrO_3 /graphite obtained at 200°C under reduced pressure, then successively washed with water, hydrochloric acid and acetone. Despite long reaction times yields of aldehydes are good (J.M. Lalancette, G. Rollin, P. Dumas, *Can. J. Chem.*, 1972, **50**, 3058). Graphite nitrate ($\text{C}_{24}^+\text{NO}_3^-$) is also recommended (H.B. Cagan, *Chem. Tech.*, 1976, **6**, 510).

(xxi) sodium hypochlorite and 2,2,6,6-tetramethylpiperidine-1-oxyl radical as catalyst, cocatalyzed by bromide ion in dichloromethane-buffered water under phase transfer conditions. Oxidation of 1-alkanols only is very rapid and quantitative at 0°C (P. Anelli *et al.*, *J. Org. Chem.*, 1987, **52**, 2559).

(xxii) N-iodosuccinimide and tetrabutylammonium iodide gives excellent yields of alkanals and 2-alkenals (S. Hanessian, D.H. Wong, M. Therien, *Synthesis*, 1981, 394).

The combination of t-butyl hydroperoxide and bis-(2,4,6-trimethylphenyl)-diselenide is also a very effective oxidant (M. Shimizu, I. Kuwajima, *Tetrahedron Lett.*, 1979, 2801).

(xxiii) the combination of nitro ethylacetate/diethyl azodicarboxylate/triphenylphosphine in refluxing tetrahydrofuran is also claimed to be a useful oxidant system (O. Mitsunobu, N. Yoshida, *Tetrahedron Lett.*, 1981, 2295).

Activated dimethylsulfoxide (DMSO) mediated oxidations of alcohols play an essential role in the preparation of carbonyl compounds (review: A.J. Mancuso, D. Swern, *Synthesis*, 1981, 165) as exemplified by the following procedures:

(xxiv) DMSO/oxalyl chloride (OC)/triethylamine (Et₃N). This combination has been extensively investigated and has wide application (A.J. Mancuso, D.S. Brownfain, D. Swern, J. Org. Chem., 1979, 44, 4148). The actual reagent in "Swern oxidations" was found to be chloro dimethylsulfonium chloride (Me₂S⁺Cl Cl⁻) also resulting from dimethyl sulfide and chlorine (E.J. Corey, C.U. Kim, J. Am. Chem. Soc., 1972, 94, 7586) or N-chlorosuccinimide (*idem*, Tetrahedron Lett., 1974, 287). The "Swern oxidation" even allows the preparation of highly reactive aldehydes which are interceptable by Wittig reactions (R.E. Ireland, D.W. Norbeck, J. Org. Chem., 1985, 50, 2198).

(xxv) DMSO/trichloromethyl chloroformate (phosgene dimer)-Et₃N gives equally good results as DMSO/OC (S. Takano, Tetrahedron Lett., 1988, 6619).

(xxvi) DMSO-thionyl chloride/Et₃N (K. Omura, D. Swern, Tetrahedron, 1978, 34, 1651). This requires precautions to prevent potential Pummerer rearrangement.

(xxvii) by DMSO/phenyl dichlorophosphate (PDCP, PhOP(O)Cl₂)-Et₃N (H.J. Liu, J.M. Nyangulu, Tetrahedron Lett., 1988, 3167).

The reagents described above are invariably employed at temperatures between -60 to -30°C.

(xxvii) DMSO/carbodiimide incorporated in a polystyrene matrix as activator (N.M. Weinschenker, C.H. Shen, Tetrahedron Lett., 1972, 3285).

In the following group of procedures transition metal reagents are used in alcohol to aldehyde oxidation reactions (reviews: A.P. Kozikowski, H.F. Wetter, Synthesis, 1976, 561; R.A. Sheldon, Bull. Soc. Chim. Belg., 1985, 94, 651):

(xxix) silver carbonate/celite, a remarkably effective supported reagent, oxidizing primary alcohols, and particularly 2-alkenols, to aldehydes in excellent yields (A. McKillop, D.W. Young, Synthesis, 1979, 401).

(xxx) palladium acetate or tetrakis(triphenylphosphine)palladium/triphenylphosphine (TPP)/aryl bromide/potassium carbonate in dimethoxyethane (DME), both forming with primary alcohols the complex RCH₂OPd(Ar)(TPP)₂ which expels

the aldehyde (Y. Tamaru *et al.*, *J. Org. Chem.*, 1983, 48, 1286). Also by the combination of palladium acetate/sodium hydrogencarbonate/tetra-n-butylammoniumbromide/iodobenzene in DMF under solid-liquid phase transfer conditions. The oxidations proceed rather slowly, but alkanals are formed in good yields (B.M. Chondary *et al.*, *Tetrahedron Lett.*, 1985, 6257).

(xxxI) tetrakis(pyridine)silver dichromate ($\text{Py}_4\text{Ag}_2\text{Cr}_2\text{O}_7$), which oxidizes 2-alkenols selectively but only in refluxing benzene (H. Firouzabadi *et al.* *Synth. Commun.*, 1984, 14, 89), or barium ferrate which shows similar selectivity under the same conditions (*idem et al.*, *ibid.*, 1986, 16, 723).

(xxxii) catalytic amounts of nonacarbonyl diiron ($\text{Fe}_2(\text{CO})_9$) in benzene, which invariably isomerizes various kinds of primary alkenols, alkenol ethers and esters with formation of aldehyde enols, enol ethers and esters. All of which are readily convertible into aldehydes (N. Iranpoor, A. Imanich, *Synth. Commun.*, 1989, 19, 2955).

(xxxiii) ruthenium dioxide/oxygen, which forms aldehydes from 2-alkenols only. It does not effect primary alkanols (M. Matsumoto, N. Watanabe, *J. Org. Chem.*, 1984, 49, 3436).

(xxxiv) ruthenium dioxide/triphenylphosphine/ phenyliodosodiacetate ($\text{PhI}(\text{OAc})_2$) which has limited selectivity. Thus carboxylic acids are formed together with alkanals (P. Müller, J. Codry, *Tetrahedron Lett.*, 1981, 2361).

(xxxv) N-methylmorpholine-N-oxide/ruthenium dichloride tris(triphenylphosphine) (TPP). This combination oxidizes primary alkanols and 2-alkenols quite selectively (K.B. Sharpless, K. Akashi, K. Oshima, *Tetrahedron Lett.*, 1976, 2503). Quite acceptable selectivities are also achieved with the ruthenium dichloride tris-TPP complex without (H. Tomioka *et al.*, *Tetrahedron Lett.*, 1981, 1605), or with addition of bis-trimethylsilyl peroxide (S. Kanemoto *et al.*, *Tetrahedron Lett.*, 1983, 2185), or with ruthenium trichloride hydrate with calcium hypochloride or sodium periodate as reoxidants (J.R. Genet, D. Pons, S. Juge, *Synth. Commun.*, 1989, 19, 1721).

(xxxvi) the trinuclear ruthenium acetate catalyst ($\text{Ru}_3\text{O}(\text{OAc})_6\text{L}_3$, L = H_2O or TPP) and oxygen under pressure at 100°C (C. Bilgrien, S. Davis, R.S. Drago, *J. Am. Chem. Soc.*, 1987, 109, 3786).

(xxxvii) tetrapropylammonium perruthenate/N-methylmorpholine-N-oxide. This self re-generating combination of reagents is very efficient and can be used under mild conditions. It allows simple workup, even in the presence of various acid

sensitive groups (W.P. Griffith, S.V. Ley, J. Chem. Soc., Chem. Commun., 1987, 1625; *idem*, Aldrichimica Acta, 1990, 23(1), 143).

(xxxviii) dicyclopentadienyl zirconium hydride (Cp_2ZrH_2) or isopropoxide ($\text{Cp}_2\text{Zr}(\text{O}-i\text{Pr})_2$) with benzophenone (T. Nakano *et al.*, Synthesis, 1986, 774) or benzaldehyde or cyclohexanone as hydrogen acceptors (T. Nakano, Y. Ishi, M. Ogawa, J. Org. Chem., 1987, 52, 4855). These reagent combinations oxidize di-primary and primary-secondary diols selectively to hydroxyaldehydes. Propargylic alcohols are unaffected.

(b) Oxidation of primary halides



Again a variety of reagent conditions can be employed including:

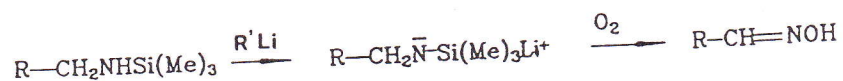
(i) dimethyl sulfoxide (DMSO)/sodium hydrogen carbonate/sodium iodide at elevated temperature with alkyl chlorides and bromides (R. Engel *et al.*, Synth. Commun., 1986, 16, 1343).

(ii) DMSO/silver tetrafluoroborate. The silver salt considerably accelerates this Kornblum-type oxidation, with primary allylic halides even reacting at ambient temperature (B. Ganem, R.K. Boeckmann, Tetrahedron Lett., 1974, 917).

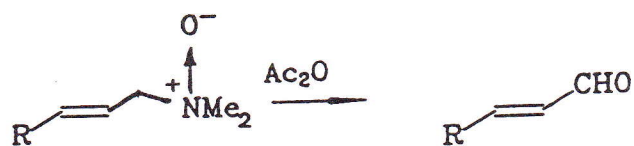
(iii) dimethylformamide (DMF)/N-ethylmorpholine-N-oxide. This is recommended for the preparation of 2-alkenals (S. Suzuki *et al.*, Bull. Chem. Soc. Jpn., 1986, 59, 3287), or 4-dimethyl-aminopyridine-N-oxide/base for the synthesis of alkanals (S. Mukaiyama, S. Inaga, M. Yamaguchi, Bull. Chem. Soc. Jpn., 1981, 54, 2221).

(c) Oxidation of amines

(i) with dry air, which reacts with the lithium salts of N-alkyl-N-trimethylsilyl metal amides yielding hydrolyzable aldoximes (H.G. Chen, P. Knochel, Tetrahedron Lett., 1988, 6701).



(ii) the formation of N,N-dimethylallylamine-N-oxides, which give 2-alkenals by a redox reaction with acetic anhydride (K. Takabe *et al.*, Chem. Lett., 1982, 1987).

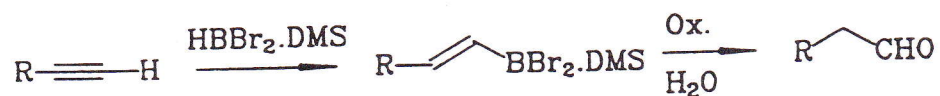


(d) From alkenes, alkynes and their derivatives

Here an addition-oxidation sequence is commonly used and may be achieved by:

(i) regioselective addition of diisoamyl borane to 1-alkenes, followed by PCC oxidation and hydrolysis of the diisoamylborinates (H.C. Brown, S.U. Kulkarni, C.G. Rao, Synthesis, 1980, 151; *idem*, J. Organomet. Chem., 1979, 172, C20).

(ii) regioselective addition of dibromoborane dimethylsulfide (DMS) to 1-alkynes, followed by oxidative hydrolysis of the alkenyl-B,B-dibromoborane dimethylsulfide complex (H.C. Brown, J.B. Campbell, J. Org. Chem., 1980, 45, 389).

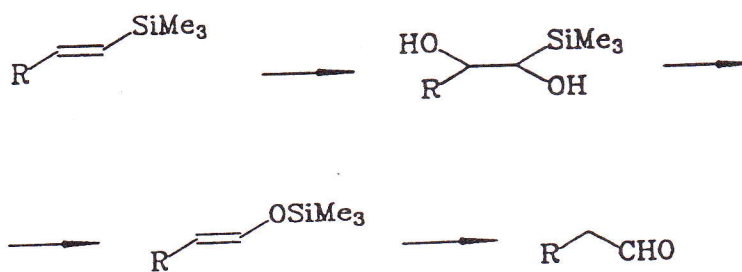


(iii) reactions of 1-alkynes with boron tribromide, followed by treatment with buffered methanolic potassium acetate and dihydrogen peroxide. This leads to the formation of 2-bromoaldehydes (Y. Satoh *et al.*, Synthesis, 1985, 406). In another approach 2-bromoaldehydes are formed by the addition of bromine to aldehyde trimethylsilyl enolethers, followed by spontaneous loss of bromotrimethylsilane (R.H. Reuss, A. Hassner, J. Org. Chem., 1974, 39, 1785).

(iv) rearrangement of propargylamines into allenylamines. These form 2-alkenals on hydrolysis (J.C. Craig, N.N. Ekwuribe, Tetrahedron Lett., 1980, 2587). This synthesis allows labelling of both alkenic carbon atoms.

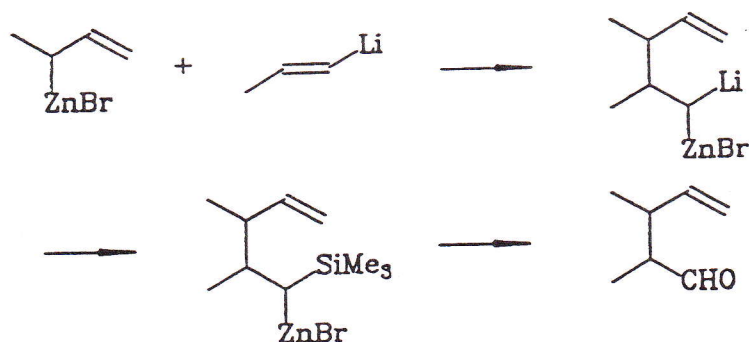


(v) treatment of 1-trimethylsilyl-1-alkenes with osmium tetroxide, followed by dehydration and concomitant C-O migration of the trimethylsilyl group. Hydrolysis of the resulting aldehyde trimethylsilyl enolethers gives the corresponding aldehydes (P.F. Hudriik, A.M. Hudriik, A.M. Kulkarni, *J. Am. Chem. Soc.*, 1985, **107**, 4260). α,β -Epoxy silanes were found to be inferior precursors.



(vi) epoxidation of 1-alkenes, followed by isomerization of the oxiranes by reaction with nickel bromide, or its bis-triphenylphosphine complex in tetrahydrofuran, or toluene (A. Miyashita *et al.*, *Chem. Lett.*, 1986, 1323).

(vii) "Carbometallation" (P. Knochel, J.F. Normant, *Tetrahedron Lett.*, 1986, 1039) of 1-metallo alkenes, by allylzinc halides in the presence of chlorotrimethyl-silane or -stannane, followed by oxidation of the resulting 1,1-dimetallo-4-alkenes. This leads to formation of 4-alkenals (P.Knochel, C. Xiao, M.C.P. Yeh, *Tetrahedron Lett.*, 1988, 6697).



(viii) regio- and stereoselective oxidation of allylic chlorides by 2-propane nitronate in the presence of tetrakis(triphenylphosphine) palladium. This method is suitable for variously substituted substrates (S. Suzuki *et al.*, *Synth. Commun.*, 1985, **15**, 1123).



(e) *Reduction of carboxylic acids and derivatives*

(Review: J.S. Cha, "Recent developments in the synthesis of aldehydes by reduction of carboxylic acids and their derivatives with metal hydrides", *Org. Prep. Proc. Int.*, 1989, **21**, 451).

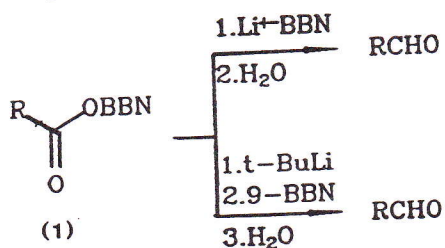
Carboxylic acids and their allies can be reduced by:

(i) isobutylmagnesium bromide in the presence of dichloro-bis-(cyclopentadienyl)titanium (for saturated carboxylic acids only) (F. Sato, T. Jiubo, M. Sato, *Synthesis*, 1981, 871). The reaction mechanism is unresolved.

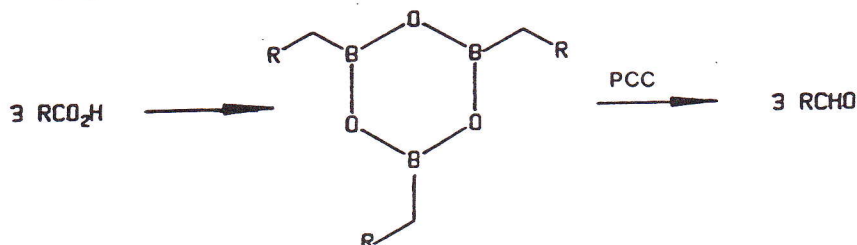
(ii) reduction of O-acyl hexyl borinic acids, formed from carboxylic acids and excess hexylbromoborane. This procedure exhibits a high degree of compatibility with various functional groups. Diacids similarly form diols (J.S. Cha, J.E. Kim, K.W.

Lee, *J. Org. Chem.*, 1987, **52**, 5030). Thexyl chloroborane can also be used (H.C. Brown *et al.*, *J. Org. Chem.*, 1987, **52**, 5400).

(iii) either by treatment of acyloxy-9-borabicyclo [3.3.1] nonanes (1) obtained from 9-BBN and carboxylic acids, with lithium 9-borabicyclo[3.3.1]nonane (Li-9BBNH) (J.S. Cha *et al.*, *Tetrahedron Lett.*, 1987, 4575), or by stepwise treatment of (1) with *t*-butyllithium and 9-BBN (*idem, ibid.*, 1987, 6231). Final hydrolysis of the products from both procedures affords aldehydes.



(iv) reduction of carboxylic acids by borane/dimethylsulfide with formation of trialkylboroxines, which are then oxidized by PCC (H.C. Brown, C.G. Rao, S.U. Kulkarni, *Synthesis*, 1979, 704).



(v) reduction with tri-*t*-butoxy-lithiumaluminum hydride of the products resulting from the reaction of carboxylic acids and chloro-*N,N*-dimethylformamidium chloride in the presence of copper(I)iodide at -78°C. Excellent compatibility with various functional groups is observed (T. Fujisawa *et al.*, *Tetrahedron Lett.*, 1983, 1543).

(vi) reduction of unsaturated esters by lithium aluminium hydride in pentane in the presence of an excess of diethylamine. This is an exceptionally facile procedure (J.S. Cha, S.S. Kim, *J. Org. Chem.*, 1987, **52**, 5486). A similar method using bis(*N*-methylpiperazinyllithium aluminium hydride is also recommended (T.D. Hubert, D.P. Eyman, D.F. Wiemer, *J. Org. Chem.*, 1984, **49**, 2279).

(vii) reduction of esters and lactones by sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH) in the presence of either N-methylpiperazine or -morpholine. Very good yields are claimed (R. Kanagawa, T. Tokoroyama, *Synthesis*, 1976, 526).

(viii) reduction of N-methoxy-N-methylamides by lithiumaluminum hydride, or by diisobutylaluminum hydride (DIBAL) (S.Nahm, S.M. Weinreb, *Tetrahedron Lett.*, 1981, 3815).

(ix) hydrogenolysis of acid chlorides in acetone, with diisopropylethylamine as acid scavenger (J.A. Peters, H. van Bekkum, *Rec. Trav. Chim. Pays-Bas*, 1971, 90, 1323).

(x) hydrogenolysis of acid chlorides in dilute solutions in the presence of equimolar amounts of 2,6-dimethylpiperidine (A.W. Burgstahler, L.O. Weigel, C.G. Schaefer, *Synthesis*, 1976, 767).

(xi) sodium borohydride reduction of acid chlorides in dimethylformamide/pyridine at -70°C (J.H. Babler, *Synth. Commun.*, 1982, 12, 839).

(xii) rapid reduction of acid chlorides by Amberlyst A-26 supported borohydride (K.Y. Cordeev *et al.*, *Zh. Org. Khim.*, 1985, 21, 2615).

(xiii) reaction of acid chlorides, or esters, with S-methyl-1,4-diphenylthiosemicarbazide with the formation of thiazolines, followed by reduction of the corresponding thiazolinium chlorides and hydrolysis (G. Doleschall, *Tetrahedron*, 1976, 32, 2549).

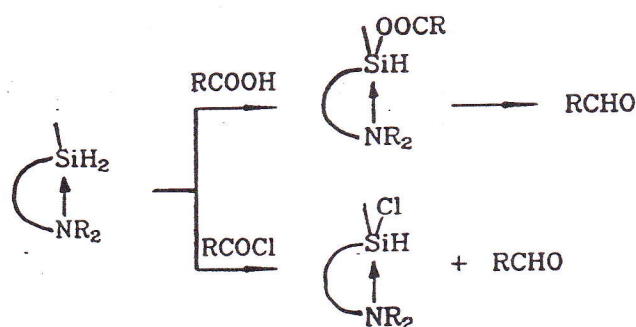
(xiv) simply by mixing acid chlorides and group 6B anionic hydrides ($\text{HM}(\text{CO})_4\text{L}^-$; M = Cr, W; L = (CO), PR_3) (S.C. Kao *et al.*, *Organometallics*, 1984, 3, 1601).

(xv) reduction of saturated acid chlorides (only) by tetramethylammonium hydridotetracarbonylferrate ($\text{Me}_4\text{N}^+\text{HFe}(\text{CO})_4^-$) in solution (T.E. Cole, R. Pettit, *Tetrahedron Lett.*, 1977, 781), or in a polymer-bound form (J.P. Collman, *Acc. Chem. Res.*, 1975, 8, 342).

(xvi) reduction of acid chlorides by μ -bis(cyantrihydroborato)-tetrakis-(triphenylphosphine)dicopper (I) ($(\text{Ph}_3\text{P})_2\text{CuBH}_3(\text{CN})_2$) under neutral conditions (R.O. Hutchins, M. Markowitz, *Tetrahedron Lett.*, 1980, 813), or by bis(triphenylphosphine)copper(I)borohydride ($(\text{Ph}_3\text{P})_2\text{CuBH}_4$) (G.W.J. Fleet, P.J.C. Harding, *Tetrahedron Lett.*, 1979, 975).

(xvii) reduction of acid chlorides by tri-n-butylstannane catalyzed by tetrakis (triphenylphosphine) palladium, or palladium dichloride/triphenylphosphine complex. These reactions are very mild, selective and allow the preparation of unsaturated, halo- and nitro aldehydes (P. Four, F. Guibe, J. Org. Chem., 1981, 46, 4439).

(xviii) reduction of carboxylic acids (R.J.R. Corriu, G.F. Lanneau, M. Perrot, Tetrahedron Lett., 1987, 3941), or acid chlorides by hypervalent silicon hydrides (*idem. ibid.*, 1988, 1271).



(xix) an indirect procedure consisting of the formylation by ethylformate of carboxylic acid dianions, followed by decarboxylation (G.K. Koch, J.M.M. Kop, Tetrahedron Lett., 1974, 603).



(xx) the reduction of N-ethyl nitrilium tetrafluoro borates, obtained from nitriles by reaction with triethyloxonium tetrafluoroborate, by trimethylsilane, followed by hydrolysis of the resulting aldimines (J.L. Frey, J. Chem. Soc., Chem. Commun., 1974, 45).

(f) *Substituted aldehydes from aldehydes*

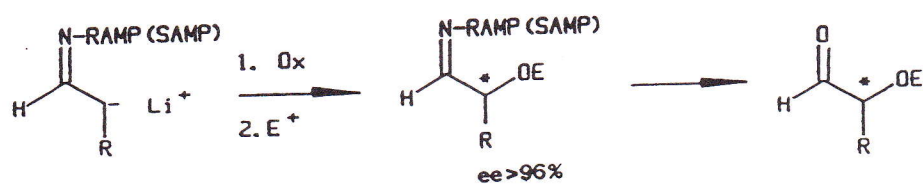
The following procedures are recommended:

(i) synthesis of α -phenylseleno aldehydes by treatment of alkanals with phenylselenenyl chloride in ethyl acetate at ambient temperature (K.B. Sharpless et al., J. Am. Chem. Soc., 1973, 95, 6137).

(ii) preparation of α -phenylseleno aldehydes by reaction of aldehyde enamines from aldehydes with piperidine, followed by treatment with phenylselenenyl chloride. Oxidation forming the selenoxide elimination and hydrolysis finally affords 2-alkenals (D.R. Williams, K. Nishitani, Tetrahedron Lett., 1980, 4417).

(iii) potassium aldehyde enolates are very good nucleophiles which can be transformed into α -iodo-, α -phenylsulfenyl-, α -alkyl- and α -allyl aldehydes (P. Groenewegen, H. Kallenberg, A. van der Gen, *ibid.*, 1979, 2817). Direct bromination of aldehydes is accomplished by 5,5-dibromo-2,2-dimethyl-4,6-dioxo-1,3-dioxane (dibromo Meldrum's acid) (R. Bloch, Synthesis, 1978, 140). Potassium enolates of 2-alkenals are readily allylated, diallylated and prenylated with formation of α -branched aldehydes (P. Groenewegen, H. Kallenberg, A. van der Gen, Tetrahedron Lett., 1978, 491).

(iv) enantioselective synthesis of α -hydroxy aldehydes by reaction of aldehydes with a homochiral hydrazine derivative ($\text{H}_2\text{N-NH-RAMP}$ or $-\text{SAMP}$), followed by metal enolate formation and oxidation (D. Enders, V. Bhushan, Tetrahedron Lett., 1988, 2437).



(v) from 2-alkenals, which are subject to exclusive 1,4-reduction with the formation of alkanals by reaction with sodium dithionite ($\text{Na}_2\text{S}_2\text{O}_4$) under phase transfer conditions in water/benzene at 80°C (O. Louis-Andre, G. Gelbard, Tetrahedron Lett., 1985, 831).

4. Syntheses with extension by one carbon atom

This and the following sub-sections deal with the preparation of aldehydes by carbon-carbon coupling reactions, considered to be "the most useful carbonyl syntheses" (W.C. Still *et al.*, J. Am. Chem. Soc., 1974, 96, 5561). (Reviews: S.F. Martin, Synthesis, 1979, 633; B.T. Gröbel, D. Seebach, Synthesis, 1977, 357; O.W. Lever, Tetrahedron, 1976, 32, 1943; P.W. Hickmott, Tetrahedron, 1982, 38, 1975; N.H. Werstink, Tetrahedron, 1983, 39, 205; T.A. Hase, J.K. Koskimies, Aldrichimica Acta, 1981, 14, 73).

(a) From alkyl halides

Alkyl halides can be converted into aldehydes either directly or indirectly by:

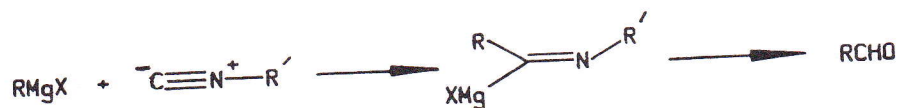
(i) an improved Bouveault-reaction which involves the treatment of primary, secondary or tertiary alkyl halides with lithium sand in mineral oil in the presence of dimethylformamide with ultrasonication and final acidic hydrolysis (C. Petrier, A.L. Gemal, J.L. Luche, Tetrahedron Lett., 1982, 3361).

(ii) reaction of Grignard reagents with anhydrous formic acid (F. Sato *et al.*, Tetrahedron Lett., 1980, 2869). In an improved version lithium or sodium formate is used (M. Bogavac *et al.*, *ibid.*, 1984, 1843).

(iii) reactions of alkyl, alkenyl or alkynyl Grignard or organolithium reagents with N-formylpiperidine (G.A. Olah, M. Arvanaghi, Angew. Chem., 1981, 93, 925).

(iv) the formylation of alkyl, alkenyl or alkynyl Grignard reagents by N-(N-formyl-N-methyl)aminopiperidine (D.L. Comins, A.I. Meyers, Synthesis, 1978, 463; W. Amaratunga, J.M.J. Frechet, Tetrahedron Lett., 1983, 1143).

(v) the preparation of metallo aldimines from isonitriles and Grignard reagents, followed by hydrolysis (H.M. Walborsky *et al.*, J. Org. Chem., 1974, 39, 600).

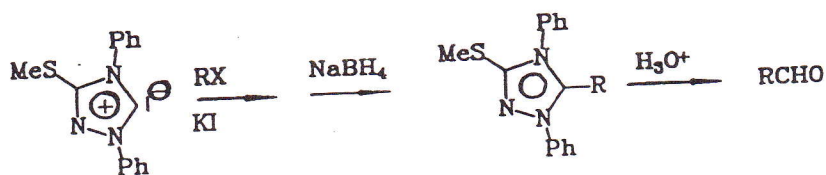


(vi) reductive formylation through reactions of alkyl halides with polymer bound tetraalkylammonium tetracarbonylferrate ($\text{P-PhCH}_2\text{N}^+\text{Me}_3 \text{HFe}(\text{CO})_4^-$) (G. Cainelli *et al.*, *J. Org. Chem.*, 1978, **43**, 1598). This is superior to the corresponding reactions in solution (M.P. Coke, *J. Am. Chem. Soc.*, 1970, **92**, 6080).

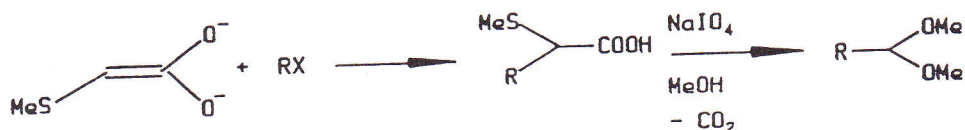
(vii) catalytic formylation of allylic halides in the presence of bis(triphenylphosphine) palladium dibromide complex and carbon monoxide/hydrogen under pressure at 100°C. (A. Kasahara, T. Izumi, H. Yanai, *Chem. Ind. (London)*, 1983, 898).

(viii) catalytic reductive formylation of allyl and alkenyl chlorides, bromides and iodides by tributylstannane/tetrakis(triphenylphosphine) palladium and carbon monoxide at 50°C under low pressure (V.P. Baillargeon, J.K. Stille, *J. Am. Chem. Soc.*, 1983, **105**, 7175). Formation of 2- and 3-alkenals.

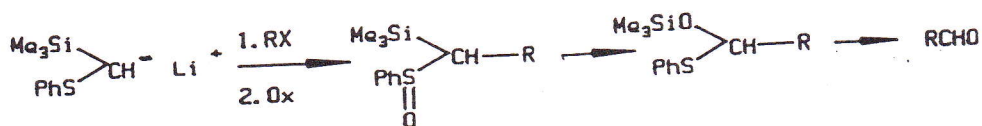
(ix) alkylation at the nucleophilic carbon atom of the 2,4-N,N-diphenyl-5-methylsulfonyl-1,2,4-triazolinium ion, followed by sodium borohydride reduction. This leads to the formation of the 3-alkyltriazolinium halide, the hydrolysis of which liberates the aldehyde (G. Doleschall, *Tetrahedron Lett.*, 1975, 1889).



(x) alkylation of the dilithium salt of methylsulfonylacetic acid, followed by sodium periodate treatment in methanol affording aldehyde dimethylacetals (B.M. Trost, *Acc. Chem. Res.*, 1978, **11**, 453).

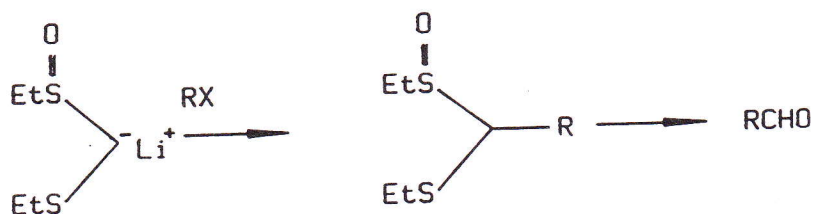


(xi) reaction of alkyl halides with lithiophenylthiomethyltrimethylsilane, followed by oxidation, thermal rearrangement of the resulting sulfonyl derivative and final hydrolysis (D.J. Ager, R.C. Cookson, *Tetrahedron Lett.*, 1980, 1677), or by a reverse approach (*idem, ibid.*, 1981, 587).



An analogous reaction sequence employs phenylselenylmethyltrimethylsilane (K. Sachdev, H.S. Sachdev, *ibid.*, 1976, 4223).

(xii) alkylations of the lithium salt of dithiomethane monosulfoxide, followed by hydrolysis with mercuric chloride in hydrochloric acid/tetrahydrofuran (J.E. Richman, J.L.Herrmann, R.H. Schlessinger, *Tetrahedron Lett.*, 1973, 3267).



This reaction sequence exemplifies the principle of formyl anion equivalents by "Umpolung" reviewed by B.T. Gröbel, D. Seebach (*Synthesis*, 1977, 357).

(b) From nitro compounds

Nitro compounds are infrequently used as substrates, however, conversion to aldehydes can be achieved by:

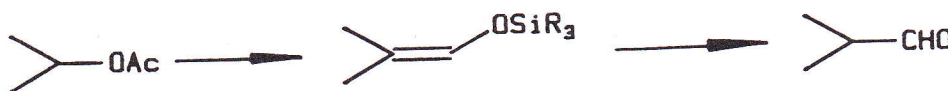
(i) reaction of an excess of a primary nitro compound with trialkyl orthoformate/zinc chloride, followed by the elimination of alcohol and hydrolysis of

the resulting 2-nitro enol ether with formation of 2-nitro-aldehydes (L. Rene, R. Royer, *Synthesis*, 1981, 878).

(c) *From carboxylic acid derivatives*

Reduction of carboxylic acids is achieved by:

(i) high temperature, pressurized dicobalt octacarbonyl catalyzed, trialkylsilane-induced carbonylations of alkyl acetates affording trialkylsilyl aldehyde enoethers which form aldehydes on hydrolysis. Lactones give ω -formyl alkanolic acids (N. Chatani, S. Murai, N. Sonoda, *J. Am. Chem. Soc.*, 1983, 105, 1370).



(ii) conversion of methyl alkanooates into methyl trimethylsilyl keteneacetals, which are treated with N-t-butylformimidoyl cyanide yielding 2-methoxycarbonyl-N-t-butylaldimines, the hydrolysis of which forms 2-formyl alkanooates (K. Okano *et al.*, *J. Chem. Soc., Chem. Commun.*, 1985, 119).

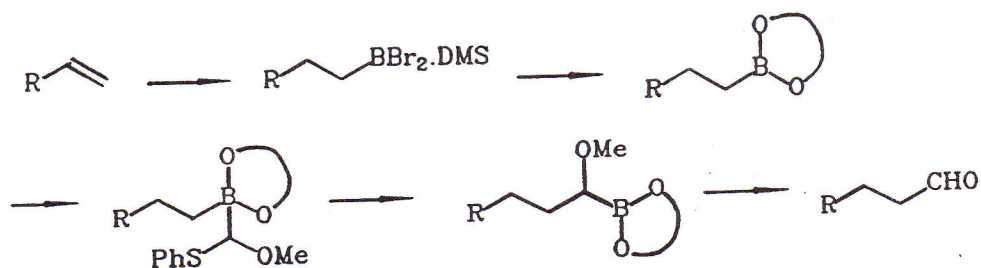


(d) *From alkenes, alkynes and derivatives*

Aldehydes may be obtained by:

(i) a sequence of reactions starting with the addition of dibromoborane to 1-alkenes, conversion into alkylboronates, reaction with methoxy(phenylthio)-

methyl lithium (MPML) to form alkylated borates, their rearrangement into chain-extended boronates by mercuric chloride, oxidation and hydrolysis (H.C. Brown, T. Imai, *J. Am. Chem. Soc.*, 1983, **105**, 6285). The syntheses of α -homochiral aldehydes is also possible by this sequence (H.C. Brown *et al.*, *J. Am. Chem. Soc.*, 1985, **107**, 4980; H.C. Brown, B. Singaram, *Acc. Chem. Res.*, 1988, **21**, 287).

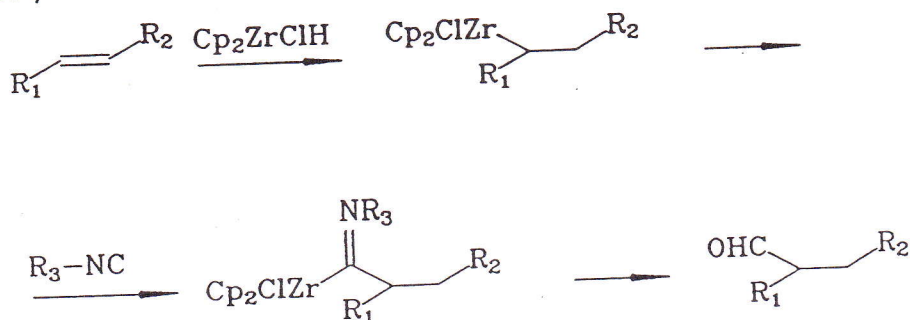


Similar homologation reactions can be performed by employing dichloro- or bromochloromethyl lithium instead of MPML (D.S. Matteson, D. Majumdar, *J. Am. Chem. Soc.*, 1980, **102**, 7588; *idem*, *Organometallics*, 1983, **2**, 1529; H.C. Brown *et al.*, *ibid.*, 1985, **4**, 1925; review: D.S. Matteson, *Tetrahedron*, 1989, **45**, 1859).

(ii) low temperature reactions of alkenyltrimethylsilanes with 1,1-dichloromethylether/titanium tetrachloride, followed by hydrolysis forming (E)-alkenals (K. Yamamoto, O. Nunokawa, J. Tsuji, *Synthesis*, 1977, 721).

(iii) hydrozirconation of different kinds of alkenes, invariably forming 1-zirconyl alkanes, followed by carbonylation with carbon monoxide under pressure and finally hydrolysis (C.A. Bertelo, J. Scharz, *J. Am. Chem. Soc.*, 1975, **97**, 228).

(iv) hydrozirconation of alkenes or alkynes, followed by isocyanide insertion and hydrolysis (E.I. Negishi, D.R. Swanson, S.R. Miller, *Tetrahedron Lett.*, 1988, 1631).

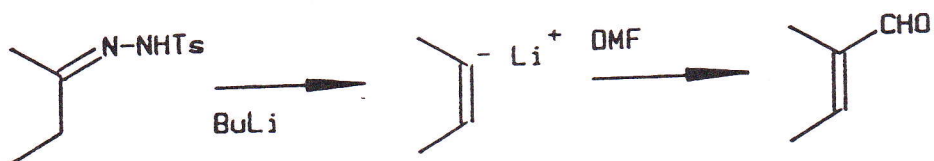


(e) From carbonyl compounds

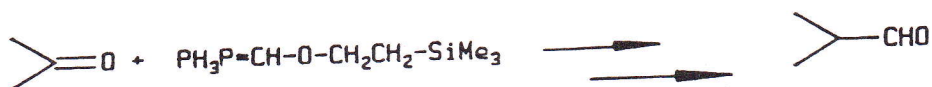
Carbonyl compounds and their derivatives are commonly used and chain extension can be effected by:

(i) homologation of aldehydes as described in section 4a (ix) for alkyl halides. Functional groups in aldehydes such as keto, ester, nitro, halo or double bonds are unaffected (G. Doleschall, *Tetrahedron Lett.*, 1980, 4183).

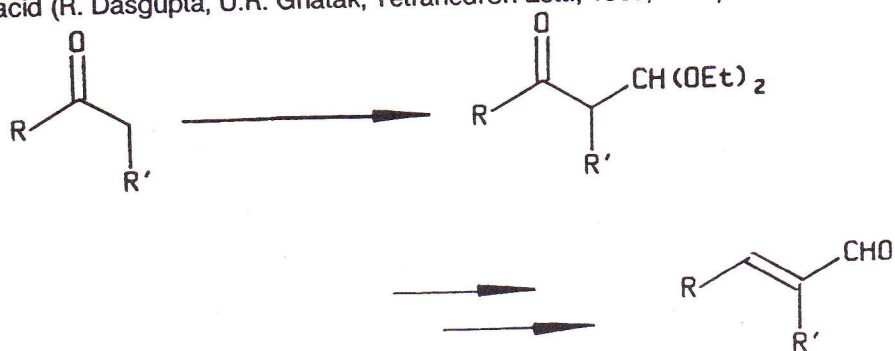
(ii) dimethylformamide mediated formylation (superior to the Vilsmeier reaction) of alkenyl anions obtained from toluenesulfonyl hydrazones by reaction with butyllithium. This procedure affords 2-alkenals (P.C. Traas, H. Boelens, H.J. Takken, *Tetrahedron Lett.*, 1976, 2287).



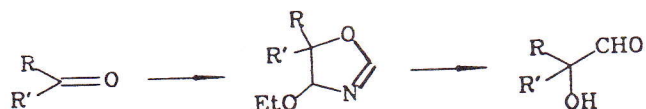
(iii) Wittig reactions of ketones with formation of intermediates readily subject to fragmentation (K. Schönauer, E. Zbiral, *Tetrahedron Lett.*, 1983, 573).



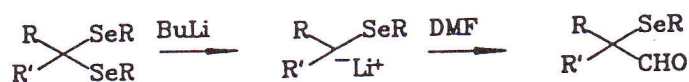
(iv) 1,3-carbonyl transposition of ketones on reaction with diethoxy carbenium tetrafluoroborate, followed by sodium borohydride reduction and treatment with acid (R. Dasgupta, U.R. Ghatak, *Tetrahedron Lett.*, 1985, 1581).



(v) conversion of carbonyl compounds with tosylmethylisocyanide (TOSMIC) and thallium ethylate in ethanol into oxazoline derivatives, affording 2-hydroxyaldehydes on hydrolysis (O.H. Oldenzel, A.M. van Leusen, *Tetrahedron Lett.*, 1974, 167).

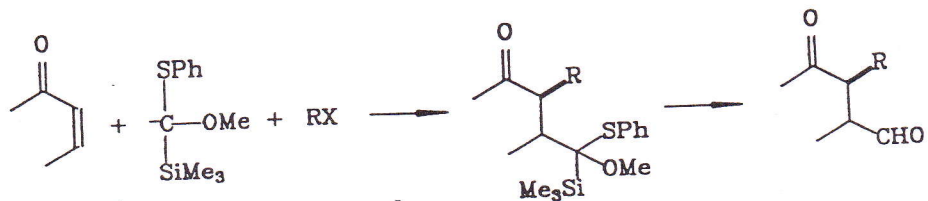


(vi) dealkylselenolithiation of seleno acetals, followed by reactions with dimethylformamide yielding 2-seleno alkanals (J.N. Denis, W.Dumont, A. Krief, *Tetrahedron Lett.*, 1976, 453).

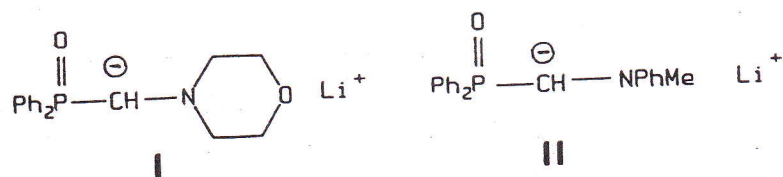


(vii) reaction of carbonyl compounds with lithiochloromethyltrimethylsilane with the formation of versatile α,β -epoxytrimethylsilanes. Their treatment with acids yields aldehydes, with methanol methylacetals, and with 1,3-propanedithiol 1,3-dithians (C. Burford *et al.*, *J. Am. Chem. Soc.*, 1977, 99, 4536).

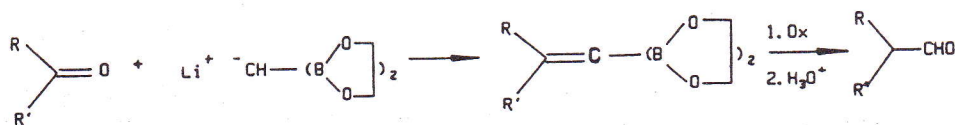
(viii) "tandem" reactions of lithio methoxy(phenylthio)(trimethylsilyl)methane (T. Mandai *et al.* *Tetrahedron Lett.*, 1985, 2675) and alkyl halides to give α,β -unsaturated carbonyl compounds, followed by desilylation and liberation of the β -alkyl γ -oxo-aldehydes (J. Otera, Y. Niibo, H. Nozaki, *J. Org. Chem.*, 1989, 54, 5003).



(ix) reactions of aldehydes with lithio N-morpholinomethyl diphenylphosphinic oxide (I) (A. van der Gen *et al.*, *Tetrahedron Lett.*, 1979, 2433), or of ketones with lithio N-methylanilinomethyl diphenylphosphinic oxide (II) (N.Boekhof, F.J. Jonkers, A. van der Gen, *Tetrahedron Lett.*, 1980, 2671), followed by elimination of diphenylphosphinic acid and hydrolysis of the resulting enamines.



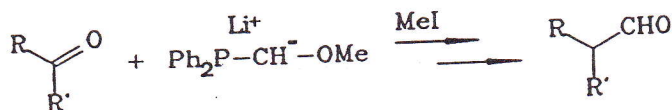
(x) reaction of carbonyl compounds with lithio bis(ethylenedioxyboryl)methide with the formation of alkenyl boronates, followed by the usual oxidative conversion into aldehydes (D.S. Matteson, R.J. Moody, *J. Org. Chem.*, 1980, 45, 1091).



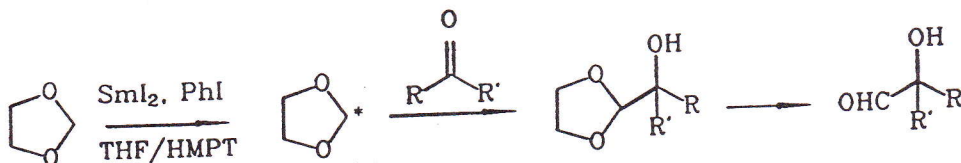
(xi) reaction of numerous different electrophiles with 2-trimethylsilylthiazole (2-TST, Dodoni's Thiazole) making available a wealth of differently and differentially substituted aldehydes through re-iterable and stereoselective syntheses (A. Dodoni *et al.*, *Gazetta Chim. Ital.*, 1988, 118, 211; *idem, ibid.*, *J. Org. Chem.*, 1988, 53, 1748).

(xii) reactions of even sterically hindered, particularly cyclic ketones with 1,1-diphenylphosphino-1-methoxymethyl lithium and iodomethane with the formation of methyl enol ethers. These suffer hydrolysis on treatment with

trichloroacetic acid releasing the corresponding aldehydes (E.J. Corey, M.A. Tius, *Tetrahedron Lett.*, 1980, 3535).



(xiii) samarium diiodide-induced cross coupling of ketones and dioxolane with formation of α -hydroxy aldehydes (M. Matsukawa, J. Inanga, M. Yamaguchi, *Tetrahedron Lett.*, 1987, 5877).



5. Syntheses with extension by two carbon atoms

(a) From alkyl halides

Three procedures are reported which are effected by:

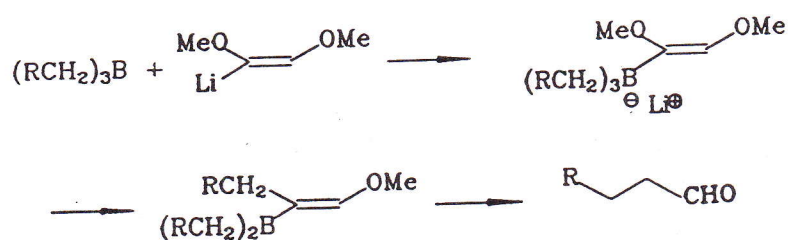
(i) alkylation of lithiated 2-methyl thiazoline, an acetaldehyde equivalent, with alkyl halides, followed by aluminum amalgam reduction and hydrolysis with aqueous mercuric chloride. This method allows the formation of long chain aldehydes (A.I. Meyers, J.L. Durandetta, *J. Org. Chem.*, 1975, 40, 2021).

(ii) reactions of β -lithio ethoxyethene with 1-iodoalkanes in HMPT, followed by hydrolysis of the enolethers formed (R.H. Wollenberg, K.F. Albizati, R. Periers, *J. Am. Chem. Soc.*, 1977, 99, 7365). For applications in natural product synthesis see R.H. Wollenberg, R. Periers (*Tetrahedron Lett.*, 1979, 297).

(iii) two carbon homologation of alkyl halides with formation of 1-phenyl-2-hydroxyalkanes. These products suffer carbon-carbon bond fission on treatment with lead tetraacetate/iodine in refluxing benzene (K. Shankaran *et al.*, Indian J. Chem., 1982, 21B, 408).

(b) From alkenes

(i) Reactions of terminal trialkylboranes with 1,2-dimethoxyethenyllithium lead to the corresponding borates, which rearrange with the formation of chain extended new boranes. Their hydrolysis yields aldehydes extended by two carbon atoms (J. Koshino *et al.*, Synth. Commun., 1983, 13, 1149; E.I. Negishi, "Organometallics in Organic Synthesis", John Wiley & Sons, New York, Vol. 1, 1980, p 286).



(c) From carbonyl compounds

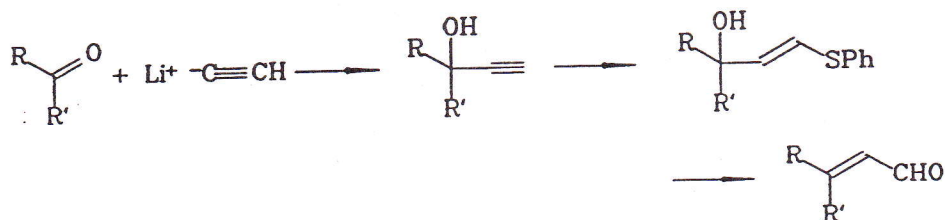
A variety of procedures are advanced which require:

(i) reactions of ketones with β -lithio ethoxyethene (c.f. subsection 5a (ii)), obtained from β -tributylstannyl ethoxyethene, followed by mild hydrolysis with formation of α,β -unsaturated aldehydes (J. Ficini *et al.*, Tetrahedron Lett., 1977, 3589).

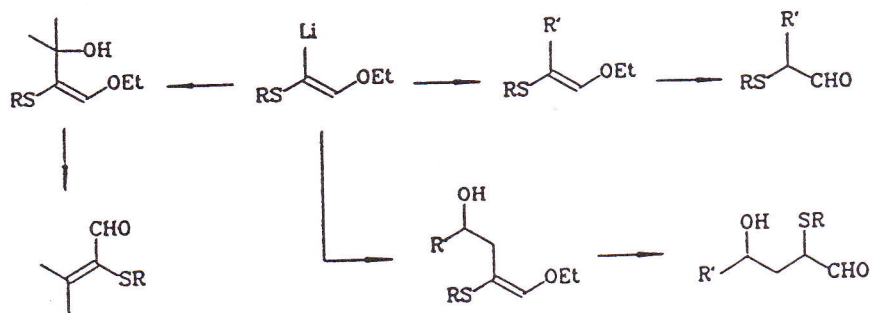
(ii) 1,3-functional group transposition through oxidation of t-allyl alcohols, which results from reactions between carbonyl compounds and vinylmagnesium halides. Interestingly, PCC (c.f. section 3a, (i)) forms α,β -unsaturated aldehydes, however,

Collins reagent (Org. Synth., 1972, 52, 5), gives α,β -epoxy-aldehydes (P. Sundararaman, W. Herz, J. Org. Chem., 1977, 42, 813; J.H. Babler, M.J. Coghlan, Synth. Commun., 1976, 6, 469).

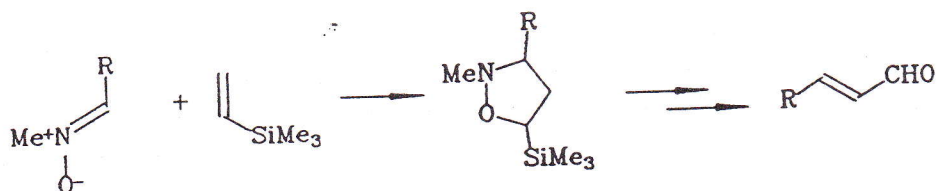
(iii) a similar sequence of reactions via the formation of secondary or tertiary propargylic alcohols, addition of thiophenol and Meyer-Schuster rearrangement of the β -phenylsulfenyl allyl alcohols yields α,β -unsaturated aldehydes (M. Julia, C. Lefebvre, Tetrahedron Lett., 1984, 189).



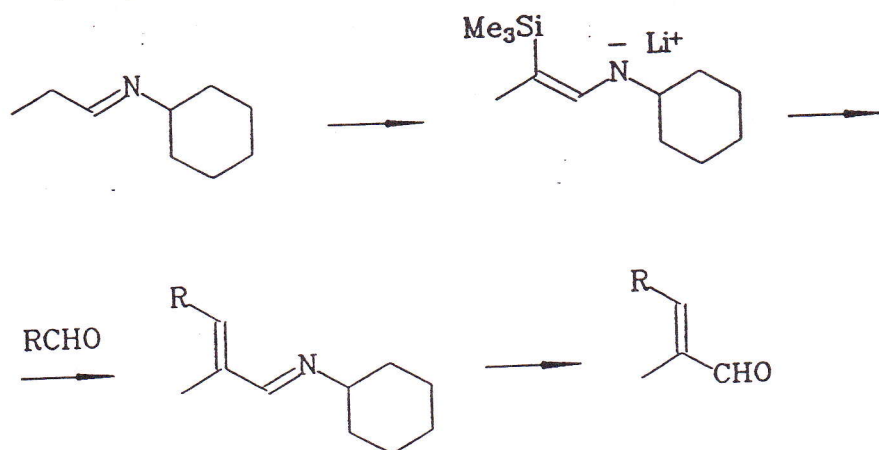
(iv) reactions of 2-(ethoxy)-1-(alkylthio)vinyl lithium with either carbonyl compounds, epoxides or alkyl halides, resulting in different intermediates, each yielding α -alkylthioaldehydes in a single step (I. Vlattas et al., J. Am. Chem. Soc., 1976, 98, 2008).



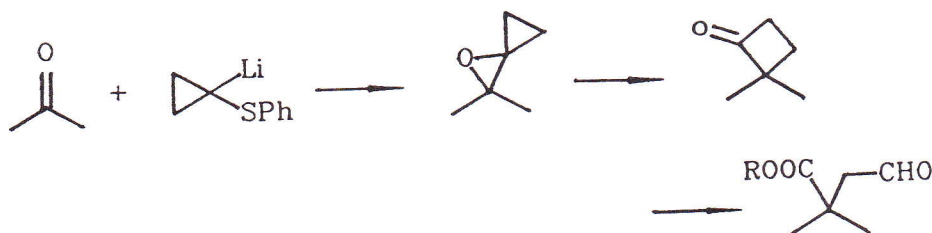
(v) the cycloaddition of aldehyde nitrones and trimethylvinylsilane, followed by a ring opening and elimination reaction with the formation of α,β -unsaturated aldehydes (P. DeShong, M. Leginus, J. Org. Chem., 1984, 49, 3421).



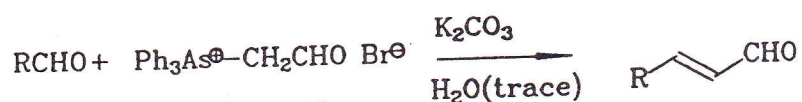
(vi) a procedure comprising the following steps: trimethylsilylation of N-cyclohexylaldimines with the formation of 2-trimethylsilyl enamines, lithiation and Peterson olefination and reaction with an aldehyde. Finally hydrolysis with trifluoroacetic acid yields α,β -unsaturated aldehydes (S.G. Mills *et al.*, *Tetrahedron Lett.*, 1988, 3895).



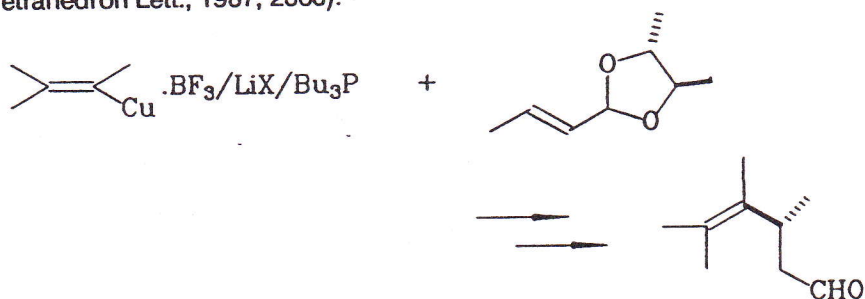
(vii) the reaction of ketones with phenylsulfenyl cyclopropyllithium *via* a spiro epoxide that rearranges with the formation of a cyclobutanone derivative. Ring opening yields β -carboxyaldehydes (B.M. Trost *et al.*, *J. Am. Chem. Soc.*, 1975, **97**, 5873).



(viii) the direct formylefination of aldehydes employing 3-formylmethyl-triphenylarsonium bromide. This is found to be superior to the corresponding Wittig reagent (Y. Huang, L. Shi, J. Yang, *Tetrahedron Lett.*, 1985, 6447).



(ix) catalytic alkenyl cuprate addition to α,β -unsaturated homochiral cyclic acetals resulting in an asymmetric synthesis of γ,δ -alkenals (P. Mangeney *et al.*, *Tetrahedron Lett.*, 1987, 2363).



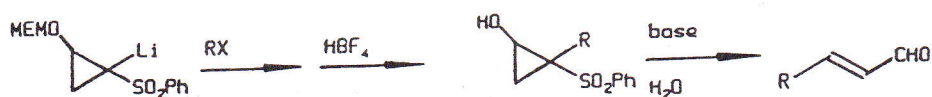
6. Syntheses with extensions by three carbon atoms

(Review: N.H. Werstiuk, "Homoenolate Anions and Homenolate Anion Equivalents", *Tetrahedron*, 1981, **39**, 205)

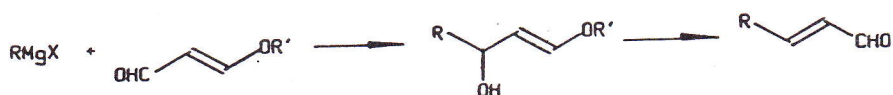
(a) From alkyl halides

There is a wealth of routes from alkyl halides which include:

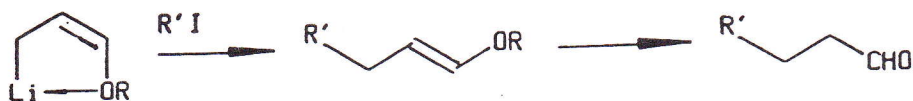
(i) homologation by a d^3 -reagent, a 3-lithioacrolein equivalent, is accomplished by reactions of alkyl halides with the lithium salt of a 2-phenylsulfonylcyclopropanoether. O-Deprotection, followed by a ring opening elimination reaction then gives α,β -unsaturated aldehydes (M. Pomakotr, S. Pisutjarocpong, *Tetrahedron Lett.*, 1985, 3613).



(ii) reactions of Grignard reagents with either 3-trimethylsilyloxy- or 3-ethoxyacroleins with formation of α -hydroxyenoethers, which on hydrolysis yield α,β -unsaturated aldehydes. Thus, oxopropenylation of carbon nucleophiles occurs via intermediate vinylogous formates (review: E. Breitmeier *et al.*, *Synthesis*, 1987, 1; C.W. Spangler *et al.*, *Synth. Commun.*, 1985, 15, 371).

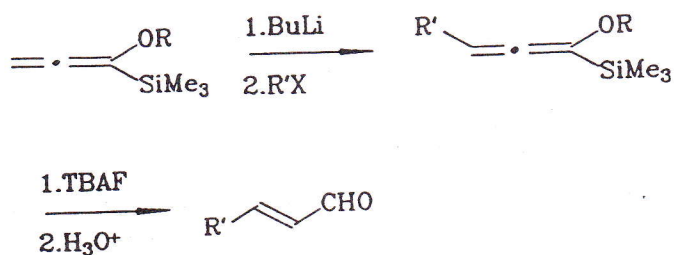


(iii) through reactions of alkyl iodides with the allyloxy carbanionic reagents derived from the triethylsilyl-, or phenyl- ether of allyl alcohol result in the formation of the respective vinyl ethers. These are valuable intermediates which give aldehydes on hydrolysis (W.C. Still, T.L. Macdonald, *J. Am. Chem. Soc.*, 1974, 96, 5561).

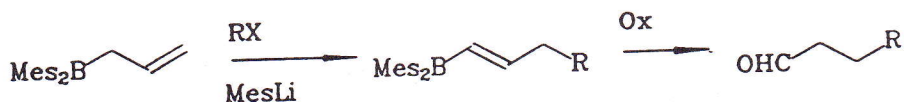


R = Ph; SiEt₃

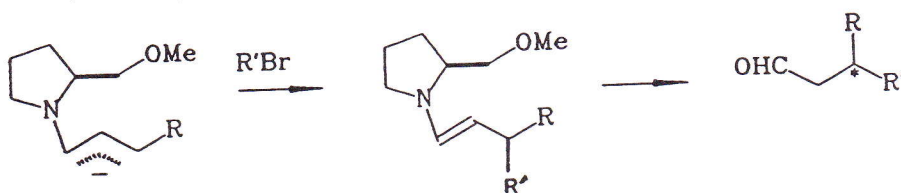
(iv) alkylation of lithiated 1-trimethylsilyl allenyl ethers, followed by fluoride mediated desilylation and hydrolysis with formation of the 2-alkenals (J.C. Clinet, G. Linstrumelle, *Tetrahedron Lett.*, 1980, 3987).



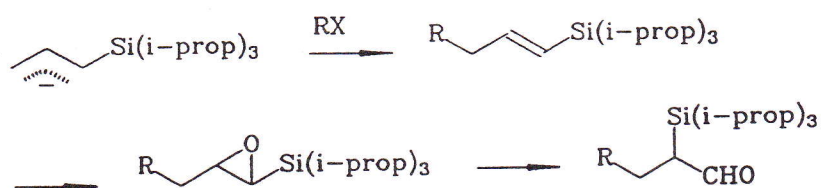
(v) alkylation of allyldimesitylborane in the presence of mesityllithium, followed by oxidation of the resulting alkenylborane (A. Pelter, B. Singaram, J.W. Wilson, *Tetrahedron Lett.*, 1983, 631).



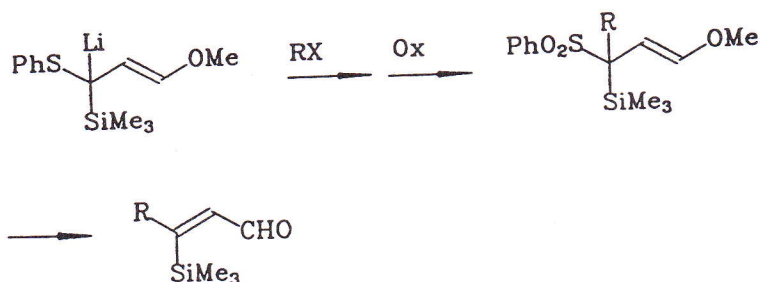
(vi) homochiral β -alkylaldehydes are obtained by alkylation of enantiomerically pure metalloallyl amines (which are homoenolate equivalents), followed by hydrolysis of the resulting enamines (H. Ahlbrecht *et al.*, *Tetrahedron Lett.*, 1980, 3175).



(vii) α -triisopropylsilylaldehydes which are rarely accessible by other methods, are synthesized by regioselective α -alkylation of the sterically demanding lithio allyltriisopropylsilane, followed by epoxidation of the intermediate enesilane and hydrolytic rearrangement (J.M. Muchowski, R. Naef, M.L. Maddox, *Tetrahedron Lett.*, 1985, 5375).

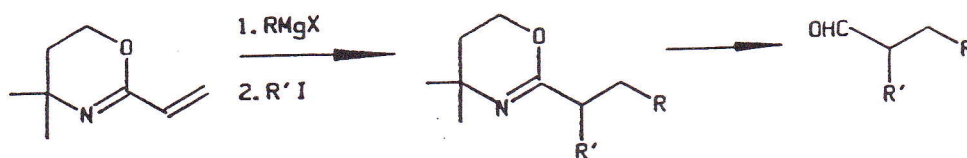


(viii) by reactions of lithio 3-phenylsulfenyl-3-(trimethylsilyl)methoxypropene, a 3-trimethylsilylacrolein equivalent, with alkyl halides, followed by oxidation and elimination yields 3-trimethylsilyl-2-alkenals (T. Mandai *et al.*, *Tetrahedron Lett.*, 1985, 2677).



(ix) *via* reaction of acrolein with 1,3-propanedithiol, triphenylphosphine and hydrobromic acid, followed by treatment with base yields 2-(2-triphenylphosphorylideneethyl)dithiane which adds alkyl halides in the presence of silver nitrate. Electroreduction liberates the aldehyde group and final treatment with triethylamine gives 2-alkenals (H.J. Christau, B. Chabaud, C. Niangoran, *J. Org. Chem.*, 1983, 48, 1527).

(x) 1H-2-vinyl-5,6-dihydro-1,3-oxazine in tandem reactions with Grignard reagents and alkyl iodides, followed by hydrolysis of the intermediates gives α -alkylaldehydes (A.I. Meyers *et al.*, J. Org. Chem., 1973, 38, 36).

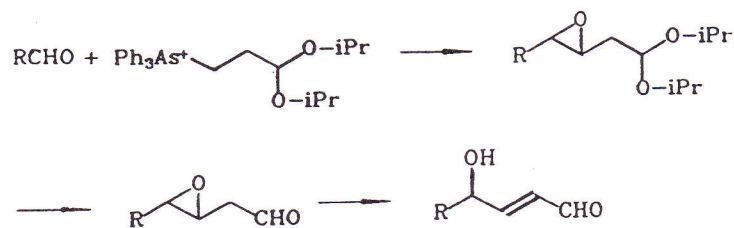


(xi) 3-hydroxy-1,5-alkadienes, readily accessible by reactions of allyl Grignard reagents with 2-alkenals, are subject to oxy-Cope rearrangement with the formation of 5-enals on treatment with potassium hydride in DMSO at ambient temperature (D.A. Evans, D.J. Baillargeon, J.V. Nelson, J. Am. Chem. Soc., 1978, 100, 2242).

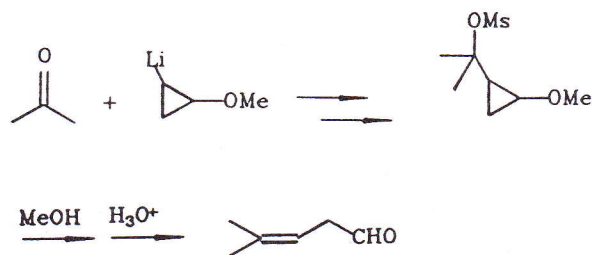


(b) From carbonyl compounds

(i) Reactions of aldehydes with (3,3-diisopropoxypropyl)triphenylarsonium ylide, a β -formylvinylanion equivalent, followed by hydrolysis and elimination yield 4-hydroxy-2-alkenals (P. Chabert, J.B. Ousset, C. Mioskowski, Tetrahedron Lett., 1989, 179).

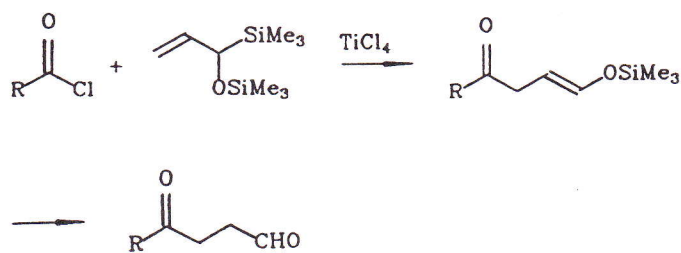


(ii) Reactions of carbonyl compounds with 2-methoxy-cyclopropyllithium, followed by mesylation of the intermediate alcohols and methanolysis, results in the formation of 3-alkenal dimethylacetals yielding 3-alkenals on hydrolysis (E.J. Corey, P. Ulrich, *Tetrahedron Lett.*, 1975, 3685).



(c) *From carboxylic acid chlorides*

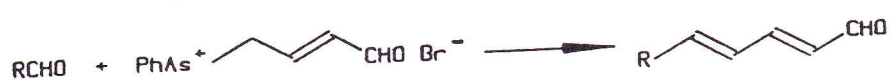
(i) α -Silyloxyallylsilanes are acylated in the presence of titanium tetrachloride and the resulting 4-oxo-silylenoethers hydrolyzed with the formation of 4-oxoalkenals (H. Sakurai, A. Hosomi, H. Hashimoto, *J. Org. Chem.*, 1978, 43, 2551).



7. Syntheses with extensions by four or more carbon atoms

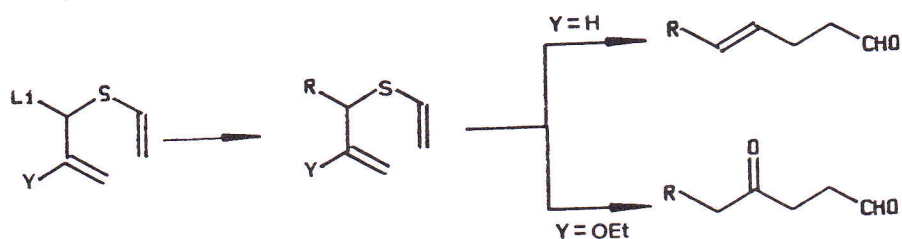
(a) From carbonyl compounds

(i) In an extension of the two-carbon homologation reaction described above (c.f. section 5c, (viii)) 3-formylallyl-triphenylarsonium bromide, (a "formyl-enyl olefination" reagent), is employed in the four carbon prolongation of aldehydes (Y. Wu, Y. Huang, *Tetrahedron Lett.*, 1986, 4583).



(b) From alkyl halides

(i) Alkylations of either vinylthioallyl- or vinylthio-(2-ethoxyallyl)-lithium with alkyl halides, followed by Thio-Claisen rearrangement result in five carbon extensions with the formation of 4-alkenals or 4-oxoalkanals (K. Oshima *et al.*, *J. Am. Chem. Soc.*, 1973, 95, 2693, 4446).



(c) From alkenes

(i) 2,5,7-Trienals can be obtained by direct Vilsmeier formylations of conjugated trienes (P.C. Traas *et al.*, *Tetrahedron Lett.*, 1977, 2129).