Organic halides

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Reviewing the literature published between 1st July 1993 and 30th June 1994

1 Introduction

Organic halides continue to be a cornerstone of organic synthesis, with new and selective methods for their preparation constantly being sought. This review covers the literature published between 1 July 1993 and 30 June 1994 and is necessarily selective, with particular emphasis being given to procedures likely to be of wide use or interest to the practising synthetic organic chemist. The chemistry of perfluoroalkyl and hypervalent iodine compounds will not be discussed here.

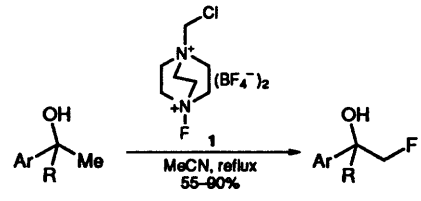
Apart from the previous review in this series,[1] no general reviews on organic halides have appeared this year. In contrast, the synthesis of organofluorine compounds has been the subject of a number of reviews,[2–5] covering such topics as nucleophilic fluoride transfer reagents[2] and fluorinated organometallics.[3] A special edition of *Tetrahedron:Asymmetry* was devoted to the enantiocontrolled synthesis of fluoro-organics.[6]

Preparative procedures of potential general interest include a convenient and economic way of producing anhydrous hydrogen bromide by heating hydrogen triphenylphosphonium bromide (Ph_3PHBr),[7] and a new method for making triphenylphosphine dichloride (Ph_3PCl_2) by reaction of triphenylphosphine with triphosgene.[8] A solid hydrogen fluoride equivalent, PVPHF [poly-4-vinylpyridinium poly(hydrogen fluoride)], has been developed and used to hydrofluorinate alkenes and alkynes, to convert secondary and tertiary alcohols into alkyl fluorides, and (when combined with an electrophilic bromine source) to effect 1,2-bromofluorination of alkenes.[9] The preparation of a range of chiral brominating and chlorinating agents has also been described,[10] although their synthetic utility has yet to be reported.

2 Alkyl halides

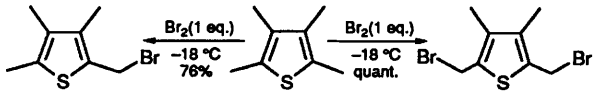
2.1 By halogenation of alkanes

The halogenation of unactivated alkanes has made limited progress since the previous review in this series.[1] Reports published this year concern the electrophilic fluorination of methane to methyl fluoride using N_2F^+ and NF_4^+ salts,[11] continuation of work in the Barton group using $GoAgg^{II}$ systems in the halogenation of cycloalkanes,[12] and a 1,2-fluorohydrin synthesis from alcohols using the 'Selectfluor' reagent F-TEDA-BF_4 (**1**, **Scheme 1**).[13]

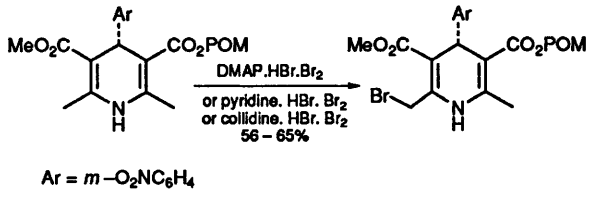


Scheme 1

Benzylic bromination of phenylalanine and tyrosine derivatives with *N*-bromosuccinimide has been used in the synthesis of diastereomers of *β*-hydroxyphenylalanine and *β*-hydroxytyrosine, but the halogenation step lacked stereoselectivity.[14] Regiocontrol has been observed in the uncatalysed benzylic bromination of polymethyl substituted thiophenes (**Scheme 2**),[15] and in the bromination of a dihydropyridine derivative for the synthesis of the calcium antagonist nivaldipine (**Scheme 3**).[16]



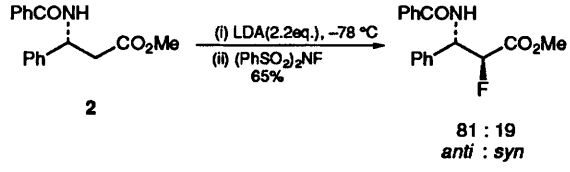
Scheme 2



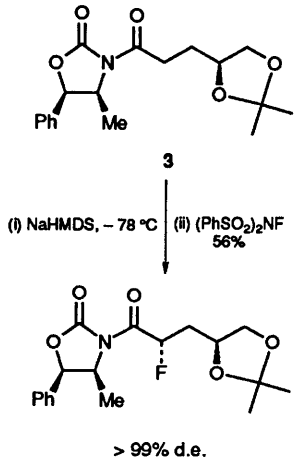
Scheme 3

The halogenation of enol derivatives, especially enolate anions, continues to be a powerful way of synthesizing α-halo-carbonyl compounds. The long-established conditions for the 2-halogenation of 1,3-dicarbonyl compounds using cupric chloride ($CuCl_2$) or cupric bromide ($CuBr_2$) have been further explored this year, with particular emphasis on their application to β-ketoesters[17] and cyclic β-diketones.[18] These mild conditions enable excellent chemoselectivity to be achieved in cases where other unsaturated functionality such as an alkene or an alkyne is present. For fluorination of 1,3-dicarbonyl systems, the Selectfluor reagent F-TEDA-BF_4(**1**) has been found to give high yields.[19]

N-Fluorobenzenesulfonimide $(PhSO_2)_2NF$ is the preferred reagent for the diastereoselective fluorination of **2** (giving a modified taxol side-chain) (**Scheme 4**),[20] and of **3**, where the stereocontrol is exerted by the homochiral oxazolidinone group (**Scheme 5**).[21]

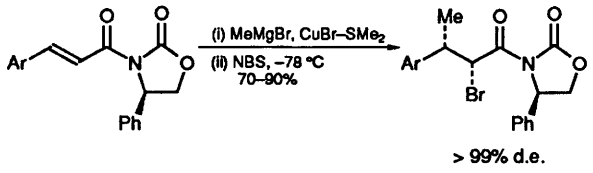


Scheme 4

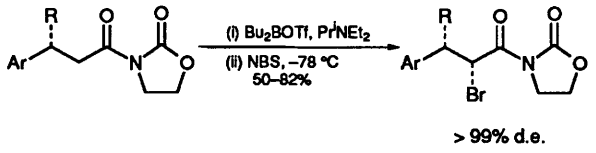


Scheme 5

The related diastereoselective bromination of enolates of oxazolidinone-derived amides continues to be a focus of the Hruby group,[22,23] but unlike the previous example, the stereocontrol is exerted by the β-alkyl substituent (**Scheme 6**). This hypothesis is supported by the chemistry depicted in **Scheme 7**, where the oxazolidinone is achiral.[24]



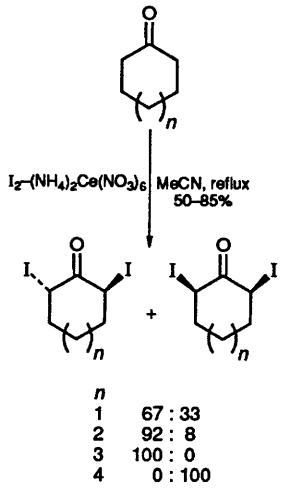
Scheme 6



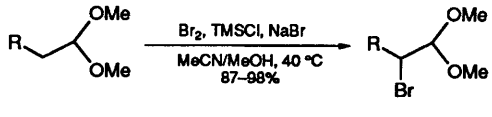
Scheme 7

Other α-halogenation procedures of note include the (diastereoselective) α,α'-diiodination of ketones with iodine and ceric ammonium nitrate (CAN) (**Scheme 8**),[25] and an α-bromination of acetals (**Scheme 9**)[26] which proceeds via a transient enol ether intermediate. The latter procedure is reported to be suitable for large scale work.

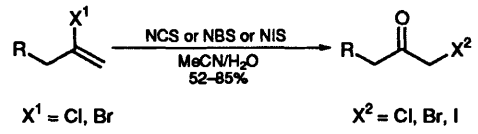
Finally, α-halomethylketones have been prepared from vinyl halides as indicated in **Scheme 10**.[27]



Scheme 8



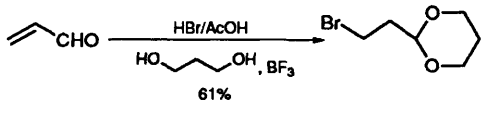
Scheme 9



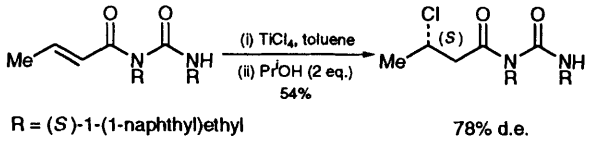
Scheme 10

2.2 By halogenation of alkenes

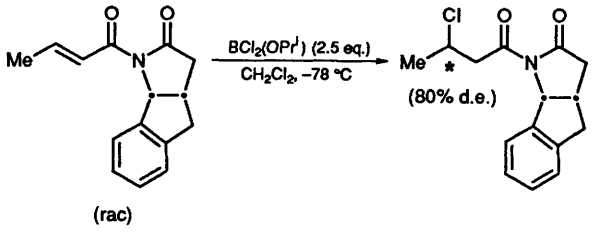
Hydrogen–halogen addition to alkenes is a relatively infrequently used synthetic approach to alkyl halides, but this year has seen a new and general hydrofluorination procedure using the solid hydrogen fluoride reagent PVPHF.[9] Hydrobromination is a key step in an improved preparation of 2-(2-bromoethyl)-1,3-dioxan (**Scheme 11**),[28] and two reports of asymmetric induction in the hydrochlorination of acrylate derivatives have appeared (**Schemes 12**[29] and **13**[30]). Although the observed diastereoselectivities in the latter chemistry may not seem particularly high by today's standards, there are very few reported methods for the asymmetric addition of halide ions to crotonates.



Scheme 11

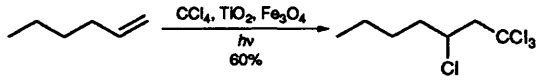


Scheme 12

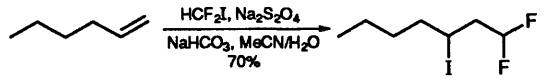


Scheme 13

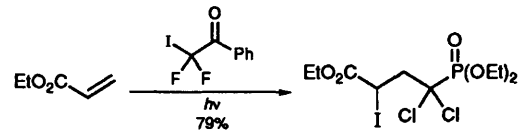
Carbon–halogen addition to alkenes is also an area of continuing interest, much of the published work has centred around radical additions of polyhaloalkanes. Some representative examples of these are shown in **Schemes 14**,[31] **15**,[32] **16**,[33] **17**,[34] **18**,[35] and **19**.[36,37] Polyhalogenated precursors are not essential, however, and additions of monohaloalkanes across double bonds have been described in both intermolecular (**Scheme 20**)[38] and intramolecular senses, the latter giving heterocycles according to the generalized transformation of **Scheme 21**.[39,40] A related



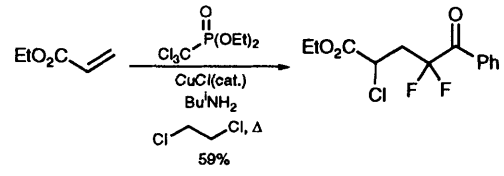
Scheme 14



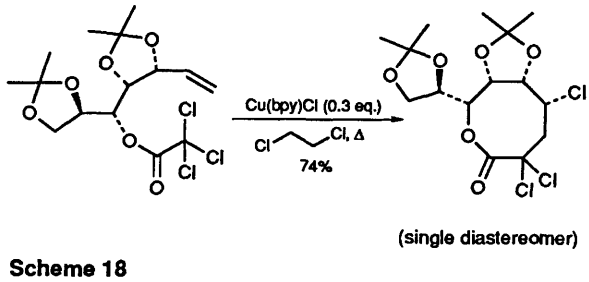
Scheme 15



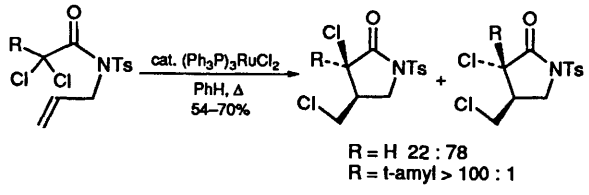
Scheme 16



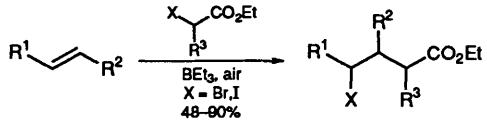
Scheme 17



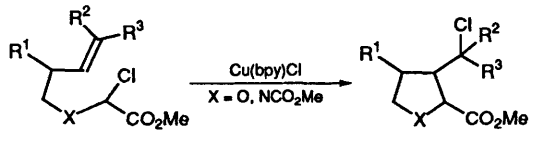
Scheme 18



Scheme 19



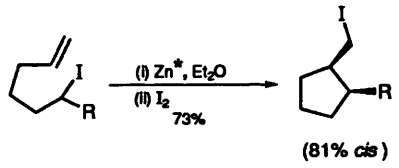
Scheme 20



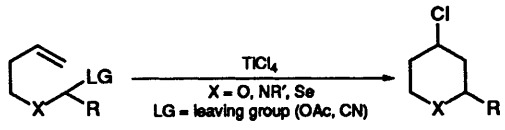
Scheme 21

transformation can also be achieved ionically (**Scheme 22**).[41]

A completely different ionic cyclization process which nevertheless results in net addition of carbon and chlorine across a double bond is depicted in **Scheme 23**. This approach has been used to prepare a wide range of oxygen-,[42] nitrogen-,[43,44] and selenium-[45] containing halogen substituted heterocycles.



Scheme 22

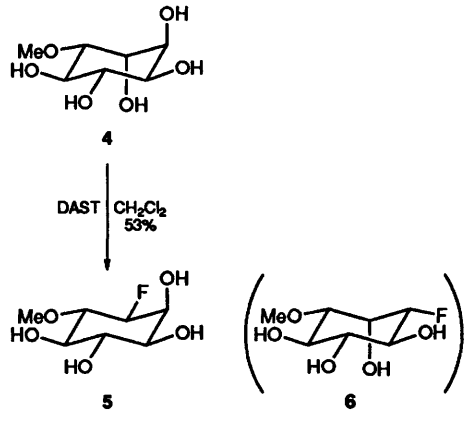


Scheme 23

2.3 By nucleophilic substitution

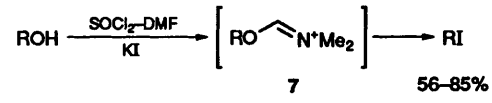
The counter-thermodynamic Finkelstein conversion of primary alkyl chlorides into bromides of high (> 99%) purity has been achieved by repeated treatment (the second after aqueous work-up) with 10 equivalents (each) of lithium bromide in refluxing pentan-2-one.[46]

The most popular precursors to alkyl halides continue to be alcohols, of course. A correction to a previously reported chemo- and stereo-selective fluorination has been published: treatment of polyol **4** with diethylaminosulfur trifluoride (DAST) gives **5** exclusively and not the isomer **6** (**Scheme 24**).[47] Meanwhile, the conversion of methanol or ethanol into the corresponding alkyl chloride by reaction with thionyl chloride has been the focus of some detailed mechanistic physical organic chemistry.[48]



Scheme 24

More general, synthetically useful procedures include the conversions of secondary and tertiary (but not primary) alcohols to the corresponding bromides or fluorides by treatment with boron tribromide[49] or PVPHF (the previously mentioned solid hydrogen fluoride source[9]) respectively. Meanwhile, primary and secondary alcohols are transformed into the corresponding iodides in good yields by treatment with thionyl chloride and potassium iodide in DMF (**Scheme 25**).[50] The use of DMF is significant, since one of the reaction intermediates is the formamidinium species **7** (as evidenced by the formation of the corresponding formate ester ROCHO under slightly different reaction conditions). DMF is also important in the conversion of alcohols into alkyl chlorides using phosphorus oxychloride ($POCl_3$).[51]

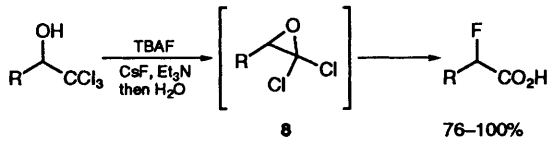


Scheme 25

Milder conditions for phosphorus-based activation of alcohols towards halide displacement continue to find regular application; examples reported this year include the combination of triphenylphosphine with CBr_4[52] and with I_2/imidazole,[53,54] smooth inversion of configuration being not unexpectedly observed in the case of a secondary alcohol.[54] In addition, triphenylphosphine iodochloride (Ph_3PICl) has been used to convert silyl ethers of perfluoroalcohols into perfluoroalkyl iodides.[55]

Examples of secondary alcohol halogenation with inversion of configuration by prior conversion into the corresponding triflate[56] or mesylate[57,58] have been described. In the latter case, it was shown that displacement with fluoride ion can be used for the stereospecific introduction of fluorine α-to a carbonyl group[57] and in benzylic positions of electron-deficient aromatics.[57,58] It was noted, however, that α-fluorophenylacetic acid could only be obtained in racemic form under these conditions because the basicity of the fluoride ion causes epimerization of the chiral centre. This deficiency might be mitigated by the use of an enzymic resolution of the α-haloester, a process whose mechanistic aspects have recently been discussed in some detail.[59]

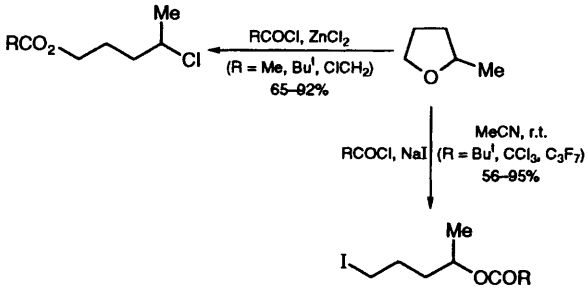
α-Fluoro-carbonyl compounds can also be prepared by way of the novel approach depicted in **Scheme 26**.[60] This transformation proceeds through the 1,1-dichloroepoxide **8**, but its stereochemical aspects have yet to be disclosed.



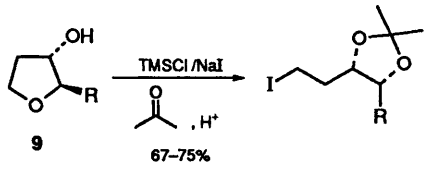
Scheme 26

The cleavage of cyclic ethers (particularly tetrahydrofurans) to halides has been studied by a number of groups. Acylative cleavage of tetrahydrofuran was reported using SmI_2,[61] and it was

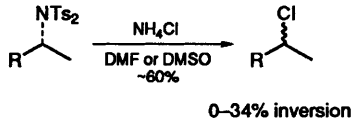
also shown that the related cleavage of 2-methyltetrahydrofuran could be controlled to give either regioisomer (**Scheme 27**).[62] Regioselective cleavage was also observed on treatment of **9** with trimethylsilyl chloride in the presence of sodium iodide (**Scheme 28**).[63] Silyl ethers themselves can be converted into fluorides (with inversion) using a piperidine analogue of DAST,[64] and a conversion of chiral amine ditosylates to secondary alkyl chlorides has been described (**Scheme 29**).[65]



Scheme 27



Scheme 28

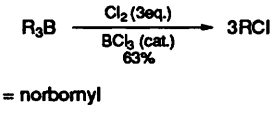


Scheme 29

Lastly, it has been found advantageous to use catechyl phosphorus tribromide instead of triphenylphosphorus dibromide or gaseous HBr for the preparation of 1,4-dibromobutane from tetrahydrofuran.[66]

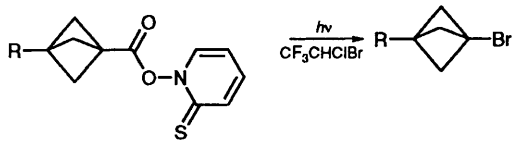
2.4 By other methods

A recent procedure for the direct conversion of trialkylboranes into alkyl halides uses elemental chlorine (or bromine) under BCl_3 catalysis (**Scheme 30**).[67] The reaction proceeds with retention of configuration and all three alkyl groups end up as alkyl halides.



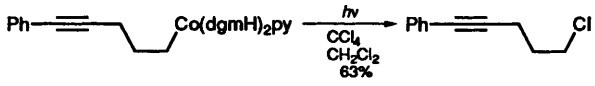
Scheme 30

Radical halodecarboxylation of acids via thiopyridylhydroxamate ('Barton') esters continues to be a method of choice for the preparation of bridgehead halides (**Scheme 31**),[68] although direct

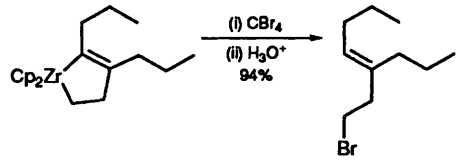


Scheme 31

fluorodecarboxylation of cyclopropane carboxylic acids has also been reported using elemental fluorine in a basic aqueous sodium fluoride solution.[69] Radical conditions can also be used to convert organocobalt species into alkyl chlorides (**Scheme 32**),[70] while by judicious choice of reagent, the zirconacyclopentene **10** can be chemoselectively converted into the homoallyl bromide **11** (**Scheme 33**).[71]



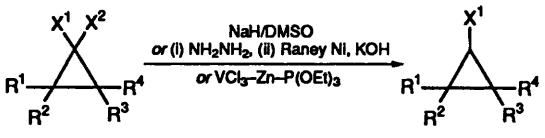
Scheme 32



10 **11**

Scheme 33

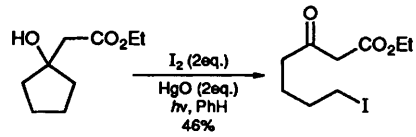
The reduction of 1,1-dihalocyclopropanes to monohalocyclopropanes (**Scheme 34**) has been reported under a number of conditions, including NaH or Bu^{t}OK in DMSO,[72] hydrazine followed by Raney nickel,[73] or VCl_3–Zn–P(OEt)$_3$.[74]



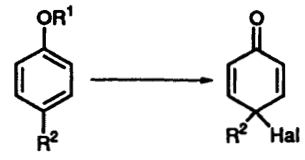
X^1, X^2 = Br, Cl

Scheme 34

Other more obscure but nevertheless interesting alkyl halide syntheses published this year include a number of oxidative fragmentation reactions[75–78] (*e.g.* **Scheme 35**[75]), and the halogenation of 4-substituted phenols (and anisoles) to give 4-halo-cyclohexadienones (**Scheme 36**) using pyridine poly(hydrogen fluoride) in combination with either iodobenzene diacetate (giving the fluoride)[79] or SbF_5 in CH_2Cl_2 [giving the chloride (sic)].[80]



Scheme 35

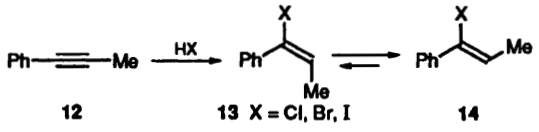


Scheme 36

3. Vinyl halides

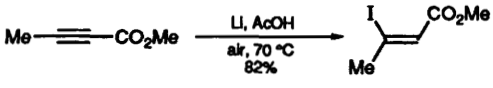
3.1 From alkynes

The hydrohalogenation of alkynes has been studied in some detail by Kropp and Crawford[81] who have found that appropriately prepared silica gel or alumina can mediate the reaction with a good degree of stereocontrol. Even more conveniently, acid halides such as $SOCl_2$, $(COCl)_2$, PBr_3, $(COBr)_2$, AcBr, PI_3, and AcI can be used as the source of hydrogen halide since, in the presence of silica or alumina, hydrogen halide is generated *in situ*. Thus, 1-propynylbenzene **12** can be converted into the *syn* addition product **13** or, on extended treatment, to the thermodynamically more stable (*Z*)-isomer **14** (partly through addition–elimination via a geminal dihalide intermediate) (**Scheme 37**). (To put this method into context, **12** does not react at all with HCl in CH_2Cl_2.) An added benefit of this heterogeneous chemistry is that HBr addition gives only the Markovnikov isomer, in contrast to the mixture of regioisomers more typically obtained under homogeneous conditions.



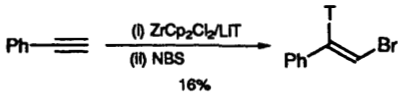
Scheme 37

Another hydrohalogenation procedure of some generality is the regio- and stereo-specific hydrohalogenation of 2-alkynoic acids and their derivatives (**Scheme 38**).[82]



Scheme 38

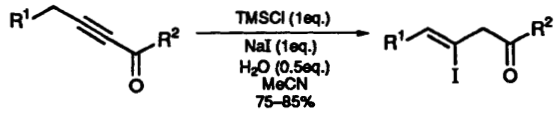
More specialized hydrohalogenation procedures reported this year include a novel supported liquid-phase rhodium catalyst for the mercury-free production of vinyl chloride from acetylene,[83] the regiospecific (but low yielding) tritiobromination of alkenes under zirconium catalysis (**Scheme 39**),[84] and



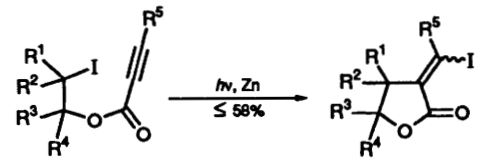
Scheme 39

a novel stereoselective hydrohalogenation–deconjugation reaction (**Scheme 40**).[85]

Carbon–halogen addition to alkynes has been widely applied to cyclizations, either radically[86,87] (*e.g.* **Scheme 41**[86]) or under palladium catalysis,[88–90]

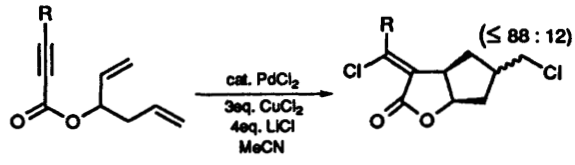


Scheme 40

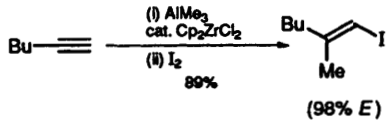


Scheme 41

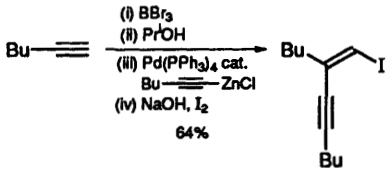
an example of the latter being depicted in **Scheme 42**.[90] Intermolecular carbon–halogen addition processes are also a powerful synthetic approach to vinyl halides, as the transformations shown in **Schemes 43**,[91] **44**,[92] **45**,[93] **46**,[94] and **47**[95] illustrate.



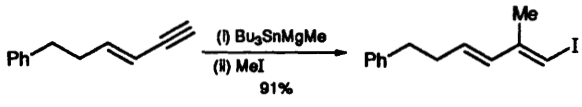
Scheme 42



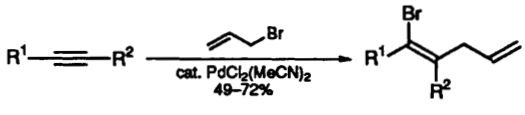
Scheme 43



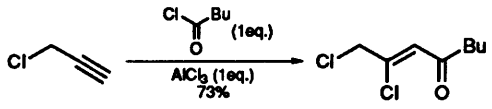
Scheme 44



Scheme 45

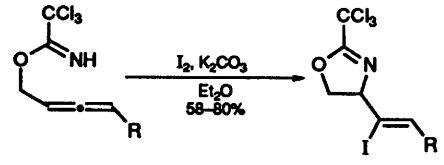


Scheme 46

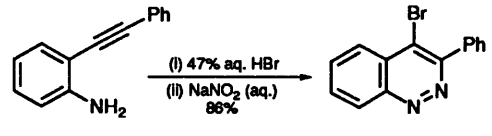


Scheme 47

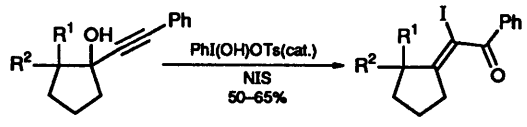
Heteroatom–halogen additions to alkenes and alkynes are exemplified by the cyclization reactions depicted in **Schemes 48**[96] and **49**,[97] while a more unusual approach to vinyl iodides from propargylic alcohols uses Koser's reagent PhI(OH)OTs as catalyst and *N*-iodosuccinimide as iodine source (**Scheme 50**).[98]



Scheme 48



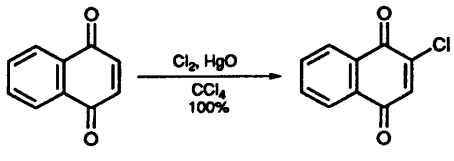
Scheme 49



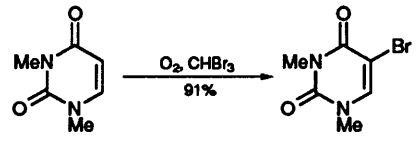
Scheme 50

3.2 From other vinyl derivatives

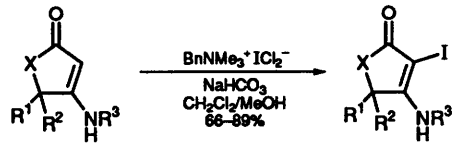
The monochlorination of quinones[99] and coumarins[100] is readily achieved with copper(II) chloride on alumina in chlorobenzene,[99,100] and with dichlorine monoxide in carbon tetrachloride,[101] the latter process being significant in that aromatic chlorination is not observed in naphthoquinone systems (**Scheme 51**). Bromination of related systems can be achieved by adaptation of the former process,[100] or by a completely different method using bromoform ($CHBr_3$) (**Scheme 52**).[102] For iodination, benzyltrimethylammonium dichloroiodate (BTMA-ICl_2) has been found particularly effective (**Scheme 53**).[103]



Scheme 51



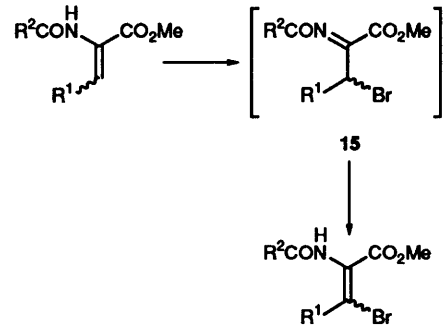
Scheme 52



X = CH_2CH_2, O, S

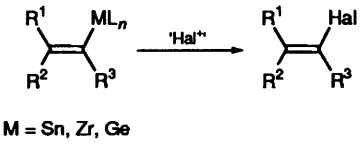
Scheme 53

An area of detailed study is the regio- and stereo-selective bromination of dehydroamino acids (**Scheme 54**), which can be carried out with controllable retention or inversion of alkene configuration.[104] The kinetically favoured (*E*)-isomers are obtained using hindered amine bases (*e.g.* lithium 2,2,6,6-tetramethylpiperidide, sodium hexamethyldisilazide) for deprotonation of the α-bromoimine intermediate **15**, whereas use of DABCO as base yields the thermodynamically favoured (*Z*)-isomer by isomerization. The picture is not quite as simple as this, however, as the nature of the brominating agent also influences the stereoselectivity.[104,105]



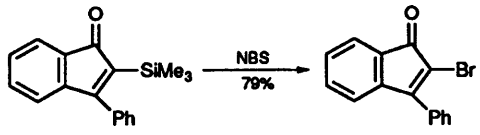
Scheme 54

Conversions of a number of alkenyl metal compounds into vinyl iodides according to **Scheme 55** have appeared regularly in the literature, the most common precursors being vinyl stannanes,[106–108] with isolated examples of vinyl zirconium[109] or germanium[110] precursors. Vinyl silanes can also be used to prepare the corresponding vinyl bromides as the example in **Scheme 56** illustrates.[111]



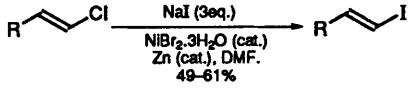
M = Sn, Zr, Ge

Scheme 55

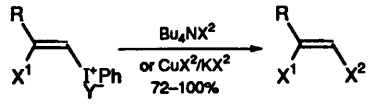


Scheme 56

Interconversion of vinyl halides is possible under certain conditions (**Scheme 57**),[112] and vinylic hypervalent iodine derivatives **16** have proved useful as synthetic precursors to (*Z*)-1,2-ethylene dihalides (**Scheme 58**).[113] Steroidal vinylic 1,2-dihalides have also been accessed from vinyl sulfides as **Scheme 59** shows.[114] Reduction of 1,1-dihaloalkenes by bromine–zinc exchange followed by protonolysis also offers access to vinyl halides (**Scheme 60**).[115]



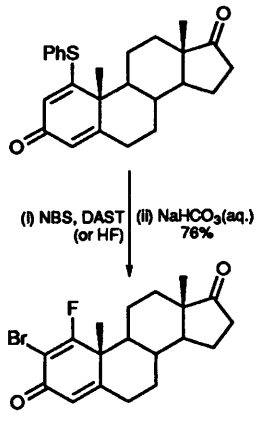
Scheme 57



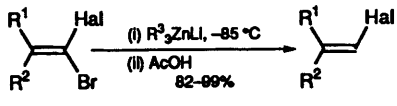
16

X^1, X^2 = Cl, Br, I

Scheme 58



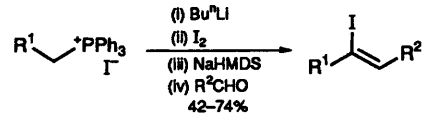
Scheme 59



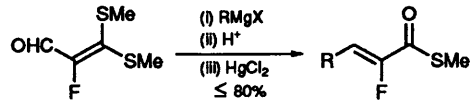
Scheme 60

3.3 By C=C bond formation

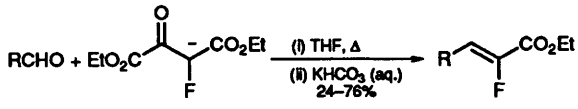
While many vinylic halide preparations start from a preformed alkyne or alkene as described in Sections 3.1 and 3.2 above, the synthesis of the carbon–carbon double bond itself offers an alternative and less widely used approach to these systems, mostly by way of Wittig-type procedures, typified by the vinyl iodide synthesis depicted in **Scheme 61**.[116] A number of syntheses of α-fluoro-α,β-unsaturated esters have been described using Wittig[117–119] and non-Wittig chemistry (**Scheme 62**),[119] as well as the unusual stereoselective transformation shown in **Scheme 63**.[120]



Scheme 61



Scheme 62

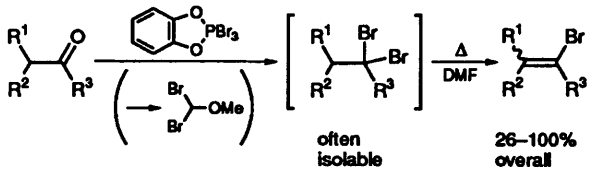


Z/*E* > 80:20

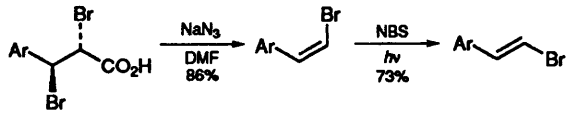
Scheme 63

3.4 By other methods

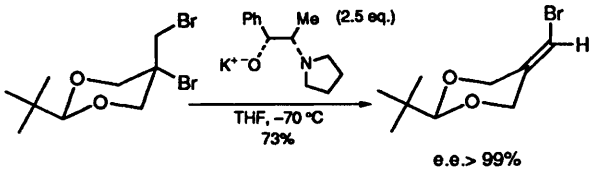
The patent literature reports the conversion of ketones into vinylic fluorides by treatment with DAST and sulfuric acid.[121] Meanwhile, more established methodology for vinyl iodide synthesis (reaction of ketone hydrazones with iodine and base) has been applied in the preparation of a calyculin fragment.[122] The direct transformation of ketones to vinylic bromides using pyrocatechyl phosphorus tribromide and methyl formate has been examined in some detail and proceeds via a geminal dibromide intermediate as shown in **Scheme 64**.[123] Related vinyl halide preparations by base-catalysed elimination of HBr from 1,1-dibromoalkanes[124] or 1,1-bromofluoroalkanes[125] have also been described. In addition, the regioisomeric 1,2-dibromides are useful vinylic bromide precursors,[126–129] with particularly interesting examples illustrated in **Schemes 65**[128] and **66**.[129]



Scheme 64

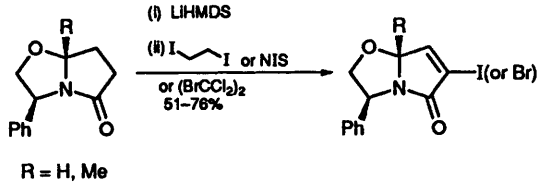


Scheme 65

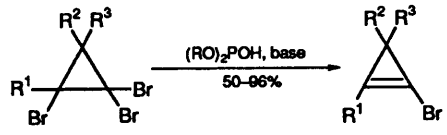


Scheme 66

A one-pot conversion of saturated lactams into α-halo-α,β-unsaturated lactams is shown in **Scheme 67**,[130] while reductive elimination of bromine can be used to synthesize strained bromocyclopropenes (**Scheme 68**).[131]

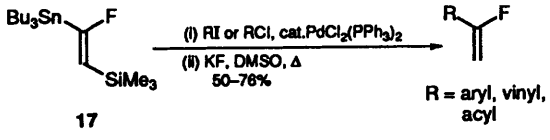


Scheme 67



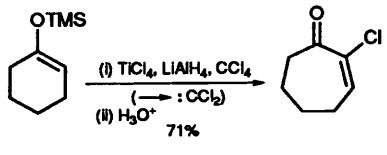
Scheme 68

A synthetic equivalent of the 1-fluoroethylene anion is the silyl stannane **17**, which undergoes a range of palladium-catalysed couplings followed by desilylation to yield vinyl fluorides (**Scheme 69**).[132]



Scheme 69

Finally, a novel one-step homologative process for the synthesis of α-chloro-α,β-unsaturated ketones has been developed with *in situ* generated dichlorocarbene as the key reactive species (*e.g.* **Scheme 70**).[133]

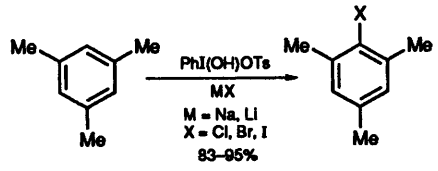


Scheme 70

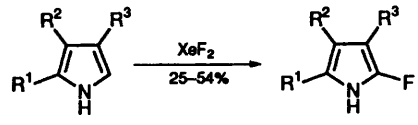
4 Aryl halides

4.1 By electrophilic substitution

Aromatic chlorination, bromination, and iodination of polyalkylbenzenes can be effected with PhI(OH)OTs ('Koser's reagent') in the presence of the requisite halide ion (**Scheme 71**).[134] Interestingly, benzene, toluene, and acetophenone do not react under these conditions, which also do not permit fluorination. Indeed, reports of electrophilic aromatic fluorination are few and far between, the most significant this year being the use of xenon difluoride to fluorinate pyrroles carrying an electron-withdrawing group and without NH protection (**Scheme 72**).[135,136]



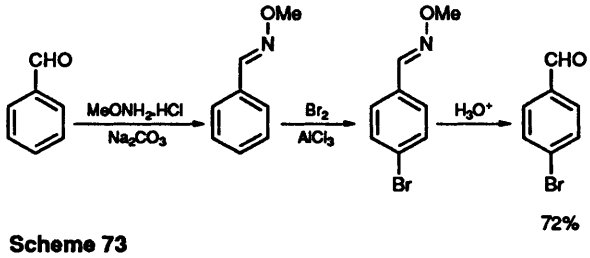
Scheme 71



Scheme 72

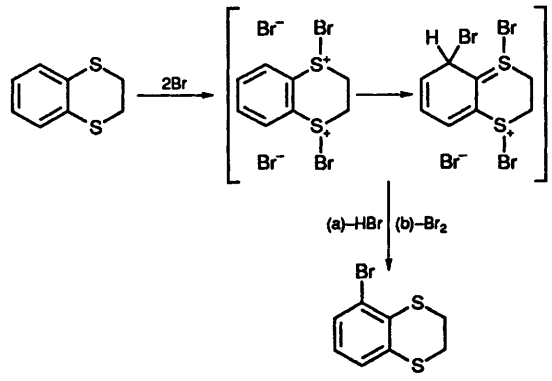
In contrast to fluorination, bromination continues to be a very active area of research. A *para*-selective, high-yielding, economical, and environmentally safe bromination of anilines, anilides, phenols, and phenol ethers has been described using an ammonium molybdate catalyst with H_2O_2/KBr,[137] and there has been a Russian report of phenol monobromination using bis(dimethylacetamido)hydrogen tribromide.[138] Attempts to control the regiochemistry of bromination of phenols and *N,N*-dialkylanilines using cyclodextrins[139] or surfactants,[140] respectively, have met with modest success.

Direct bromination of benzaldehyde usually gives the *meta*-substituted product, but temporary masking of the aldehyde as an *O*-methyl oxime allows *para*-bromination to be achieved in high overall yield (**Scheme 73**).[141] Regiocontrolled chlorination can also be achieved using this methodology.



Scheme 73

Theoretical chemists continue to challenge the mechanistic understanding of synthetic chemists, this time with calculations suggesting that the rapid bromination of 1,4-benzodithian proceeds by way of vicarious nucleophilic substitution rather than electrophilic substitution (**Scheme 74**).[142]



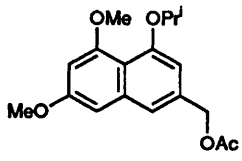
Scheme 74

The trialkoxynaphthalene **18** can be converted into any one of three possible monobromination products by combinations of selective bromination, debromination, and bromine migration;[143] and enzymatic bromination of the pyrrole ring of compounds such as **19** using chloroperoxidase and H_2O_2/MBr has also been described.[144]

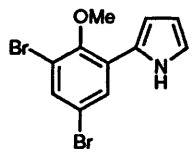
Turning to aromatic iodination, procedures have appeared using iodine in combination with mercury(II) salts[145] or silver(I) sulfate.[146]

While the electrophilic methods described above all involve replacement of hydrogen with halogen, silanes and stannanes also continue to be useful precursors to halides. In particular, iodination of furans is often best achieved via a silane,[147] and thanks to advances in regioselective silylation, iodobenzenes with less-common substitution patterns are now more readily accessible.[148] A straightforward and general method for the preparation of aryl fluorides from aryl silanes has been described using xenon difluoride,[149] while 2- and 3-fluoroindoles have been prepared by treatment of the corresponding 2- and 3-trimethylstannylindoles with either caesium fluoroxysulfate or with the Selectfluor reagent F-TEDA-BF_4(**1**).[150] Aryl stannanes have also been used as precursors to radiolabelled aryl iodides using iodine-125.[151] More unusual preparations of aryl halides reported this year include the conversion of aryl lead triacetates into aryl fluorides using boron trifluoride etherate,[152] and a palladium-catalysed conversion of arylsulfonylchlorides into aryl iodides.[153]

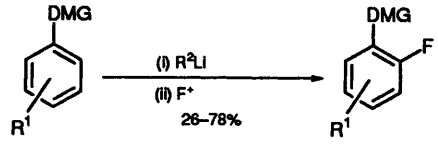
The other common approach to aryl halides using electrophilic halogens is via directed lithiation, which has proved particularly useful for the *ortho*-fluorination of aryl amides, carbamates, phenol ethers, sulfoxides, sulfones, sulfonamides, and oxazolines (**Scheme 75**).[154,155] With *N,N*-diethylbenzamide as substrate, and using *N*-fluorobenzenesulfonimide, $(PhSO_2)_2NF$, as the electrophilic fluorine source, unexpected transfer of



18

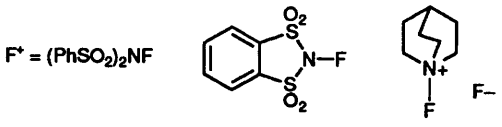


19



DMG = directed metallation group

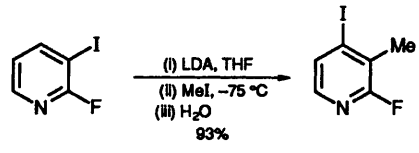
$CONHBu^t$	$OCSNEt_2$
OMe	SO_2NHMe
oxazoline	$SO_2NR^3_2$ (R^3 = Me, Et)
$CONEt_2$	$S(O)_nBu^t$ (n = 1, 2)



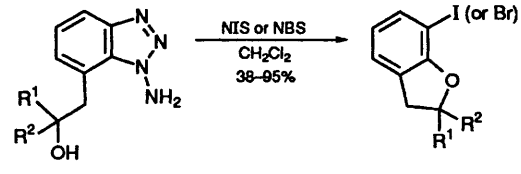
Scheme 75

the $PhSO_2$ group was observed,[154] whereas use of *N*-fluoroquinuclidinium fluoride gave the expected fluoride.[155]

Other examples of metallation–halogenation have been described in pyrrole[156] and pyridine[157] systems, and an interesting 'halogen dance' has been observed (**Scheme 76**).[158] Finally, an unusual cyclization of substituted benzotriazoles to halogenated dihydrobenzofuranyl systems has been described (**Scheme 77**).[159] A transient aryne intermediate is proposed.



Scheme 76



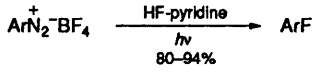
Scheme 77

4.2 By nucleophilic substitution

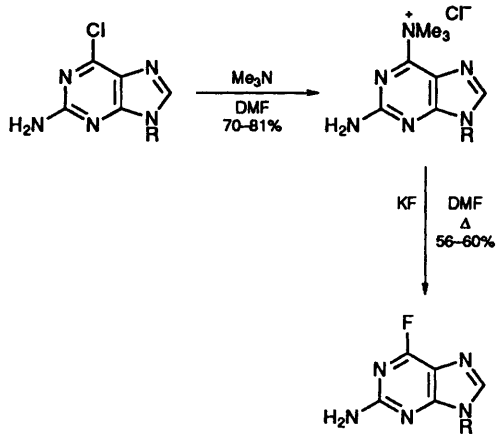
Nucleophilic substitution with halide ion is a less common approach to aryl halides. The synthesis of fluorides by this approach has been the subject of a review which places particular emphasis on

mechanistic aspects.[160] Perhaps the most significant development in the area is a high-yielding and facile preparation of aryl fluorides from aromatic diazonium tetrafluoroborates under photochemical conditions (**Scheme 78**).[161] The transformation can also be achieved thermally, but yields are much more variable (and often poor).

The substitution of heterocyclic chlorides with fluoride ion via quaternary ammonium intermediates has been applied to the synthesis of potential prodrugs of acyclovir and ganciclovir (**Scheme 79**).[162]



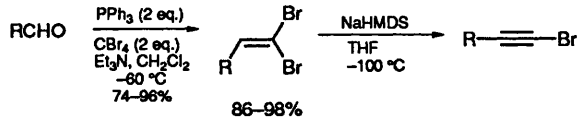
Scheme 78



Scheme 79

5 Alkynyl halides

The only new literature in this area describes an improved procedure for aldehyde to alkyne homologation via 1,1-dibromoalkenes (**Scheme 80**).[163]

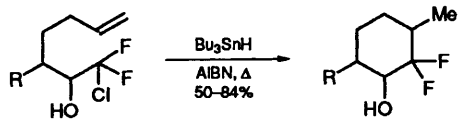


Scheme 80

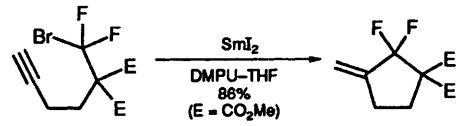
6 1,1-Dihalo compounds

The preparations of some 1,1-dihaloalkanes from 1,1,1-trihalomethyl units have already been mentioned in this review (*e.g.* **Schemes 15–18**, Section 2.2). While in those examples the radical resulting from the alkene addition step was trapped with a halogen radical, trapping with a hydrogen radical has also been reported (**Scheme 81**).[164] Another variation on the same theme is the cyclization of the 1,1,1-bromodifluoro alkyne **20** (**Scheme 82**).[165]

The most widely used approach to the synthesis of 1,1-dihaloalkanes starts from carbonyl compounds or their derivatives. During the period under review, the conversion of aldehydes to geminal difluoroalkanes



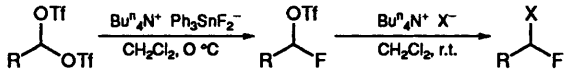
Scheme 81



20

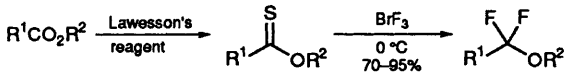
Scheme 82

using DAST has been described,[166] as well as the preparation of 1,1-halofluoroalkanes from geminal bis-triflates (**Scheme 83**).[167] Geminal difluoroalkanes were prepared from ketones via oximes [using $NOBF_4$ and pyridine poly(hydrogen fluoride)],[168] imines (using BrF_3),[169] and dithioacetals [using SO_2Cl_2 and pyridine poly(hydrogen fluoride)],[170] while related transformations were also reported for higher oxidation state carbonyl compounds such as esters (**Scheme 84**),[171] amides,[172] and thiocarbonates.[173,174] In addition to these procedures, a method for the synthesis of 1,1-dibromoalkanes from ketones has already been mentioned in Section 3.4 (**Scheme 64**).[123]



X = Cl, Br, I (53–94% overall)

Scheme 83

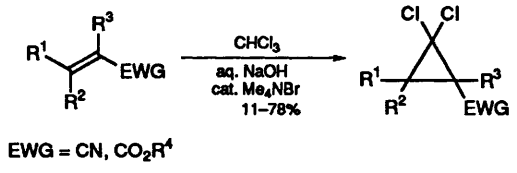


Scheme 84

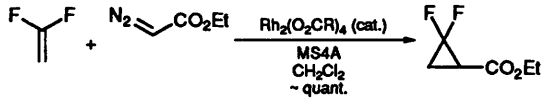
A detailed study of the photochemical benzylic di- and tri-bromination of methyl-, dimethyl-, and trimethyl-benzenes with *N*-bromosuccinimide has been made;[175] it was found that 1,1,1-tribromination was facile, except in the presence of an *ortho* substituent, in which case 1,1-dibromination was preferred.

1,1-Dihalocyclopropane derivatives can be prepared either by phase-transfer catalysed addition of dichlorocarbene (from $CHCl_3$/NaOH) to acrylates and crotonates (**Scheme 85**),[176] or by the addition of ethyl diazoacetate to 1,1-difluoroethylene (**Scheme 86**).[177]

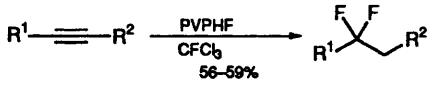
Other approaches to 1,1-dihaloalkanes include the double hydrofluorination of alkynes using the solid hydrogen fluoride source PVPHF (**Scheme 87**),[9] and the oxidative acetal halogenations shown in **Scheme 88**.[178,179]



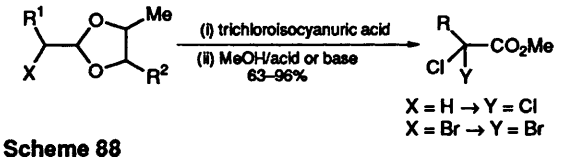
Scheme 85



Scheme 86

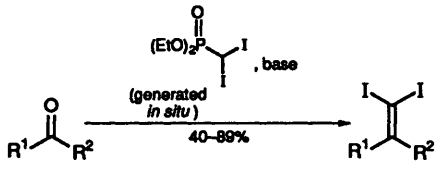


Scheme 87

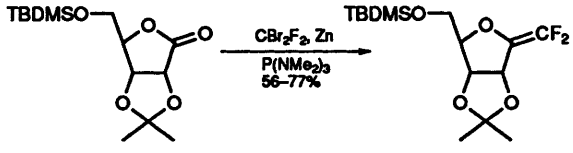


Scheme 88

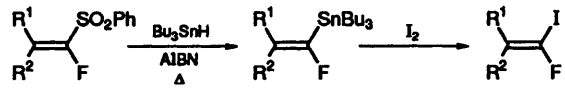
Syntheses of vinylic geminal dihalides appeared regularly in the year's literature. In addition to that already mentioned in Section 5 above, a general preparation of 1,1-diiodoalkenes by Wittig type procedures (**Scheme 89**),[180] an unusual approach to geminal difluoroenol ethers (**Scheme 90**),[181] a synthesis of 1,1-fluoroiodoalkenes by functional group manipulation of 1-fluoro-1-sulfonylalkenes (**Scheme 91**),[182] and further examples of previously described[1]



Scheme 89

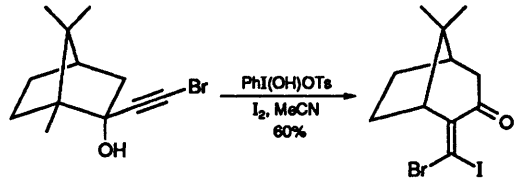


Scheme 90

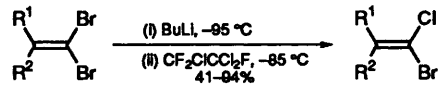


Scheme 91

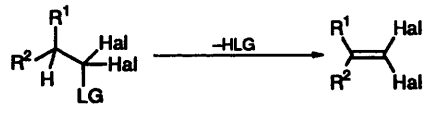
rearrangement reactions to give 1,1-bromoiodoalkenes (**Scheme 92**)[183] were reported. 1,1-Bromochloroalkenes are readily prepared from 1,1-dibromoalkenes as shown in **Scheme 93**.[115] Other vinylic dihalides arose from elimination reactions (**Scheme 94**) in rather specialized systems[184–187] and will therefore not be discussed here.



Scheme 92



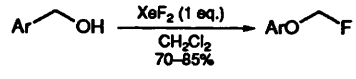
Scheme 93



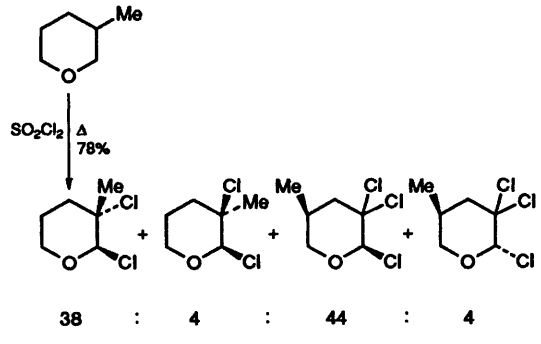
Scheme 94

7 1,1-Halohydrins and related compounds

Non-glycosidic 1,1-fluorohydrins are not particularly common, but a novel method for the preparation of fluoromethyl phenol ethers has been reported (**Scheme 95**).[188] Meanwhile, another unusual and not particularly chemoselective approach to 1,1-halohydrins is the chlorination of ethers with sulfuryl chloride (**Scheme 96**).[189]

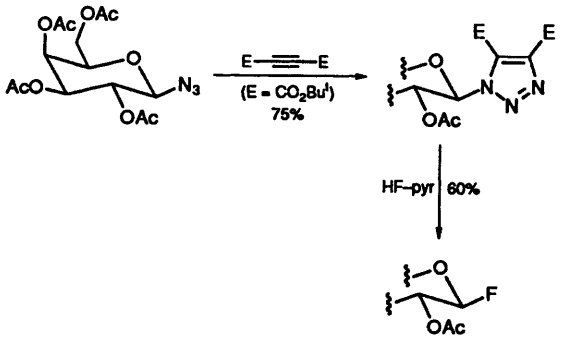


Scheme 95

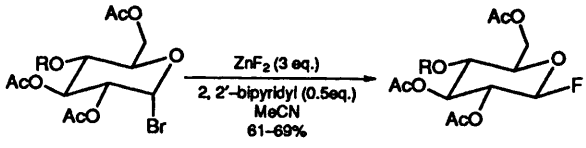


Scheme 96

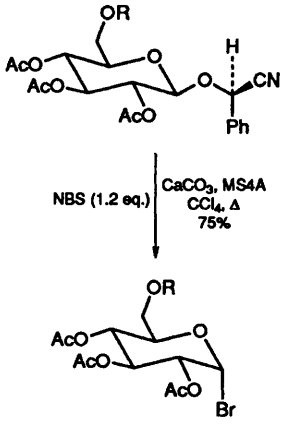
Of wider synthetic interest are the glycosyl halides. There have been reports of glycosyl fluoride preparations from a range of different precursors, including glycosidic acetals ($HF/MeNO_2$),[190] azides (**Scheme 97**),[191] and bromides, the latter proceeding with inversion of configuration at the anomeric centre as indicated in **Scheme 98**.[192] Inversion of configuration is also observed in the preparation of α-glycosyl bromides from acetals containing mandelonitrile as the anomeric activating group (**Scheme 99**).[193] α-Glycosyl bromides are the preferred products of glycal bromination with tetraalkylammonium tribromides as **Scheme 100** indicates.[194]



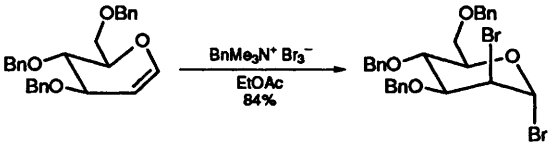
Scheme 97



Scheme 98

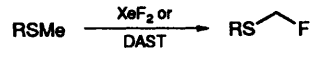


Scheme 99



Scheme 100

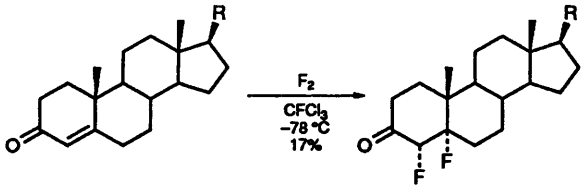
Fluoromethylsulfides are readily prepared from methyl thioethers by treatment with either xenon difluoride[195] or diethylaminosulfur trifluoride (DAST)[196,197] (**Scheme 101**).



Scheme 101

8 1,2-Dihalo compounds

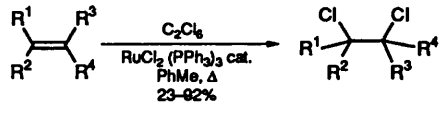
The direct fluorination of alkenes with molecular fluorine[198] is a difficult and rarely used synthetic procedure, the capricious nature of which was borne out by a recent attempt to repeat a literature fluorination of 4-cholesten-3-one. While earlier workers have reported a 70% yield of the *cis*-difluoride **22** from **21**, the repeat reaction proceeded in only 17% yield (**Scheme 102**).[199] This was nevertheless used as a fairly direct way of introducing a fluorine atom β to a carbonyl group as indicated in the Scheme. Xenon difluoride can also be used to difluorinate alkenes, but phenyl substitution of the alkene is required.[200]



21 **22**

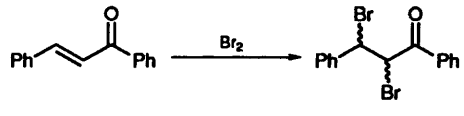
Scheme 102

A new transition metal catalysed alkene 1,2-dichlorination has been described which proceeds in the presence of a number of functional groups such as hydroxyl, carboxyl, and activated methylene (**Scheme 103**).[201,202]



Scheme 103

Bromination of alkenes has once again been the focus of theoretical calculations,[203] and the influence of cyclodextrins on the bromination of chalcone has been investigated and shown to be very modest (**Scheme 104**).[204]



without β-cyclodextrin ⟶ 100 : 0 (*erythro* : *threo*)
with β-cyclodextrin ⟶ 80 : 20 (*erythro* : *threo*)

Scheme 104

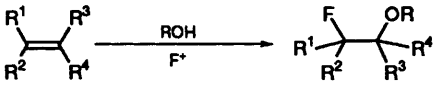
Bromofluorination of alkenes can be effected with the new solid hydrogen fluoride source PVPHF, when combined with NBS or DBH.[9]

9 1,2-Halohydrins and related compounds

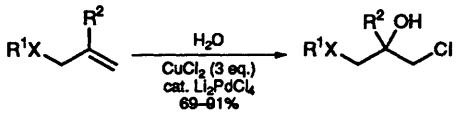
9.1 By addition to alkenes

This year saw the publication of a detailed review on the intermolecular addition of halogen and either oxygen or nitrogen nucleophiles to alkenes (a transformation termed 'cohalogenation').[205] The review discusses the regio-, chemo-, and stereo-selectivity of the process, and presents examples of cohalogenation with a wide variety of nucleophiles (water, hydrogen peroxide, carboxylic acid derivatives, alcohols, ethers, nitriles, amines, and pseudohalogens).

New procedures in the primary literature include the application of the Selectfluor reagent F-TEDA-BF_4(**1**)[206] (or $CsSO_4F$[200]) to the preparation of vicinal fluoro ethers (**Scheme 105**), and the first practical method for selective heteroatom-directed chlorohydroxylation of alkenes (**Scheme 106**).[207] In the latter paper, up to 76% diastereomeric excess was reported for allylic amines carrying a chiral (R^3 = α-methylbenzyl) substituent.

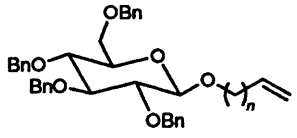


Scheme 105



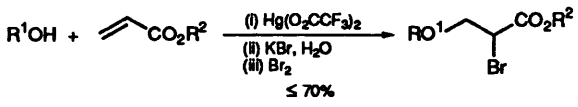
Scheme 106

The formation of bromohydrins from ω-alkenyl glycosides **23** has been studied in some detail,[208] and this paper contains an interesting account of the transfer of Br^+ from cyclic bromonium ions to alkenes.



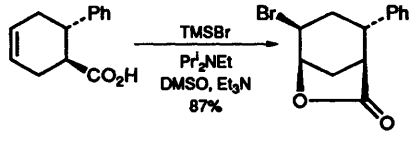
23 (*n* = 3, 4)

A one-pot procedure for regioselective bromine–alcohol addition to acrylates has been described (**Scheme 107**).[209] Although this method accommodates a wide variety of alcohols, the generally modest yields and the stoichiometric use of mercury bis(trifluoroacetate) will probably limit its wider application.

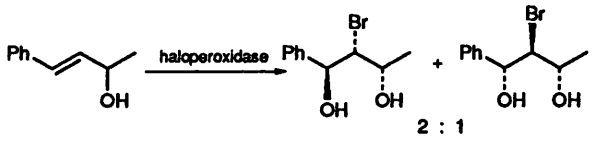


Scheme 107

Bromolactonization with an unexpected stereochemical outcome has been described (**Scheme 108**),[210] as well as biocatalytic bromohydrin formation using haloperoxidase enzymes (**Scheme 109**).[211] The products obtained in the latter case were racemic.

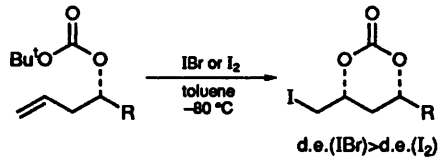


Scheme 108

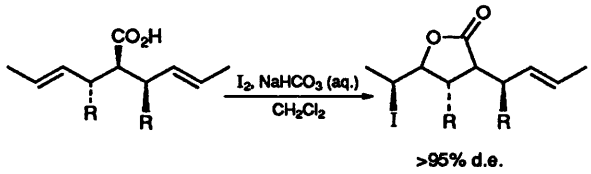


Scheme 109

Perhaps not surprisingly, the halogen most widely used in cohalogenation chemistry continues to be iodine. Iodolactonization is regularly applied in synthesis,[212] and many of the iodolactonization protocols described in the previous review in this series[1] have been developed further. These include seven- to eleven-membered ring-forming procedures[213] enhanced by geminal dimethyl substitution,[214] and the enhancement of diastereoselectivity in intramolecular iodocarbonation by using IBr instead of I_2 (**Scheme 110**).[215] There have been other publications concerning the stereochemistry of iodocarbonation,[216] iodocarbamation,[217] and iodolactonization (*e.g.* double diastereoselectivity, **Scheme 111**),[218] but space limitations preclude further discussion of these. An interesting use of iodolactonization chemistry for the mild hydrolysis of γ,δ-unsaturated amides is depicted

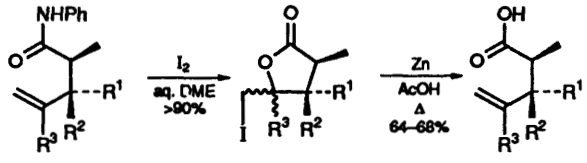


Scheme 110



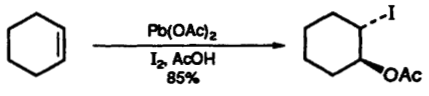
Scheme 111

in **Scheme 112**.[219] Of perhaps more general interest is a new and general iodolactonization procedure for β,γ- and γ,δ-unsaturated carboxylic acids via the oxidation of iodide with sodium persulfate in aqueous solution.[220] This method is fast, very high yielding, and exceptionally clean.

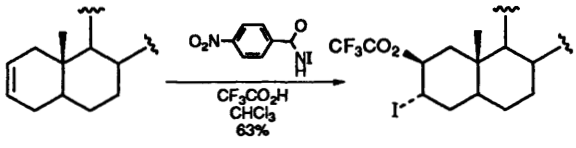


Scheme 112

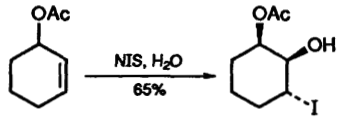
Intermolecular iodoacylation can be mediated by lead (**Scheme 113**),[221] and by the use of *N*-iodo-*p*-nitrobenzamide as electrophilic iodine source (**Scheme 114**).[222] Meanwhile, diastereospecificity is observed in the iodohydroxylation of 1-acetoxycyclohexene by way of intramolecular oxygen delivery (**Scheme 115**).[223] Regioselective alkoxy- and, more unusually, nitrato-iodination of α,β-unsaturated carbonyl compounds has also been described, using iodine and ceric ammonium nitrate (**Scheme 116**).[224]



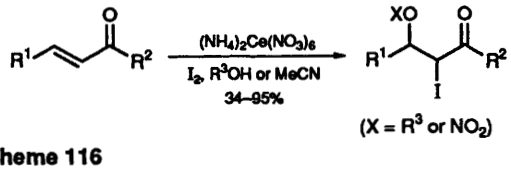
Scheme 113



Scheme 114

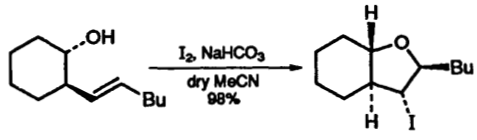


Scheme 115

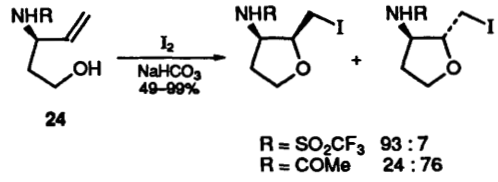


Scheme 116

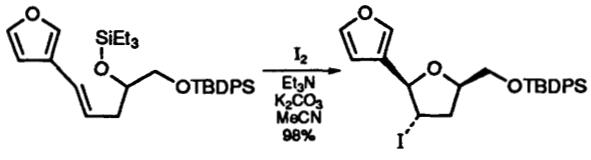
Intramolecular iodoetherification has been widely used in the synthesis of tetrahydrofuranyl systems.[225-230] For example, high levels of stereocontrol can be realized in the formation of bicyclic systems by using strictly anhydrous conditions (**Scheme 117**),[227] and electronic effects can strongly influence the stereoselectivity of cyclization of the allylic amines **24** (**Scheme 118**).[228] Other unusual and interesting stereoselective examples are illustrated in **Schemes 119**[229] and **120**.[230] Finally, *cis*-selective iodoetherification has been applied in the synthesis of *N*-aryl morpholinyl systems, although concomitant aromatic iodination also occurs unless the *para* position of the *N*-aryl group is blocked (**Scheme 121**).[231]



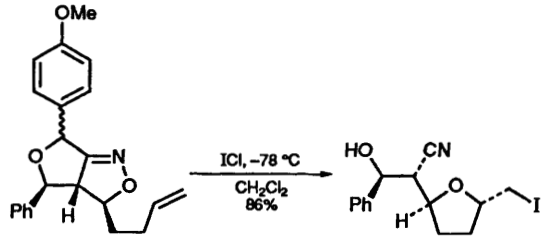
Scheme 117



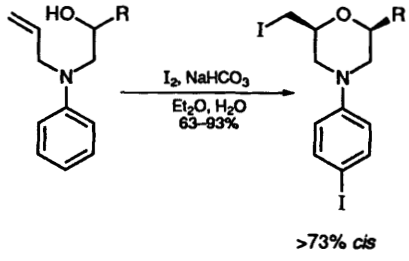
Scheme 118



Scheme 119



Scheme 120



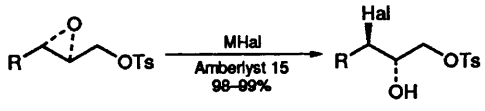
Scheme 121

Other heteroatoms which have been added across alkenes simultaneously with halide include nitrogen[232-234] and selenium,[235] but these will not be discussed further in this review.

9.2 By epoxide opening

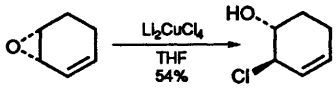
The regio- and chemo-selective synthesis of 1,2-halohydrins by the cleavage of epoxides with metal halides has been the subject of a detailed review by experts active in the area.[236] The review covers a range of metal counter-ions and discusses the influence of proximate functional groups such as alcohols and carbonyl groups.

The reaction of 2,3-epoxy-1-tosylates with chloride, bromide, or iodide ion has been shown to occur chemoselectively as shown in **Scheme 122**,[237] while cyclohexene epoxides can be opened regioselectively using dilithium tetrachlorocuprate (Li_2CuCl_4) or dilithium tetrabromonickelate (Li_2NiBr_4) (*e.g.* **Scheme 123**).[238]



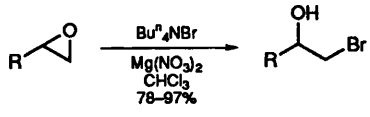
Hal = Cl, Br, I

Scheme 122



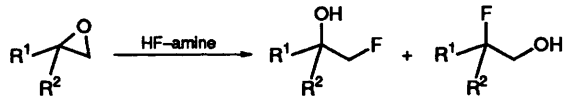
Scheme 123

A general and regioselective conversion of epoxides into 1,2-bromohydrins has been developed using tetrabutylammonium bromide and magnesium nitrate (**Scheme 124**).[239] The very high regioselectivity of this particular process is underlined by the observation that styrene oxide (R = Ph), which under most conditions affords the *secondary* halide (not shown) by nucleophilic attack at the benzylic position, gives the primary halide preferentially (83:17 mixture).

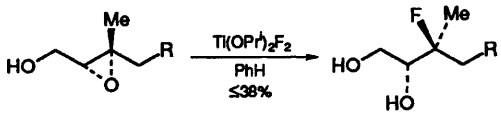


Scheme 124

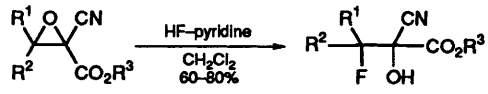
The levels of stereo- and regio-control in the conversion of optically active epoxides into vicinal fluorohydrins by treatment with HF-amine mixtures (**Scheme 125**) have been examined in some detail.[240] Depending on the nature of R^1 and R^2 and the precise conditions used, this reaction may proceed with reasonable (and sometimes excellent) regioselectivity, and also with clean inversion, or with partial racemization owing to carbonium ion formation. A number of other papers describe regioselective epoxide openings with fluoride, and examples of these are shown in **Schemes 126**,[241] **127**,[242] **128**,[243] and **129**.[64]



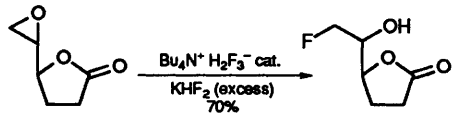
Scheme 125



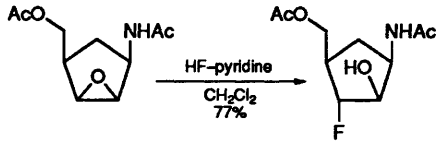
Scheme 126



Scheme 127

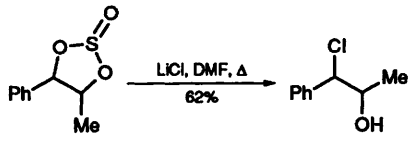


Scheme 128

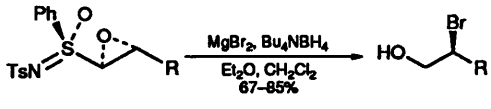


Scheme 129

Cyclic sulfites are useful epoxide surrogates in the synthesis of halohydrins, as the example in **Scheme 130** shows.[244] Meanwhile, a novel approach to enantiomerically enriched bromohydrins from homochiral *N*-tosylsulfoximino-oxiranes **25** has been described, which gives products of 70 to 91% e.e. (**Scheme 131**).[245] Finally, ring opening of aziridines[246] and thiiranes[247] with halide ion have also been reported in the period under review.



Scheme 130

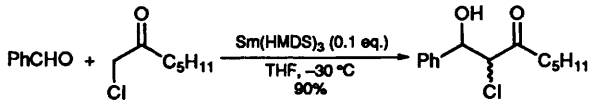


25 **70–91% e.e.**

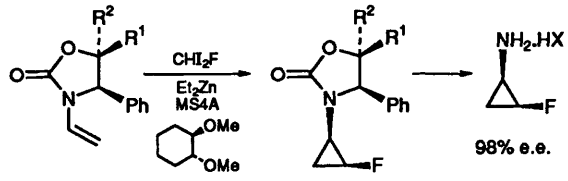
Scheme 131

9.3 By other methods

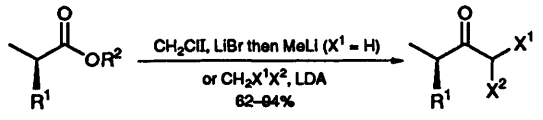
An unusual fluorohydrin synthesis has already been mentioned in Section 2.1 (**Scheme 1**), and while Sections 9.1 and 9.2 above cover the chemistry used most widely in the synthesis of 1,2-halohydrins and related compounds, there are nevertheless other methods available. These range from reactions of aldehydes with α-halo carbanion equivalents,[248-251] as exemplified by **Scheme 132**,[252] to the asymmetric cyclopropane synthesis depicted in **Scheme 133**.[253,254] α-Halo- (and α,α-dihalo-) ketones have been accessed by way of the chemistry shown in **Scheme 134**,[255] while a novel synthesis of fluoromethylketones from aldehydes has been demonstrated (**Scheme 135**).[256] The high temperatures required for the latter approach render it perhaps less useful than it first appears.



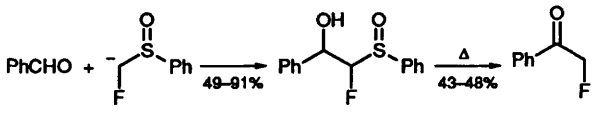
Scheme 132



Scheme 133

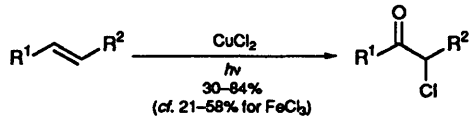


Scheme 134



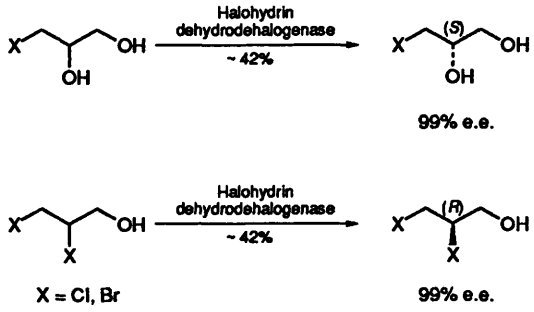
Scheme 135

Yield improvements in the photooxidation of alkenes to α-chloroketones have been achieved by using $CuCl_2$ instead of $FeCl_3$ (**Scheme 136**).[257]



Scheme 136

Lastly, a novel enzymatic resolution of halohydrins has been reported using halohydrin dehydrodehalogenase to selectively dehydrohalogenate one enantiomer (**Scheme 137**).[258]



Scheme 137

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