Organic halides

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Reviewing the literature published between 1 July 1992 and 30 June 1993

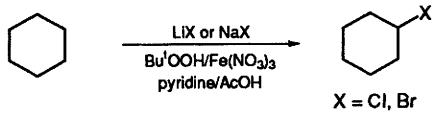
1 Introduction

The huge synthetic potential of organic halides puts them in a unique position within organic chemistry. Whether through palladium catalysis, by halogen–metal exchange, by conversion into radicals, or by good old-fashioned nucleophilic substitution, organic halides play a key role in much of contemporary organic synthesis. This coverage does not attempt to be fully comprehensive, but it is hoped that the chemistry selected for presentation is that which will be of particular utility or interest to the practising synthetic organic chemist. The area of perfluoroalkyl chemistry[1,2] will not be discussed, as it will be reviewed in this journal at a future date. No general reviews on the preparation of organic halides appeared during the review period, but some reviews specifically concerning fluorination were published.[3–5]

2 Alkyl halides

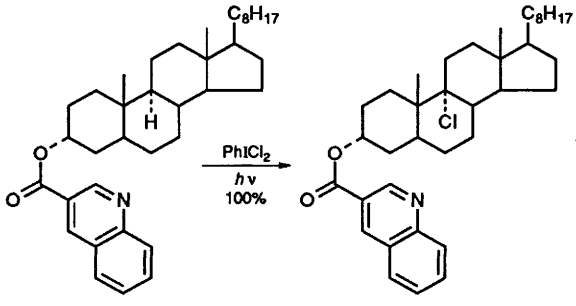
2.1 By halogenation of alkanes

The direct halogenation of unactivated alkanes using 'Gif-type' chemistry has continued to be developed in the research group of Barton,[6–9] but the lack of substrate functional group requirement for this chemistry does rather restrict its use to highly symmetrical systems such as cycloalkanes (**Scheme 1**).[9]



Scheme 1

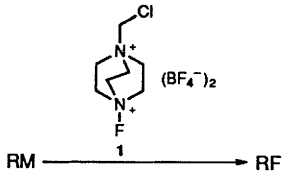
A review on this and related chemistry has been published.[8] Breslow's template-directed radical functionalization of apparently unactivated positions of steroids continues to prove synthetically useful, giving regioselectively chlorinated derivatives in impressively high yields (**Scheme 2**).[10] Alkyl chlorides can also be prepared by hydrochlorination of alkenes with thionyl chloride in a surface-mediated reaction on silica.[11]



Scheme 2

α-Halogenations of ketals and acetals have been described by a number of research groups, using MnO_2, TMSCl;[12] Br_2, ROH;[13] and Br_2, CCl_4;[14] the latter being part of a detailed study of the stereochemistry of spiro-ketal brominations and their subsequent elimination products.

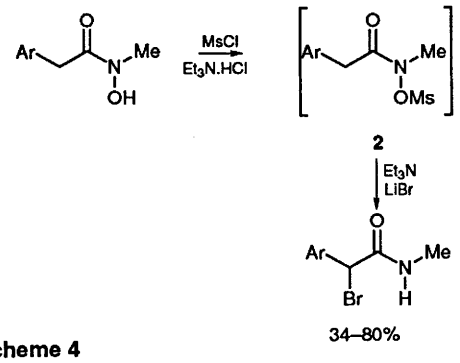
Halogenation by quenching of organometallic species with elemental halogen (*i.e.* $RLi + F_2 \rightarrow RF$[15]) has shown occasional utility,[16] and can be achieved with one of the latest additions to the battery of electrophilic fluorinating agents, the *N*-fluoro-DABCO derivative **1**,[17] which has been named a 'Selectfluor' reagent (**Scheme 3**). It is a virtually non-hygroscopic, high-melting solid with considerable synthetic potential, as will be seen in later sections of this review.



M = MgBr, Na, K; R = alkyl, aryl

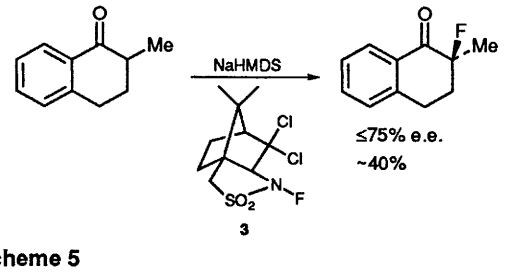
Scheme 3

The most frequently halogenated sp^3 carbon atoms are of course those stabilized by an adjacent carbonyl group, and a number of examples of this chemistry can be found in the literature under review, including lactams (TMSI, I_2 (or Br_2), Et_3N;[18] LDA then $ClSO_2Ph$[19]), α-thiolactams (by electrochemical means[20,21]), malonate derivatives (CCl_4, TBAF;[22] Selectfluor reagents;[17] I_2, K_2CO_3, Phase transfer catalysis[23]), ketoesters (TMSCl, $KBrO_3$,[24] Selectfluor reagents[17]), and sensitive 2-furyl ketones.[25] An interesting new method for the preparation of α-chloroamides is outlined in **Scheme 4**.[26] Use of only one equivalent of triethylamine allows the reaction to stop at the *N*-mesyloxyamide intermediate **2**. Treatment of **2** with LiBr and Et_3N then gives the α-bromoamide. Note, however, that a conjugating group at C-2 is essential for this reaction to proceed.

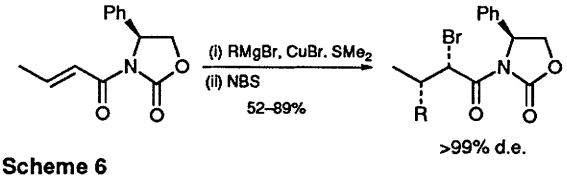


Scheme 4

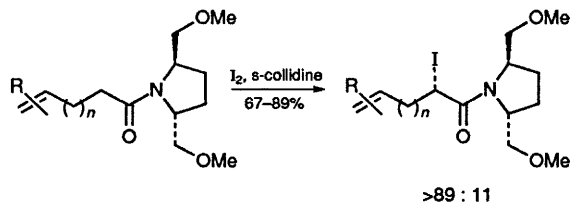
Asymmetric fluorination of enolates has been described using the Davis *N*-fluoro-camphorsultam derivative **3** (**Scheme 5**),[27] while asymmetric bromination[28] and iodination[29] of enolates have been achieved using covalently bound chiral auxiliaries (**Schemes 6 and 7**).



Scheme 5

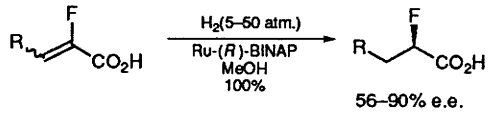


Scheme 6

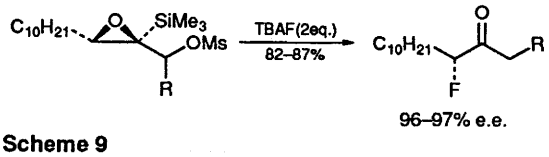


Scheme 7

α-Fluorocarboxylic acids of up to 90% e.e. have been prepared by asymmetric hydrogenation of α-fluoroacrylates (**Scheme 8**).[30] Lastly, a completely novel approach to enantiometrically pure α-fluoroketones has been developed which uses a Sharpless asymmetric epoxidation as the original source of chirality (**Scheme 9**).[31]



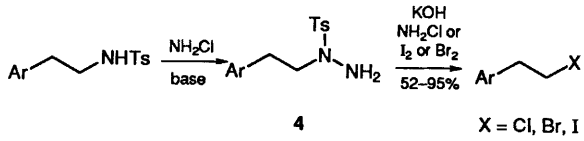
Scheme 8



Scheme 9

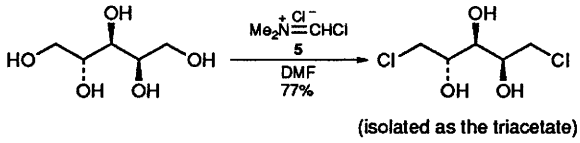
2.2 By nucleophilic substitution

The Finkelstein reaction between alkyl halides and aqueous HCl, HBr, or HI has been shown to be strongly accelerated under phase transfer catalysis,[32] while a new method for the conversion of alkyl chlorides or bromides into fluorides (PbF_2, NaBr, MeCN) has been reported, although this is restricted to benzylic systems only.[33] While not strictly a nucleophilic substitution a mild, cheap, and apparently general method for converting alkyl tosylamines to alkyl halides has been described (**Scheme 10**).[34] When the chloride is desired, this is a one-pot procedure. However, the bromide and iodide can also be prepared in high yield by isolation of the intermediate tosylhydrazine **4** followed by treatment with bromine or iodine.



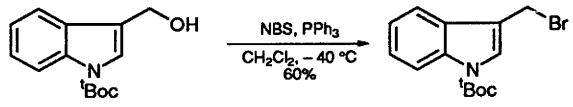
Scheme 10

The most common precursors to alkyl halides are, of course, alcohols. Selective halogenations of primary alcohols in the presence of secondary ones have been studied in detail, chlorination being achieved with the Vilsmeier-Haack reagent **5** in DMF (**Scheme 11**),[35] and bromination with HBr in acetic acid.[36]



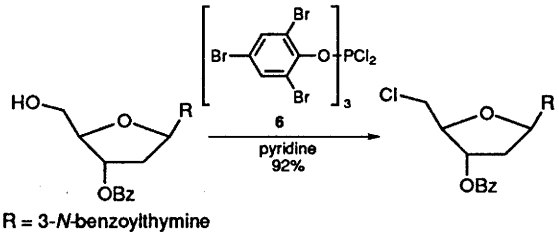
Scheme 11

The patent literature contains a report of a phosphine oxide mediated conversion of alcohols into alkyl chlorides with phosgene.[37] This is complemented by a report on the use of triphosgene and PPh_3 which has been shown to give excellent yields of alkyl chlorides from a wide range of alcohols.[38] The triphenylphosphine–bromine adduct PPh_3Br_2 continues to find use, particularly when sensitive functionality is also present in the starting alcohol,[39] and the combination of NBS and PPh_3 at low temperature has been shown to effect the previously difficult transformation shown in **Scheme 12**.[40]



Scheme 12

For less sensitive systems, a high-yielding and economical large-scale preparation of bromides from alcohols with inversion of configuration has been described, using the simple reagent combination of $SOCl_2$, pyridine, and HBr(g).[41] A reagent originally devised for the conversion of nucleoside phosphates to phosphorochloridates, [tris(2,4,6-tribromophenoxy) dichlorophosphorane/pyridine] **6**, has been shown to convert primary alcohols to alkyl chlorides in high yield (**Scheme 13**),[42] while one of the other halogenation reagents used in nucleoside chemistry (methyl-triphenoxyphosphonium iodide and HMPA) has proved useful in simple aliphatic chemistry where more traditional procedures failed.[43] Alkyl iodides can also be prepared from carboxylic acids, aldehydes, ketones, and alcohols by treatment with $BHI_2.Me_2NPh$ (prepared by treating borane–dimethylaniline complex with iodine).[44] This reagent system effects the necessary reduction(s) before iodination occurs.

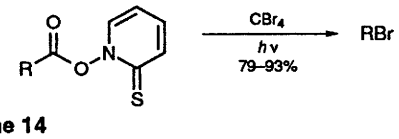


R = 3-*N*-benzoylthymine

Scheme 13

2.3 By other methods

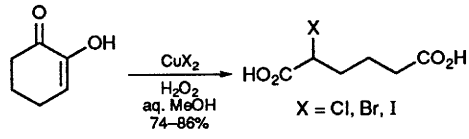
'Texan sunshine' has entered the field of 'not-universally-available' reagents for the photochemical halodecarboxylation of carboxylic acids *via* their thiopyridyl hydroxamate derivatives (**Scheme 14**).[45] Fortunately, other sources of light are also suitable, and a report of an application of this procedure in Europe has already appeared.[46] The old-fashioned Hunsdiecker reaction nevertheless still finds its advocates.[47]



Scheme 14

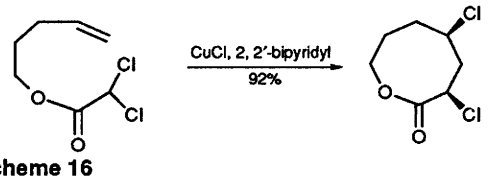
Bromomethylation of polymethylated benzenes (CH_2O, HBr, AcOH) can be controlled to give mono-, di-, or tri-bromomethylated products in high yields,[48] while aromatic chloromethylation can be achieved with MOM chloride at low temperature.[49]

1,1-Dihalocyclopropanes are a useful source of monohalocyclopropanes either by classical reduction (Raney Ni, NH_2NH_2, KOH),[50] or by monometallation and quenching with electrophiles.[51,52] Meanwhile, copper-catalysed oxidative cleavage of 1,2-cyclohexanediones in the presence of halides has been shown to give the open chain 2-halo diacids (**Scheme 15**).[53]



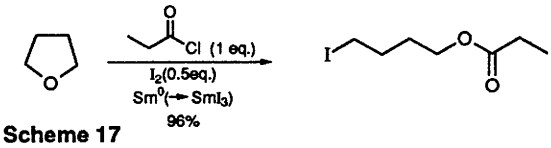
Scheme 15

A number of examples of radical atom transfer additions of *geminal*-polyhaloalkanes to olefins, both inter-[54] and intra-molecular[55–59] have been reported. This is illustrated by one example[59] (**Scheme 16**) which is particularly interesting since it allows the preparation of often-difficult eight- and nine-membered ring lactones in high yield.

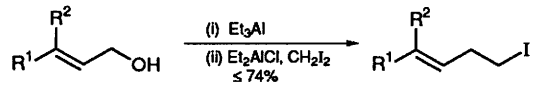


Scheme 16

Other potentially useful transformations resulting in alkyl halides are illustrated in **Schemes 17**[60] and **18**.[61] Also noteworthy is a paper describing efficient procedures for the synthesis of tertiary alkyl fluorides by successive introduction of three different alkyl groups onto a fluorine-bearing prototertiary carbon fragment.[62]



Scheme 17



Scheme 18

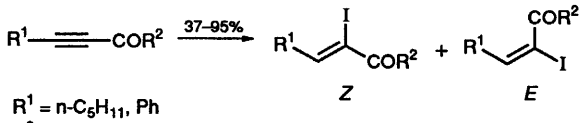
R^1 or R^2 = silyl

3 Vinyl halides

3.1 From alkynes

α-Iodoacrylates have been prepared by a one-pot hydrostannylation–iododestannylation procedure

(**Scheme 19**).[63] Generally, separable mixtures of *E* and *Z* isomers were obtained, although in one case (R^1 = Ph, R^2 = Me) > 99% *Z*-isomer was obtained.

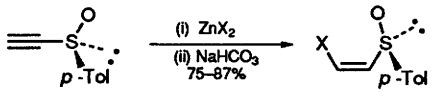


R^1 = n-C_5H_{11}, Ph
R^2 = Me, Ph

Reagents: (i) Bu_3SnH, $Pd(PPh_3)_4$; (ii) I_2; (iii) aq. KF, Et_2O

Scheme 19

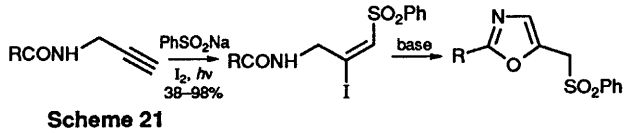
The addition of halides to a chiral α,β-acetylenic sulfoxide has also been reported to give the *Z*-β-halovinylsulfoxides without affecting the configuration of the chiral centre (**Scheme 20**).[64]



X = Cl, Br, I

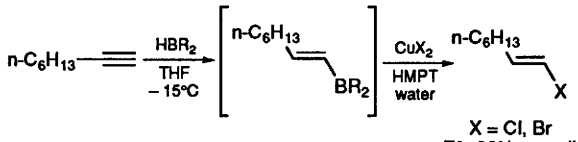
Scheme 20

In related chemistry, *E*-β-iodovinylsulfones, prepared by photochemical addition of sodium benzenesulfonate and iodine to an alkyne, have been used in isoxazole synthesis (**Scheme 21**).[65]



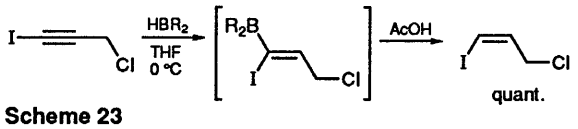
Scheme 21

Formal addition of HCl or HBr to unactivated terminal alkynes to yield *E*-vinyl halides can be achieved in high yield by regio- and stereo-selective hydroboration followed by treatment with copper(II) halide (**Scheme 22**).[66] By starting with a haloalkyne, hydroboration followed by protonolysis leads to *Z*-vinyl halides (**Scheme 23**).[67]



X = Cl, Br
70–89% overall

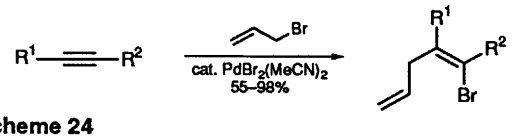
Scheme 22



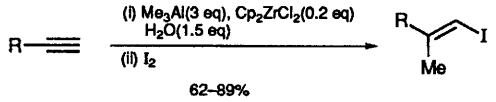
quant.

Scheme 23

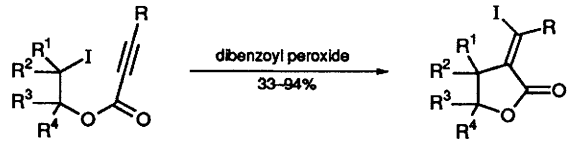
A novel palladium-catalysed addition of allyl bromide to alkynes has been described (**Scheme 24**),[68] while the Negishi carboalumination of alkynes has been shown to be accelerated by the addition of 1.5 equivalents of water, thus improving access to unactivated vinyl iodides (**Scheme 25**).[69]
Turning to intramolecular reactions, a radical atom-transfer reaction has been shown to give the *E*-iodoalkylidene lactones **7** in good yield (**Scheme 26**).[70]



Scheme 24



Scheme 25

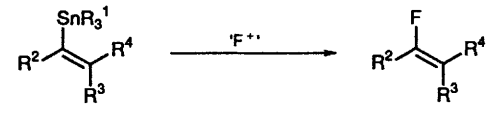


7

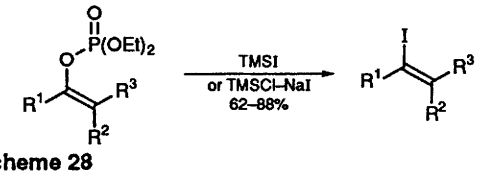
Scheme 26

3.2 From other vinyl derivatives

Vinyl stannanes have proved to be a fruitful source of vinyl fluorides (**Scheme 27**), by treatment with caesium fluoroxysulfate ($CsSO_4F$);[71] XeF_2, $AgPF_6$;[72] or the Selectfluor reagent **1**.[73] Meanwhile, vinyl phosphates have been shown to be useful precursors to vinyl iodides (**Scheme 28**).[74]

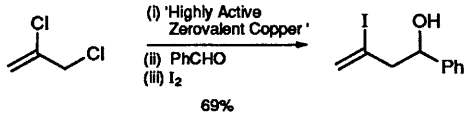


Scheme 27

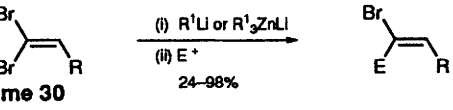


Scheme 28

Another approach to vinyl iodides uses highly active, zero-valent copper to generate a vinyl cuprate which can be quenched with iodine (**Scheme 29**).[75] In related work, halogen–metal exchange on 1,1-dibromoalkenes has been shown to occur stereoselectively at the sterically more hindered bromine position, thus facilitating the stereospecific synthesis of substituted vinyl bromides (**Scheme 30**).[76,77]

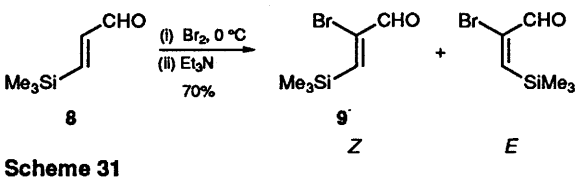


Scheme 29



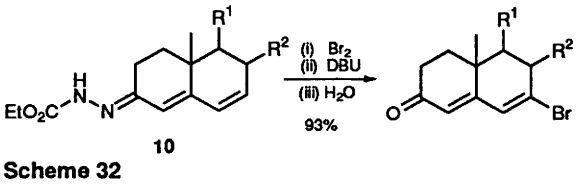
Scheme 30

α-Halogenation of α,β-unsaturated carbonyl compounds continues to be popular, and recent examples of this approach include the 3-iodination of flavones, thioflavones, and chromones with I_2/CAN,[78] α-chlorination of enones with HCl-mCPBA in DMF,[79] and halogenation of 1,4-benzoquinones with $CuCl_2$ or $CuBr_2$ adsorbed on alumina, to give mono-, di-, tri-, and tetra-haloquinones, depending on the substrate and reaction conditions.[80]
Bromination–dehydrobromination of 3-silylacrolein **8** (**Scheme 31**)[81] gives a mixture of geometric isomers, but equilibration under the reaction conditions gives predominantly the *Z*-isomer **9**, a compound which has great synthetic potential.

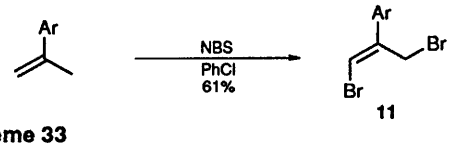


Scheme 31

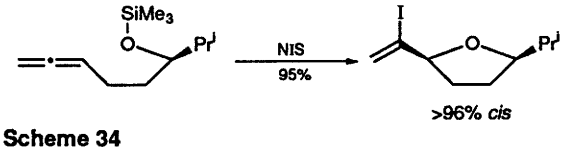
δ-Bromination of a dienone has also been reported, utilizing an ethoxycarbonylhydrazone derivative **10** (**Scheme 32**),[82] while conditions for the selective conversion of α-methyl styrenes into the useful synthon **11** (**Scheme 33**) have also been optimized.[83] Allenes have also proved to be useful precursors to vinyl iodides, by treatment with iodine (followed by further reaction of the resulting 2-iodoallyl iodide)[84,85] or by *N*-iodosuccinimide treatment in the presence of an internal nucleophile (**Scheme 34**).[86]



Scheme 32



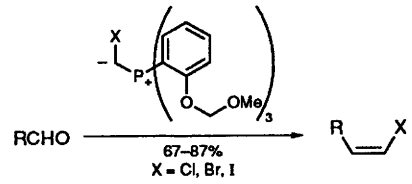
Scheme 33



Scheme 34

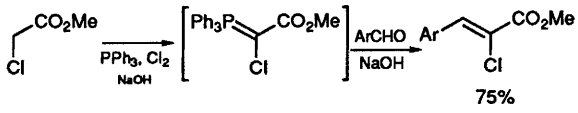
3.3 By C=C bond formation

A general method for the preparation of *Z*-vinyl halides by Wittig chemistry has been described (**Scheme 35**).[87] The yields and stereoselectivities are high, and chlorides, bromides, and iodides can all be prepared this way. Note, however, that yields and stereoselectivities were much lower when vinyl fluorides were prepared in this way.

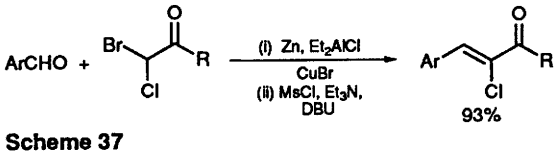


Scheme 35

An interesting Wittig synthesis of α-chloro-α,β-unsaturated esters has also been reported (**Scheme 36**),[88] while Reformatsky-type chemistry can yield similar products (**Scheme 37**).[89] Unfortunately, the latter cannot be extended to α-bromoenones, since reductive debromination of the bromohydrin intermediate also occurs.

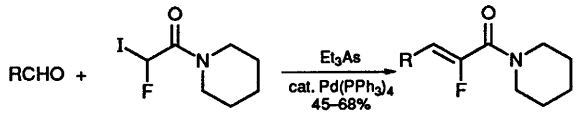


Scheme 36

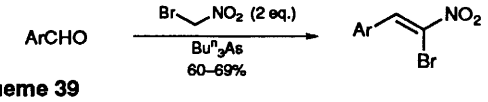


Scheme 37

Related α-fluoro-α,β-unsaturated carbonyl compounds can be accessed by related chemistry using palladium catalysis (**Scheme 38**).[90] Lastly, a Knoevenagel-type condensation between aldehydes and bromonitromethane has been reported (**Scheme 39**),[91] but the risk of explosion associated with this procedure may limit its use.



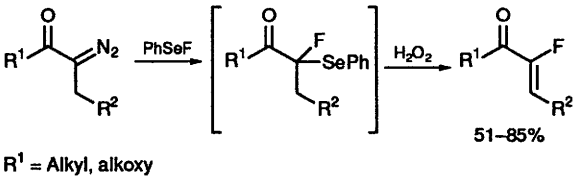
Scheme 38



Scheme 39

3.4 By other methods

A novel approach to α-fluoro-α,β-unsaturated carbonyl compounds *via geminal* fluoro-selenation followed by oxidative selenoxide elimination is depicted in **Scheme 40**.[92] Sulfoxide elimination from α-fluoro-α-sulfoxido carbonyl compounds has also been used to generate vinyl halides.[93]

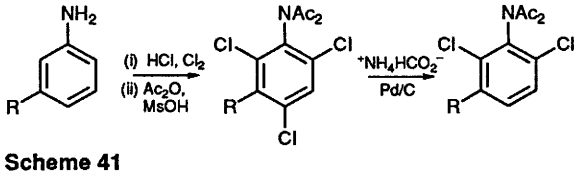


R^1 = Alkyl, alkoxy

Scheme 40

4.1 By electrophilic halogenation

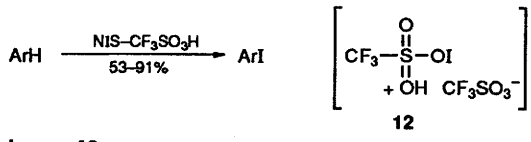
The search for selective electrophilic aromatic halogenation procedures has continued unrelentlessly, and has yielded some useful results. Regioselective monobromination of anilines has been achieved with pyridinium hydrobromide perbromide in THF, giving minimal polybromination, and predominantly *para*-selectivity (75–95% yields).[94] The use of molecular bromine with a catalytic tetraethylammonium chloride (0.1 equivalents) and methanol (0.5 equivalents) system has also given high *para*-regioselectivity in the bromination of anilines.[95] In addition, it has been shown that heating an isomeric mixture obtained by the bromination of aniline with a deficiency of bromine in the presence of HBr leads to isomerization, giving 4-bromoaniline as essentially the only product.[96] *para*-Selective monoiodination of aniline derivatives has been achieved with iodine and silver sulfate in generally excellent yields.[97] Under these conditions, aniline itself gave only 46% yield, while acetanilide gave 91%. Interestingly, these conditions also work for nitroanilines. The preparation of 2,6-dichloroanilines *via* 2,4,6 trichlorination followed by regioselective hydrogenolysis of the 4-chloro group has also been described (**Scheme 41**).[98]



Scheme 41

High-yielding 2,4,6-tribromination of anilines and phenols can be readily achieved using bis(dimethylacetamide)hydrotribromide,[99] while selective *ortho*-bromination of phenols has been effected by the inclusion of diisopropylamine or dibutylamine in a reaction mixture containing the arene and *N*-bromosuccinimide.[100] The effective halogenating agent is believed to be the *N*-bromoamine. The *ortho*-selectivity of ferric chloride catalysed chlorination of toluene has also been shown to be enhanced by using alcohols as co-catalysts.[101]

Electrophilic halogenation procedures of fairly broad scope (with respect to substrate) and generally high yield include the use of *N*-chloro- or *N*-bromo-succinimide with catalytic perchloric acid,[102] hexamethylenetetramine hydrotribromide,[103] *N*-bromo- or *N*-chloro-saccharin with pyridinium poly(hydrogen fluoride),[104] and bis(pyridine)iodine monofluoroborate (IPy_2BF_4) with HBF_4.[105,106] The latter reagent system can also be used to controllably generate polyiodinated compounds.[107] Substitution of the HBF_4 with trifluoromethane sulfonic acid also allows deactivated arenes to be effectively iodinated with IPy_2BF_4.[106] Indeed, triflic acid also facilitates iodination of deactivated arenes with *N*-iodosuccinimide (**Scheme 42**).[108] It is believed that the active agent is 'superelectrophilic' iodine(I) triflate **12** which is generated *in situ*.



Scheme 42

A novel bromination procedure which is only suitable for use on *de*activated arenes uses BrF_3 and Br_2.[109] This avoids problems associated with the use of BrF, and it is also interesting to note that until now BrF_3 has only been used as a fluorinating agent. Meanwhile, an aqueous medium (NaOH) has been used for the *N*-bromosuccinimide- or dibromodimethylhydantoin-mediated bromination of substituted benzoic acids.[110] Hypervalent iodine reagents are beginning to find use in the catalysis of electrophilic halogenations. In particular, PhI(OH)OTs (Koser's reagent) has been found effective for halogenation of polyalkylbenzenes with *N*-iodo- and *N*-bromo-succinimide.[111]

Fluorination of toluene or xylenes with the previously mentioned 'Selectfluor' reagent **1** (**Scheme 3**) shows poor regioselectivity, although this reagent does show potential for the synthesis of aryl fluorides by reaction with aryl Grignard species.[17]

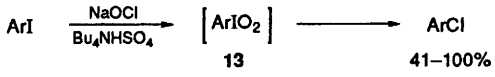
Regiospecific preparation of aryl halides can also be achieved by halodesilylation of aryltrimethylsilanes. A review on this and related chemistry has been published,[112] while the specific case of iodination of arylsilanes with ICl and silver salts has been studied in some detail.[113]

Aryl boronates can be converted to aryl fluorides in moderate yields by treatment with caesium fluoroxysulfate ($CsSO_4F$),[114] while the quenching of certain arylmanganese species with NBS or NIS has also shown some synthetic utility.[115]

4.2 By nucleophilic substitution

Heteroaromatic chlorides such as 2-chloro-pyridines and pyrimidines and 2,4-dinitrochlorobenzene undergo counter-thermodynamic halogen-exchange fluorination on treatment with HF or HF–pyridine or HF–collidine.[116] Similar results are achieved with tetrabutylphosphonium hydrogendifluoride ($Bu^n_4P^+HF_2^-$),[117] by an extension of a previously described method for fluorination of heat- or base-sensitive substrates in non-polar solvents.[118] Proton sponge hydrofluoride also acts as a useful source of fluoride ion, it being soluble in acetonitrile. This is especially useful for the nucleophilic substitution of heteroaryl chlorides, since the by-product proton sponge hydrochloride is insoluble, allowing ready recovery of the base.[119] The use of caesium fluoride for related halogen exchange fluorination has been recently highlighted.[120] Meanwhile, treatment of aryl diazonium salts with BF_3 under photochemical or thermal conditions has been shown to be another effective approach to aryl fluorides.[121] In addition, new conditions for fluoro-denitration of nitroarenes have also been reported, using dry tetramethylammonium fluoride in DMSO.[122] Finally, aryl iodides can be readily

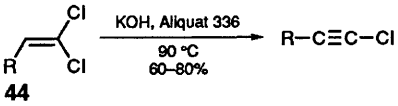
converted *via* the iodylarene intermediate **13** into the corresponding aryl chlorides by treatment with hypochlorite under phase transfer conditions (**Scheme 43**).[123] The explosive nature of iodylarenes may limit the use of this protocol.



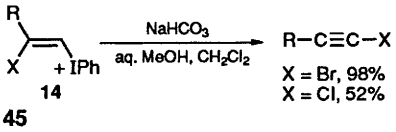
Scheme 43

5 Alkynyl halides

While not a particularly active area, three groups have made noteworthy contributions. Firstly, bromination of terminal alkynes in a novel triphase brominating–oxidizing system (NaBr, NaOCl, Bu_4NHSO_4) has been shown to give alkynyl bromides (in stark contrast to the use of Bu_4NBr_3, which gives 1,1-dibromoalkenes).[124] Secondly, further developments in the elimination of HCl from 1,1-dichloroalkenes have been described (**Scheme 44**),[125] and thirdly, rearrangement of the hypervalent iodine species **14** under basic conditions gives the alkynyl bromide (or chloride) (**Scheme 45**).[126]



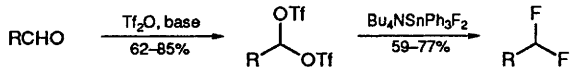
Scheme 44



Scheme 45

6 1,1-Dihalo compounds

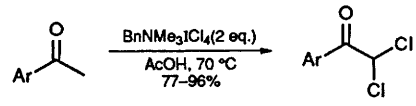
A variety of methods for the preparation of *geminal* dihalo compounds have been described in the period under review. 1,1-Difluorides are readily obtained from aldehydes by initial conversion to the *geminal*-bis-triflate followed by treatment with $Bu_4NSnPh_3F_2$ (**Scheme 46**).[127] This reagent is non-hygroscopic, non-toxic, easy to handle, and requires relatively mild conditions compared to many other fluorinating agents. Complementary to this is a CBr_2F_2/Zn reagent system which allows access to *geminal* difluorides from ketones, and indeed fails when applied to aliphatic aldehydes.[128]



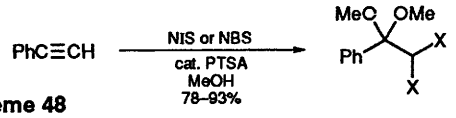
Scheme 46

Other ketone derivatives which have been successfully converted into *geminal* dihalides include oximes (Cl_2, $BF_3.OEt_2$),[129,130] 1,1-nitrosohalides (HX, CH_2Cl_2; X = F, Cl, Br)[130] and thioketals (electrochemical anodic desulfurization/$Et_3N.3HF$).[131]

α-Dihalocarbonyl compounds have been derived from ketones (**Scheme 47**)[132] and alkynes (**Scheme 48**),[133] by 2 + 2 cycloaddition of dichloroketene with alkenes,[134] and by controlled reduction of 1,1,1-trichloroalkanes.[135]



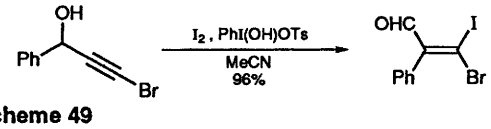
Scheme 47



Scheme 48

A variety of examples of *geminal*-dihalocyclopropane formation by base-induced carbenoid addition of either CH_2Br_2[136] or $CHBr_3$,[137] or $CHCl_3$[138] to alkenes have also been described.

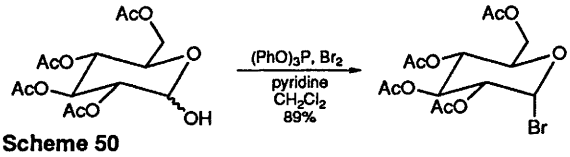
Various bromo-propargylic alcohols have been converted *via* a rearrangement reaction into 1-bromo-1-iodoalkenes,[139,140] and an example[140] is illustrated in **Scheme 49**. The high level of functionality in these products suggests that they could be useful synthetic precursors.



Scheme 49

7 1,1-Halohydrins and related compounds

The most common occurrence of 1,1-halohydrins in organic chemistry is, of course, in carbohydrate systems. Two selected examples which would appear to have general synthetic applicability include the reaction of aldoses with $(PhO)_3P$, Br_2, and pyridine to give the α-bromo anomer (**Scheme 50**),[141] and the conversion of α-bromoglycosides into the corresponding β-fluoro anomers by treatment with triethylamine trishydrofluoride (**Scheme 51**).[142]



Scheme 50

Scheme 51

8 1,2-Dihalo compounds

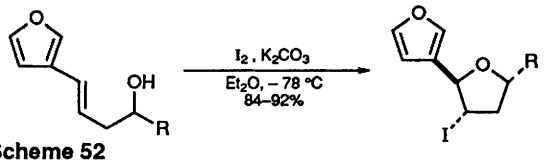
The addition of bromine or bromine plus nucleophile across a double bond continues to fascinate the physical chemist, with a number of detailed mechanistic studies being published.[143–145] Of greater

interest to the synthetic chemist, are the previously-mentioned Selectfluor reagents (**1**, **Scheme 3**) which, when combined with HF–pyridine, give 1,2-difluoroalkanes from alkenes.[17] For mixed 1,2-dihalides, *N*-bromo- (or *N*-iodo-) succinimide or dibromodimethylhydantoin in combination with either $Bu_4PH_2F_3$[146] or $Bu_4NH_2F_3$[147] have been found to be effective. Finally, alkene iodofluorination using I_2 and AgF has proved beneficial in the synthesis of fluorinated nucleoside derivatives.[148]

9 1,2-Halohydrins and related compounds

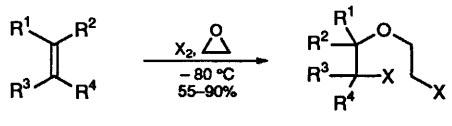
9.1 By addition to alkenes

Semi-empirical molecular orbital calculations have indicated that bromonium ions may not, after all, be intermediates in the intramolecular bromoetherification of alkenes (or indeed intermolecular bromohydrin reactions), but instead a rather weak alkene–Br^+ π-complex.[149] Whatever the true detail of the reaction mechanism, this type of chemistry continues to be a rich source of diverse functionality. For example, the Selectfluor reagents (**1**, **Scheme 3**) previously described in this review can also be used to generate a range of fluorohydrin derivatives, specifically ethers, esters, and fluorohydrins themselves.[17] Additionally, t-butyl ethers of fluorohydrins have been prepared by reaction of alkenes with Bu^{t}OF.[150] Intramolecular iodoetherification can be controlled to give *anti*-2,5-disubstituted tetrahydrofurans (**Scheme 52**).[151]

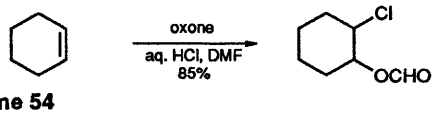


Scheme 52

Classical iodohydrin formation has found continued use in carbohydrate chemistry,[152,153] while a less common mode of alkene functionalization, in which a molecule of ethylene oxide becomes incorporated into the product, has also been described (**Scheme 53**).[154] Potassium monoperoxysulfate ('Oxone®') continues to find applications in many areas of organic chemistry, and alkene oxidation is no exception. Specifically, treatment of an alkene with oxone in acidic DMF gives halohydrin formate esters (**Scheme 54**).[155]

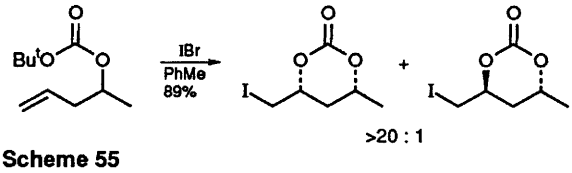


Scheme 53

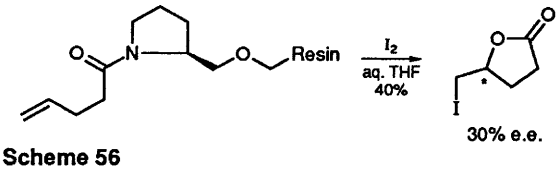


Scheme 54

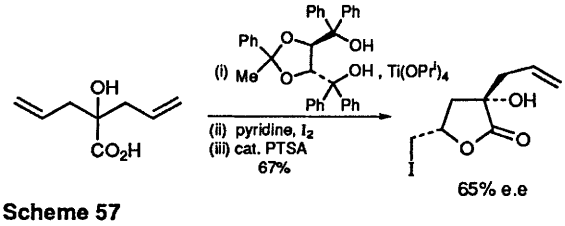
Another area of fruitful research has been that of halolactonization. The formation of simple four-membered[156] and seven- to eleven-membered rings[157] by bromo and iodolactonization respectively have been studied, while much of the other literature in the field concentrates on five- and six-membered ring formation (including cyclic carbonates[158] and carbamates[159]) with particular emphasis on diastereoselectivity. Space precludes detailed discussion of much of this chemistry,[160,161] but three examples of particular interest are illustrated in **Schemes 55, 56**, and **57**. In the first (**Scheme 55**),[158] IBr is found to give much greater levels of diastereoselectivity than I_2, while in the second (**Scheme 56**),[162] a polymer-supported chiral auxiliary is used to induce asymmetry (although the stereoinduction was not spectacular). The third example (**Scheme 57**)[163] makes use of a chiral Lewis acid as the source of asymmetry.



Scheme 55



Scheme 56

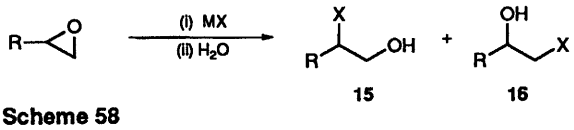


Scheme 57

Other heteroatoms which have been added across alkenes concomitantly with a halide include sulfur,[164,165] selenium,[166,167] and nitrogen,[168,169] but these will not be discussed further in this review.

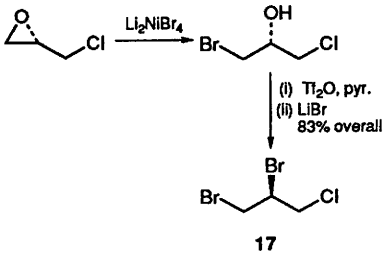
9.2 By epoxide opening

This is perhaps the most widely-studied approach to 1,2-halohydrins, in which stereo- and regio-selectivity are of course the major issues. In the case of epoxides derived from terminal alkenes, a detailed study of the effect of varying the Lewis acid has been performed.[170] It was shown that strong Lewis acids, *e.g.* $TiCl_4$ or $TiBr_4$, give the 2-halogenoprimary alcohol **15** (**Scheme 58**), while Lewis bases such as $TiBr_2(NEt_2)_2$ give the regioisomeric secondary alcohol **16**.
The synthetic importance of this work is underlined by the fact that reagents and conditions have been found which enable either regioisomer to be prepared in high yield with about 95% regioselectivity.



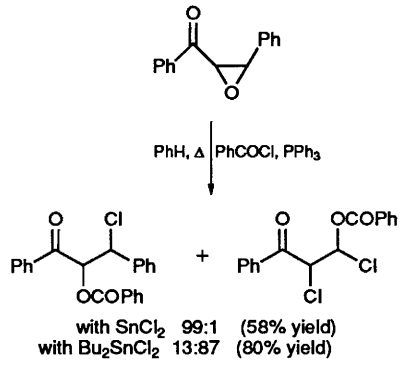
Scheme 58

Halogenative ring-opening of 2,3-epoxy alcohols (*i.e.* epoxides derived from allylic alcohols) gives a variety of regio- and stereo-isomers with the selectivity strongly dependent on the substrate and reaction conditions.[171-173]. Regioselective epoxide opening has been used to prepare enantiomerically pure 1,2-dibromo-3-chloropropane **17** from enantiomerically pure epichlorohydrin (**Scheme 59**).[174]

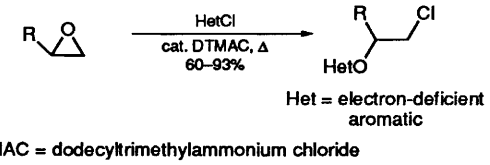


Scheme 59

In certain cases, the regioselectivity of epoxide opening can be switched by judicious choice of reagents (**Scheme 60**).[175] Aryl ethers of 1,2-chlorohydrins can be prepared directly from epoxides as long as the aryl group is electron-deficient (**Scheme 61**),[176] while further versatility is added to the epoxide reaction manifold by the use of Swern conditions for direct oxidative conversion of epoxides to α-chloroketones in good yields.[177] It is also perhaps worth mentioning that there are sometimes cases where it is more practical to prepare a 1,2-halohydrin by regioselective hydrolysis of a 1,2-dihalide.[178]



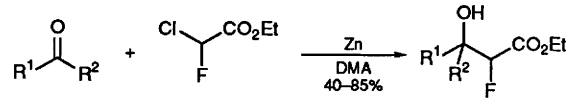
Scheme 60



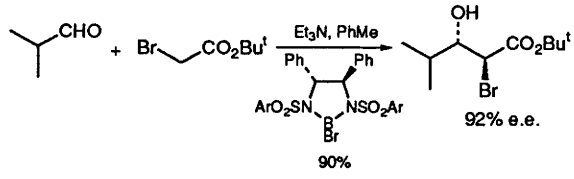
Scheme 61

9.3 With C–C bond formation

Two examples suffice to illustrate this approach. The first, an apparently general method for α-fluoro-β-hydroxyester synthesis, uses Reformatsky-type chemistry (with or without $CeCl_3$ catalysis) (**Scheme 62**),[179] while the second (**Scheme 63**)[180] uses an asymmetric boron ligand for the aldol condensation of an α-bromoacetate residue. The latter example has been described previously in the literature, but the reference cited herein includes key experimental improvements for larger scale work.



Scheme 62



Scheme 63

10 References

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