Organic halides

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Reviewing the literature published between 1 July 1994 and 30 June 1995
Continuing the coverage in *Contemporary Organic Synthesis*, 1995, **2**, 85

1 Introduction

This review presents developments in the synthesis of organic halides which have appeared in the literature between 1 July 1994 and 30 June 1995. The strategic importance of organic halides as synthetic intermediates or as compounds in their own right is undiminished, and is reflected in the vast number of new or improved methods for their preparation since the last review in this series.[1] The methods highlighted here have been chosen as those most likely to gain recognition from the synthetic chemist, or those offering economic and/or environmental advantages over existing methods. As in the previous reviews,[1,2] the chemistry of perfluoroalkyl and hypervalent iodine compounds will not be discussed.

A number of review articles covering aspects of organic halide chemistry have been published this year. These include articles concerning the bromination of olefins[3] and synthetic applications of α-monohalo ethers.[4] Additionally, advances in the synthesis of fluorinated heterocycles[5] and amino acids[6] have both been reviewed, as have the synthetic applications of xenon difluoride[7] and complexes of hydrogen fluoride.[8]

Convenient preparations of two useful fluorinating agents have been reported this year. Triphenylphosphine difluoride (Ph_3PF_2) has been prepared in good yield by the ultrasonification of triphenylphosphine and potassium hydrogen fluoride in the presence of diisopropyl azodicarboxylate,[9] while anodic oxidation of aryl iodides in the presence of triethylamine/HF complex results in the formation of hypervalent iodobenzene difluoride derivatives.[10] Additionally, DeShong has introduced tetrabutylammonium (triphenylsilyl)-difluorosilicate [Bu_4N^+ $(Ph_3SiF_2)^-$, TBAT] as a non-hygroscopic equivalent of tetrabutylammonium fluoride (TBAF).[11] Yields of a range of nucleophilic substitution reactions carried out with the new reagent were at least comparable to, and in many cases outstripped, those obtained with TBAF or potassium fluoride as the fluoride source. Another new, highly reactive nucleophilic fluoride ion source is cobaltocenium fluoride ([Cp_2Co]F), prepared by the reaction of cobaltocene with perfluorodecalin.[12] This reagent rapidly displaces chloride from alkyl or acyl chlorides and polychlorinated aromatics to yield the corresponding fluorides.

Additions to the battery of polymer supported reagents include: (i) poly(styrene/4-vinylpyridine) supported bromine, which gave excellent yields in bromine addition to styrene derivatives, *para*-bromination of anisole and side chain bromination of toluene;[13] and (ii) polystyryl diphenylphosphino iodine, which has been used in the efficient conversion of amino alcohols into β-iodoamines.[14]

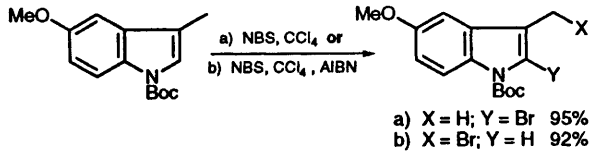
2 Alkyl halides

2.1 By halogenation of alkanes

Reports on the halogenation of unactivated alkanes include a study of the iron(III) picolinate catalysed bromination of cyclooctane by bromotrichloro-methane from the Barton group,[15] and an interesting cobalt(II) porphyrin mediated chlorination of alkanes using sulfuryl chloride.[16] The regioselectivity of chlorination in the latter case was

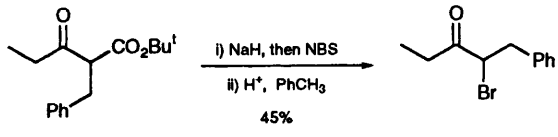
best explained by the intermediacy of an alkyl cobalt(III) species.

Cook and co-workers examined the regioselectivity of bromination of several *N*-protected 3-methylimidazoles, achieving excellent regiocontrol for side chain or ring bromination in some cases (**Scheme 1**).[17]



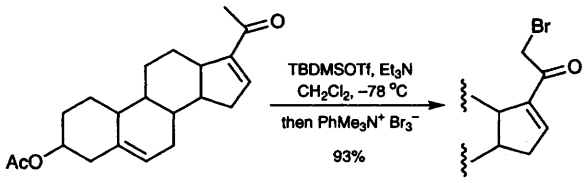
Scheme 1

The synthesis of α-halocarbonyl compounds continues to be of interest. Moderate to good regiocontrol in the direct bromination of unsymmetrical ketones can be achieved by varying the order of addition of the reagents.[18] Thus, addition of bromine to the ketone in refluxing methanol favours bromination at the least hindered carbon, while the more hindered carbon is brominated by addition of the ketone to a solution of bromine. An indirect but more rigorous solution to the problem of regiocontrol in bromination utilises β-keto-*tert*-butyl esters, the enolate of which may be brominated with NBS and decarboxylated under anhydrous acidic conditions to furnish the unsymmetrical bromoketone (**Scheme 2**).[19] The regioselective α-bromination of enones has been achieved in a one pot process, involving the quenching of a silyl enol ether with

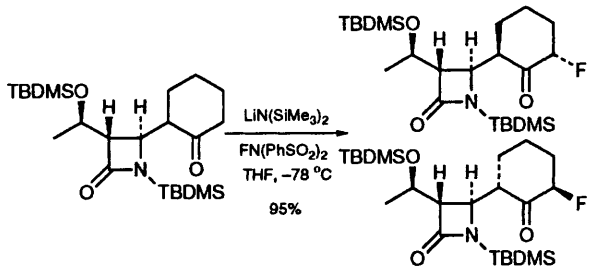


Scheme 2

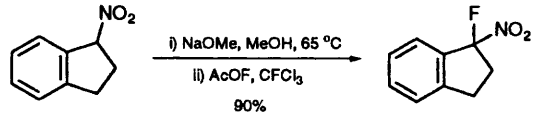
phenyl(trimethyl)ammonium tribromide.[20] The latter brominating agent is sufficiently mild that the reaction is successful in the presence of additional unsaturation in the molecule (**Scheme 3**). A report in the Japanese patent literature shows that the α-iodination of amides may be achieved in the presence of remote olefins using iodine and 2,4,6-collidine.[21] In the area of diastereoselective halogenation of enolates, trapping of the lithium enolate of a 2-substituted cyclohexanone with *N*-fluorobenzenesulfonimide $(PhSO_2)_2NF$ gave exclusively the 2,6-*trans*-isomers in the synthesis of a fluorinated tribactam (**Scheme 4**),[22] while modest control of the stereochemistry of bromination of ketones bearing the DiTOX auxiliary was shown to be possible through judicious choice of enolising agent.[23] Related to the halogenation of enols and enolates, the fluorination of a nitro-stabilised anion



Scheme 3



Scheme 4

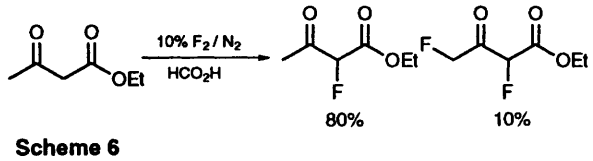


Scheme 5

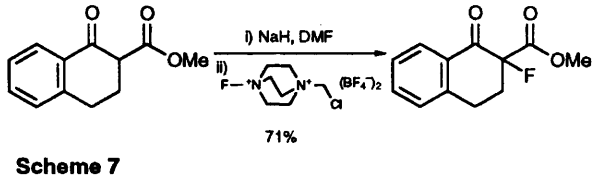
using acetyl hypofluorite has been reported this year (**Scheme 5**).[24]

The fluorination of 1,3-dicarbonyl compounds has been achieved directly with gaseous fluorine (**Scheme 6**),[25] and by the reaction of the derived enolates with the Selectfluor reagent (**Scheme 7**).[26]

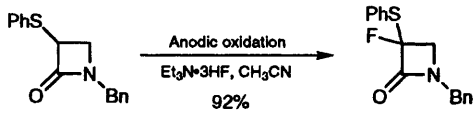
Electrochemical oxidation of α-arylthio ketones and esters[27,28] and amides[29] may be achieved using the triethylamine/hydrogen fluoride complex as an electrolyte (**Scheme 8**). The mechanism is proposed to involve the Pummerer-like rearrangement of a fluorosulfonium cation.



Scheme 6



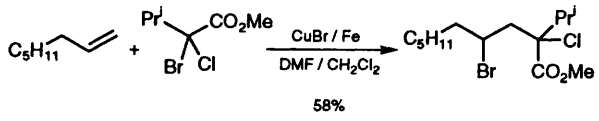
Scheme 7



Scheme 8

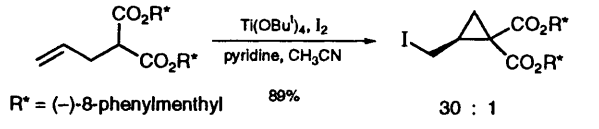
2.2 By halogenation of alkenes

There have been some interesting developments in the area of atom transfer carbon–halogen addition to alkenes. Hiemstra and Speckamp have reviewed their success in the copper catalysed cyclisation of ω-alkenyl di- and tri-chloroacetates[30] and reported the high yielding synthesis of eight- and nine-membered lactones by this method.[31] A related intermolecular coupling, utilising a copper(I)/iron couple, was also successful (**Scheme 9**),[32] as was the photolytic radical atom transfer cyclisation of an ω-alkenyl-α-iodo-nitro compound.[33]

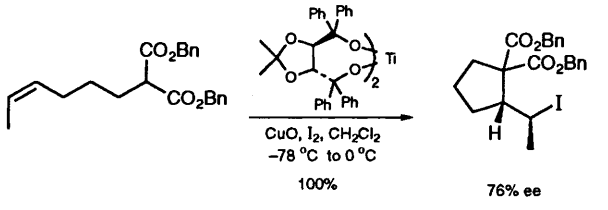


Scheme 9

Taguchi has investigated two approaches to asymmetric iodocarbocyclisation reactions. The use of chiral ester groups as auxiliaries allowed the preparation of a cyclopropyl iodide with a good diastereoisomeric excess (**Scheme 10**),[34] while a chiral titanium catalyst promoted the analogous construction of a cyclopentane with a 76% enantiomeric excess (**Scheme 11**).[35]



Scheme 10

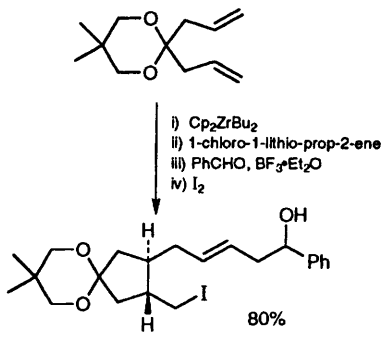


Scheme 11

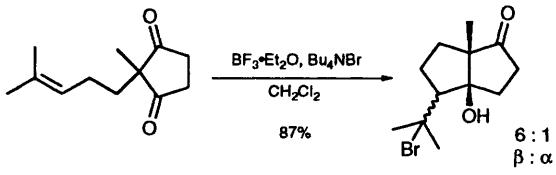
Transition metal mediated cyclisations coupled with a halogen quench continue to be a valuable method for the construction of complex alkyl halides. In one such example, Luker and Whitby demonstrated a remarkable one pot sequence of reactions mediated by the Negishi reagent, leading to a highly functionalised iodide in excellent yield (**Scheme 12**).[36]

Halide ion terminated electrophilic olefin cyclisation reactions have also received much attention this year, leading to syntheses of halogenated tetrahydropyrans,[37] cyclopentanes[38] and fused bicyclic systems (**Scheme 13**).[39]

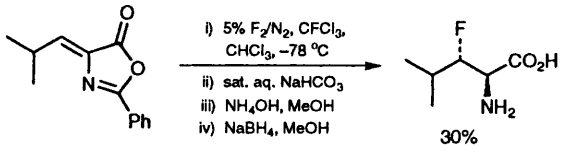
The electrochemical difluorination of an enol camphanate ester followed by separation of the diastereoisomeric products and careful hydrolysis



Scheme 12



Scheme 13

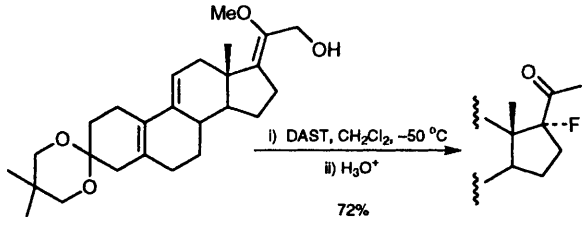


Scheme 14

provides an asymmetric route to α-fluoroketones.[40] Addition of molecular fluorine to azlactones provides a method of synthesising fluorinated amino acids by way of an intermediate fluorinated α-ketoacid (**Scheme 14**).[41]

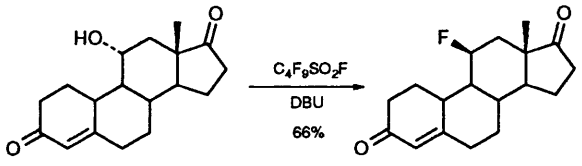
2.3 By nucleophilic substitution

The *in situ* activation of alcohols and nucleophilic displacement by halide ions has again received significant attention this year. Diethylaminosulfur trifluoride (DAST) continues to be the most widely used reagent for the direct conversion of an alcohol to a fluoride and has been applied to the synthesis of, *inter alia*, fluorinated sugars,[42] deoxythiopyrimidine nucleosides,[43] taxanes[44] and, by an allylic transposition, 17-α-fluoroprogesterones (**Scheme 15**).[45] A report on the fluorination of diols

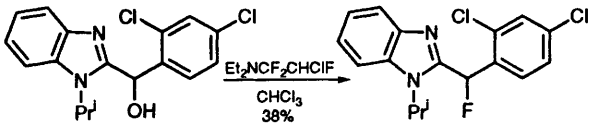


Scheme 15

using DAST warns that, depending on the chain length separating the alcohols, cyclic sulfites or cyclic ethers can be formed as significant by-products or even major products.[46] Other reagents which have been used for the direct synthesis of fluorides from alcohols include perfluorobutanesulfonyl fluoride (**Scheme 16**),[47] and (2-chloro-1,1,2-trifluoroethyl)diethylamine (the Yarovenko reagent), which has again been demonstrated to be the superior reagent for the fluorination of benzylic alcohols (**Scheme 17**).[48] The direct conversion of alcohols into iodides has been achieved in moderate yields by simple treatment with iodine in hydrocarbon solvents.[49]

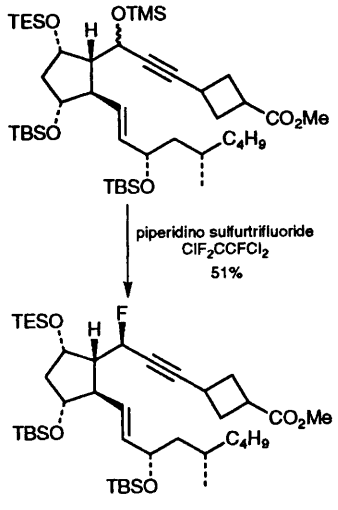


Scheme 16



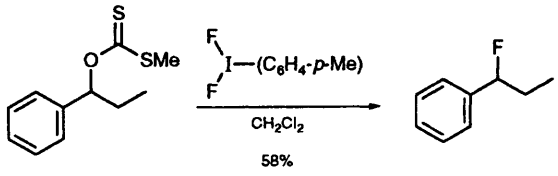
Scheme 17

The conversion of silyl ethers to halides has been demonstrated on silylated cyclodextrins using triphenylphosphine dibromide[50] and in the synthesis of a potent anti-anginal prostaglandin with piperidino sulfurtrifluoride (**Scheme 18**).[51]

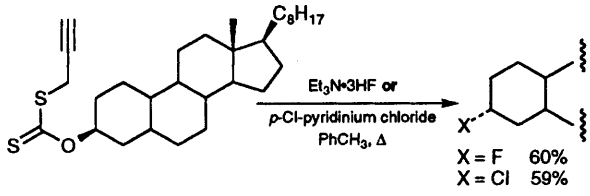


Scheme 18

The nucleophilic displacement of sulfonates by halide ions continues to be a popular method, particularly in the case of chiral secondary sulfonates, where clean inversion of configuration is normally observed. Spray dried KF in warm ethylene glycol has been shown to be an excellent source of fluoride ion for such substitution reactions.[52] There have also been two reports of the displacement of xanthates by halide ions. Motherwell describes the activation of simple *S*-alkyl xanthates with 4-methyl(difluoroiodo)benzene, with subsequent displacement by the liberated fluoride (**Scheme 19**).[53] Zard employs propargyl xanthates, which undergo a thermal rearrangement to a betaine which may be trapped by mild acid and displaced by appropriate counterions such as fluoride or chloride (**Scheme 20**).[54]

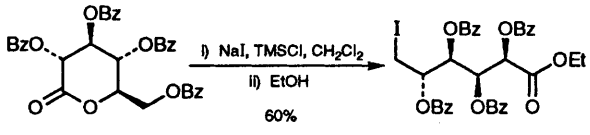


Scheme 19

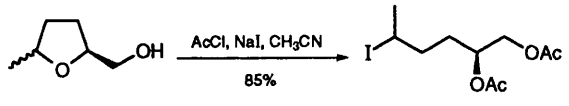


Scheme 20

The trimethylsilyl iodide (TMSI) mediated cleavage of lactones[55] and cyclic ethers[56] has again found widespread application in the synthesis of functionalised alkyl iodides. The unexpected participation of a benzoyl group allowed the synthesis of 6-iodo sugars from sugar lactones using this method (**Scheme 21**).[57] Good regiocontrol in the acylative cleavage of 2,5-disubstituted tetrahydrofurans has been demonstrated if one of the substituents contains a mildly electron withdrawing group such as an alcohol (**Scheme 22**).[58]



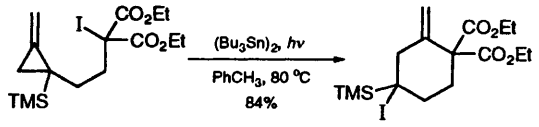
Scheme 21



Scheme 22

2.4 By other methods

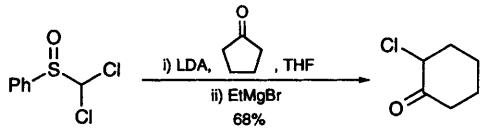
Kilburn has synthesised iodinated cyclohexanes in high yield using iodine atom transfer chemistry upon substrates containing methylene cyclopropanes (**Scheme 23**).[59] The radical decarboxylation of



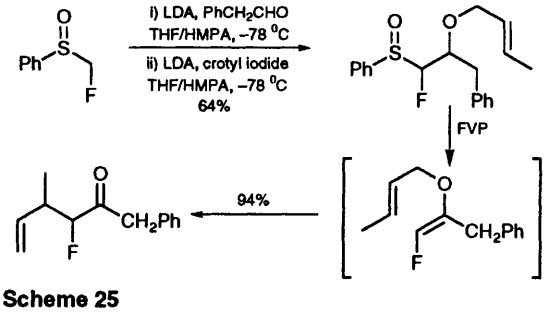
Scheme 23

tricyclodecadienones[60] and cyclopropanes[61] via thiopyridylhydroxamate (Barton) esters, facilitates the synthesis of the corresponding bromide using bromotrichloromethane as the radical trap.

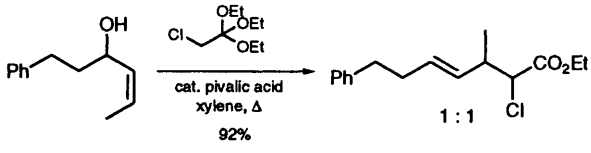
Lithiated (dichloromethyl)phenyl sulfoxide forms the basis of a new homologative synthesis of α-chloroketones (**Scheme 24**).[62] Lithiated (fluoromethyl)phenyl sulfoxide has been used to synthesise fluoromethylketones via addition to aldehydes followed by flash vacuum pyrolytic (FVP) sulfoxide elimination.[63] The FVP step represents an improvement over a previously reported synthesis involving simple thermolysis in a sealed tube. In addition, allylation of the initially formed hydroxy sulfoxide gives a substrate which, on FVP, undergoes a tandem sulfoxide elimination/Claisen rearrangement to yield substituted fluoroketones (**Scheme 25**).[64] The Johnson variant of the Claisen rearrangement has also been employed in the synthesis of α-chloro-, bromo- and fluoro-esters (**Scheme 26**).[65]



Scheme 24

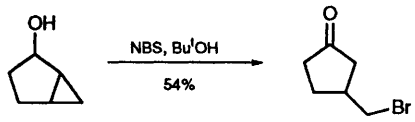


Scheme 25



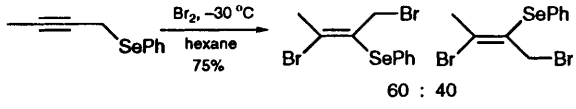
Scheme 26

The known ring-opening of cyclopropyl ketones with trimethylsilyl iodide has been spectacularly coupled with an intramolecular Michael addition reaction to yield complex fused tricyclic iodides.[66] Cossy has reported the oxidative ring opening of cyclopropyl carbinols by NBS, which has been shown to proceed by nucleophilic addition to the corresponding ketone (**Scheme 27**).[67]

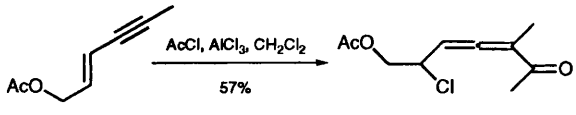


Scheme 27

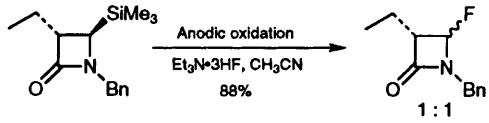
Dibromination and dichlorination of propargylic selenides has been investigated, and leads to the production of halovinyl selenides bearing an allylic halide, the reaction proceeding via the addition of PhSeX to an intermediate haloallene (**Scheme 28**).[68] The synthesis of chlorinated allenic ketones may be achieved by the overall addition of acetyl chloride across a 1,3-enyne (**Scheme 29**).[69] Finally, an interesting electrochemical oxidation of silylated azetidinones has been achieved, leading to the corresponding fluorinated heterocycle (**Scheme 30**).[70]



Scheme 28



Scheme 29



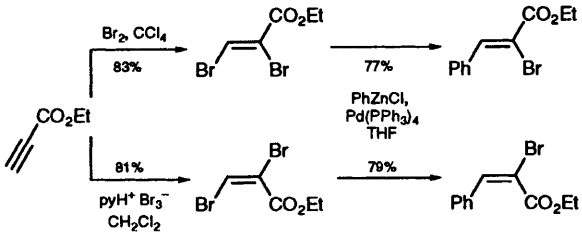
Scheme 30

3 Vinyl halides

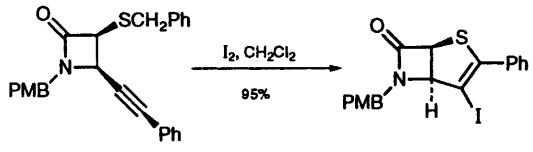
3.1 From alkynes

The stereoselective synthesis of (*Z*) or (*E*)-1,2-dibromoolefins by direct bromination of ethyl propynoate under controlled conditions has been reported (**Scheme 31**).[71] The terminal bromide participates in palladium catalysed cross couplings with complete retention of stereochemistry, allowing access to the monobromides which could only be obtained as isomeric mixtures by Horner–Wadsworth–Emmons technology. Iodination of an alkene with intramolecular nucleophilic trapping by a sulfide was the key step in a synthesis of penem analogues (**Scheme 32**).[72]

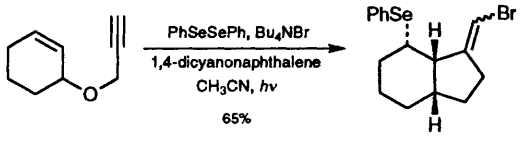
Radical methods remain popular for the halo-functionalisation of alkynes. Interesting examples include the cyclisation/bromoselenation of an ω-enyne (**Scheme 33**)[73] and a synthesis of iodomethylene lactones involving the atom transfer



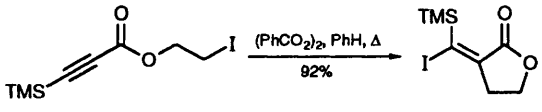
Scheme 31



Scheme 32



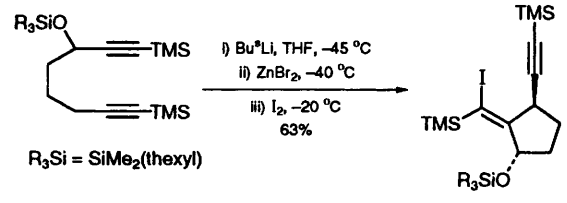
Scheme 33



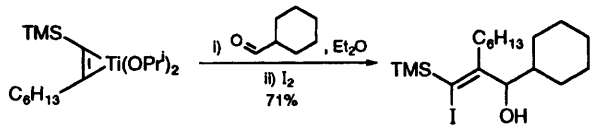
Scheme 34

cyclisation of an iodo alkyne (**Scheme 34**).[74] Weavers and co-workers have studied the latter reactions mechanistically and identified the optimal cyclisation conditions.[75]

Normant and Marek have developed a stereoselective synthesis of iodomethylene cyclopentanes, involving the cyclisation of an organozinc species onto an alkyne and quenching of the resulting vinyl zinc with iodine (**Scheme 35**).[76] The Sato group studied the nucleophilic addition of low valent titanium alkoxide alkyne complexes to carbonyl compounds.[77] Quenching the resulting σ-bonded vinyl titanium with iodine yields functionalised (*Z*)-vinyl iodides, the olefin geometry being controlled by complexation of the titanium to the allylic oxygen function (**Scheme 36**). Studies on

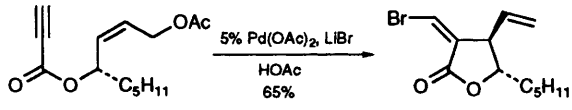


Scheme 35



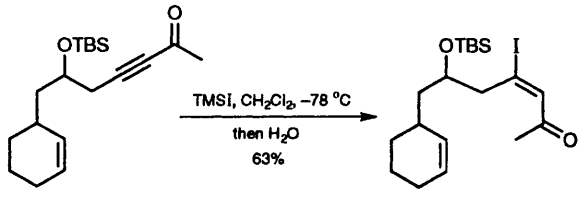
Scheme 36

the synthesis of halomethylene γ-lactones by the palladium mediated oxidative cyclisation of ω-enynes have been extended this year.[78,79] In addition, a non-oxidative version of the reaction starting from an allylic acetate has also been demonstrated and employed in a synthesis of the antibiotic methylenolactone (**Scheme 37**).[80]



Scheme 37

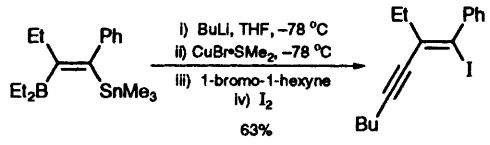
Finally, the stereoselective hydrohalogenation of alkynyl ketones may be achieved using sodium iodide/acetic acid under the optimised conditions of Piers,[81] or through the conjugate addition of trimethylsilyl iodide followed by hydrolytic work up (**Scheme 38**).[82]



Scheme 38

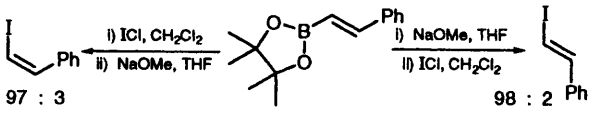
3.2 From other vinyl derivatives

The popularity of vinyl silanes, stannanes and boranes as precursors to vinyl halides remains undiminished, and several significant examples reported this year illustrate the reasons for this popularity. A stannyl vinyl borane was exploited to achieve the stereospecific synthesis of a vinyl iodide intermediate on the way to an enediyne system (**Scheme 39**).[83] Initial metallation takes place at the boronyl carbon, facilitating a copper catalysed cross coupling with a bromoalkyne, before final iodinative cleavage of the vinyl stannane. Complete control of regio- and stereochemistry was observed. Bromodienes were synthesised by the NBS mediated desilylation of 1-silyl-1,3-dienes,[84] and bis(pyridine)iodonium tetrafluoroborate has been introduced as an agent for the stereoselective desilylation of vinyl silanes.[85] Stewart and Whiting found that iodine monochloride was an effective agent for the cleavage of hindered pinacol



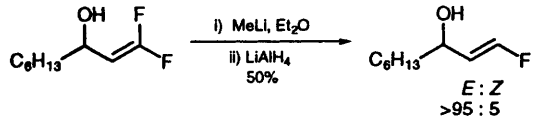
Scheme 39

boronates, where iodine had been shown to be unreactive.[86] Retention or inversion of configuration can be attained cleanly by varying the order of addition of reagents (**Scheme 40**). Stereoselective fluorinative destannylation of vinyl stannanes can be achieved with silver triflate and xenon difluoride, the mechanism of which has been studied in detail this year.[87]

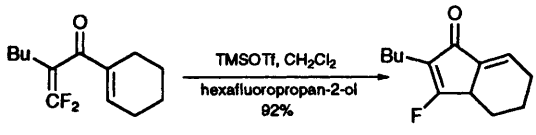


Scheme 40

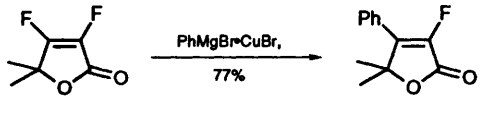
1,1- or 1,2-Dihaloalkenes are often used to prepare vinylic monohalides. Sequential treatment of 1,1-difluoroallylic alcohols with methyllithium and lithium aluminium hydride leads to (*E*)-vinyl fluorides of excellent isomeric purity (**Scheme 41**).[88] An interesting synthesis of cyclic vinyl fluorides exploits the β-cation destabilising effect of a difluoromethylene unit to direct Nazarov cyclisations (**Scheme 42**).[89] Fluorine substitution of 2,3-difluorobutenolides by organometallic or alkoxide nucleophiles provides entry to the corresponding 2-fluoro-3-substituted butenolides (**Scheme 43**).[90] Clean α-iodination of enones can be achieved using iodine and catalytic pyridinium dichromate.[91]



Scheme 41

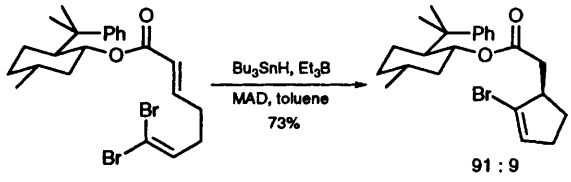


Scheme 42

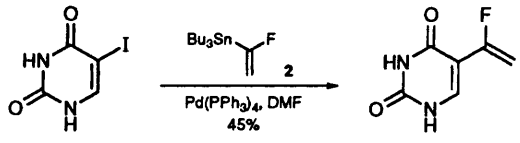


Scheme 43

1,1-Dibromoolefins are valuable precursors to 1-bromovinyl radicals. The cyclisation of a bromovinyl radical onto a chiral α,β-unsaturated ester occurred with a reasonable level of diastereoselectivity in the presence of the bulky Lewis acid MAD (**Scheme 44**).[92] 1-Fluoro-1-tributylstannylethene **2** has been introduced for the incorporation of fluorovinyl units via palladium catalysed cross coupling reactions, exemplified by the synthesis of a modified nucleoside base (**Scheme 45**).[93]

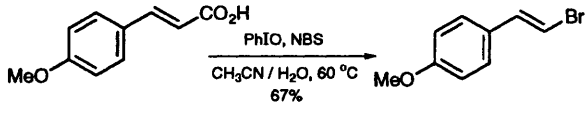


Scheme 44

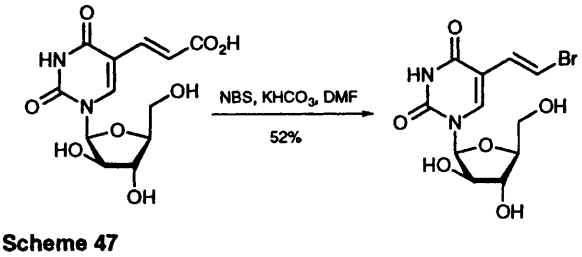


Scheme 45

The Hunsdiecker reaction, the classical method for decarboxylative bromination, usually fails with unsaturated acids. Two alternative, non-radical based decarboxylative brominations have appeared this year. Both involve treatment of the unsaturated acid with NBS, with subsequent decarboxylation being promoted either by iodosyl benzene (**Scheme 46**)[94] or potassium bicarbonate (**Scheme 47**).[95]

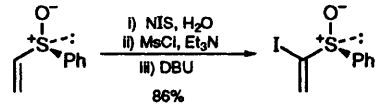


Scheme 46

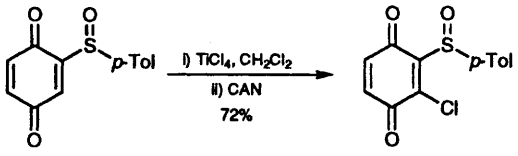


Scheme 47

Novel iodovinyl sulfoxides have been synthesised by the addition of cuprates to alkynyl sulfoxides, trapping with *N*-iodosuccinimide (NIS), and also by dehydration of the iodohydrin of vinyl sulfoxides (**Scheme 48**).[96] Finally, 3-chloro-2-sulfinyl-1,4-benzoquinones have been synthesised as asymmetric Diels–Alder dienophiles, by addition of



Scheme 48

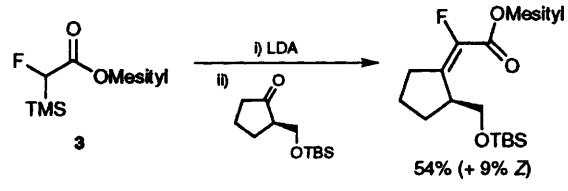


Scheme 49

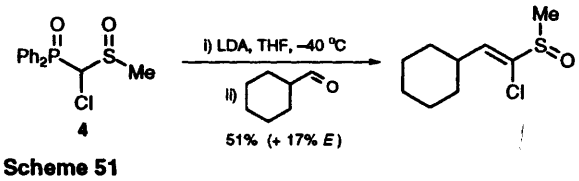
chloride to the parent benzoquinone and subsequent oxidation of the intermediate dihydroquinone (**Scheme 49**).[97]

3.3 By C=C bond formation

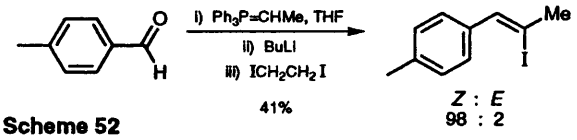
Vinyl halide synthesis via carbon–carbon double bond formation is a relatively little used strategy, largely due to the low levels of stereocontrol generally attainable through such approaches. For example, the synthesis of vinyl fluorides by the direct condensation of ethyl fluoroacetate with aldehydes proceeds with isomeric ratios typically of only 2:1.[98] The chromium(II) chloride/iodoform system for the iodomethylenation of aldehydes has been utilised in a synthesis of bullaticin, but with *E*:*Z* ratios of only 4:1.[99] Elsewhere, a fluorinated Peterson type reagent **3** (**Scheme 50**)[100] and a chlorinated Horner–Wittig reagent **4** (**Scheme 51**)[101] have been reported, but again variable degrees of stereocontrol in their reactions with carbonyl compounds limit their general use. Good levels of stereocontrol have been achieved, however, by the iodination of Schlosser type β-oxido ylides with 1,2-diiodoethane, followed by phosphine oxide elimination (**Scheme 52**).[102] Another interesting



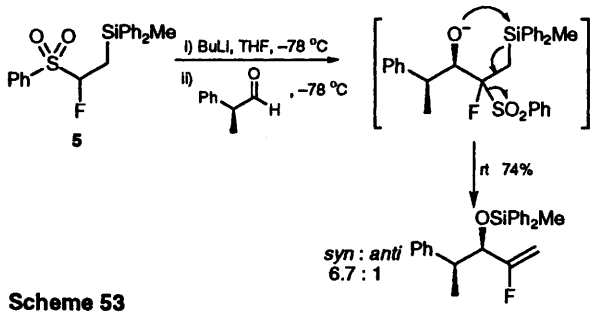
Scheme 50



Scheme 51



Scheme 52

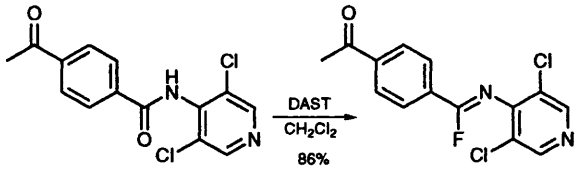


Scheme 53

reagent is the silylated fluorosulfone **5**, which achieves the overall addition of a fluorovinyl unit to aldehydes as shown (**Scheme 53**).[103]

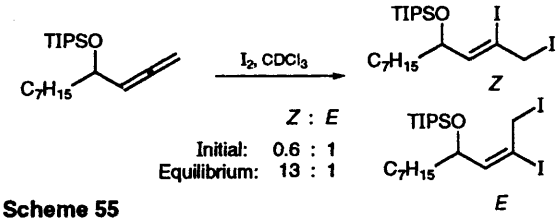
3.4 By other methods

Vinyl fluorides are often produced during the attempted preparation of 1,1-difluorides from carbonyl compounds by treatment with DAST or synthetic equivalents. In some cases the vinyl fluoride is the exclusive product, a fact exploited in a synthesis of fluorodehydroepiandrosterones as potential antitumour agents.[104] A related example, although not a vinyl fluoride, is the exclusive production of fluoro-imines from secondary amides (**Scheme 54**).[105]



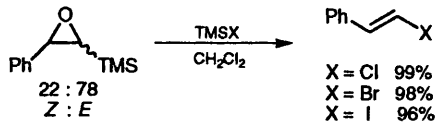
Scheme 54

Friesen has studied the iodination of allenic alcohols, and found that the excellent levels of stereocontrol for the (*Z*)-isomer of the vinyl iodide observed are due to the isomerisation of an initial mixture rich in the (*E*)-isomer (**Scheme 55**).[106] Treatment of allenic esters with aqueous NBS leads, on cyclisation of the initially formed hydroxy ester, to β-bromobutenolides.[107]



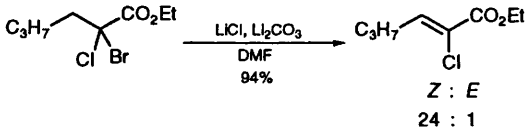
Scheme 55

Vinyl iodides have been synthesised by the treatment of 1-trimethylsilyl epoxides with TMSI (**Scheme 56**).[108] The production of a single geometric isomer from a mixture of (*Z*)- and (*E*)-epoxides indicates that the reaction proceeds by the E_1 elimination of hexamethyl disiloxane from an intermediate silylated iodohydrin. The elimination



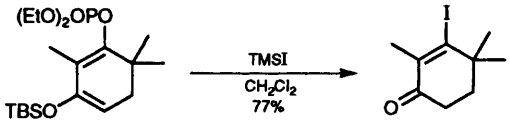
Scheme 56

of water or hydrogen halide from 1,2-halohydrins and 1,2-dihalides respectively has been used in the synthesis of fluorinated analogues of abscisic acid[109] and eugenol.[110] An improved method for the synthesis of α-chloro acrylates by lithium chloride promoted elimination of HCl from α-bromo–α-chloro esters has been reported, with *Z*:*E* ratios better than 20:1 observed in all cases examined (**Scheme 57**).[111] Mechanistic studies show that it is the chloride ion which catalyses the elimination step, and that the lithium carbonate present simply neutralises the HCl thus formed.

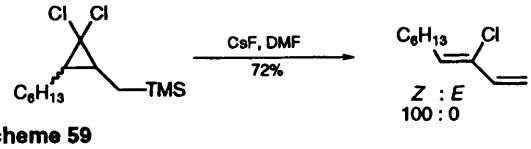


Scheme 57

The synthesis of β-iodo enones from cyclic 1,3-diones classically leads to iodination at the position corresponding to the most sterically accessible ketone. Kishi has developed a method for the synthesis of the regioisomeric iodo enones, involving silylation of the most reactive ketone, formation of the enol phosphonate of the remaining ketone and treatment with trimethylsilyl iodide (**Scheme 58**).[112] 2-Chloro-1,3-dienes are formed stereoselectively and in good yield by the fluoride mediated ring opening of α-silyl dichlorocyclopropanes (**Scheme 59**).[113]



Scheme 58

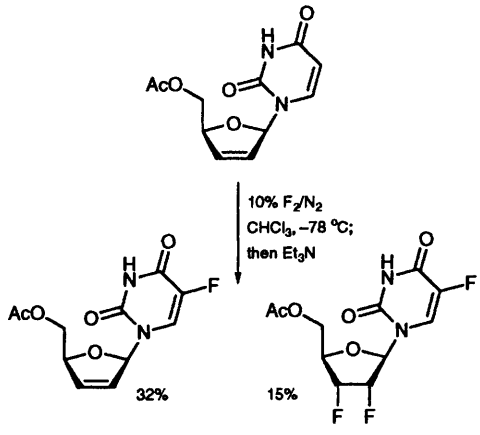


Scheme 59

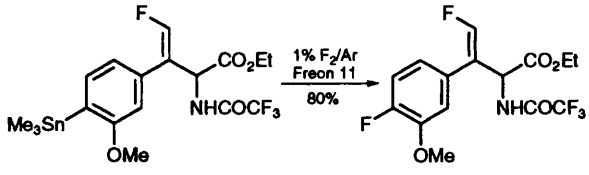
4 Aryl halides

4.1 By electrophilic substitution

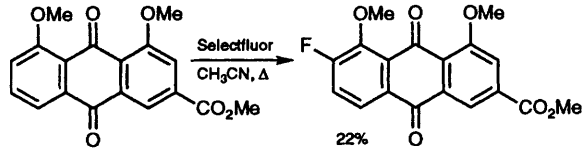
The indiscriminate reactivity of molecular fluorine has led to it being comparatively little used in electrophilic aromatic fluorination reactions. Reports this year, however, have demonstrated that direct fluorination can indeed by performed in good yields, provided that a protic acidic solvent such as trifluoroethanol, trifluoroacetic acid[114] or formic acid[115] is used to temper the reactivity of the fluorine. Direct fluorination of an intact nucleoside with molecular fluorine has also been achieved, albeit in modest yield (**Scheme 60**).[116] Fluorination of a tyrosine analogue for PET studies has been achieved in excellent yield by the destannylation of an aryl stannane with fluorine (**Scheme 61**).[117] Elsewhere, the Selectfluor reagent has been used in the chemoselective fluorination of analogues of the antiarthritic agent rhein, again in modest yield (**Scheme 62**).[118]



Scheme 60



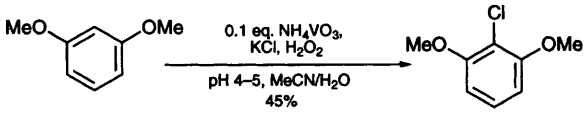
Scheme 61



Scheme 62

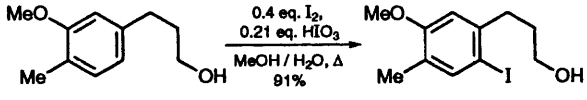
Reports this year show that the efficiency of NBS as a reagent for aromatic bromination can be greatly increased either by ultrasonication[119] or by the addition of a zeolite catalyst.[120] Dibromodimethylhydantoin has been introduced as a more efficient synthetic equivalent of NBS, when used in conjunction with triflic acid.[121] Developments in the area of aromatic chlorination include the use of calcium hypochlorite as an electrophilic chlorine source, in a cheap large scale preparation of 5-chloroanthranilic acid.[122] Thionyl chloride is often used to *para*-chlorinate phenols, but Sheldon has shown that the addition of catalytic amounts of a bulky secondary amine leads to a complete reversal

of regioselectivity in favour of the *ortho*-isomer.[123] He explains this result by invoking the formation of a chloramine, which hydrogen bonds to the phenolic hydroxy group. An interesting new aromatic chlorination procedure employs ammonium metavanadate in the presence of hydrogen peroxide and potassium chloride as the halide source (**Scheme 63**).[124] The metavanadate is proposed to act as a mimic for vanadate dependent metalloenzyme systems.



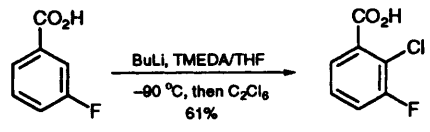
Scheme 63

Aromatic iodination has been achieved with elemental iodine by bubbling gaseous fluorine through the reaction mixture.[125] The nature of the iodinating agent is not known, but is suggested to be either a hypervalent iodine species or iodine monofluoride. The latter species, created *in situ* by treatment of iodide salts with fluorine, has been used to incorporate radioactive iodine into aromatic rings for radiotracing applications.[126] Pyridine/iodine monochloride complex, in conjunction with mercury(II) nitrate, provides a potent iodinating agent which successfully iodinates a wide range of aromatic substrates.[127] Finally, a mixture of iodine and periodic acid has been used to iodinate aromatic rings efficiently (**Scheme 64**).[128]

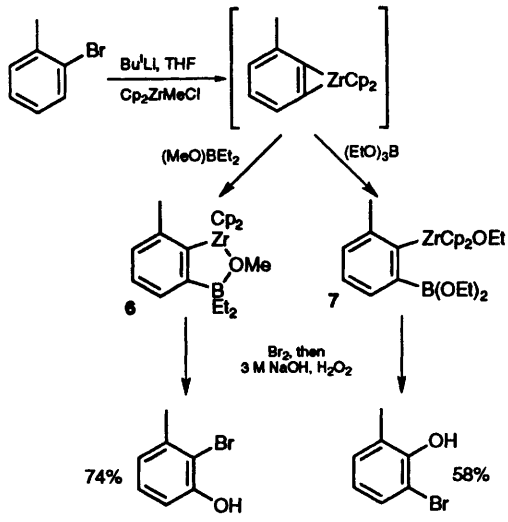


Scheme 64

Directed lithiation protocols have proven extremely useful for the regiospecific synthesis of aromatic halides when used in conjunction with an electrophilic halogen quench. Chlorination and bromination of benzoic acids have been achieved, using the acid as a directing group for lithiation.[129] The presence of a halogen atom on the benzoic acid further directs lithiation to a single *ortho*-position, allowing the regioselective synthesis of 2,3-dihalobenzoic acids (**Scheme 65**).[130] Buchwald has exploited the chemistry of zirconocenyl benzyne complexes to devise synthetic routes to isomeric halophenols (**Scheme 66**).[131] Treatment of the complex with diethylmethoxyborane gives the



Scheme 65

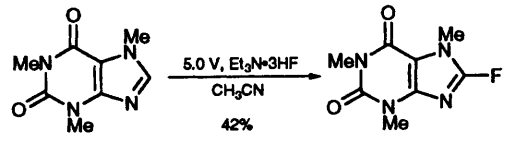


Scheme 66

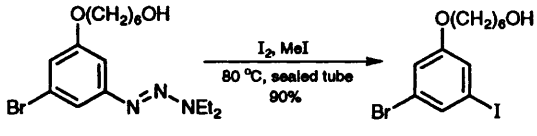
kinetic aryl boron species **6**, while treatment with triethyoxyborane gives the thermodynamic isomer **7**. Halogenative cleavage of the aryl–zirconium bond is followed by oxidation of the aryl–boron bond to furnish the isomeric halophenols.

4.2 By nucleophilic substitution

The nucleophilic displacement of nitro groups from aromatic rings has been achieved with tetramethylammonium fluoride[132] or potassium fluoride/[2.2.2]cryptand,[133] the latter system being sufficiently rapid to be of use in the synthesis of ^{18}F radiotracers. 2-Fluoroimidazoles have been prepared from the corresponding bromides using spray dried KF as the fluoride source.[134] An interesting approach to the synthesis of fluorinated purine molecules involves the anodic oxidation of the parent compound in the presence of the triethylamine/HF complex (**Scheme 67**).[135] Aryl triazenes are often employed as stable equivalents of diazonium salts in nucleophilic aromatic substitutions, but their activation usually requires strongly acidic conditions. A mild alternative reported this year involves the use of iodine in iodomethane at moderate temperatures (**Scheme 68**).[136]



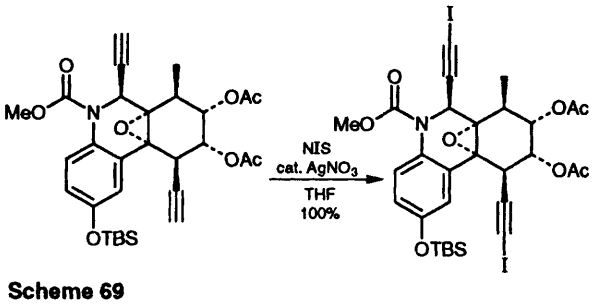
Scheme 67



Scheme 68

5 Alkynyl halides

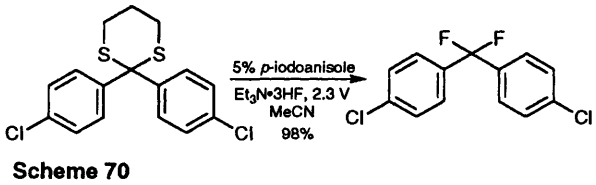
The strategic value of alkynyl halides in organic synthesis, and particularly as partners in transition metal catalysed coupling reactions, has been highlighted by Danishefsky's preparation of a bisiodoalkyne for use in a synthesis of the core unit of dynemicin (**Scheme 69**).[137] Practical improvements in the area this year include the introduction of bis(*sym*-collidine)iodine(I) hexafluorophosphate as a reagent for the direct iodination of alkynes[138] and a report of optimised conditions for the iodinative quenching of magnesium acetylides.[139]



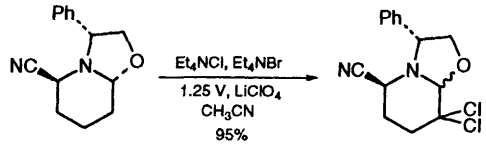
Scheme 69

6 1,1-Dihalo compounds

Interest in the area of 1,1-dihalo compounds largely concerns 1,1-difluoro derivatives, undoubtedly stimulated by the potential use of such units as isosteric replacements for carbonyl groups in medicinal chemistry. Direct conversion of carbonyl groups into the $-CF_2-$ unit by treatment with DAST has again proved a popular method.[140,141] Several new or improved protocols for the conversion of dithioketals into difluoromethylene groups have been reported, including the combinations of 1,3-dibromo-5,5-dimethylhydantoin and (hexafluoropropene)diethylamine (an *in situ* source of HF),[142] and iodine and gaseous fluorine.[143] Anodic oxidation of *p*-methoxyiodobenzene in the presence of the triethylamine/hydrogen fluoride complex produces an iodosodifluoride derivative which carried out the difluorination *in situ* (**Scheme 70**).[10] An interesting electrochemical chlorination of an oxazoline has also been reported (**Scheme 71**).[144]

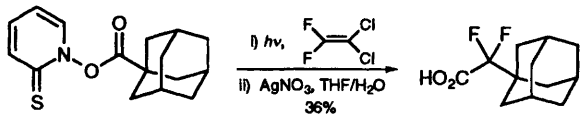


Scheme 70

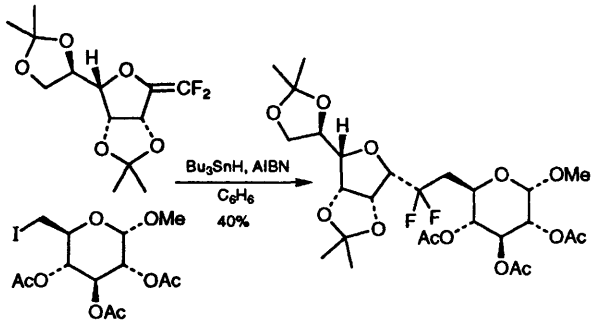


Scheme 71

Difluoroalkenes have proved to be competent radical acceptors, providing alternative routes to difluoromethylene containing carboxylic acids (**Scheme 72**)[145] and carbohydrate analogues (**Scheme 73**).[146]

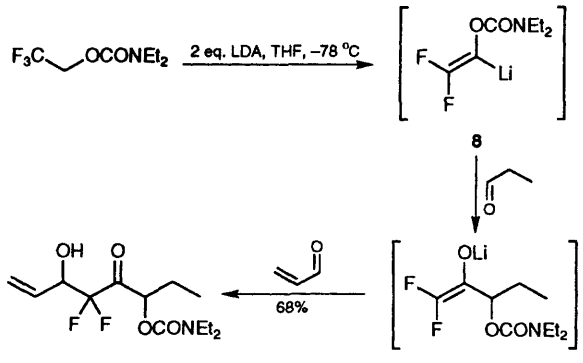


Scheme 72



Scheme 73

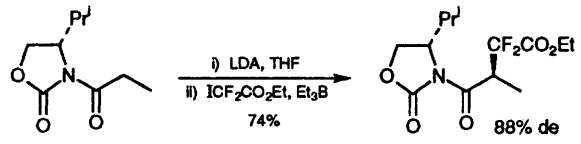
Lithiated diethyl (difluoromethyl)phosphonate $[(EtO)_2P(O)CHF_2]$ has been used as a nucleophile for the introduction of $-CF_2-$ units by the displacement of triflates,[147] addition to aldehydes[148] and cerium(III) mediated conjugate addition to nitroolefins.[149] Synthetically useful aldol reactions of difluoroenolates, generated *in situ* by the addition of difluorovinyllithium **8** to aldehydes or ketones, have been demonstrated (**Scheme 74**).[150] Treatment of chlorodifluoromethyl groups with samarium(II) iodide generates a reactive entity, presumed to be either a free difluoromethyl radical or an organosamarium(III) species, which adds to ketones and olefins in reasonable yields.[151] Dichloromethylene Reformatsky type reagents have been formed from trichloroacetic esters using a lead(II) chloride and gallium bimetallic redox system,[152] and bromofluoromethylene reagents from dibromofluoroacetic esters using a zinc/diethylaluminium chloride system.[153] Both reagents react cleanly with carbonyl compounds. Dibromomethyl lithium has been



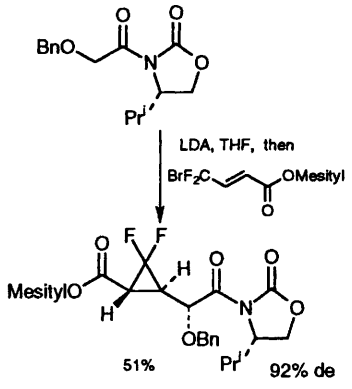
Scheme 74

demonstrated to add in good yield to cyclic sulfates[154] and in a 1,2-fashion to a cyclic enone.[155]

The use of difluoromethylene electrophiles has received somewhat less attention than their nucleophilic counterparts. The diastereoselective alkylation of chiral oxazolidinone based enolates with ethyl difluoroiodoacetate and triethylborane has been reported, the reaction having been shown to proceed via a radical mechanism (**Scheme 75**).[156] Michael addition of a chiral enolate to a bromodifluoromethyl substituted acrylate leads to the asymmetric synthesis of a difluorocyclopropane (**Scheme 76**).[157]

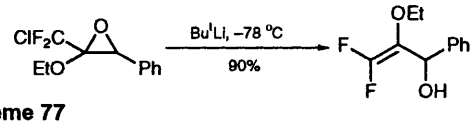


Scheme 75



Scheme 76

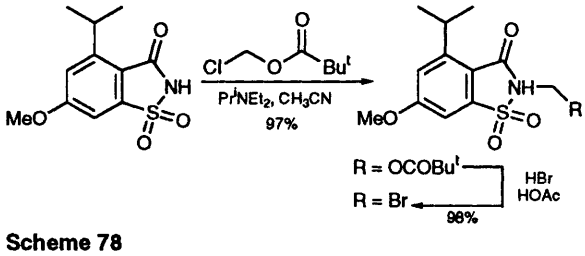
1,1-Difluoroalkenes have been prepared by the S_N2' displacement of fluoride from trifluoromethyl substituted alkenes with lithium amides.[158] Treatment of chlorodifluoromethyl substituted epoxides with Bu^{t}Li leads to a surprisingly facile metal–halogen exchange with subsequent ring opening to furnish difluoroenol ethers (**Scheme 77**).[159] The high yielding dichloromethylenation of lactones has been achieved using triphenylphosphine and carbon tetrachloride,[160] an improvement on previous methods which produced the carcinogenic hexamethylphosphoric triamide as a by-product.



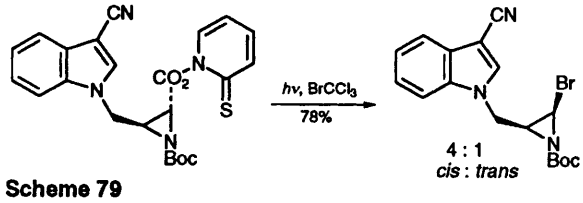
Scheme 77

7 1,1-Halohydrins and related compounds

By far the most abundant examples of 1,1-halohydrin derivatives are the glycosyl halides. For reasons of brevity, these entities will not be discussed in this review. There have, however, been other significant developments in the area this year. A clean and safe preparation of methoxymethyl chloride from dimethoxymethane and hexanoyl chloride has been reported, which gives material free from the normal impurity, the highly carcinogenic bis(chloromethyl) ether.[161] In a similar vein, a new method for the *N*-bromomethylenation of imides and isothiazolones has been developed and applied to the synthesis of antiemphysemic compounds (**Scheme 78**).[162] A brominated aziridine required for a mitomycin synthesis has been prepared from the corresponding carboxylic acid via photolysis of its Barton ester and trapping of the resultant radical with bromotrichloromethane (**Scheme 79**).[163]



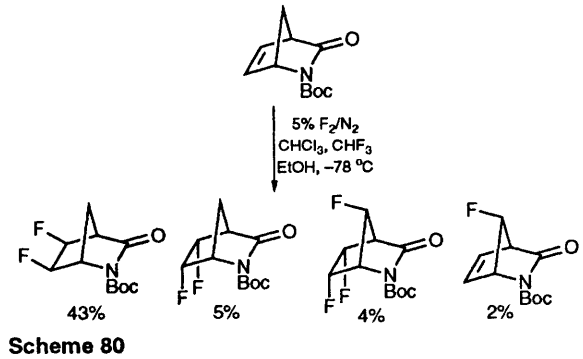
Scheme 78



Scheme 79

8 1,2-Dihalo compounds

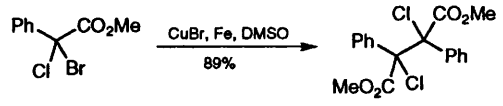
The direct addition of fluorine to various aza[2.2.1]heptenes has been studied in the context of the synthesis of fluorinated carbocyclic nucleosides (**Scheme 80**).[164] Although the desired product dominated, the presence of several by-products demonstrates the indiscriminate reactivity of fluorine towards alkenes. Two novel metal mediated protocols for the 1,2-dibromination of alkenes have been reported. Clean *trans*-dibromination has been achieved with trimethylsilyl bromide and tetradecyltrimethylammonium permanganate.[165] In a model for vanadium dependent bromoperoxidases (*vide supra*), ammonium vanadate will also achieve the dibromination of olefins in the presence of potassium bromide and hydrogen peroxide.[166,167]



Scheme 80

The bromofluorination and chlorofluorination of alkenes by the interception of halonium ions with fluoride has received much attention this year. Reagent combinations for this transformation include DBH/HF, pyridine,[168] DBH/KH_4F_5,[169] and *N*-chlorosaccharin/HF·pyridine.[170] In all cases, mixtures of stereo- and/or regio-isomers were obtained.

A reductive homocoupling of α-bromo-α-chloroesters has been reported, mediated by a copper(I)/iron redox couple, leading to 1,2-dichlorides as shown in **Scheme 81**.[171,172]

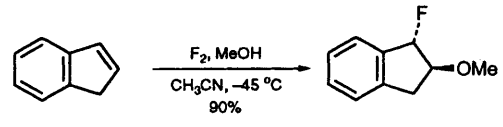


Scheme 81

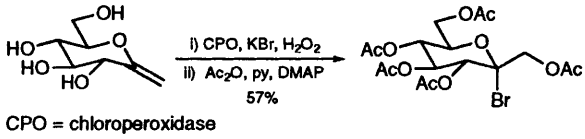
9 1,2-Halohydrins and related compounds

9.1 By addition to alkenes

In the last review of this series, the application of caesium fluoroxysulfate ($CsSO_4F$) to the synthesis of vicinal fluoroethers was reported. This year a detailed study of the effect of alkene and alcohol on the rate and stereochemical outcome of this reaction has appeared.[173] An alternative approach to these compounds has been reported by Rozen and co-workers, who have investigated the reaction of alkenes with methyl hypofluoride (**Scheme 82**).[174] This compound, prepared by the reaction of methanol and fluorine at low temperatures, reacts as 'MeO^+ F^-', and is thus regiocomplementary to the $CsSO_4F$/MeOH system which has the opposite polarity. The use of chloroperoxidase enzymes for the synthesis of halohydrins has been extended to include higher sugar anomeric bromides (**Scheme 83**).[175]



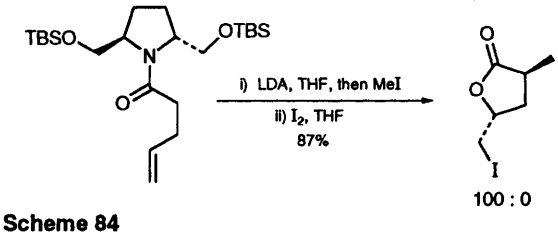
Scheme 82



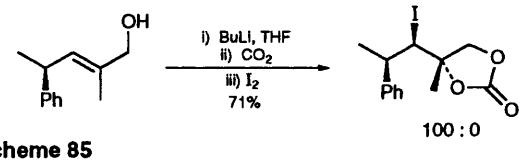
CPO = chloroperoxidase

Scheme 83

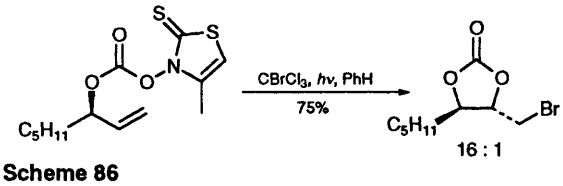
Interest in halonium ion mediated electrophilic cyclisations remains intense. The use of bis(*sym*-collidine)iodine(I) hexafluorophosphate as an agent for medium ring iodolactonisations has been described, with excellent yields reported for seven-membered ring formation.[176] An interesting strategy for the asymmetric synthesis of iodolactones has been reported, involving the use of a C_2-symmetric pyrrolidine as a chiral auxiliary for sequential alkylation and iodocyclisation reactions (**Scheme 84**), both proceeding with excellent stereocontrol.[177] The method has also been shown to be successful with the chiral auxiliary attached to a polymeric support, offering an attractively facile method of auxiliary recycling.[178] In the related area of iodocarbonation, a remarkably diastereoselective cyclisation has been attributed to intramolecular delivery of iodine by an allylic aromatic group, prior to cyclisation (**Scheme 85**).[179] An interesting variation in halocarbonation reactions involving radicals rather than ionic species is shown in **Scheme 86**.[180] The cyclisation proceeds with the same sense of asymmetric induction as the polar equivalent, but a greater level of selectivity (16:1, *cf.* 4:1).



Scheme 84

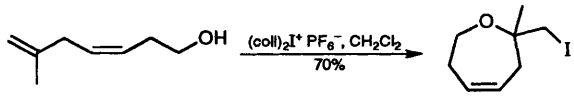


Scheme 85

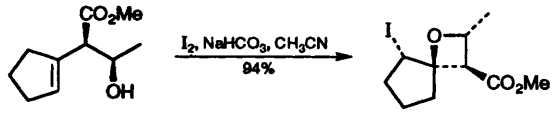


Scheme 86

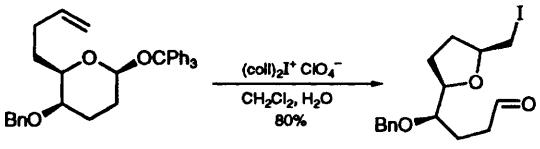
Iodoetherification reactions have again been widely used in the preparation of tetrahydrofurans (including tetrasubstituted[181] and 2,2,4-trisubstituted[182] examples) as well as in the synthesis of oxepanes (**Scheme 87**)[183] and oxetanes (**Scheme 88**).[184] An interesting approach to the synthesis of functionalised tetrahydrofurans involves the use of ring oxygen of derivatised furanosyl[185] and pyranosyl[186] sugars as the nucleophilic partner in iodocyclisations, with subsequent rupture of the sugar ring (**Scheme 89**).



Scheme 87

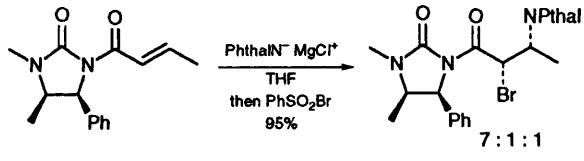


Scheme 88

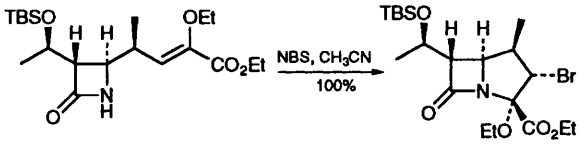


Scheme 89

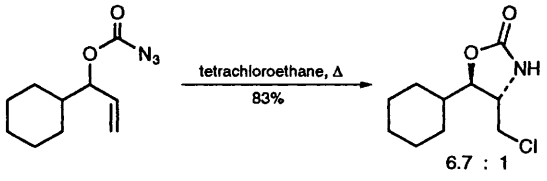
As in previous years, this review will not cover the co-addition of halides and heteroatoms such as sulfur and selenium to olefins. However, several interesting examples of the azahalogenation of olefins have appeared this year and are worthy of mention. The diastereoselective Michael addition of phthalimide to chiral enamides, trapping with a bromine source, leads to a mixture of three isomeric adducts, the major isomer having the stereochemistry shown in **Scheme 90**.[187] The nitrogen of β-lactams proves to be a competent nucleophile for halonium ions, facilitating a novel carbapenem synthesis (**Scheme 91**). Gallagher has investigated the synthesis of 8–11 membered azacycles by the iodocyclisation of sulfonamides onto allenes.[189] Finally, an interesting formal addition of a nitrogen nucleophile and a halide across an olefin has been reported upon thermolysis of an azido olefin (**Scheme 92**).[190] The reaction proceeds via interception of an intermediate aziridine by HCl produced by the chlorinated solvent.



Scheme 90



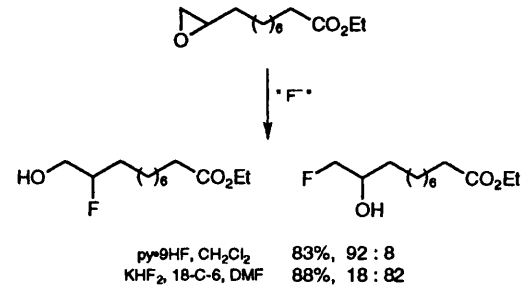
Scheme 91



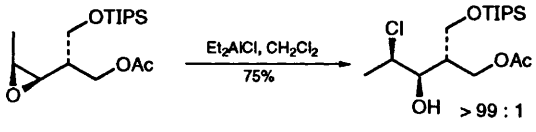
Scheme 92

9.2 By epoxide opening

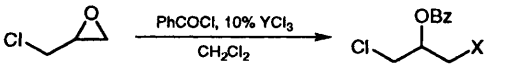
Epoxide opening remains a popular method of halohydrin synthesis. A comparative study of the effects of fluoride source on the regioselectivity of ring opening of terminal epoxides reveals that good regiocontrol is possible in either sense by appropriate choice of reagent (**Scheme 93**).[191] More challengingly, an investigation of the ring opening of 1,2-disubstituted epoxides has shown that chelation to nearby oxygen functionality can be used to direct halide delivery from metal halides with very high regiocontrol (**Scheme 94**).[192] Yttrium(III) chloride and its dicyclopentadienyl analogue have been found to be excellent catalysts for the acylative ring opening of epoxides.[193] Using benzoyl chloride as the acylating agent, both chlorohydrins and, by the addition of sodium iodide, iodohydrins are formed in excellent yield (**Scheme 95**).



Scheme 93

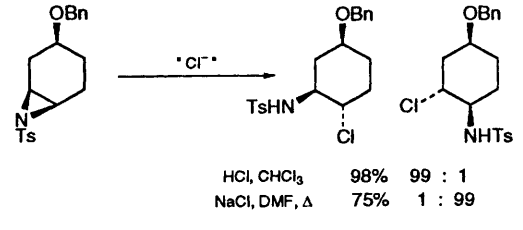


Scheme 94



Scheme 95

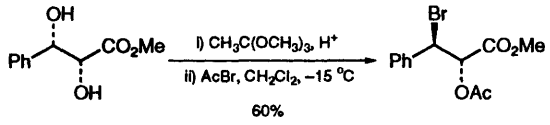
In the area of halide ion opening of aziridines, total control of the regiochemistry of ring opening of a bicyclic aziridine was demonstrated by appropriate choice of reagents (**Scheme 96**).[194]



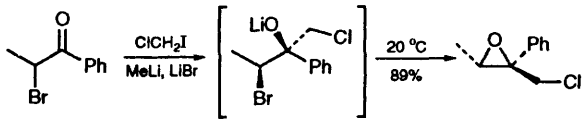
Scheme 96

9.3 By other methods

The regioselective formation of acetoxy chlorides[195] and bromides[196] from diols via their derived orthoformates have been reported, the latter being employed in a large scale asymmetric synthesis of the Taxol® side chain (**Scheme 97**). The addition of haloalkyl organometallic reagents to aldehydes and ketones provides an entry into 1,2-halohydrins.[197] In one report, the stereoselective addition of (chloromethyl)lithium to α-bromoketones furnishes glycidyl chlorides on warming the reaction mixture (**Scheme 98**).[198]

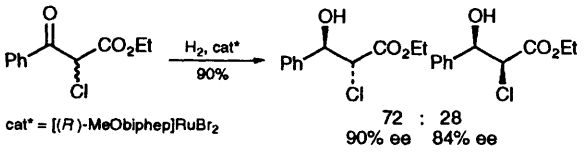


Scheme 97



Scheme 98

Finally, the Gênet group have achieved the dynamic resolution of α-chlorinated-β-ketoesters by catalytic asymmetric hydrogenation, leading to 1,2-halohydrins of reasonable purity (**Scheme 99**).[199]



Scheme 99

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