Organic halides

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Reviewing the literature published between 1 July 1995 and 30 June 1996
Continuing the coverage in *Contemporary Organic Synthesis*, 1996, **3**, 133

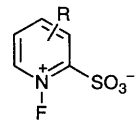
1 Introduction

This fourth review in the series aims, like its predecessors,[1-3] to highlight developments in methodology for the preparation of organic halides which have appeared in the literature over the past year. Particular emphasis has been placed on those methods which are either conceptually novel or which demonstrate superior chemo-, regio- or stereo-selectivities over existing protocols. Given the current level of interest in the development of 'clean' chemical reactions, it is of little surprise that the use of technologies such as electrochemistry, ultrasound and heterogeneous catalysis in halogenation reactions has increased manifoldly in the past year, and this will be reflected in the number of examples which feature such methods. For reasons of brevity, and in line with the previous reviews, the chemistry of perfluoroalkyl and hypervalent iodine compounds will not be reviewed; additionally, there have been no significant developments in alkynyl halide synthesis this year, and so this area will not feature in the review.

Several areas of organic halide preparation have been reviewed in the past twelve months. A *Tetrahedron* 'Symposium in Print' was dedicated to synthetic and medicinal aspects of fluoroorganic chemistry.[4] The synthesis of fluorinated porphyrins for use in photodynamic cancer therapy has been reviewed,[5] as has the use of aryl- and vinylstannanes as precursors for the introduction of radioisotopic halides into pharmaceuticals for *in vivo* imaging studies.[6] A comprehensive review of methods for the synthesis of 1,1-difluoroalkanes and alkenes has been published,[7] as has a smaller review concerned with the synthesis of optically active fluoroorganics.[8] The synthesis of organic fluorides by anodic fluorination has been reviewed,[9] as have the applications of reagents including elemental fluorine,[10] triethylamine tris(hydrogen fluoride)[11,12] and tetrabutylammonium hydrofluoride.[13]

Several new electrophilic fluorinating agents have been introduced this year. These include *N*-fluoropyridinium-2-sulfonate **1**,[14] perfluoro[*N*-(4-pyridyl)acetamide] **2**[15] and *N*-fluorooxathiazinone dioxides **3**,[16] based around the commercial sweetener Acesulfam K. All of these agents are effective in the electrophilic fluorination of electron rich aromatics, malonate salts, enamines *etc.*

Ammonium and phosphonium perfluorocyclobutane ylides **4** have been introduced as masked fluoride sources,[17] which have proven to be effective in several reactions including nucleophilic aromatic substitution. *N*-Methylhexamethyleneammonium fluoride **5** is another new agent for S_NAr reactions, especially fluorodenitration.[18]



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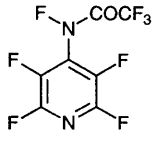

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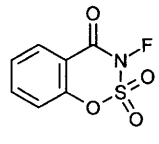

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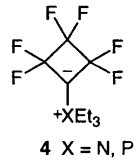

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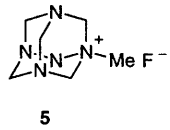


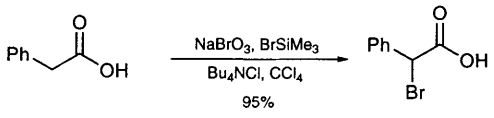
5

2 Alkyl halides

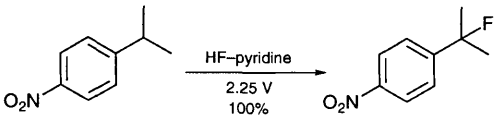
2.1 By halogenation of alkanes

There have been relatively few new developments in the halogenation of unactivated alkanes. In one example, the ionic bromination of alkanes using the carbon tetrabromide–aluminium tribromide superacid as promoter has been studied in detail.[19]

In contrast, several new benzylic halogenation reactions have been reported. The use of sodium bromate–trimethylsilyl bromide in conjunction with a phase transfer catalyst has been reported to give excellent yields of monobrominated materials (**Scheme 1**).[20] Anodic oxidation using Olah's reagent (70% HF–30% pyridine) as both solvent and electrolyte is an efficient route to benzylic fluorides (**Scheme 2**).[21] Imines and alkyl substituted pyridines can be α-fluorinated in moderate yield using *N*-fluorobis(trifluoromethylsulfonyl)imide, although in the case of the imines some difluorinated material is formed.[22]



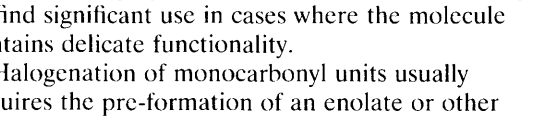
Scheme 1



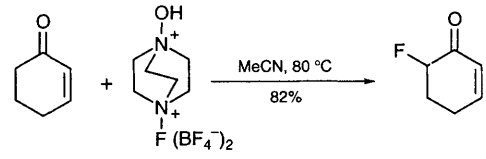
Scheme 2

Halogenation of activated methylene units of 1,3-dicarbonyl compounds remains a fruitful approach to haloalkanes. A high yielding method for the bromination of β-keto esters using copper(II) bromide and Koser's reagent [PhI(OH)OTs] has been reported.[23] The direct fluorination of a range of 1,3-dicarbonyl compounds in formic acid provides a rapid route to fluoroalkanes.[24] A more elaborate approach to fluorinated β-keto esters involves the dephosphinylative acylation of fluorinated phosphonoacetates (**Scheme 3**).[25] The relatively mild conditions employed mean that this method is likely to find significant use in cases where the molecule contains delicate functionality.

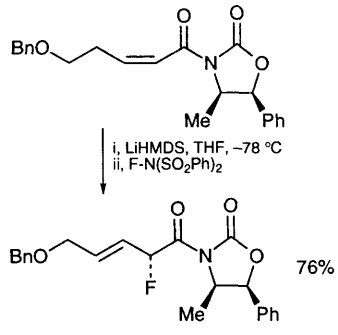
Halogenation of monocarbonyl units usually requires the pre-formation of an enolate or other activated derivative. Two methods which avoid this requirement have been reported this year, namely the use of Accufluor™ in acetonitrile at elevated temperatures[26] (**Scheme 4**) and the use of HF–SbF_5 superacids in inert solvents.[27] Fluorinated prostaglandin analogues have been prepared by treatment of the lithium enolate of a bicyclic lactone with acetyl hypofluorite.[28] The regioselective fluorination of 1,3-dienolates in both α- and γ-positions has been demonstrated. Treatment of a lithium dienolate with *N*-fluorobis(phenylsulfonyl)imide [$FN(SO_2Ph)_2$] at low temperature gave the α-fluorinated product, as part of a synthesis of fluorinated nucleosides (**Scheme 5**).[29] Conversely, addition of triphenylborane to a potassium dienolate gave a dienyloxyboronate which yielded exclusively the γ-fluorinated regioisomer on exposure to $FN(SO_2Ph)_2$ (**Scheme 6**).[30]



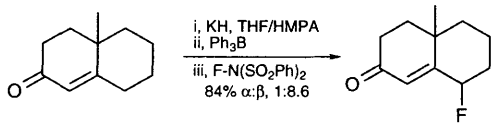
Scheme 3



Scheme 4



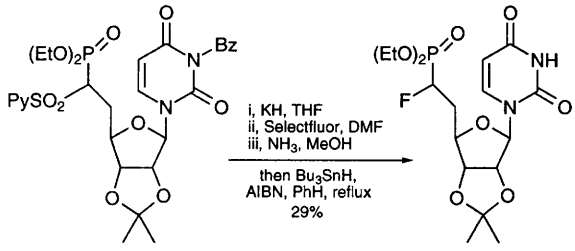
Scheme 5



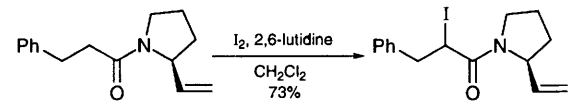
Scheme 6

Fluorinated nucleoside phosphonates have been prepared by electrophilic fluorination of α-pyridylsulfonyl phosphonate anions, followed by tin hydride excision of the sulfone (**Scheme 7**).[31]

Finally, an unusual iodination of *N*-allylic amides and lactones has been demonstrated by simply using iodine and 2,6-dimethylpyridine (**Scheme 8**).[32] This remarkable and unexpected transformation involves an initial iodocyclisation of the lactam carbonyl, followed by loss of a proton to give a ketene aminal which is then electrophilically iodinated.



Scheme 7

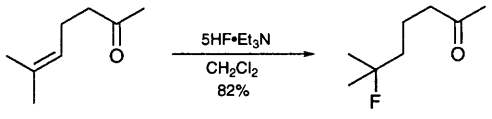


Scheme 8

Retroiodocyclisation furnishes the observed product in good yield.

2.2 By halogenation of alkenes

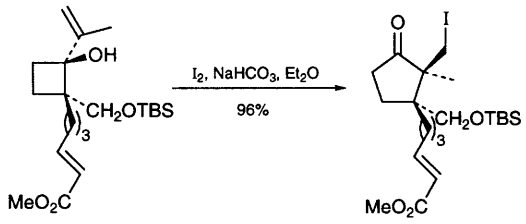
The synthesis of alkyl halides by direct addition of HX to an alkene is a relatively little used strategy in the modern era, largely due to the harsh nature of the conditions employed. Nevertheless, an alkyl chloride intermediate in a synthesis of necic acid was prepared from an alkene and concentrated HCl.[33] Useful yields of alkyl fluorides can be obtained from alkenes and an HF–triethylamine complex (**Scheme 9**),[34] or by using potassium hydrogen difluoride in the presence of an activating agent such as SiF_4.[35]



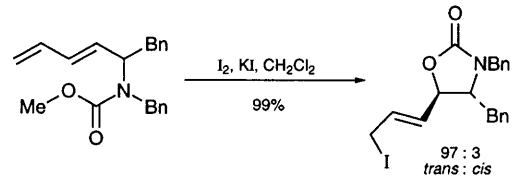
Scheme 9

Iodination of exocyclic allylic alcohols or silyl ethers[36–38] can be a useful method for the synthesis of ring expanded cyclic ketones (**Scheme 10**). Iodocyclisation of carbamates to dienes has been demonstrated to give the product of 1,4-addition exclusively, providing intermediates which have been used in the synthesis of sphingosines (**Scheme 11**).[39] Taguchi has optimised his catalytic asymmetric iodocarbocyclisation reaction, discussed in the last of these reviews, with the discovery that the use of 2,6-dimethoxypyridine as a base with a titanium TADDOLate catalyst (TADDOL = α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol) gives reproducibly high ees.[40]

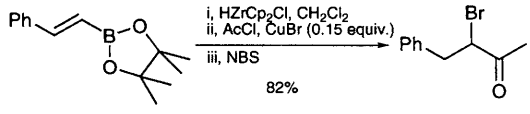
In an impressive demonstration of the power of 1,1-bimetallic reagents in synthesis, Srebnik has achieved the conversion of vinylboronates to α-bromo ketones, in a process involving hydro-



Scheme 10



Scheme 11



Scheme 12

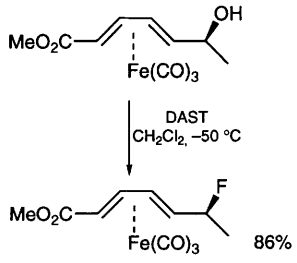
zirconation, acylation, 1,3-boron migration and finally electrophilic bromination (**Scheme 12**).[41]

2.3 By nucleophilic substitution

The substitution of hydroxy groups by halogens is one of the most popular and reliable methods for the synthesis of functionalised alkyl halides, and alkyl fluorides in particular. Pertinent examples this year include the synthesis of fluorinated leukotriene analogues[42] and 2-fluoro-2-arylpropionic acids as anti-inflammatory agents[43] using dimethylaminosulfur trifluoride and diethylaminosulfur trifluoride (DAST) respectively. A new reagent system for the *in situ* activation–substitution of hydroxy groups is the combination of trimethylsilyl halides with catalytic bismuth(III) chloride.[44] The reaction proceeds with predominant inversion of configuration with chiral secondary alcohols, although S_N1 and S_N2' modes have been observed with appropriate substrates. Benzylic sulfides have been substituted by fluoride, using a combination of nitrosonium tetrafluoroborate as activating agent and pyridinium poly(hydrogen fluoride) as the fluoride source.[45]

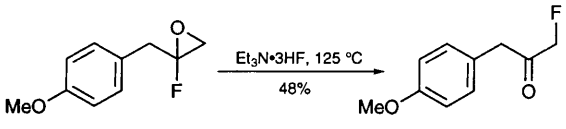
The substitution of allylic alcohols with reagents such as DAST frequently leads to problems of allylic transposition and loss of stereochemical integrity at chiral centres. An elegant example from the laboratories of Gree uses η^4-diene iron carbonyl complexes to give single regioisomers of the product fluorides with exclusive retention of stereochemistry (**Scheme 13**).[46]

The synthesis of α-halocarbonyls by ring-opening of functionalised epoxides with halide has been

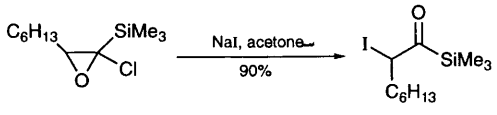


Scheme 13

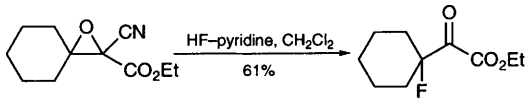
demonstrated in several reports. Treatment of 2-fluoro-2-alkyl epoxides with fluoride sources yields the α-fluoro ketones in moderate yields (**Scheme 14**).[47,48] α-Haloacyl silanes, useful precursors for Reformatsky reactions, have been prepared by attack of halide on 2-halo-2-trimethylsilyloxiranes (**Scheme 15**).[49] In a versatile new method, nucleophilic attack on *gem*-dicyanooxiranes gives intermediate α-haloacyl nitriles, which can undergo further substitution of cyanide by a second nucleophile to give α-halo acids, esters, amides and hydroxamic acids.[50,51] 3-Fluoropyruvates have been prepared by an analogous route, involving ring-opening of 1-cyano-1-ethoxycarbonyloxiranes with fluoride (**Scheme 16**).[52] The intermediate cyanohydrins require nickel(II) catalysis to effect their breakdown to the ketone. Finally, a mechanistically related example involves the asymmetric synthesis of α-halo acids from chiral α-trichloromethyl alcohols (**Scheme 17**).[53] These proceed *via* halide-mediated ring-opening of intermediate 1,1-dichlorooxiranes formed under the reaction conditions.



Scheme 14

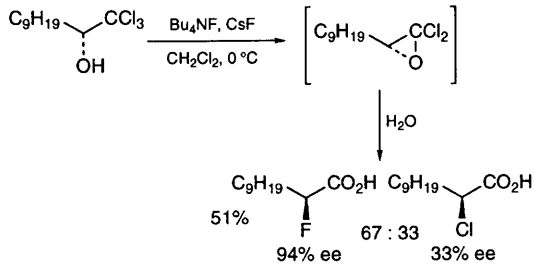


Scheme 15

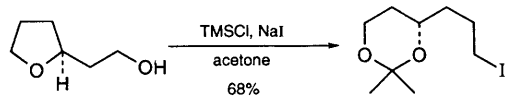


Scheme 16

The TMSI-promoted ring opening of cyclic ethers remains a useful approach to halogenated synthons, in this case as part of a synthesis of α-lipoic acid (**Scheme 18**).[54]



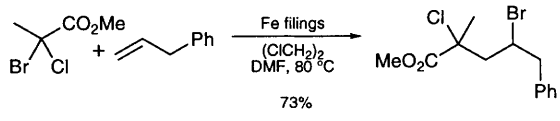
Scheme 17



Scheme 18

2.4 By other methods

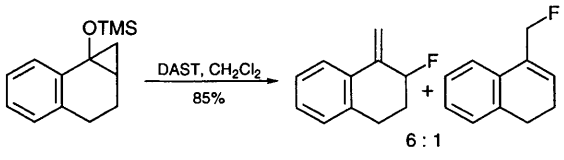
Intermolecular atom transfer additions of α,α-dihalo esters to alkenes have been further investigated this year, using the previously reported iron filings–copper(I) bromide system as promoter,[55] as well as a new system using iron filings alone (**Scheme 19**).[56] In this latter case, the reaction is only successful in the case of terminal alkenes, and careful control of the amount of iron and temperature is needed to minimise the formation of radical dimers.



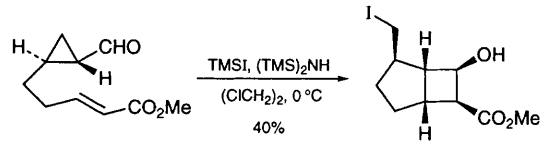
Scheme 19

Allylic fluorides have been prepared by treatment of trimethylsilyloxycyclopropanes with DAST, the reaction proceeding through an allylic cation intermediate (**Scheme 20**).[57] Treatment of cyclopropyl-substituted alcohols with HBr gives homoallylic bromides with good to excellent *E*:*Z* ratios.[58] An elegant and stereocontrolled cascade synthesis of a bicyclic [3.2.0] system has been reported, triggered by the homo-Michael addition of iodide to a cyclopropanecarbaldehyde (**Scheme 21**).[59]

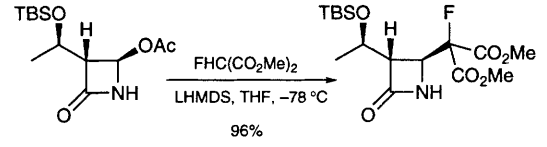
The introduction of fluoride into complex target molecules through the intermediacy of simple fluorinated nucleophiles is a popular strategy.



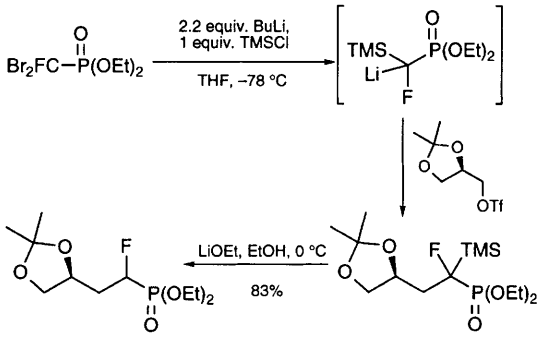
Scheme 20



Scheme 21



Scheme 22

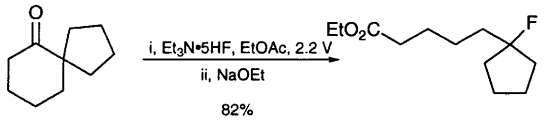


Scheme 23

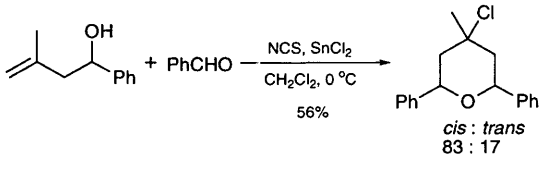
Examples include the synthesis of fluorinated carbapenems from fluoromalonates (**Scheme 22**),[60] and *sn*-glycerol-3-phosphate analogues from fluorinated phosphonate anions (**Scheme 23**).[61]

An interesting example of electrochemical synthesis involves the fluorinative cleavage of cyclic ketones (**Scheme 24**),[62] although the reaction is limited to α,α-disubstituted ketones.

Finally, the use of a halide trap for the cation formed in an intramolecular Prins-type reaction allows access to 4-halotetrahydropyrans (**Scheme 25**).[63]



Scheme 24

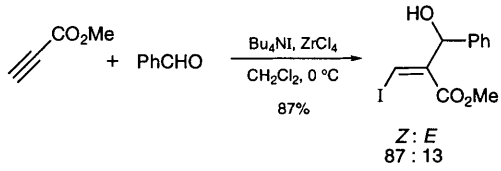


Scheme 25

3 Vinyl halides

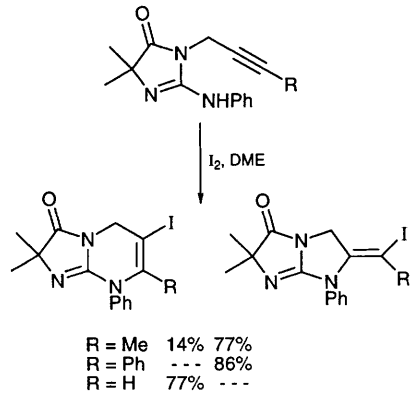
3.1 From alkynes

Highly functionalised vinyl iodides have been prepared by the Michael addition of iodide to methyl propiolate in the presence of carbonyl compounds, which efficiently trap the resulting enolates (**Scheme 26**).[64] Modest to good *E*:*Z* ratios were obtained.



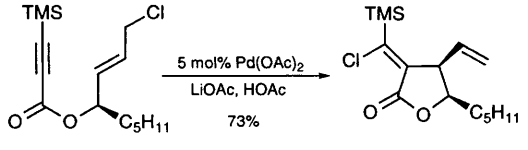
Scheme 26

The electrophilic addition of iodine to alkynes, with either inter- or intra-molecular trapping by nucleophiles, remains a commonly used route to vinyl iodides. A decalin containing two vinyl iodide units was prepared by exposure of cyclodeca-1,6-diyne to iodine.[65] The regiochemistry of cyclisation of 2-aminoimidazolin-4-ones to pendant alkynes is dependent upon the substitution of the alkyne (**Scheme 27**).[66]



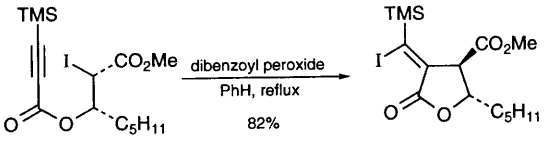
Scheme 27

The palladium-catalysed oxidative cyclisation of enynes, terminated by halide ions, continues to serve as a facile route to *exo*-halomethylene substituted carbo- and hetero-cycles.[67] A related non-oxidative cyclisation of an alkyne to an allylic chloride has been used in a total synthesis of phaseolinic acid (**Scheme 28**).[68] An alternative route



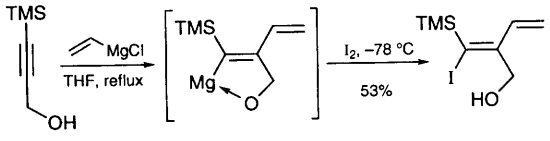
Scheme 28

to *exo*-halomethylene lactones is based upon the radical atom transfer cyclisations of ω-iodoalkynes, and the value of this approach has been demonstrated in a synthesis of methylenolactocin (**Scheme 29**).[69]



Scheme 29

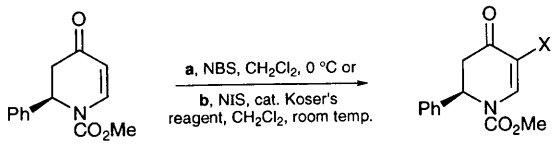
The addition of Grignard reagents to prop-2-ynyl alcohols gives configurationally defined vinylmagnesium species, which can be quenched with iodine to afford isomerically pure vinyl iodides (**Scheme 30**).[70]



Scheme 30

3.2 From other vinyl derivatives

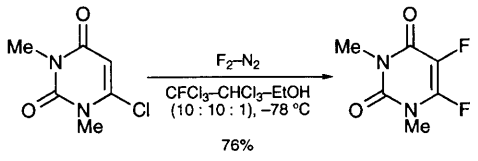
α-Haloenones are of increasing synthetic importance, largely due to their ready participation in palladium-catalysed cross-coupling reactions. Comins has determined efficient conditions for the α-halogenation of *N*-acyl-2,3-dihydro-4-pyridones, to form partners for cross-couplings with arylstannanes (**Scheme 31**).[71] A convenient method for the



a X = Br, 93%
b X = I, 90%

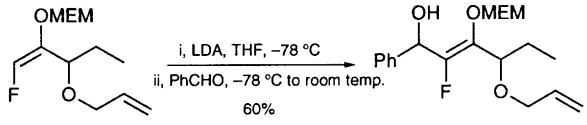
Scheme 31

generation of chlorine or bromine in acidic media involves mixing Oxone with sodium halides.[72] The resulting mixtures effect halogenation of cyclic enones if the intermediate dihalides are treated with mild base on work-up. The direct fluorination of β-chloroenones in Rozen's solvent followed by treatment with base allows access to α,β-difluoroenones, including fluorouracils, which are antitumour agents (**Scheme 32**).[73]



Scheme 32

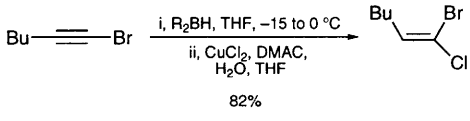
The alkylation of metallated vinyl fluorides is proving to be a popular method for the construction of functionalised fluoroalkenes. Percy has developed routes to both 1-lithio-2,2-difluoro enol ethers[74] (initially reported last year) and 2-fluoro-2-lithio enol ethers (**Scheme 33**).[75] Both types of organolithium react efficiently with a range of electrophiles (*e.g.* alkyl halides, halogens, carbon dioxide, carbonyl compounds). A similar range of electrophiles can be used to quench trifluorovinyllithium, prepared by treatment of 1,1,1,2-tetrafluoroethane with butyllithium.[76]



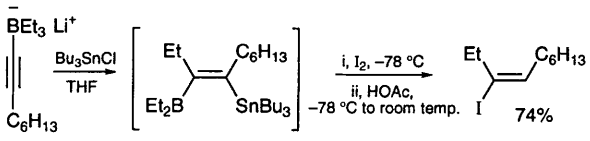
3 : 1 mixture of diastereomers

Scheme 33

Vinyl-boronates, -silanes and -stannanes are popular precursors to vinyl halides, since they can be prepared with very high stereochemical purity, which is often translated faithfully in the halogenation step. Petasis has studied the halogenation of vinylboronic acids of varying substitution patterns and stereochemistry, and identified the *N*-halosuccinimides (chloro-, bromo- and iodo-) as the reagents of choice.[77] Stereodefined 1,1-dihaloalkenes have been prepared by the regioselective hydroboration of haloalkynes, followed by cleavage of the resulting vinylborane with copper(II) halide salts (**Scheme 34**).[78] Alkynylboronate complexes rearrange on treatment with stannyl halides to give mixed vinyl stannane–boranes. Quenching of the more reactive C–B bond with iodine, followed by acidic destannylation provides an excellent, high-yielding route to stereochemically defined internal vinyl iodides (**Scheme 35**).[79] α-Fluorinated steroidal enones have been prepared from the corresponding stannylated enone using caesium fluoroxysulfate.[80]

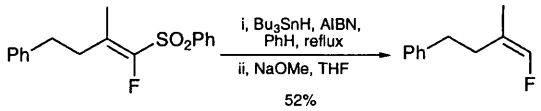


Scheme 34

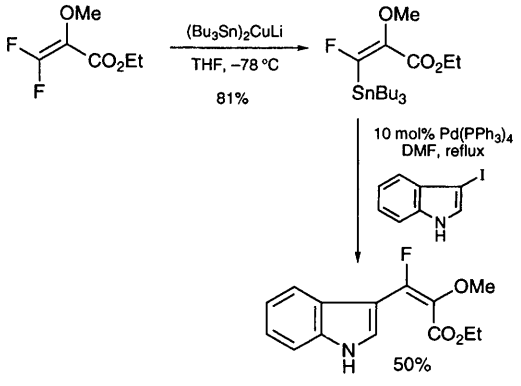


Scheme 35

A highly stereoselective synthesis of 1-fluoro-olefins has been reported based upon the two-step desulfonylation of readily available 1-fluoro-1-sulfonylalkenes (**Scheme 36**).[81] This process involves the protonolysis of an intermediate fluorinated vinyl stannane. Unsurprisingly, the potential of these compounds as partners in palladium-catalysed cross-couplings has been exploited in the preparation of polysubstituted fluoroolefins (**Scheme 37**).[82]

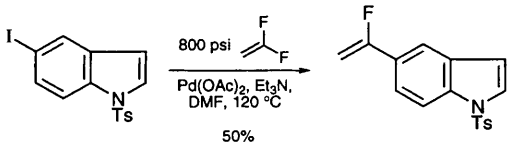


Scheme 36



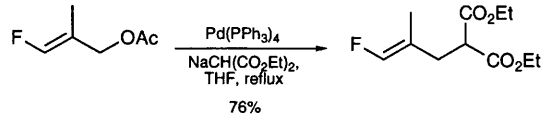
Scheme 37

1,1-Difluoroethene has been utilised as the olefinic partner in a Heck reaction with an iodoindole derivative (**Scheme 38**).[83] The regio-selectivity of the coupling is atypical, which allows the introduction of a monofluorovinyl unit by elimination of a fluoropalladium species, rather than the usual palladium hydride. Fluoroolefins bearing allylic acetates are substrates for the formation of



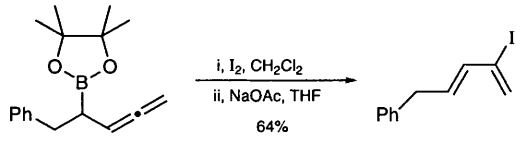
Scheme 38

fluorinated π-allyl palladium complexes, albeit at greatly reduced rates as compared to their non-fluorinated analogues. Nucleophiles such as malonate anions attack at the non-fluorinated terminus with good and often complete selectivity (**Scheme 39**).[84]



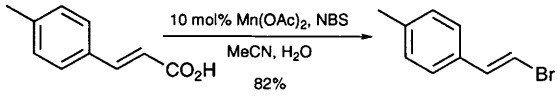
Scheme 39

2-Iodinated 1,3-dienes have been prepared from allenes bearing an allylic boronate group by simple exposure to iodine (**Scheme 40**).[85] The allenes themselves are prepared by reaction of Srebnik's mixed borane–zirconocenyl 1,1-bismetalloalkanes with prop-2-ynyl halides under copper catalysis.



Scheme 40

The brominative decarboxylation of α,β-unsaturated carboxylic acids fails under traditional Hunsdiecker conditions, and several imaginative solutions to this problem were reviewed last year. A further example this year involves the manganese(II) acetate-catalysed reaction of enoic acids with *N*-bromosuccinimide (**Scheme 41**).[86] At present the mechanism of this transformation is still unclear.

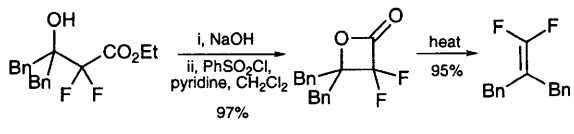


Scheme 41

3.3 By C=C bond formation

As in previous years, the lack of stereocontrol associated with the synthesis of monohaloalkenes by this method has severely limited its utility. Nevertheless, the ready availability of fluorinated phosphonates[87] or α-silyl esters[88] makes the route attractive in cases where control of olefin geometry is not vital.

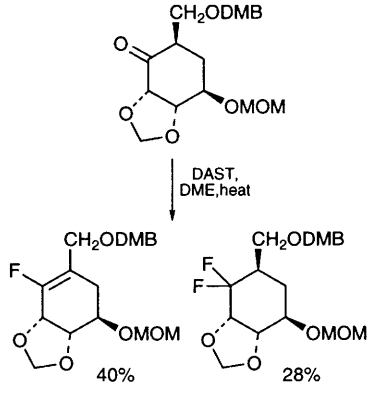
A new approach to 1,1-difluoroolefins is based upon the thermolytic extrusion of carbon dioxide from α,α-difluoro-β-lactones (**Scheme 42**).[89] The β-lactones themselves are prepared by the Reformatsky reaction of ethyl bromodifluoroacetate and carbonyl compounds.



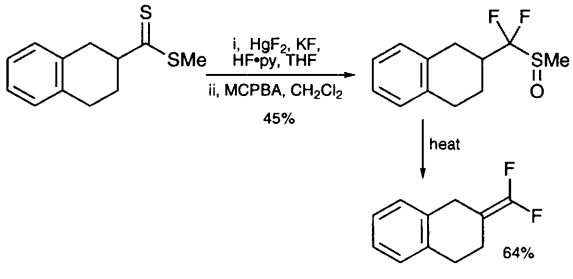
Scheme 42

3.4 By other methods

Treatment of β-keto sulfones with phosphorus pentachloride provides ready access to β-chlorovinyl sulfones.[90] Similarly, treatment of chalcone epoxides with Vilsmeier's salts furnishes β-chloroenones.[91] Vinyl fluorides are often formed as undesired by-products in the formation of 1,1-difluorides from ketones using DAST, but this reaction has been exploited in a synthesis of 2-fluoroshikimic acid (**Scheme 43**).[92] An effective route to 1,1-difluoroolefins from carboxylic acids has been reported, based upon their conversion to dithioesters and subsequent difluorination (**Scheme 44**).[93] Oxidation and pyrolytic elimination of sulfenic acid furnishes the olefin.

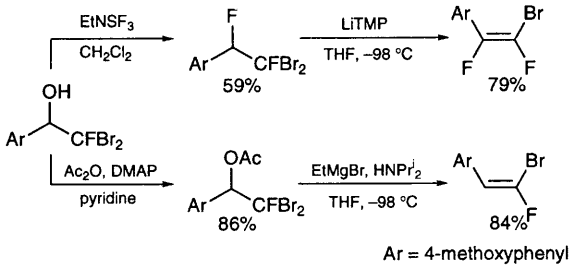


Scheme 43



Scheme 44

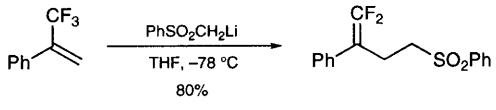
The synthesis of 1,1-difluoroalkenes by dechlorinative ring opening of 1-chlorodifluoromethyl-substituted epoxides, initially reported last year, has been extended to include 2,2-dialkyl derivatives.[94] 1-Bromo-1-fluoroalkenes and 1-bromo-1,2-difluoroalkenes are both available from 1-dibromofluoromethyl alcohols, depending



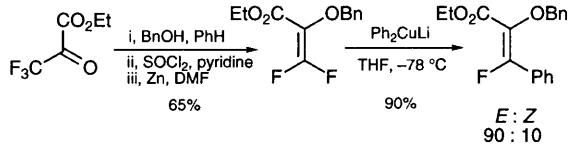
Scheme 45

upon the method of activation of the hydroxy group used before treatment with strong bases or Grignard reagents (**Scheme 45**).[95]

1,1-Difluoroalkenes have previously been prepared by the allylic displacement of fluoride from trifluoromethyl-substituted olefins by amide nucleophiles. This work has been extended to include organolithiums as the nucleophile (**Scheme 46**).[96,97] The order of addition of reagents (alkyllithium to olefin) is crucial to the attainment of clean reactions. Tetrasubstituted vinyl fluorides are available from β,β-difluoroenoates, readily prepared from ethyl trifluoropyruvate, by the displacement of one fluoride by cuprate reagents (**Scheme 47**).[98]



Scheme 46



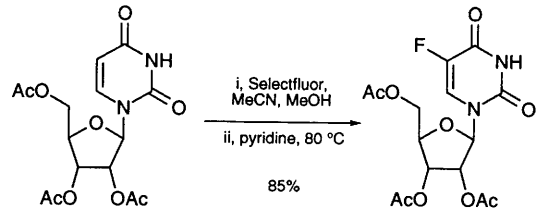
Scheme 47

4 Aryl halides

4.1 By electrophilic substitution

A comprehensive study of the conditions for the direct electrophilic fluorination of aromatic substrates has revealed that acidic media (98% H_2SO_4 or aqueous formic acid) give the highest yields.[99] Fluorinated pyrimidines can be prepared by treatment of the protected nucleoside with Selectfluor™ in methanolic media, followed by base-induced elimination of methanol (**Scheme 48**).[100]

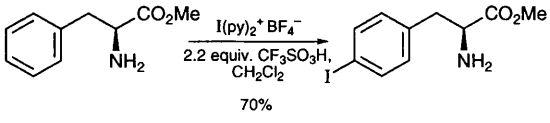
The increasing interest in ultrasound promoted reactions is reflected in improved methods for the formation of aryl halides. The chlorination of arenes by the acetyl chloride–manganese(III) acetate system was greatly accelerated by ultrasound,[101] while



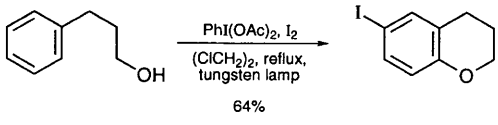
Scheme 48

N-bromosuccinimide in carbon tetrachloride gave high yields of aromatic bromination under sonication with no catalyst required.[102]

Bis(2,4,6-trimethylpyridine)iodonium hexafluorophosphate[103] and bis(pyridine)iodonium tetrafluoroborate[104] have both been demonstrated to be effective reagents for the iodination of electron rich aromatics such as phenols, phenolic ethers and anilines. The former reagent is notably effective in the iodination of anilines in comparison with other methods, while the latter reagent will also effect the iodination of less reactive arenes in the presence of trifluoromethanesulfonic acid as an activator (**Scheme 49**). An elegant approach to the synthesis of iodinated dihydrobenzopyrans involves oxidative cyclisation of 3-phenylpropan-1-ols with iodine and phenyl(iodosyl) acetate (**Scheme 50**).[105] Although the reaction shows some generality in terms of the substituents tolerated, it is only effective for the construction of six-membered rings.

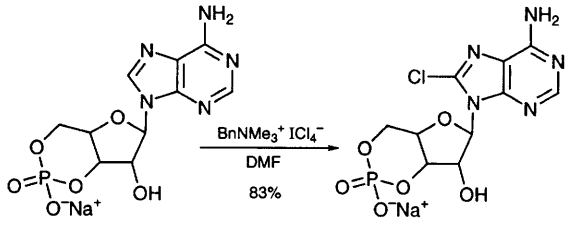


Scheme 49



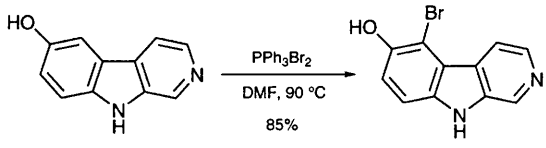
Scheme 50

Mercuric oxide[106] and lead tetraacetate[107] have both been used to activate iodine to effect the high yielding iodination of phenolic ethers. In the latter case, the active intermediate is assumed to be iodosyl acetate. Lead tetraacetate–tin(IV) chloride also effects the chlorination of phenolic ethers, possibly *via* the *in situ* generation of chlorine.[108] In these examples, no benzylic chlorination of alkyl substituents was observed. Iodine monochloride is normally an effective electrophilic iodinating agent, but its use as a chlorinating agent in reactions with alkoxy triphenylenes has been reported.[109] A single electron transfer mechanism is invoked to explain the unusual chemoselectivity. An industrial scale preparation of chlorinated adenosine phosphates as anticancer agents uses tetraalkylammonium tetrachloroiodides as the chlorinating agent (**Scheme 51**).[110]



Scheme 51

The use of acetonitrile as solvent dramatically increases the yields of bromination[111] and iodination[112] of electron rich benzenes and naphthalenes by the appropriate *N*-halosuccinimides, partly by shutting off benzylic halogenation pathways. The nature of the surfactant group in the aromatic bromination of dialkylanilines by tetraalkylammonium tribromide was shown to have a great effect on the *ortho*:*para* ratios of the products (*o*:*p* from 85:15 to 0:100).[113] Similarly, excellent regioselectivity in *para*-brominations using bromine were achieved by performing the reactions in the presence of a reusable zeolite.[114] Finally, the regioselective bromination of a β-carboline using bromine–triphenylphosphine was a key step in the synthesis of the anti-viral natural product eudistomin D (**Scheme 52**).[115]

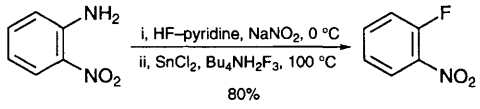


Scheme 52

4.2 By nucleophilic substitution

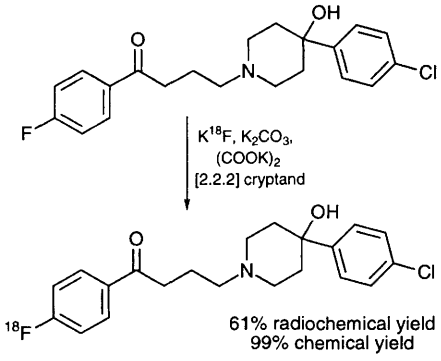
Anilines are useful starting materials for the synthesis of aromatic fluorides, since the readily derived diazonium salts undergo nucleophilic substitution by fluoride. A new reagent system for this reaction employs KHF_2–SiF_4 with *tert*-butyl nitrite as the diazotisation agent.[116] The addition of a mixture of stannous chloride and tetrabutylammonium hydrofluoride increased the yield of aryl fluorides from diazonium cleavage reactions performed in HF–pyridine (**Scheme 53**).[117]

The high yields and rapid reactions often associated with nucleophilic aromatic substitutions makes them attractive methods for the introduction of short half-life ^{18}F to tracer molecules for PET scanning. Fluoride–halogen exchange was studied as a possible route to ^{18}F labelled neuroleptic agents,



Scheme 53

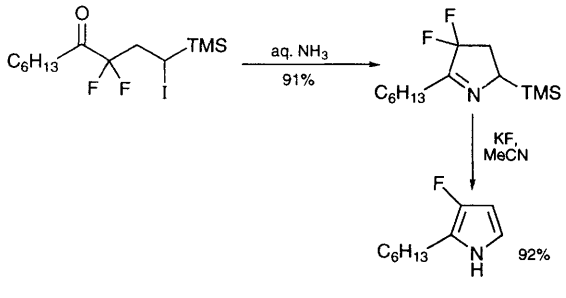
the highest yields being obtained with fluoride as the leaving group (**Scheme 54**).[118] Diaryliodonium salts were also shown to be effective substrates for nucleophilic displacement.[119] The use of an electron rich arene as one of the substituents facilitates a highly chemoselective attack by fluoride at the other ring.



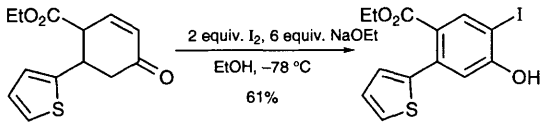
Scheme 54

4.3 By other methods

The electrochemical fluorination of purine bases reviewed last year has been further examined and extended to α,β-unsaturated hydrazones and *N*-acyl lactams, albeit in low yield.[120] Burton and co-workers have described a general synthesis of 3-fluorinated pyrroles, which makes use of a fluoride-promoted desilylation to effect aromatisation (**Scheme 55**).[121] Previous syntheses required electron withdrawing substituents on the ring to effect this step. Substituted 2-iodophenols are often difficult to prepare in good yield by iodination of phenols. An interesting *de novo* approach to these compounds involves the diiodination of ester-substituted cyclohexenones, followed by aromatisation through the elimination of HI (**Scheme 56**).[122]



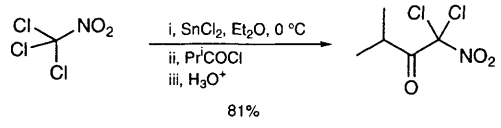
Scheme 55



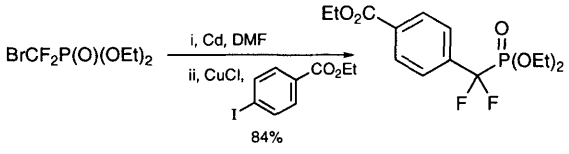
Scheme 56

5 1,1-Dihalo compounds

A common entry to this class of functionality involves the coupling of aldehydes or ketones with dihalomethyl anions. These species have been generated from trihalomethyl units by metal–halogen exchange with alkyllithiums (on fluorotribromomethane),[123] samarium(II) iodide (on bromodifluoroacetates)[124] or zinc metal (on bromodifluoromethylalkynes).[125] Dihaloalkyltin reagents, generated by the action of tin(II) chloride on trichloronitromethane, add smoothly to acid halides to give α,α-dichloroketones (**Scheme 57**).[126] Difluoroalkylcadmium reagents have been prepared by reaction of cadmium metal with bromodifluoromethylphosphonates, and shown to participate in copper-promoted cross-couplings with aryl halides (**Scheme 58**).[127]

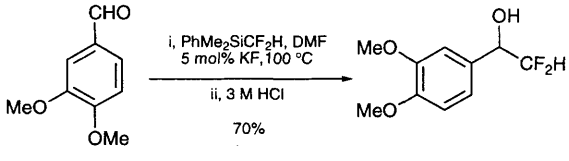


Scheme 57

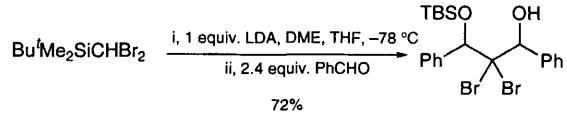


Scheme 58

A novel, non-basic approach to non-stabilised difluoromethyl anions involves the fluoride mediated desilylation of difluoromethylsilanes (**Scheme 59**).[128] Lithiated (dihalomethyl)silanes have been shown to act as 1,1-dihalodianion equivalents in reactions with aldehydes (**Scheme 60**).[129] This surprising outcome originates from the silyl group undergoing a 1,3-Brook rearrangement following



Scheme 59

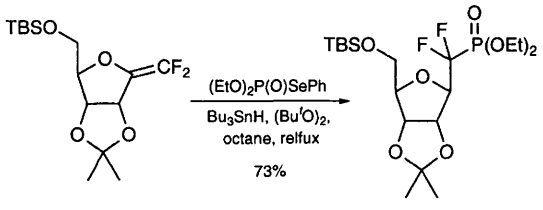


Scheme 60

initial addition to the aldehyde, generating a second alkyllithium species. If the reaction is performed in diethyl ether, the reaction can be halted after the first addition.

α,α-Difluoro-β-keto phosphonates have been prepared from lithiodifluoromethyl phosphonates either by transmetallation with cerium(III) chloride followed by addition to carboxylic esters,[130] or by addition to aldehydes followed by PDC oxidation of the resulting alcohol.[131] These units are valuable in their own right as mimics of phosphate esters, but in the second case the phosphonate groups were also hydrolytically cleaved to give unsubstituted difluoromethyl ketones. Treatment of difluoromethyl phosphonates with Lawesson's reagent allows access to novel fluorinated phosphonothionic acids, which may be deprotonated with strong base and quenched with electrophiles in the same manner as their oxygenated counterparts.[132]

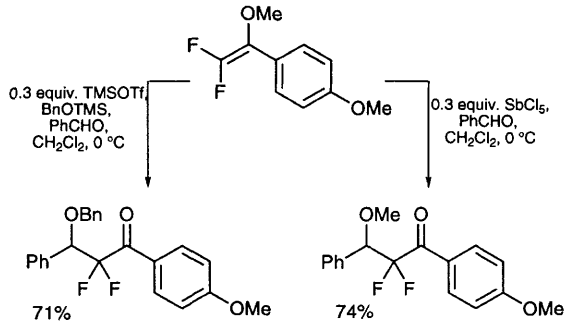
α,α-Difluorophosphonates have also been prepared from α-keto phosphonates by treatment with DAST,[133] and by the addition of phosphonyl radicals derived from dialkyl phosphonites to difluoroolefins.[134] Motherwell has developed an improved system for this latter transformation, based upon the use of (phenylseleno)phosphonates and tributyltin hydride (**Scheme 61**).[135]



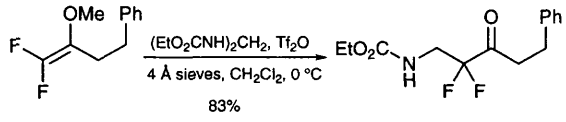
Scheme 61

Difluoroalkyl units have also been introduced *via* nucleophilic 1,1-difluorovinyl alkenes. Difluoroenol ethers have been shown to participate in aldol reactions in the presence of antimony pentachloride or trimethylsilyl trifluoromethanesulfonate (**Scheme 62**).[136] The use of a new, highly reactive iminium ion source allows the first participation of difluoroenol ethers in Mannich reactions (**Scheme 63**).[137] Fluorinated allylsilanes are also excellent nucleophilic olefins and add efficiently to aldehydes (**Scheme 64**).[138]

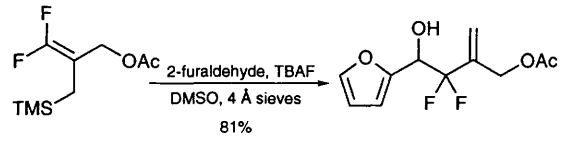
The [2+2] cycloaddition of dibromoketene to olefins provides useful access to dibromocarbonyl compounds.[139] The related condensation of dichloroketene with α-alkoxy and α-amino aldehydes



Scheme 62

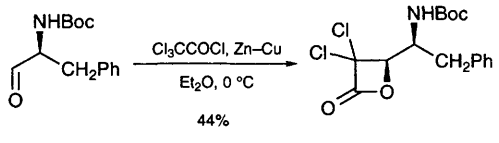


Scheme 63

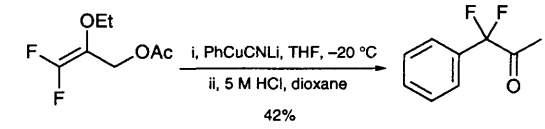


Scheme 64

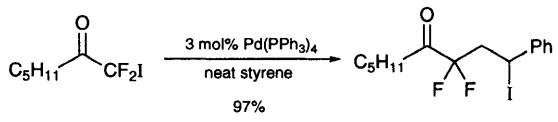
has been shown to proceed with excellent levels of stereoselectivity, according to the Felkin–Anh chelate model (**Scheme 65**).[140] Novel approaches to α,α-difluoro ketones appearing this year include the S_N2' reaction of cuprates with fluorinated allylic acetates (**Scheme 66**)[141] and the palladium mediated addition of iododifluoromethyl ketones to olefins (**Scheme 67**).[142] This latter reaction has been shown to proceed *via* a radical mechanism. Difluoromethylene radicals can also be generated electrochemically from dibromodifluoromethane if a single electron transfer reagent such as diphenyl diselenide is added to inhibit carbene formation (**Scheme**



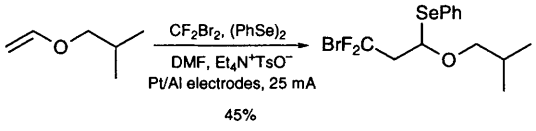
Scheme 65



Scheme 66



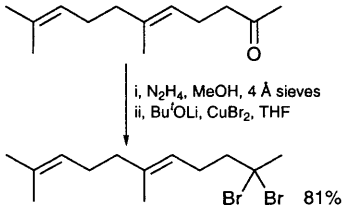
Scheme 67



Scheme 68

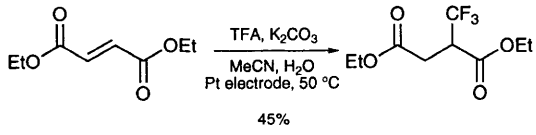
68).[143] Difluorocyclopropanes bearing electron withdrawing substituents are difficult to prepare, since difluorocarbene reacts only sluggishly with electron poor olefins. They can, however, be prepared indirectly by nucleophilic substitution of the corresponding dichlorocyclopropanes using TBAF or potassium fluoride.[144]

Diaryldichloromethanes were the unexpected product of an attempted Friedel–Crafts alkylation using trifluoromethylarenes and aluminium trichloride, presumably *via* preliminary transhalogenation to trichloromethylarenes.[145] The α,α-dichlorination of cyclic imines with *N*-chlorosuccinimide is a key step in a new synthesis of pyridines.[146] The transformation of ketones to dibromides can be performed by initial conversion to the hydrazone derivative, which is then exposed to lithium *tert*-butoxide and copper(II) bromide (**Scheme 69**).[147] This reaction, which presumably proceeds *via* a diazoalkane, is more general than previously reported methods using bromine.



Scheme 69

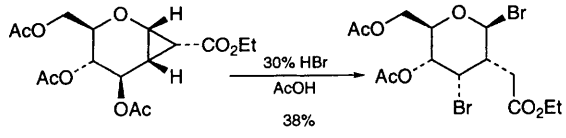
The ready availability of difluoroolefin units bearing allylic hydroxy groups makes them attractive starting points for difluoromethylene synthesis by rearrangements involving allylic transposition. Examples appearing this year include halogenation with thionyl halides,[148] Claisen rearrangements[149,150] and [2,3] Wittig rearrangements.[151] Finally, an electrochemical method for the generation of trifluoromethyl radicals from trifluoroacetic acid has been developed.[152] These radicals add competently to electron poor olefins such as fumarate esters (**Scheme 70**).



Scheme 70

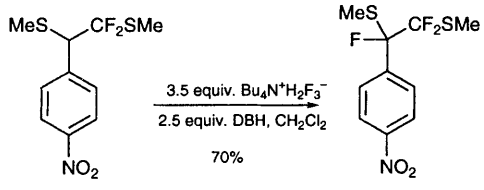
6 1,1-Halohydrins and related compounds

As in previous years, the synthesis of anomeric halides will not be reviewed in detail for reasons of brevity. Three unusual examples appearing this year, however, include the homo-Michael addition of bromide to a glucal-derived cyclopropyl carboxylate (**Scheme 71**),[153] the exchange of anomeric sulfides or selenides for fluorine using *p*-tolyliodonium difluoride,[154] and the synthesis of 4′-fluoroadenosine by treatment of an *exo*-glycal with silver fluoride and iodine.[155]



Scheme 71

α-Fluoro sulfides may be prepared from the corresponding sulfides by the fluoro-Pummerer reaction (**Scheme 72**).[156] α-Sulfenyl acetates can also be α-fluorinated by anodic oxidation in the presence of fluoride electrolytes.[157] Modest asymmetric induction is possible if chiral acetates are used.[158] α-Fluoro sulfones are available by direct fluorination of sulfoxides, the reaction presumably proceeding by formation of sulfur(IV) difluoride intermediates.[159,160]

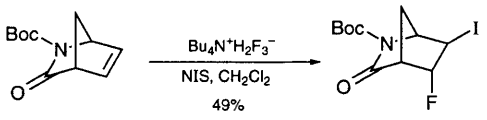


Scheme 72

7 1,2-Dihalo compounds

The dibromination of chalcone derivatives with tetrabutylammonium tribromide has been studied in various solvents.[161] Ultrasonication of the mixture was shown to have a beneficial effect on both the yield and rate of reaction. Potassium dichloroiodate(I) has been introduced as an excellent reagent for the iodochlorination of alkenes in aqueous media.[162] The iodofluorination of alkenes

has been achieved using *N*-iodosuccinimide in the presence of triethylamine tris(hydrogen fluoride),[163] 1 M hydrogen fluoride–TBAF[164] or tetrabutylammonium dihydrogen trifluoride[165] as the nucleophilic fluoride source. The latter system was used in the synthesis of intermediates for the preparation of fluorinated carbocyclic nucleosides (**Scheme 73**).

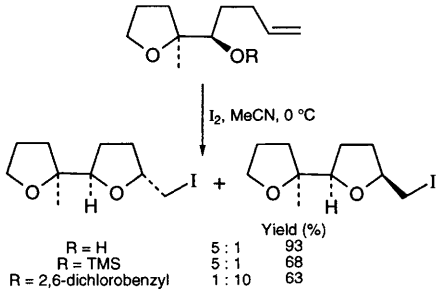


Scheme 73

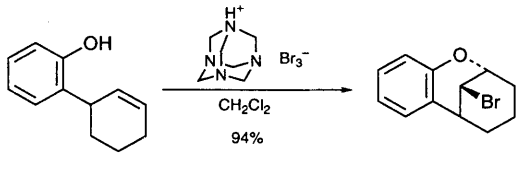
8 1,2-Halohydrins and related compounds

8.1 By addition to alkenes

A study of the stereo- and regio-chemistry of the reaction of substituted styrenes with Selectfluor™ and alcohols has been published.[166] However, the majority of 1,2-halohydrin syntheses from alkenes involve electrophilic halocyclisations. Iodoetherification reactions have been used to prepare bicyclic trisubstituted tetrahydrofurans[167] and 2-substituted-3-amino tetrahydrofurans.[168] An interesting and synthetically useful inversion of stereoselectivity in the preparation of 2,5-linked tetrahydrofurans *via* iodoetherifications occurs with an increase in bulk of the substituent on the nucleophilic oxygen (**Scheme 74**).[169] The participation of phenols in intramolecular bromoetherifications has been studied in detail, and hexamethylenetetramine hydrotribromide identified as the reagent of choice to minimise competing phenolic ring bromination (**Scheme 75**).[170,171]

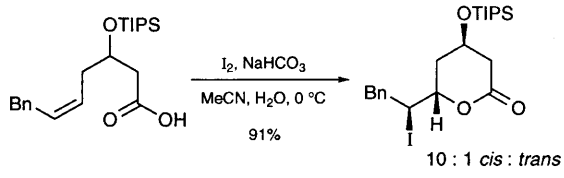


Scheme 74



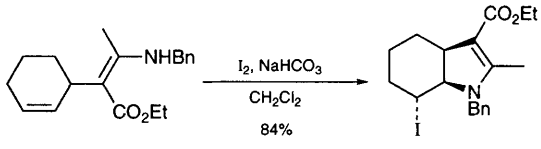
Scheme 75

Copper(II) bromide on alumina has been introduced as an effective new agent for bromolactonisation.[172] Examples of iodolactonisation reactions in synthesis this year include the further functionalisation of α-allyl-α-substituted amino acids, prepared *via* Claisen rearrangements,[173] and an examination of the stereochemistry of cyclisation of 3-silyloxyalk-5-enoic acids (**Scheme 76**).[174] In the latter examples, the unusual preference for the formation of a 1,3-*trans* substitution pattern is explained by hydrogen bonding between the acid and the siloxy group, which forces the latter group into a pseudo-axial position during the cyclisation.

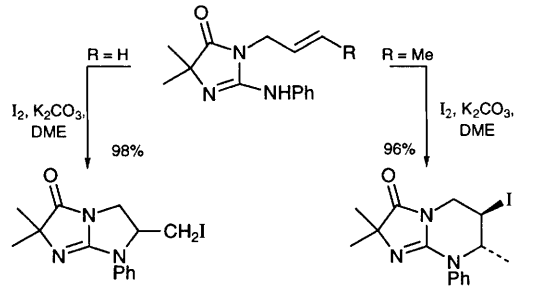


Scheme 76

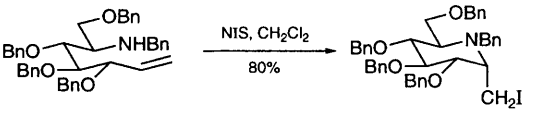
Nitrogen heterocycles are also readily available by halocyclisation protocols. Cyclic β-enamino esters have been prepared by 5-*exo* iodocyclisations (**Scheme 77**),[175] while pyrrolidines have been prepared by the 5-*endo* cyclisations of allylic sulfonamides.[176] The regiochemistry of cyclisation of 3-allyl-2-aminoimidazolin-4-ones was observed to be dependent on the level of substitution on the olefin undergoing attack, allowing access to fused 5,5- and 5,6-ring systems (**Scheme 78**).[177] Aza-*C*-glycosides are conveniently prepared by 6-*exo* halocyclisations of sugar derived ω-aminoalkenes (**Scheme 79**).[178]



Scheme 77

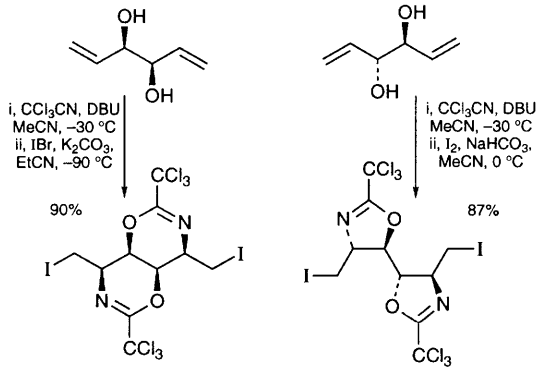


Scheme 78



Scheme 79

Cyclisations of allylic and homoallylic trichloracetimidates are useful approaches to amino alcohols. Kang has studied issues of regioselectivity in the cyclisations of alkenes bearing both allylic and homoallylic substituents, and found that the relative stereochemistry of the two groups governed which functionality reacted. Thus, six-membered rings were formed by the preferential reaction of the homoallylic acetimidate in *erythro*-diol derived systems,[179] whereas *threo*-derived systems gave five-membered rings through reaction of the allylic acetimidate (**Scheme 80**).[180] These double iodoaminations were useful in the preparation of potential inhibitors of HIV protease.



Scheme 80

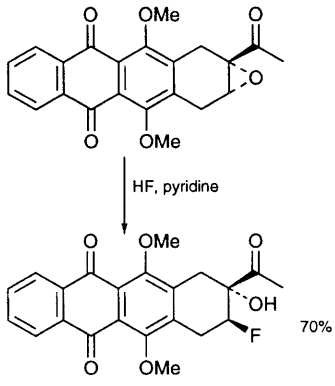
8.2 By epoxide opening

The key issue in the synthesis of halohydrins from epoxides is of course the regioselectivity of the ring opening. Further work on the synthesis of β-bromo-α-hydroxycarboxylic esters by reaction of the corresponding epoxides with magnesium bromide has appeared.[181] The reverse regiochemical outcome (*i.e.* attack of halide at the α-position) may be obtained by employing sodium halides and Amberlyst 15 in acetone at low temperatures.[182] The use of magnesium halides adsorbed on silica gel to open various epoxides gives excellent selectivity for attack at the least hindered end, except in the case of activated systems such as styrene oxides.[183]

A variety of halogenated sugars have been prepared by ring opening of 2,3-epoxy-1,6-anhydrogalactose derivatives.[184] Olah's reagent proved to be of use in the synthesis of A-ring fluorinated anthracyclines (**Scheme 81**).[185]

8.3 By other methods

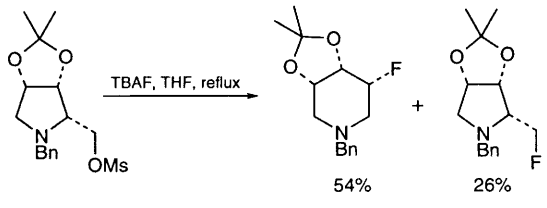
One of the most reliable methods for the stereo- and regio-specific synthesis of 1,2-halohydrins and their amino analogues is the nucleophilic displacement of activated hydroxy groups from 1,2-diols or amino alcohols. This strategy is particularly widely used in the area of sugar chemistry. Examples of the displacement of hydroxy groups by DAST include syntheses of 3-fluoroaspartic acid,[186] 2-fluoro-



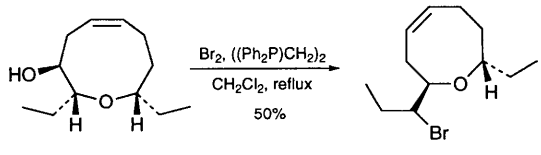
Scheme 81

6-aminodeoxynojiromycin[187] and 4-deoxy-4-fluoro-*myo*-inositol, the latter reaction proceeding with retention of configuration due to neighbouring group participation.[188] An alternative to the expensive '*in situ*' activating agents such as DAST is to pre-activate the hydroxy group, *e.g.* as an imidazolyl sulfonate, then displace with a fluoride source. This has been achieved in the synthesis of 2-deoxy-2-fluoroarabinose units from ribose for the preparation of anti-hepatitis agents, using triethylamine tris(hydrogen fluoride)[189] or potassium hydrogen difluoride[190] as the fluoride source.

Fluorinated piperidines can be synthesised by ring expansion of activated 2-(hydroxymethyl)pyrrolidines, through intermediate aziridinium ions (**Scheme 82**).[191] A similar rearrangement involving a bridged oxonium ion was seen in the attempted bromination of a hydroxy group in a projected laurenan synthesis, using bromine–1,2-(diphenylphosphino)ethane (**Scheme 83**).[192] In this case, the major product of the reaction was the ring contracted 3,4,7,8-tetrahydro-2*H*-oxocine, accompanied by the small amounts of the epimeric brominated 1,2,3,6,7,8-hexahydrooxonines.

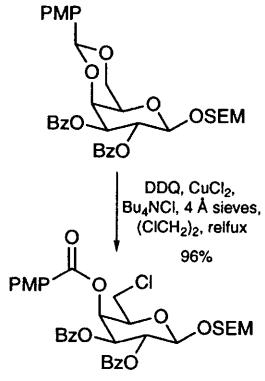


Scheme 82

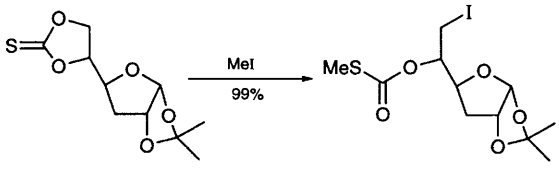


Scheme 83

The Hanessian oxidative ring opening of benzylidenes with *N*-halosuccinimides has found application in the regioselective synthesis of 3-benzoyloxy-4-bromohexahydroazepines[193] and 3-chloroshikimic acid.[194] Employing 4-methoxybenzylidenes allows the use of alternative conditions, with DDQ as the oxidant and halide salts as the nucleophilic trap (**Scheme 84**).[195] An alternative method for the conversion of diols to protected iodohydrins involves the activation of cyclic thiocarbonates with alkyl halides, the displaced halide acting as a competent nucleophile to attack the thionium cation at the least hindered site (**Scheme 85**).[196]



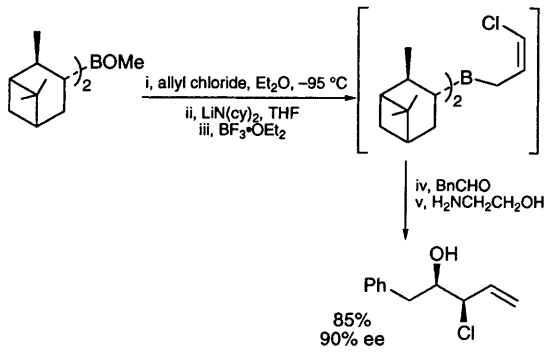
Scheme 84



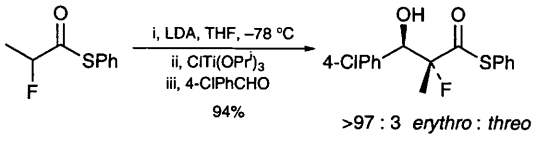
Scheme 85

The generation of halogenated nucleophiles capable of attacking carbonyl compounds is another fruitful area for the synthesis of halohydrins. Organoindium species generated from 1,1-dichloroprop-2-ene give predominantly *syn*-chlorohydrins on reaction with aldehydes.[197] The preparation of chiral chlorinated allylboranes provides a useful asymmetric approach to *syn*-chlorohydrins (**Scheme 86**).[198]

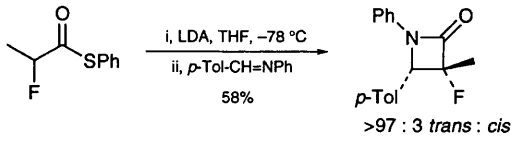
α-Bromoenolates may be generated from α,α-dibromo ketones by debromination with phenylmagnesium bromide. These enolates add to aldehydes to give a stereorandom mixture of bromohydrins.[199] *erythro*-Selective aldol reactions of lithium and titanium enolates of α-fluoropropanethiolates have been reported, the latter species exhibiting slightly higher selectivity (**Scheme 87**).[200] The lithium enolates have also been used to attack imines, with subsequent displacement of thiolate by the amide anion, giving fluorinated β-lactams with excellent degrees of stereocontrol (**Scheme 88**).[201] Finally,



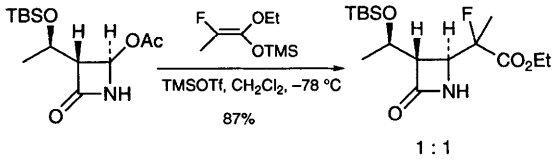
Scheme 86



Scheme 87



Scheme 88



Scheme 89

fluorinated ketene acetals react with cyclic iminium ions, allowing access to fluorinated carbapenems (**Scheme 89**).[202]

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