Organic halides

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REVIEW PERKIN 1

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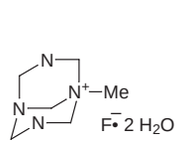
1 Introduction

This article continues a series of annual reviews on the synthesis of organic halides previously published in *Contemporary Organic Synthesis*. In common with previous reviews,[1–4] the aim is to present novel or topical methods for the synthesis of organic halides. In this respect, particular emphasis has been placed on techniques which present advantages over existing methods, either in terms of yield or selectivity, and those which may be adopted by synthetic chemists. The format from previous years has been retained in order to maintain consistency between the reviews. Organic halides continue to play a key role as intermediates in synthesis, and as important compounds in their own right. In particular, organofluorine compounds are seeing increasing use in the pharmaceutical industry due to the unique electronic nature of the fluorine atom. This has prompted an extra section to be added to the review this year. In line with previous articles, the chemistry of hypervalent iodine and long chain perfluoroalkanes will not be assessed. However, due to their increasing importance, the final section will deal with methods for the construction of compounds containing the trifluoromethyl (CF_3) group. While this will by no means be exhaustive, novel and useful techniques for placing the CF_3 group at strategic points in organic structures will be highlighted.

The importance of organofluorine compounds is perhaps best reflected by the fact that *Chemical Reviews* set aside an entire issue for fluorine chemistry last year.[5] Several new fluorinating agents have been reported this year. 1-Methylhexamethylenetetramine fluoride **1** has been shown to be a source of naked fluoride ions,[6] while a user-friendly class of site-selective reagents are the 1-alkyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane salts **2**.[7] 4-Dimethylamino-1-trifluoroacetylpyridinium trifluoroacetate **3** has been reported as a stable and easy to handle reagent for the trifluoromethylation of both aromatic rings[8] and 1,3-dicarbonyl compounds.[9] Harwood *et al*. have shown that the morpholine equivalent of DAST (diethylaminosulfur trifluoride) **4** can produce different selectivity and yields from the more established reagent.[10] Katritzky *et al*. have introduced 2-bromo-3,3,3-trifluoropropene **5** as a trifluoromethylacetylene anion synthon.[11]



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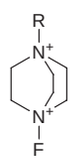

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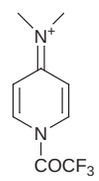

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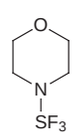

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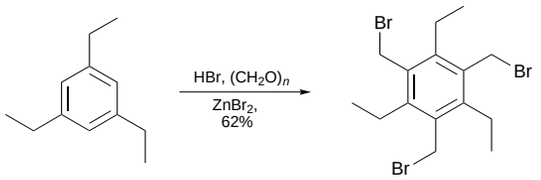
2 Alkyl halides

2.1 By halogenation of alkanes

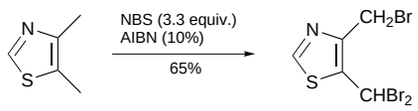
Halogenation of alkanes continues to be an area of interest with several new or improved methods being reported. Shaw *et al*. have found that free radical addition of bromine to organic compounds can be induced in water under photolytic conditions.[12] Activation through the use of high temperatures has allowed the bromination of decalin and some of its derivatives.[13] The action of hydrobromic acid and formaldehyde on triethylbenzene has produced the novel 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene, a potentially useful precursor for the assembly of dendrimers[14] (**Scheme 1**). Benzylic bromination is well known and by using a lanthanide reagent, the reaction can be carried out in heptane to produce a reasonable yield of 2-bromomethylnaphthalene.[15] This avoids the use of carbon tetrachloride, the solvent used for the analogous NBS bromination. A quick and easy route to tribromo derivatives of thiazoles has been reported[16] (**Scheme 2**). Reaction with NBS produced the desired compound in a reasonable 65% yield. While exploring the chemistry of bicyclo[3.3.1]nonanes, Srikishna *et al*. reported a site selective allylic bromination with NBS[17] (**Scheme 3**). 1,2,4-Trioxanes and trioxepanes have been synthesised by the NBS mediated intramolecular cyclisation of unsaturated hydroperoxy acetals.[18] The direct fluorination of β-keto esters using iodotoluene difluoride in an HF–pyridine solvent has been reported,[19] as has the regioselective synthesis of 19-fluorovitamin D.[20] An interesting enantioselective synthesis of (α-chloroalkyl)boronates has been achieved[21] (**Scheme 4**). By using a chiral ligand, differentiation of the prochiral chlorides was possible.

2.2 By halogenation of alkenes

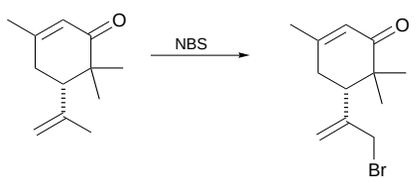
Use of a hydroxymethylene group both to activate and direct the α-fluorination of carbonyl compounds has been reported[22] (**Scheme 5**). Using elemental fluorine at low temperatures, this presents an alternative to direct fluorination of 1,3-dicarbonyl



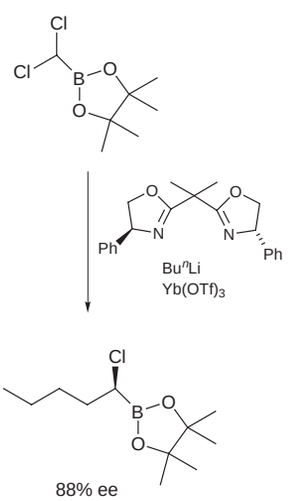
Scheme 1



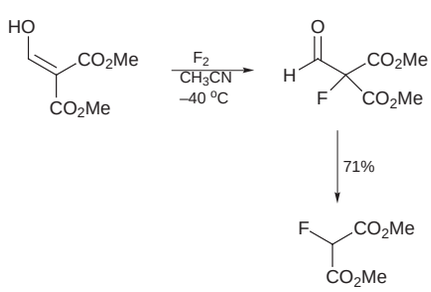
Scheme 2



Scheme 3



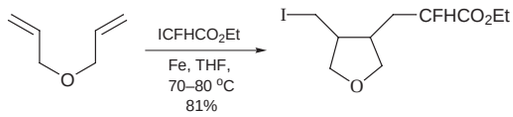
Scheme 4



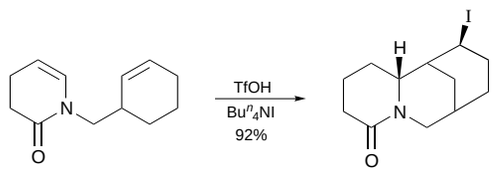
Scheme 5

systems. An asymmetric addition of HBr *via* a radical mechanism has been used during a stereoselective synthesis of (2*S*,3*S*)-hydroxyvaline.[23]

In an elegant approach towards the propellane systems, Dave *et al*. have utilised the bromination of exocyclic dienes in diazabicyclo[3.3.0]octane moieties.[24] Bromination of norbornadiene under high temperature conditions has been reported.[25] A novel preparation of α-fluoro functionalised esters from fluoroiodoacetates has been shown to occur on reaction with diallyl ether. The resultant cyclisation produces 3,4-disubstituted tetrahydrofuran systems[26] (**Scheme 6**). Overman has reported a strategy for the construction of the aloperine ring system by reaction of an unsaturated lactam with triflic acid and tetrabutylammonium iodide[27] (**Scheme 7**). The halogenation of 1-trifluoromethyl enamines has been used in the synthesis of α-halo trifluoromethyl ketones.[28]



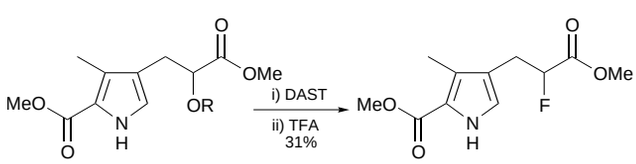
Scheme 6



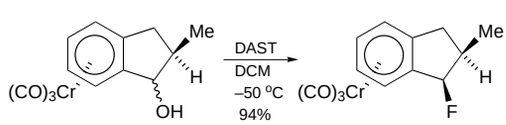
Scheme 7

2.3 By nucleophilic substitution

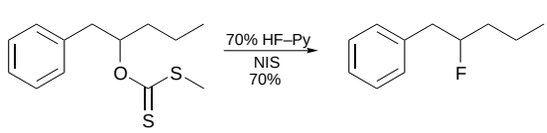
The use of DAST to activate alcohols and related functionalities towards fluoride displacement has continued this year. Relevant examples include the synthesis of an allylic fluoride, en route to 19-fluororetinol,[29] and during the preparation of the first fluorinated bilirubin[30] (**Scheme 8**). An interesting article has shown that enantiomerically enriched benzylic fluorides can be obtained using the chromium tricarbonyl group to block one face[31] (**Scheme 9**). The stereochemistry of the alcohol group did not affect the course of the reaction. Along similar lines, an oxidative desulfurisation–fluorination of alkyl dithiocarbonates has been reported[32] (**Scheme 10**).



Scheme 8

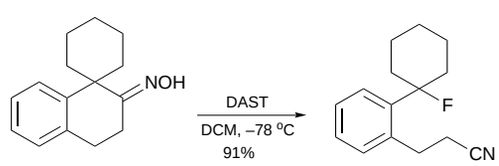


Scheme 9



Scheme 10

Fluorinated nitriles have been prepared by cleavage of cyclic ketoimines with DAST[33] (**Scheme 11**). Routes towards α-fluorophosphonates have appeared which use the phosphonate as an efficient nucleophile capable of attacking alkyl iodides[34] or prop-2-ynylic ketones.[35]



Scheme 11

The catalytic decomposition of alkyl chloroformates by hexaguanidinium chloride has been shown to proceed through an S_N2 type mechanism.[36]

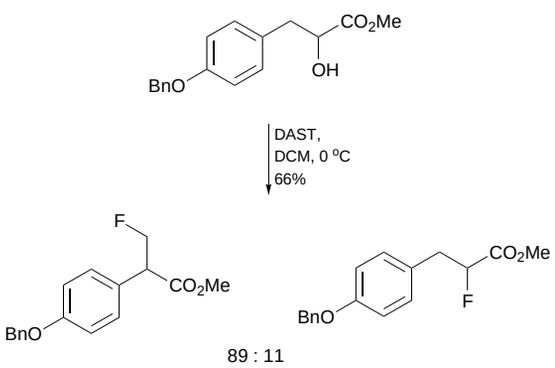
Using microwave irradiation, efficient preparation of benzylic bromides has been achieved without solvent using sodium bromide and doped K-10 clay.[37] The synthesis of α-halogeno phosphonates has been accomplished using thionyl chloride or bromide to produce the chloride and bromides respectively. The iodide species were obtained by using phosphorus(III) iodide with a catalytic amount of triethylamine.[38] The synthesis of 1-chloroalkylphosphinates has also been achieved.[39]

2.4 By other methods

Several structurally interesting fluoro compounds have been reported this year.

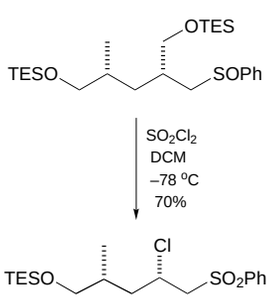
Atropisomeric fluorohexadienones have been synthesised by *ipso*-fluorination of tetrahydrobinaphthol derivatives.[40] A fluorinated analogue of 1-aminocyclopropanecarboxylic acid has been prepared by Sloan and Kirk,[41] and the synthesis of fluorinated nucleoside analogues has been reported.[42]

Following the use of DAST to replace hydroxy functionalities as described above, an unexpected product was observed[43] (**Scheme 12**).

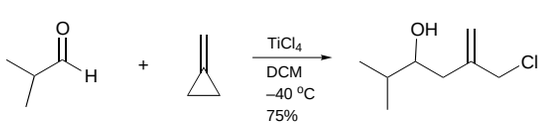


Scheme 12

Oddon and Uguen have accomplished a silyl-Durst chlorination of hydroxy sulfoxides[44] (**Scheme 13**). The titanium tetrachloride promoted addition of methylenecyclopropanes to aldehydes and ketones has produced an interesting route to allyl chlorides[45] (**Scheme 14**). By opening α,α-dicyano epoxides with methylamine hydrochloride, a simple and general route for α-chloroamides has been achieved.[46]



Scheme 13

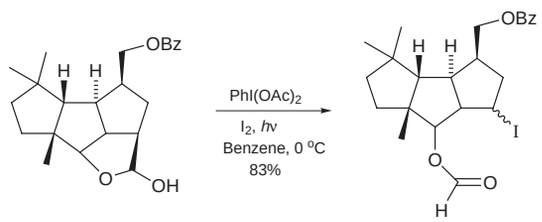


Scheme 14

An unexpected rearrangement reaction has been noted during the halogenation of a bicyclic ketone with boron tribromide[47] (**Scheme 15**).

Scheme 15

The ceric ammonium nitrate mediated iodination of ketones has been reported.[48] 1,5-Hydrogen atom transfer reactions have been used to explain the radical rearrangement of α-iodoalkyl phenyl sulfones.[49] Tanaka and Ogasawara have reported an oxidation–iodination of a lactol on the way towards (−)-capnellene[50] (**Scheme 16**). Finally, use of sodium iodide and mCPBA to create an α-iodo carbonyl group was used in the synthesis of (−)-dendrobine.[51]

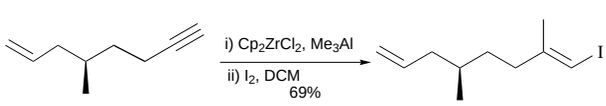


Scheme 16

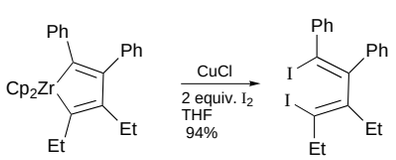
3 Vinyl halides

3.1 From alkynes

The strategy of addition of organometallic/metalloid reagents across a triple bond, followed by quenching of the reactive intermediate with a halogen electrophile continues to be an important method of accessing vinylic halides. The hydrozirconation of an enyne followed by iodine quench gave rise to a vinyl iodide, which was further utilised in the synthesis of (+)-curacin A[52] (**Scheme 17**). Also, difunctionalisation of a zirconacycle intermediate, produced from the coupling of two alkynes, has allowed the production of a 1,4-diiododiene[53] (**Scheme 18**). Liu and Negishi have produced a route to cyclobutenes through cyclisation of 4-iodoalk-1-yne derivatives with zirconocene dichloride.[54] Ma *et al*. also report an aluminium mediated addition across an alkyne, quenching of which produced an iodosubstituted homoallylic alcohol.[55]



Scheme 17

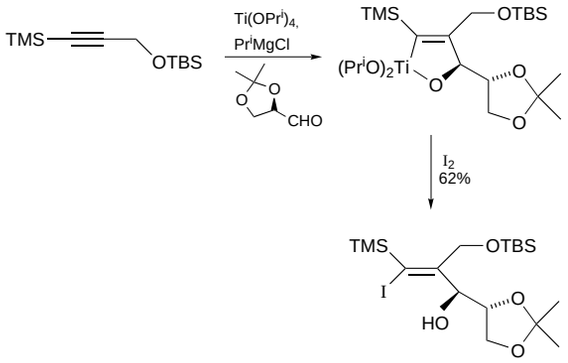


Scheme 18

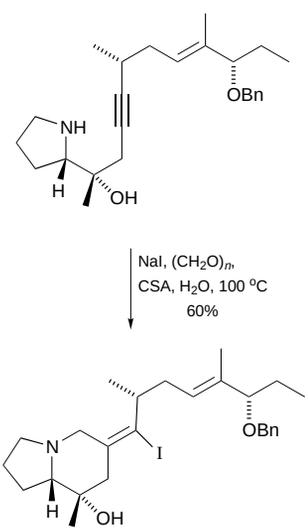
Sato *et al*. have reported a highly diastereoselective route to heavily functionalised iodoalkenes through his elegant titanium mediated coupling reaction[56] (**Scheme 19**). Using optically pure glyceraldehyde, excellent control can be achieved to produce a good yield of the olefin.

Overman *et al*. have shown an exciting variation of addition across alkynes[57] (**Scheme 20**). In the synthesis of pumilotoxins A and B, they used an iodide promoted iminium ion–alkyne cyclisation to construct the alkaloid framework.

A radical based 5-*exo*-*dig* cyclisation allowed the preparation of haloalkylidene cyclopentanones in good yields with high stereoselectivity.[58] Caddick and co-workers have shown that

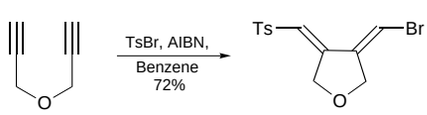


Scheme 19

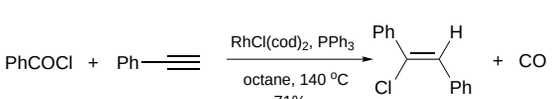


Scheme 20

bromodienes can be made efficiently by a radical cyclisation of diynes[59] (**Scheme 21**). An interesting rhodium catalysed coupling of aroyl chlorides with alkynes gave chlorostilbenes with loss of carbon monoxide[60] (**Scheme 22**).



Scheme 21

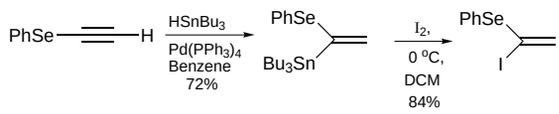


Scheme 22

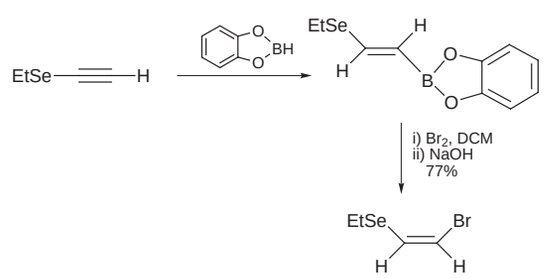
3.2 From other vinyl derivatives

In a similar vein to that outlined above, boron and tin reagents have been utilised to provide access to vinyl halide species. However in these cases the intermediates can be isolated. Vinylic iodides have been synthesised from the corresponding stannanes, these being derived from the bromoalkyne derivatives.[61] As part of a strategy to synthesise (−)-haliclonadiamine, Taber and Wang converted a vinylstannane to the iodide in good yield.[62] Two approaches to haloselenylalkenes have been reported. Hydrostannylation of an arylselenoethyne, followed by reaction with iodine gave a 1,1-substituted product[63] (**Scheme 23**), whereas reaction with catecholborane, followed by bromine provided access to 1,2-substituted derivatives[64] (**Scheme 24**).

1,2-Difluoroethenyl stannanes have been produced from the corresponding silicon species in a stereospecific fashion.[65]

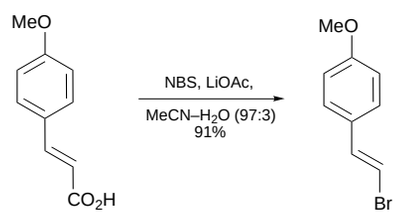


Scheme 23



Scheme 24

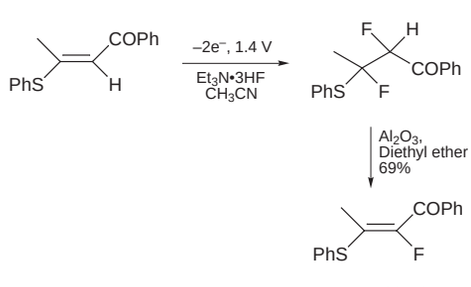
Reaction of vinylsilanes with NIS gave good yields of the corresponding vinyl iodides, again with retention of stereochemistry.[66] Kim *et al*. have reported that β-nitro olefins can be chlorinated in good yield by reaction with HCl in DMF in the presence of Oxone.[67] A catalytic version of the Hunsdiecker reaction has been used to synthesise β-halostyrenes[68] (**Scheme 25**).



Scheme 25

3.3 By C=C bond formation

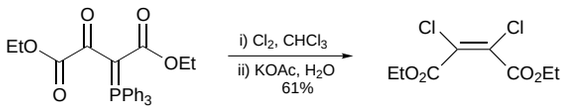
Long chain fluoroalkenoic esters have been synthesised by reaction of the alkenoic esters with NBS in the presence of HF, followed by elimination of HBr to regain the double bond.[69] These were then converted to fluoroalkenoic acids which have been shown to possess antifungal activity. Anodic fluoridation of α,β-unsaturated ketones followed by elimination of HF on alumina gave rise to fluoroalkenes, although the stereochemistry of the double bond was not controlled[70] (**Scheme 26**). Fluorinated retinols have been made by a Wittig reaction on a fluoro substituted aldehyde.[71]



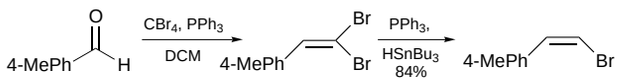
Scheme 26

1,2-Dichloroalkenes were prepared by reaction of a phosphoranylidene butanedioate with chlorine. Extrusion of triphenylphosphine oxide gave the desired 2,3-dichlorobutenedioates in reasonable yield[72] (**Scheme 27**). A Wadsworth–Emmons type reaction has been used to provide a convenient route to aryl substituted chloro- and bromo-olefins.[73] The yield of the chloride was significantly greater than that for the bromo derivative and the authors note that the principal advantage of the method is the lack of formation of acetylenes. A general

route for synthesis of geometrically pure bromoalkenes has been reported[74] (**Scheme 28**). Dibromoolefination of an aldehyde followed by reduction of the trans bromide proceeded with excellent selectivity, and in moderate to excellent yield.



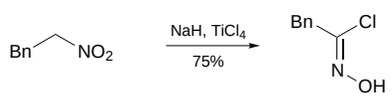
Scheme 27



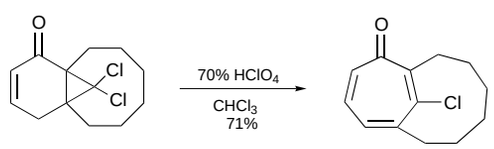
Scheme 28

3.4 By other methods

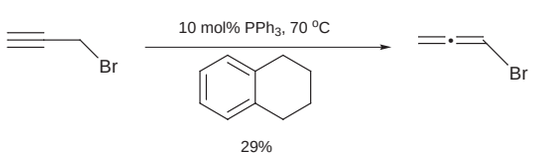
A new synthetic route to 6,7-dichloro-5,8-quinoxalinedione has been reported.[75] The unexpected reaction of tertiary enaminones with benzyltrimethylammonium dichloroiodate has introduced a new α-chlorination method for these compounds. The usual products are those derived by iodination.[76] Using nitroalkenes as a starting material, Kumaran and Kulharni have achieved a route to hydroxyiminoyl chlorides by reaction with titanium chloride[77] (**Scheme 29**). An unusual troponophane has been characterised after reaction of a dichlorocyclopropane with perchloric acid[78] (**Scheme 30**). Isomerisation of 3-bromoprop-2-yne with a catalytic amount of triphenylphosphine has resulted in the production of an allene derivative albeit in modest yield[79] (**Scheme 31**).



Scheme 29



Scheme 30

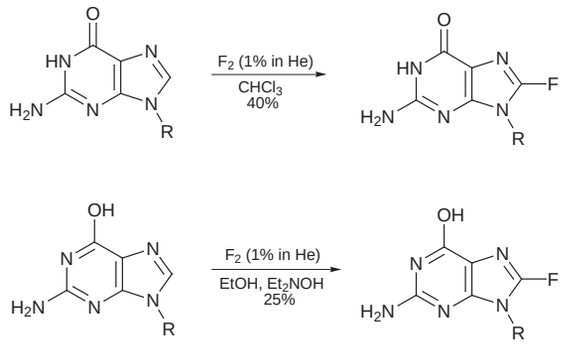


Scheme 31

4 Aryl halides

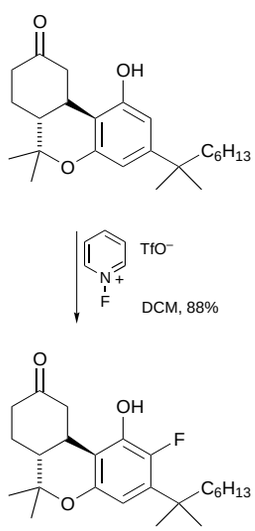
The use of fluorine substituents to alter the electronic properties of aromatic compounds continues to be of importance in the pharmaceutical industry. With this in mind, methods for the placement of fluorine onto aromatic rings are of importance. Bois-Choussy[80] and co-workers have used enzymatic resolution to access fluoro-substituted phenylalanine. Regioselective fluorination of both guanine[81] and purine[82] bases has been achieved with dilute solutions of fluorine in helium (**Scheme 32**). Although the yields are modest, this provides a mild one-step route to these intermediates. Also reported were the routes to ribofuranosyl fluoropyridines,[83] and halogenation of the chromophoric moiety of pyoverdins.[84]

Tius *et al.*[85] have used *N*-fluoropyridinium triflate to introduce a fluorine probe in the nabilone structure (**Scheme 33**). The good yield in this scheme is in contrast to electrophilic

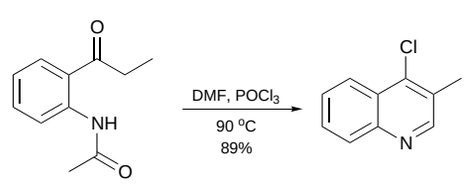


Scheme 32

bromination of the same molecule, which only proceeded in 38%. An improved large scale preparation of 2-amino-4-chloropyridine has been reported.[86] This has also been used to prepare various polychlorinated 2-aminopyridines. A simple route to *o*-chloro hydroxypyridines has been achieved.[87] This used a strategic halogen exchange since the electrophilic bromination is regioselective, whereas the chlorination is not. A new route to 4-chloro-3-methylquinolines using the Vilsmeier reagent has provided access to 1-(2-aminophenyl)propanes[88] (**Scheme 34**) while *o*-methoxylated phenylisopropylamines were elaborated after bromination with bromine in acetic acid.[89]



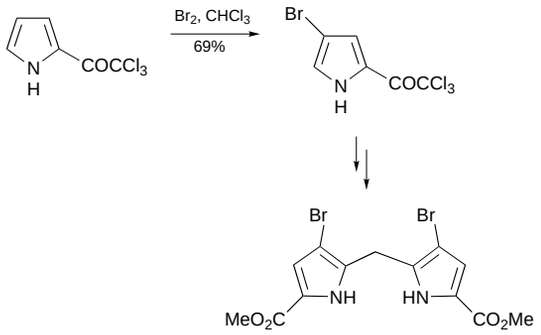
Scheme 33



Scheme 34

Mubarak and Peters have reported what they term a halogen dance around thiophene. By subjecting 2,5-dibromothiophene to an electrochemical reduction, they have been able to isolate a number of different halogen containing products.[90] The synthesis of 3,3′-dibromodihydrodipyrrins has been reported[91] (**Scheme 35**). Bromination of the pyrrole was achieved and the product carried on to give a potentially useful target product.

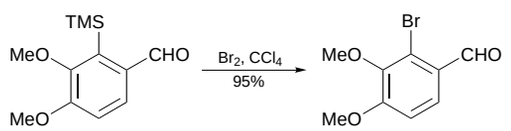
Bromothiophenes have also been synthesised by Kim and Rieke.[92] Starting with 3,4-dibromothiophene, they have reacted one of the bromides with activated manganese and coupled this to provide access to substituted bromothiophenes. The bis(*sym*-collidine) reagents have been used to halogenate pyridols.[93] Both bromination and iodination have been achieved with



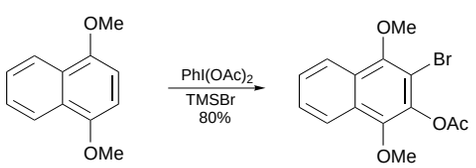
Scheme 35

success. Bromination of pyrimidines has been reported to proceed with bromine and monoperoxysulfate.[94]

Costa and co-workers have reported the chemoselective electrophilic replacement of bromine for silicon at an aromatic centre[95] (**Scheme 36**). Montmorillonite clay has been used to direct electrophilic bromination at an aromatic ring and reduce side chain reactions.[96] Using dimethyl sulfoxide and hydrobromic acid, site specific bromination of substituted benzenes has been reported,[97] while a hypervalent iodine species has produced a novel haloacetoxylation of 1,4-dimethoxynaphthalenes[98] (**Scheme 37**).

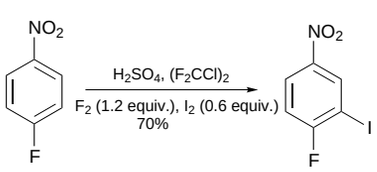


Scheme 36



Scheme 37

Elemental fluorine has been used in the iodination of nitrobenzenes[99] (**Scheme 38**). Depending on the solvent used, a mixture of chloro and iodo products was produced, however, with a fluoro directing group, iodine substitution can proceed in good yield. Brazdil and Cutler have produced a clean route to diiodinated benzenes.[100] Both the iodine atoms come from elemental iodine, so there is no waste metal iodide to dispose of. Using iodine in dimethylformamide, Sheldrake *et al*. have prepared 5-hydroxy-2-iodopyridine, albeit in moderate yield.[101] Finally, *ortho* deprotonation and subsequent halogen quench has been used to access 3,4-dihalopyridines.[102] These were then elaborated to give 3-alkylfluoropyridines *via* an intramolecular palladium coupling reaction.

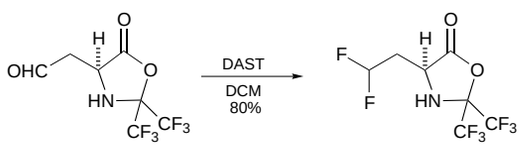


Scheme 38

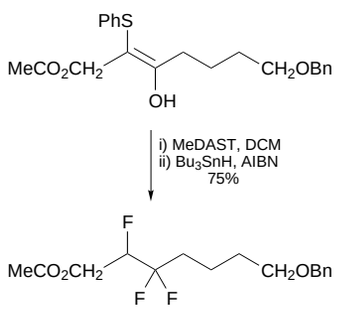
5 1,1-Dihalo compounds

A considerable volume of work has been published in the area of 1,1-dihalo compounds in the past year, with the vast majority being concerned with difluoro compounds. A general method for the synthesis of *gem*-difluoroalkanes has been reported using iododifluoromethylated compounds.[103]

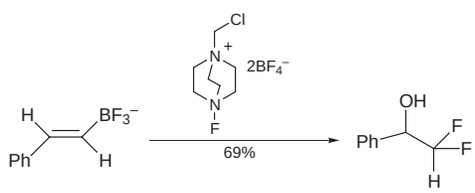
Elemental fluorine has been used for the fluorination of 1,3-dicarbonyl compounds.[104] DAST has been used for both the direct conversion of a carbonyl group to -CF_2- (**Scheme 39**) in the synthesis of arenomycin[105] and in the fluorination of an alkene in a route towards 5,6-difluoroarachianic acid[106] (**Scheme 40**). The related reagents Selectfluor and Accufluor have seen increased useage. Selectfluor has been used to provide access to fluorine containing alkenes, amides and alcohols by electrophilic fluorination of alkenyl boronic acids and trifluoroboronates[107] (**Scheme 41**). Accufluor has been used to convert alkynes directly to ketones with an α-difluoromethyl group[108] (**Scheme 42**). Electrochemically induced ring expansion of cycloalkylidenes has produced β,β-difluoro compounds.[109]



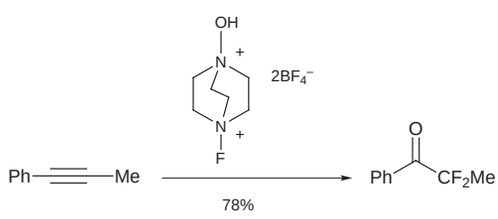
Scheme 39



Scheme 40

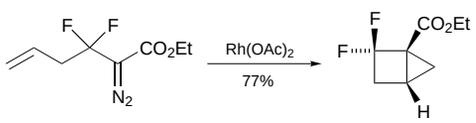


Scheme 41



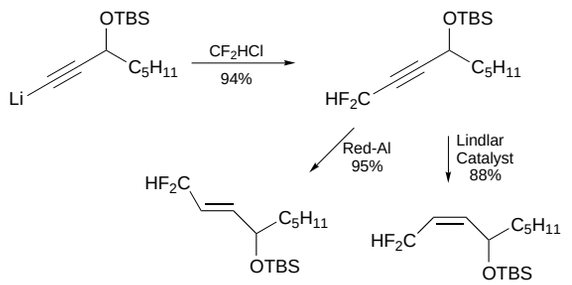
Scheme 42

Bicyclo[2.1.0] ring systems with difluoro substituents have been synthesised by the rhodium catalysed decomposition of diazo esters[110] (**Scheme 43**). Toyota *et al*. have reported the stereoselective synthesis of *cis*-2-fluorocyclopropane-1-carboxylic acid.[111] Fluorine containing 1,4-dihydropyridines have been synthesised as potential calcium channel modulators.[112]

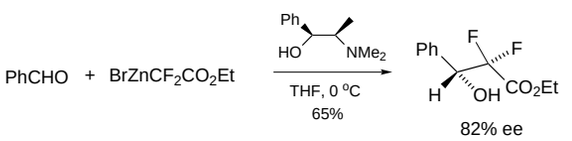


Scheme 43

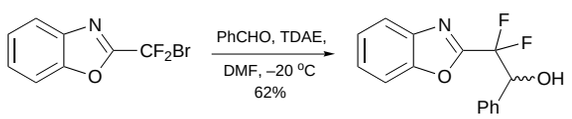
By reacting alkynyl anions with a chlorofluorocarbon, Konno and Kitazume have accessed a fluorinated alkyne in good yield[113] (**Scheme 44**). Through standard reduction with either RED-Al or Lindlar catalyst, these were reduced to either the *E*- or *Z*-alkene. An enantioselective Reformatsky reaction coupled the β,β-difluoroester with an aldehyde in good enantiomeric excess[114] (**Scheme 45**). In a similar manner, reaction of the benzoxazole with tetrakis(dimethylamino)ethylene (TDAE) and an aldehyde gave the coupled reaction product[115] (**Scheme 46**).



Scheme 44



Scheme 45

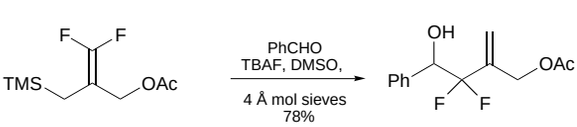


Scheme 46

Electrochemical removal of a dithiane protecting group occurred in the presence of hypervalent iodobenzene derivatives.[116] Stereoselective introduction of fluorine containing methyl groups at the 2-position of glucose has been achieved,[117] and a new strategy for the synthesis of difluoromethyl α-hydroxy and α-amino acids has also been reported.[118] Takeda *et al*. have transformed ketones and aldehydes to *gem*-dihalides by first converting to the hydrazone.[119] Reaction with a copper source gave the desired products in good yield under mild conditions.

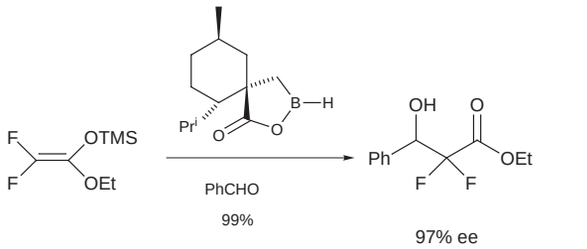
Phase transfer conditions for the addition of dichlorocarbene to alkenes have been shown to be dependent on the catalyst used.[120]

Shi and Huang have demonstrated the use of 2-(acetoxymethyl)-1,1-difluoro-3-trimethylsilyl)propene as a novel bifunctional reagent[121] (**Scheme 47**). On reaction with TBAF and aldehydes, a nucleophilic attack occurs at the carbonyl through the carbon bearing the fluorines. Iseki *et al*. have isolated an α,α-difluoroketene silyl acetal and used it in an asymmetric aldol reaction[122] (**Scheme 48**). Using a chiral catalyst, excellent enantiocontrol was achieved, as well as good chemical yield. Percy *et al*. have reported a [2,3]-rearrangement of difluoroallylic alcohols that also involves carbon–phosphorus or carbon–sulfur bond formation[123] (**Scheme 49**).

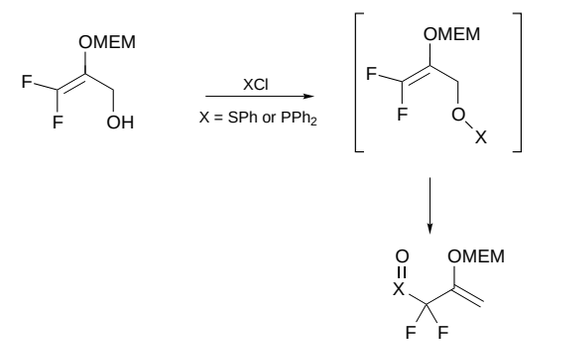


Scheme 47

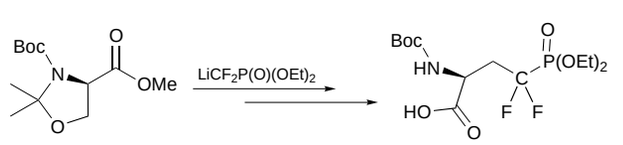
Interest in fluorinated phosphonates continues, mainly for use as mimics of secondary phosphonates and potential use in the pharmaceutical industry. To this end, use of lithiated diethyl (difluoromethyl)phosphonate [$(EtO)_2P(O)CHF_2$] has been the reagent of choice in a number of areas. Nucleophilic addition to ketones has prompted a reinvestigation of the Wadsworth–Emmons reaction[124] while reaction with aldehydes has provided access to difluoromethyl ketones.[125] The same nucleophile has also been utilised in the reaction with quinones to provide a DAST free route to (aryldifluoromethyl)phosphate esters,[126] and with oxazolines to give functionalised α-amino acids[127] (**Scheme 50**). Synthesis of (difluoromethyl)phosphonate azasugars has been achieved *via* nucleophilic attack at the pseudoanomeric position and subsequent cyclisation[128] (**Scheme 51**).



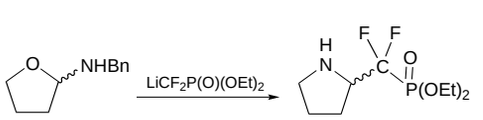
Scheme 48



Scheme 49

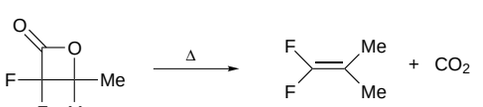


Scheme 50

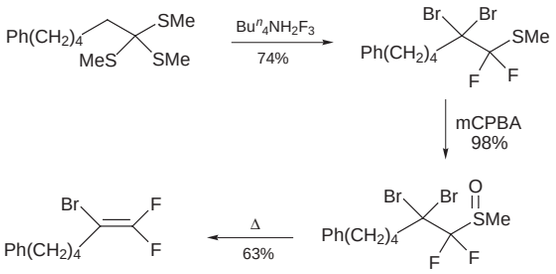


Scheme 51

1,1-Difluoroalkenes have also received substantial attention this year. Serafinowski and Barnes have incorporated this unit in a new AZT analogue[129] while Xu *et al*. have reported a new fluoroalkene building block.[130] The thermal decarboxylation of β-lactones has been used to access fluorinated alkenes[131] (**Scheme 52**), and a desulfurization–fluorination reaction has provided a new route to partially fluorinated olefins[132] (**Scheme 53**).



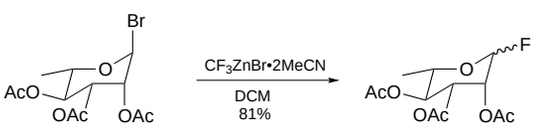
Scheme 52



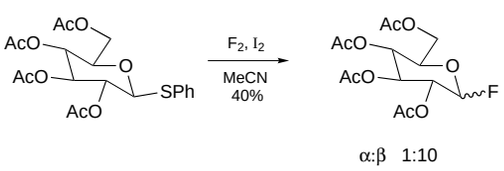
Scheme 53

6 1,1-Halohydrin and related compounds

The area of glycosyl halides will only be touched on briefly here for reasons of space. However, two methods worthy of comment for the production of glycosyl fluorides are the use of trifluoromethylzinc bromide[133] (**Scheme 54**), which gave the desired compounds in good yield under mild conditions, and a mixture of elemental fluorine and iodine which reacted with thioglycosides to give a good ratio of anomers[134] (**Scheme 55**).



Scheme 54



Scheme 55

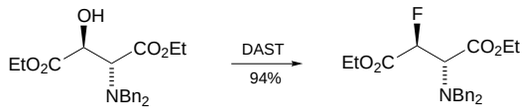
Regioselective anodic monofluorination of tetrahydrooxindole has been achieved.[135] Finally, a novel rearrangement has been reported in the fluoridation of pyranosides.[136] Using DAST, the furanosides were produced with some degree of diastereocontrol.

7 1,2-Dihalo compounds and 1,2-halohydrins

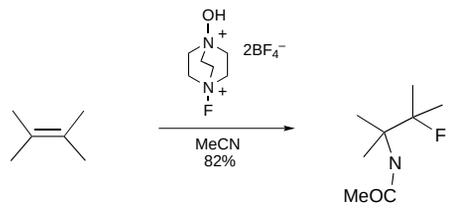
Little has been reported in the area of 1,2-dihalo compounds, so 1,2-dihalo compounds and 1,2-halohydrins will be discussed together. Bromination of α-chlorocarboxylic acids with NBS has been reported by Shaw and Tan, to give good yields of the corresponding dihalo derivatives.[137]

Charvillan and Amourous have synthesised enantiomerically enriched 3-fluoroaspartic acids[138] (**Scheme 56**). The reagent of choice was DAST, which was used either to replace the hydroxy group, or to degrade a sulfate to a fluorohydrin. Routes to enantiomerically pure 3-fluoromethylthreonines have been reported.[139] A Ritter type reaction with Accufuor has proven an effective method for the generation of vicinal fluoroamides[140] (**Scheme 57**). Differding's *N*-fluorosulfonamide has been used as an electrophilic quench to place fluorine in a β-lactam structure[141] (**Scheme 58**). A zinc carbenoid reagent containing fluorine has been used to react with aldehydes. Importantly the reagent has good selectivity for aldehydes over ketones in the same molecule[142] (**Scheme 59**). In a similar vein, (chlorodifluoromethyl)trimethylsilane has been reported as a moisture and air stable compound. By reacting with TBAF, a method for the fluoroalkylation of aldehydes in good yields has been achieved.[143]

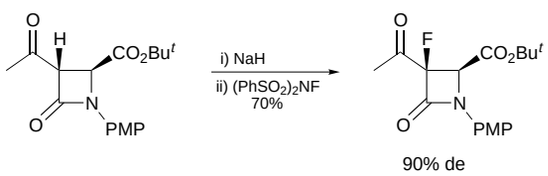
Selective reduction of an oxetan-2-one has produced a key intermediate in the synthesis of carnitine and amino-3-



Scheme 56



Scheme 57



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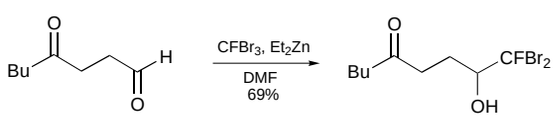
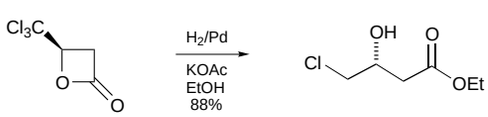
Scheme 58

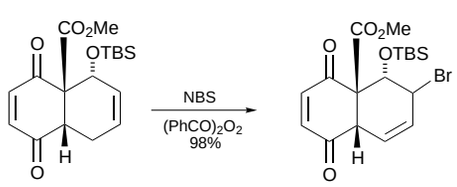


Scheme 59

hydroxybutyric acid[144] (**Scheme 60**). A regioselective radical addition of chlorine to a phthalimide substituted anhydride with sulfuryl chloride has been reported.[145] Joachim and Raphael have synthesised a key intermediate in the synthesis of monocyclofarnesyl using a bromoacetaldehyde equivalent.[146] In the total synthesis of the polyols (±)-euonyminol and (±)-3,4-dideoxymaytol, White *et al*. reported a radical based addition of bromine that proceeded with translation of the double bond[147] (**Scheme 61**). A photochemical rearrangement of 2-bromovinyl selenides has been shown to occur by Morley.[148]



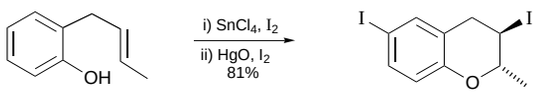
Scheme 60



Scheme 61

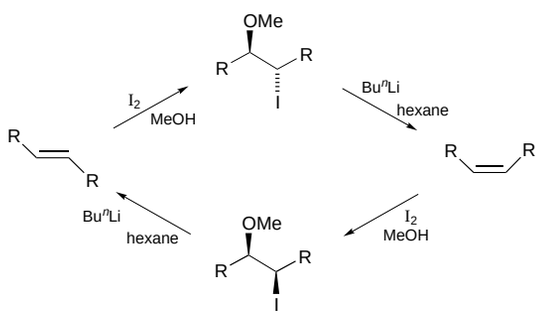
The combination of iodine and ceric ammonium nitrate has proven successful in the generation of iodohydrins.[149] Trapping of iodonium species continues to be a popular route to cyclic intermediates. The synthesis of iodobenzofurans and pyrans by the attack of a phenol on an ortho allylic olefin activated by tin chloride and iodine has been reported to progress in good yield[150] (**Scheme 62**). Similarly oxepanes and oxocanes have been made by iodoetherification of suitable substrates using bis(*sym*-collidine)iodine hexafluorophosphate.[151] Imines have also been used in a similar cyclisation to afford tetrahydropyridines[152] (**Scheme 63**). This latter method was used on the way to the total synthesis of (−)-anisomycin and (+)-polyoxamic acid.

Finally, a stereospecific olefin inversion process which allows *E*- and *Z*-isomers of di-substituted double bonds to be interconverted has been published[153] (**Scheme 64**). Reaction of one of the olefins with iodine in methanol followed by elimination with butyllithium produces the other isomer through an E2 *syn* mechanism.



Scheme 62

Scheme 63



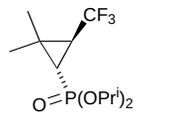
Scheme 64

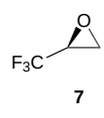
8 Trifluoromethyl compounds

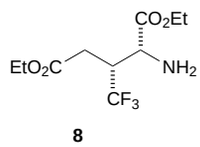
The importance of the trifluoromethyl group in organic and medicinal chemistry continues to grow at a significant rate. This section has been added to address the growing use of the group. However, an exhaustive review would be too consuming in terms of space, therefore an overview of some important advances in the area will be presented.

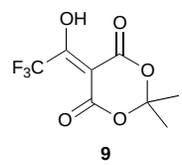
Several useful small building blocks containing CF_3 groups have been synthesised this year. These include a cyclopropyl phosphonate **6**,[154] 2-(trifluoromethyl)oxirane **7**,[155] diethyl 3-(trifluoromethyl)glutamate **8**[156] and a trifluoroacetyl derivative of Meldrum's acid **9**.[157] The different chemistry of the CF_3 group is illustrated by the opposite sense of reduction induced on methyl and trifluoromethyl aromatic ketones by alcohol dehydrogenase[158] (**Scheme 65**). (Trifluoromethylacetyl)-benzotriazole has been introduced by Katritzky *et al*. as a convenient reagent for trifluoroacetylating alcohols and amines.[159] Trifluoroacetanyl radicals have been used to produce trifluoromethyl ketones.[160] Billard and co-workers have accessed trifluoromethyl thio or seleno ethers either from the disulfide (diselenide)[161] or from the nitrile compound[162] (**Scheme 66**). Germanium reagents have been used to induce nucleophilic attack of trifluoromethyl anion on aldehydes[163] and imines.[164] Trifluoromethyl substituted alcohols have been accessed by reaction of allyl bromides with indium and a suitable electrophilic quench[165,166] (**Scheme 67**). Trifluoromethyl silanes have been used to derivatise amino ketones.[167] The electrochemical reduction of acrylonitrile in the presence of trifluoroacetic acid has been reported.[168]

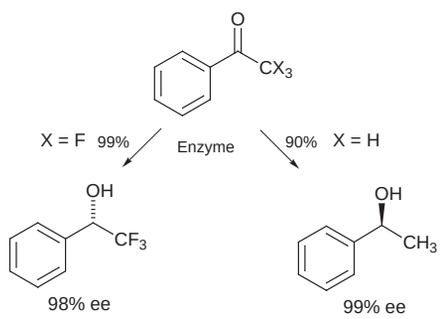
Several useful rearrangements have been highlighted this year which provide access to useful trifluoromethyl derivatives. A fluoral-ene reaction with vinyl sulfides[169] and Wittig[170] and Ireland–Claisen[171] rearrangements have produced the appropriate CF_3-substituted products with high levels of stereo-



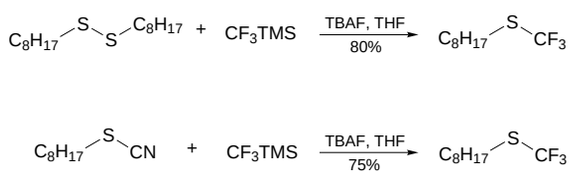




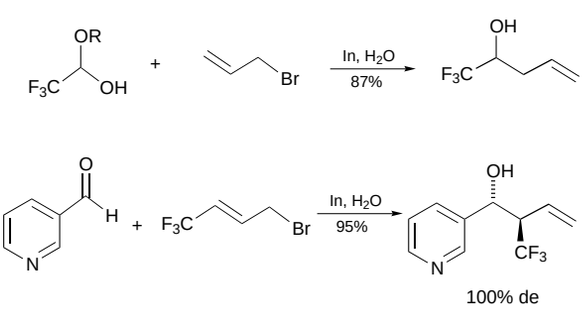




Scheme 65



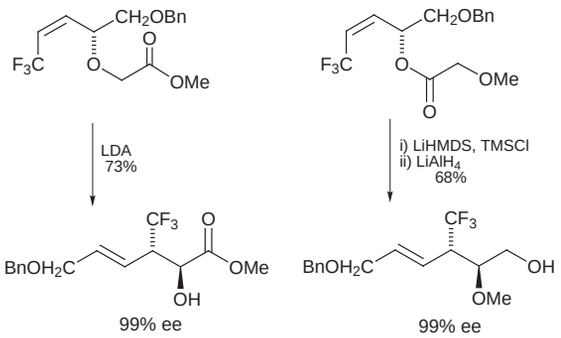
Scheme 66



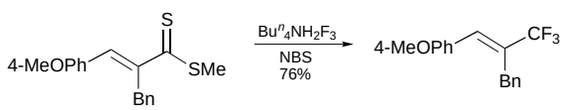
Scheme 67

control (**Scheme 68**). Trifluoromethyl substituted alkenes have received some attention this year. A stereoselective approach to CF_3-substituted unsaturated esters and nitriles has been reported,[172] as has a desulfurisation–fluorination of dithiopropenates to produce trifluoropropenes[173] (**Scheme 69**). Azadienes have been produced by the reaction of trifluoromethylated enamines with iminium chlorides.[174] Cycloaddition reactions of trifluoromethylated alkenes have been used to produce optically active products. The Diels–Alder reaction of trifluoromethylated alkenes under high pressure has been demonstrated[175] (**Scheme 70**), as has the 1,3-dipolar addition to nitrones[176] (**Scheme 71**).

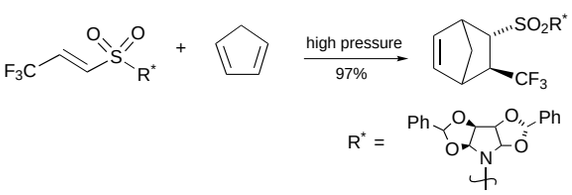
The area of trifluoromethyl substituted heterocycles is one of the most actively researched areas in organic halide chemistry. Trifluoromethyl substituted imidazoles have been synthesised by Derstine *et al*.[177] (**Scheme 72**), and a simple synthesis of 3-substituted 5-trifluoromethylpyrroles by a modified Hantzsch reaction has been reported[178] (**Scheme 73**). A novel trimerisation reaction of trifluoromethyl isocyanides has been used to produce dihydropyrimidine derivatives[179] (**Scheme 74**). Finally, routes towards trifluoromethyl substituted benzo[*h*]quinolines,[180] pyrimidines,[181] azacyanins[182] and pyridines[183] have all been reported.



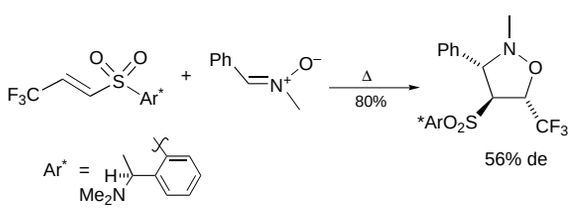
Scheme 68



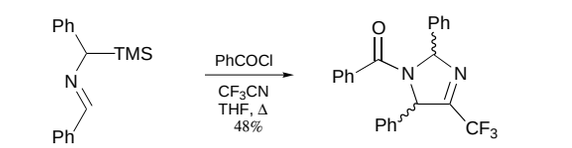
Scheme 69



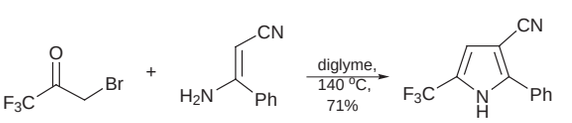
Scheme 70



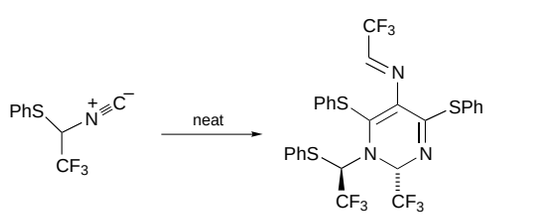
Scheme 71



Scheme 72



Scheme 73



Scheme 74

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