2-Fluoromalonate esters: fluoroaliphatic building blocks for the life sciences

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ABSTRACT The majority of fluorinated pharmaceutical products bear structurally simple fluoro- and trifluoromethyl-aromatic subunits, in part, due to the ready availability of a wide range of fluoro and trifluoromethyl aryl derivatives for both drug discovery and manufacturing campaigns. As life-science programmes are increasingly seeking more three-dimensional structures as hit-to-lead compounds, the requirement for complex organic molecules bearing fluorine attached to sp_3 carbon in aliphatic systems and monofluorinated heterocycles is becoming more important. Consequently, the incorporation of new polyfunctional fluorinated building blocks into drug discovery projects is required, to drive the development of new generations of fluorinated pharmaceuticals in much the same way as the availability of fluorinated aromatic systems did in the past. Fluoromalonate esters are potentially very versatile fluorine containing building blocks that may be used for the introduction of fluorine atoms into aliphatic and heteroaromatic systems. The syntheses of fluoromalonate derivatives using commercially available fluorinating reagents on both research and manufacturing scales are described and the use of fluoromalonates for appropriate alkylation, acylation, Michael addition, annelation and biotransformation processes are presented, providing an indication of the synthetic possibilities available for accessing novel selectively fluorinated structures.

1.   Introduction

In 1952, Fried and Sabo published their seminal paper concerning the enhanced biological activity possessed by a fluorocortisoid derivative compared to both the parent and corresponding halogenated steroid systems.[1] This discovery gave added impetus to the development of methodology for the introduction of fluorine atoms into organic systems and, today, around 20% of commercially significant pharmaceuticals and 30 % of all agrochemicals contain fluorinated groups within their structures that perform a variety of functions such as increasing metabolic stability, increasing lipophilicity and bioavailability.[2]

Analysis of the 140 fluorine containing active pharmaceutical ingredients that have been approved for general use by the FDA since the 1950's shows that by far the most common fluorinated motifs present in pharmaceutical structures[3] are fluoroaromatic sub-units, principally 4-fluorophenyl (e.g. Atorvastatin (Lipitor), Ezetimibe (Zetia), Escitalopram (Lexapro) etc.) and trifluoromethyl aryl systems (e.g. Fluoxetine (Prozac), Dutasteride (Avodart), Travoprost (Travatan Z), etc.) (Fig. 1).
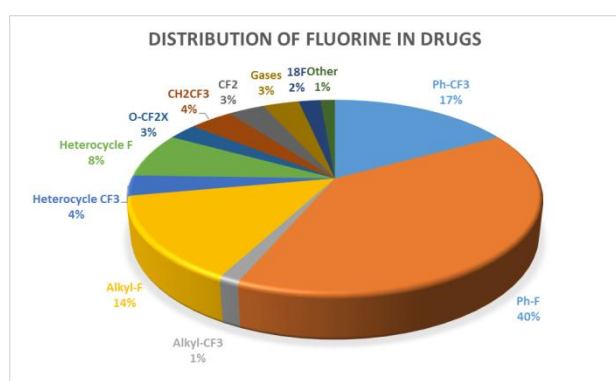

FIGURE 1. Fluorine containing motifs in FDA approved active pharmaceutical ingredients (1950-present)

Both fluoro and trifluoromethyl aromatic derivatives are synthesised on the large scale using anhydrous hydrogen fluoride for the key carbon-fluorine bond forming stage and usually in the early stages of the synthetic construction of the pharmaceutical product by commodity chemical manufacturers. Both Balz-Schiemann[4] and Swart's halogen exchange[5] processes are very well developed for the manufacture of a wide range of fluoro and trifluoromethyl aromatic building blocks respectively.

As the pharmaceutical industry seeks to further develop new pharmaceuticals that have more three-dimensional structure in design strategies that are moving away from aromatic 'flatland',[6] methodology for the incorporation of fluorine atoms located at sp_3 centres is gaining in importance. The major class of fluoroaliphatic pharmaceuticals are the anti-inflammatory fluorosteroids (18 out of 21 in the example set) such as Fluticasone propionate (Advair) and Difluprednate (Durezol).[3] Reagents such as DAST and Selectfluor[TM] are now used widely in drug discovery programmes[2,7] and, consequently, a wider range of fluorinated aliphatic motifs are being incorporated into drug design. Of course, the ready availability of polyfunctional, stable fluorinated aliphatic building blocks that have established, robust chemistry[8] will further aid discovery and manufacturing campaigns and, in time, widen the types of fluorinated structural units in pharamaceuticals beyond mainly existing fluorinated aromatic derivatives.

This review considers the synthesis and subsequent chemistry of polyfunctional, selectively fluorinated dialkyl fluoromalonate esters as substrates for the preparation of structurally more sophisticated fluorine containing systems, with a particular emphasis on fluorinated derivatives where fluorine is attached to sp_3 carbon. Of course, the chemistry of non-fluorinated malonic esters is very well developed[9] and a wide range of, for example, alkylation, acylation, Knoevenagel, aldol, reduction, Michael addition, nucleophilic substitution and annelation processes are utilised in many important syntheses. Malonate esters frequently appear in restrosynthetic planning strategies[10] from

3

University sophomore classes onwards. In comparison, however, corresponding chemistry of dialkyl fluoromalonate esters is not developed to any great extent and the relatively few patents using diethyl fluoromalonate as a fluorinated building block for the synthesis fluorinated biologically active systems have only begun to appear in the past 10 years (Fig. 2), providing an indication of the relatively undeveloped potential of these polyfunctional selectively fluorinated systems.
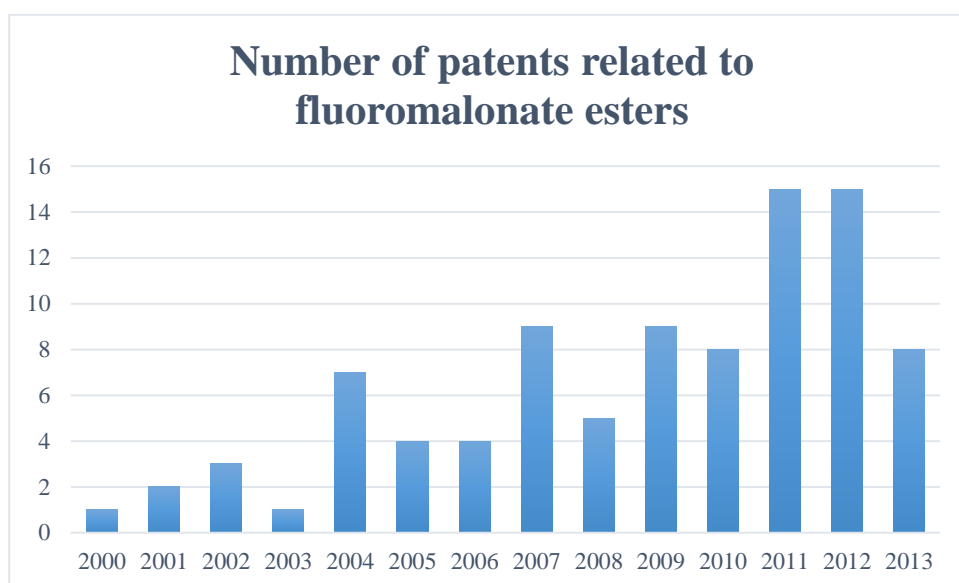
FIGURE 2. Diethyl fluoromalonate esters in patents (2000-present)

The relatively recent developments in fluoromalonate chemistry is most probably due to the recent commercial availability of dimethyl and diethyl fluoromalonate at very reasonable prices from the usual speciality chemical suppliers. No special handling procedures are required when using fluoromalonate esters for synthetic processes beyond employing the usual laboratory and industrial safety precautions.

Here, we discuss the synthesis of fluoromalonate esters and the use of these potentially versatile fluorinated substrates as fluorinated-building blocks in synthesis to aid synthetic strategy planning for the preparation of fluorinated derivatives that will provide opportunities to access new

fluorinated chemical space for life-science applications, in particularly systems where fluorine is attached to sp$_3$ carbon in aliphatic systems.

2. Synthesis of dialkyl 2-fluoromalonate esters

2.1 Electrophilic fluorination of malonate enol derivatives

Replacement of enolic hydrogen atoms by fluorine using an electrophilic fluorinating agent offers the most direct method for the synthesis of fluoromalonate esters and, over the last 60 years, several procedures have been developed using the fluorinating reagents available at the time. The first example of fluorination of malonate esters using perchloryl fluoride (FClO$_3$) was published in 1958.[11] When FClO$_3$ was passed through an ethanolic solution of sodium diethyl malonate, a 50 : 50 mixture of diethyl malonate and diethyl 2,2-difluoromalonate was obtained rather than the expected diethyl 2-fluoromalonate while two equivalents of NaOEt and FClO$_3$ gave pure diethyl 2,2-difluoromalonate in high yield. Fluorination of a small range of 2-substituted malonic esters gave the corresponding fluoromalonate product (Scheme 1a) but this fluorination methodology was not widely adopted because of the highly oxidising and potentially explosive nature of perchloryl fluoride.
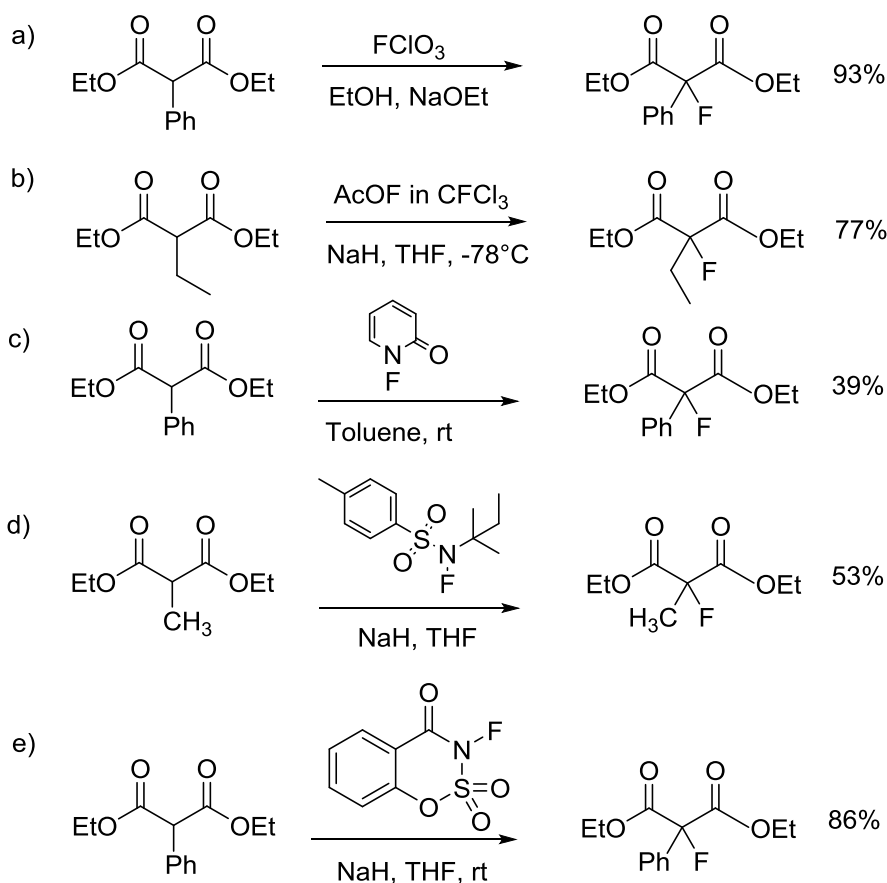
SCHEME 1. Initial processes for the synthesis of 2-fluoromalonate esters using (a) FClO$_3$; (b) acetyl hypofluorite; (c) *N*-fluoropyridone; (d) *N*-fluoro-*N*-alkylsulfonamide; (e) benz-1,2,3-oxathiazin-4-(3-F)-one 2,2-dioxide.

In the 1980's, the development of novel electrophilic fluorinating reagents of the O-F and N-F class allowed the synthesis of a wider range of 2-fluoro-1,3-dicarbonyl systems. Acetyl hypofluorite (CH$_3$COOF), developed by Rozen, was the first successful reagent to monofluorinate 1,3-dicarbonyl systems in reasonable yield and purity (Scheme 1b).[12]

N-Fluoro-2-pyridone can conveniently be prepared from 2-trimethylsiloxy pyridine with elemental fluorine (5% in N$_2$)[13] and is capable of fluorinating sodium dialkyl malonates, but yields are poor, reaching only 39% in the case of diethyl 2-phenylmalonate (Scheme 1c). *N*-Fluoro-*N*-alkylsulfonamides, introduced by Barnette[14] in the early 1980s, are prepared by passing dilute (3-5

% in N$_2$) fluorine gas through a solution of the corresponding sulfonamide in an inert solvent. Their fluorinating power was demonstrated by reaction with a series of carbanion sytems, most of which gave the desired monofluorinated product in good yield (Scheme 1d).[14] Similarly, DesMarteau synthesised a range of *N*-fluoro-perfluoroalkylsulfonimides[15] from elemental fluorine. These reagents readily react with carbanionic substrates and essentially give the fluorinated product in quantitative yield (96 % for diethyl 2-methylmalonate) but their hazardous preparation (use of neat fluorine that is liquefied during the reaction) precludes widespread use of these reagents. More recently another class of *N*-fluorosulfonamide was developed that uses oxathiazione dioxides as easily accessible starting materials.[16] The most stable and promising fluorinating reagent is benz-1,2,3-oxathiazin-4-(3-F)-one 2,2-dioxide which fluorinates various carbon nucleophiles (Scheme 1e). Similarly, for the fluorination of carbanions, *N*-fluoro-2,4,6-trimethylpyridinium triflate (trifluoromethanesulfonate) was found to react with the diethyl malonate sodium salt to give diethyl 2-fluoromalonate and other, substituted malonates provided access to the corresponding fluorinated products in high yield.[17]

In the past few years, *N*-fluorobenzenesulfonimide (NFSI) and Selectfluor[TM] have emerged as the most effective electrophilic fluorinating reagents of the N-F class because they are shelf stable, solid, commercially available reagents that do not require any additional handling procedures beyond the usual precautions taken in a research laboratory. *N*-Fluorobenzenesulfonimide (NFSI) is used for the asymmetric fluorination of prochiral malonate esters[18] (Scheme 2) and reaction of Selectfluor[TM] with diethyl 2-phenylmalonate salt afforded fluorinated product in almost quantitative yield (93 %)[19]. Similarly, several fluoromalonate derivatives have been prepared using Selectfluor[TM], for use as liquid crystal compounds[20] and potential pharmaceutical targets (Scheme 2).[21]
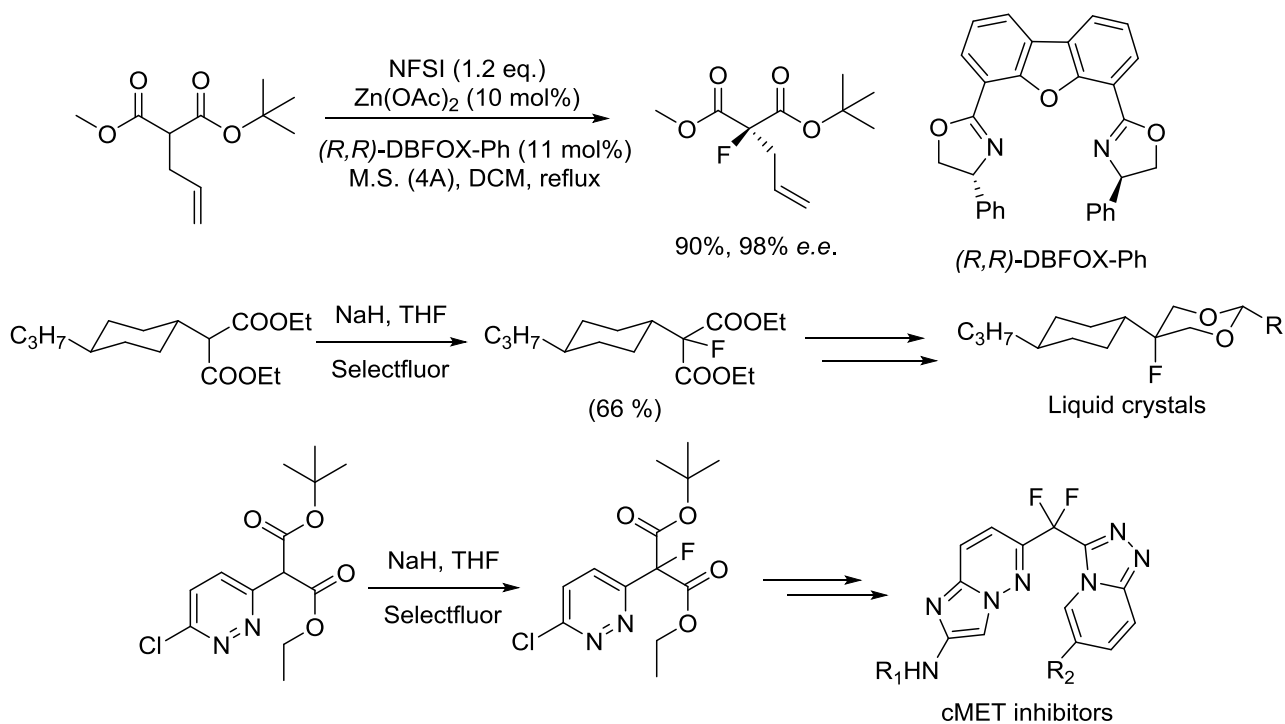
SCHEME 2. Synthesis of fluoromalonates using *N*-fluorobenzenesulfonimide (NFSI) and Selectfluor[TM].

The direct fluorination of malonates with elemental fluorine gas was believed to be impractical until it was demonstrated by Purrington that it is possible to selectively fluorinate trimethylsilyl-malonate derivatives.[22] The starting material in this case was the corresponding silyl enol ether that was fluorinated with dilute (5% in N_2) fluorine gas in an inert Freon solvent (Scheme 3a). The use of elemental fluorine for the synthesis of fluoromalonate esters was further developed by Chambers.[23] Fluorination of several dialkyl sodio-malonates in acetonitrile solution gave a product mixture that contains mono and difluorinated product and their relative ratio depends upon the number of base equivalents used. With one equivalent of NaH, 37 % mono- and 23 % difluorinated malonate esters were obtained while when adding 2.25 equivalents of NaH, the difluorinated product was the major product (37 %) with 14 % monofluoro malonate. Substituted dialkyl malonate salts react with elemental fluorine to provide high yields of the corresponding fluorinated derivatives (Scheme 3b).[23]
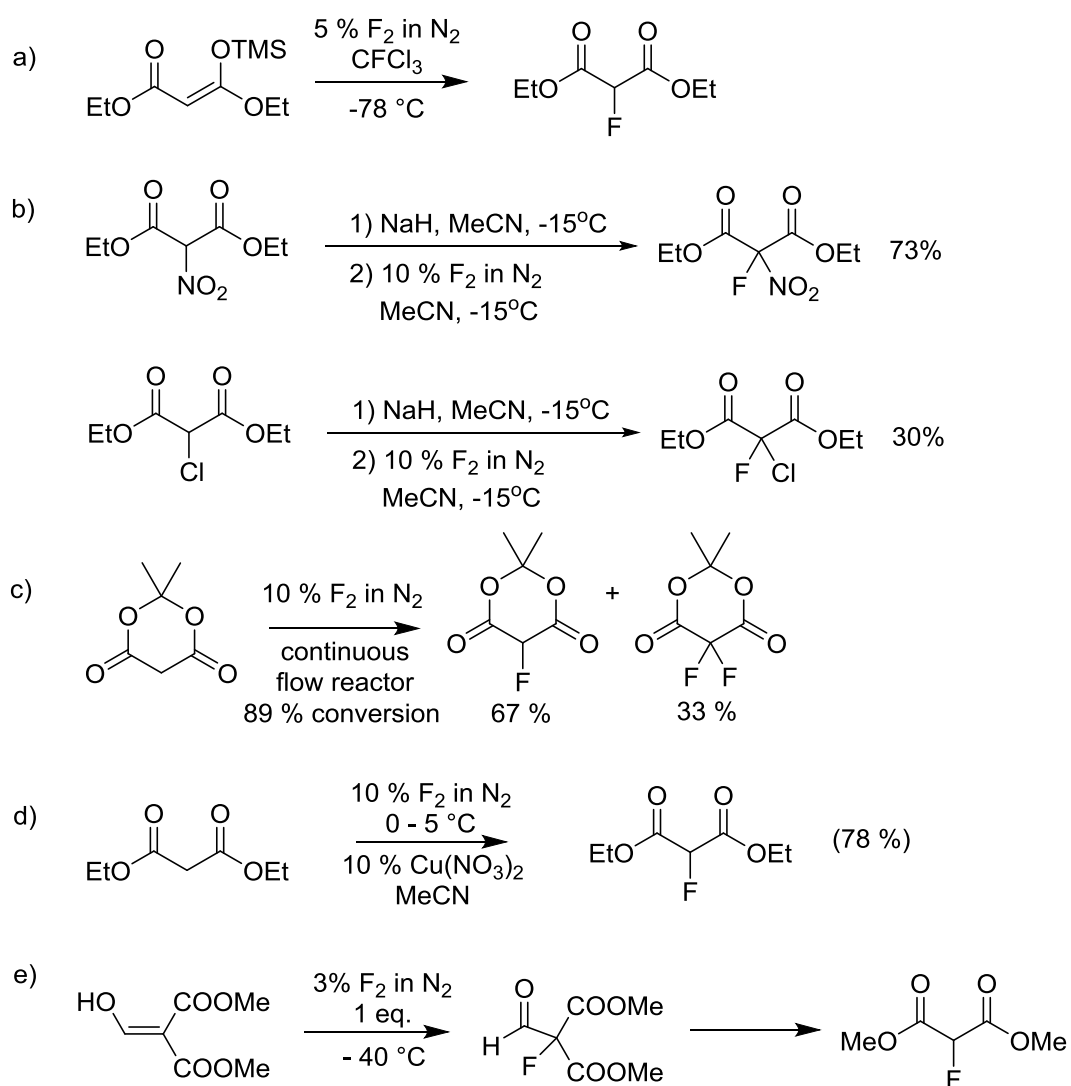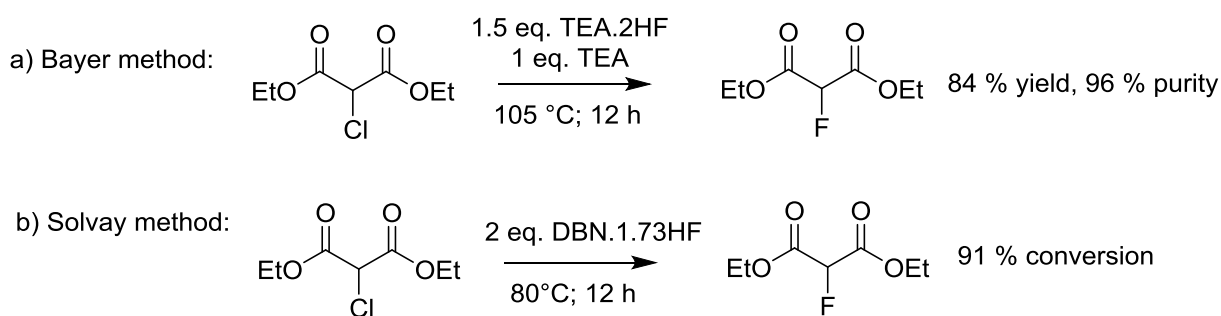
SCHEME 3. Synthesis of fluoro malonate esters using fluorine gas.

Fluorination of diethyl malonate in a continuous flow microreactor using acetonitrile as reaction medium gave several mono- and difluorinated products but with low selectivity.[24] The change of substrate to Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) followed by treatment of the crude reaction mixture with ethanol before the work-up stage gave mono- and difluoromalonate derivatives which could be easily separated (Scheme 3c). However, the selectivity problem for direct fluorination of malonate substrates was solved when it was discovered that the addition of a catalytic amount of copper nitrate (Cu(NO$_3$)$_2$.2.5 H$_2$O) could activate the malonate substrate towards direct fluorination (Scheme 3d).[25] As an alternative approach, dialkyl 2-formyl malonates

readily react with elemental fluorine to yield dialkyl 2-fluoro-2-formyl malonates that can easily be deformylated to yield exclusively the monofluorinated product in good yield (Scheme 3e).[26]

2.2   Halogen exchange reactions

Halogen exchange of chlorine by fluorine using a suitable source of fluoride ion offers an alternative approach to the synthesis of fluoromalonate derivatives. In the early 2000s' several patents were filed by Bayer[27] and Solvay[28] concerning reactions of base and amine-hydrogen fluoride complexes with diethyl chloromalonate (Scheme 4).


SCHEME 4. Synthesis of fluoromalonates by Halogen exchange processes.

Bayer's procedure uses triethylamine and triethylamine.3HF to give diethyl 2-fluoromalonate in 82 % yield while Solvay's process uses DBN (1,5-diazabicyclo[4.3.0]non-5-ene) HF complex as the fluoride ion source to give diethyl 2-fluoromalonate in 91% conversion on a large scale, as stated in the relevant patent descriptions.
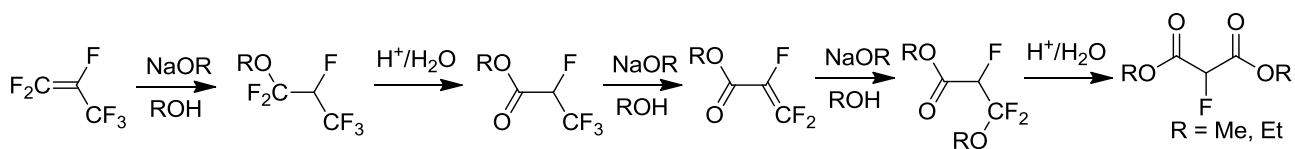
2.3   Miscellaneous preparations

The condensation of fluoroacetic acid derivatives with alkyl chloroformate is another possible route for the synthesis of dialkyl fluoromalonate derivatives.[29] In an early procedure, ethyl chloroformate and the sodium enolate of ethyl fluoroacetate gave diethyl 2-fluoromalonate in low yield (21 %). A similar procedure was developed using less toxic ethyl bromofluoroacetate[30] which was reacted with tributylphosphine to form an ylid that was acylated using ethyl chloroformate, to give diethyl 2-fluoromalonate (Scheme 5).
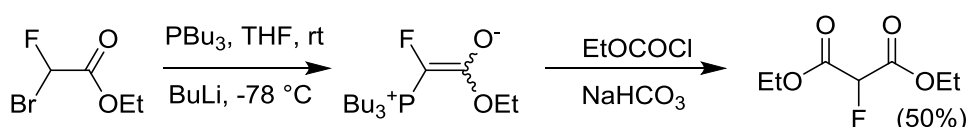
SCHEME 5. Acylation of ethyl bromofluoroacetate.

A method involving sequential solvolysis of hexafluoropropene to give dialkyl 2-fluoromalonates in good yield was published by Japanese authors in the early 1980s (Scheme 6).[31] Since hexafluoropropene (HFP) is manufactured on a very large scale for the production of various fluoropolymers, it is an inexpensive starting material. When HFP is reacted with an alcoholic solution of sodium alkoxide conjugate addition of an alcohol leads to an ether that can be hydrolysed by concentrated sulfuric acid to give alkyl 2,3,3,3-tetrafluoropropanoate. When this ester is reacted with an alcoholic sodium alkoxide solution, HF elimination gives the corresponding acrylic acid derivative that immediately undergoes further substitution followed by acidic hydrolysis to give the desired dialkyl fluoromalonate.

F$_2$C=CF$_3$/F →(NaOR, ROH)→ RO/F$_2$C–CF$_3$ →(H$^+$/H$_2$O)→ RO–CF$_3$ →(NaOR, ROH)→ RO–CF$_2$ →(NaOR, ROH)→ RO–CF$_2$ →(H$^+$/H$_2$O)→ RO–CH(F)–OR

R = Me, Et

SCHEME 6. Sequential solvolysis of hexafluoropropene.[31b]

In summary, simple fluoromalonate derivatives such as dimethyl and diethyl fluoromalonate are synthesised on a large scale using halogen exchange or hydrolysis processes described above and are available at reasonable prices from the usual chemical suppliers. More complex fluoromalonate systems, particularly for research scale processes, may be synthesised most readily by reaction of the corresponding malonate with either NFSI or Selectfluor[TM], thus providing access to a wide range of fluoromalonate building blocks to all laboratories for life-science applications.

3. Reactions of fluoromalonate ester derivatives

3.1 Reactions with carbon electrophiles

The alkylation of fluoromalonate esters using simple alkyl halides as electrophiles may be mediated using sodium ethoxide in ethanol but, predictably, alkylation proceeds more slowly than the non-fluorinated malonate due to the lower stability and nucleophilicity of the fluoromalonate ion. Dialkyl fluoromalonates are alkylated[32] in the syntheses of a carbopeptidase U inhibitor[33] and enzymatically triggered chemiluminescent probes.[34] Similarly, synthesis of bicyclo[3.1.0]hexane based anti-anxiety drug candidates involves a related early stage epoxide opening step[35,36] with diethyl fluoromalonate as the substrate (Scheme 7). Ring opening of aziridines by reaction of fluoromalonate anions provides a useful method for the synthesis of α-fluoro-γ-amino acids after appropriate deprotection.[37] While related ring opening of β-lactone derivatives gives access to α-fluoro-dicarboxylic acids.[38]
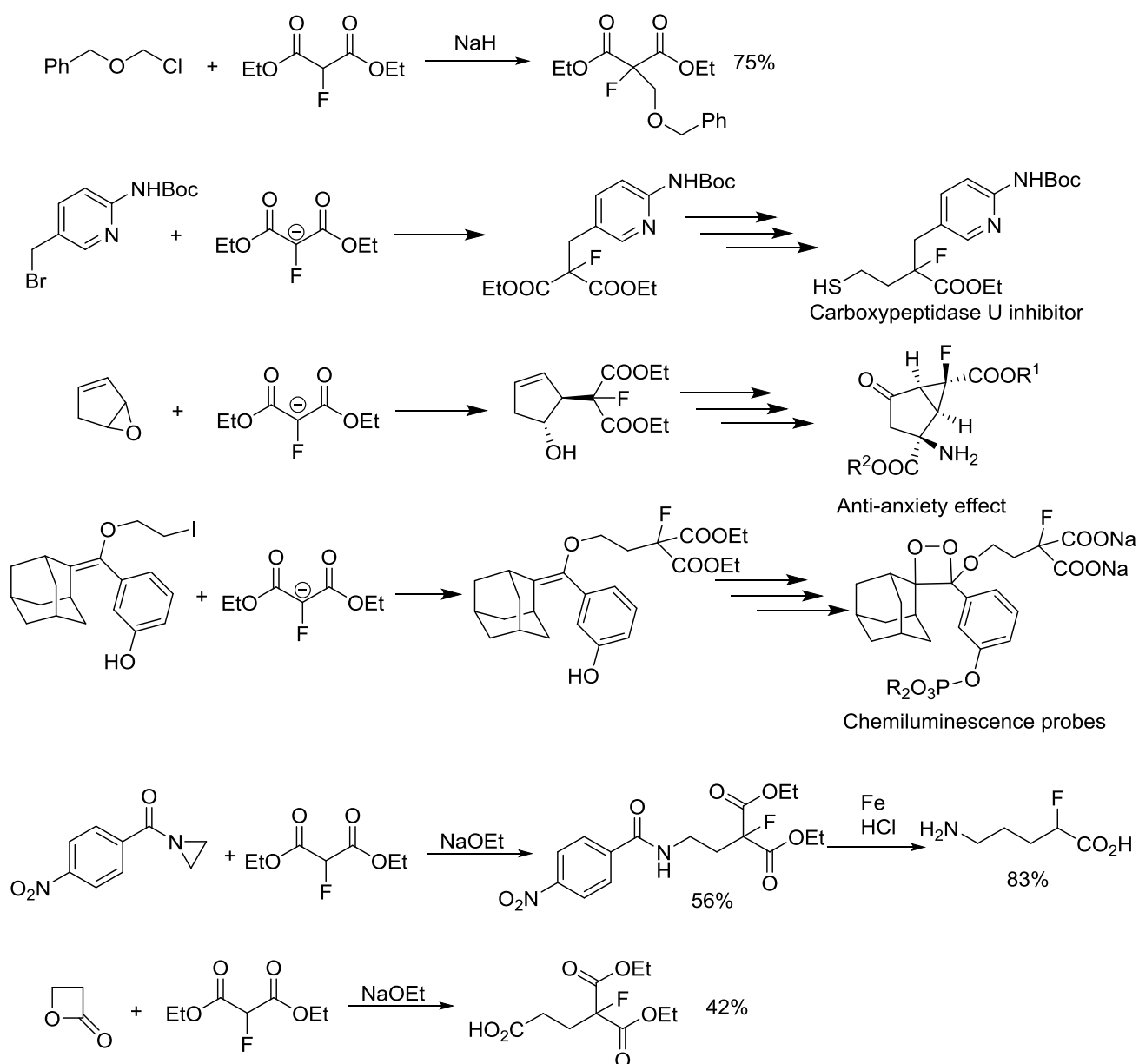
SCHEME 7. Alkylation of fluoromalonate derivatives.

Palladium catalysed allylation of fluoromalonate can also be utilised for the attachment of allyl groups to the fluorinated carbon centre.[39]
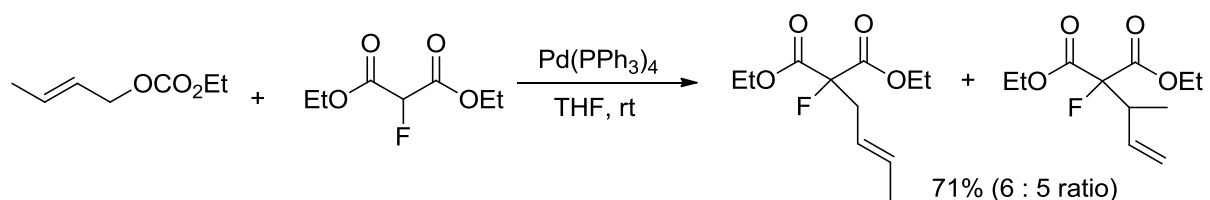

SCHEME 8. Palladium catalysed allylation of fluoromalonate.

Related reaction of fluoromalonate with formaldehyde has been used for the synthesis of fluorinated acrylic ester monomers[40] in which 2-fluoroacrylic chloride was prepared in three steps from dimethyl 2-fluoromalonate (Scheme 9). Similar synthesis of related 2-fluoroacrylate derivatives was used for the preparation of fluorinated porphobilinogens.[41]
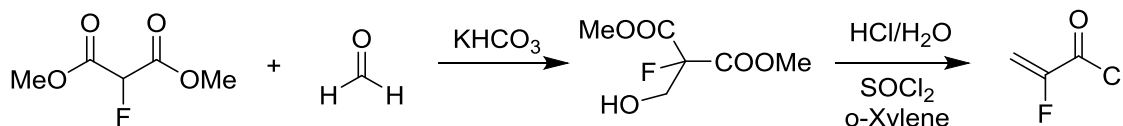

SCHEME 9. Synthesis of 2-fluoroacrylic chloride form dimethyl fluoromalonate.

Addition of 2-fluoromalonate anions to C=N bonds lead to α-fluoro-β-aminoacid precursors which are effectively generated from aldimines or their synthetic equivalents. A simple synthesis of racemic 2-fluoro-2-(α-Cbz-aminobenzyl)malonates used diethyl fluoromalonate and α-amido p-tolylsulphones as the Mannich base equivalent reagents[42] while enantioselective addition of diethyl fluoromalonate to N-Boc aldimines was performed using a chiral thiourea based organocatalyst (Scheme 10).[43]
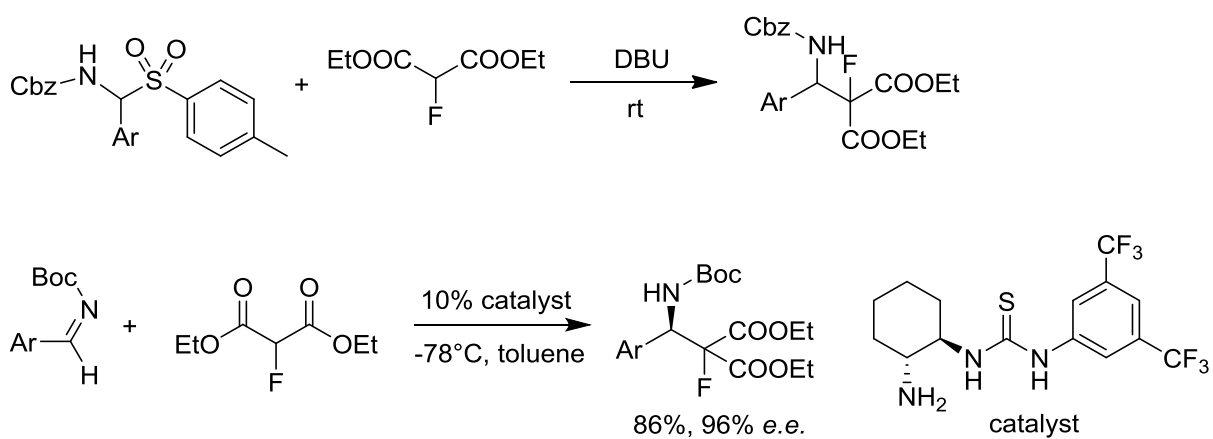
SCHEME 10. Reaction of fluoromalonate with C=N bonds.

A very efficient 2-fluoroacrylate ester synthesis is based on a domino reaction where the first step is the addition of fluoromalonate to an α,β-unsaturated ketone followed by elimination to give a fluoroacrylate derivative.[44] Although the yields vary from poor to excellent, the *E/Z* selectivity of the reaction is very good (Scheme 11).
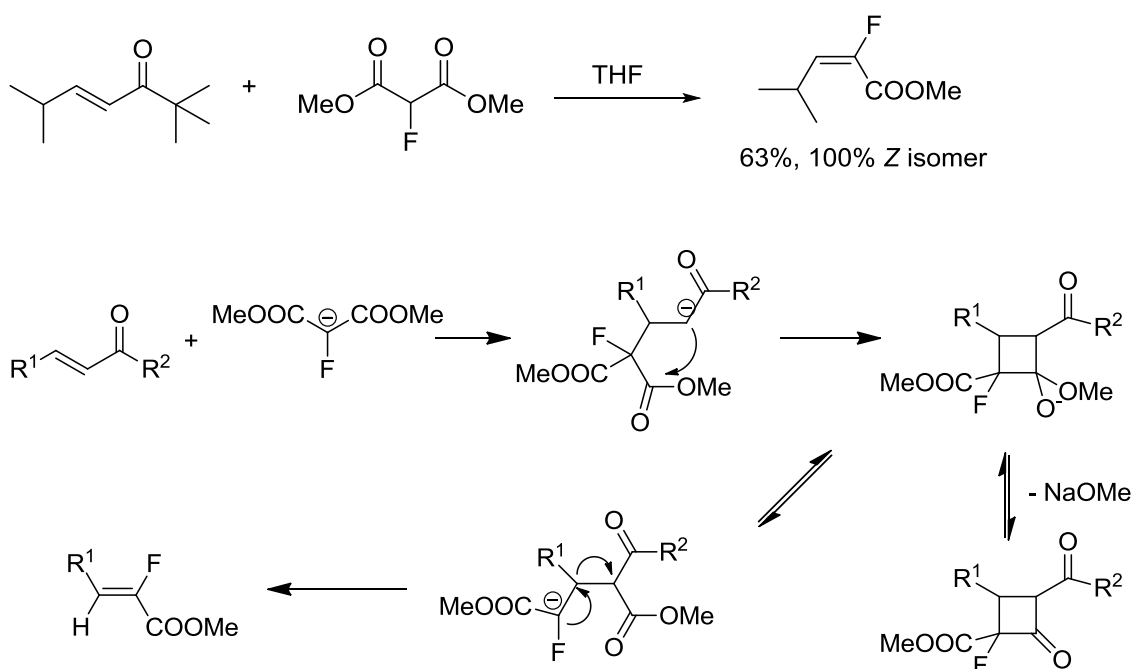
**SCHEME 11**. Synthesis of fluoroacrylates from fluoromalonates.

Of all the possible reactions of fluoromalonate systems, enantioselective addition of dialkyl fluoromalonate derivatives to different Michael-acceptors has attracted the most attention. The first reported example described the use of an efficient cinchonine derived quaternary ammonium salt catalyst for addition of fluoromalonate to chalcone derivatives but, unfortunately, the enantioselectivty was mediocre.[45] Similarly, the enantioselective addition of diethyl fluoromalonate to α,β unsaturated aldehydes was carried out in the presence of a simple prolinol organocatalyst that proceeded in good yield and enantiopurity (Scheme 12).[46]
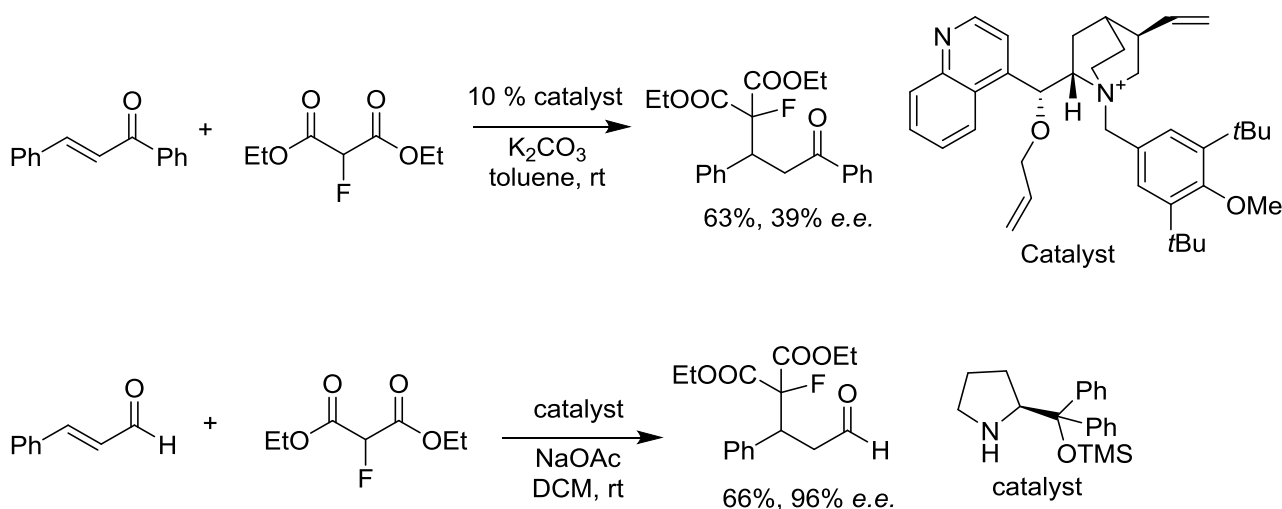
SCHEME 12. Enantioselective Michael addition of diethyl fluoromalonate to α,β-unsaturated carbonyl derivatives.

Nitroalkenes are Michael-acceptors that are often used in the testing of novel chiral catalyst systems and, in 2009, three different catalysts were shown to be very effective for the addition of fluoromalonates to nitroalkene substrates[47-49] (Scheme 13).
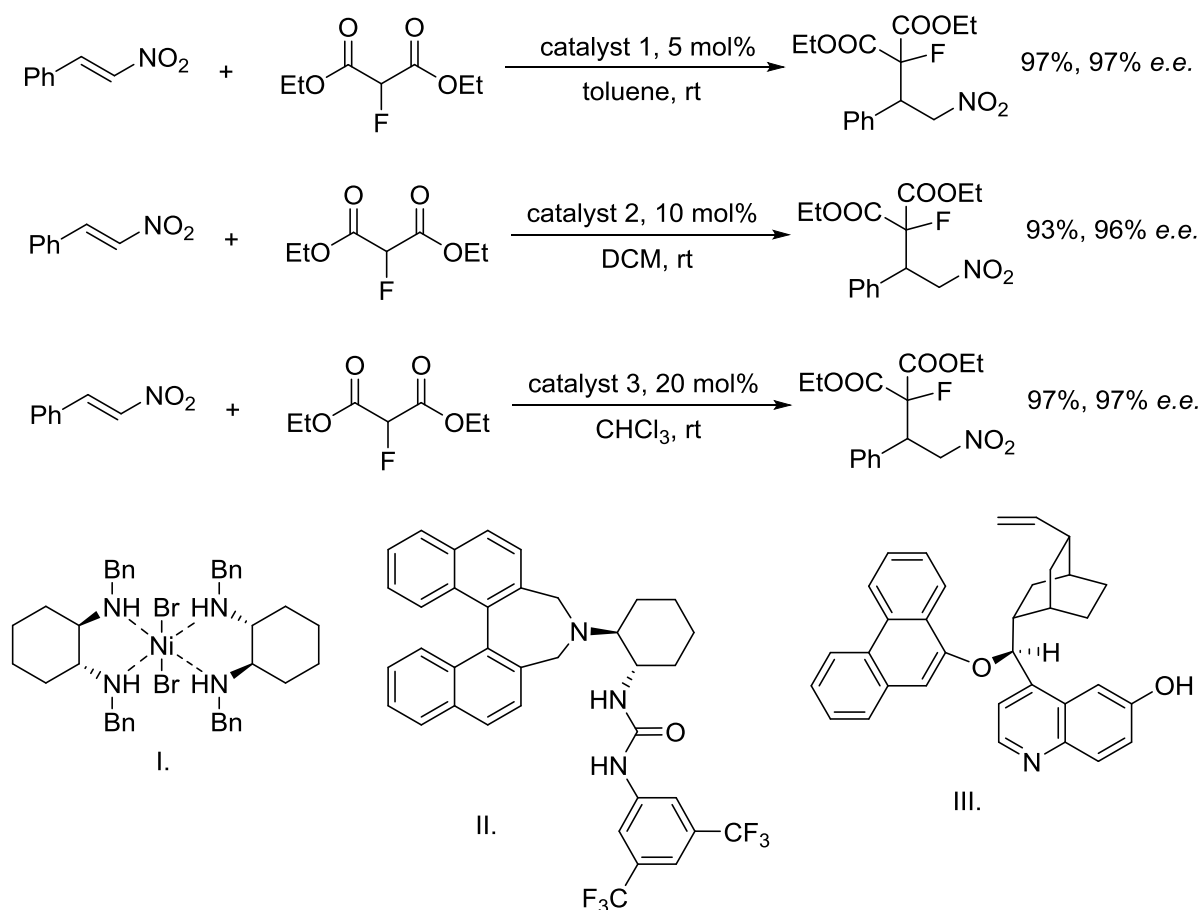
SCHEME 13. Enantioselective addition of dialkyl fluoromalonates to nitroalkenes.

Although the yields and enantiopurities are very similar, the nickel complex catalyst appears to be more effective than the organocatalysts for these addition reactions since the reaction times are significantly shorter and the catalyst load is lower (5 mol% vs 10 and 20). While the organocatalysts react slowly with related *ortho*-substituted benzene derivatives, the nickel catalyst is not found to be affected by steric effects. The absolute configuration of these products was found to be *S* in all cases.

Michael addition of fluoromalonates to related systems have been used in the synthesis of several complex monofluorinated structures such as α-fluoro-γ-aminoacids[37], 4-fluoroglutamates[50] and 4-fluoro-5,5'-dihydroxyleucine derivatives[51], that find use as herbicides,[52] immuno-modulators[53] and potassium channel deactivator[54] compounds (Scheme 14).
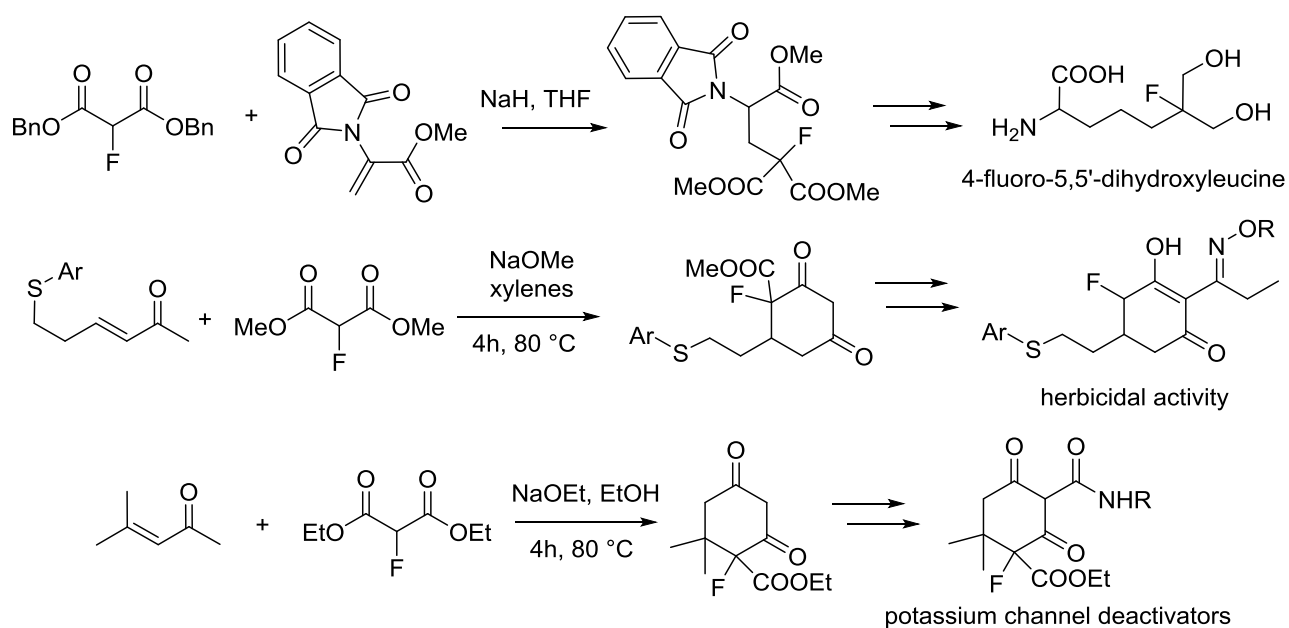
SCHEME 14. Michael addition reactions of fluoromalonates.

Arylation by nucleophilic aromatic substitution processes involving reaction of fluoromalonate anion with 2-fluoronitrobenzene and nitrobenzyl bromide derivatives provides convenient access to unusual 3-fluoroxindole[55] and 3-fluorotetrahydroquinolone[56] derivatives respectively (Scheme 15).
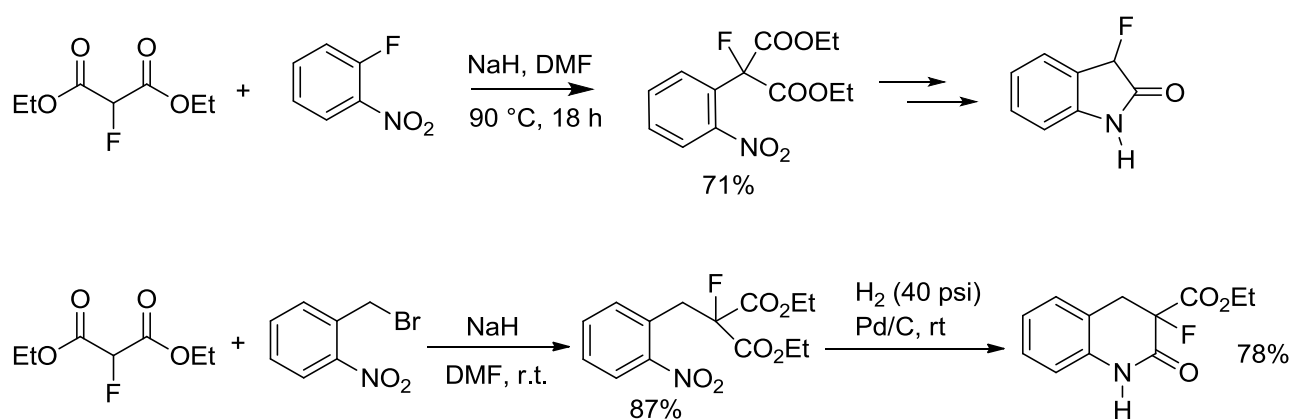
SCHEME 15. Synthesis of 3-fluoroxindole and 3-fluorotetrahydroquinolone derivatives.

Using a more generally applicable procedure, palladium catalysed reactions allow cross-coupling of diethyl fluoromalonate with a variety of aryl bromides (Scheme 16).[57] This methodology has already been employed for the synthesis of novel fluorinated arylamide derivatives that are potential cancer treatment drug candidates.[21a]
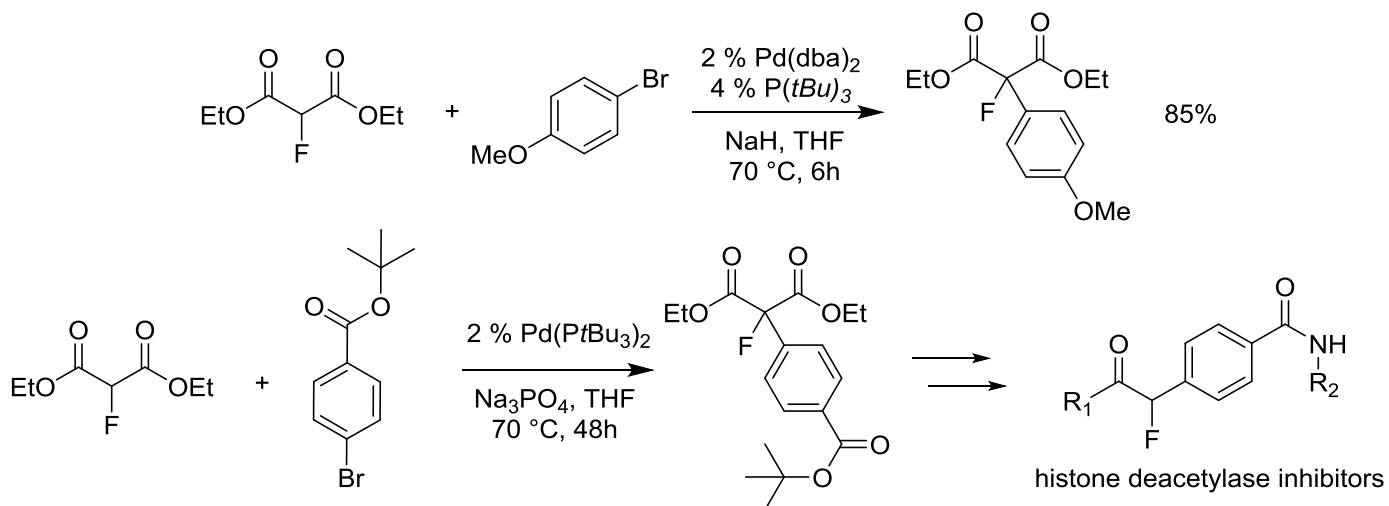
SCHEME 16. Pd catalysed arylation of diethyl fluoromalonate.

3.2   Functional group interconversion reactions

Hydrolysis of one of the ester groups of fluoromalonate systems can be achieved by heating in aqueous acidic media enabling, for example, the simple synthesis of α-fluorocarboxylic acid derivatives and, despite the simplicity of these reactions, only a few examples of this chemistry have been reported. Early publications discussed the synthesis of 2-fluoroalkanoic acids[12,38] and 2-fluoro-2-phenylacetic acid[22] and several similar syntheses of bioactive compounds such as anti-cancer system 2-fluoro-6-benzothiophenyl acetic acid,[21a,58] 2-aryl-5-fluoromethyl-1,3,4-oxadiazol[21b] derivatives, 3-aryldifluoromethylpyridazines[59] and α-fluorovalerolactone containing steroids[60] (Scheme 17) have been reported in the patent literature.
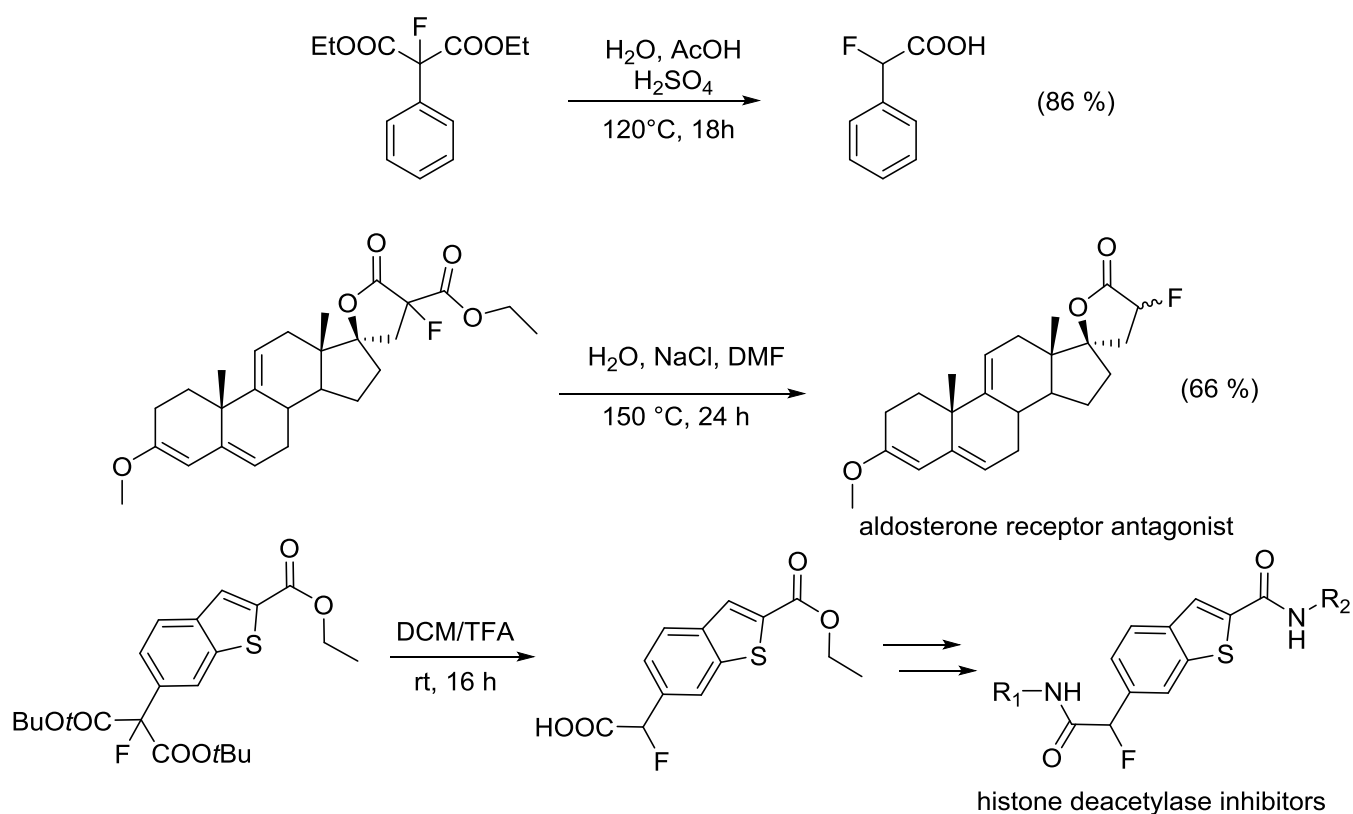
SCHEME 17. Acid hydrolysis of fluoromalonate systems.

Possibly the only practical syntheses of 2-fluoro-1,3-propanediol derivatives are reductions of appropriate fluoromalonate derivatives using diborane in tetrahydrofuran[61] or calcium borohydride.[62] Similarly, fluoromalonates can be reduced to 2-fluoro-3-hydroxypropanoates if the monoester is first prepared by partial hydrolysis of the corresponding diesters (Scheme 18).[63]
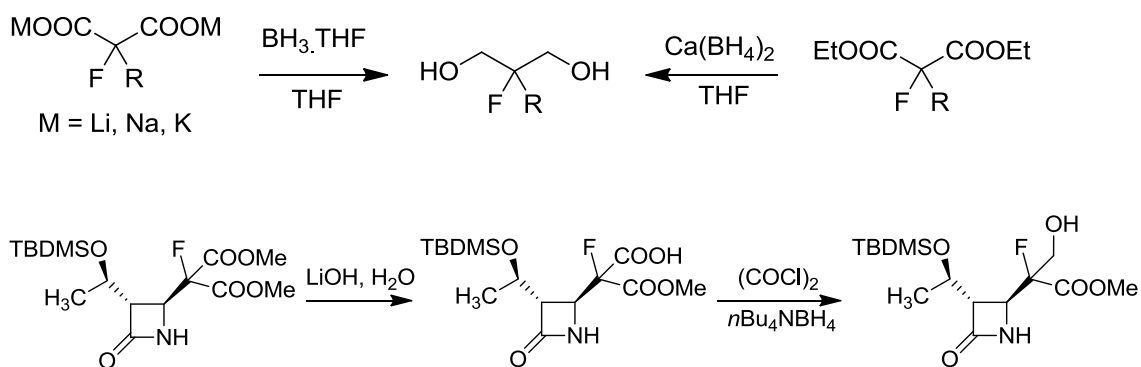
SCHEME 18. Reduction of fluoromalonate esters

Malonamides and propane 1,3-diamines are practical building blocks for the synthesis of more complex structures such as heterocycles and macrocycles. The fluorinated analogues can easily be prepared from dialkyl fluoromalonates by reaction with amines and reduction as appropriate. An early example of this chemistry was the synthesis of several fluorinated cyclam (1,4,8,11-tetraazacyclotetradecane) systems that form metal ion complexes.[64] The incorporation of 2-fluoro- or 2,2-difluoro-1,3-diaminopropyl segments into complex bioactive structures such as potential antitumor,[65-67] Alzheimer's disease,[68,69] cardiovascular disease,[70] immunosuppressant activity,[71] and enzyme inhibition[72] systems. Similarly, fluorinated 1,4-benzodiazepines were successfully synthesised from diethyl fluoromalonates when reacted with appropriate 1,2-diaminobenzenes (Scheme 19).[31b,73]
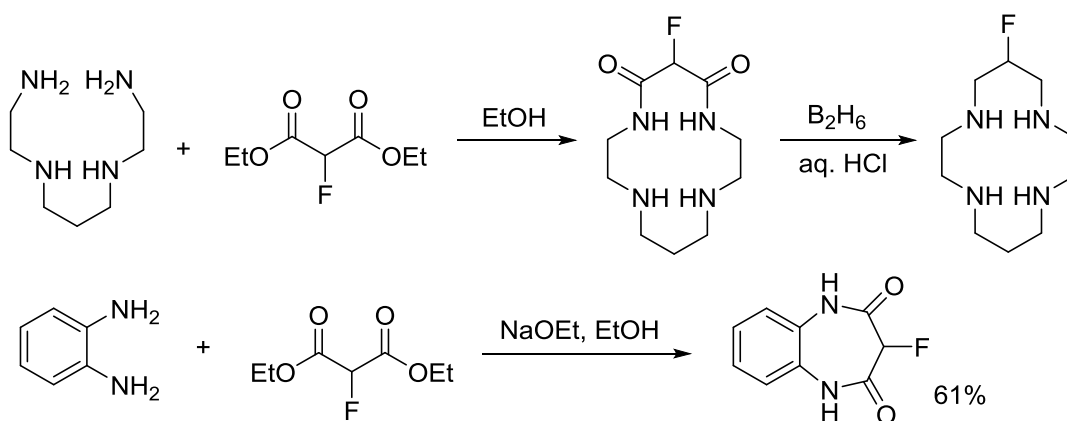
SCHEME 19. Synthesis of fluorinated diamides and cyclam.

Arguably, the most important applications of fluoromalonate derivatives are for the synthesis of different heterocyclic structures and the earliest fluoroheterocycle synthesis using diethyl fluoromalonate was the preparation of 2-ethylthio-5-fluoro-4,6-dihydroxypyrimidine by reaction of diethyl fluoromalonate with *S*-ethyl *iso*thiouronium bromide.[29] In 2009, a novel antibacterial drug family bearing a 5-fluoropyrimidine unit was patented by GSK.[74] The synthesis of this drug family is based on condensation of dialkyl fluoromalonates with amidines followed by halogenation to give a 2-substituted 4,6-dichloro-5-fluoropyrimidine drivative that can be further functionalised using standard synthetic transformations. 4,6-Dihydroxypyrimidines can easily be converted to the corresponding dichloropyrimidines using phosphorus based halogenating reagents such as PCl_3, $POCl_3$ or PCl_5.[75] Fluoxastrobin, a commercially significant herbicide, is synthesised from fluoromalonate[76] by Bayer CropScience by a similar strategy (Scheme 20).

Fluoxastrobin (Bayer).
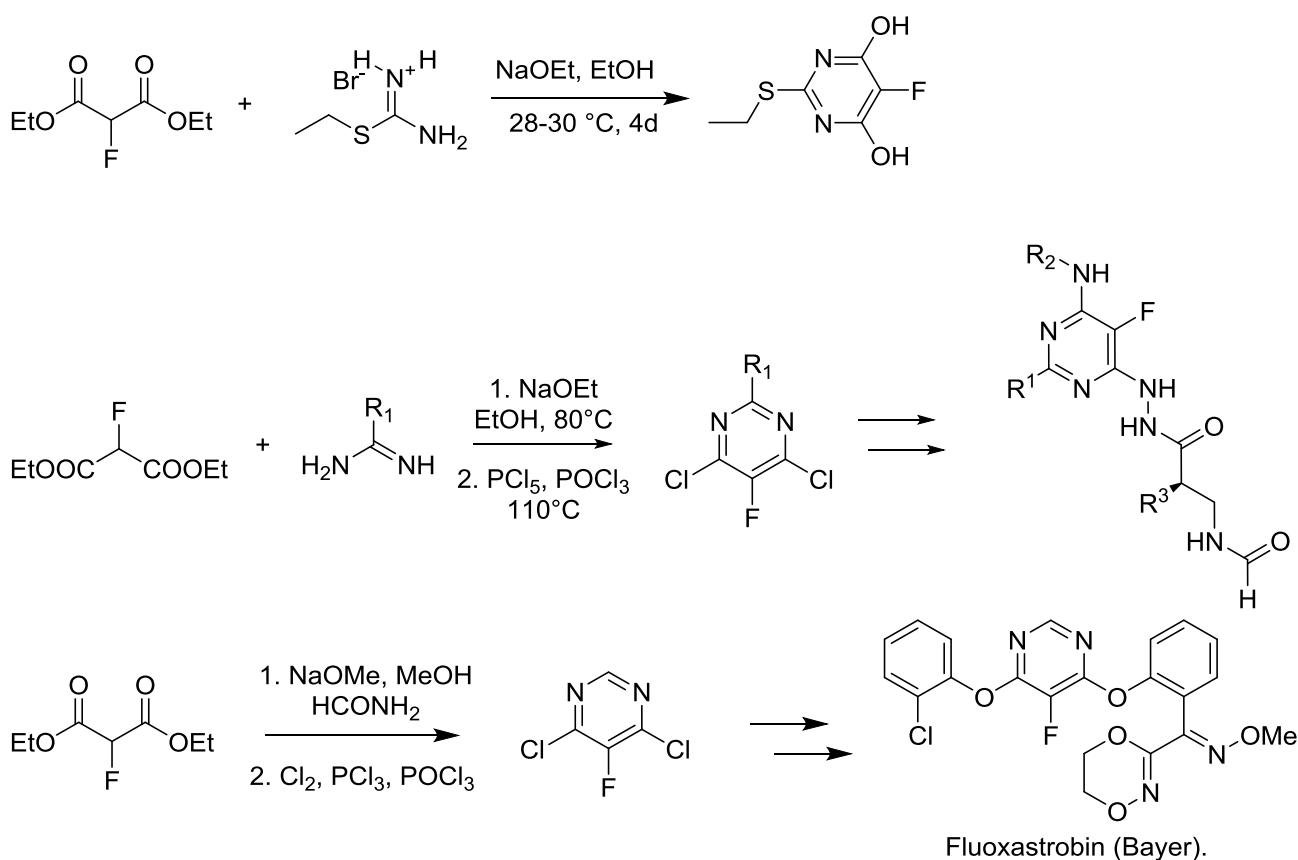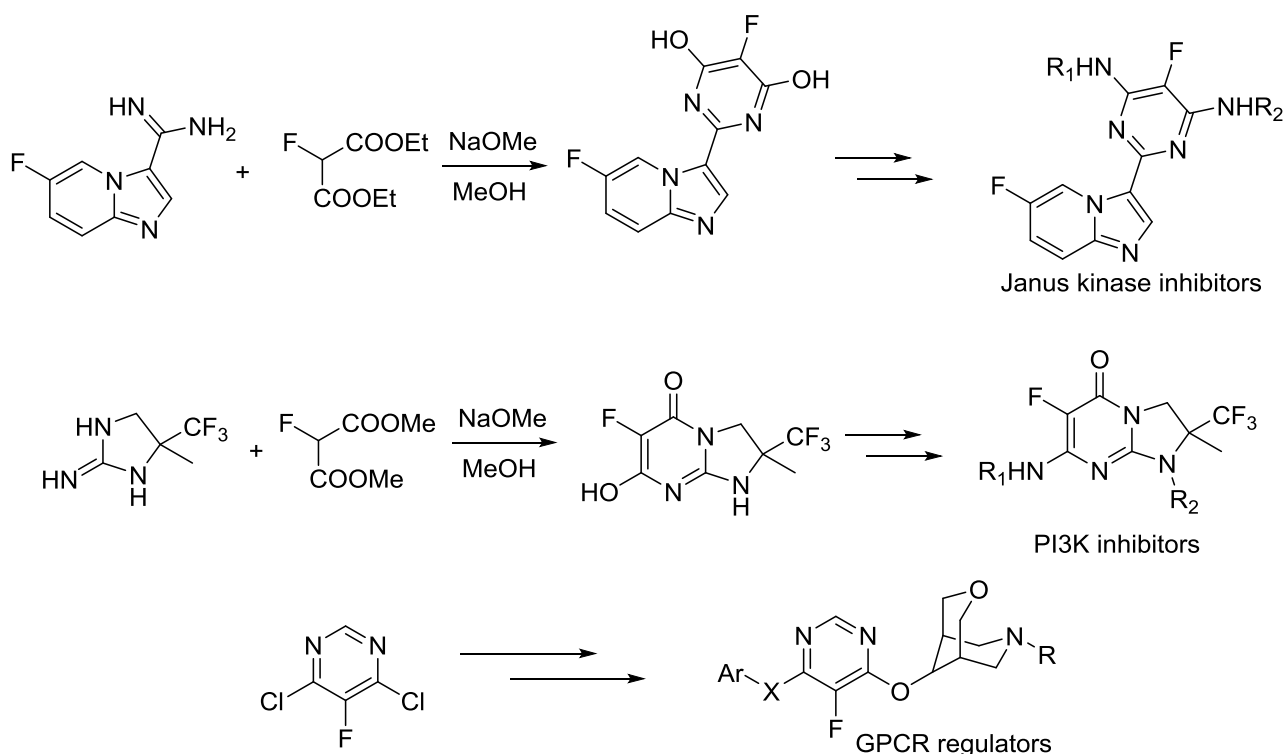
SCHEME 20. Synthesis of 5-fluoro-pyrimidine derivatives.

Since 2005, several further pharmaceutical and agrochemical patents have described biologically active systems bearing the 5-fluoropyrimidine sub-unit within more complex systems. In most of these cases compounds are derived from 4,6-dichloro-5-fluoropyrimidine derivatives including Janus kinase inhibitor,[77] orexin receptor modulator,[78] anti-cancer,[79] GPCR inhibitor,[80] RAF kinase inhibitor,[81] calcium channel antagonists[82] and chronic obstructive pulmonary disease treatment systems.[83]

Dimethyl 2-fluoromalonate was used in the large scale synthesis of 3-fluoroquinoline derivatives that were used in the synthesis of novel anti-bacterial drug candidates (Scheme 21).[84]
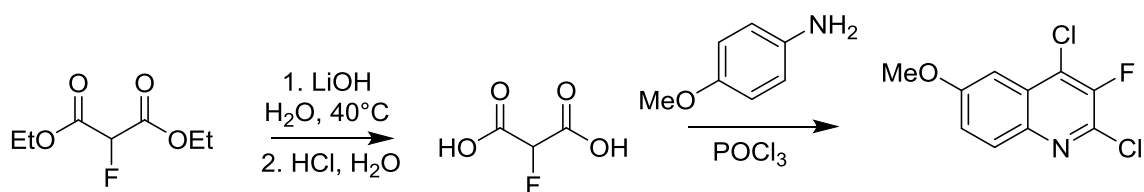
SCHEME 21. Synthesis of 3-fluoro-6-methoxyquinoline using dimethyl fluoromalonate.[84]

A recent report from Takeda Pharmaceuticals discusses the synthesis of 3,5-disubstituted 6-fluoro-8-methylpyrido[2,3-d]pyrimidine-4,7-(3H,8H)-diones which are active pharmaceutical ingredients used for the synthesis of various drug candidates (Scheme 22).[85]
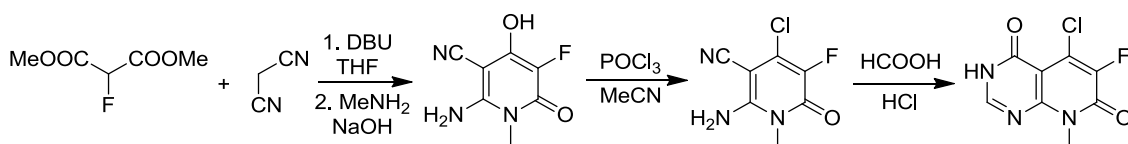
SCHEME 22. Synthesis of 6-fluoro-8-methylpyrido[2,3-d]pyrimidine-4,7-(3H,8H)-dione.

3.3 Biotransformations for the synthesis of chiral fluorinated building blocks

The first reported use of fluoromalonates for the synthesis of chiral building blocks was the enantioselective enzymatic hydrolysis of malonate esters to malonate monoesters[86] using esterase (*Candida Cylindracea*) and cellulase (*Trichoderma Viride*) enzymes (Table 1).

TABLE 1. Enzymatic asymmetric hydrolysis of fluoromalonates.[86]

Substrate	Origin of enzyme	Yield (%)		%ee
MeCF(COOEt)$_2$	*Candida Cylindracea*	87	(-)	91
MeCF(COOEt)$_2$	*Trichoderma Viride*	60	(+)	56
MeCF(COOMe)$_2$	*Candida Cylindracea*	74	(-)	95
MeCF(COOMe)$_2$	*Trichoderma Viride*	83	(+)	46
EtCF(COOEt)$_2$	*Candida Cylindracea*	87	(-)	93
EtCF(COOEt)$_2$	*Trichoderma Viride*	No reaction		-
EtCF(COOMe)$_2$	*Candida Cylindracea*	87	(-)	99
EtCF(COOMe)$_2$	*Trichoderma Viride*	No reaction		-
CHF(COOEt)$_2$	*Candida Cylindracea*	70	(+)	62
CHF(COOEt)$_2$	*Trichoderma Viride*	51	(+)	58
n-PrCF(COOEt)$_2$	*Candida Cylindracea*	No reaction		-
n-BuCF(COOEt)$_2$	*Candida Cylindracea*	No reaction		-

The results clearly indicate that, with the selection of the appropriate enzyme, chiral fluoromalonate monoesters can be obtained in excellent yield and enantiopurity. Using appropriate enzymes, both enantiomers may be synthesised, but the lipase from *Candida Cylindracea* appears to be a more efficient catalyst for this transformation. The scope of this hydrolysis reaction is very limited because alkyl chains longer then ethyl completely inhibit the reaction due to steric inhibition. The absolute configurations were determined by reducing (+)-2-fluoromalonate monoethyl ester to the corresponding known *R*-ethyl 2-fluoropropionate.[87] Substitution of a hydrogen atom by fluorine does not affect the highly stereo-controlled enzymatic reactions.[88]

A practical approach to asymmetric 2-aryl-2-fluoro-1,3-propanediol monoacetate derivatives was developed using enzymatic hydrolysis of 2-aryl-2-fluoromalonate esters.[89] In these reactions, Celite supported porcine pancreatic lipase (S-PPL) was used for the asymmetric hydrolyses that ultimately led to 1-(O)-benzyl-2-aryl-2-fluoro-1,3-propanediol products with good enantiopurity. The substrate scope was later extended to 2-methoxy systems but in this case microbial lipase Amano AY, (AYL) was utilised (Scheme 23).[90]
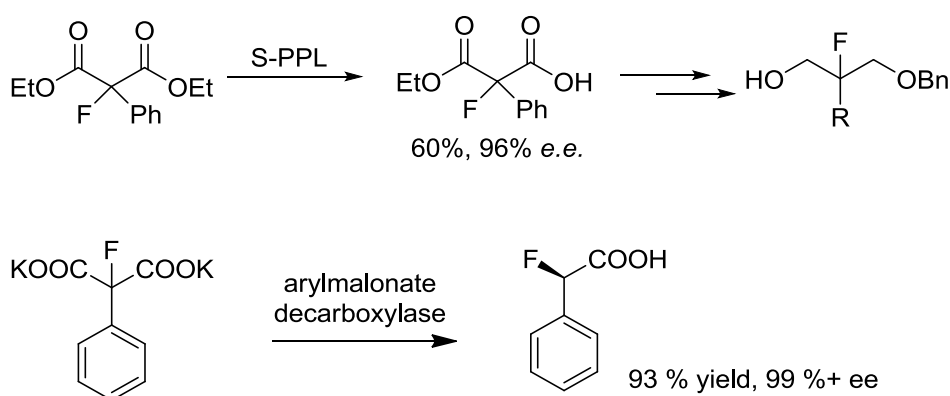
SCHEME 23. Asymmetric hydrolysis and decarboxylation of 2-substituted fluoromalonates.

Enantiopure 2-fluoro-2-phenylacetic acid is used as a chiral derivatising agent to determine enantiomeric excess by ^{19}F NMR.[91] A very efficient and selective synthesis of (R)-2-fluoro-2-phenylacetic acid was developed by Japanese researchers when an arylmalonate decarboxylase enzyme (expressed from *E. coli* JM 109) was used to decarboxylate dipotassium 2-fluoro-2-phenylmalonate.[92] The crude product of the reaction already was 99.1% pure *R* isomer, but after one recrystallization (69% recovery) enantiopure product was obtained.

The first use of synthetic biology for the synthesis of fluorinated systems has been reported by Chang and co-workers. In this process, fluoromalonyl-CoA was used to synthesise fluorinated polyketides avoiding the use of highly toxic fluoroacetyl-CoA (Scheme 24).[93]
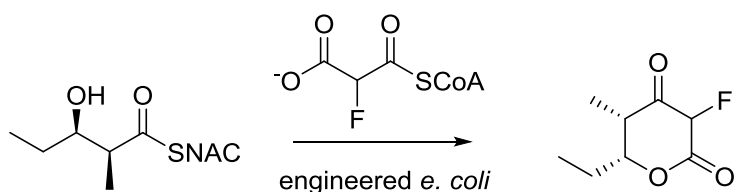
SCHEME 24. Synthesis of fluorinated polyketides

4.   Conclusions

Fluoromalonate esters are readily synthesised on a large scale and a variety of transformations allowing the preparation of structurally more sophisticated fluoro-aliphatic and heterocyclic derivatives have been described. Given the importance of fluorine containing structural sub-units in pharmaceuticals and the synthetic versatility of fluoromalonate systems, it is perhaps surprising that only a relatively few publications and patents describing the chemistry of fluoromalonates have been reported. This review has outlined the potential for the use of fluoromalonates in synthesis as a contribution to the development of new generations of fluorinated pharmaceuticals.

5.   References

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