Synthesis and Applications of Fluorinated Multi-Carbonyl Systems via Batch and Flow Processes

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Synthesis and Applications of Fluorinated Multi-Carbonyl Systems via Batch and Flow Processes

by

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One never notices what has been done,
one can only see what remains to be done.

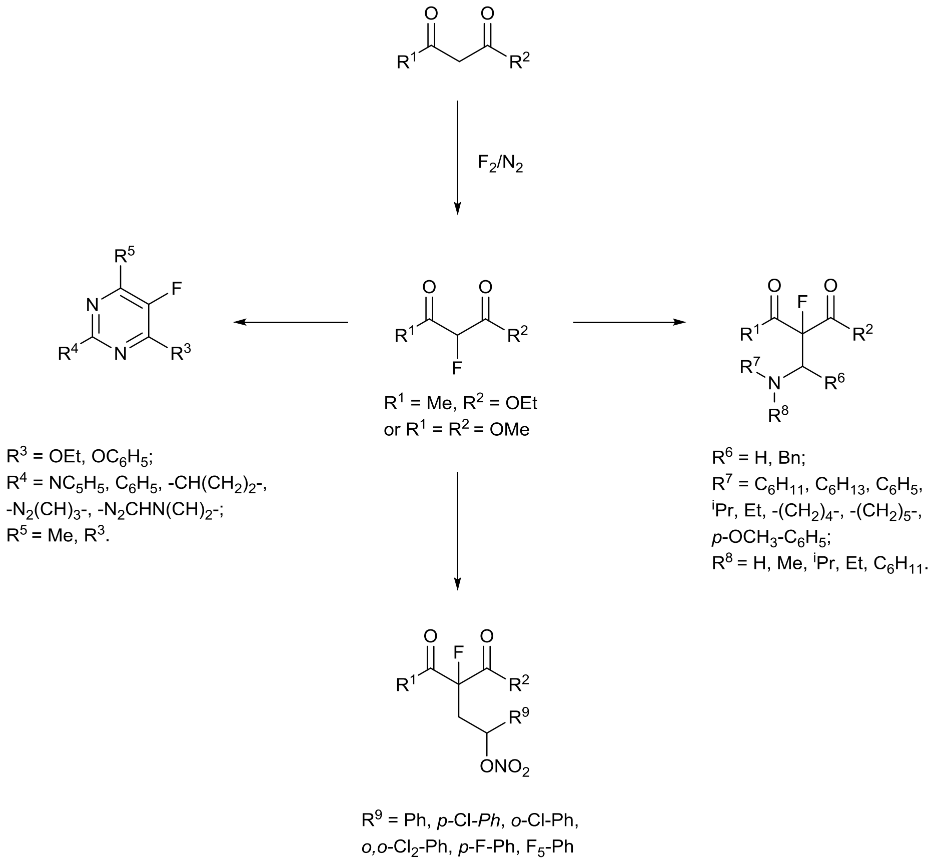
- Marie Curie

A mes grands-parents

Abstract

Organofluorine chemistry has played a significant role in the majority of the spectacular scientific and technological developments of the past century. Two key challenges in organofluorine chemistry remain selective methods for the formation of carbon-fluorine bonds and the synthesis of complex fluorinated molecules under mild conditions.

The incorporation of fluorine atoms into a pharmaceutical candidate is a well established approach to, for example, affect lipophilicity, pKa and metabolic stability of new chemical entities as part of drug discovery programs. Consequently, effective and inexpensive methodologies for the synthesis of selectively fluorinated multifunctional building blocks for incorporation into drug synthesis campaigns are very desirable.



***Scheme 1** Various fluorinated molecular systems investigated in this thesis*

In the context of developing the use of 2-fluoro-1,3-dicarbonyl substrates for the synthesis of more structurally complex fluorinated intermediates, we investigated routes to various fluorinated systems. As part of a general strategy aimed at assessing the effect of the carbon-fluorine bond attached to the reactive enolic site of the 2-fluoro-1,3-dicarbonyl system, we used this reactivity profile for the synthesis of pharmaceutically relevant fluorinated intermediates (Scheme 1).

Several APIs present a fluoro-pyrimidinone structure, therefore a synthetic pathway giving access to functionalized fluorinated pyrimidinones has been established. Secondly, after testing various radical initiators, we applied a free radical chemistry strategy to reactions of 2-fluoro-1,3-dicarbonyl systems using Ceric Ammonium Nitrate (CAN) and various olefins, affording fluorinated nitro-oxy products by a catalytic oxidative addition. Finally, as the value of multicomponent reactions (MCRs) in drug development gives rapid access to large libraries of molecules possessing a high degree of functionality and structural diversity, we developed a synthetic strategy using β-fluoroketoesters and β-fluoromalonate substrates as MCR components in Mannich reactions involving various aldehydes and amines, using both batch and flow processes.

Additionally, we investigated the potential use of fluorinated 1,3-dicarbonyl systems to act as nucleophiles in nucleophilic substitutions involving poly-fluorinated aromatic systems and also studied the direct fluorination of functionalized tri-carbonyl systems.

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My thanks firstly go to Professor Graham Sandford who supervised and mentored my work, for his attention, his availability, his interest in my studies, for all his answers to many of my questions, for all the knowledge he helped me deepen and all the time he awarded to me. Despite my “french” way of working, I thank him for all his advices, encouragements and “keep going” enthusiastic comments, especially when the chemistry was giving me tough moments.

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Memorandum

The work described in this thesis was carried out at Durham University between September 2014 and September 2017. This thesis is the work of the author, except where acknowledged by reference, and has not been submitted for any other degree. The copyright of this thesis rests with the author. No quotation from it should be published without the prior written consent and information derived from it should be acknowledged.

Parts of this work have been the subject of the following publication:

- E. Lisse, G. Sandford, *J. Fluorine Chem.* **2018**, *206*, 117-124

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- 17th RSC Postgraduate Symposium in Fluorine Chemistry, Leicester, UK, 18-19th September 2017, *oral presentation*
- European Symposium on Organic Reactivity, Durham, UK, 3-8th September 2017, *poster presentation*
- 18th Tetrahedron Symposium, Budapest, Hungary, 27-30th June 2017, *poster presentation*
- Durham Chemistry Postgraduate Gala Symposium, 15th June 2017, *oral presentation*
- RSC Organic Division North East Regional Meeting, Durham, 29th March 2017, *poster presentation*
- “Fluorine as Key Element” Symposium, Berlin, Germany, 24-25th November 2016, *oral presentation*
- 16th RSC Postgraduate Symposium in Fluorine Chemistry, Oxford, UK, 22-23th September 2017, *poster presentation*

Abbreviations

σ	substituent constant
Å	Angström
abs.	absolute
Ac.	Acetyl
AIBN	Azobisisobutyronitrile
Ar	aryl
ASAP	Atmospheric solid analysis probe
atm.	Atmosphere
Boc	tert-Butyloxycarbonyl
bp	boiling point
Bu	butyl
Cat.	Catalytic
CAN	Ceric ammonium nitrate
CFC	chlorofluorocarbon
conc.	Concentrated
COSY	Correlation spectroscopy
DAST	Diethylaminosulfur trifluoride
DBU	Diazabicycloundecene
DBN	1,5-Diazabicyclo(4.3.0)non-5-ene
DCC	N,N'-dicyclohexylcarbodiimide
DCM	Dichloromethane
Deoxofluor^{TM}	Bis(2-methoxyethyl)aminosulfur trifluoride
DFT	Density Functional Theory

dist.	Distilled
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxyde
e.e.	enantiomeric excess
EI	Electronic ionisation
eq.	equivalent
ESI	Electrospray ionisation
Et	ethyl
FBDD	fragment-based drug discovery
FEP	Iron(III) perchlorate nonahydrate
g	gram
GC	Gas chromatography
GC-MS	Gas chromatography - Mass spectrometry coupling
h	hour
hv	photochemical
HCFC	hydrochlorofluorocarbon
HTS	high-throughput screening
Hz	Hertz [s^{-1}]
i-pr	isopropyl
IR	infrared
Lit.	literature
Ln	ligand
m-	meta

M	molar
m/z	relationship mass/charge
MCP	methylenecyclopropane
MCR	multi-component reaction
Me	Methyl
MHz	Megahertz
min	minute
mp	melting point
M.S.	molecular sieve
MS	Mass spectrometry
MW	Micro Wave
NBA	Nitrobenzoic acid
NFOBS	N-fluoro-*o*-benzenedisulfonimide
NFSI	N-fluorobenzenesulfonimide
NMR	Nuclear magnetic resonance spectroscopy
o-	ortho
p-	para
Ph	Phenyl
ppm	parts per million
psi	pounds of force per square inch of area
PTFCE	Polychlorotrifluoroethene
PTFE	Poly(tetrafluoroethylene)
PTSA	p-Toluenesulfonic acid
quant.	Quantitative

Rf	Retention factor
r.t.	Room temperature
Selectfluor^{TM}	1-Chloromethyl-4-fluoro-diazonia[2.2.2]bicyclooctane-bis(tetrafluoroborate
SET	single electron transfer
TBAF	Tetra-n-butylammonium fluoride
TBDMS	tert-butyldimethylsilyl
t-Bu	tert-Butyl
TEA	triethylamine
temp.	temperature
THF	Tetrahydrofuran
TMS	Trimethylsilane
Ts	Tosyl
VNS	Vicarious Nucleophilic Substitution

Table of contents

Chapter 1 Organofluorine chemistry: importance and properties

Apart from a few exceptions, molecules containing a carbon-fluorine bond are not present in nature, thus making organofluorine chemistry largely “man-made”. Interestingly, even if not noticeable, fluorinated organic molecules are present pretty much everywhere in our daily life, such as chlorofluorocarbon refrigerants, recently replaced by ozone-friendly hydrofluorocarbons, which are present in everybody’s kitchens. Moreover, the medical and pharmaceutical industries have been revolutionized by the appearance of fluorinated anaesthetics or products such as the well-known antidepressant Prozac®. In fact, the presence of fluorine atoms in those molecules conferred them their respective specific properties and biological activities. Applications of fluorinated molecules are also really diverse, fluoro-polymers such as Teflon®, developed by DuPont, for non-stick coatings on cookware or Goretex®, invented by W. L. Gore, for the waterproof clothing are among the best proofs. Perfluorinated materials made supersonic flights and space travel possible and perfluorocarbon fluids were recently used as imaging agents for the diagnosis of heart disease and as oxygen-carrying blood substitutes.

In the past few decades, organofluorine chemistry therefore appears to be quite successful in a wide variety of applications, opening a free space for further synthetic investigations and transformations, so broadening access to a full variety of fluorinated molecules is important. In this thesis, we are firstly going to describe briefly in this chapter the history of organofluorine chemistry and the specific properties conferred by fluorine atoms when present in molecules. The development of direct fluorination towards desired key fluorinated intermediates will also be discussed.

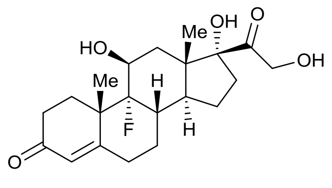
1. Historical review

The fluorine atom possesses some extreme properties, such as high electronegativity and oxidation potential, as predicted from its position on the periodic table of elements. Therefore, elemental fluorine is difficult prepare by chemical reaction, but Henri Moissan managed to isolate it in 1886 using scientific ingenuity, which gave him the Nobel Prize in 1906 thanks to the method he developed using electrolysis, which is still in use for industrial production of fluorine gas.[1,2]

However, many experts able to handle fluorine gas using specific laboratory equipment struggled to develop the field of fluorine chemistry really quickly after Moissan's achievement and the first fluorinated chemicals were only synthesized on industrial scale in the late 1930s.[3]

In fact, a really larger scale production of elemental fluorine was achieved due to the necessity of producing fissile Uranium 235. At this stage, uranium hexafluoride UF_6 was found to possess optimal physicochemical properties to separate the fissile U-235 from heavier U-238 using a centrifugation processing strategy. As UF_6 is a really corrosive compound, developing inert fluorine-based special materials, like polymers such as Teflon® was mandatory to achieve its production. At the same time, many methodological discoveries were made, such as developing electrophilic fluorinating agents, electrochemical fluorinations or strategies to deal with the violent reactivity of fluorine gas. Those approaches helped in a large part to develop synthetic organofluorine chemistry and to give access to fluorine-containing building blocks.[4]

The idea of introducing fluorine atoms to alter properties of natural product molecules was almost unconceivable before the 1950s due to the abiotic properties of fluorine, and its applications were therefore limited to military and special materials needs. However, at this stage, the quite poisonous properties of a few naturally occurring fluorinated organic compounds were well-known and the first known fluorine-containing pharmaceutical compounds fludrocortisones **1** were discovered following a systematic study of series of 9α-halogenated cortisone derivatives (Figure 1).



1

Figure 1 *Molecular structure of fludrocortisone*

A link between the size of the halogen atom and the bioactivity of 9α-halogenated cortisones was discovered by Fried and Sabo in 1953.[5] Analyzing the anti-inflammatory activity of 9α-halo-17α-hydroxycorticosterone acetates, Fried and Sabo, after studying the chlorinated, brominated and iodinated derivatives, were investigating the properties of the 9α-fluorinated derivative, also known as fludrocortisone, and prepared it by reaction of the corresponding alcohol with anhydrous hydrogen fluoride. It indeed possessed a remarkable gluco-corticoid activity, which was ten times superior to the parent hormones.[6]

Following this work, Heidelberger and coworkers demonstrated in 1957 that 5-fluorouracil **2** was acting as an antimetabolite of natural uracil (Figure 2). 5-Fluorouracil and many of its derivatives were also mechanism based inhibitors of thymidylate synthase, the enzyme responsible for transformation of 2-deoxyuridine-5-monophosphate into 2-deoxythymidine-5-monophosphate.[7,8]

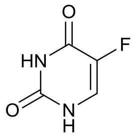


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Figure 2 *Molecular structure of 5-fluorouracil*

Pointing to the remarkable antitumor-inhibiting activity of 5-fluorouracil, the development of easier synthetic strategies to obtain more potent and tumor-selective analogs as useful pharmaceuticals remains an active research area. Indeed fludrocortisone and 5-fluorouracil constituted the starting point in terms of fluorine's place in biology-related research, and the role of fluorine in life sciences has never ceased to increase since then, such as an enhancement of the therapeutic efficacy and improvement of pharmacological properties.[9]

To summarize, it was clearly difficult before the 1960s to expect that introducing fluorine into natural products can result in beneficial biological properties, despite the fact that a certain number of past and current pharmaceutical products were either directly derived from or inspired by natural products.[10] But, in fact, until 1943, fluorine-containing natural products were not known in science and sodium monofluoroacetate was described to be hugely toxic and poisonous, despite the fact that it was the first isolated fluorinated naturally occurring compound.[11]

2. Relevance of fluorine containing molecules

2.1. General properties of fluorine atoms

Nowadays organofluorine chemistry plays a significant role in the majority of the spectacular and technological developments of the past century, due to the specific properties of the fluorine atom. Synthesis of fluoro-organic compounds has become a brand new research area and gives opportunity to access new fluorinated chemical space for different applications. The key step in developing new products and applications, involving fluorinated derivatives, is the synthesis of carbon-fluorine bonds by different fluorinating agents or using fluorinated “building blocks”.

Bearing in mind the fact that fluorine is the most electronegative element in the periodic table, it forms the strongest bonds in organic chemistry, when attached to a carbon atom, material science became attractive for the incorporation of fluorine. Although highly polarized, the C-F bond gains stability from the resultant electrostatic attraction between C and F atoms. Application to materials is mostly based on the properties derived from the fluorine-carbon bonds, which are hardly attacked by any oxidants or chemicals. One of the main results is that such strong bonds between fluorine and carbon atoms inhibit normal metabolism in a living body.

Fluorine is the 13th most common element on Earth’s crust, which is significantly more abundant than the other halogens but fluorine-containing natural products are extremely rare. Indeed, fluorine can be found on Earth in the form of insoluble salts fluorspar CaF_2 or cryolite Na_3AlF_6, thus explaining the limitations to delivery to aqueous biological systems. Compared to other halogen elements, fluorine possesses the highest oxidation potential: -3.06V compared to -1.36V for chlorine, -1.07 for bromine, -0.54 for iodine. Fluorine has also the highest hydration energy: 117 kcal/mol compared to 84 kcal/mol for chlorine, 78 kcal/mol for bromine and 68 kcal/mol for iodine, giving it a very poor nucleophilic behavior under aqueous biological conditions. The C-F bond is one of the strongest chemical bonds and its biological formation/cleavage requires extremely activated intermediates which are difficult to generate under biological conditions.[12]

On the other hand, the van der Waals radius of fluorine is not significantly longer than hydrogen. Accordingly, organofluorine compounds are similar in steric size to non-fluorinated derivatives but quite different in electronic nature. The mimic effect of the fluorine atom compared to hydrogen is also an important aspect of fluorinated molecules, because enzymes cannot make any steric distinction between the fluorinated and the non-fluorinated molecule and, therefore, they can be incorporated into metabolic sequences. However the C-F bond strength stops the normal metabolism in a living body to cause various biological effects, due to the opposite polarization.[13]

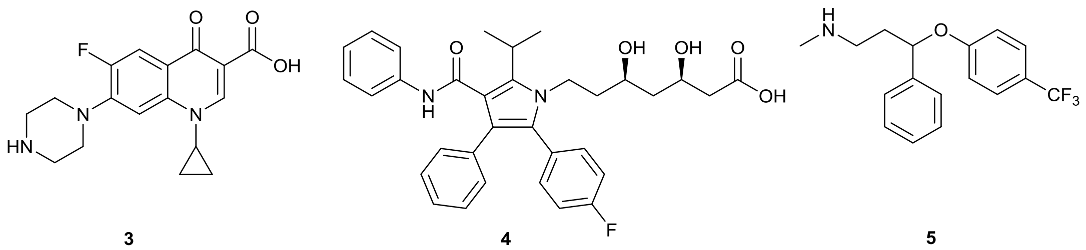
Properties of organic compounds can be largely affected by fluorine or fluorine-containing substituents. Fluorine's electronegativity, size, lipophilicity and electrostatic interactions can clearly impact the chemical reactivity of a synthesized intermediate molecule. To give a few examples, replacing a methyl group by a CF_3 group leads to a completely different chemical outcome, especially during a metabolic cascade of reactions where even the presence of only one fluorine atom can modify all the properties of the resulting compound. Despite the fact that modified properties are sometimes difficult to predict, there are few examples where the fluorine element modified all initial properties, such as for mono-fluoroacetic acid.[14]

Acidic or basic properties of organic molecules can also be affected by the presence of a fluorine atom, which can lead to modifications dealing with binding affinity, pharmacokinetic properties or bioavailability of any drug candidate.[15] The presence of $-CF_3$, $-S-CF_3$ or $-O-CF_3$ groups can also clearly modify the lipophilicity of corresponding non-fluorinated molecules, which can be explained by the alterations of electrostatic repulsive interaction or attraction between the fluorine atoms and the surrounding functional groups, leading to the access of different conformers.[16]

On aromatic rings, switching hydrogen atoms for fluorine atoms appears to be an effective strategy to modulate the metabolic stability and slow down significantly the oxidative metabolic step of a given drug by Cytochrome P450 monooxygenase enzymes. Fluorination has moreover an effect on hydrolytic metabolism by the electron-withdrawing property of fluorine, particularly affecting reaction rates, and the stability of intermediate metabolites.[17]

2.2. Fluorine in pharmaceuticals

Fluoro-organic molecules are key components in an ever increasing number of high-value commercially important products particularly in the life science industries. The use of fluorinated systems in drug discovery programs has continued to grow and, at present, 20% of commercially available pharmaceuticals and 30% of agrochemicals contain a fluorinated group. Among all fluorinated pharmaceuticals, some of them are well-known pharmaceutical compounds sold all around the world.[17-19] Among the top-selling pharmaceuticals, we can find: Lipitor® as the best-selling drug in 2008, Atorvastatin used for treatment against high cholesterol and triglyceride level and for the prevenetion of heart attacks and strokes, antidepressant fluoxetin, also known as Prozac® and the antibacterial ciprofloxacin, well-known by its name Ciprobay (Figure 3).



3 Ciprofloxacin

4 Lipitor

5 Fluoxetin (Prozac®)

Figure 3 *Examples of well-known fluorinated drugs*

The most common fluorinated systems in pharmaceutical structures contain fluoroaromatic sub-units or trifluoromethyl aryl systems (Figure 4), and can be synthesized using anhydrous hydrofluoric acid. However, new methodology for the incorporation of fluorine atoms located at sp^3 centres is needed and synthetic conditions using fluorinating agents have been investigated. New selective fluorination processes by using both innovative chemoselective methodology and synthetic biochemistry can provide new synthetic strategies to introduce a fluorine atom into an organic system.

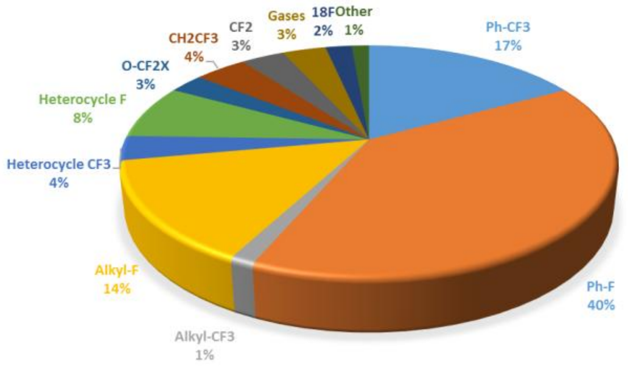
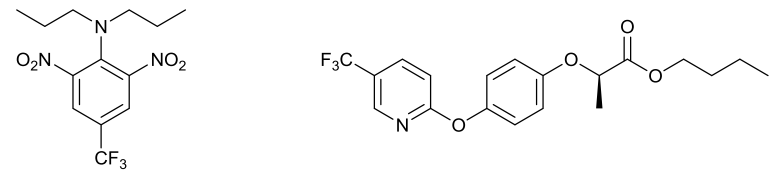


Figure 4 *Distribution of fluorine in drugs*

Developing fluorinated drug candidates firstly involves the design of molecules with the fluorine element in the right position. All the synthetic studies around fluorinated biological and medicinal fluorinated molecules allow us to predict the impact of the presence of the fluorine atom for a structural type of synthesized molecule.[20]

2.3. Fluorine in agrochemicals and liquid crystals

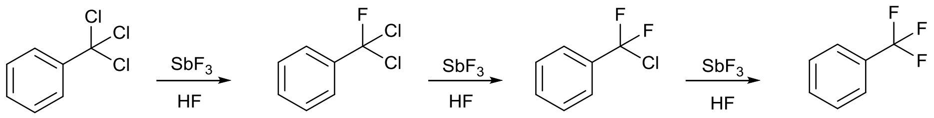
Among many other different applications of fluorinated systems, we can cite: aryl-CF_3 containing herbicides (Figure 5) synthesized by halogen exchange reaction (Scheme 2), anti-bacterial agents and insecticides synthesized by Balz-Schiemann (Scheme 3) or aromatic halogen exchange reactions (Scheme 4).[21]



6, Treflan, herbicide (Eli Lilly)

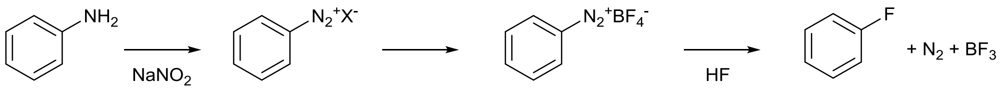
7, Fusilade, herbicide (ICI)

Figure 5 *Examples of aryl-CF_3 containing commercial herbicides*



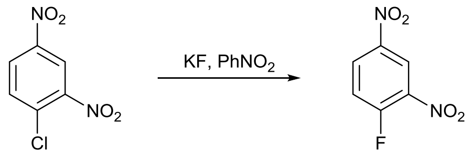
8 **9** **10** **11**

Scheme 2 *Reaction between benzotrichloride and SbF_3 via halogen exchange process*



12 **13** **14** **15**

Scheme 3 *Balz-Schiemann synthetic strategy towards fluorinated aromatics via diazotization in acidic conditions*



16 **17**

Scheme 4 *Nucleophilic halogen exchange used in fluoroarene synthesis*

Liquid crystals are also largely synthesized using aromatic halogen exchange process which produces aromatic intermediate building blocks with low fluorine content.[22] Other applications are in thin film transistor – liquid crystal display, transparent fluorinated resin for plastic optical fiber or for semi-conductor manufacturing process and last but not least new lubricants used for hard disc drives.[23]

3. Development of direct fluorination reactions

Introducing carbon-fluorine bonds into the various systems previously reported is largely using multistep nucleophilic fluorination processes. Even if alternative electrophilic fluorination methods exist, it seems that the potential for using fluorine gas as a reagent becomes more and more popular and recognized as a unique 2nd generation efficient fluorinating agent, aside of the first generation represented by HF and third generation, whose main examples are Selectfluor, or DAST (Figure 6). Indeed, there is a clear lack of reagents for the large scale transformation of a C-H bond to a C-F bond and elemental fluorine appears to be a fluorinating agent viable for industry scale applications.

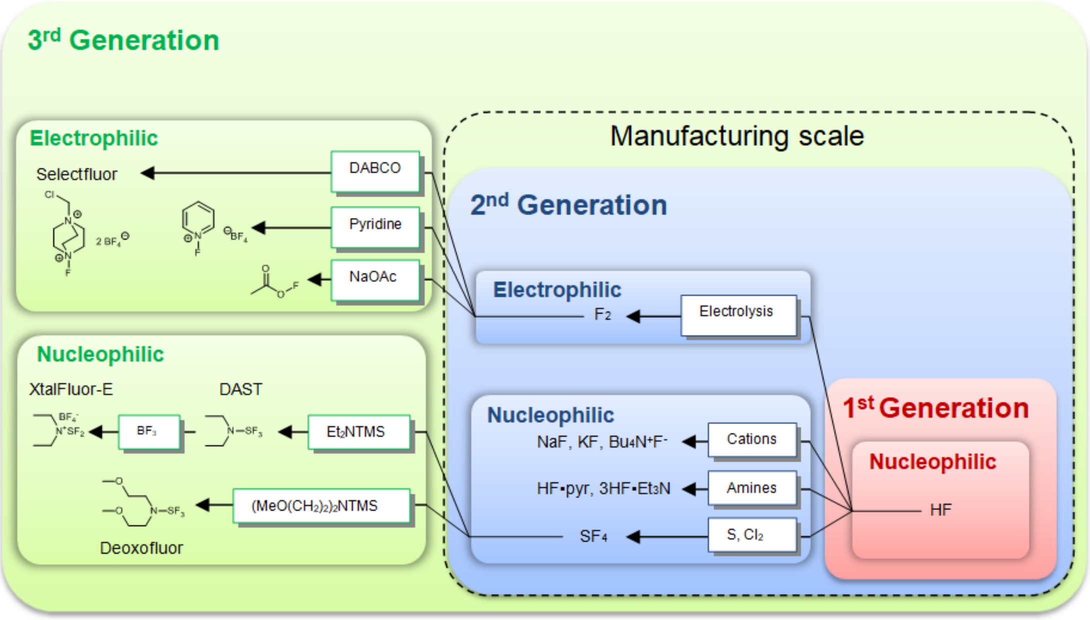


Figure 6 *Generations of fluorinating agents used in organofluorine chemistry*

In this part, a brief history of the development of direct fluorination reactions using fluorine gas, some recent resulting synthetic challenges and a quick overview of alternative fluorinating agents will be presented.

3.1. Historical overview of the use of elemental fluorine

Henri Moissan in 1886 synthesized for the first time elemental fluorine in small quantities by electrolysis of anhydrous hydrogen fluoride. He was one of the pioneers carrying out reactions between neat fluorine and several organic compounds, but in the late 19th century, only decomposed products and explosions were obtained.[24,25]

Controlling the reactions using fluorine was one of the main challenges of the early 20th century. One of the reported examples of explosions was the work of Bancroft and Jones in 1929 attempting the fluorination of benzene and toluene with molecular fluorine. Bancroft and coworkers repeated the same fluorination reaction two years later avoiding any explosions by using fluorine diluted by inert gases, only giving access to tarry products with high fluorine content though; confirmed a few years later by similar work by Beckmüller on several aromatic molecules.[26]

Opening a new chapter through the investigations around fluorination conditions, the first samples of fluorocarbons were made during World War II by reaction between carbon and elemental fluorine catalyzed by mercury. The direct fluorination of benzene with elemental fluorine in the vapor phase over a copper catalyst was achieved by Bigelow and Fukuhara, and perfluorocyclohexane was synthesized by this way despite moderate degradation. Important to be noticed were the yields up to around 60% of perfluorocyclohexane from benzene, encouraging chemists to find a more suitable preparation of fluorocarbons, such as the CoF_3 method that was reported few years later.[27,28]

At this stage, modifying the high reactivity of fluorine appeared to be a key point to study and different apparatus was created to control direct fluorination, such as the vapor-phase apparatus, developed by Bigelow, which was reported to be more efficient for the synthesis of low-molecular-weight fluorocarbons. An interesting fact was the scaled-up production of perfluoropropane, commonly used as a dry plasma etchant in microelectronics industry.[29]

Approximatively twenty years later, after trying to develop multiple fluorination apparatus, fluorination technique was improved by the appearance of the low temperature gradient fluorination, so called “LaMar” fluorination, named after Lagow and Margrave. The process was developed with various substrates which were condensed at low temperature into a tube packed with copper turnings through which fluorine, initially highly diluted in either helium or nitrogen, was passed. The concentration of fluorine and the reaction temperature were slowly increased over a period of several days to permit perfluorination. The only reported problems were the long reaction times required.[30]

Trying to find an ideal combination between the process and its corresponding apparatus, a flow version was reported. The selected substrate was adsorbed onto the surface of fine sodium fluoride particles in a fluorination apparatus into which fluorine is introduced and the apparatus is warmed and UV irradiated to complete perfluorination.[31]

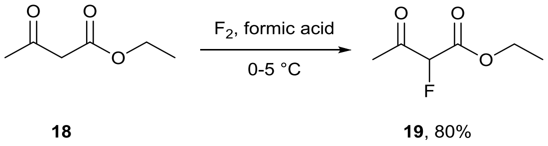
None of the methods described so far were as efficient as the one developed by Exfluor-Lagow, who claimed a perfluorination of ethers and esters without UV irradiation, with the principle of a slow inverse addition of hydrocarbon substrates into an inert liquid dissolving excess fluorine gas. Development of this method showed that adding a tiny amount of a highly reactive hydrocarbon such as benzene, which reacted spontaneously with fluorine to produce a very high concentration of fluorine radicals, ensured perfluorination of the chosen substrates. The liquid-phase fluorination process developed by Exfluor-Lagow was providing products in high yields with the only drawback of using CFCs as solvents due to solubility problems, which are now fully regulated as part of the global environmental strategy.[32]

Nowadays, fluorine gas is commercially available in various forms (pure or diluted with an inert gas, such as nitrogen) and on different scales, but large scale industry users prefer on-site generation (Figure 7).

Figure 7 *Fluorine cell room used in the manufacture of perfluorocarbon gases and fluids, at F2 Chemicals Ltd, Preston, UK*

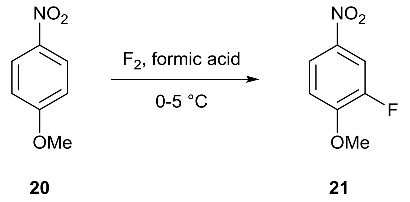
3.2. Selective fluorination challenges

In the last part of this chapter, we are going to describe the relatively recent work on selective direct fluorination methodology. The development of convenient, safe, efficient and economic methods to introduce fluorine into organic species opens a large field of investigations. The main problem with direct fluorination reactions is the large amount of heat generated by transforming the C-H bond into a C-F bond, which could lead to uncontrolled reactions. Nowadays, fluorine has been tamed by dilution into an inert gas like nitrogen, and a lot of direct fluorinations have been reported to be effective using low temperature and appropriate solvents. Among those, the Durham group reported direct fluorinations in acidic media such as formic acid, i.e. the preparation of fluorinated 1,3-dicarbonyl compounds, scaled up by F_2 Chemicals Ltd (Scheme 5).[25,33]



***Scheme 5** Direct fluorination of ethylacetoacetate in formic acid*

The chemistry of fluoro-dicarbonyl systems will be developed in the next chapter but other direct fluorination reactions of many systems effectively carried out in acidic media have been reported. It gives access to synthetic strategies involving controlled selective fluorination of various systems such as heterocycles, aromatics and carbohydrate derivatives using recently developed techniques (Scheme 6).[34]

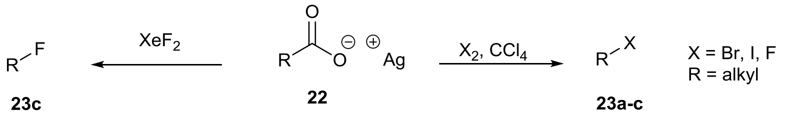


***Scheme 6** Direct fluorination of 1-nitro-4-methoxy-benzene in formic acid*

The last parts of this chapter will be dedicated to present various processes involving fluorination associated with further transformations, as it is relevant to our field of research, and a quick description of alternative fluorinating agents, for comparison with direct fluorination using elemental fluorine.

4. Alternative fluorinating agents

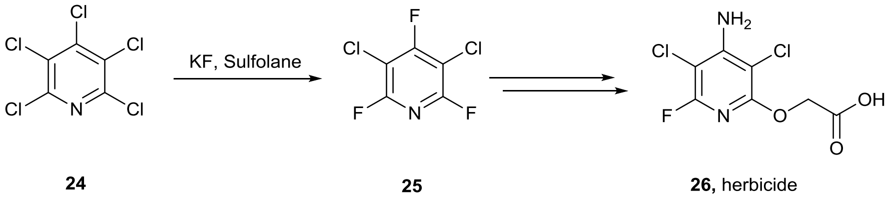
Considering the development of fluorination throughout the past decades, many other fluorinating agents have been developed, for fluorination of organic compounds. Among those, xenon di-, tetra-, and hexafluoride are known to be selective monofluorinating reagents, but they are unstable and quite expensive, which make them less popular than organic fluorinating agents, though they can be used, for example, in the fluoro-decarboxylation of carboxylic acids, giving a good alternative to the Hunsdiecker reaction shown in Scheme 7.[35,36]



Scheme 7 *Hunsdiecker reaction*

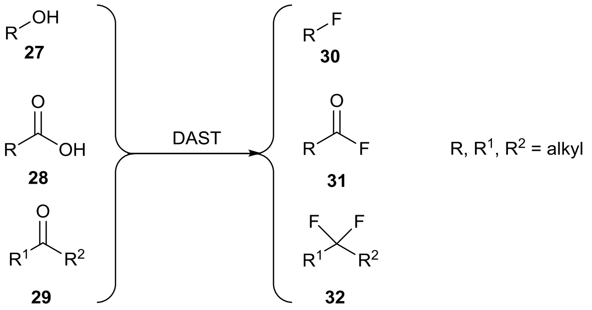
Many nucleophilic fluorinations have been reported using inorganic ionic fluorides, such as cesium or potassium fluoride, which are synthetic reagents for achieving a fluorination step. In terms of using those metal fluorides, dipolar aprotic solvents often give the best results and addition of a crown-ether can sometimes be really beneficial, due to the low solubility of metal fluorides.

Antimony fluoride plays an important role in the fluorocarbon industry and was widely used as synthesis of chlorofluorocarbons CFC's or hydrochlorofluorocarbons HCFC's.[37] The Balz-Schiemann chemical conversion, dealing with the use of fluoroborates, involving the formation of a diazonium tetrafluoroborate, is particularly useful for the conversion of arylamines to aryl fluorides (Scheme 3).[38,39] Halogen exchange (Halex) reaction between an activated chlorinated aromatic compound and a nucleophilic fluoride source like KF has also been reported as a possible method for the synthesis of fluoroarenes, despite being too expensive for large scale applications (Scheme 8).[39]



Scheme 8 *Halogen exchange fluorination of pentachloropyridine*

Last but not least, sulfur fluorides are powerful fluorinating agents, highly toxic in case of sulfur tetrafluoride, but diethylaminosulfur trifluoride (DAST) is more selective and easier to handle. A lot of fluorinations with DAST has been reviewed by Hudlicky, especially from alcohols to alkyl fluorides, carboxylic acids to acyl fluorides and carbonyl compounds to gemdifluorides (Scheme 9).[40]



Scheme 9 *General examples of fluorinations with DAST*

5. Conclusion

The unique properties of fluorine-containing molecules have been showcased and we showed that the direct fluorination processes possess various advantages in comparison to many other fluorinating agents, either nucleophilic or electrophilic. It seems that nature has never learned how to use the fluorine element, but as its properties have demonstrated over many years that this element brings huge benefits to health and sciences field, especially in agrochemicals and pharmaceuticals.

Chapter 2 Fluorination of various 1,3-dicarbonyl systems and further applications

1. Introduction

Developing new methodologies for the formation of new C-F bonds represents an important topic in organofluorine chemistry and many fluorinating agents have already been developed over the past years. Many of them will be presented and discussed in the following review, with a focus on fluorination of 1,3-dicarbonyl systems such as malonic esters and acids, or various ketoesters, as they are particularly convenient and useful “building blocks” for the synthesis of fluorinated sophisticated heterocycles.

Malonates and related 1,3-dicarbonyl compounds are very useful substrates in organic synthesis and often appear in many classic chemical reactions and retrosynthetic strategies. As a quick comparison between fluorinated and non-fluorinated 1,3-dicarbonyl molecules, 1,3-dimethyl malonate represents a widely applied organic synthetic key intermediate and is an important raw material for the synthesis of medicine, agrochemicals, spices, dyestuff, antioxidant, light stabilizer, bauxite flotation desiccation chelating collector and hydrazine nitrate by various chemical reactions.

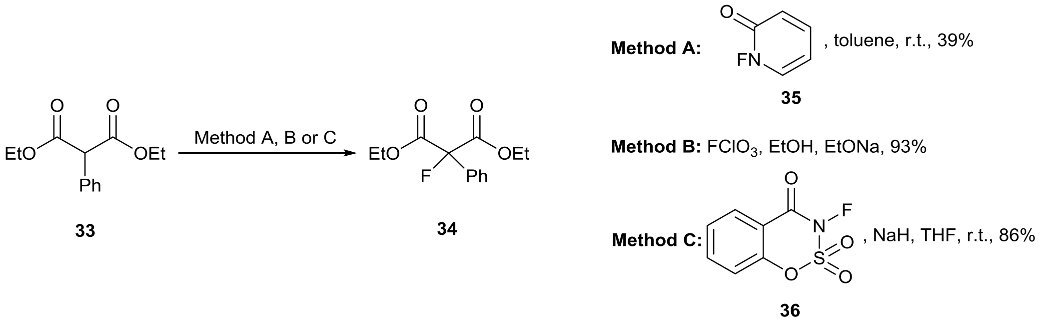
Most of the processes that have already been developed and reported concerning the production of the 1,3-dimethyl-2-fluoromalonate are mainly involving the 1,3-dimethylmalonate. As a quite recent type of fluorinated intermediate, 1,3-dimethyl-2-fluoromalonate has synthetic potential in the application of agrochemicals, drugs, materials, aerospace and many more, and is clearly drawing attention from industries in the domain of biological engineering and science, due to its potential versatile reactivity and high selectivity. However, nowadays, only a few patents are dealing with the use of fluoro-malonates as building blocks for the synthesis of fluorinated biologically active systems.[41,42]

This thesis describes the various fluorination processes towards fluorinated 1,3-dicarbonyl products, their reported applications and our investigations to afford more sophisticated fluorinated intermediates using various new synthetic methodologies.

2. Fluorinations of 1,3-dicarbonyl compounds

2.1. Synthetic strategies using fluorinating agents

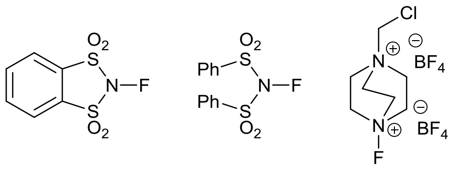
Fluorine gas and hydrogen fluoride are highly hazardous and reactive compounds, thus introducing fluorine into organic molecules presents a real challenge to synthetic chemists and has led to the development of specialized fluorination technologies and specific fluorinating reagents. Due to the relative weakness of the F-F bond (159 kJ/mol) and the great strength of bonds to most other elements, including hydrogen (566 kJ/mol), carbon (484 kJ/mol) and silicon (582 kJ/mol), elemental fluorine is one of the most reactive chemicals known.



***Scheme 10** Electrophilic fluorination of malonate enol derivatives*

Consequently, the first strategy for the synthesis of fluoromalonate derivatives that was developed was the replacement of the enolic hydrogen atom by fluorine using an electrophilic fluorinating agent. A few examples are listed in Scheme 10, and show different N-fluoro reagents, either N-fluoro-2-pyridone **35**, prepared by fluorination of trimethylsiloxy-pyridine (method A), or N-fluoro-perfluoro-alkylsulfonimides **36** reacting with carbanionic substrates (method C), and perchloryl fluoride (method B), not widely adopted because of its highly oxidising and potentially explosive nature.[43,44,45]

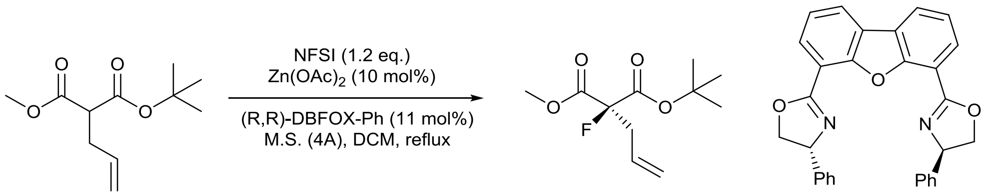
N-Fluoro agents are usually stable, easily handled solids, have different fluorinating reactivity, from mild to moderate, depending on the molecular structure of the reagent and, of course, the nature of the substrate. Using those types of fluorinating agents has another huge advantage, free anhydrous hydrogen fluoride is not a major by-product in fluorination reactions, so specialist equipment is not required.



37 NFOBS **38** NFSI **39** Selectfluor®

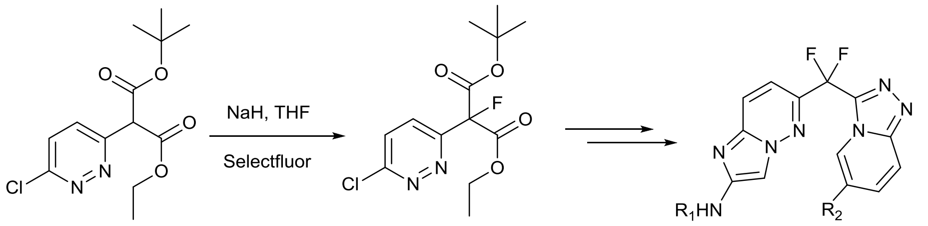
Figure 8 *N-Fluoro reagents*

During the past decade, two main N-fluoro reagents have been developed and often used as fluorinating agents. Among these, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane-bis-tetrafluoroborate **39**, known as Selectfluor®, and N-fluorobenzenesulfonimide **38** (NFSI), N-fluoro-*o*-benzenedisulfonimide **37** (NFOBS), whose structures are presented in Figure 8, often appear as fluorinating agents in many publications, such as those presented in Schemes 11 and 12.[46,47]



40 **41**,90%, 98% e.e. **42**, (R,R)-DBFOX-Ph

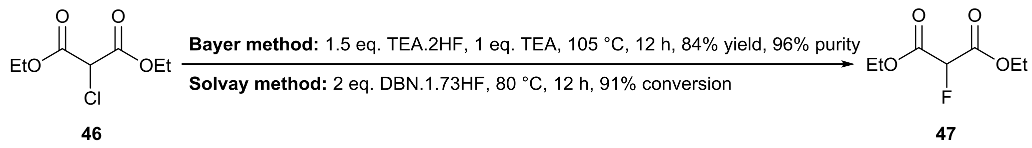
Scheme 11 *NFSI used for the asymmetric fluorination of prochiral malonate esters*



43 **44** **45**, cMET inhibitors

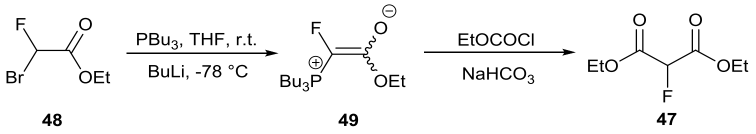
Scheme 12 *Fluoro-malonate prepared using Selectfluor®, towards potential pharmaceutical targets*

A few other synthetic strategies for the synthesis of fluorinated malonates have been investigated, including halogen exchange of chlorine by fluorine using a suitable source of fluoride ion. This method has been developed by Solvay and Bayer using amine hydrogen fluoride complexes starting from diethyl chloro-malonate **46** (Scheme 13). HF-amine complexes are most of the time liquids and thus less volatile and easier to handle than HF itself, and appear to be more nucleophilic than HF. The two complexes used by Solvay or Bayer differ from the most frequently used HF-pyridine, also known as Olah's reagent, which is known as a reagent in the preparation of alkyl fluorides from alcohols or alkenes.[48,49]

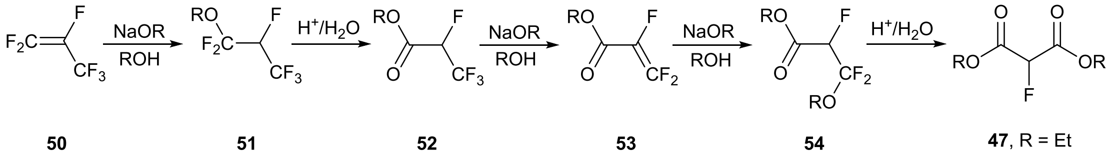


Scheme 13 *Fluorination strategies developed by Bayer and Solvay*

Among others, the condensation of fluoroacetic acid derivatives with alkyl chloroformate allows the preparation of the desired fluorinated compound. Moreover, an early procedure deals with the reaction between ethyl chloroformate and sodium enolate of ethyl fluoroacetate to give 1,3-diethyl-2-fluoromalonate **47** in low yield. A similar procedure has been developed using the less toxic ethyl bromofluoroacetate **48** as starting compound, and reaction with tributylphosphine to form an acylated ylid which, combined with ethyl chloroformate, provides fluoro-malonate (Scheme 14).[50,51]



Scheme 14 *Synthesis of fluoro-malonate from ethyl bromofluoroacetate*

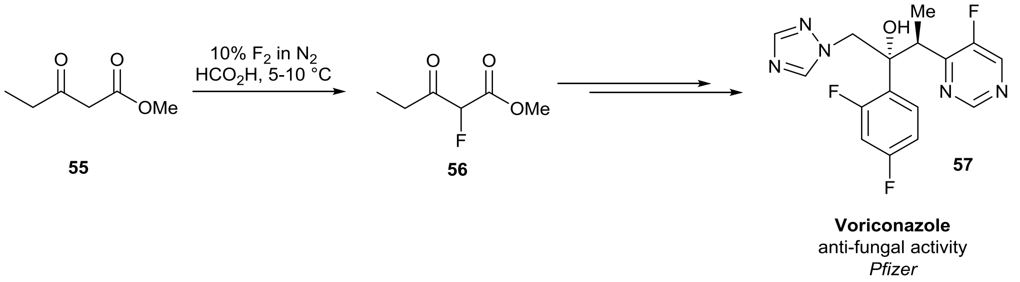


Scheme 15 *Sequential solvolysis of hexafluoropropene*

By a sequential solvolysis of hexafluoropropene, dialkyl 2-fluoromalonates can be easily synthesized, as shown in Scheme 15, representing a good way of synthesizing fluoro-malonates, as hexafluoropropene is an inexpensive starting material.[52]

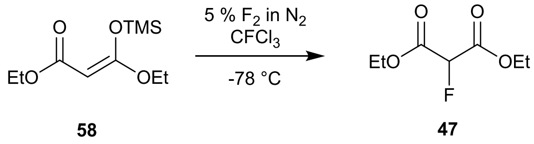
2.2. Elemental fluorine: versatile reagent for 2-fluoromalonate ester synthesis

New synthetic strategies involving direct fluorination have been investigated to give access to a wide range of precursors of potentially bioactive molecules. Among those, a process for the synthesis of a fluoro-ketoester, first carried out in Durham University, was developed by F_2 Chemicals Ltd (UK) for Pfizer company and forms a key starting material in the multi step synthesis of the widely used anti-fungal agent Voriconazole, which is one of the global top 100 best selling pharmaceutical products (Scheme 16).[53]



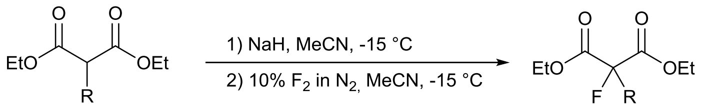
Scheme 16 *Synthesis of the fluoro-ketoester precursor of Voriconazole by direct fluorination*

Many examples of direct fluorination of different substrates, especially 1,3-dicarbonyl systems, have been published recently, giving access to fluorinated dicarbonyl systems by using diluted fluorine gas into nitrogen. Direct fluorination of malonates using fluorine gas was believed to be impossible until it was developed on trimethylsilyl-malonate derivatives, fluorinated with 5% fluorine gas diluted in nitrogen in $CFCl_3$ solvent (Scheme 17).[54]



Scheme 17 *Selective fluorination of trimethylsilyl malonate derivative*

Mono and difluoro-compounds were synthesized by direct fluorination of sodium dialkyl malonate salts using acetonitrile, and it was proved that the amount of NaH used modifes the ratio between obtained mono and difluoro-compounds. Indeed, more molar equivalents of NaH provide a larger amount of synthesized difluorinated malonate. Substitution at the 2-position of dialkylfluoro-malonate has also been proved to have an impact on the obtained yield (Scheme 18).[55]



59a, R = NO_2
59b, R = Cl

60a, R = NO_2, 73%
60b, R = Cl, 30%

Scheme 18 *Reaction of substituted dialkyl malonate salts with elemental fluorine*

Studies around the fluorination of various ketoester and malonate substrates have been done by Chambers and coworkers. Their investigations focused on the different catalysts that can be used to achieve this process in the best possible conversion and yield towards the desired product. The results obtained for the fluorination of ethyl acetoacetate indicated that hydrated copper(II) nitrate catalysed the reaction to a significant extent in acetonitrile, but less efficiently than compared to the corresponding 1,3-dimethylmalonate.

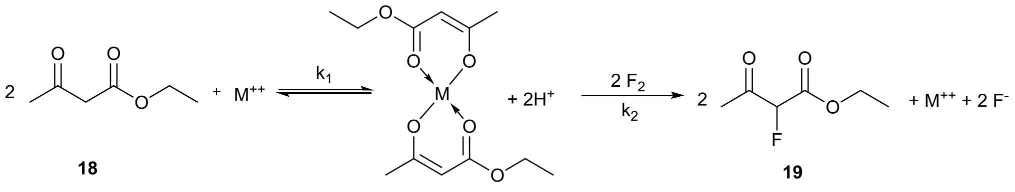
Table 1 *Fluorination of 1,3-dicarbonyl molecules using various catalysts*[a]

Entry	Catalyst	Substrate	Conversion [%]
1	$Cu(NO_3)_2.2.5H_2O$	1,3-diethylmalonate	100
2	$Ni(NO_3)_2.3H_2O$	1,3-diethylmalonate	70
3	$Co(NO_3)_3.6H_2O$	1,3-diethylmalonate	5
4	$Mn(NO_3).6H_2O$	1,3-diethylmalonate	5
5	$CuCl_2.2H_2O$	1,3-diethylmalonate	5
7	$Cu(OOCCH_3)_2.2H_2O$	1,3-diethylmalonate	5
8	$Cu(NO_3)_2.2.5H_2O$	Ethyl acetoacetate	45

[a] Substrate (20 mmol), catalyst (2 mol%), F_2 (32 mmol over 2h), MeCN, 0-5°C

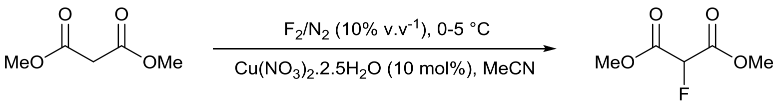
Table 1 summarizes the different catalysts that have been tested and the resulting yields of the corresponding fluorination processes, showcasing that copper nitrate is clearly the most reliable option for such a process. Hydrated nitrates of manganese, cobalt, nickel and other salts of copper were evaluated but didn't show any significant catalytic activity. Having a look on the mechanism of such a fluorination process, the importance of the catalyst used in the different synthetic conditions that were applied needs to be assessed. Scheme 19 shows that fluorine reacts with the enol form of the corresponding substrate and that enolisation appeared to be the rate-limiting step. Therefore, the catalytic activity of a salt must stem from the ability of the cation to accelerate the formation of the enolate. The quick release of the metal cation also remained crucial during this process, therefore being able to complex again with the starting dicarbonyl molecule to complete the cycle. Noticable is the impact of the side groups next to the carbonyl functional groups on k_1 and k_2

rates, in addition to the influence of the nature of the anion, cation and used solvent.[56]



Scheme 19 *Proposed mechanism of the fluorination of 2-ethylacetoacetate*

More recently, the synthetic conditions for the fluorination of 1,3-dimethylmalonate have been optimized, affording the dimethyl-2-fluoromalonate in a high yield, using $Cu(NO_3)_2.2.5H_2O$ as a catalyst, and elemental F_2 (10% diluted in nitrogen, $v.v^{-1}$), in a flow of 40mL/min. A direct batch fluorination system has been designed to complete the fluorination at 0 °C during 5 h on a 0.5 mol scale. After distillation, the 1,3-dimethyl-2-difluoromalonate was separated from the dimethyl-2-fluoromalonate, providing a yield close to 90% for a >99% pure mono-fluoro product (Scheme 20).[57]



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Scheme 20 *Fluorination of 1,3-dimethylmalonate using F_2/N_2*

The synthesis of 2-fluoro-1,3-dimethylmalonate has been completed around 20 times over the three years of this project, either in large scale (up to 300 mmol) or in smaller scale (down to 20 mmol), using the corresponding glass batches fitted with PTFE tubings and connection to a soda-lime scrubber neutralizing the excess of fluorine. Figures 9 and 10 show the two batch equipment used for these processes, with mechanical stirring for the larger scale and magnetic stirring (a large cross shaped magnetic stirrer) for the smaller scale.

These two figures also show both inlets and outlets for the fluorine gas, as supplied from a commercial cylinder containing 20% F_2 in nitrogen ($v.v^{-1}$) and transferred or diluted if required in smaller cylinders with an overall pressure not exceeding 5 bar.

Figure 9 *Large scale fluorination process set-up with mechanical stirring*

Figure 10 *Small scale fluorination process set-up with magnetic stirring*

Figure 11 shows the main commercially available F_2/N_2 (20% v.v^{-1}) cylinder (bottom right) connected to nitrogen inlets and a four-valve system using stainless steel tubing able to dispatch fluorine gas to smaller storage cylinders (up to 5 bar) that are connected to fluorination set-ups. The two set-ups are provided with fluorine dispensed from storage cylinders at regulated flow rates controlled by Brooks mass-flow controllers, typically from 10 to 200 mL/min and introduced under the liquid surface in the reactor through a narrow bore (1/8” OD) FEP tube.

Figure 11 *Pressure-controlled system between the commercially available* F_2/N_2 *(20% v.v*$^{-1}$*) and smaller storage cylinders connected to reactive batch glass systems*

Excess gases containing residual fluorine, HF and solvent are directed to a solid scrubber filled with granular soda lime (mixture of CaO and $CaCO_3$) to neutralize all corrosive and volatile waste. Work-up procedures for this method involved extracting solvent, pouring the reaction mixture into water and extracting with ethyl acetate, with classic washings with water, saturated sodium bicarbonate solution and drying over magnesium sulfate, before evaporating the solvent again resulting in a crude fluorinated mixture, ready for a further purification using distillation under reduced vacuum (approx. 10 mbar). Purification of the resulting crude mixture from the fluorination of 1,3-dimethylmalonate by distillation, afforded the desired 1,3-dimethyl-2-fluoromalonate with a 98% purity (Figure 12).

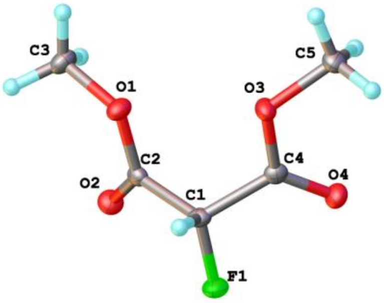


Figure 12 *Molecular structure of 1,3-dimethyl-2-fluoromalonate* ***62***

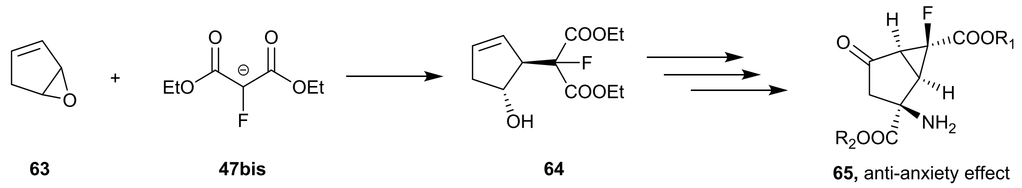
To summarize the results previously obtained in the Durham group by A. Harsanyi for the optimization of the fluorination of 1,3-dimethylmalonate, it has been proved that the concentration of the malonate ester substrate in acetonitrile has no apparent effect on the outcome of the reaction, although solvent was required because malonate esters couldn't dissolve the copper nitrate catalyst. Basically the use of high dielectric constant media such as acetonitrile was proved to be beneficial to control the selectivity of the electrophilic direct fluorination process. Moreover, the percentages of fluorine gas diluted into nitrogen, between 10% and 20% ($v.v^{-1}$) does not impact the quality of the obtained fluorinated product, but reactions carried out at room temperature instead of 0-5 °C showed a decomposition of the copper catalyst, resulting in some insoluble copper species blocking the inlet gas tube, while processing at room temperature impacted the reactive mixture with a temperature increase, due to the exothermic nature of this fluorination strategy. Of course, lowering the amount of copper nitrate catalyst that was used avoided a quick reaction and required larger excess fluorine gas to be able to reach similar conversions as observed in previous optimized synthetic conditions.[58]

As a summary on the fluorination process towards fluorinated dicarbonyl molecules, such as 2-fluoroethylacetoacetate or 2-fluoro-1,3-dimethylmalonate, the equipment used for batch processes enabled controlled reaction and the importance of solvent choice, cooling, dilution and mixing has been showcased.

3. Reactions of 2-fluoro-1,3-dicarbonyl ester derivatives with carbon electrophiles

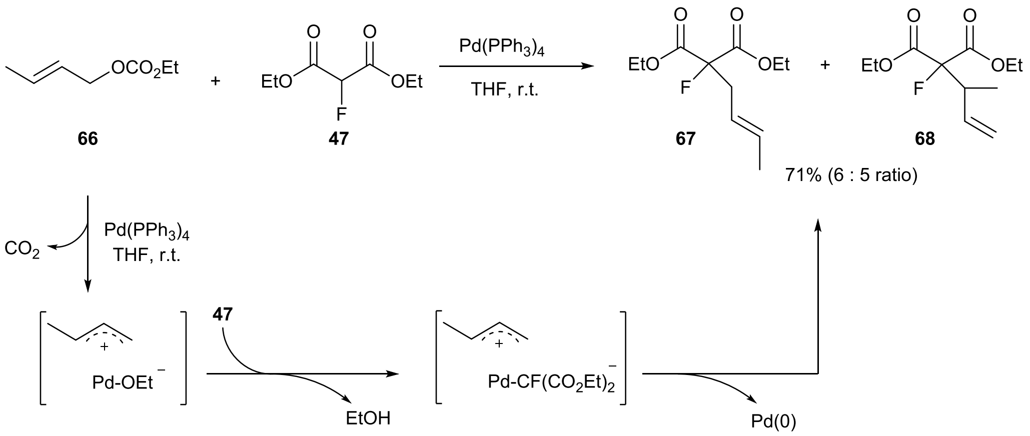
2-Fluoro-1,3-dicarbonyl compounds appear to be useful “building blocks” for the preparation of potentially biological active molecules and have already been investigated as valuable reagents to build molecular structures, either reacting with carbon electrophiles or affording fluoro-heterocycles, as discussed briefly below.

The reactivity of 1,3-dicarbonyl systems is mainly linked to the nucleophilicity of the corresponding carbanion. For this reason, due to the electron withdrawing fluorine atom removing the electron density from the carbanion, thus making it becoming a poorer nucleophile, alkylation reactions of fluoromalonates are slower than those using other malonate molecular systems. Scheme 21 shows an example of alkylation of fluoro-malonate, affording a precursor of an anti-anxiety drug molecule, involving an epoxide opening step with 1,3-diethyl-2-fluoro-malonate as starting substrate.[59]

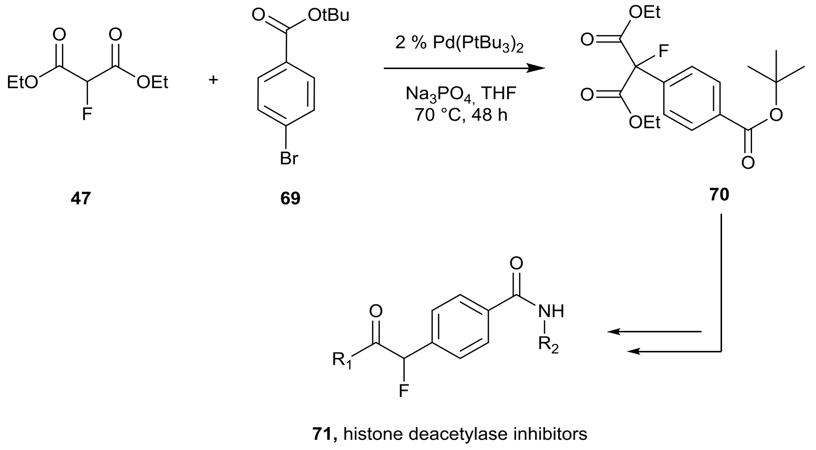


***Scheme 21** Alkylation of 1,3-diethyl-2-fluoro-malonate carbanion*

A few other possible reactions involving fluoro-malonate esters and carbon electrophiles have already been investigated during the last decade, most of them deal with the use of a catalytic system, especially palladium-catalyzed, in either allylation or arylation processes (Schemes 22 and 23).[60]



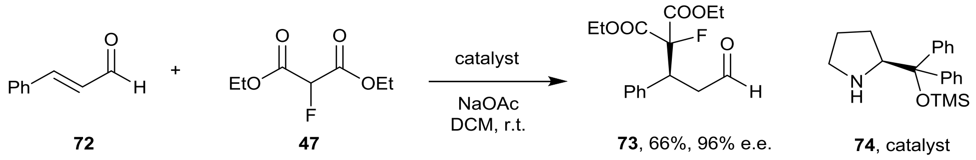
Scheme 22** Palladium-catalyzed allylation of 1,3-diethyl-2-fluoro-malonate **47



***Scheme 23** Palladium-catalyzed arylation of diethyl fluoro-malonate*

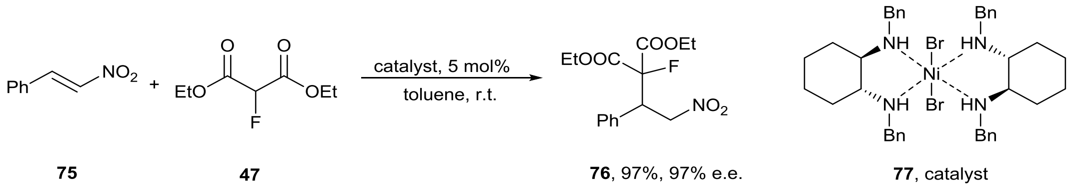
Palladium-catalyzed reactions allow cross-coupling of diethyl fluoromalonate with aryl bromide, employed for the synthesis of an aryl amide, used as potential cancer treatment drug candidates (Scheme 23).[61] Among these catalyzed reactions, a few of them are Michael addition reactions, leading to the synthesis of a chiral product, using a chiral catalyst.

One of the main examples of asymmetric Michael addition reactions of fluoromalonate deals with the reaction of an α,β-unsaturated aldehyde with diethyl fluoromalonate, catalyzed by a chiral pyrrolidine derived compound, giving access to the desired product with a good enantiomeric excess (Scheme 24).[62]



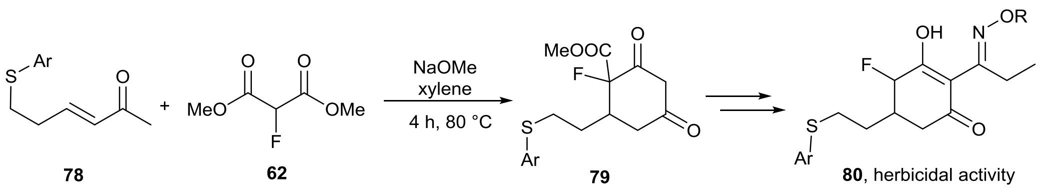
Scheme 24 *Enantioselective Michael addition of 1,3-diethyl-2-fluoro-malonate to α,β-unsaturated carbonyl derivatives*

Other chiral catalytic systems have already been reported, such as a chiral nickel complex catalyst and reactions between diethyl fluoromalonate and nitroalkenes provide the phenyl alkene product in good yield with good enantiomeric excess (Scheme 25).[63]



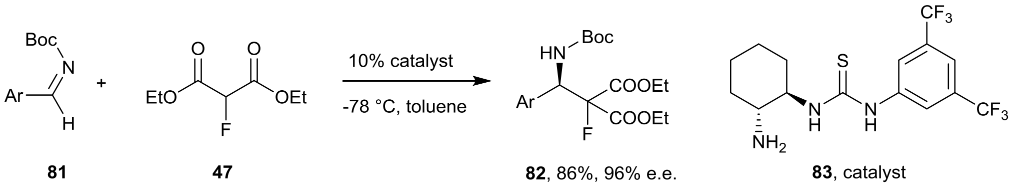
Scheme 25 *Enantioselective addition of dialkyl fluoro-malonates to nitroalkenes*

Beside the use of a catalytic system, Michael additions of fluoro-malonate to related systems have been used for the synthesis of more complex fluorinated structures, such as precursors of molecules with potential herbicidal activity (Scheme 26).[64]



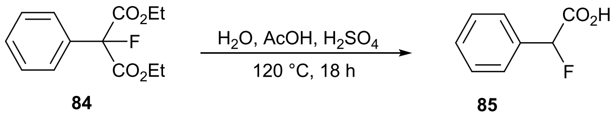
Scheme 26 *Michael addition reaction of 2-fluoro-1,3-dimethylmalonate*

Dealing with other catalytic systems used in reactions involving fluoro-malonates as starting substrates, enantioselective addition of diethyl fluoro-malonate to N-Boc aldimines were reported using a chiral thiourea based organo-catalyst and show that fluoro-malonates can easily react with molecular structures comprising a C=N bond, in a good yield and really good enantiomeric excess (Scheme 27).[65]

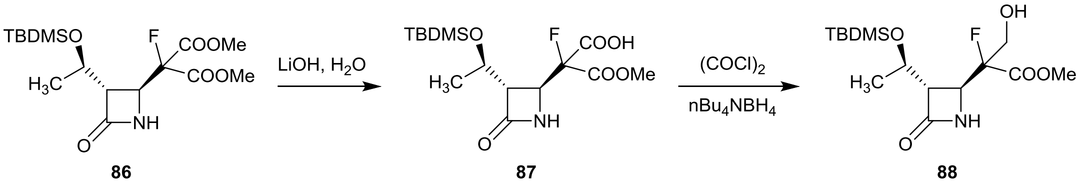


Scheme 27 *Reaction of fluoro-malonate with C=N bond*

2-Fluoromalonates can be used as starting substrates for functional group interconversion reactions, such as hydrolysis of one ester group of the fluoro-malonate molecular system, by heating in an aqueous acidic media, allowing the simple synthesis of 2-fluoro-2-phenylacetic acid (Scheme 28).[66] They can also be reduced to 2-fluoro-3-hydroxypropanoates, when the monoester is firstly prepared by partial hydrolysis of the starting diester (Scheme 29).[67]



Scheme 28 *Acid hydrolysis of fluoro-malonate system*

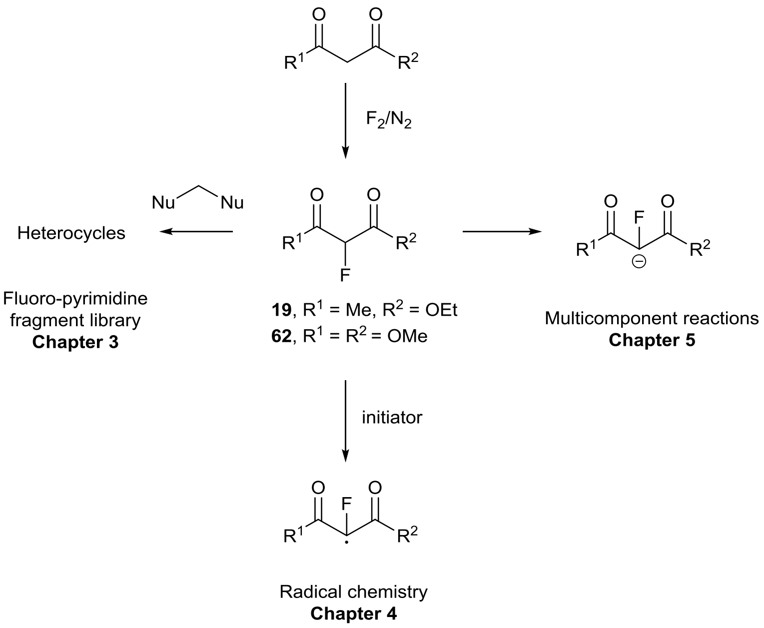


Scheme 29 *Reduction of fluoro-malonate esters*

4. Conclusion

As a quick summary on the interest of fluorinated 1,3-dicarbonyl building blocks for further transformations, 2-fluoro-1,3-dialkylmalonate and 2-fluoro-alkylacetoacetate show that they are potentially versatile building blocks. However, not much of their chemistry is known despite their quick synthesis and potential applications. Despite the fact that a series of various reactions remain possible, the range of synthetic applications has still not been fully explored.

The aims of this thesis are to repeat the direct fluorination processes to gain 2-fluoro-1,3-dicarbonyl systems and to develop different types of chemistry on these substrates: building new fluorinated heterocycles, using radical initiators or finally developing multicomponent reactions and using a flow-process system with adapted conditions (Scheme 30).



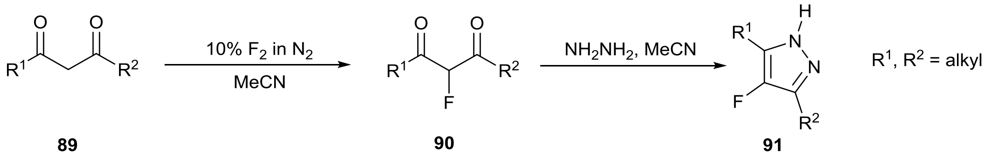
Scheme 30 *Synthesis of fluorinated 1,3-dicarbonyl substrates and aims of this thesis*

Chapter 3 Functionalized fluoro-pyrimidinones and fragment-based screening

A huge variety of possible reactions from 2-fluoro-1,3-dicarbonyl building blocks exists. In this chapter, we are going to present the high potential of 2-fluoro-1,3-dicarbonyl derivatives as building blocks in the formation of fluorinated heterocyclic systems. The carbonyl carbons of the fluoro-malonate molecular structures are susceptible to nucleophilic attack, yielding in many cases different heterocyclic structures, which are going to be presented in this chapter, followed by our work on building a library of fluorinated pyrimidines to test them as potential bioactive fragments.

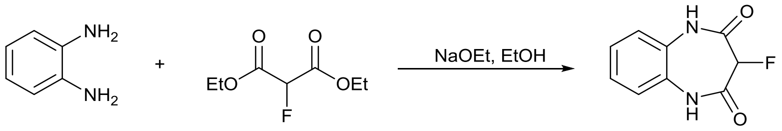
1. Synthesis of fluorinated heterocycles from 2-fluoro-1,3-dicarbonyl derivatives

Fluorination of diketones has been recently investigated, affording cyclization of the intermediate fluoro-diketone by reaction with hydrazine derivatives, giving access to new 4-fluoropyrazoles using a flow process (Scheme 31).[68]



Scheme 31 *Synthesis of 4-fluoro-3,5-dimethylpyrazole derivatives* ***91*** *using designed flow reactor system*

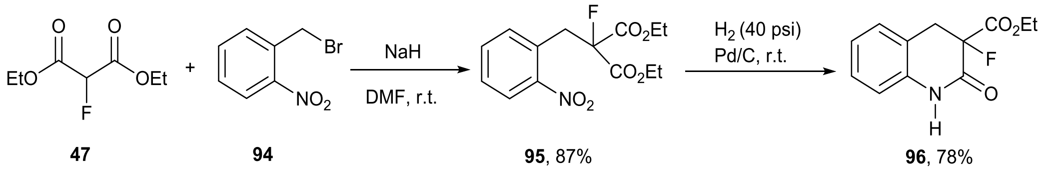
Besides this flow process chemistry affording fluoro-heterocycles, reactions of 2-fluoro-malonate and diamines provides the formation of a fluorinated seven-membered heterocycle (Scheme 32).[69]



Scheme 32 *Synthesis of fluorinated diamides*

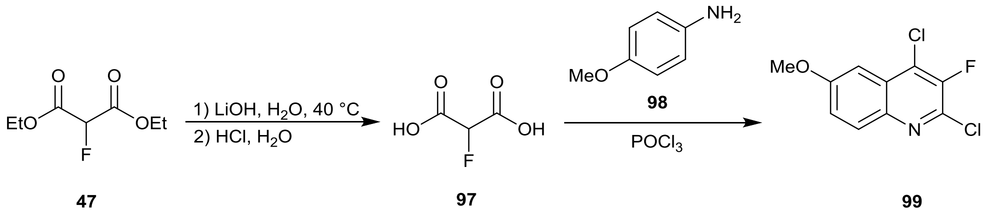
Moreover, the Durham group has recently reported the synthesis of fluorinated heterocycles by a two step reaction, involving firstly alkylation of fluoromalonate by a

2-nitrobenzyl bromide derivative and secondly, after reduction, nucleophilic attack at the carbonyl carbon by the amine group, giving access to a new range of tetrahydroquinolone derivatives (Scheme 33).[70] A similar process using 1-fluoro-2-nitrobenzene instead of 2-nitrobenzyl bromide has also been reported for the synthesis of 3-fluoroxindole.[71,72]



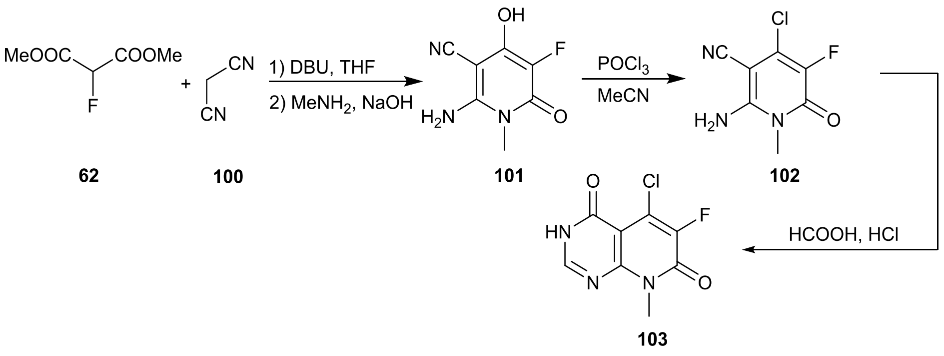
Scheme 33 *Synthesis of 3-fluorotetrahydroquinolone derivatives*

Dealing with the synthesis of potential antibacterial drug molecules, diethyl 2-fluoro-malonate has been reported by Pfizer as a starting substrate for the large scale synthesis of 3-fluoroquinoline derivatives (Scheme 34).[73]



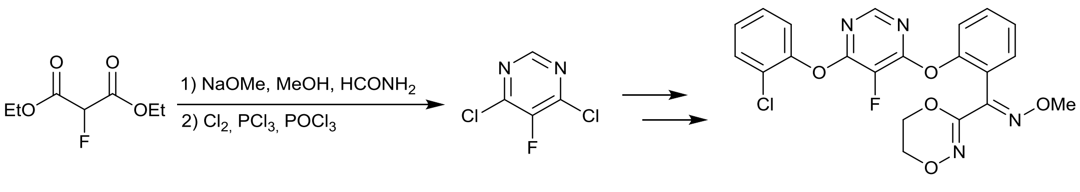
Scheme 34 *Synthesis of 3-fluoro-6-methoxyquinoline* ***99*** *using 1,3-diethy-2-fluoromalonate*

In the field of the synthesis of pyrimidines or derivatives, fluoro-malonates and 2-fluoro-1,3-dicarbonyl derivatives play an important role. Indeed, a few syntheses affording different pyrimidine-based structures have been recently reported by different companies. Takeda Pharmaceuticals developed the synthesis of a potentially active pharmaceutical ingredient (Scheme 35).[74]



Scheme 35 *Synthesis of 6-fluoro-8-methylpyrido[2,3-d]pyrimidine-4,7-(3H,8H)-dione*

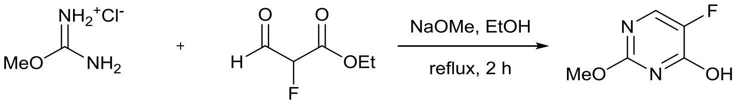
Bayer CropScience achieved the synthesis of a fluorinated precursor to Fluoxastrobin, a commercially significant herbicide (Scheme 36).[75]



47 **104a** **105**, Fluoxastrobin (Bayer)

Scheme 36 *Synthesis of 5-fluoro-pyrimidine derivatives*

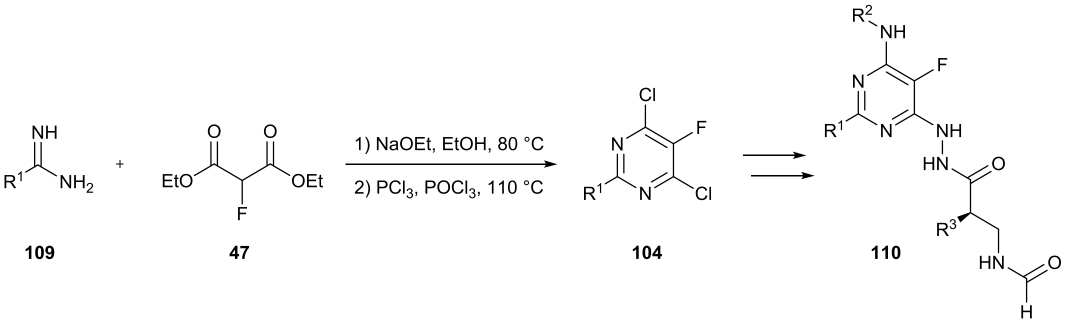
One of the earliest examples of fluorinated heterocycle formation from a fluorinated dicarbonyl starting material was reported by Duschinsky and coworkers in 1957, who reacted pseudo urea salts with α-fluoro-β-ketoesters to produce a 5-fluoropyrimidine derivative, which was reduced to form 5-fluorouracil, an effective anti-cancer agent, as presented in earlier chapters (Scheme 37).[76]



106 **107** **108**

Scheme 37 *Synthesis of a 5-fluoropyrimidine from a 2-fluoro-1,3-dicarbonyl starting material, as reported by Duschinsky et al.*

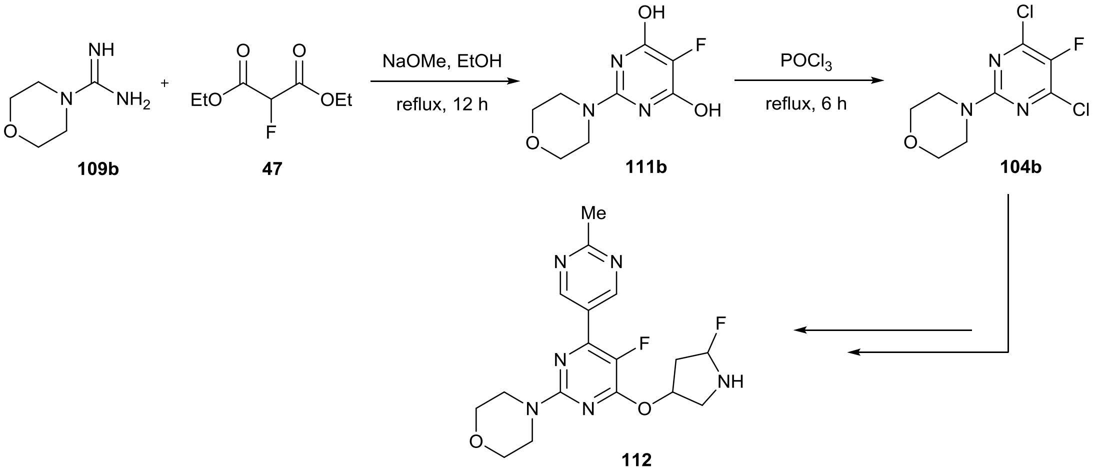
Narrowing the heterocycles synthesis to fluorinated pyrimidines, the first example of 4,6-hydroxy-5-fluoropyrimidine synthesis was presented by Bergmann et al. in 1959, followed by many different synthetic strategies towards fluoropyrimidine compounds, especially over the last decade.[50] For example, GlaxoSmithKline Plc. conducted a condensation reaction between various amidines and 2-fluoro-dialkylmalonate followed by further functionalization (Scheme 38).[77]



109 **47** **104** **110**

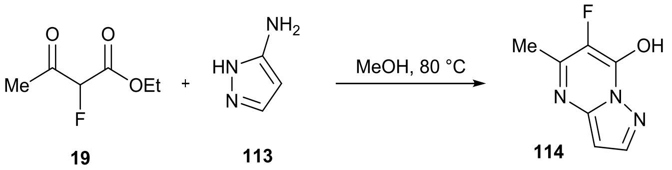
Scheme 38 *GSK's synthesis of a functionalized 5-fluoropyrimidine derivative*

Aiming for a variety of bioactive molecules, the use of 4,6-dichloro-5-fluoropyrimidine scaffold has been developed. Among all those methods, we were particularly interested in the synthesis of a potential cancer treatment from 2-fluoro-1,3-diethylmalonate, developed by Pfizer Inc. in 2017 (Scheme 39). Indeed 5-fluoropyrimidine shows anticancer properties.[78,79]



Scheme 39 *Pfizer Inc.'s synthesis of a potential cancer treatment, starting from diethyl fluoromalonate and proceeding via a 4,6-dichloro-5-fluoropyrimidine intermediate*

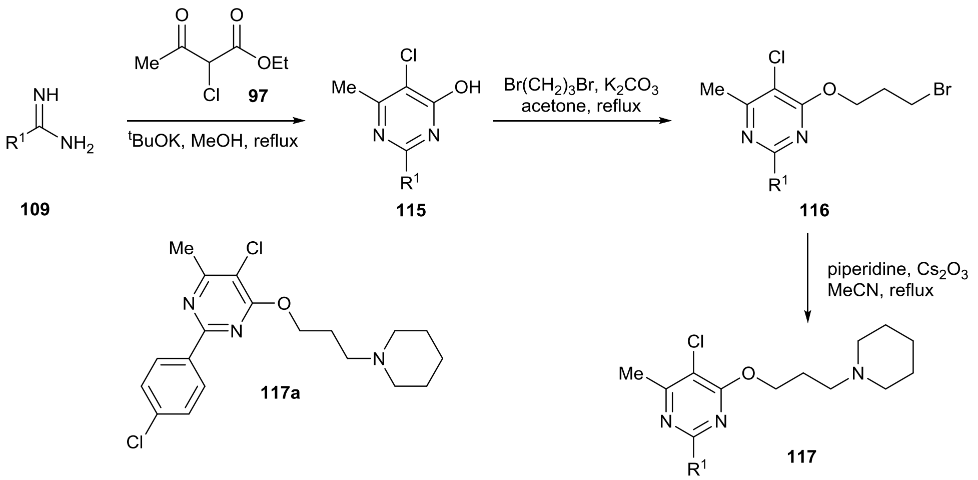
As well as 2-fluoro-1,3-dialkylmalonate, 2-fluoro-ketoesters are also convenient starting substrates for the synthesis of fluorinated heterocycles. As an example, Alantos Pharmaceuticals reacted 1H-pyrazol-5-amine with 2-fluoroethylacetoacetate to form an unusual library of fluorinated pyrazolo-(1,5a)-pyrimidines (Scheme 40).[80]



Scheme 40 *Synthesis of fluorinated pyrazolo-(1,5a)-pyrimidine* ***114*** *performed by Alantos Pharmaceuticals*

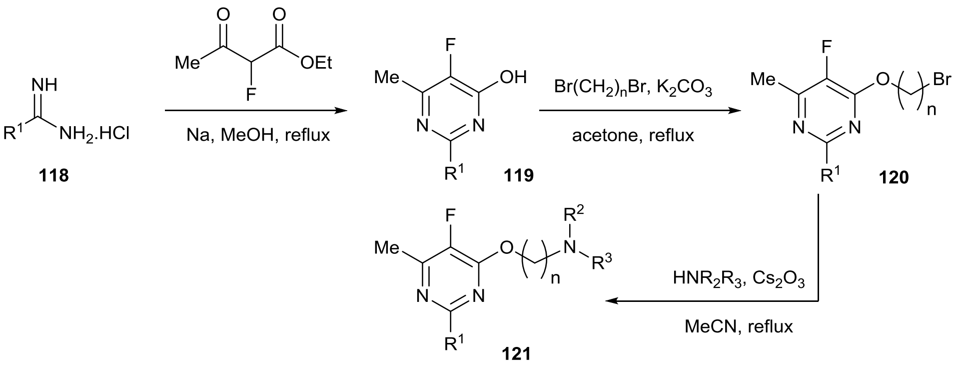
Deriving from 1,3-dicarbonyl 2-halogenated molecules, other new series of pyrimidines have been recently discovered to be potential sigma-1 receptor (σ_1R) antagonists, which have been found to be associated with pharmacological antineuropathic pain activity. Those compounds have been evaluated *in vitro* in σ-1 and σ-2 receptor binding essays. The molecular structure of the tested pyrimidines has been proved to be essential to the activity of such molecules and finally, the most promising derivative was 5-chloro-2-(4-chlorophenyl)-4-methyl-6-(3-(piperidin-

1-yl)propoxy)pyrimidine **117a** which shows a high binding activity to σ_1 receptor and acceptable pharmacokinetic properties (Scheme 41).[81]



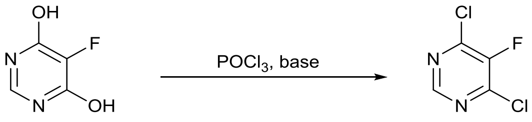
Scheme 41 *Synthetic pathway towards pyrimidine derivatives from halogenated 1,3-dicarbonyl compounds*

Among the various 2,4,6-substituted pyrimidines, fluorinated derivatives have been reported by Lan and coworkers (Scheme 42), which could be used in pain relief therapy, as the corresponding chlorinated system has shown pharmacological activity.[81]



Scheme 42 *Generation of 2,4,6-substituted fluorinated pyrimidines as selective σ^1 antagonists*

Aside of the synthesis of fluorinated pyrimidine scaffolds, interest is in the functionalization of fluoro-pyrimidines, especially further chlorination reactions of the hydroxy functional groups, as those positions can undergo further reactions like C-C bond formation, catalytic hydrogenation or, last but not least, reactions with O-, N- or S- nucleophiles. Industry has previously developed chlorination of fluorinated pyrimidines *via* the use of highly toxic phosgene, in yields up to 90%, which is difficult in laboratory-scale processes.[82]



111a **104a**

Scheme 43 *Chlorination of 4,6-dihydroxy-5-fluoropyrimidine* ***111a*** *using POCl$_3$*

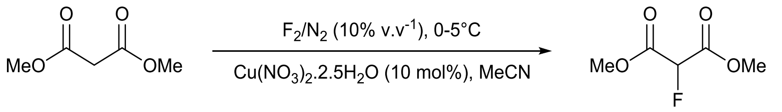
Zeneca Ltd. reported the use of neat POCl$_3$ to achieve effective chlorination of pyrimidines (Scheme 43). Recent adaptations of the neat POCl$_3$ chlorination method were using bases, such as N,N-dimethylaniline and NEt$_3$, to catalyze the reaction. The group of Cheng and coworkers has used a combination of POCl$_3$ and toluene as the solvent to ease extraction of the product. And finally in 2011, Sun et al. reported pyridine as an effective base, to reduce the attack at the chlorine site, therefore, increasing the reaction yield of the fluorinated dichloro-pyrimidines by reducing side-reactions.[83]

We showed that fluorinated 1,3-dicarbonyl substrates have been recently used in a lot of various applications but lots of synthetic opportunities still remain possible towards the synthesis of fluorinated functionalized heterocycles, especially with a pyrimidine-based scaffold. The first part of our investigations is dedicated to the synthesis of a library of new fluorinated heterocycles possessing the pyrimidine molecular scaffold, starting from our previously synthesized fluorinated 1,3-dicarbonyl substrates, and to optimize further effective substitutions to gain specific functionalized fluorinated intermediates.

2. Towards the synthesis of various functionalized fluorinated pyrimidines

2.1. Synthesis of 2-substituted-5-fluoro-pyrimidines

2-Fluoro-1,3-dimethylmalonate and 2-fluoro-ethyl acetoacetate were synthesized using F$_2$ methodology and used as starting substrates to develop the synthesis of a fluorinated pyrimidine fragment library. 2-Fluoro-1,3-dimethylmalonate and 2-fluoroethylacetoacetate were used after purification by distillation, to remove the difluorinated analogue, as explained in the previous chapter in the method developed by Harsanyi et al. (Scheme 44). The purity of the starting fluorinated compounds was checked by ^{19}F-NMR before further synthetic steps.



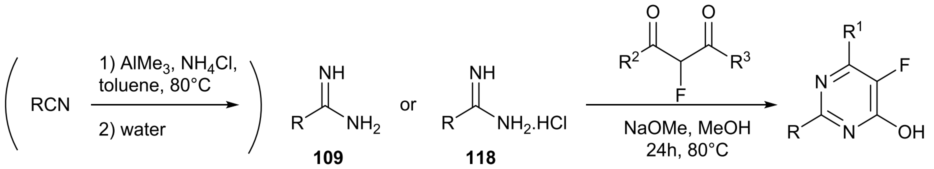
61

62, 90%, >99% purity

Scheme 44 *Synthetic strategy by direct fluorination towards 2-fluoro-1,3-dimethylmalonate*

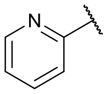
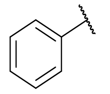
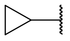
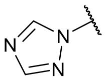
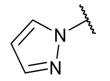
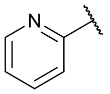
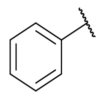
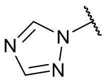
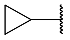
Cyclization of 2-fluoro-1,3-dimethylmalonate or 2-fluoro-ethyl acetoacetate with a series of amidines was studied and attention was put on the structural shape of the obtained molecules (Table 2). We had the option to synthesize various amidines reactants using the Garigipatis procedure but we chose first to use commercially available amidines hydrochloride salts.[84]

Table 2 *Synthesis of fluoro-pyrimidinones from various synthesized amidines and fluorinated dicarbonyl systems*



109 **118**

119c-e, R^1 = Me
111c-f, R^1 = OH

Entry	R	R^2	R^3	Yield [%][a]
1		OCH_3	OCH_3	**111c**, 72[b] (88)[c]
2		OCH_3	OCH_3	**111d**, 76[b] (63)[c]
3		OCH_3	OCH_3	**111e**, 89[b] (81)[c]
4		OCH_3	OCH_3	**111f**, 51[b] (57)[c]
5		OCH_3	OCH_3	– [b] (–)[c]
6		CH_3	OCH_2CH_3	**119c**, 97[b] (91)[c]
7		CH_3	OCH_2CH_3	**119d**, quant.[b] (91)[c]
8		CH_3	OCH_2CH_3	– [b] (–)[c]
9		CH_3	OCH_2CH_3	**119e**, 97[b] (95)[c]

[a] Isolated; [b] Isolated mixture of tautomers after acidic work-up; [c] Addition of 2-fluoro-1,3-dicarbonyl substrate diluted in MeCN and multiple filtration-evaporations in EtOH during work-up (less acidic work-up)

We firstly achieved these reactions in methanol as the solvent and worked all the crude products up using dilute aqueous HCl and a single filtration. As an example, by this methodology, the ^{1}H-NMR spectrum from fluorinated pyrimidinone **119d** synthesized from benzamidine hydrochloride and 2-fluoro-ethyl acetoacetate shows two series of peaks, due to the keto and enol forms from the resulting pyrimidinone, which was due to the acidic work-up that has been tested. We observe an average ratio 65:35 between the keto and enol forms in Figure 13, which has been described in Scheme 45.

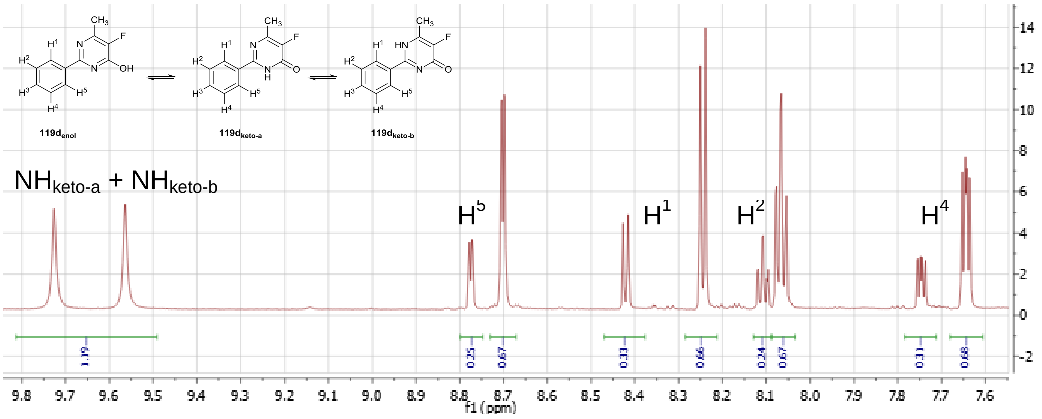
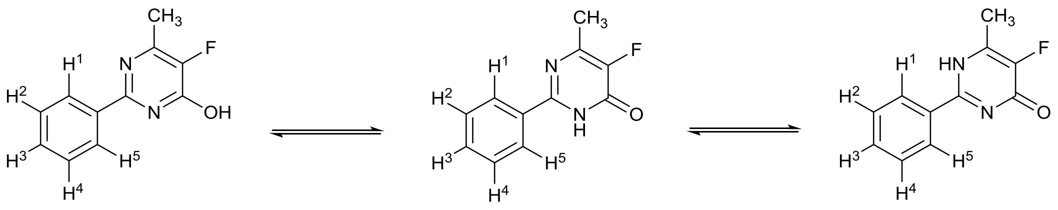


Figure 13 *^{1}H-NMR of fluorinated pyrimidinone* ***119d*** *from benzamidine and 2-fluoro-ethyl acetoacetate*



119d$_{enol}$ **119d$_{keto-a}$** **119d$_{keto-b}$**

Scheme 45 *Keto-enol isomers formed in case of using 2-fluoro-ethyl acetoacetate as starting substrate*

Optimization of the reaction led us to perform the addition of the 2-fluoro-1,3-dicarbonyl substrate diluted in acetonitrile, and after completion of the reaction and addition of dilute aqueous HCl, process multiple filtrations and evaporations under reduced pressure of the different filtrates from multiple washings with ethanol, yielding only the desired pyrimidines without any keto-isomers (Table 2)

After optimizing the reaction and work-up procedure to a less acidic one to avoid any keto-enol products to be formed, the reactions were finally carried out in acetonitrile at 80 °C. Sodium was dissolved in methanol to generate sodium methoxide *in situ*, then the base activated the amidine to attack one of the electrophilic carbonyl groups of the 1,3-dicarbonyl species, followed by an intramolecular ring-closure on the second carbonyl by the second nitrogen of the amidine group. Methanol, or ethanol and water, were released as by-products, depending on the substrate used.

From the results presented in Table 2, it generally seems that higher yields are obtained in the case of using 2-fluoro-ethyl acetoacetate instead of 2-fluoro-1,3-dimethylmalonate, while aromaticity of the chosen amidine plays a role on the stability of the resulting product and therefore on the obtained yield. However, all the products obtained by this synthetic method were isolated after filtration, considering their respective ^{1}H-, ^{19}F- and ^{13}C-NMR spectra and mass analyses showed >99% purity for all those compounds, indicating an efficient optimization of the process and work-up for those reactions, avoiding any keto-enol equilibrium to be shown on NMR spectroscopy. As an example, by this method, the ^{1}H-NMR spectrum of fluorinated pyrimidinone from benzamidine hydrochloride and 2-fluoro-1,3-dimethylmalonate only shows two sets of multiplets, for protons H^{1} and H^{5}, and for H^{2}, H^{3} and H^{4} respectively (Figure 14).

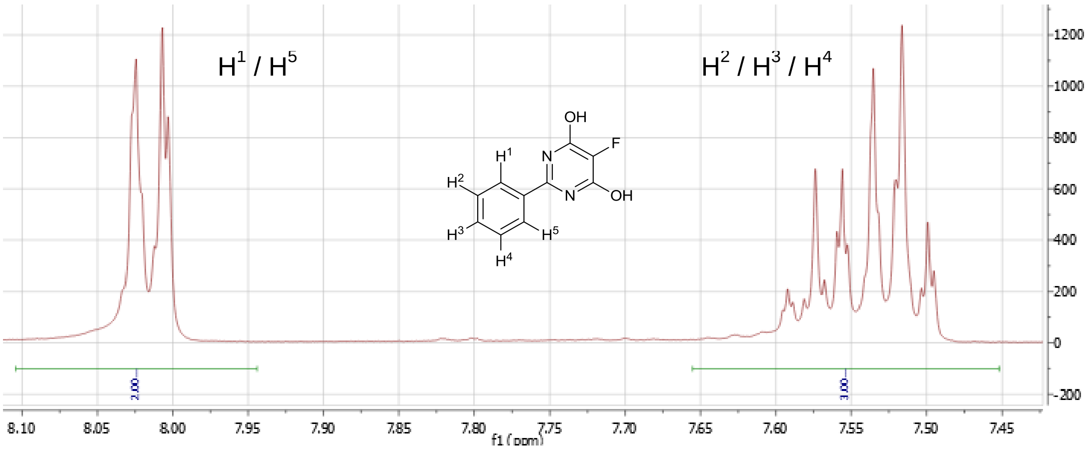


Figure 14 *^{1}H-NMR of fluorinated pyrimidinone from benzamidine and 2-fluoro-1,3-dimethylmalonate*

Acquisition of the NMR data was often problematic for these fluoro-pyrimidine compounds, as they are insoluble in most of the classic organic solvents, partially soluble in water and methanol, and only soluble in DMSO. Addition of sodium deuteroxide to D_2O was required to increase the aqueous solubility of compounds via hydroxyl group-deprotonation. Efficient π-stacking of the planar compounds and hydrogen bond-donating -OH groups might be responsible for very high melting points obtained (> 180 °C). However, all compounds were obtained in convenient to high yields, giving access to a first fragment library (Figure 15).

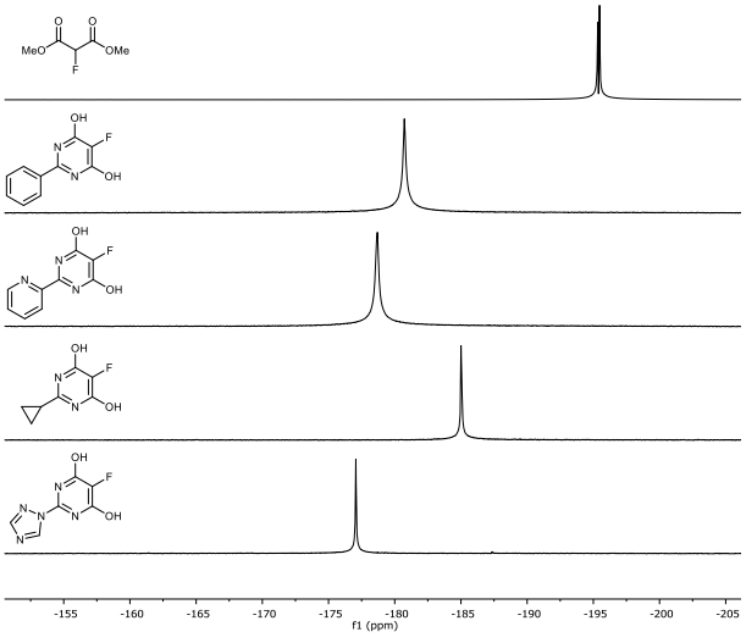


Figure 15 *^{19}F-NMR of the fluorinated dihydroxy-pyrimidinone fragment library*

^{13}C-NMR spectra of all the synthesized fluoro-pyrimidine fragments showed different doublets which can be easily assigned due to the various C-F couplings. Indeed carbons coupling to the fluorine atom resulted in various observable C-F coupling constants: $^{1}J_{CF}$ = ~ 220-280 Hz, $^{2}J_{CF}$ = ~ 12-16 Hz and $^{4}J_{CF}$ = ~ 6-10 Hz. As an example, figure 16 shows the ^{1}H- and ^{13}C-NMR spectra of the 2-cyclopropyl-5-fluoropyrimidine-4,6-diol **111e** with the different observed C-F coupling in the ^{13}C-NMR spectrum, while in the ^{1}H-NMR spectrum, we observed that the protons on each face of the cyclopropyl ring are diastereotopic and magnetically inequivalent, resulting in a second order spectrum and two different multiplets for both -CH$_2$ of this cyclopropyl ring at around 0.65 ppm.

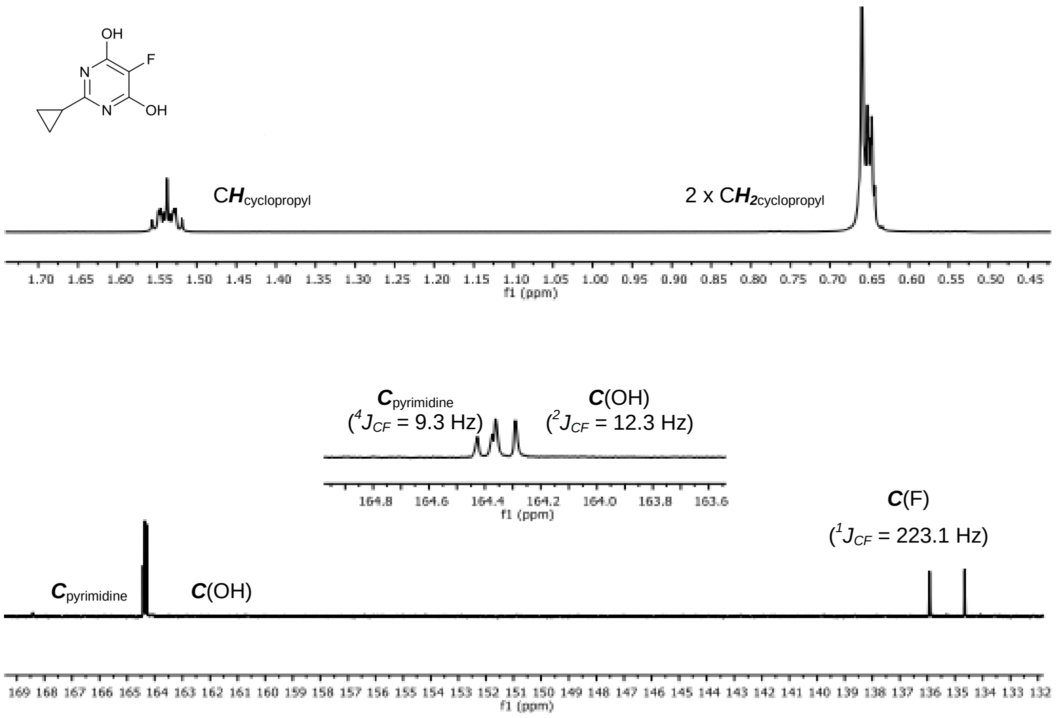
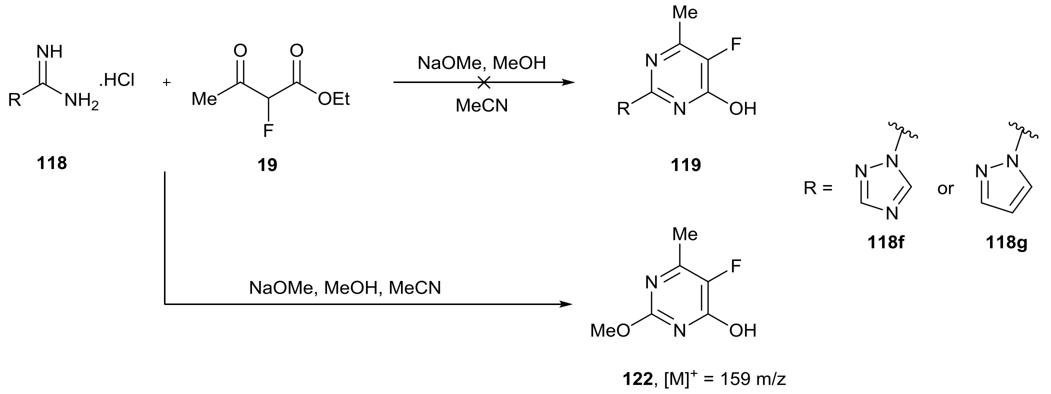


Figure 16 For 2-cyclopropyl-5-fluoropyrimidine-4,6-diol **111e**: ^{1}H-NMR (D_2O, 700 MHz, 298 K, 0.45-1.70 ppm, top); ^{13}C-NMR (D_2O, 176 MHz, 298 K, 132-169 ppm, bottom)

It has to be noticed that only a few attempts using different amidine structures were unsuccessful. Among them, the cyclization of *1H*-pyrazole-1-carboxamidine hydrochloride **118g** and 2-fluoro-1,3-dimethylmalonate **62** produced a highly insoluble pale pink powder, which might be due to the formation of poly-substituted products.



***Scheme 46** Reaction between 2-fluoroethylacetoacetate and either 1H-1,2,4-triazole-1-carboxamidine hydrochloride or 1H-pyrazole-1- carboxamidine hydrochloride*

Identical mass spectrometry results were obtained from the reaction of 2-fluoroethylacetoacetate **19** and both 1H-1,2,4-triazole-1-carboxamidine hydrochloride **118f** and 1H-pyrazole-1-carboxamidine hydrochloride **118g**, with an $[M]^+$ peak at 159 m/z, showing that both reactions gave the same unexpected product, coming from substitution of the azole groups by aromatic nucleophilic substitution with sodium methoxide (Scheme 46). In fact, triazole groups have already been reported as good leaving groups by Larsen and Harpp.[85] Therefore we focused our work on the use of non sensitive amidine substrates.

Reactions between 2-fluoro-1,3-dimethylmalonate **62** and either malonamamidine hydrochloride **118h** or chloroacetamidine hydrochloride **118i** formed insoluble polymeric material, probably due to the low chemoselectivity of the chosen amidine in the first case or due to reaction at the alkyl halide centre in the second case. The insoluble properties of the resulting crude products made it difficult to obtain enough spectroscopic data to prove the structure of the products. Therefore, to limit side-reactions and widen the scope of amidine derivatives suitable for cyclization, the amidine must either be linked to a non-reactive substituent or a protecting group should be previously introduced to the system.

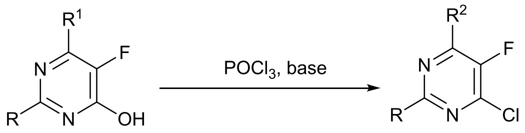
To briefly summarize this starting step, seven fluoropyrimidine compounds were successfully synthesized and fully characterized according to a procedure that has been conveniently optimized. An interesting side-reaction was observed, whereby sodium methoxide was suspected to substitute azole substituents of intermediate pyrimidines.

2.2. Chlorination of 2-substituted 5-fluoropyrimidines

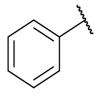
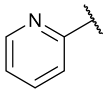
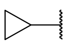
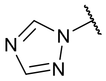
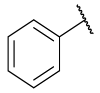
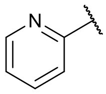
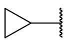
Chlorination of the synthesized fluorinated pyrimidines was achieved by replacement of the hydroxyl groups (Table 3). The purpose of this reaction step was to place a halogenic group on the structural shape of the fragment library to gain access to a useful synthetic handle for further functionalization. Optimization of the synthetic conditions included modifications of temperature, reagents and addition mode. After obtaining the first chlorinated 2-benzo-5-fluoropyrimidinone (Table 3, entry 5), this part of the project was achieved by Alexander Melvin, a 4th year student in our research group in Durham University.

Table 3 *Synthesis of chlorinated 5-fluoropyrimidine derivatives*

119c-e, R^1 = Me
111c-f, R^1 = OH



123c-e, R^2 = Me
104c-f, R^2 = Cl

Entry	R	R^1	R^2	$POCl_3$ [eq.]	Yield [%][c]
1[a]		OH	Cl	15	**104d**, 31[d]
2[b]		OH	Cl	15	**104c**, 27
3[b]		OH	Cl	20	**104e**, 37
4[b]		OH	Cl	10	-
5[b]		Me	Me	15	**123d**, 56
6[b]		Me	Me	10	**123c**, 15
7[b]		Me	Me	15	**123e**, 41

[a] $POCl_3$, N,N-dimethylaniline (1 eq.), reflux, 3 h; [b] $POCl_3$, triethylamine (1.1 eq. per –OH), inert atm., 80 °C, 105 min; [c] Isolated; [d] Crude

First attempts to chlorinate the fluorinated pyrimidines were performed using neat $POCl_3$ with N,N-dimethylaniline at 120 °C and 5-fluoro-4,6-dichloro-2-phenylpyrimidine **104d** was obtained in a crude yield of 31%. After trying to improve the crude yield by the addition of triethylbenzylammonium chloride as an extra source of chloride ions resulted in an unsuccessful attempt, forcing conditions promoted the formation of side-products.

Looking for a model compound to test and optimize the different synthetic conditions, we focused our work on the 5-fluoro-6-methyl-2-phenylpyrimidin-4-ol substrate **119d**, as it contains only one hydroxyl group to chlorinate. Softening the reaction conditions by using lower temperatures appeared to be beneficial. Due to the fact that triethylamine is a stronger base than N,N-dimethylaniline (pKa 10.78 compared to pKa 5.07), further optimization was done using this stronger base. The mechanism of the chlorination step goes through the formation of a phosphate intermediate, followed by an aromatic nucleophilic substitution of the phosphate group by the formed chloride anion.[86]

Therefore, a stronger base such as triethylamine should encourage the deprotonation of the hydroxyl group attached to the pyrimidine scaffold. The nucleophilic ability of the hydroxyl group to attack $POCl_3$ and form the phosphate intermediate was increased by the induced deprotonation, and this was the reason for the reaction speed and efficiency to be increased. Further optimization of the reaction was achieved by stirring the reaction mixture at room temperature for 15 minutes, followed by adding triethylamine and increasing the reaction temperature to 80 °C while mixing. The synthesis of the new chlorinated fluoro-fragment was monitored by GC-MS (Figure 17).

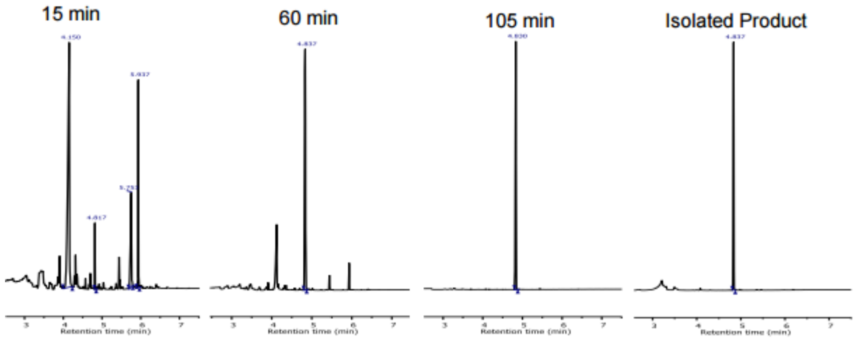


Figure 17 *GC-monitoring of the synthesis of fragment* ***123d*** *(retention time = 4.83 min) from fragment* ***119d*** *using $POCl_3$, NEt_3 under inert atmosphere*

Optimized conditions for the chlorination to occur were found as follows: neat $POCl_3$ (15 eq.) was used and triethylamine (1.1 eq. per hydroxyl group attached to the pyrimidine scaffold) was added. After 15 minutes of stirring at room temperature, a number of different species were present in the reaction solution, including a small amount of product at a retention time of 4.83 minutes. After heating up to 80 °C and adding the triethylamine over a period of 45 minutes, significant conversion to the desired product was observed. Finally, after heating for a further 45 minutes at 80 °C, full conversion to the desired product was obtained. Decreasing the reaction time, reducing the temperature, working under an inert atmosphere and adding a stronger base dropwise promoted an isolated crude yield of 80%, dropping to 56% after recrystallization in a chloroform-hexane solvent system.

Table 3 summarizes the different conditions used for the syntheses of other chlorinated fluoro-pyrimidines in relatively moderate yields, except for two compounds. One of them decomposed (Table 3, entry 4), without any product being observed by NMR or GC-MS, basically due to the triazole functional group attached to the pyrimidine scaffold, which is quite unstable. We were able to confirm the structures of few synthesized products using X-ray crystallography (two examples in Figure 18).

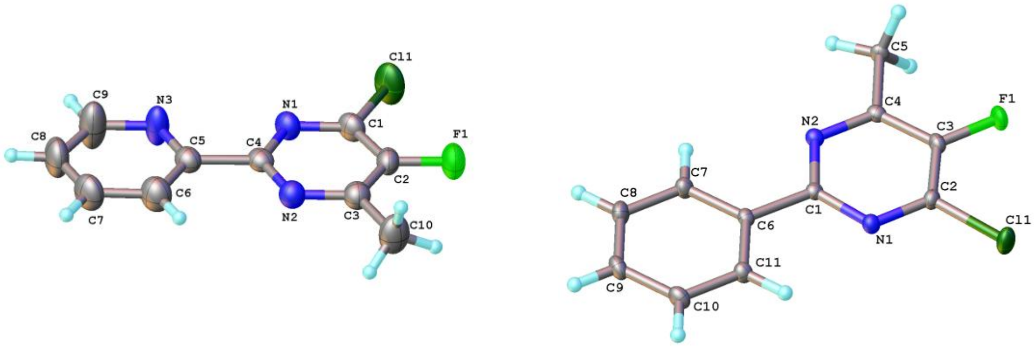


***Figure 18** Molecular structures of fragments **123c** (left) and **123d** (right) (confirmed by X-ray crystallography)*

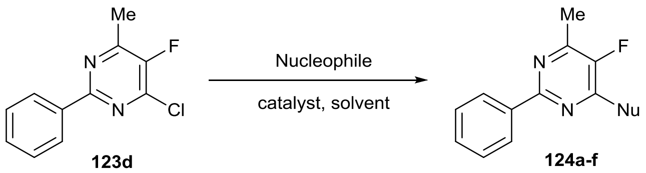
As a brief summary, the chlorination of various 2-substituted 5-fluoropyrimidines has been optimized and six different products have been isolated, fully characterized and ready for further transformations.

2.3. Nucleophilic aromatic substitution of chlorinated 5-fluoropyrimidine compounds

The final step of functionalization achieved by A. Melvin was to attach a nucleophile by replacing the chlorine atom of the fluoro-pyrimidine scaffolds. Finalizing the fragment library we built, we investigated suitable synthetic conditions for aromatic nucleophilic substitutions with O- and N- nucleophiles. The 4-chloro-5-fluoro-6-methyl-2-phenylpyrimidine **123d** was selected as a model compound to develop omtimized conditions. Aromatic nucleophilic substitutions results of fragment **123d** with ethanol, phenol, piperidine, piperazine, benzylamine and aniline are summarized in Table 4.

Mild basic conditions were used during those transformations, except with the use of aniline as nucleophile, which necessitated the use of a catalytic amount of concentrated hydrochloric acid. Due to their non-nucleophilic properties, carbonate catalysts were getting the priority as catalysts for these transformations. None of the tested reactions showed any significant competing side-reaction, therefore, promoting an efficient conversion of the starting material. However, using phenol and aniline as nucleophiles provided the desired products in low yields. Further purifications by recrystallization in an hexane-chloroform solvent system was necessary in the case of using aromatic nucleophiles during this transformation step, *i.e.* phenol, benzylamine or aniline, whereas after-work-up NMR and MS analyses showed pure products when using aliphatic nucleophiles, *i.e.* ethanol, piperidine or piperazine.

***Table 4** Aromatic nucleophilic substitution of chlorinated fluoro-pyrimidine **123d** (achieved by A. Melvin)*



123d **124a-f**

Entry	Nucleophile	Cat.	Solvent	Time [h]	Temp. [°C]	Conv. [%]	Yield [%]^a
1	Ethanol	K_2CO_3	-	19	78	97^b	**124a**, 76
2	Phenol	Cs_2CO_3	MeCN	16	75	full^b	**124b**, 44
3	Piperidine	Cs_2CO_3	DMF	16	50	98^b	**124c**, 71
4	Piperazine	-	EtOH	16	78	98^c	**124d**, 91
5	Benzylamine	NEt_3	MeCN	16	r.t.	full^c	**124e**, 84
6	Aniline	HCl	EtOH	30	78	96^c	**124f**, 69

^{a} Isolated; ^{b} By GC-MS analysis; ^{c} By LC-MS analysis

Again, we were able to confirm the structures of few synthesized products by X-ray crystallography (two examples in Figure 19).

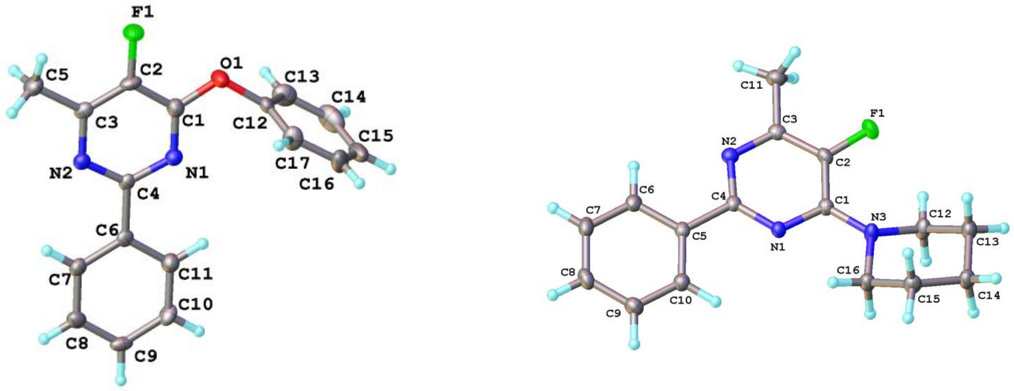
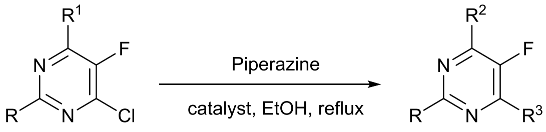


***Figure 19** Molecular structures of fragments **124b** (left) and **124c** (right) (confirmed by X-ray crystallography)*

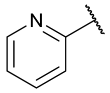
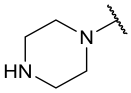
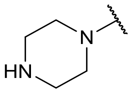
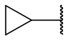
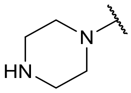
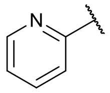
Almost full conversion was observed in case of using piperazine as nucleophile, requiring only little purification afterwards and providing almost quantitative yield. The piperazine moiety is a common functional group present in many commercial drugs, including Ciprofloxacin and Fluphenazine.[87,88] Piperazine's four sp^3–hybridised carbons increase the fragments' inherent 3D character, potentially raising target compound selectivity.[89]

Table 5 *Nucleophilic derivatisation of various pyrimidine scaffolds using piperazine as nucleophile*



123c, R^1 = Me
104c-e, R^2 = Cl

125-127

Entry	R	R^1	R^2	R^3	Time [h]	Yield [%][a]
1		Cl			72	**125**, 74
2		Cl	Cl		16	**126**, 71
3		Me	Me	OEt	96	**127**, 38[b]

[a] Isolated; [b] Corresponding to the non-desired product

The same synthetic conditions with various reaction times were applied to fragments **123c**, **104c** and **104e** (Table 5). In case of substituting the two chlorine atoms with a pyridinyl group attached to the main aromatic ring (Table 5, entry 1), we obtained a full ^{19}F-NMR conversion after 72 hours. The expected product was isolated after an aqueous work-up. On the other hand, the same reaction with a cyclopropyl group attached to the aromatic ring (Table 5, entry 2), we only obtained a mono-substitution after 16 hours and full conversion. Purification of the resulting product by column chromatography provided the isolated product in relatively high yield. The mono-substitution of the chlorine atome for the piperazine was ensured by the one-to-one addition stoichiometry (Table 5, entry 2).

Low conversion was obtained by using fragment **123c** as starting substrate after 72 hours mixing (Table 5, entry 3). Cesium carbonate was added during this test reaction to increase the nucleophilicity of the piperazine ring, however it only enhanced the ethanol to act as a nucleophile, resulting in getting a full conversion to give fragment **127**.

Full characterization of all the different obtained products was achieved by 1D- and 2D-NMR spectroscopy and mass spectrometry. Only one example out of all these fragments is presented in Figures 19, 20 and 21 as the same method was used for the attribution of all the different peaks corresponding to the respective fragments.

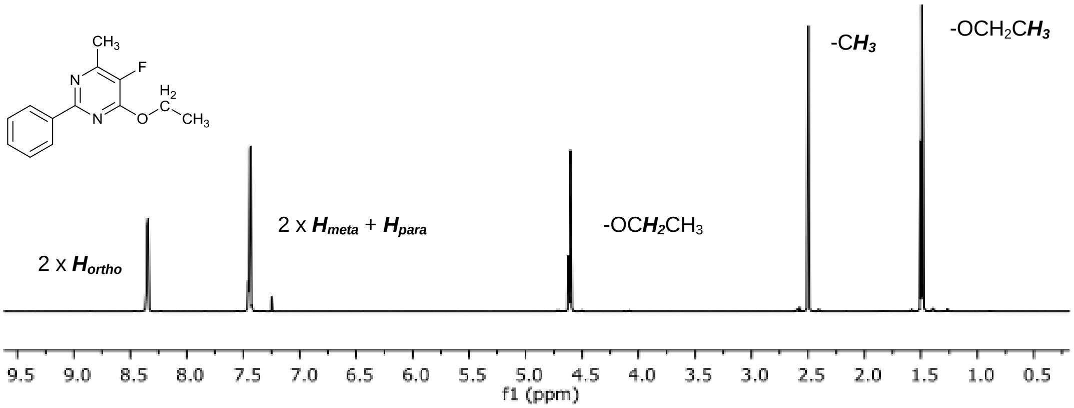


Figure 19 *^{1}H NMR spectrum (CDCl$_3$, 700 MHz, 298 K) of fragment* ***127***

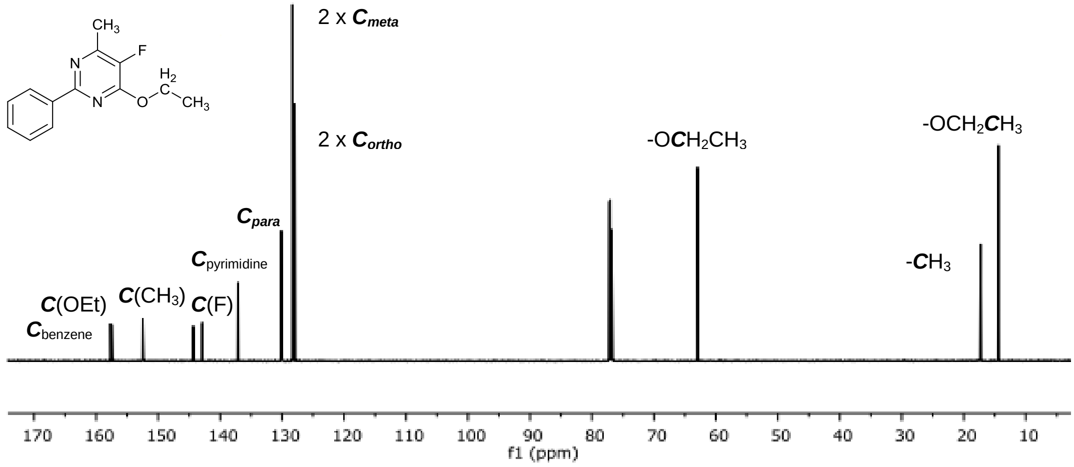


Figure 20 *^{13}C-NMR spectrum (CDCl$_3$, 176 MHz, 298 K) of fragment* ***127***

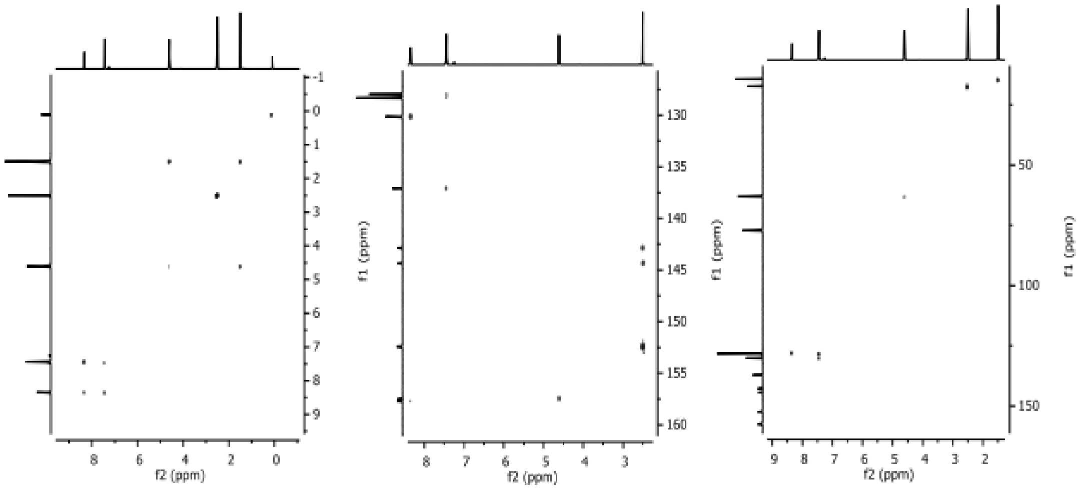
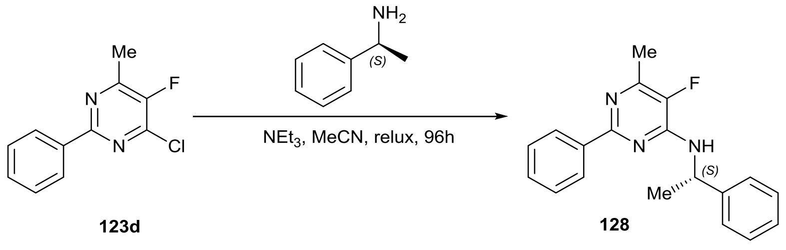


Figure 21** From left: COSY, HMBC and HSQC spectra of fragment **127

We then conducted further synthetic studies around the development of new fragments for our functionalized fluorinated library. It quickly came that introducing chirality in those fragments was the next step in our research project. Indeed incorporating sp^3 centres to fluorinated fragments appears interesting as part of the development of 3D-like molecules in a fragment-based drug discovery program. As the previously synthesized pyrimidine scaffolds possessed a planar molecular structure, adding chirality to those molecules was automatically linked to the molecular shape of the chosen nucleophile. We already introduced sp^3 centres in a few of our previously synthesized fragments, i.e. by using cyclopropyl, piperidine or piperazine functional groups which all contain -CH$_2$ moieties, but none of the previously synthesized fragments contained chiral centres.



Scheme 47** Synthesis of 5-fluoro-6-methyl-N-[(1S)-1-phenylethyl]-2-phenylpyrimidin-4-amine **128

We chose (*S*)-(-)-phenylethylamine as a chiral nucleophile to achieve the nucleophilic aromatic substitution with previously synthesized fragment **123d** (Scheme 47). The increased steric hindrance of the nucleophile relative to benzylamine (Table 4, entry 5) significantly increased the reaction time from 16 hours to four days, after which we obtained 93% ^{19}F-NMR conversion to the expected product (Figure 22). The resulting crude product was then purified by flash column chromatography to yield 43% pure material.

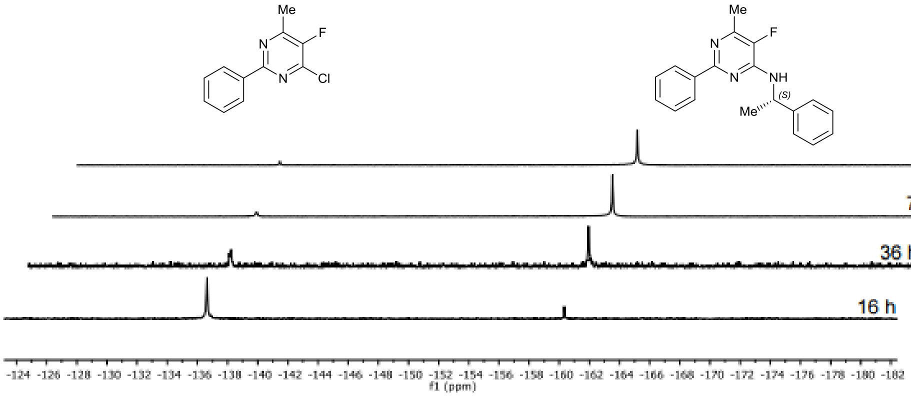


Figure 22 *^{19}F-NMR spectroscopy monitoring of the conversion of* ***123d*** *to* ***128***

In summary, we managed to synthesize various functionalized fluoro-pyrimidine fragments, starting either from 2-fluoro-1,3-dimethylmalonate or 2-fluoro-ethyl acetoacetate, and built a small library of fluoro-pyrimidines possessing a similar structure, that could be suitable to be part of a fragment-based drug discovery strategy. The concepts of fragment based drug discovery are described briefly below, followed by the screening of our fluoro-pyrimidine fragments.

3. Fluorine and fragment-screening in drug discovery

3.1. Advantages of fragment-screening in drug discovery

New approaches for the development of chemical leads for novel drugs are required, despite the success of high-throughput screening (HTS). Various options such as screening low molecular weight weakly-binding molecules against a protein target, so called fragment-based drug discovery (FBDD), have emerged (Figure 23).

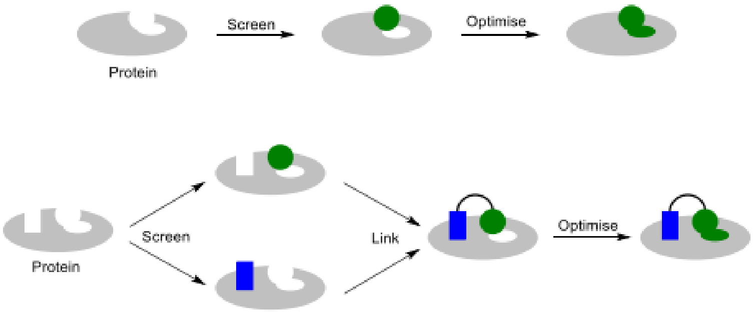


Figure 23 *Illustration of the concept of fragment-based drug discovery (the green circle and blue rectangle represent binding fragments that can be optimized and, sometimes, linked to form a high-affinity ligands)*

This dry screening process uses easy-access biophysical techniques, such as NMR spectroscopy and X-ray crystallography, to monitor the binding properties of synthesized fragments to the chosen protein targets and provides a better understanding of the binding-mechanism at the correct binding site to create lead-like molecules. Furthermore, weak affinity binding fragments can sometimes be linked together to form a highly potent ligand. FBDD recently was taking an active part in the development of several drug candidates discovered in the last decades, such as FDA-approved drug Vemurafenib, which is a treatment for melanoma.[90,91] To compare the different screenings, FBDD interestingly presents different advantages. Firstly, the theoretical space that could be occupied by all possible compounds for a given set of conditions is indeed bigger in the FBDD strategy, as it can be covered by using various smaller fragments than by an extensive library of larger compounds prepared by parallel synthesis.[92]

Limiting the size of molecules is providing a more efficient sampling of the chemical space available, and needs fewer systems to be tested to obtain final hits, which has been showcased by Hadjuk and coworkers in their work on combining 10000 fragments in pairs with ten different linkers would generate one billion compounds.[93] Studies by Scanlon and coworkers also showed that major pharmaceutical companies fragment screening campaigns revealed high hit rates (around 8%) from their fragment libraries, suggesting efficient sampling of their chemical space.[94]

Higher ligand efficiency was also obtained by FBDD technique, as compared with HTS hits. As ligand efficiency is defined as a ratio of the free energy of ligand binding against the number of non-hydrogen atoms in the ligand, Kuntz and coworkers studied the influence of the proportion of atoms on protein binding and they showed that the higher this proportion was, the better the contribution to the protein-binding event for molecules with up to 15 heavy atoms, compared to molecules with higher molecular weights.[95,96]

Filtering fragment libraries by removing molecules which contain reactive or disruptive functional groups can reduce the time spent on screening non-drug-like molecules, which has been reported by Vulpetti and Dalvit. On another hand, Hann et al. reported that extra functionality present in complex molecules may direct or limit the extent of elaboration possible on a high molecular weight hit that is being developed into a lead.[97]

Promising FBDD hits can be progressed with much more design control than HTS hits to lead-like molecules, giving the synthetic chemist more synthetic options and avoiding potential intellectual property violations. The easy access to FBDD strategy compared to industry HTS processes finally makes FBDD an efficient process in academia.[98]

3.2. Physicochemical properties of synthesized and pharmaceutical fragment libraries

To explore the required parameters in FBDD libraries, a basic analysis of the various criteria for fragment library synthesis was performed on all our combined small size synthesized fragments (Figure 24).

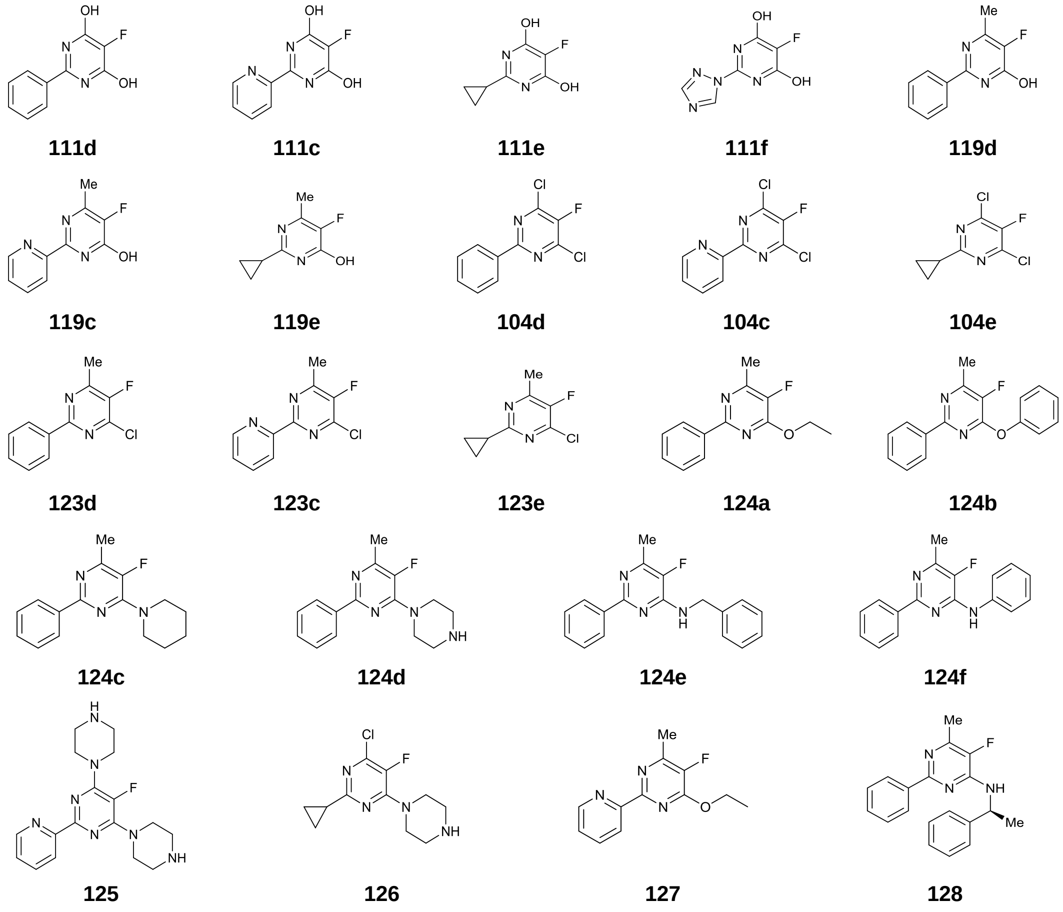


Figure 24 *Synthesized fluorinated pyrimidine derivatives fragment library*

All the synthesized fragments should respect a few criteria, such as not containing any reactive functional group able to form covalent bonds with biological nucleophiles in the target protein backbone, as they are the source of many false positives in screening essays and not contain any common reactive groups such as acyl chlorides, aldehydes or epoxides, as they induce side reactions in screening assays. Effective fragments should have chemical handles or linkers, *i.e.* -OH, -Cl, -NH functional groups for further elaboration, which is the case of 19 of our synthesized molecules out of 23.[99]

Moreover, for large, non-fluorinated fragment libraries, Congreve et al. proposed a revised version of Lipinski's famous "Rule of Five": the "Rule of Three" (RO3). Based on analysis of the properties of common fragment hits, RO3 advises binding fragments usually have MW ≤ 300 Da, hydrogen bond donors ≤ 3, hydrogen bond acceptors ≤ 3, number of rotatable bonds ≤ 3, total polar surface area ≤ 60 Å^2 and a value of log(P) ≤ 3, where P is the lipophilicity of the fragment. Additionally, a lower molecular weight limit of 150 Da is often implemented to reduce the chance of nonspecific binding.[100]

A computational study was undertaken by A. Melvin on the full library of synthesized fluoro-pyrimidine derivatives to assess their RO3 properties (Table 6). We used JoeLib descriptors of physicochemical properties, performed with the chem-informatics toolkit ChemMine Tools to assess the computational predictions.[101]

Table 6 *Comparison of physicochemical properties from up to twelve pharmaceutical fragment libraries with the synthesised fragment library*[a]

Library	Molecular weight [g/mol]	Heavy atom count	Log(P)[b]	Hydrogen bond donors
Pharma	199.4[c]	13.9[d]	1.2[e]	1.1[f]
Fluoro-pyrimidine library	240 ± 50	17 ± 4	4 ± 2	0.8 ± 0.4

Library	Hydrogen bond acceptor	Number of rotatable bonds	Rings	Topological polar surface area [Å^2]
Pharma	2.8[f]	2.0[e]	1.6[g]	59[f]
Fluoro-pyrimidine library	3 ± 1	2 ± 1	2.0 ± 0.6	50 ± 20

[a] Data for the literature-reported libraries was compiled from studies by Scanlon;
[b] Calculated atomic logP; pharmaceutical library data averaged from [c] Ten, [d] Seven,
[e] Twelve, [f] Six, [g] Five literature reported pharmaceutical fragment libraries

The various physicochemical properties are largely looking similar between both libraries, except the lipophilicity character expressed by log(P). Indeed we previously discussed that the presence of fluorine in molecular scaffolds has an impact on the liphophilicity on such molecules, especially with an extreme proximity with nitrogen atoms. Linking the high lipophilicity (log(P) > 3) and the low topological surface area (< 75 $Å^2$), studies by Pfizer Inc. showed a significant increase of the likelihood of *in vivo* toxicity. High values of log(P) can also indicate that the synthesized compound may bind to multiple targets with moderate affinity.[102]

Interestingly, the error values for each physicochemical parameters are relatively high, dealing with the fact that the fragments obtained by nucleophilic aromatic substitution using various -O or -nucleophiles possessed larger values for each parameter than the starting fluorinated pyrimidines and fluorinated chloro-pyrimidines. The molecular weight limits set out by Jordan, indeed getting a molecular weight between 150 Da and 300 Da, are respected by 21 out of 23 synthesized fragments.[103]

Only the 2-cyclopropyl-5-fluoropyrimidine-4,6-diol **111e** was fulfilling all the RO3 rules, but if we removed the lipophilicity requirement, as it is largely modified by the presence of the fluorine atom, 14 synthesized fragments out of 23 are respecting the remaining five RO3 rules, when 17 of them are obeying at least four of the RO3 remaining requirements. Finally, the computational comparison to the minimum parameters of a virtual screening showed that the fragments display most of the properties required for any industrial fragment library design program.

3.3. ^{19}F-NMR-based screening of the fragment library against β-catenin

^{19}F-NMR spectroscopy is particularly well suited to FBDD techniques due to the 100% abundance of the spin ½ ^{19}F nucleus and a sensitive transverse relaxation rate called R_2. This R_2 sensitivity parameter is the origin of ^{19}F-NMR's intrinsic sensitivity to weak protein-ligand interactions. R_2 increases on binding, causing significant line broadening of the ^{19}F-NMR signal and allowing easy determination whether the fluorinated compound is binding to the protein or not (Figure 24).

Figure 24 *Illustration of the line-broadening effect, where b = bound molecule, f = free molecule and c = control molecule in A) presence of protein and B) absence of protein*

During the ligand binding, the main cause of the lengthening of R_2 parameter is the fact that the rotation-correlation time (τ_c), one of the main contributors to R_2, increases because molecular tumbling of the large ligand-protein complex is now slow, compared to the free ligand. This causes an uneven magnetic field around the ^{19}F nucleus called chemical shift anisotropy (CSA) and results in line broadening of the ligand's signal during any binding event.[104]

As part of the Fluor21 Network European project, we developed a partnership with the University of Vienna to assess screening of the synthesized fluorinated pyrimidine fragments against β-catenin. This part of the project has been developed by Màté Solmyay, a PhD student in the University of Vienna, who carried out the NMR experiments. The main conclusions are recorded briefly here for completeness.

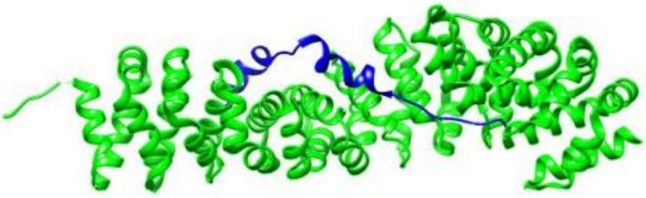


Figure 25 *Structure of β-catenin (green) bound to the transcription factor, Tcf4 (blue); structural data obtained from the Protein Data Bank (PDB – 1JDH)*

In fact, β-catenin is a well-known protein which forms a complex with Tcf4, a transcription factor, in the Wnt signaling pathway of colonic cancer cells (Figure 25). This β-catenin-Tcf4 complex is indeed promoting the transcription of many genes involved in cell proliferation, giving the result of a growth of malignant tumours. Investigations have been focussed on disrupting the binding between β-catenin and Tcf4 by attaching high affinity β-catenin ligands discovered through screening techniques. Since, 2,4-substituted-5-fluoropyrimidines have already been reported to have an anticancer activity, β-catenin was seen as a suitable target to choose for subsequent screening of our synthesized fragment library.

A first criterion was applied to all the synthesized fragments: a solubility filter *via* quantitative ^{19}F-NMR spectroscopy. Indeed, the assays were carried out in specific conditions in which the protein was stable (7.45 pH in 5% DMSO, 95% aqueous tris(hydroxymethylaminomethane) buffer solution) and, therefore, all the screened compounds had to be soluble in the same environment. Each compound was dissolved in a 1mM and 250 μM solution and their ^{19}F-NMR signals were observed relative to 1mM and 250 μM NaF respectively. If the ^{19}F-NMR signals of each compound were the same integrals (with a chosen ± 25% integral range) relative to the reference at each concentration, they were judged to be sufficiently soluble.

Out of the twelve fragments analyzed, seven passed the solubility filter (**111c-e**, **119c-d**, **124c-d**), however, four substrates out of the seven compounds showed broad ^{19}F-NMR signals (**111e**, **119c-d**, **124c**) rendering them unsuitable for further analysis. This line-broadening effect was potentially due to a large exchange contribution to the relaxation time caused by tautomerisation of the pyrimidine ring.

The three remaining pyrimidine fragments fulfilling all the required criteria were then screened against β-catenin (**111c-d**, **124c**). 60 μM of each compound was dissolved in both a reference solution and a mixture containing 20 μM of β-catenin. In each assay, 0.5 mM dithiothreitol was used as a reducing agent to ensure that disulfide bonds didn't cause the protein to aggregate in the presence of oxygen. Monitoring of these experiments was done by ^{19}F-NMR spectroscopy, revealing a potential reduction in intensity and increase in line-broadening of a fragment signal, compared to the initial reference. In the case of observing these two phenomena, it was assumed that the fragment was bonding to β-catenin. Figure 26 shows that three tested fluoropyrimidine fragments showed a weak binding affinity but not sufficiently strong to merit further investigations.

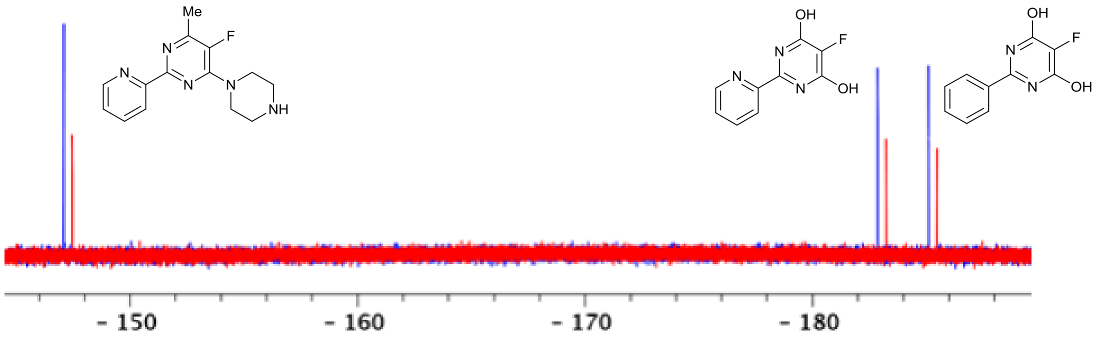


Figure 26 *^{19}F-NMR spectrum of the screening results: blue signal = 60 μM compound in the reference solution; red signal = 60 μM compound in 20 μM β-catenin (red signal shifted downfield by 0.2 ppm for clarity)*

4. Screening of the fragment library with *Cunninghamella elegans*

As well as the ^{19}F-NMR spectroscopy screening studies against β-catenin, the Fluor21 Network project allowed us to conduct studies on biotransformation of the synthesized fluorinated compounds using *Cunninghamella elegans*. This part of the project has been done in collaboration with the research group of Dr. C. Murphy in UCD Dublin, especially Shruti Mani, who identified how the synthesized fluorinated fragments were undergoing biotransformation when incubated with *C. elegans* (for 72 hours at 28 °C with shaking at 200 rpm). The biotransformation pattern of these compounds was assessed by analyzing the results obtained by ^{19}F-NMR spectroscopy and GC-MS spectrometry techniques.

4.1. Studies around the microbial model of mammalian drug metabolism involving *Cunninghamella elegans*

Several studies have suggested that microorganisms have the potential to mimic mammalian metabolism of drugs, as firstly observed by Smith and Rosazza in 1976.[105] Further studies revealed that some microorganisms possess similar enzymes that carry out phase I and phase II metabolism of drugs in mammals.[106]

As already known, phase I drug metabolism involves chemical reactions such as oxidation, reduction, and hydrolysis, but extensive pharmacokinetic and pharmacodynamic testing is required for a drug to be successfully approved for human consumption. Knowing the metabolism of a drug in mammalian system plays a vital role in determining its safety and efficacy and further evaluation of its pharmacological and toxicological activities. Therefore, metabolic studies allow the microorganisms to be used in toxicity assessment during drug development and subsequently reduce animal testing. Many microorganisms, including the soil fungus *Cunninghamella* and *Actinomycetes* bacteria are known to metabolize xenobiotic compounds in a similar way to those occurring in mammalian systems.[107]

Microorganisms have been proved to be efficient models of mammalian metabolism, however, few of them can generate useful quantities of drug metabolic intermediates. Using microbes for this purpose is more desirable than extracting metabolic intermediates from dosed animals.[108]

Cunninghamella have been largely studied for their ability to metabolise xenobiotics owing to the presence of cytochrome P450 enzymes and other associated enzymes present in mammals.[109] Studying the different phases of metabolism, it's clear that phase 1 metabolism involves oxidation, reduction and hydrolysis of the drug into various metabolites, whereas phase 2 metabolism involves chemical reactions altering the drug or the metabolites formed during phase 1 metabolism to soluble molecules, classically excreted in urine. Metabolites formed in phase 2 are generally pharmacologically inactive.[110]

Only a few studies on fluorinated drugs related to their metabolisms in microorganisms such as *C. elegans* have been conducted so far. These models of metabolism if successful can be used to produce metabolites that will otherwise be strenuous to synthesize.[111] Fungi cannot only metabolize pharmaceutical compounds in the comparable way to large quantities of metabolites as in mammals but they also offer an easy scaling-up.[112,113]

Monitoring the metabolism of fluorinated compounds still remains challenging but ^{19}F-NMR spectroscopy has improved this process in several studies on the microbial biotransformation of fluorinated compounds. In our case, ^{19}F-NMR was used for observing the degradation of fluorinated compounds and to determine which catabolic pathway is involved by revealing identities of the fluorine containing metabolites that accumulate in the culture medium, as it was previously used by the Murphy group in UCD Dublin to identify metabolites of Flurbiprofen.[114]

4.2. Biotransformation of the synthesized fluorinated pyrimidine fragments using *C. elegans*

Incubation of 5-fluoro-6-methyl-2-phenylpyrimidin-4-ol **119d** and 5-fluoro-6-methyl-2-(pyridine-2-yl)pyrimidin-4-ol **119c** with *C. elegans* gave different products. ^{19}F-NMR spectroscopy and GC-MS spectrometry analyses indeed revealed two different behaviors of the selected fluorinated fragments.

5-Fluoro-6-methyl-2-(pyridine-2-yl)pyrimidin-4-ol **119c** was not completely biotransformed, giving only access to a single fluorometabolite, identified by a singlet in ^{19}F-NMR spectroscopy, showing that the methyl group had been altered from -CH_3 to -CO_2H (Figure 27). On the other hand, biotransformation of 5-fluoro-6-methyl-2-phenylpyrimidin-4-ol **119d** was completed, resulting in the formation of 4 different fluorometabolites, each giving quartets by ^{19}F-NMR, indicating that the initial CH_3 group is unchanged (Figure 28).

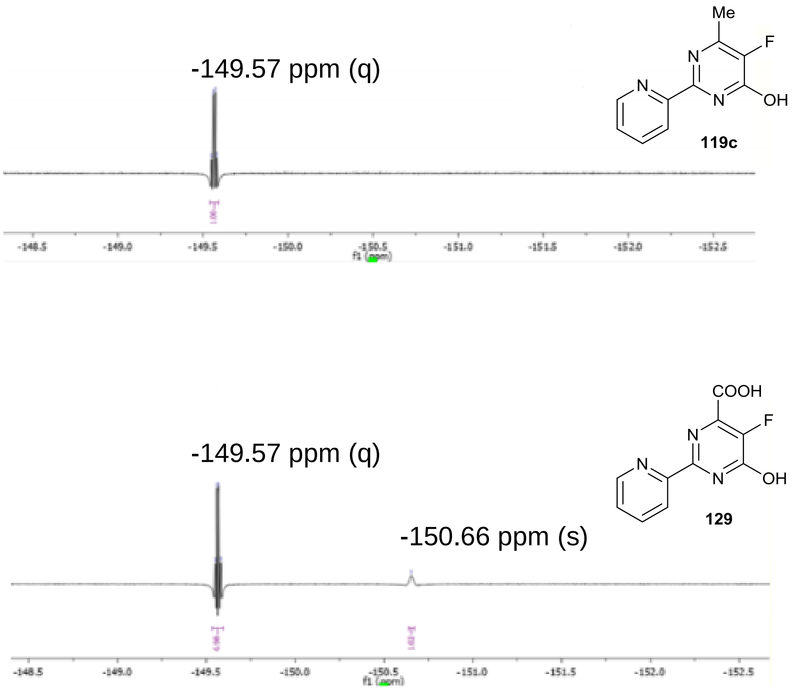


Figure 27 *^{19}F-NMR spectra of 5-fluoro-6-methyl-2-(pyridine-2-yl)pyrimidin-4-ol **119c** standard (top), and product **129** of uncomplete biotransformation of 5-fluoro-6-methyl-2-(pyridine-2-yl)pyrimidin-4-ol **119c** with C. elegans (bottom)*

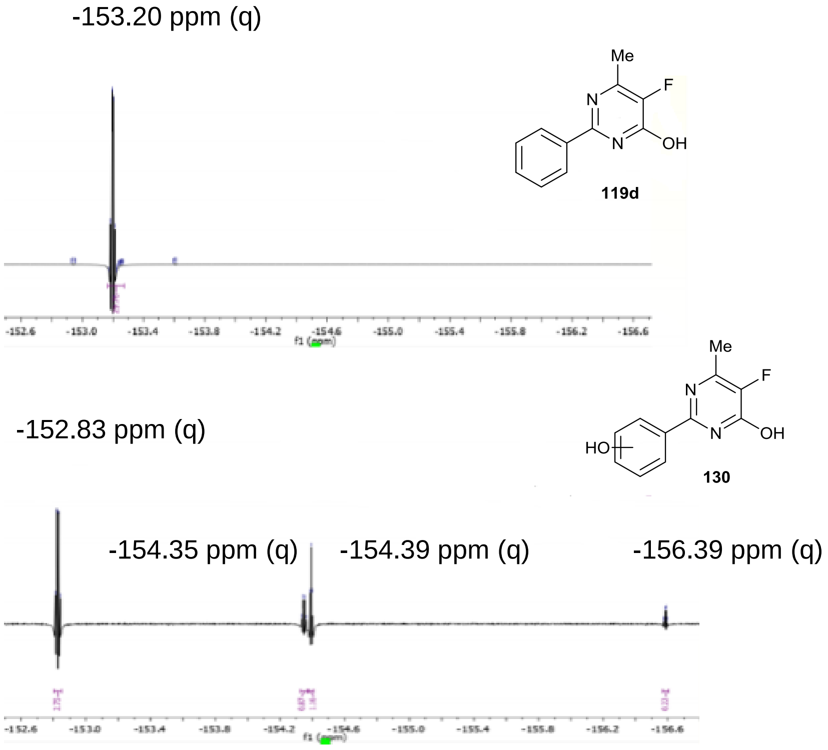


Figure 28 *^{19}F-NMR spectra of* 5-fluoro-6-methyl-2-phenylpyrimidin-4-ol ***119d*** *standard (top), and product **130** of complete biotransformation of 5-fluoro-6-methyl-2-phenylpyrimidin-4-ol **119d** with C. elegans (bottom)*

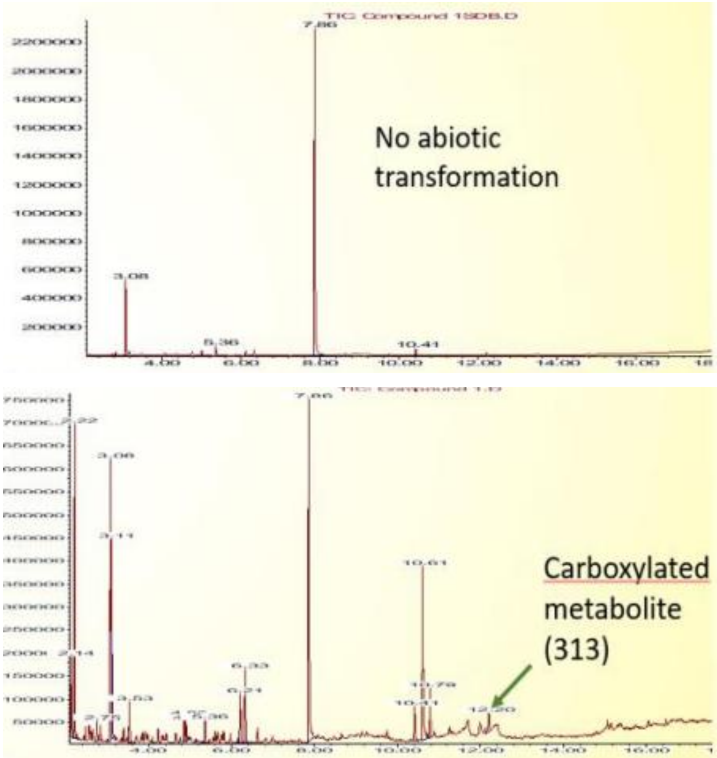


Figure 29 *GC-MS analysis of 5-fluoro-6-methyl-2-(pyridine-2-yl)pyrimidin-4-ol* ***119c*** *(abiotic control, top) and of the resulting mixture from the biotransformation of 5-fluoro-6-methyl-2-(pyridine-2-yl)pyrimidin-4-ol* ***119c*** *and C. elegans (bottom)*

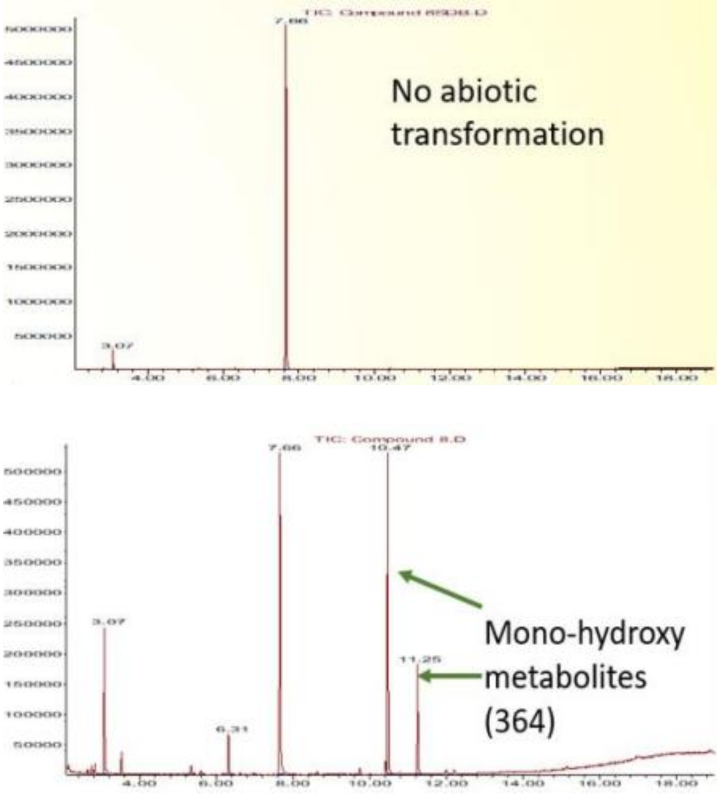


Figure 30 *GC-MS analysis of 5-fluoro-6-methyl-2-phenylpyrimidin-4-ol* ***119d*** *(abiotic control, top) and of the resulting mixture from the biotransformation of 5-fluoro-6-methyl-2-phenylpyrimidin-4-ol* ***119d*** *and C. elegans (bottom)*

GC-MS analyses of the resulting mixtures confirmed these observations and revealed the presence of carboxylated metabolite in a tiny amount in the first case, and monohydroxylated metabolites in the second case (Figures 29 and 30).

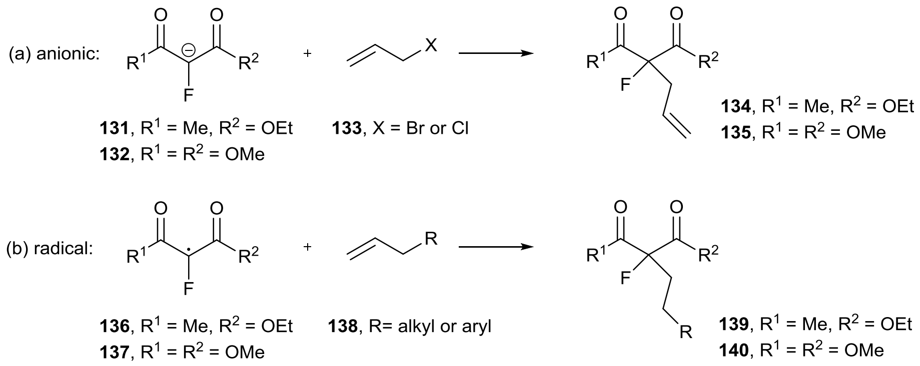
This comparison demonstrated how a single structural change, a replacement of aromatic ring by pyridine, can alter the biotransformation pattern drastically, reflecting the less easily oxidation of the electron poor pyridine ring compared to the phenyl ring. These results confirmed the potential of the fungus *Cunninghamella* to transform a wide range of xenobiotic compounds.[115]

5. Conclusion

Over this part of the project, we described and optimized easy access to various fluorinated pyrimidine structures using 2-fluoro-1,3-dicarbonyl systems. Diverse functionalizations have been conducted on the obtained structures, giving access to a range of 23 various fluorinated pyrimidine fragments. As the molecular shapes of the obtained fragments has biological activity, they have been studied as potential linkers to β-catenin, using a ^{19}F-NMR screening developed in the University of Vienna, which highlighted three fragments out of the full library as weak binders. Last but not least, biotransformation studies have been conducted at the UCD in Dublin, to investigate the impact of the functional groups attached to the pyrimidine ring of the synthesized fragments, and revealed different behaviors of such molecules when reacted with *Cunninghamella elegans*.

Chapter 4 Free radical chemistry of 2-fluoro-1,3-dicarbonyl building blocks

While all the reactions presented in the previous chapters mainly involve anionic additions or substitutions, radical chemistry represents an interesting alternative synthetic strategy, possessing a huge potential to achieve many reactions involving 2-fluoro-1,3-dicarbonyl compounds (Scheme 48).



Scheme 48 *Addition of olefin to 2-fluoro-1,3-dicarbonyl substrates via (a) anionic strategy and (b) radical chemistry*

Developing catalytic systems involving radical initiators has never been explored in the case of using 2-fluoro-1,3-dimethylmalonates or 2-fluoroketoesters as substrates, which may offer a large opportunity to access new strategies to fluorinated “building blocks”. For this reason, a brief literature review on the use of different radical initiators, especially related to reactions involving 1,3-dicarbonyl compounds, is going to be presented in this chapter, followed by our synthetic investigations on the oxidative addition of various olefins to 2-fluoro-1,3-dicarbonyl substrates.

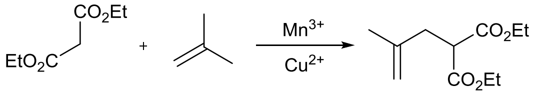
1. Overview of the oxidative addition of various olefins to dicarbonyl substrates

Oxidative addition of carbonyl compounds to alkenes has been largely investigated in the last decade, especially using reactions promoted by metal ions. Indeed, a wide range of different metal salts, such as manganese(III), cobalt(II), copper(II), silver(I), vanadium(V) and cerium(IV), has been used to generate carbon-centred radicals.[116] Oxidative strategies involving metal salts as radical initiators have received most attention for linking many different alkenes to 1,3-dicarbonyl compounds. A few papers have shown the different ability of radical initiators to afford the desired addition compounds.[117]

1.1. Additions to olefins initiated by Manganese salts

For literature procedures using 1,3-dimethylmalonate as substrate, $Mn(OAc)_3$ is known as the most common oxidant/initiator for plenty of radical reactions, but in the termination step, its oxidative ability is limited. Indeed γ-carboxy-radicals (secondary and tertiary) will be oxidized to carbocations, tertiary radicals will be oxidized to carbocations to give alkene or to form a tertiary acetate, allylic radicals will be oxidized to allylic acetates, but primary and secondary radicals won't be oxidized. If no oxidant is present they will be quenched by H-abstraction from the solvent. $Cu(OAc)_2$ oxidizes secondary radicals 350 times faster than $Mn(OAc)_3$, reacts rapidly with radicals (~ 106 M/sec) to form alkyl-Cu(III) species, primary and secondary radicals are taken to alkenes via direct oxidative elimination from the alkyl-Cu intermediate (E-olefins and the less substituted alkene), allylic tertiary radicals are oxidized to carbocations.[117]

Acetic acid is the most common solvent used with $Mn(OAc)_3$, but DMSO, MeOH, dioxane, and acetonitrile can also be used although they require higher temperature and the yields are sometimes lower. EtOH is a better H-donor than acetic acid so it is preferred when vinyl radicals are involved in the termination step (vinyl radicals cannot be oxidized so they need to be quenched). Radical chemistry involving manganese(III) acetate as a radical initiator, combined with copper(II) acetate, to link nucleophilic alkenes to 1,3-diethyl-malonates has already been reported (Scheme 49).[118]

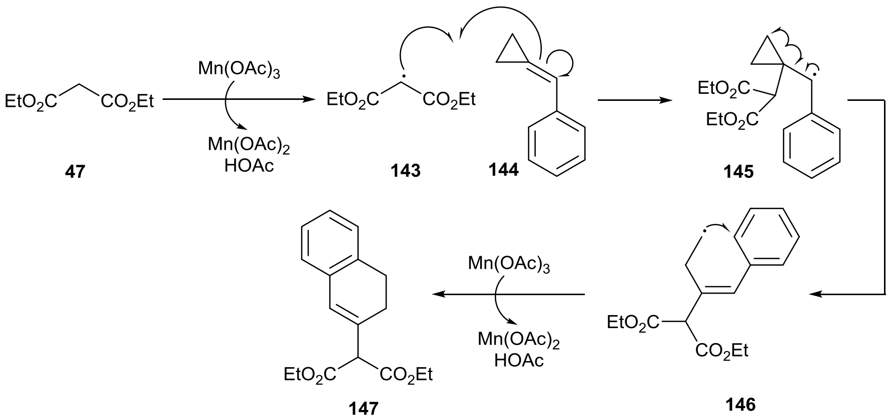


47 **141** **142**

Scheme 49 *Reported radical chemistry with diethylmalonate using Mn(II)/Cu(II) catalytic system*

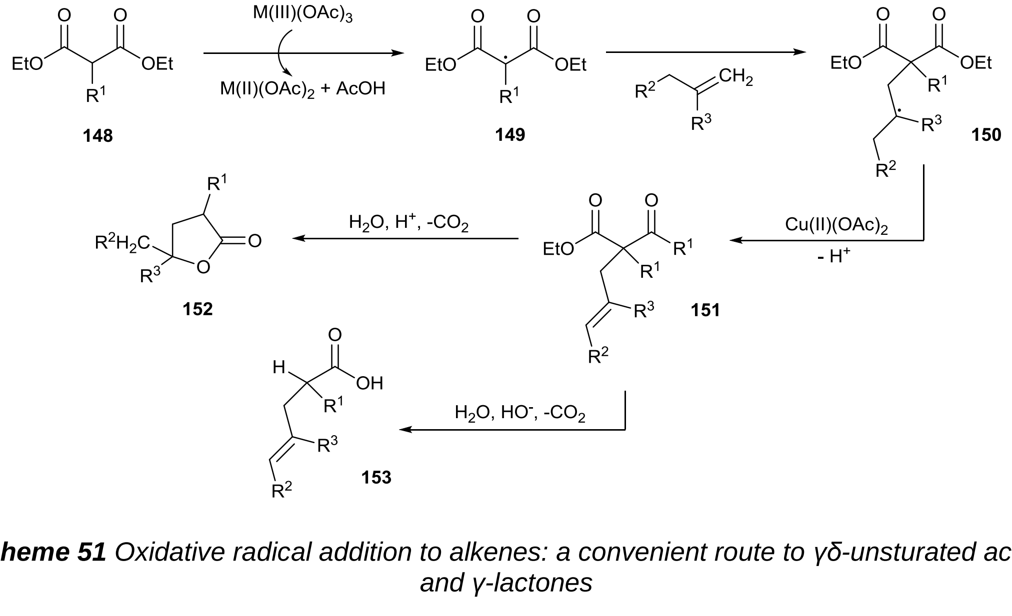
Among all the metal oxidants, $Mn(OAc)_3$ has received particular attention and its use often appears in different synthetic strategies for various oxidative additions. Moreover, its use has most of the time been associated with the synthesis of different precursors of natural products showing biological activities.[119] 1,3-Dicarbonyl compounds have been investigated as substrates in manganese(III)-

mediated oxidative free radical cyclizations of alkenes. Indeed, new C-C bonds can be easily made using an efficient oxidative method mediated by metal salts. For example, cyclization of methylenecyclopropanes (MCPs) has been reported using a manganese(III)-mediated free radical strategy for the synthesis of precursor skeletons of many natural products (Scheme 50).[120]



***Scheme 50** Reaction mechanism of the synthesis of (Z)-2,4-dihalobutenes*

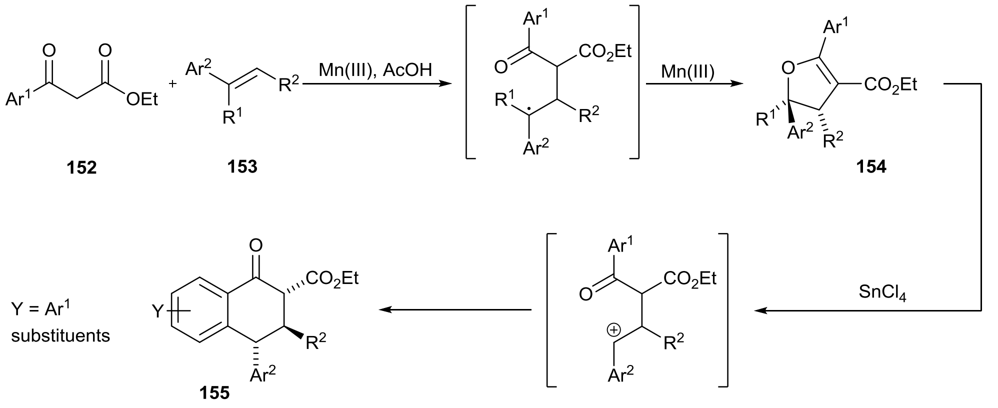
Diethyl malonate and diethylalkyl malonates react with olefins and manganese(III) or cobalt(III) acetates in the presence of copper(II) acetate to give diethyl-alk-2-enylmalonates which produce, upon hydrolysis, γδ-unsaturated acids and γ-lactones (Scheme 51).[118]



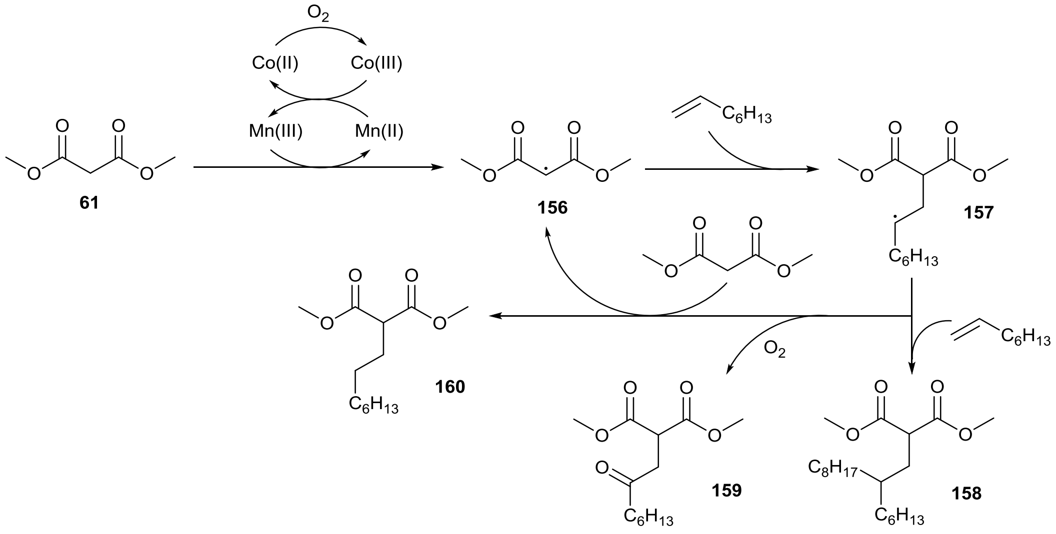
***Scheme 51** Oxidative radical addition to alkenes: a convenient route to γδ-unsturated acids and γ-lactones*

In this reported process, catalytic amounts of copper(II) acetate alter the course of the reaction initiated by Mn(OAc)$_3$ and only diethyl hept-2-enylmalonate **151** was isolated. Oxidation of the radical intermediate **150** gives selectively the isomer **151**, showing that the elimination of the hydrogen in the δ-position is preferred to the β-position, due to the polar effect of the CO_2R group preventing the nucleophile from attracting the β-hydrogen atom.

Similarly, ketoesters have been used as starting substrates with manganese(III) acetate catalytic systems, especially in the synthesis of substituted tetralones, via a two step route combining oxidative addition and cyclization (scheme 52). This method has been reported to afford molecular skeletons generally used for the synthesis of 4-arylnaphtalenes, which are known biologically active molecules.[121]



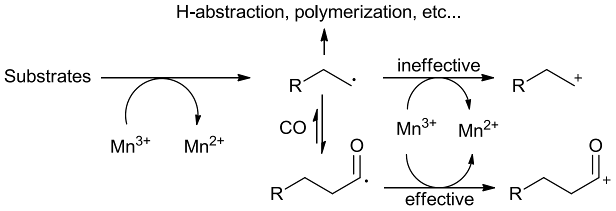
Scheme 52 *Synthesis of substituted tetralones*



Scheme 53 *Catalytic radical addition of carbonyl compounds to alkenes by Mn(II)/Co(II)/O_2*

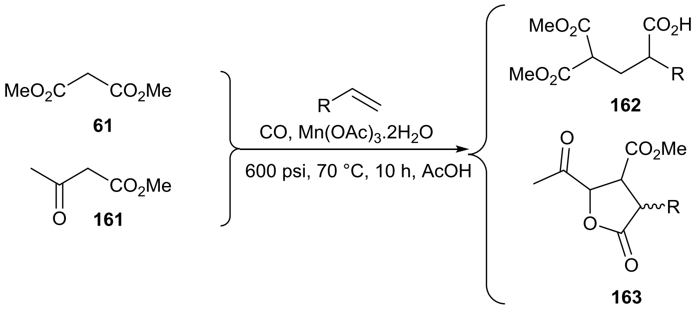
Radical addition to alkenes was also successfully achieved through a catalytic process using a system combining manganese(II), cobalt(II) and dioxygen. The mechanistic pathway for this reaction was studied and is reported in Scheme 53.[122]

On another hand, a few of the processes reported in the literature also showcased a trapping strategy involving different functional groups, either -CO or -OH. The manganese(III)-induced oxidative addition of carbonyl compounds to alkenes has attracted renewed attention in recent years and some other procedures involving malonates have been developed, using other synthetic conditions to find an alternative to the use of copper(II) salts to assist in the termination step. For example, carbon monoxide trapping in manganese(III)-induced oxidation processes have been reported (Scheme 54).[123]



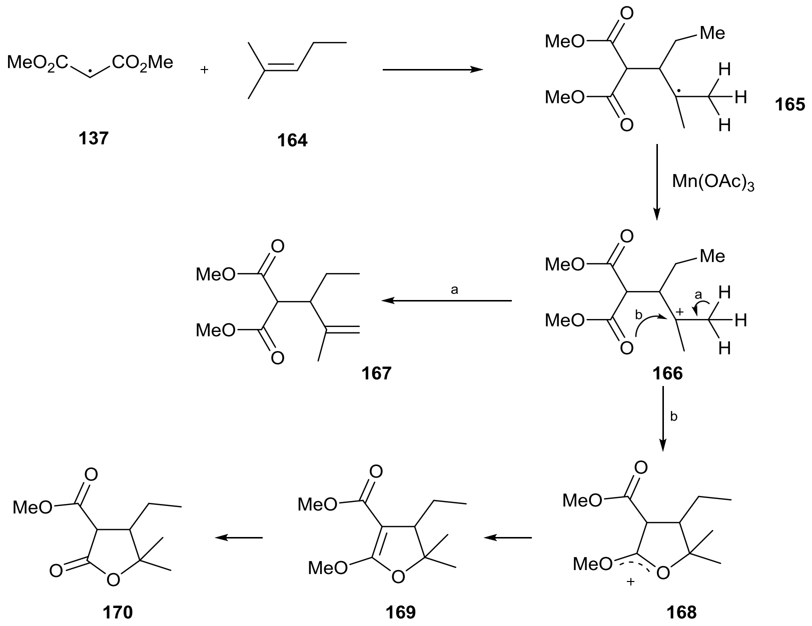
***Scheme 54** Carbon monoxide trapping in a manganese(III)-induced oxidation system*

Scheme 55 shows the different products obtained either from malonates or ketoesters using a manganese(III) acetate and carbon monoxide catalytic system.



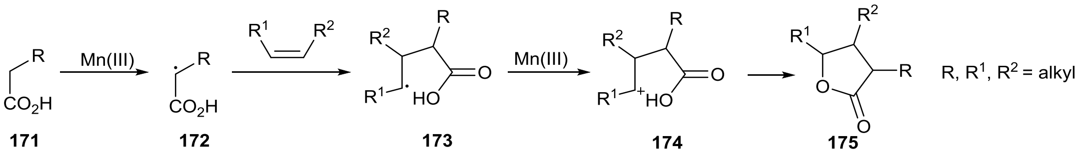
***Scheme 55** Products obtained from ketoesters or malonates with $Mn(OAc)_3$/CO*

In a similar procedure, manganese(III) acetate mediated reaction of dimethyl malonate with 2-methyl-pent-2-ene has been reported to give two products due to an alternative cylization affording a stabilized cation, following the synthetic pathway shown in Scheme 56.[116]



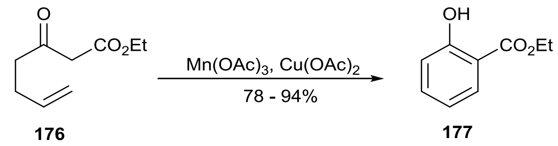
Scheme 56 *Suggested mechanistic pathways for the reaction between dimethyl malonate and 2-methylpent-2-ene in methanol*

Another $Mn(OAc)_3$ catalytic system has been developed for the one-step synthesis of γ-lactones. A SET synthetic strategy is involved and provides carboxyalkyl radicals first, followed by oxidation of the radical adduct to a carbocation species, affording compound **175** (Scheme 57). Related stimulations by ultrasound irradiation have also been investigated, and reported to afford α-substituted-γ-lactones in good yields and short reaction times.[124]



Scheme 57 *Sonochemical lactonization of olefins*

Finally, dealing with an intramolecular strategy, a few other examples using manganese(III) acetate combined with copper(II) acetate as a radical initiator system have been reported. Among these examples, one of them describes an intramolecular addition of an olefin to a ketoester function (Scheme 58).[125]



Scheme 58 *Oxidation of acetoacetate towards a 6-endo-cyclization*

1.2. Cerium ammonium nitrate as radical initiator

Several comparisons have been done between catalytic systems involving different transition metal oxidant species, among which is cerium ammonium nitrate (CAN) (Figure 31). Ceric ammonium nitrate has proved to be an efficient SET reagent and widely used as an α-carbonyl alkyl radical generator.

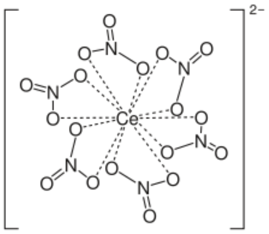
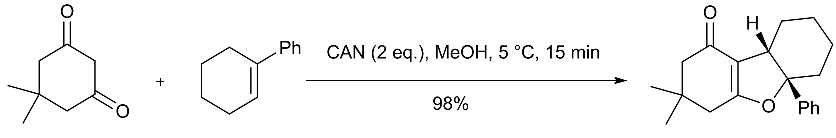


Figure 31 *Molecular structure of Ceric Ammonium Nitrate (CAN)*

Ceric ammonium nitrate is known due to recent work on oxidative addition of ketones and carboxylic acids to alkenes. Indeed, CAN possesses huge synthetic potential to form C-C bonds and was firstly reported as a reagent in the addition of 1,3-dicarbonyl compounds to buta-1,3-diene and malonylation of arenes. CAN-mediated addition of dicarbonyl compounds to cyclic and acyclic alkenes to afford 2,3-dihydrofurans in good yield has also been previously reported (Scheme 59).[116]

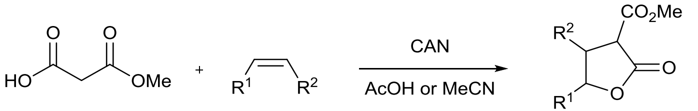


178 **179** **180**

Scheme 59 *Ceric ammonium nitrate-mediated addition of dicarbonyl compounds to cyclic alkene*

The efficiency of CAN in the synthesis of α-carbomethoxy-γ-lactones from olefins has been reported, when combined with $Cu(OAc)_2$, which is a fast oxidizer of the secondary alkyl radical to the carbocation, avoiding side-products.[126] Table 7 shows the effect of ultrasound irradiation on the reaction. Indeed, the trend is that ultrasound irradiation provides better yields for styrene derivatives and cyclohexene.

***Table 7** Lactonization of alkenes with monomethyl ester of malonic acid and ceric ammonium nitrate*



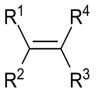
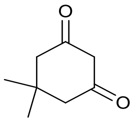
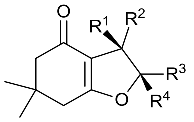
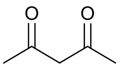
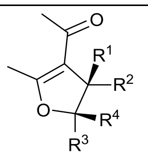
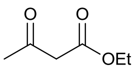
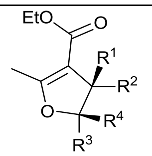
181 **182-185** **186-189**

Entry	Olefin	MeCN / yields [%]		AcOH / yields [%]	
		Mechanical stirring[a]	Ultrasound irradiation[b]	Mechanical stirring[a]	Ultrasound irradiation[b]
1	1-Octene **182**	25	20	8	9
2	Cyclohexene **183**	15	25	12	22
3	Styrene **184**	15	52	38	50
4	α-Methyl styrene **185**	30	49	41	51

[a] At room temperature; [b] At 5-10 °C

The CAN-mediated addition of dimedone, acetylacetone and ethyl acetoacetate to alkenes presents a simple method for the synthesis of dihydrofurans in good yields, and the addition of 1,3-dimethyl-malonate to alkenes provides lactones in moderate yields. The solubility of CAN in organic solvents such as methanol, acetonitrile, and THF, milder reaction conditions, experimental simplicity, generally higher yields of products, suggests that CAN is a superior alternative to commonly used manganese(III) acetate (Table 8).

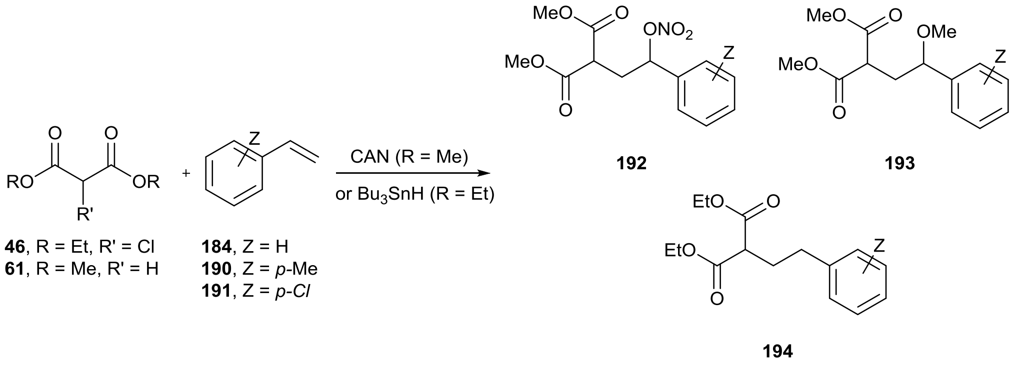
***Table 8** CAN- or Mn(OAc)$_3$-induced oxidative addition of 1,3-dicarbonyl systems to olefins*

Entry	Substrate		Product	Yields [%][a]
1		R^1 = H, R^2 = R^3 = $(CH_2)_4$, R^4 = Me		57 (47)
2		R^1 = H, R^2 = Et, R^3 = R^4 = Me		60 (41)
3		R^1 = H, R^2 = R^3 = $(CH_2)_4$, R^4 = Me		40 (39)
4		R^1 = H, R^2 = Et, R^3 = R^4 = Me		60 (39)
5		R^1 = H, R^2 = R^3 = $(CH_2)_4$, R^4 = Me		20 (33)
6		R^1 = H, R^2 = Et, R^3 = R^4 = Me		37 (45)

[a] Yields obtained with Mn(OAc)$_3$-mediated reactions are given in parentheses

Relative rates for the addition reactions of the malonyl radical to substituted styrenes have been reported, using either cerium(IV) ammonium nitrate or tributyltin hydride as the radical initiator. The two processes exhibit practically identical ρ^+ values, suggesting that the coordination between the metal and the radical does not play a significant role in the CAN-promoted oxidative addition to styrene-based olefins. Table 9 shows the yields obtained for the products **192** to **194** corresponding to the reaction between dimethylmalonate and a styrene derivative with CAN, and to the reaction between diethyl-chloromalonate and a styrene derivative with tributyltin hydride.[127]

***Table 9** Reactions between malonyl radical and substituted styrenes induced by CAN or Bu_3SnH*



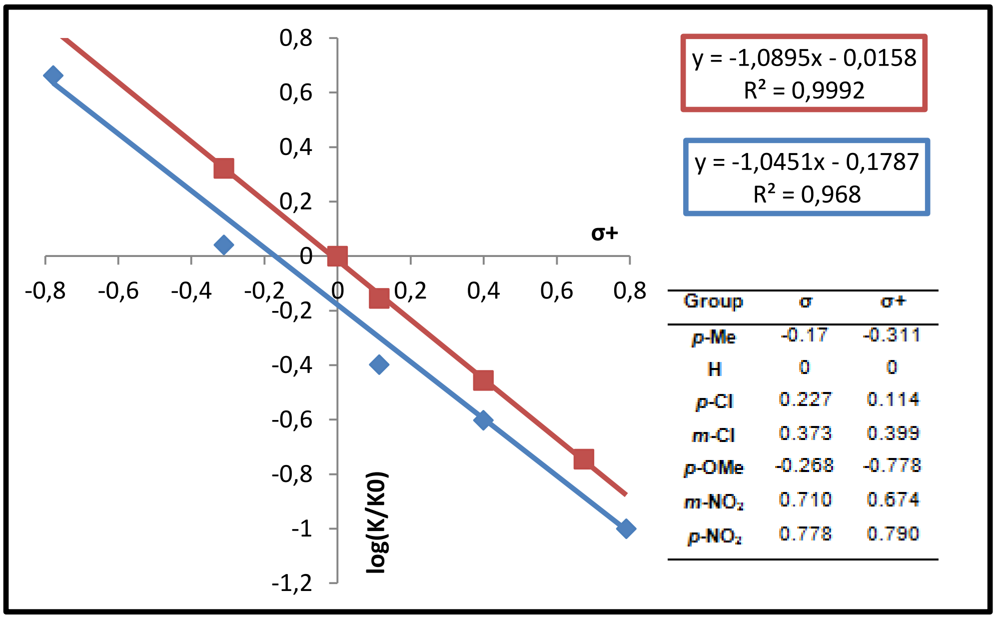
Entry	Olefin	Reaction induced by CAN {192+193} [%][a]	Reaction induced by Bu_3SnH {194} [%]
1	*p*-Methylstyrene **190**	90 (0.7)	40
2	Styrene **184**	93 (2.9)	50
3	*p*-Chlorostyrene **191**	86 (2.7)	50

[a] In parentheses the ratio [**192**/**193**]

Relative rates for both reactions are reported in Table 10, electron-donating groups increase and electron-withdrawing groups retard the reaction rate. Applying the Hammett equation to these values, with corrected σ^+ substituent constants, ρ^+ values from the Hammett trend plot don't show so much difference between the reaction induced by CAN (-1.0895) and that induced by Bu_3SnH (-1.0451), showing an identical selectivity for the two reactions (Figure 32).

***Table 10** Relative reactivities in the addition reactions of malonyl radicals to Z-substituted styrenes*

Entry	**Z**	**Reaction induced by CAN**	**Reaction induced by Bu_3SnH**
1	*p*-CH_3	2.1	1.1
2	H	1.0	1.0
3	*p*-Cl	0.70	0.40
4	*m*-Cl	0.35	0.25
5	*p*-OMe	/	4.6
6	*m*-NO_2	0.18	/
7	*p*-NO_2	/	0.10

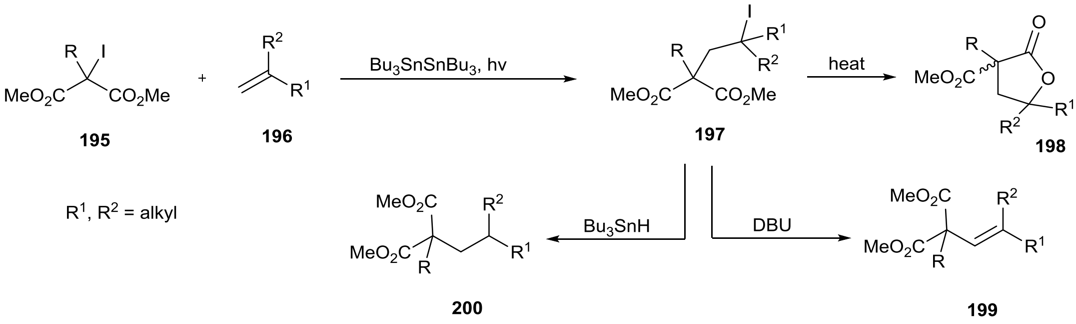


Group	σ	σ+
p-Me	-0.17	-0.311
H	0	0
p-Cl	0.227	0.114
m-Cl	0.373	0.399
p-OMe	-0.268	-0.778
m-NO_2	0.710	0.674
p-NO_2	0.778	0.790

***Figure 32** Hammett plots and trend plots of the CAN- (red) and Bu_3SnH-induced (blue) addition of malonyl radical to substituted styrenes*

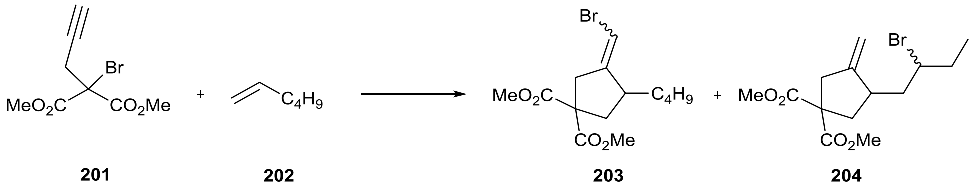
1.3. Other radical initiators

2-Halogenated malonates, such as iodo-malonates, have already been investigated as excellent substrates for radical cyclizations by an atom transfer strategy. Indeed, several alkenes have been previously tested as acceptors for the addition reactions to iodo-malonates using tributyltin hydride as a radical initiator (Scheme 60). Malonyl radicals are considered as electrophilic and pair with electron rich alkene acceptors in additions, whereas most radical reactions pair nucleophilic alkyl radicals with electron-deficient alkene acceptors.[128]



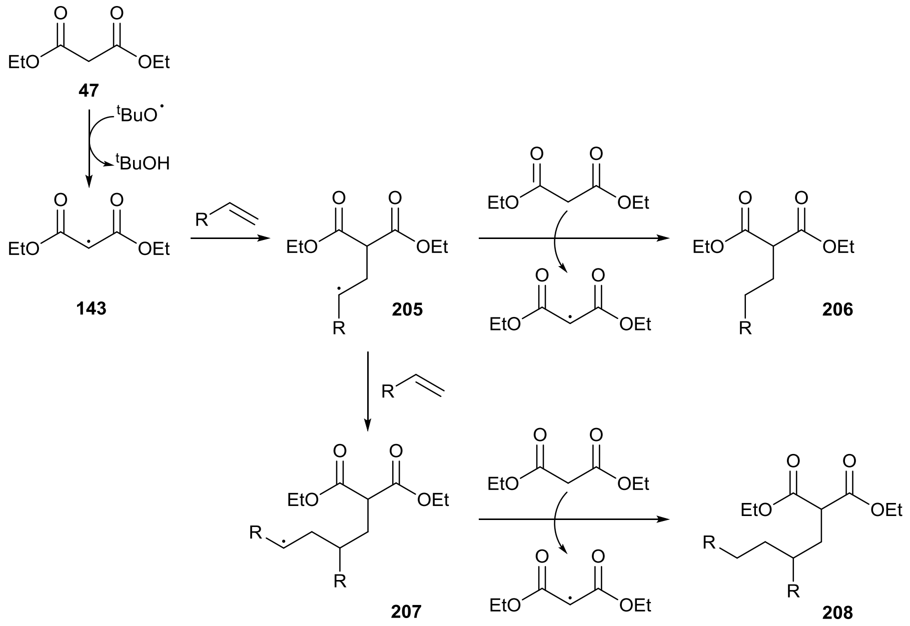
Scheme 60 *Addition reactions of iodomalonates to various alkenes*

The addition of alkenes to bromo-malonates has also been reported in an annulation experiment (Scheme 61).[128]



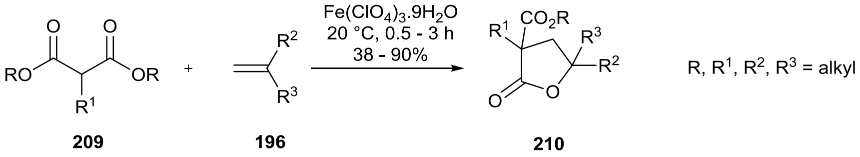
Scheme 61 *Annulation experiment with bromo-malonate*

On another hand, free radical addition of an ester to an olefin in the presence of peroxide initiators can be used for the synthesis of aliphatic acids from malonic acids. Radical alkylation of malonic ester and related 1,3-dicarbonyl compounds, such as ketoesters, has also been reported using peroxides, as the radical initiator. An efficient, convenient and direct alkylation of diethyl malonate has been developed, using a one-step process involving a free radical initiated addition of the reactive species to suitable olefins. This synthetic strategy has been applied to few olefin substrates such as 1-octene, cyclohexene or 1-decene and the synthetic pathway is shown in Scheme 62.[129]



***Scheme 62** Radical-alkylation of malonic ester using ditertbutylperoxides*

Last but not least, oxidation of malonic esters in the presence of olefins has been reported using iron(III) perchlorate nonahydrate (FEP) in acetonitrile. Inter- and intramolecular additions of dialkyl malonates to olefins such as styrenes or dienes can be achieved to provide 3,5,5-trisubstituted-2-oxotetrahydrofuran-3-carboxylic esters in high yields or γ-lactones with low selectivity from other alkenes (Scheme 63). This process shows another alternative to commonly used metal oxidants such as manganese(III) acetate or ceric ammonium nitrate (CAN), as the FEP reagent is relatively inexpensive.[130]



***Scheme 63** Efficient oxidation of enolizable carbonyl compounds to α-carrbonylalkyl radicals by iron(III) salts*

All the free radical initiation methods that have been reported are used in reactions with non-fluorinated dicarbonyl substrates or intermediates and their respective applications, corresponding synthetic approaches have never been tested on 2-fluorinated starting molecules and our research on this topic will be presented in the next part.

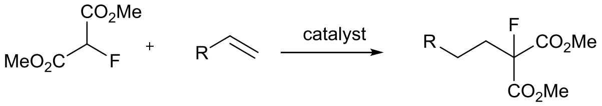
2. Catalytic oxidative addition of fluorinated 1,3-dicarbonyl compounds to olefins using radical chemistry

Throughout this next part, we present our different synthetic investigations to achieve the oxidative addition of our synthesized fluorinated 1,3-dicarbonyl substrates to various olefins, studying the nature of the catalytic system to process such reactions.

2.1. Manganese acetate $Mn(OAc)_3$ as initiator

By similar procedures to those reported in the literature, we tested a range of different manganese(III)-based catalysts, $Mn(OAc)_3$, Mn_2O_3, or $Mn(acac)_3$ using previously synthesized 2-fluoro-1,3-dimethylmalonate, with two different olefins, either cyclohexene or 1-octene. $Cu(OAc)_2$ was used as a co-catalyst in some cases (Table 11). No conversion was obtained in the cases of using either Mn_2O_3 or $Mn(acac)_3$ as catalyst, even with a reaction time of 3 days. Adding $Cu(OAc)_2$ as a co-catalyst didn't improve the conversion of the starting substrate into the desired product.

***Table 11** Optimization table for the addition of alkene to 2-fluoro-1,3-dimethylmalonate with different Mn-based catalysts*[a]



62 **182** or **183** **140a-b**

Entry	Olefin [eq.]	Catalyst [eq.]	Time [h]	Yield [%][c]
1	1-Octene **182** [0.5]	$Mn(OAc)_3$ [0.5]	5	-
2	1-Octene **182** [0.5]	$Mn(OAc)_3$ [0.5]	20	17
3[b]	1-Octene **182** [0.5]	$Mn(OAc)_3$ [0.5]	20	18
4	Cyclohexene **183** [0.5]	$Mn(OAc)_3$ [0.5]	24	7
5[b]	Cyclohexene **183** [0.5]	$Mn(OAc)_3$ [0.5]	24	10
6	1-Octene **182** [1.0]	Mn_2O_3 [1.0]	72	-
7	1-Octene **182** [1.0]	$Mn(acac)_3$ [1.0]	72	-
8	1-Octene **182** [1.0]	$Mn(OAc)_3$ [1.0]	120	48

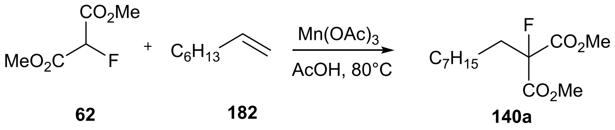
[a] AcOH, 80°C; [b] With $Cu(OAc)_2$ (10 mol%) as co-catalyst; [c] By ^{19}F-NMR

Using cyclohexene lowers the conversion, therefore longer chain alkenes, such as 1-octene were used in the further reactions. Longer reaction times and more molar equivalents of $Mn(OAc)_3$ gave better conversion and it has been shown that the efficiency of the electron transfer to generate radicals is mainly dependent on the olefin used.[131]

***Figure 33** Picture of reaction mixtures containing 2-fluoro-1,3-dimethylmalonate, olefin and $Mn(OAc)_3$ with and without $Cu(OAc)_2$ as co-catalyst*

Before attempting any further purification, improving the synthetic conversion of linking alkenes to 2-fluoro-1,3-dimethylmalonates using $Mn(OAc)_3$ was done by heating the mixture up to 100 °C and adding the alkene at 100 °C. Different synthetic conditions were tested (Table 12). More molar equivalents of 2-fluoro-1,3-dimethylmalonate gave higher conversion of the 1-octene to the desired product. Using 2-fluoro-1,3-dimethylmalonate as a solvent, without acetic acid, provides really good conversion (Table 12, entries 6 to 10), and more molar equivalents of the Mn(III) catalyst also improve the conversion (Table 12, entries 8, 9 and 10).

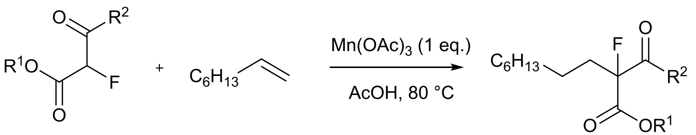
***Table 12** Addition of alkene to 2-fluoro-1,3-dimethylmalonate using $Mn(OAc)_3$ catalyst*



Entry	Reaction time [h]	62 [eq.]	$Mn(OAc)_3$ [eq.]	Yield [%][b]
1	24	1	1	22
2	72	1	2	77
3	72	2	2	20
4	72	2	1	25
5	72	4	1	45
6[a]	72	10	1	39
7[a]	72	15	1	50
8[a]	72	20	2	93
9[a]	72	30	2	95
10[a]	72	40	2	quant.

[a] Without AcOH; [b] Isolated

Various attempts at purification of the addition product were carried out, combining distillation under reduced pressure and column chromatography, providing the corresponding product. Whereas the purification of the crude product by a distillation method on a larger scale makes this synthetic strategy potentially interesting, problems of huge excess of 2-fluoro-1,3-dimethylmalonate made this an unrealistic synthetic process.



140a, R^1 = Me, R^2 = OMe, 68% conv., 45%
139a, R^1 = Et, R^2 = Me, full conv., 76%

19, R^1 = Et, R^2 = Me
62, R^1 = Me, R^2 = OMe

182, 1 eq.

Scheme 64 *Synthetic comparison between 2-fluoroacetoacetate and 2-fluoro-1,3-dimethylmalonate substrates*

Investigations around the impact of the starting fluorinated substrate were made (Scheme 64) and the use of fluorinated malonate gave less than full conversion towards the desired product but 2-fluoro-ethyl acetoacetate gave full conversion, accessing the desired molecule in convenient yield after very difficult purification (Figure 34).

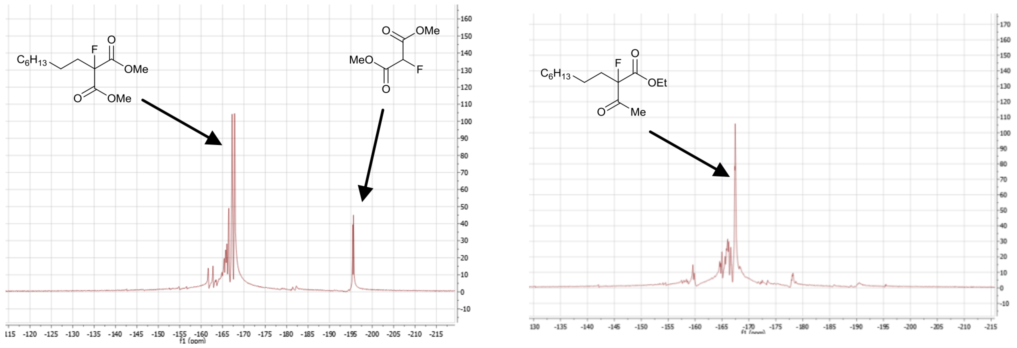
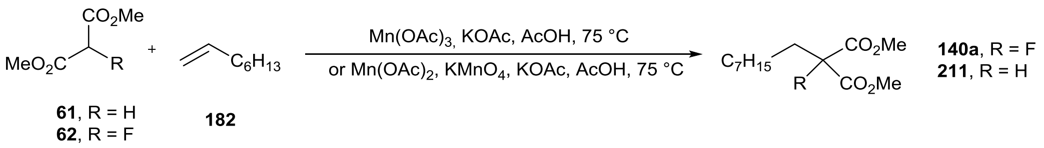


Figure 34 *^{19}F-NMR (-215 to -130 ppm) of crude products from Mn(OAc)$_3$-induced addition of 1-octene to 2-fluoro-1,3-dimethylmalonate (left) or 2-fluoroethylacetoacetate (right)*

2.2. Other Manganese-based radical initiators

Improving the conversion of linking alkenes to fluorinated malonates was investigated using two other procedures (Scheme 65), involving the use of Mn(OAc)$_2$, or KMnO$_4$.[132] Both procedures, either using 1,3-dimethylmalonate or 1,3-dimethyl-2-fluoromalonate, gave full conversion of the 1-octene but the desired products were only obtained when the non-fluorinated malonate was used as a starting substrate. Due to the presence of many by-products (^{19}F-NMR), purification of the crude mixtures was not achieved. Similar conditions were tested using a different olefin, cyclohexene, but again gave poor conversion and many by-products were observed (^{19}F-NMR).

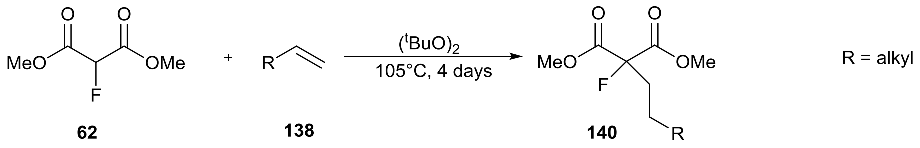


***Scheme 65** Radical chemistry involving fluoro- and non fluoro-malonates using other manganese-based radical initiators*

We also tested the catalytic radical addition of carbonyl compounds to alkenes by a Mn(II)/Co(II)/O_2 system (previously shown in Scheme 53), and we tested 1,3-dimethyl-2-fluoromalonate as a potential substrate using this combination. Whereas using 1,3-dimethylmalonate was reported to give the desired product,[122] the presence of the fluorine atom did not allow any conversion of the substrate and the yield of the desired product could not be determined due to the large amount of by-products, when the fluorinated malonate (15 eq.) was the starting compound. For this reason, this method was not investigated further.

2.3. Ditertbutylperoxide (^{t}BuO)$_2$ as initiator

Synthetic aspects of free-radical addition of alkenes to 1,3-dicarbonyl compounds has been reported in a few literature reviews, but the influence of the fluorine atom in the α-position has never been investigated for ^{t}BuO$^\cdot$ initiator processes (Scheme 66).

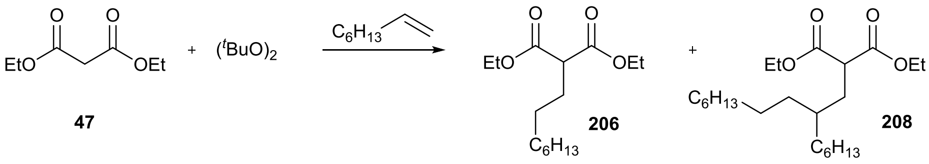


***Scheme 66** Addition of alkene to 2-fluoro-1,3-dimethylmalonate using ditertbutyl peroxide as radical initiator*

To discover the optimal conditions of the addition of 1,3-dicarbonyl substrates such as malonates to alkenes, a series of experiments were previously reported by Allen and coworkers,[129] with varied temperatures, reactions times, ratios of reactants and nature of the peroxide initiator (Table 13). It has been reported that peroxidic initiation at elevated temperatures is more effective than photo-initiation at room temperature and high ratios of reactive methylene compound to olefin are essential for good conversions.

Table 13 shows the reported results of addition of 1,3-diethylmalonate to 1-octene induced by peroxide. Clearly, to avoid the formation of the product **208**, the best synthetic strategy (Table 13, entry 4), that has been reported for 1,3-diethylmalonate, involved addition of a mixture of the olefin (1 mol), the reactive malonate compound **47** (1 mol) and ditertbutylperoxide (0.1 mol) over 6 hours to the same reactive malonate compound **47** (7 mol) at around 150°C. At those temperatures, ditertbutyl peroxides decompose to give methyl radicals in addition to tertbutoxy radicals, modifying the efficiency of the initiation processes. Entries (5) and (6) showed that reducing the amount of peroxide has no impact on the obtained yields corresponding to both products. Finally, the best conditions to give higher yield of product **206**, were found in entry (7), and these synthetic conditions were applied to 1,3-dimethyl-2-fluoro-malonate.

Table 13 *Addition of 1,3-diethylmalonate to 1-octene (1 mol) induced by ditertbutyl-peroxide (0.15 mol) at 105 °C (reaction time: 4 days)*

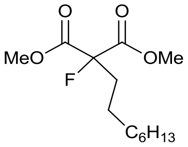


Entry	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
1,3-diethylmalonate [mol]	2	5	8	8[a]	20	20[b]	30	40	50
206 [%]	6	11	13	47	67	67	79	60	73
208 [%]	6	6	11	/	14	11	6	11	10

[a] Malonate (1 mol), 1-octene (1 mol), peroxide (0.1 mol) added to malonate (7 mol) at 150 °C during 6 hours then heated for a further 1.5 hour; [b] Ditertbutylperoxide (0.05 mol)

Following the conditions of entry (7), a similar addition to 1,3-dimethyl-2-fluoromalonate was achieved and, after Kugelröhr distillation of excess 1,3-dimethyl-2-fluoromalonate, the resulting crude mixture shows by ^{19}F-NMR the presence of the desired product in some cases (Table 14). Unfortunately, related processes using ditertbutylperoxide with substrates such as styrene derivatives did not provide any desired product, but afforded a crude product with a polymeric texture.

Table 14 *Addition of 1,3-dimethyl-2-fluoromalonate to olefin induced by ditertbutyl-peroxide*[a]

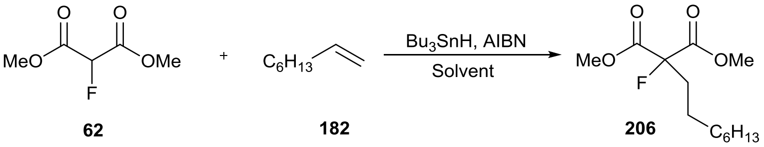
Entry	**Olefin**	**(^{t}BuO)$_2$**	**Yield [%]**[b]	**Product**
1	1-octene [0.033 eq.]	0.005 eq.	66	
2	Styrene [0.1 eq.]	0.01 eq.	-	-
3	vinyl-cyclohexane [0.1 eq.]	0.01 eq.	-	-
4	Cyclohexene [0.1 eq.]	0.01 eq.	-	-
5	4-methyl-styrene	0.1 eq.	-	-

[a] 105°C, 4 days; [b] By ^{19}F-NMR

These experiments have only been done on a µL-scale, and a good purification method of the resulting crude mixtures was not possible, especially in case of using styrene derivatives as substrates, which gave polymerization.

2.4. Tributyltin hydride/Azobisisobutyronitrile (Bu_3SnH/AIBN) as initiator

Tin initiators dominate free radical chemistry and they have proved particularly serviceable to replace hydrogen by hydroxyl, amino, nitro, thiol, selenide, carboxylate, and halogen groups.[133] Tributyltin hydride combined with azobisisobutyronitrile (AIBN) is most commonly used in synthetic sequences and so we tested this initiator combination in reactions between 1,3-dimethyl-2-fluoromalonate and 1-octene (Scheme 67).



Scheme 67 *Addition of 1-octene to 1,3-dimethyl-2-fluoromalonate using tributyltinhydride/AIBN*

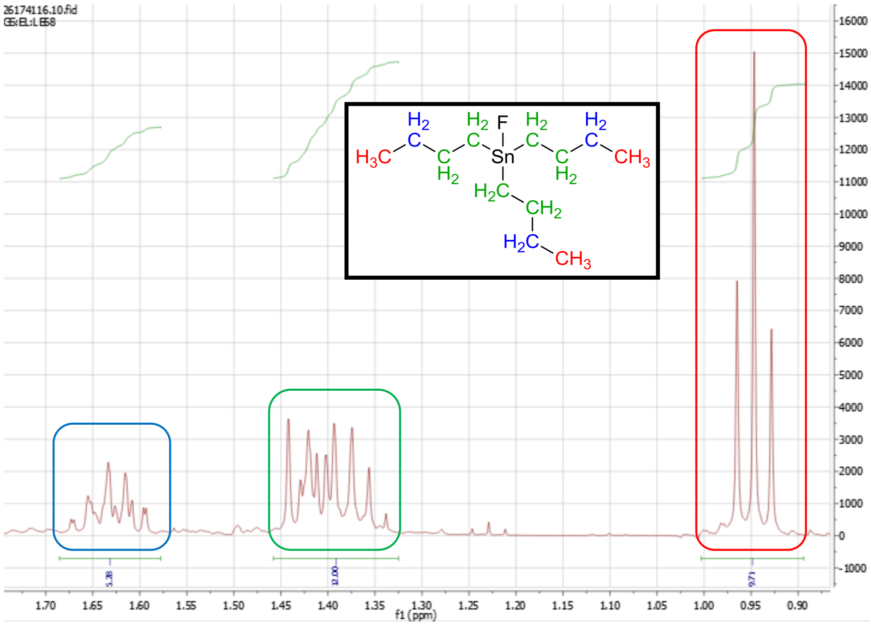
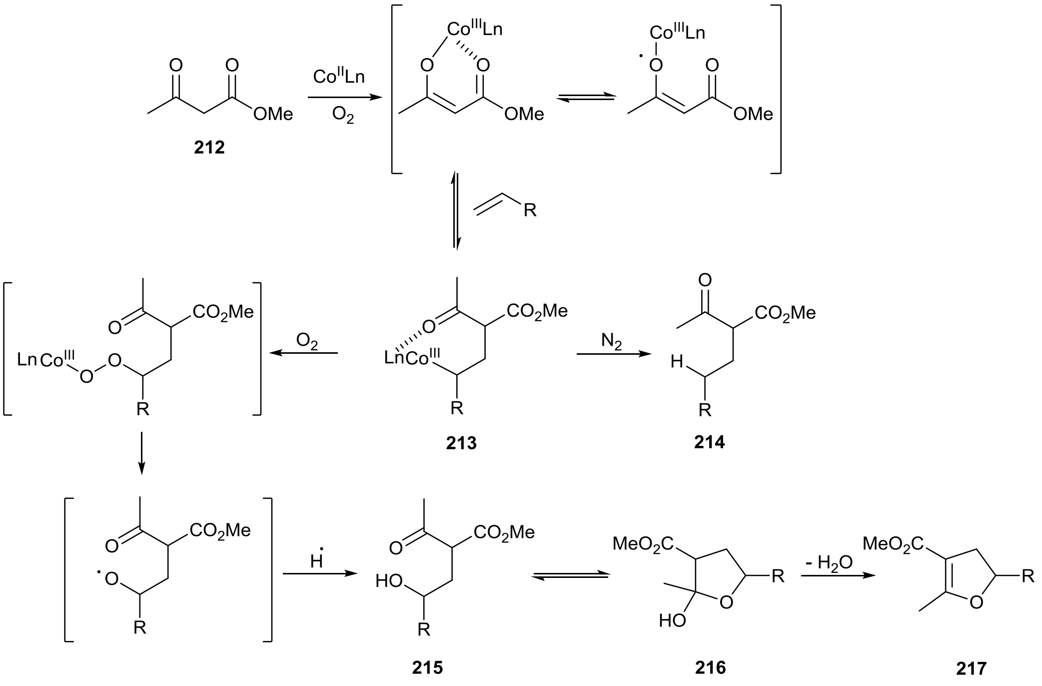


***Figure 35** ^{1}H-NMR of resulting product from the addition of 2-fluoro-1,3-dimethylmalonate to 1-octene using tributyltin hydride as radical initiator*

Different synthetic conditions have been tested on the 1,3-dimethyl-2-fluoromalonate:1-octene (1:1) substrates system, using 1, 2 or 3 molar equivalents of tributyltin hydride either in benzene or toluene. After work-up, only Bu_3SnF was obtained in all the tested experiments (^{1}H- and ^{19}F-NMR) (Figure 35). Those results can be explained by the fact that KF is used during the work-up of the reaction to get rid of the unreacted tributyltin hydride, after converting unreacted Bu_3SnH to Bu_3SnI by using iodine, meaning that Bu_3SnF can be formed during the work-up, so this method has not been investigated further.

2.5. Cobalt acetate $Co(OAc)_2$ initiator and fluoro-ketoester as substrates

Cobalt(II) acetate promoted oxidative addition of 1,3-dicarbonyl compounds to alkenes under aerobic conditions has already been reported (Scheme 68).[134] Cobalt(II) acetate oxidizes the acetoacetate to give a cobalt(II) enolate, likely to behave as an enol radical and react with the chosen alkene to yield an organocobalt compound. Anaerobic conditions provides the compound **214**, while the insertion of dioxygen in the carbon-cobalt bond gives the peroxo-cobalt(III) complex, giving the alkoxy radical by homolytic cleavage. This radical abstracts an hydrogen atom to give hydroxy compound **216**, which undergoes an intramolecular ketalisation to yield the hemi-ketal **217**.

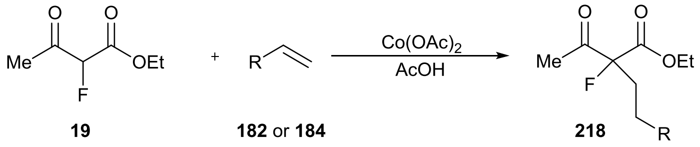


Scheme 68 *Mechanistic pathway of the addition of acetoacetate to alkene using* $Co(OAc)_2$

Figure 36 *Picture of the reaction mixture containing 2-fluoroacetoacetate, olefin and* $Co(OAc)_2$

A molar ratio [2:2:3] for [$Co(OAc)_2$:fluoro-ketoester:alkene] was used and different synthetic conditions were tested to find a suitable procedure (Table 15). Choosing a longer chain alkene with the double bond in the terminal position, such as 1-octene, provided a better yield than styrene derivatives and heating up the reaction mixture gave higher yields.

Table 15 *Addition of 2-fluoroacetoacetate to various olefins using Co(OAc)$_2$*



Entry	R	Temp.	Time [days]	Yield [%][a]
1	C_6H_{13}	r.t.	3	24
2	C_6H_5			15[b]
3	C_6H_{13}	90°C	4	67

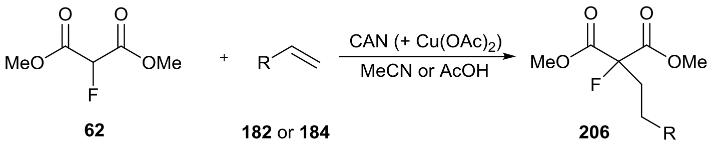
[a] Isolated ; [b] By ^{19}F-NMR

Those tested synthetic conditions showed that fluorinated ketoester are probably a much better option as a starting compound for any type of radical initiator system, but purification was very difficult.

2.6. Ceric ammonium nitrate (CAN) as initiator

Ceric ammonium nitrate is well-known as an efficient SET reagent and literature procedures have reported that the molecular system CAN:alkene:mono-methyl ester malonic acid has been used in a 4:1:5 molar ratio for 2 hours at room temperature, using either acetonitrile or acetic acid combined with the use of Cu(OAc)$_2$ as a co-catalyst.[126] We tested these synthetic conditions on 1,3-dimethyl-2-fluoromalonate using two types of olefin, 1-octene or styrene (Table 16).

Table 16 *Addition of 2-fluoro-1,3-dimethylmalonate to olefins using CAN[a]*



Entry	R	Co-catalyst (10 mol%)	Solvent	Yield [%][d]
1[b]	C_6H_{13}	-	MeCN	-
2[b]	C_6H_{13}	Cu(OAc)$_2$	AcOH	11
3[b]	C_6H_5	-	MeCN	-
4[b]	C_6H_5	Cu(OAc)$_2$	AcOH	12
5[c]	C_6H_5	-	MeCN	-
6[c]	C_6H_5	Cu(OAc)$_2$	AcOH	10

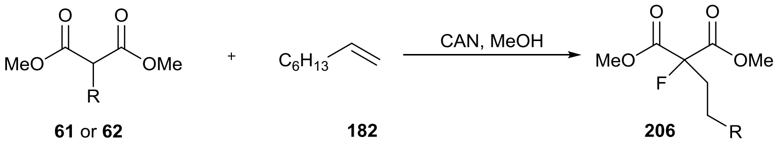
[a] 3 Days, r.t.; [b] 2-Fluoro-1,3-dimethylmalonate:styrene:CAN with molar ratio 5:1:4; [c] 2-Fluoro-1,3-dimethylmalonate:styrene:CAN with molar ratio 1:1:1; [d] By ^{19}F-NMR

Figure 36 *Picture of the color monitoring of the reaction from the resulting reaction mixtures containing 2-fluoroacetoacetate, olefin and CAN with or without Cu(OAc)$_2$*

The obtained results show that using acetonitrile avoided the formation of any expected product, and that acetic acid combined to Cu(OAc)$_2$ provided only a small amount of desired product, thus confirming the previous observation that using 1,3-dimethyl-2-fluoromalonate was probably a less efficient option as a starting substrate than a 2-fluoroketoester. As previously written, these results showed the importance of an eventual co-catalyst, because Cu(OAc)$_2$ possesses a quicker oxidizing power of secondary alkyl radicals. No further purification was attempted here as the resulting yields were too low.

Another literature review has reported another procedure using CAN in methanol,[135] and, therefore, CAN has been tested with 1-octene and 1,3-dimethyl-2-fluoromalonate in a molar ratio of 2:4:1 in methanol (Table 17). The obtained results showed that using CAN in methanol gave low conversion of the starting 1,3-dicarbonyl compound, even with heating or longer reaction times, and so this method was not investigated further.

Table 17 *Addition of 1,3-dimethyl-2-fluoromalonate to olefin using CAN in methanol*

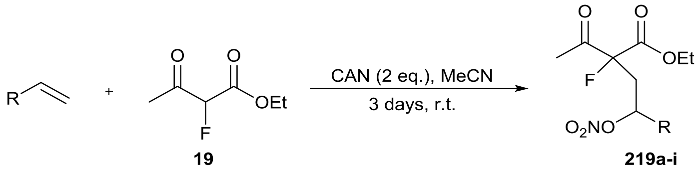


Entry	**R**	**Temperature [°C]**	**Time [h]**	**Yield [%]**[a]
1	F	r.t.	24	-
2	F	60	24	5
3	H	r.t.	3	4

[a] By ^{19}F-NMR

The same synthetic procedure has been tested on the molecular system [2-fluoroacetoacetate:styrene:CAN] using a molar ratio of [5:2:4]. After purification by column chromatography, a mixture of diastereomers was clearly obtained as the major product in moderate yield (Table 18). ^{1}H-, ^{13}C- and ^{19}F-NMR analysis of the obtained product was consistent with the mixture of diastereomers. Elemental analysis was also confirming the molecular structure of these products.

Table 18 *Addition of various olefins to 2-fluoroacetoacetate using CAN radical initiator*



Entry	R	Yield [%][a]	Diastereomers ratio [major:minor][b]
1	Ph	**219a**, 56	1:1
2	C_6H_{13}	**219b**, 35	1:1
3	cyclohexyl	**219c**, 31[b]	3:2
4	*p*-Cl-Ph	**219d**, 56	1:1
5	*o*-Cl-Ph	**219e**, 57	1:1
6	*o,o*-Cl_2-Ph	**219f**, 59	1:1
7	*p*-F-Ph	**219g**, 60	1:1
8	F_5-Ph	**219h**, 62	5:4
9	*p*-Me-Ph	**219i**, 20[b]	1:1
10	*p*-^{t}Bu-Ph	-	-

[a] Isolated; [b] By ^{19}F-NMR

Indeed, ^{19}F-NMR clearly showed two doublet of doublet of quadruplets (Figure 35), confirming the presence of diastereomers and the three fluorine-hydrogen couplings, 4.5 Hz, 11.4 Hz and 29.1 Hz for the doublet of doublet of quadruplets at -166.95 ppm, and 5.0 Hz, 15.0 Hz and 22.4 Hz for the doublet of doublet of quadruplets at -167.18 ppm. Thus we observe accurately the couplings between fluorine and protons in α- and β-positions characterized by their $^{3}J_{H\text{-}F}$ and $^{4}J_{H\text{-}F}$ coupling constants. The presence of diastereomers was confirmed by the analysis of the ^{1}H-NMR (Figure 36), clearly showing that every peak was consistent with a pair of diastereomers and the presence of a proton around 6 ppm, representative of a proton in α-position of a -ONO_2 functional group.

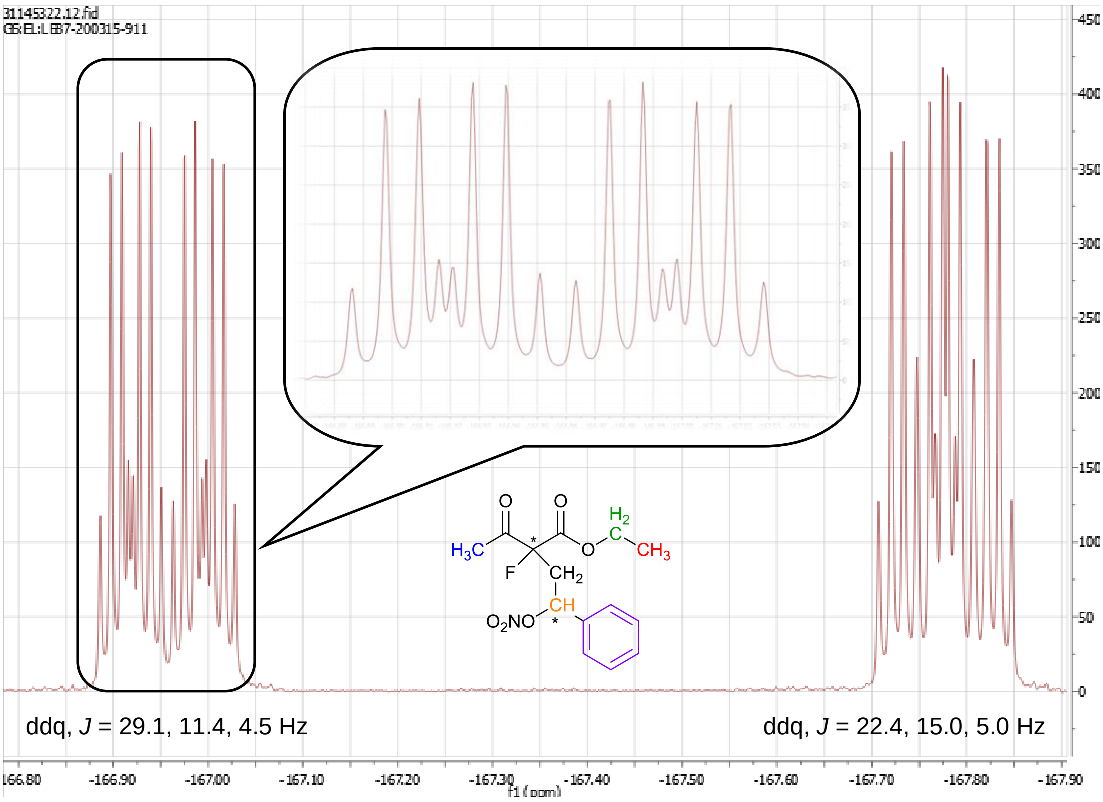


Figure 35 ^{19}F-NMR of ethyl 2-acetyl-2-fluoro-4-(nitrooxy)-4-phenylbutanoate **219a**

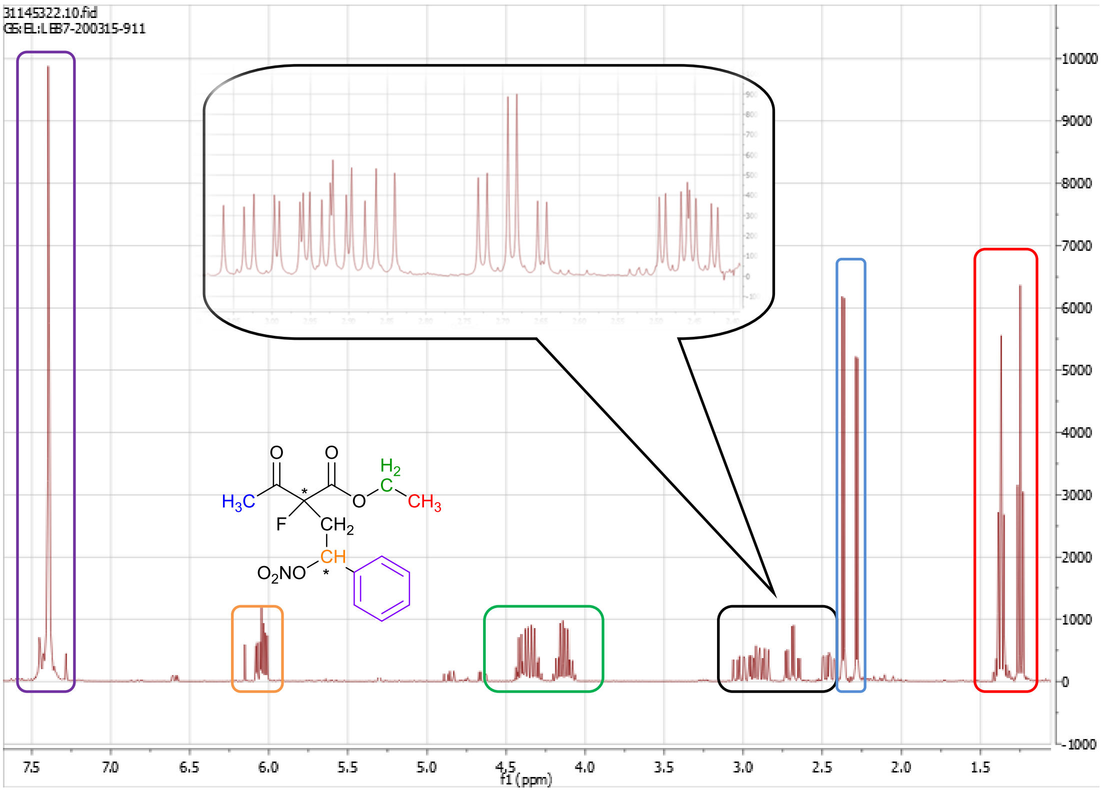
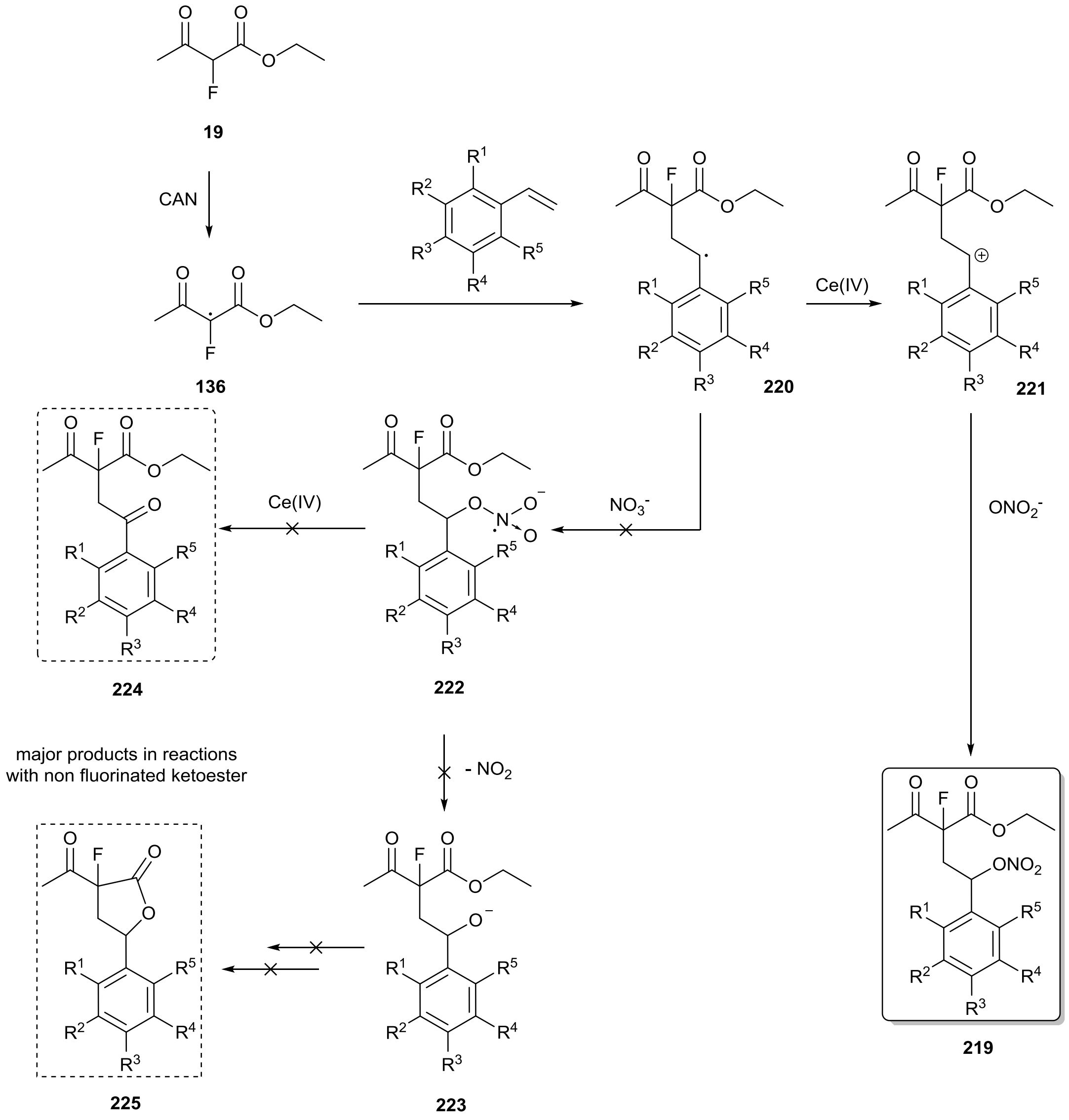


Figure 36 ^{1}H-NMR of ethyl 2-acetyl-2-fluoro-4-(nitrooxy)-4-phenylbutanoate **219a**

In the present work, we compared three different structures of olefins, indeed 1-octene, vinyl cyclohexane and styrene. Reaction with styrene derivative clearly shows a higher yield, due the relative lower stabilizing effect of the octyl and cyclohexyl groups on the synthesized radical intermediate. The presence of the fluorine atom on the β-position of the fluorinated ketoester seemed to stabilize the radical intermediate **220**, and that stabilization was enhanced by the structure of the styrene derivative, as long chain alkenes provided less efficient conversion towards the desired nitro-oxy products (Scheme 68).



***Scheme 68** Mechanistic pathways of CAN mediated addition of 2-fluoroacetoacetate to styrene derivatives*

To rationalize the obtained results, a tentative mechanism has been established for 2-fluoro-ethyl acetoacetate (Scheme 68). The addition of ketoester radical, generated by Ce(IV), to styrene, would give the radical **220**. The formation of the mixture of diastereomers is due to the oxidation of **220** and the trapping of the cation **221**, resulting from the Ce(IV) oxidation by NO_3^-, consistent with additions involving non-fluorinated malonates shown in Table 9 (page 83). Major products from non-fluorinated 1,3-dicarbonyl systems are the corresponding non-fluorinated **224** and **225** but non-fluorinated equivalent of **219** was observed, either as trace or minor by-product.[135]

$NO_3^{\cdot}$ radicals possess a high electrophilicity combined with a high oxidation potential (E_{red} = 2.0V), so they can react with hydrocarbons with a relative high selectivity, due to substantial polarization of the transition structure for CH-hydrogen abstraction.[127] Ceric ammonium nitrate photo-initiation has already been studied to prove the generation of $NO_3^{\cdot}$ radicals and the low oxidation potential of CAN and $NO_3^{\cdot}$ radicals has been demonstrated not to be high enough to oxidize saturated hydrocarbons, meaning that the $NO_3^{\cdot}$ radical may attack directly the strained hydrocarbon moiety.[127]

After getting the proof that styrene substrate was the only one providing nitro-oxy diastereomers as main products in relatively convenient yields, it was also important to investigate the presence of different electron donating and electron withdrawing functional groups on the different positions of the styrene ring. We observed that in the case of the presence of halogeno-groups such as chlorine or fluorine atoms, reactions gave the desired products, whereas methyl and tertbutyl functional groups, whatever the position they were attached to the benzene ring, did not afford any significant transformation towards these molecules.

This mechanistic pathway has precedent, although other oxidizing species deriving from CAN can be present in the reaction crude mixture. Nevertheless, a similar mechanistic pathway has been already reported using 1,3-dimethylmalonate as starting substrate affording similar products, but using a non-fluorinated substrate was providing some different major products. Indeed corresponding lactone **225** and further oxidized product **224**, which were not obtained at all in our studied case, showing that fluorinating the starting 1,3-dicarbonyl substrate was impacting the reaction.[135]

3. Conclusion

Throughout this chapter, we reviewed the various radical initiators to accomplish the oxidative addition of olefin to fluorinated 1,3-dicarbonyl substrates and revealed that starting from 2-fluoroketoester appeared to be more successful. After many synthetic investigations, we developed a significant methodology reacting 2-fluoro-ethyl acetoacetate and various olefins using Ceric ammonium nitrate as radical initiator, and CAN-mediated reactions of styrenes and 2-fluoro-1,3-dicarbonyl compounds gave reasonable yields to generate the corresponding radical fluoro-intermediate to access the desired nitro-oxy products. Importance of the halogeno-groups attached to the benzene ring of styrene derivatives has been largely showcased, in comparison to various alkyl groups in the different positions of the benzene rings.

Chapter 5 Multicomponent reactions from fluorinated dicarbonyl systems

As the main idea of our general project was to develop the use of fluorinated dicarbonyl substrates in synthetic chemistry, after developing the synthesis of fluorinated heterocycles and applying radical chemistry methods, we then focused our work on processes to transfer fluorine to more complex functionalized molecules, which could be obtained in easy synthetic one-pot processes in high yields. Multicomponent reactions remain perhaps the best option to rapidly access complex fluorinated molecular scaffolds. Therefore, in this chapter we present the various advantages of multicomponent processes, describing recently reported multicomponent methods on fluorinated substrates, and showcase a method to access functionalized fluoro-products from 2-fluoro-1,3-dicarbonyl synthesized molecules *via* various three-component Mannich-type synthetic strategies.

1. Multicomponent reactions: introduction

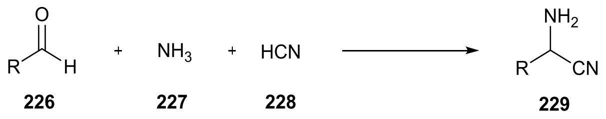
Multicomponent reactions (MCRs) can be described as any synthetic process with more than two substrates generating a simple and flexible building block. The main advantages of such processes are their practical, time-saving and one-pot reaction conditions. Therefore, multicomponent strategies can build libraries of various compounds, especially in the field of drug discovery and automated synthesis.[136] Many areas of chemistry are taking advantages of MCRs properties, such as electron paramagnetic resonance (EPR)-spin labeling, synthesis of biocompatible materials (artificial eye lenses for example), polymers with novel properties, chiral phases for HPLC analytical methods, natural product synthesis, peptide-nucleic acids or even agrochemicals synthesis.

An inherent formation of various bonds in one procedure summarizes the MCR synthetic strategy without isolating the corresponding intermediates while being able to switch various reaction parameters and adding additional reagents. Multicomponent reactions can be defined as convergent reactions in which three or more starting materials react to form a product, where basically all or most of the atoms contribute to the newly formed product (Figure 37). By a series of simple chemical reactions, the final product can be obtained via an irreversible step in most cases.

Figure 37 *Comparison between (left) divergent one-component reaction and (right) convergent five-component reaction*

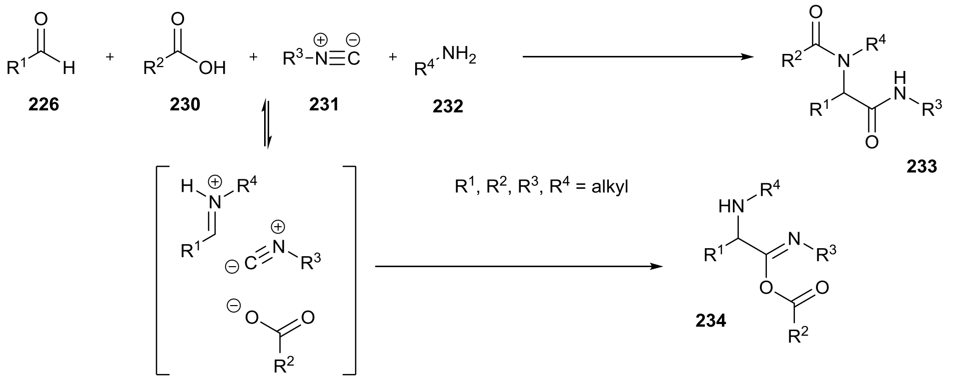
However, the multicomponent process always appears challenging as it needs to be conducted in such a way that the network of pre-equilibrated reactions give the main desired product and do not yield side products. This challenging process explains why the result is so dependent on experimental conditions, *i.e.* the solvents, reaction temperatures, substrate concentrations, potential need of an identified catalyst, presence of any specific functional groups and, of course, the starting materials. All these criteria together are linked to the success of the design and discovery of new multicomponent processes.

As a brief history of multicomponent reactions, the first officially reported MCR was the Strecker synthesis of α-amino acid in 1850, which began a large number of syntheses being developed from isocyanides (Scheme 69).[136]



Scheme 69 *Strecker synthesis, first reported by Laurent and Gerhardt (1838) and Strecker (1850)*

However, one of the pioneers of the development of a four-component reaction was Ivar Ugi (Scheme 70), followed by a few other contributors who developed variations of this multicomponent synthetic strategy from the Ugi reaction, such as Bienayme, Weber, Schreiber, Armstrong and Bossio. So far, the Ugi reaction appears to be the most extensively studied and applied MCR in the drug discovery process nowadays.

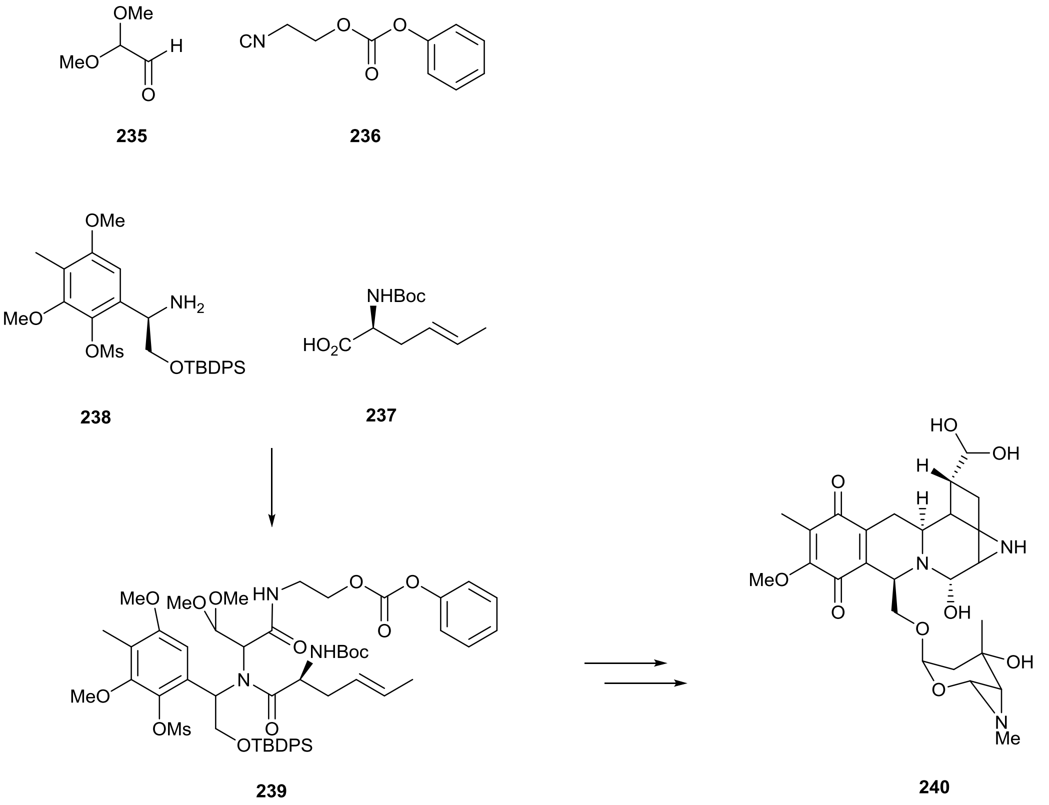


Scheme 70 *Four-component reaction developed by Ugi (1959)*

The most useful MCRs have been reported to be isocyanide-based MCRs, also called IMCRs, as previously shown in the Ugi four-component reaction. They mainly involve commercially available substrates allowing the synthesis of a large number of easy-accessible molecular scaffolds. The topological nature of isocyanides confer them a significant particular reactivity, making the IMCRs quite different from the MCRs, indeed these functional groups can react with both electrophiles and nucleophiles on the same atom to form a reactive α-adduct intermediate, which is the starting point of further rearrangements and synthetic transformations towards the desired products, especially in the field of natural product synthesis. This way they appear similar to carbon monoxide and carbenes. Among all the reported syntheses involving IMCRs, Scheme 71 shows one of the different synthetic approaches towards natural products reported by Fukuyama using a four-component reaction.[137]

Assembling complex molecules in one-pot is clearly the main advantage of MCRs, conferring MCRs with many applications in areas of applied chemistry, as accessing target molecules requires a minimum of synthetic effort, when efficiently optimized and simply processed.

Starting from a certain amount of starting materials (S_m), the number of different products that can be obtained by a N-component process becomes high really quickly, indeed S_m^N. As an example, a three-component reaction with 10 starting materials of each class will result in a library of 1000 compounds from a simple one-pot reaction.[138]



Scheme 71 *Total synthesis of the natural product (-)-lemonomycin using four-components reaction IMCR by Fukuyam**a***

Ugi and coworkers also showcased that MCR strategies represent an easy access to large collections of compounds to assess structure-activity relationship by varying functional groups contained in the target molecules. This work was pursued further on an industrial scale to access an enormous chemical structure space for patent applications, especially in the field of drug discovery. For example, a linear 6 step synthesis will typically take 6 months to be fully optimized and achieved, when the same process applied to MCRs strategy can reduce considerably development time and give access to a wide variety of molecular scaffolds. “Hit-to-lead” transitions can be accomplished promptly and physicochemical properties can also be modified easily, *i.e.* the lipophilicity, solubility, molecular weight, number of hydrogen donors or acceptors, number of rotatable bonds and polar surface area, either on a laboratory scale or to industrial amounts.[139]

Performing one-pot reactions is synonymous to performing the addition of reagents, controlling, quenching, extracting, and purifying the reaction at one time. Last but not least, analyzing the resulting products is also carried out only once. The preferred approach for such MCR strategies remains a solution phase approach, which allows an automatic process with multiple liquid dispensers.

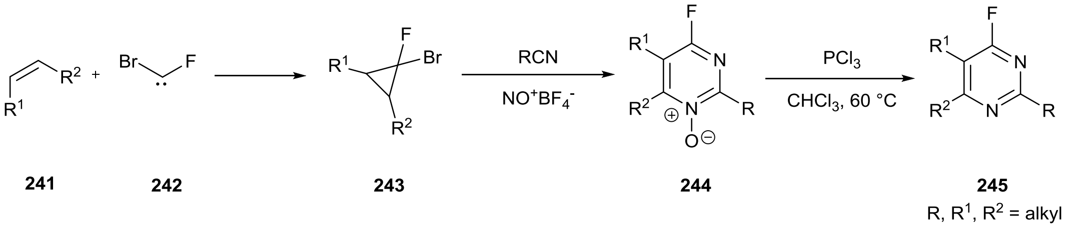
Bond forming efficiency, developed by Tietze and coworkers,[140] is one of the key criteria to determine the quality of a mutlicomponent reaction, related to forming several bonds in one operation without isolating the intermediates, changing the reaction conditions or adding further reagents.

2. Organofluorine chemistry and multicomponent reactions

2.1. Multicomponent reaction on fluorinated substrates

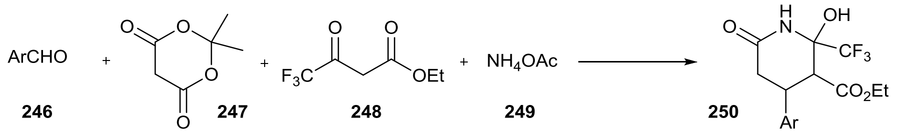
In this part, we have summarized the different multicomponent processes as applied to fluorine-containing compound synthesis. Various fluorinated heterocycles have already been reported to be synthesized via the application of MCRs, especially in the fields of agrochemical and pharmaceutical industries.[141]

The synthesis of fluoropyridine-N-oxide from Averina et al. gave route to fluoro-pyrimidines. This approach has been made through the use of 1-bromo-1-fluoro-cyclopropanes and $NOBF_4$ in the presence of a selected nitrile as solvent (Scheme 72). Dihalocarbene are first treated with an olefin to access the cyclic intermediate followed by heterocyclization via ring opening. The products scope was extended by the use of PCl_3/chloroform to reduce the N-oxide functional group to give various fluorinated pyrimidines.[142, 143]



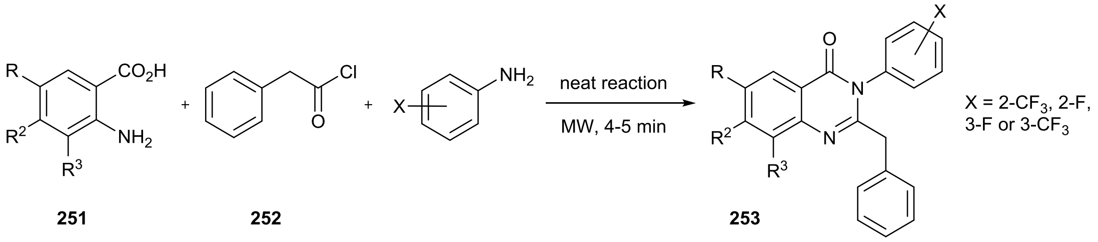
Scheme 72 *Synthesis of fluorinated N-oxide-pyrimidine and fluorinated pyrimidine*

Moreover, Song et al. developed a one-pot four-component synthesis of dihydropyridine derivatives using an aromatic aldehyde, Meldrum's acid, ethyl-4,4,4-trifluoro-1,3-dioxobutanoate **248** and ammonium acetate, to afford ethyl 2-hydroxy-6-oxo-4-aryl-2-(trifluoromethyl)piperidine-3-carboxylate **250**, a useful CF_3-containing substrate used for the synthesis of a wide variety of heterocycic compounds with potential biological activity (Scheme 73).[144, 145]



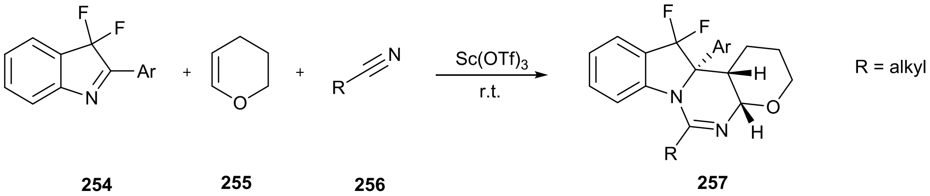
Scheme 73 *Synthesis of 1,4-dihydropyridine with trifluoromethane analogs*

Various fluoro-2,3-substituted quinazolin-4-(*3H*)-ones **253** have an antifungal activity and were synthesized in 2004 by Dandia and coworkers. The three components they used were anthranilic acid, phenyl acetyl chloride and substituted anilines under microwave irradiation and neat reaction conditions (Scheme 74). All the synthesized compounds showed antifungal activity with different pathogenic fungi.[146]



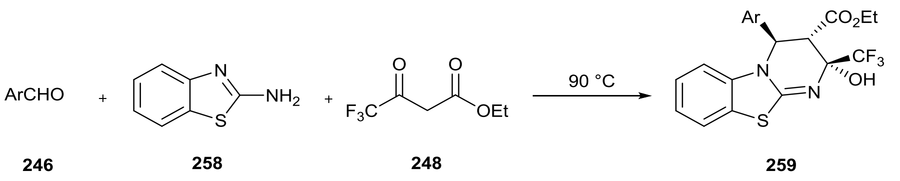
Scheme 74 *Fluorinated derivatives of quinazolines by MCRs in a microwave*

We were particularly interested in the recent development of Mannich-type reactions via a multicomponent process and Lavilla et al. reported a Mannich-Ritter transformation towards fluorinated heterocycles, using aromatic or functionalized nitriles to achieve the formation of cyclic amidine (Scheme 75).[147]



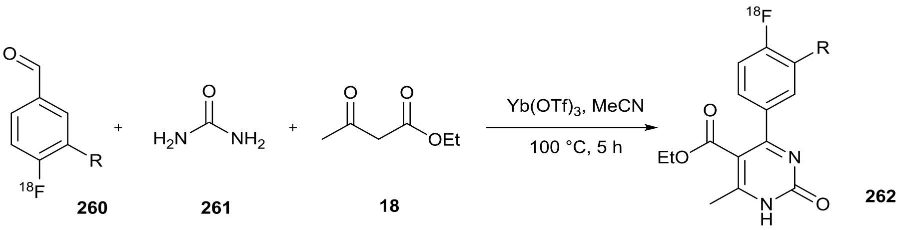
Scheme 75 *Amidine synthesis from reaction of dihydropyrane, various fluorinated cyclic imines and alkyl nitriles*

The use of fluorinated derivatives of ketoesters in MCRs is already developed. Shaabani and coworkers reported the synthesis of fluorinated tetrahedropyrimido-[1,2-β]-benzothiazole **259** by a three-component process under solvent-free conditions (Scheme 76).[148]



Scheme 76 *Three component reaction towards the fluoro-tetrahedronpyrimido[1,2-β] benzothiazole*

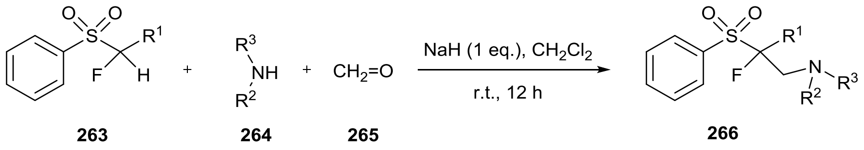
Multicomponent reactions can also be applied to ^{18}F-fluorine radiolabelling, as radiolabeled probes are often required for in vivo studies by PET. Increasing the synthetic efficiency and diversity of ^{18}F-labeled radiotracers can be performed by rapid construction of functionalized ^{18}F-radiotracers from ^{18}F-labeled starting materials with the label positioned on an aryl motif. A significant example showcasing the use of keto-ester towards the formation of a fluorinated pyrimidine scaffold by a classic Biginelli three-component process involving radiolabeled 4-(^{18}F)benzaldehyde **260** is shown in Scheme 77.[149]



Scheme 77 *Three-component Biginelli reaction performerd using ^{18}F-benzaldehyde derivative*

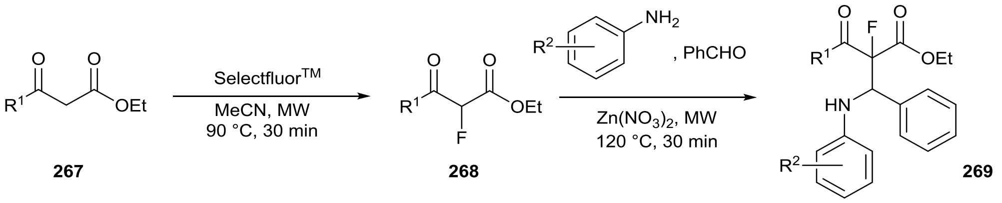
2.2. Mannich-type three component reaction from 2-fluoro-1,3-dicarbonyl substrates

While carbonyl compounds have played a crucial role in the development of multi-component reactions, the corresponding use of α-fluorinated carbonyl compounds have been much less investigated as MCR substrates. Applications of Mannich-type reactions utilizing related fluorinated substrates have been reported previously such as, for example, the synthesis of β-fluoronitro(phenylsulfonyl)ethylamines from fluoro-ketosulfone substrates described by Prakash and Olah (Scheme 78).[150] Of particular relevance to the research reported here, during the course of this thesis research, Zhang and coworkers developed a Mannich reaction involving various fluoro-ketoesters catalyzed by zinc nitrate and irradiated by microwave at high temperature, to which our work will be compared to in the next part (Scheme 79).[151]



$R^1 = NO_2$ or SO_2Ph
$R^2 = CH_3$, CH_2CH_3, $(CH_2)_2CH_3$, CH_2Ph, $-(CH_2)_4-$, $CH(CH_3)_2$, $(CH_2)_3CH_3$, $(CH_2)_5CH_3$, cyclopentyl, Ph, *p*-OCH_3-Ph
$R^3 = H$, CH_3, CH_2CH_3, $CH(CH_3)_2$, $(CH_2)_2CH_3$

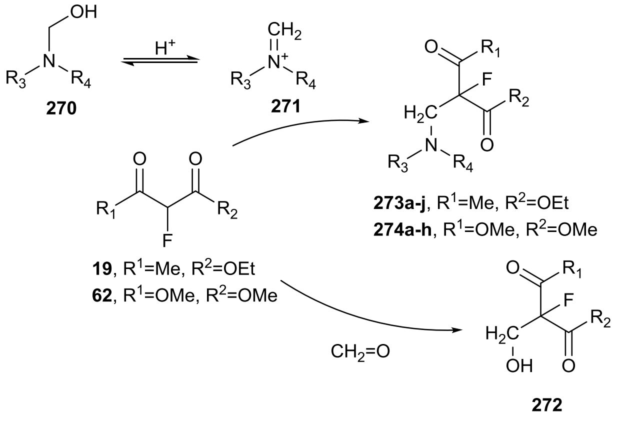
***Scheme 78** Direct synthesis of diverse β-fluoroethylamines by a mutlicomponent protocol by Prakash and coworkers*



***Scheme 79** One pot reactions of β-ketoesters developed by Zhang et al.*

Our aims of this part of our work is dedicated to the use of 2-fluoro-ethyl acetoacetate and 2-fluoro-1,3-dimethylmalonate as MCR components in Mannich reactions involving formaldehyde and different types of amines as educts to give poly-functional fluorinated products bearing amine and carbonyl functionalities using batch protocols in simple, scalable reaction processes.

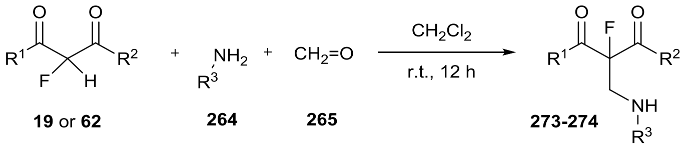
In initial studies we investigated reactions of 2-fluoro-ethyl acetoacetate with an amine and formaldehyde in multi component Mannich-type processes. Reactions were carried out by first mixing both amine and formalin together before addition of the fluorinated dicarbonyl substrate which limits the formation of any alcohol by-product by aldol condensation with residual formaldehyde (Scheme 80).

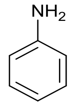
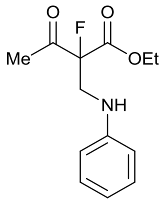
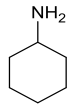
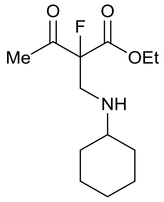
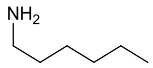
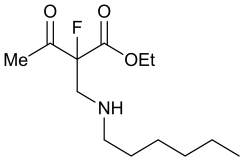
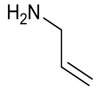
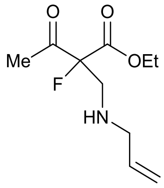
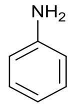
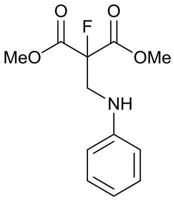
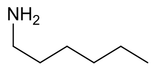
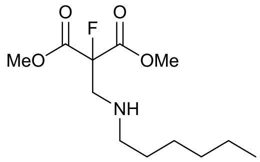


***Scheme 80** Competing formation of fluoroalcohol by-products **272** involved in the three-components Mannich-type reaction*

The first tested reactions were achieved using primary amines (Table 19), and a quick comparison was made with the use of 2-fluoro-1,3-dimethylmalonate as starting substrate.

Table 19 *Three-component Mannich-type reaction of 2-fluoro-ethylacetoacetate or 2-fluoro-1,3-dimethylmalonate, formaldehyde and a chosen primary amine*



Entry	Amine	Product	Yield [%]^a
1			**273a**, 35
2			**273b**, 64
3			**273c**, 67
4			**273d**, 63
5			**274a**, 15
6			**274b**, 30

[a] By ^{19}F-NMR

The low reactivity of the primary amines did not give good conversion of the starting fluorinated substrate, only allowing us to observe the desired product by ^{19}F-NMR in a low yield, encouraging us to use forcing conditions using primary amines (by reflux) and secondary amines. ^{19}F-NMR of one example of the obtained crude product from reaction with allylamine is presented in Figure 38. Purifications of Mannich products were not attempted at this stage due to the low conversions.

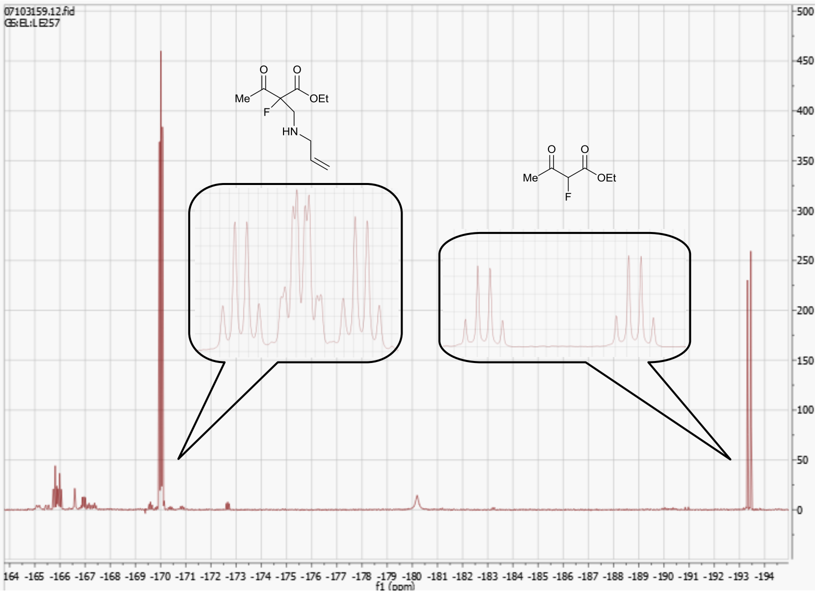
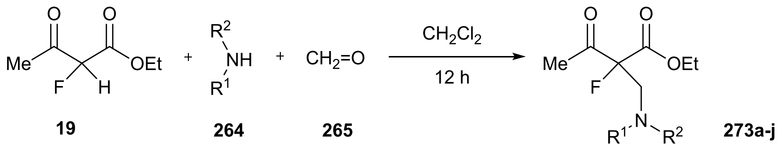


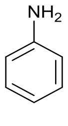
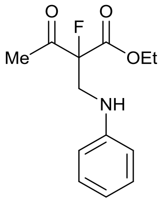
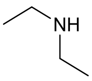
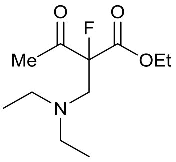
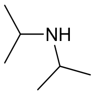
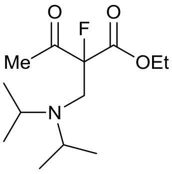
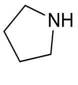
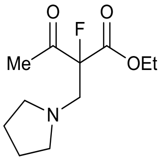
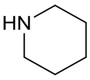
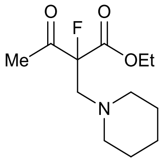
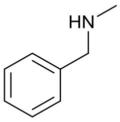
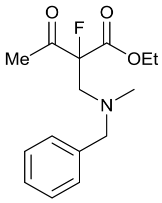
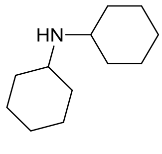
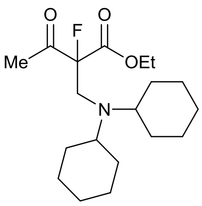
Figure 38 *^{19}F-NMR spectrum of crude product from Mannich-type reaction between 2-fluoro-ethylacetoacetate, formaldehyde and allylamine*

We then achieved successfully Mannich-type reactions of 2-fluoro-ethylacetoacetate, formaldehyde and various more nucleophilic secondary amines in significantly high yields under different conditions of solvent, and reflux conditions (Table 20).

Our optimized conditions were found to be 1.7 molar equivalents of amine and 1.5 molar equivalents of formaldehyde, stirred together for two hours, preceding the addition of the 2-fluoro-ethyl acetoacetate and further reaction at room temperature. In addition, reactions involving less reactive amines such as benzylamine were carried out at 90 °C, providing the corresponding Mannich products in full conversion (Table 20, entry 1). Use of additional NaH as a base was also tested on similar reactions, without any significant increase of the resulting yields.

Table 20 *Three-component Mannich-type reaction of 2-fluoro-ethylacetoacetate, formaldehyde and a chosen amine*



Entry	Amine	Product	Yield [%][a]
1[b]			**273a**, 79
2			**273e**, 98 (75)[c] (quant.)[d]
3			**273f**, 90 (95)[d]
4			**273g**, 98 (98)[d]
5			**273h**, 98 (97)[d]
6			**273i**, 95 (98)[d]
7			**273j**, 92

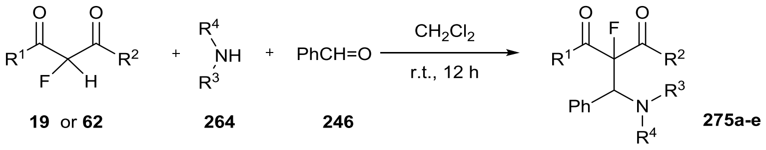
[a] Isolated; [b] At reflux temperature; [c] Carried out in MeCN;
[d] Using NaH (1 eq.) as a base

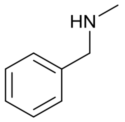
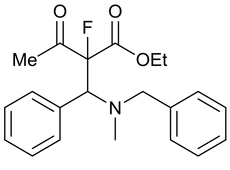
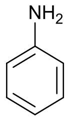
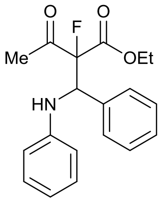
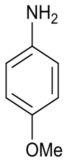
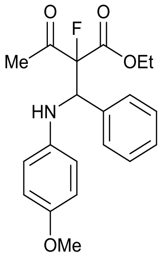
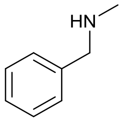
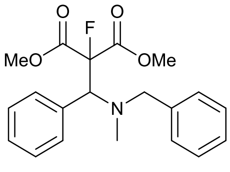
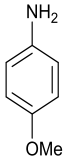
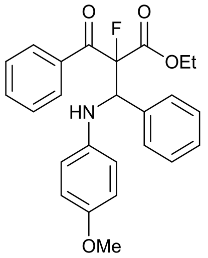
During the course of this work, related Mannich reactions of fluorinated 1,3-dicarbonyl compounds catalyzed by $Zn(NO_3)_2$ using microwave irradiation at 120 ^oC were reported.[151] However, the method we have described above does not require such vigorous heating and allows access to various products, for example **275b** and **275c**, which reportedly cannot be obtained by the zinc nitrate catalyzed method. Furthermore, Mannich reactions of 2-fluoro-1,3-dimethylmalonate ester were not described. Moreover, in the method described by Zhang and coworkers,[151] zinc nitrate has surprisingly been chosen as a second step catalyst in the corresponding process despite the fact that it can decompose over 110 °C and when heated, it forms zinc oxide, nitrogen dioxide and oxygen.

Noticing that some of the desired molecules were not obtained by Zhang's method, especially involving para-methoxyaniline as the amine substrate, and that the method we previously developed did not require any catalysts, heating or microwave process, analogous reactions between fluorinated dicarbonyl systems with a secondary amine and benzaldehyde were also performed leading to high yields of Mannich products (Table 21).

We observed that the synthesis of the desired products can be achieved without any heating of the reaction mixture, showing that primary amines can be used with aromatic aldehydes, such as benzaldehyde, and afford desired products in high yields and full conversions.

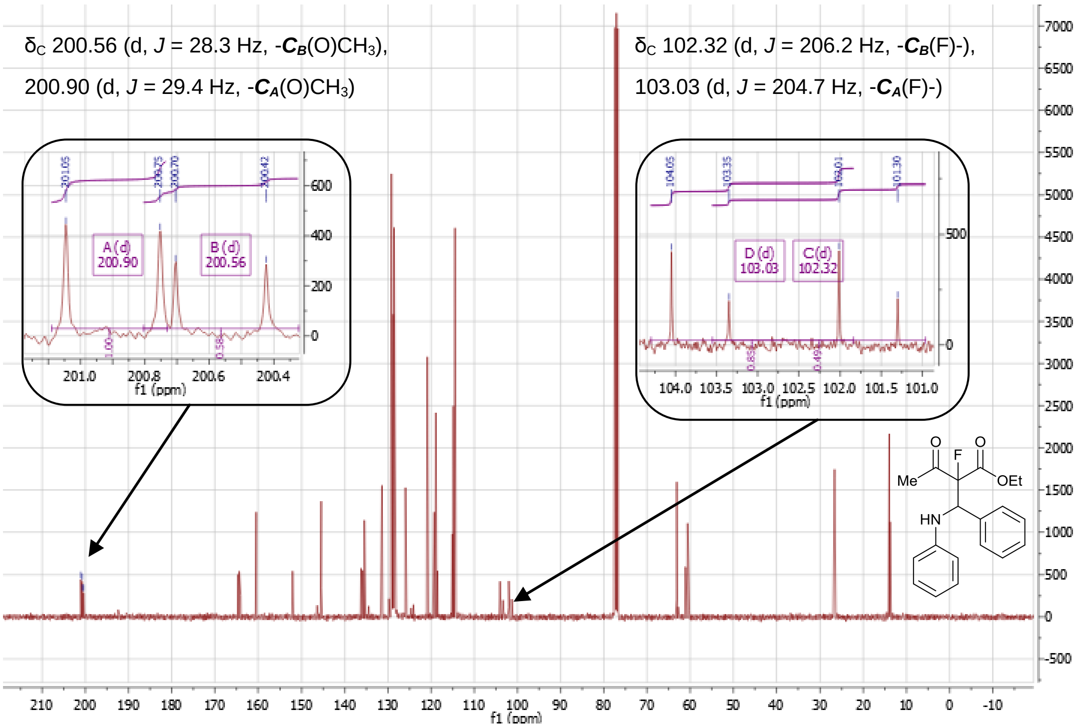
***Table 21** Three-component Mannich-type reaction of fluorinated dicarbonyl system, benzaldehyde and a chosen amine*



Entry	Amine	Product	Yield [%][a]	Diastereomers ratio [major:minor]
1			**275a**, 79	3:2
2			**275b**, 84	2:1
3			**275c**, 92	1:1
4			**275d**, 80	-
5[b]			**275e**, 87	1:1

[a] Isolated; [b] Starting ethyl 2-fluoro-3-oxo-3-phenylpropanoate substrate commercially available

At this stage of our investigations, we observed the formation of diastereomers from the three-component Mannich-type reactions and we were easily able to observe the diastereomers using NMR spectroscopy. Indeed, as a selected example, Figure 39 shows the two sets of multiplets that have been identified for the corresponding diastereomers of compound **275b** (two sets of doublets have been selected in the inset).

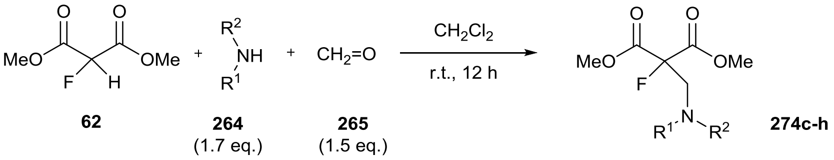

δ_C 200.56 (d, J = 28.3 Hz, -C_B(O)CH_3), 200.90 (d, J = 29.4 Hz, -C_A(O)CH_3)

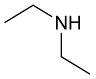
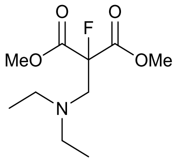
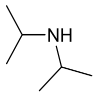
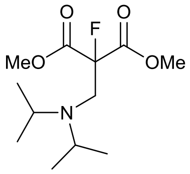
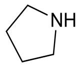
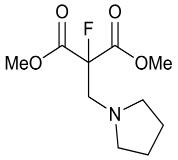
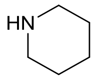
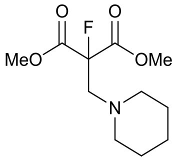
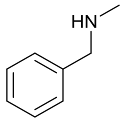
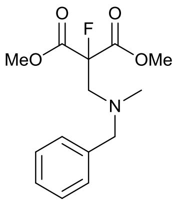
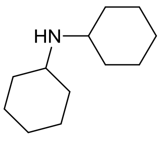
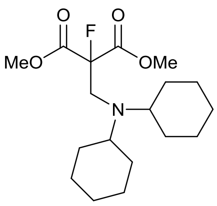
δ_C 102.32 (d, J = 206.2 Hz, -C_B(F)-), 103.03 (d, J = 204.7 Hz, -C_A(F)-)

Figure 39 *^{13}C-NMR of Ethyl-2-(phenyl(phenylamino)methyl)-2-fluoro-3-oxobutanoate* ***275b***

The synthetic conditions developed above were then applied to reactions between 2-fluoro-1,3-dimethylmalonate ester and a range of amines (Table 22), resulting in analogous products but in lower yield reflecting the lower nucleophilicity of the diester substrate.

Table 22 *Three-component Mannich-type reaction of 2-fluoro-1,3-dimethylmalonate, formaldehyde and a chosen amine*

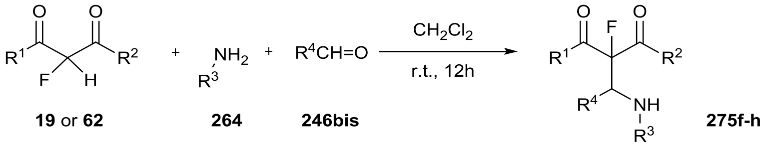


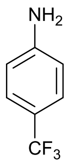
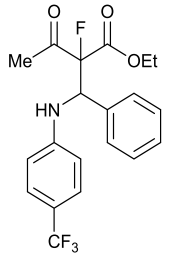
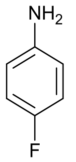
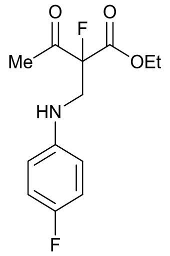
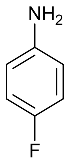
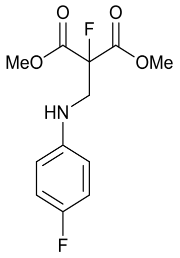
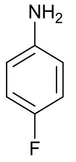
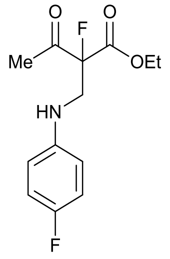
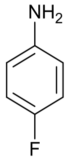
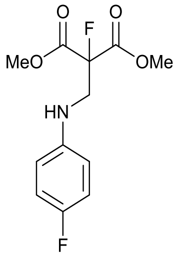
Entry	Amine	Product	Yield [%][a]
1			**274c**, 98
2			**274d**, 71 (75)[b]
3			**274e**, 78 (80)[b]
4			**274f**, 97 (97)[b]
5			**274g**, 95 (94)[b]
6			**274h**, 80

[a] Isolated; [b] Using NaH (1 eq.) as a base

Functionalization by various fluorinated groups on the *para*-position of the primary benzo-amines allowed us to test the developed conditions towards more sophisticated fluorinated molecular systems. Using 2-fluoro-1,3-dimethylmalonate as substrate did not provide any desired product, despite reflux conditions, confirming our general observation that fluorinated di-esters give low conversion, whereas reflux conditions on 2-fluoroethylacetoacetate substrate afforded better conversion (Table 23).

Table 13 *Synthesis of β-fluoro(dicarbonyl)alkylamines from 2-fluoro-1,3-dicarbonyl systems, fluorinated primary benzo-amines and formaldehyde or benzaldehyde*



Entry	Amine	Product	Yield [%][a]
1			**275f**, 10
2			**275g**, 60
3			no product
4[b]			**275h**, 80
5[b]			no product

[a] By ^{19}F-NMR; [b] Reaction carried out under reflux

3. Conclusion

A direct Mannich-type three component MCR reaction has been developed for the ready synthesis of β-fluoro(dicarbonyl)ethylamines starting from fluorinated dicarbonyl substrates further demonstrating that fluorinated 1,3-dicarbonyl molecular systems are particularly useful as starting substrates for further transformations or functionalization, opening up opportunities for the synthesis of more complex fluorinated systems for life science projects from simple, readily accessible fluorinated systems.

With this idea in mind, we then referred to the synthesis of tropinone as a double-Mannich type of reaction, which was reported by Robinson in 1917, to adapt this multicomponent process to an intramolecular synthetic strategy.[152] Therefore, it rapidly came that the fluorination of multi-carbonyl molecules, with similar molecular scaffolds as the previously reported keto-esters or malonates, appears as the next part of our research project, in the following chapter. The idea of such a process is to adapt the same approach to a fluorinated version of the starting tricarbonyl system and develop the same Mannich-type multicomponent reactions, using fluorinated tricarbonyl substrates.

Chapter 6 Fluorination of functionalized multi-carbonyl systems

After investigating the fluorinations of dicarbonyl substrates and their different applications on various fields such as the synthesis of fluorinated heterocycles, radical chemistry or multicomponent synthetic strategies, we focused our research project on the potential fluorination of carbonyl starting material possessing a different functionality.

Therefore, this chapter shows our investigations on getting fluorinated multi-carbonyl systems with different functional groups via direct fluorination using F_2 (Figure 39) and further potential applications of the synthesized 2-fluoro-1,3-dicarbonyl compounds.

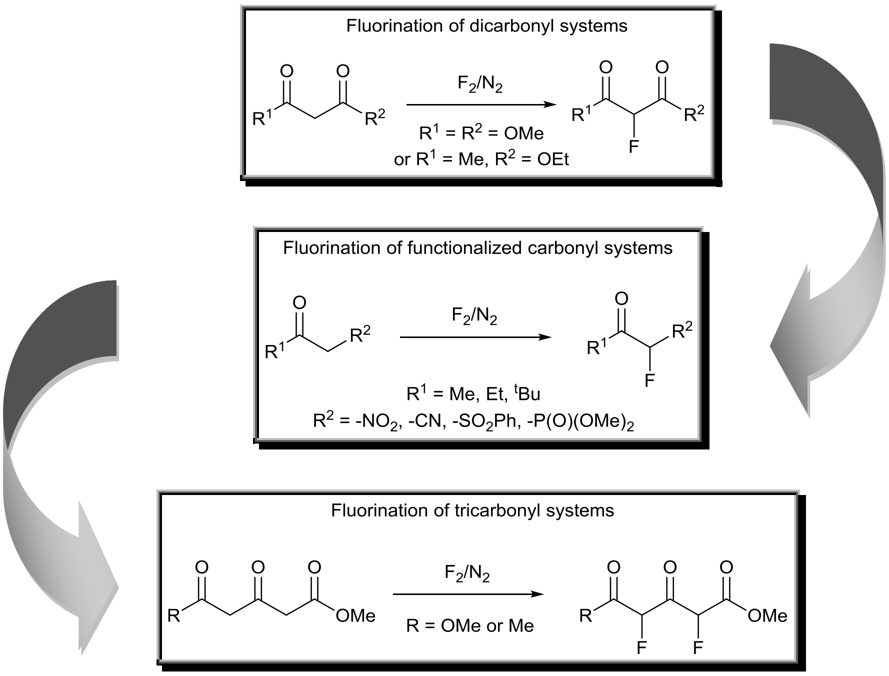


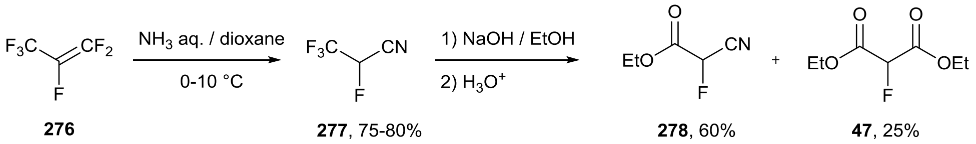
***Figure 39** Development of the direct fluorination process from known direct fluorination of 1,3-dicarbonyl systems*

1. Functionalized fluoro-carbonyl systems

1.1. Synthesis of fluorinated functionalized carbonyl systems and applications

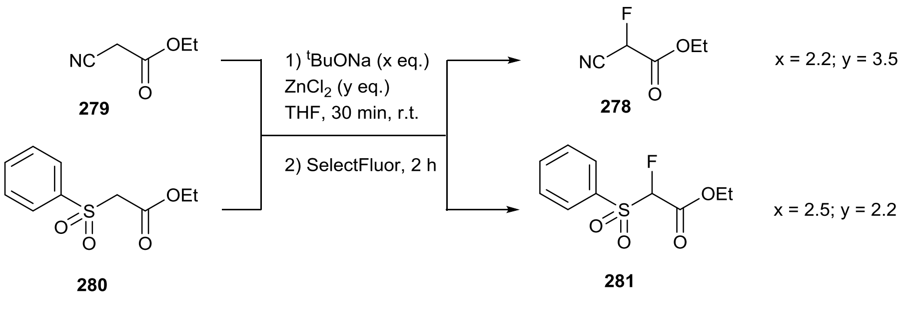
Mono-carbonyl functionalized molecular systems are molecules possessing, for example, either a nitro, cyano, phosphono or sulfono group on the other side of the ester functional group. These molecules present a structural shape close to the 1,3-dicarbonyl structures described in previous chapters, therefore of interest in our project. Few fluorination processes of these systems and applications of the resulting products have been featured in recent reviews, because there is a clear lack of simple methods to access them.

First on the list of such molecules are the cyano-esters, whose fluorination and applications have been rarely reported, despite a chemically interesting potential. Most of the synthesis methods previously described exhibited the use of fluorinated substrates such as hexafluoropropene as starting materials, leading to the desired alkyl α-fluoro-α-cyanoacetate **278** via a two step process (Scheme 81). This reaction shows the use of the nitrile **277**, produced from hexafluoropropene bubbling into an ammonia-dioxane solution, following by a reaction with alcoholic potassium hydroxide solution and acidic work-up.[153]



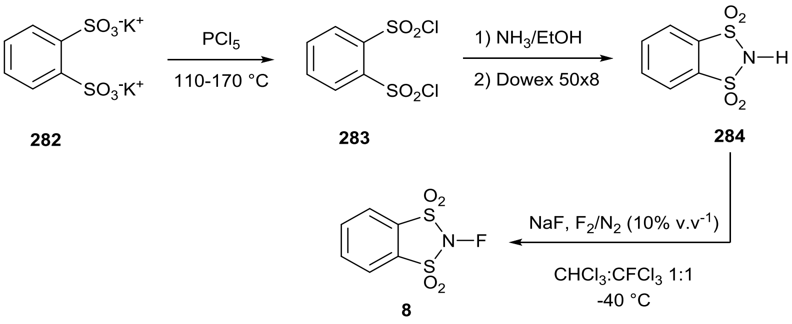
Scheme 81 *Synthesis of ethyl-α-fluoro-α-cyanoacetate from hexafluoropropene*

Electrophilic monofluorination of active methylene compounds has been reported by J. Hu and coworkers, especially on active methylene cyano and sulfonyl substrates (Scheme 82). This work revealed that the presence of zinc chloride activates the fluorination of such molecules and lowered undesired overfluorination. Mechanistic studies showed the crucial role of the zinc chloride catalyst through its interaction with a Brönsted base to control the deprotonation of the starting substrates over the corresponding mono-fluorinated products.[154]

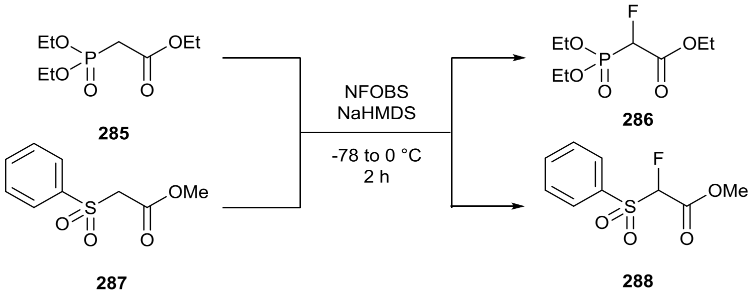


Scheme 82 *$ZnCl_2$-mediated monofluorination of active methylene cyano and sulfonyl compounds*

Similarly, fluorination of different enolates has been reported by Davis et al., but this method was developed using NFOBS fluorinating agent (Schemes 83 and 84).[155]

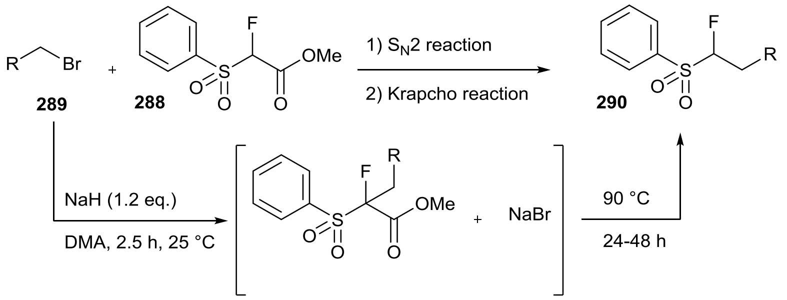


***Scheme 83** Synthesis of NFOBS by fluorination of o-benzenedisulfonimide*



***Scheme 84** Fluorination of phosphono and sulfono enolates using NFOBS*

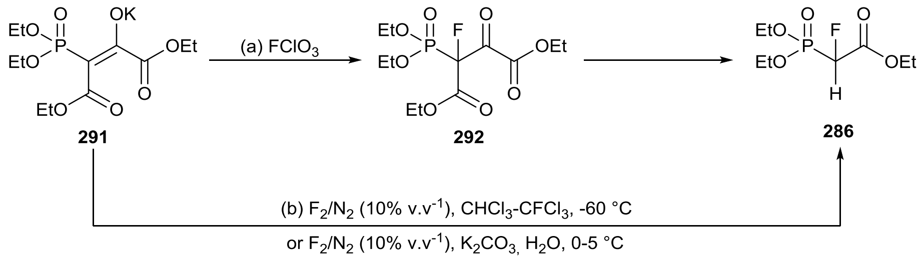
To show briefly an application of 2-fluoro-2-(phenylsulfonyl)acetate **288**, the synthesis of α-fluorinated sulfones **290** using a one-pot tandem substitution/Krapcho reaction sequence in acceptable yield has been reported (Scheme 85).[156]



***Scheme 85** Synthesis of α-fluorinated sulfones from fluoro-2-(phenylsulfonyl)acetate*

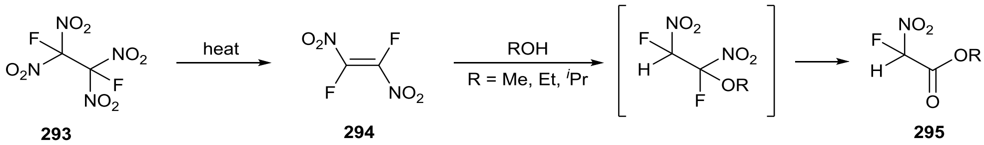
On another hand, the direct fluorination of an alkyl phosphono substrate has never been investigated. However, the process developed by Grell and Machleidt showed the use of perchloryl fluoride on the potassium enolate of diethyl phosphono diethyl oxo acetate to gain access to the mono fluorinated phosphono-product (Scheme 86).157]

Secondly, the work of J. Tessier and coworkers promoted the use of direct fluorination by F_2/N_2 (10-20% $v.v^{-1}$) with good yields, and surprisingly avoiding any difluorinated product being formed (Scheme 86).[158]



Scheme 86 *Synthesis of (O,O-diethylphosphono)-2-fluoro-2-ethylacetate (a) by Grell and Machleidt and (b) by Tessier, Demoute and Truong*

Last but not least on the list of various functionalized carbonyl molecules, the fluorinated nitro-esters represent a large category and their chemistry have been reported in a few reviews. Their syntheses have been reported by Baum and coworkers, following previous research done by Martynov in 1965. They described the synthesis of the desired fluoro-nitro-esters **295** from 1,2-difluoro-tetranitroethane, which can be obtained by the direct fluorination of the di-potassium salt of tetranitroethane in a aqueous solution. The main property of the 1,2-difluorodinitroethylene intermediate **294** was its ability to be handled under normal ambient conditions indefinitely in a freezer, despite its slight hygroscopicity, unlike tetrahydroethylene (Scheme 87).[159]



Scheme 87 *Synthesis of 2-fluorinated nitro-esters from difluorotetranitroethane*

Two main reports on asymmetric synthesis of α-fluoro-α-nitro esters have appeared; first of all, Togni et al. reported an asymmetric electrophilic fluorination of α-nitro esters to synthesize chiral α-fluoro-α-nitro esters with up to 40% enantiomeric excess.[160]

Catalysis of the fluorination of a range of 2-substituted carbonyl compounds have already been studied by Chambers and Hutchinson, such as the fluorination of diethyl-2-fluoromalonate by hydrated copper nitrate. Fluorinations of other 2-substitued carbonyl compounds such as phosphonates, sulphones and nitriles have also been discussed, showing the importance of the choice of the catalytic system. Indeed, the use of hydrated copper nitrate appeared in many cases as the one providing higher yields in the synthesis of the mono-fluoro desired product (Table 24).[161]

Table 24 *Fluorination of 2-substituted carbonyl compounds developed using various conditions*

Entry	**Substrate**	**Conv. [%]**	**Yield [%]**[d]	
			Mono-fluorinated	**Di-fluorinated**
1[a]	$NCCH_2CO_2Et$	46	50	8
2[a]	$O_2NCH_2CO_2Et$	54	52	20
3[b]	$NCCH_2CO_2Et$	73	40	25
4[b]	$O_2NCH_2CO_2Et$	62	50	7
5[c]	$(EtO)_2P(O)CH_2CO_2Et$	73	35	15
6[c]	$MeSO_2CH_2CO_2Et$	62	36	7

[a] F_2 (3.2 eq. over 4 h), $Cu(NO_3)_2.2.5H_2O$, MeCN, 0-5 °C; [b] F_2 (2.7 eq. over 4 h), anhydr. KF, MeCN, 0-5 °C; [c] F_2 (3.2 eq. over 4 h), $Cu(NO_3)_2.2.5H_2O$, NaH, MeCN, 0-5 °C; [d] by GC-MS

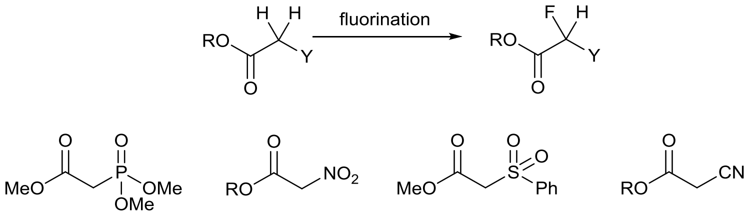
In this part of our research, we tried to optimize the access to various fluorinated functionalized carbonyl intermediates for the development of subsequent chemistry.

Neither of the methods developed in this previous work gave satisfactory conversions and yields, but pre-reactions with sodium hydride forming the corresponding anions, which then were applied to fluorination, were giving fair yields, despite few C-S and C-P cleavages (Table 24, entries 5 and 6).[161]

1.2. Fluorination of various functionalized mono-carbonyl substrates

In this project, fluorinations using similar synthetic conditions as fluorination of dimethylmalonate were attempted ($Cu(NO_3)_2.2.5H_2O$ used as a catalyst, F_2/N_2 (10% v.v^{-1}, 40 mL/min)) in a small batch reactor at 0 °C (Figure 40) and different substrates have been tested (Scheme 88).

Figure 40 *Small-scale fluorination set-up using F_2/N_2 (10% v.v^{-1})*



296

297a, R = Me
297b, R = Et

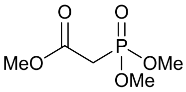
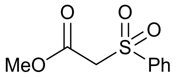
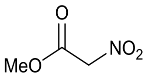
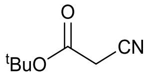
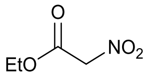
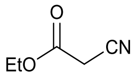
287

298, R = tBu
279, R = Et

Scheme 88 *Carbonyl substrates applied to direct batch fluorination*

^{19}F-NMR of the different crude resulting mixtures show the presence of either the monofluoro-product, the difluoro-product and in some cases the presence of by-products, but the monofluoro-product appears to be the major product (Table 25).

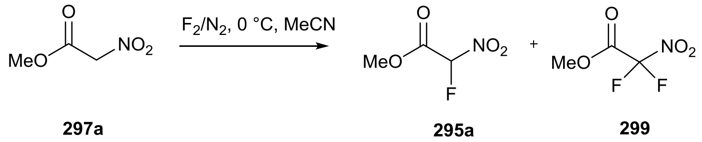
Table 25 *^{1}H-NMR yields of the fluorination of functionalized carbonyl compounds*

Entry	Substrate	Yield [%][a]	Entry	Substrate	Yield [%][a]
1		48	4		37
2		95	5		37
3		81	6		35

[a] By ^{1}H-NMR, corresponding to the mono-fluorinated product

Table 25 shows that better yields were obtained when using alkyl-nitroacetates as starting compounds, assessed by NMR of the crude product mixture. It has already been shown that the lower yields for fluoro-methylphosphonoacetate and fluoro-methylsulfonylacetate can be in part explained respectively by C-P bond and by C-S bond cleavages.

Attention was put on the purification of fluoro-methylnitroacetate by distillation, providing different fractions with different ratios of 2-methyl-2-fluoro-nitroacetate to other by-products. Large batch fluorination of methylnitroacetate at 0 °C under F_2/N_2 (20%, 80 mL/min) flow gave mainly two products (Scheme 89), and separation was attempted using a micro-distillation strategy.



Scheme 89 *Resulting compounds from the fluorination of methylnitroacetate*

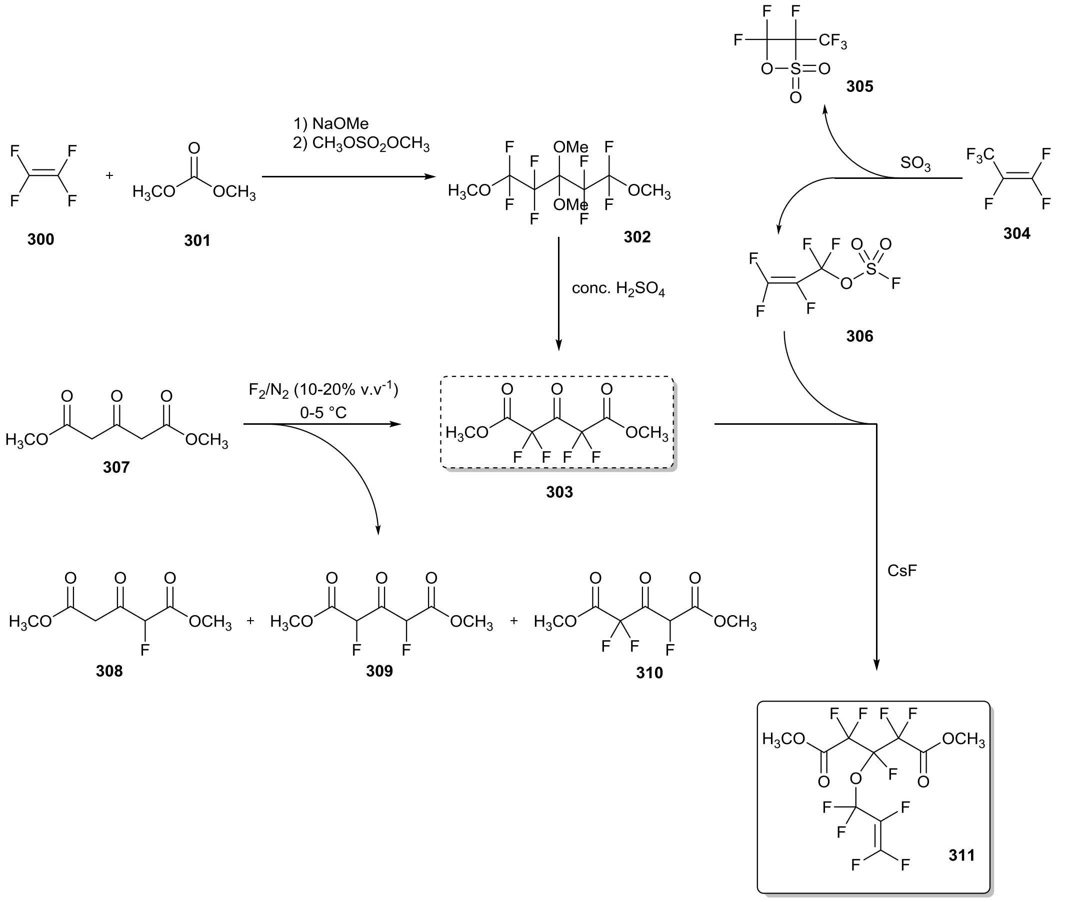
Repeated attempts at distillation only allowed us to enrich the fractions of mono-fluorinated product up to 85% of mono-fluorinated methyl-nitroacetate **295a** but gave no pure product due to similar boiling points, meaning that, so far, 2-fluoromethylnitroacetate is not a viable building-block.

2. Development of the fluorination of tricarbonyl substrates

The chemistry of fluorinated tricarbonyl systems remains unexplored, compared to the chemistry of simple fluorinated mono- or di-carbonyl molecules, so we aimed to develop a more efficient method to access fluorinated tricarbonyl derivatives.

2.1. Fluorinated tricarbonyl molecules

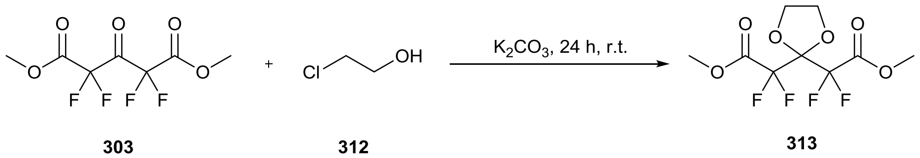
Poly-fluorinated tricarbonyl derivatives have been reported as products of acid-catalyzed hydrolysis of substrates possessing a molecular structure similar to intermediate **302**, coming from tetrafluoroethylene **300**. These tricarbonyl systems have been developed as part of a wider research program dealing with the synthesis of poly-fluorinated monomers **311**, affording water-wettable, dyeable and electrically conductive copolymers (Scheme 90).[162]



Scheme 90 *Process towards poly-fluorinated monomers and alternative direct fluorination pathway*

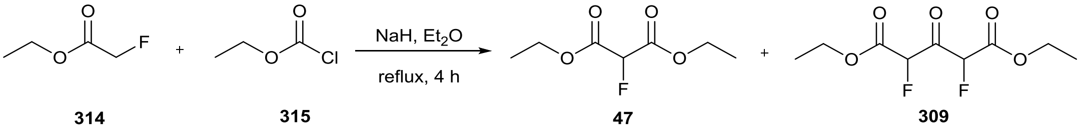
The disadvantages of this process is the lower yields obtained during the synthesis of intermediate **302** (52%), and the dimethyl tetrafluoroacetone-1,3-dicarboxylate **303** (69%), resulting in a 36% overall yield for the multistep process (Scheme 90).

Dimethyl tetrafluoroacetone-1,3-dicarboxylate **303** has been already showcased in different industrial patents used for the synthesis of fluorinated dioxolanes (Scheme 91), developed by C. G. Krespan. In this report, polyfluoroalkyl-1,3-dioxolanes are considered to be potential inhalation anaesthetics, despite the fact that they received little attention compared to fluoroethers anaesthetics. [163]



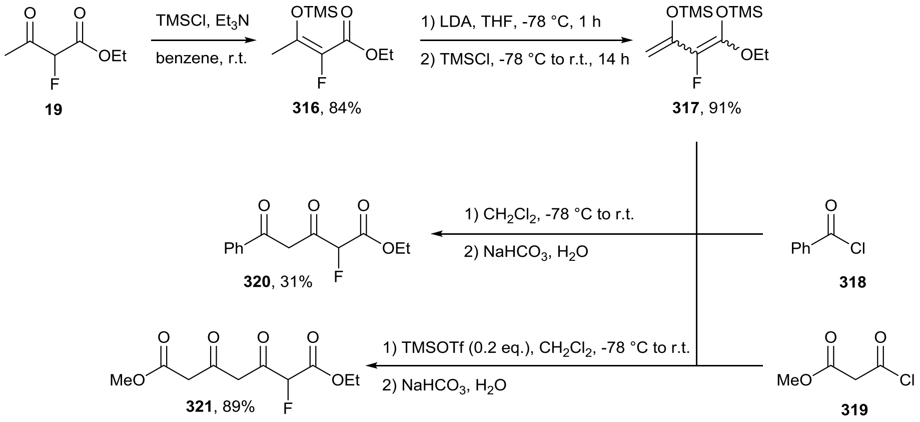
Scheme 91 *Synthesis of fluorinated dioxolane systems from dimethyl tetrafluoroacetone-1,3-dicarboxylate* ***303***

The preparation of 2-fluoro-1,3-diethylmalonate also revealed that a similar type of fluorinated diethylacetone-1,3-dicarboxylate could be obtained as a side product (21%) by the reaction of ethyl-fluoroacetate with ethyl-chloroformate (Scheme 92).[164]



Scheme 92 *Diethylacetone-1,3-dicarboxylate synthesis as a side product of the condensation of ethyl-fluoroacetate and ethyl-chloroformate*

Looking at a potential link between 2-fluoro-1,3-dimethylmalonate or 2-fluoro-ethyl acetoacetate, it has been reported that asymmetric one-sided fluorinated multi carbonyl systems can be accessed from a key intermediate **317**, which is synthesized in two steps from the previously described 2-fluoro-ethyl acetoacetate via the use of trimethylsilyl chloride and LDA in a satisfying yield (Scheme 93).[165]

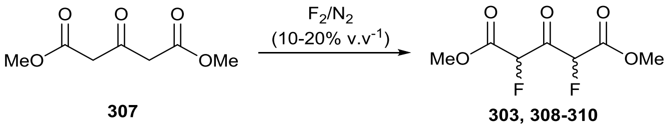


Scheme 93 *Access to fluorinated multi-carbonyl products from 2-fluoro-ethylacetoacetate*

Nevertheless, none of the processes previously described were involving a direct fluorination of the tricarbonyl susbstrates using F_2 in nitrogen. Therefore we conducted studies around the synthetic conditions of this direct fluorination strategy.

2.2. Comparative fluorination of symmetric and asymmetric tricarbonyl compounds

Similar studies to those conducted in the case of the direct fluorination of malonate esters have been conducted using tricarbonyl substrates. Our focus was on finding the right synthetic conditions in terms of fluorine gas molar equivalents, flow rates, and reaction times, to achieve firstly the direct fluorination of dimethylacetone-1,3-dicarboxylate **307**. In contrast to the direct fluorination of malonate esters, we can expect that fluorinating dialkylacetone-1,3-dicarboxylate molecules (Scheme 94) could afford four different fluorinated products, i.e. α-monofluoro- **308**, bis-α,β-monofluoro- **309**, α-mono-β-difluoro- **310**, bis-α,β-difluoro- **303** compounds, and their respective enol forms, thus affording a total of eleven potential fluorinated products (Figure 41). We also postulated that different stereoisomers could be obtained by this method.



Scheme 94 *Direct fluorination of dimethylacetone-1,3-dicarboxylate* ***307***

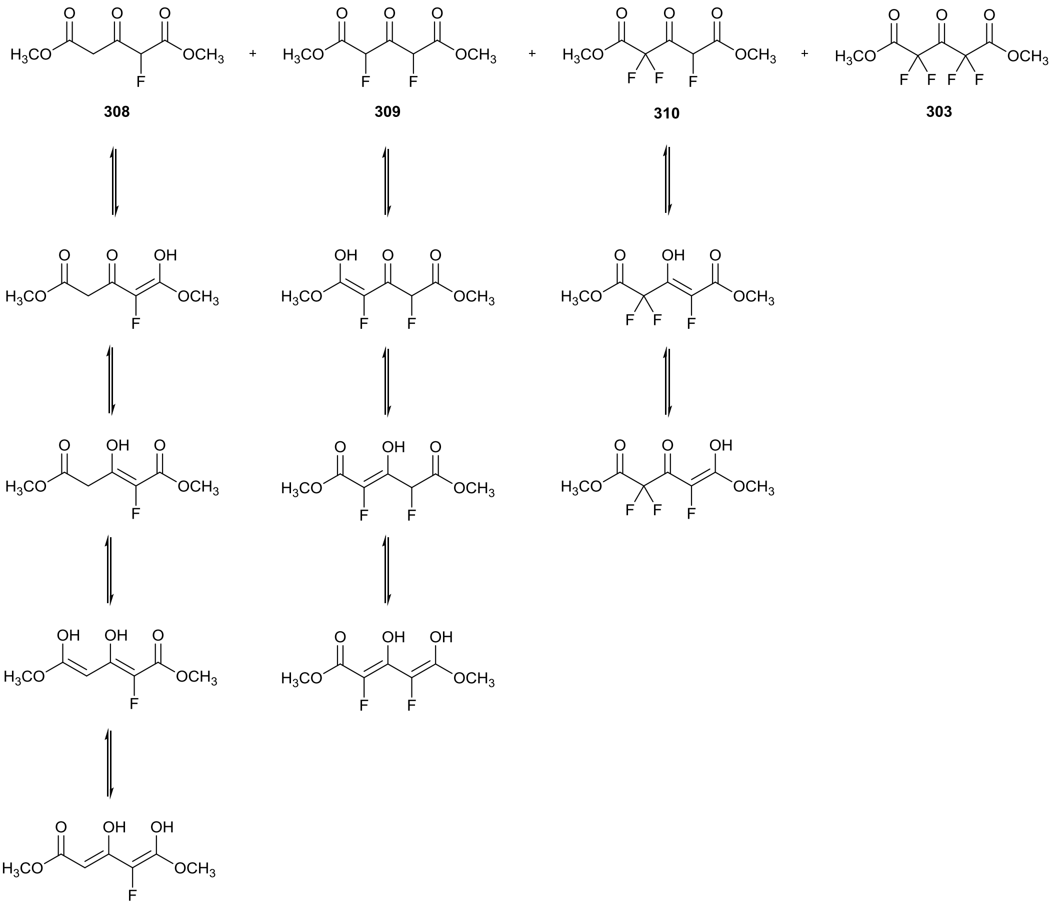


Figure 41 *Potential fluorinated products from direct fluorination of dimethylacetone-1,3-dicarboxylate*

Computational DFT-calculations conducted by Dr Mark Fox (Durham University), dealing with the potential ^{1}H- and ^{19}F-NMR chemical shifts showed that the fluorine atoms may have different shifts, resulting from the stereochemistry at the carbon atoms (Figure 42).

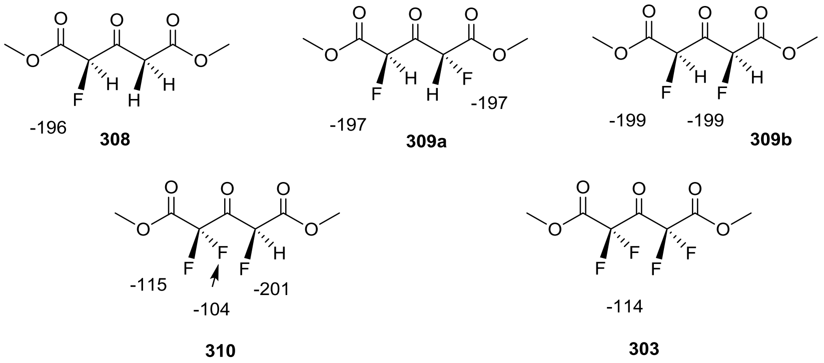
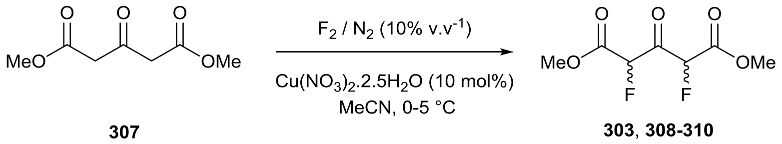


Figure 42 *Calculated* ^{19}*F-NMR shifts of respective fluorinated species from the fluorination of dimethylacetone-1,3-dicarboxylate* ***307***

We carried out numerous direct fluorinations on tricarbonyl substrates, varying the conditions, and the collected fractions extracted from the different purifications, either by distillation or by column chromatography, were then analyzed by NMR spectroscopy and compared with the obtained DFT-calculations (Scheme 95).



Scheme 95 *Direct fluorination of dimethyl-1,3-dicraboxylate* ***307***

In the first experiment, we applied a large excess of F_2/N_2 to be able to identify the different ^{19}F-NMR shifts of the resulting products by analyzing their abilities to couple with the potential protons nearby resulting in different *J* coupling constants. Figure 43 presents the ^{19}F-NMR spectrum from the crude product from direct fluorination of the dimethylacetone-1,3-dicarboxylate using a large excess of F_2/N_2, which we can assign by comparison with calculated ^{19}F-NMR shifts (Figure 42).

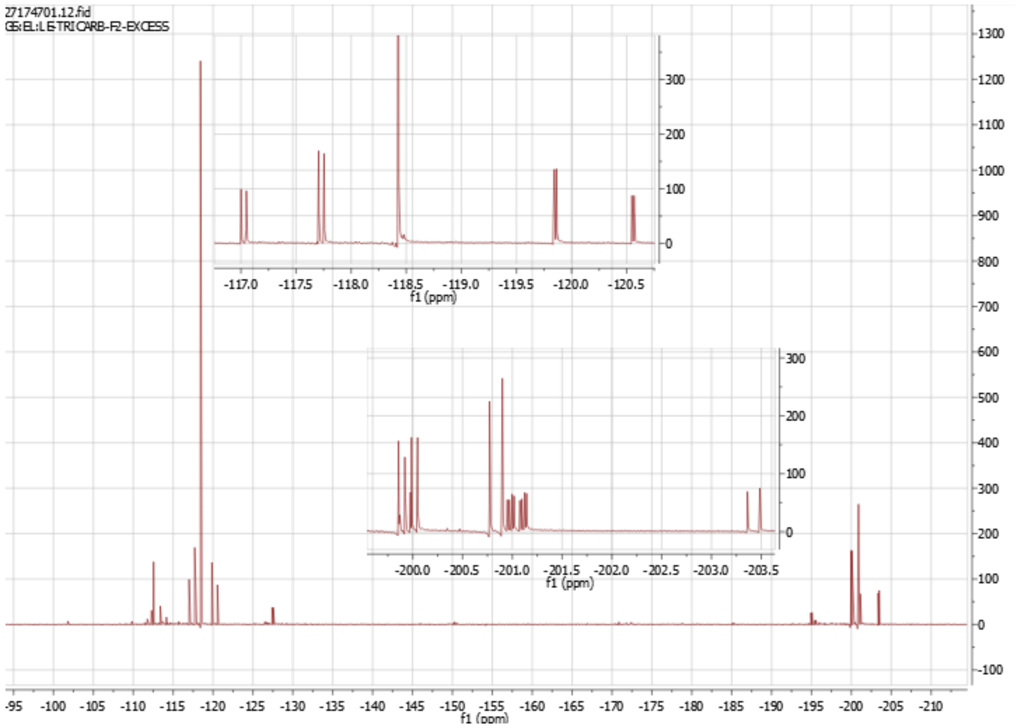
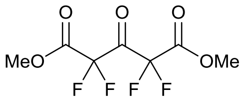
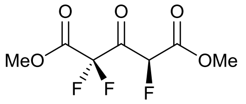
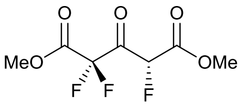
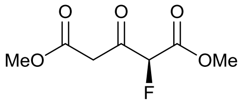
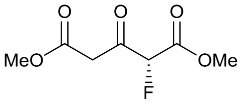
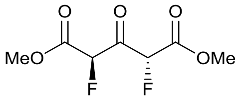
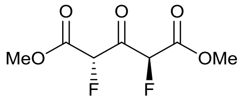
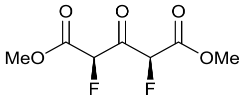


Figure 43 *^{19}F-NMR of the crude product from direct fluorination of dimethylacetone-1,3-dicarboxylate **307** using large excess F_2/N_2 (10% v.v^{-1})*

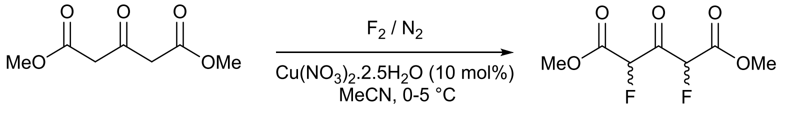
Analyzing the ^{19}F-NMR spectrum obtained by this method, we could easily identify a few products which are listed in Table 26. The shift corresponding to the bis-difluorinated product **303** (Table 26, entry 1) has been easily identified due to the absence of H-F coupling, both enantiomers of **310** (Table 26, entry 2) and their respective E/Z enol forms have been identified by the associated coupling constants J_{FF} and J_{HF} but differentiating these two enantiomers by their shifts at this stage is impossible using ^{19}F-NMR spectroscopy. The compounds **308** and their respective E/Z enol forms (Table 26, entry 3) in addition to the compounds **309a-b** (Table 26, entries 4-5) have been identified as their shifts give a single coupling H-F but we are unable to unambiguously identify each of them at this stage. The ratio 2:1 between the ^{19}F-NMR shifts corresponding to compounds **309a** (Table 26, entry 4) and the bis-monofluorinated compound **309b** (Table 26, entry 5) allowed us to identify their respective shifts. We also observe that the various shifts obtain match in the large majority to the DFT-calculations, as the ^{19}F-NMR shifts obtained by experimental processes only differ from DFT-calculated shifts by ± 4 ppm.

Table 26 *^{19}F-NMR shifts of the corresponding products from direct fluorination of dimethylacetone-1,3-dicarboxylate* ***307*** *using large excess F_2/N_2 (10% v.v^{-1})*

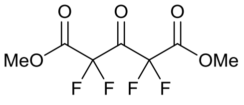
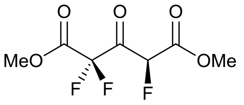
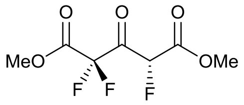
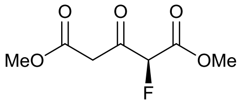
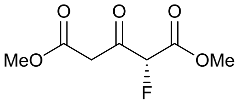
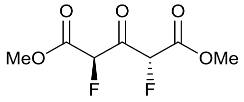
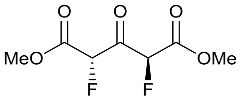
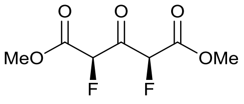
Entry	**^{19}F-NMR shift [ppm]**		***J* [Hz]**	**Product**
	-CF$_2$	**-CFH**		
1	-118.43 (s)	-	-	 **303**
2	-117.03 (d) -117.73 (d) -119.85 (d) -120.56 (d)	-201.04 (ddd)	$^{4}J_{FF}$ (Z$_{enol}$) 7.5 $^{4}J_{FF}$ (E$_{enol}$) 18.3 $^{2}J_{HF}$ 47.4	 **310** 
3	-	-203.42 (d) -200.84 (d)	$^{2}J_{HF}$ 46.8 $^{2}J_{HF}$ 48.4	 **308** 
4	-	-199.98 (d) -199.92 (d)	$^{2}J_{HF}$ 48.3 $^{2}J_{HF}$ 49.0	 **309a** 
5	-	-199.98 (d) -199.92 (d)	$^{2}J_{HF}$ 44.6 $^{2}J_{HF}$ 41.2	 **309b**

Having identified the different shifts for the corresponding mono- and bis-fluorinated products, we then applied different synthetic conditions to this fluorination reaction to be able to identify which product can be obtained in major proportion depending on the amount of F_2/N_2 used, either higher or lower molar equivalents and higher or lower percentage of F_2 in N_2, but also the length of the reaction and the flow rate.

Table 27 *Fluorination of dimethylacetone-1,3-dicarboxylate in batch using various conditions*



307 **303**, **308-310**

	Entry	1[a]	2[a]	3[a]	4[b]	5[b]	6[b]
	F_2/N_2 [%]	10	10	10	20	20	10
	Flow rate [mL/min]	20	40	20	80	20	40
	Reaction time [min]	180	180	300	180	168	168
	F_2 [eq.]	0.49	0.98	0.80	4.69	1.10	1.10
Products [^{19}F-NMR %]	 **303**	6	8	9	39	29	1
	 **310** 	9	20	18	31	29	6
	 **308** 	15	17	24	7	14	8
	 **309a** 	60	47	35	20	21	65
	 **309b**	8	8	8	2	7	20

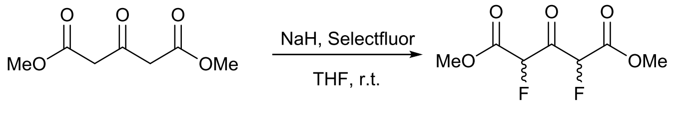
[a] Reaction achieved on 30 mmol scale; [b] Reaction achieved on 25 mmol scale

The results presented in Table 27 showcased that the major products after applying the different tested synthetic conditions are always the bis-mono-fluorinated enantiomers **309a** (*R,S*) and (*S,R*). It clearly appears that more equivalents of F_2/N_2 using similar reaction time increased the formation of *α*-mono-*β*-di-fluorinated isomers **310** (entry 1 compared to entry 2). However, slower addition of F_2/N_2 encouraged the formation of *α*-mono-fluorinated isomers, while still achieving *α*-mono-*β*-di-fluorinated enantiomers **310** formation in higher yields, due to the larger molar equivalents of F_2/N_2. By using forced conditions via F_2/N_2 (20% $v.v^{-1}$), we then synthesized more *α*-mono-*β*-di-fluoro- and *α*-difluoro-*β*-difluoro- products, respectively **310** and **303** (entries 4 and 5), whose ratios are more than 50% of the overall present products. By a more controlled experiment on the reaction time and molar equivalents, we were able to gain the bis-mono-fluorinated enantiomers **309a** (*R,S*) and (*S,R*) as major products again in similar ^{19}F-NMR ratios as entry 1 (entry 6), with the exception of being able to obtain one-sided bis-mono-fluorinated isomer **309b** in a larger proportion.

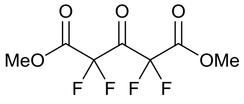
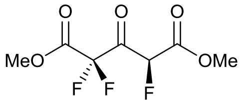
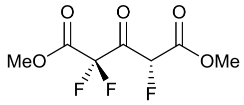
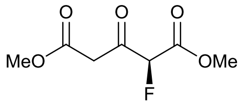
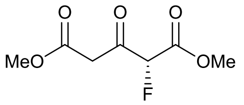
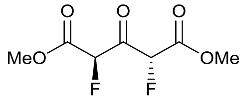
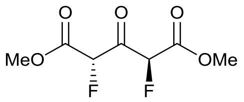
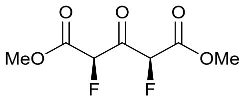
To compare the results with another fluorinating agent, fluorination was achieved using Selectfluor®. Indeed the chosen dimethyacetone-1,3-dicarboxylate was mixed with THF, and this solution was added to a suspension of NaH in THF, to get the resulting suspension stirred at room temperature until no more hydrogen evolved, Selectfluor® (2.2 eq.) was then added and the resulting mixture stirred overnight at room temperature. After work-up, the crude product was then analyzed by NMR spectroscopy and the resulting spectra were compared to the corresponding reported ^{19}F-NMR shifts (Table 28).

The obtained results showed that similar ^{19}F-NMR shifts were obtained for the previously listed fluorinated products and the molar equivalents of fluorinating agent has a large impact on major products formed. In the case of using Selectfluor®, more di-fluorinated products were obtained.

Table 28 *Fluorination of dimethylacetone-1,3-dicarboxylate using Selectfluor® and NaH*



307 **303**, **308-310**

	Entry	1
	NaH [eq.]	1.1
	Selectfluor® [eq.]	2.2
Products [^{19}F-NMR %]	 **303**	61
	 **310** 	24
	 **308** 	6
	 **309a** 	6
	 **309b**	2

At this stage, it appeared impossible to selectively mono-fluorinate and di-fluorinate one side of the symmetric tricarbonyl molecule. Therefore, we combined most of our obtained fluorinated products from the direct fluorination of dimethylacetone-1,3-dicarboxylate using F_2/N_2 and submitted them to a further purification by distillation under reduced pressure, in an attempt to purify one product, and we analyzed all the different fractions collected by NMR spectroscopy. We indeed managed to separate fractions possessing a richer percentage of corresponding fluorinated entities, in order of low to high boiling points: bis-α,β-difluoro-richer (**303**) fractions, followed by α-mono-β-difluoro-richer (**310**) fractions, then bis-α,β-monofluoro-richer (**309a-b**) fractions to end the distillation by collecting the α-monofluoro-richer (**308**) fractions (Figure 44).

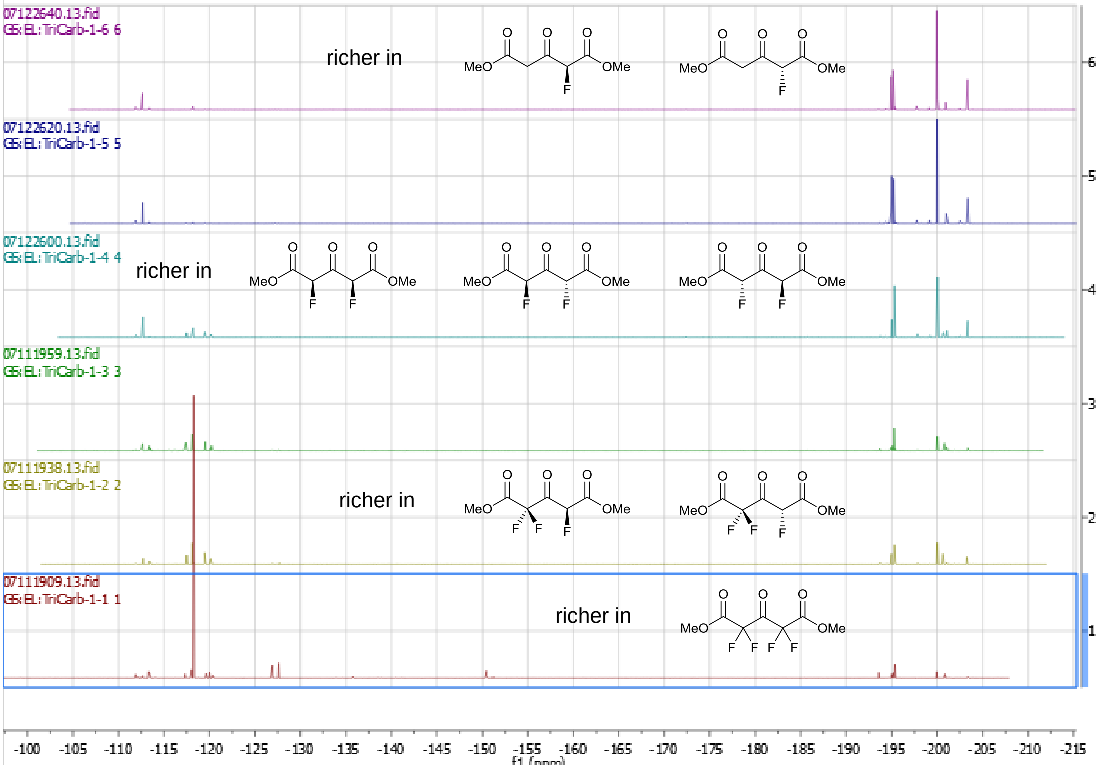
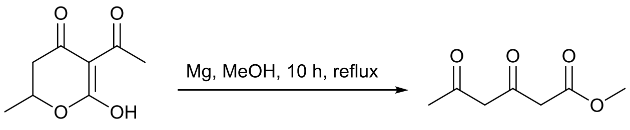


Figure 44 *^{19}F-NMR spectroscopic monitoring of the distillation of combined crude products from direct fluorination of* dimethylacetone-1,3-dicarboxylate **307** using F_2/N_2

This distillation strategy included forcing conditions to collect the last fractions under reduced pressure, but this gave a large amount of black tar, considerably reducing any potential yield. However, it seemed at this stage that working on different substrates with a similar molecular scaffold was necessary to gain a better selective fluorination methodology.

We decided to synthesize an asymmetric version of the tricarbonyl molecule, hoping for better selectivity at the CH_2 positions. The methyl 3,5-dioxohexanoate **323** was synthesized by the literature method (Scheme 96) and we then tested different conditions of the direct fluorination on this synthesized asymmetric substrate, indeed the molar equivalents of F_2, to gain different results presented in Figure 45.[166]



322

323, 80%

Scheme 96 *Synthesis of methyl 3,5-dioxohexanoate* ***323***

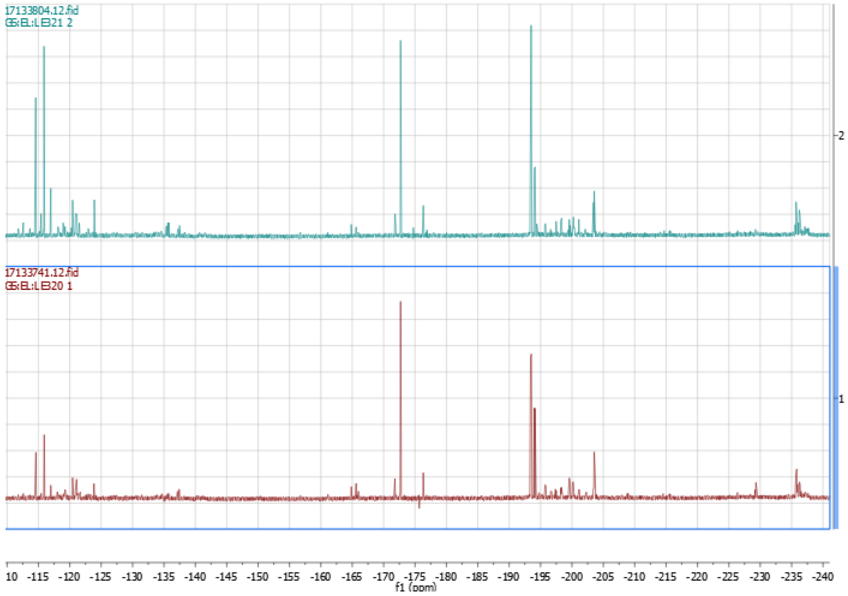
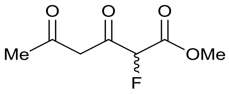
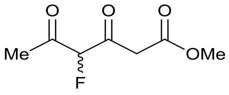


Figure 45 *^{19}F-NMR spectra of crude product from the direct fluorination of methyl-3,5-dioxohexanoate* ***323*** *with F_2/N_2 (10% v.v^{-1}) (2.2 eq.; top) (1.1 eq.; bottom)*

As predicted, adding more F_2/N_2 to the reaction mixture allowed us to obtain more di-fluorinated products, as the corresponding ^{19}F-NMR shifts (around -115 ppm) increased. We were also able to identify the main mono-fluorinated products formed after analyzing the multiplicity of the signals (Table 29).

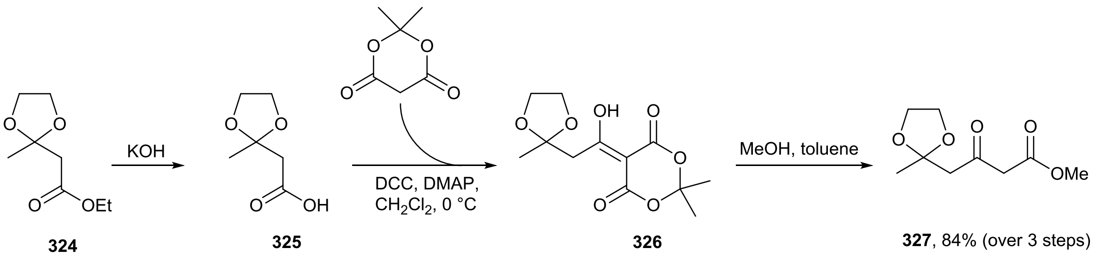
Table 29 *^{19}F-NMR shifts of the corresponding mono-fluorinated products from direct fluorination of methyl-3,5-dioxohexanoate* ***323*** *using F_2/N_2 (10% v.v^{-1})*

Entry	**^{19}F-NMR shift [ppm]**	***J* [Hz]**	**Product**	**Ratio major/minor** **F_2/N_2 [eq.]**	
				1.1	**2.2**
1	-194.06 (dt)	$^2J_{HF}$ 47.4 $^4J_{HF}$ 3.9	 minor	1	1
2	-193.45 (dddd)	$^2J_{HF}$ 49.7 $^3J_{HF}$ 16.2 $^4J_{HF}$ 7.1 $^4J_{HF}$ 3.8	 major	1.7	3.2

Summarizing this part of our investigations, we were able to fluorinate symmetric and asymmetric tricarbonyl substrates and showed the clear impact of the amount of F_2/N_2 and its corresponding flow rate on the resulting fluorinated products ratios. However, at this point, we were looking at an alternative strategy, involving a quick modification of the substrate to be able to achieve this fluorination selectively.

2.3. Towards the fluorination of a one-sided protected asymmetric tricarbonyl substrate

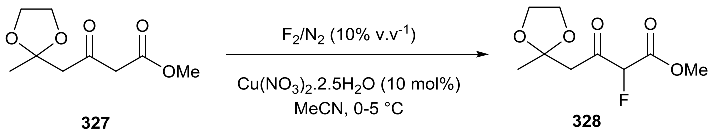
Analyzing the effects of the molecular shape of the tricarbonyl structure, we decided to modify the keto-group by protecting it with a dioxolane functional group before fluorination. Accessing such an intermediate in a 84% isolated yield was possible by a three steps process starting from the commercially available ethyl 2-(2-methyl-1,3-dioxolan-2-yl) acetate **324** via successful reaction with potassium hydroxide firstly and then synthetic conditions using Meldrum's acid, DCC and DMAP followed by mixing in methanol and toluene to access the desired mono-protected tricarbonyl system (Scheme 96).[167]



Scheme 96** Synthesis of methyl 4-(2-methyl-1,3-dioxolan-2-yl)-3-oxobutanoate intermediate **327** from ethyl 2-(2-methyl-1,3-dioxolan-2-yl) acetate **324

Fluorination of the resulting protected dicarbonyl system **327** was achieved on different scales at 0-5 °C using 10 mol% of hydrated copper nitrate catalyst. Table 30 summarizes the controlled fluorination as assessed using ^{1}H-NMR and ^{19}F-NMR sampling. The percentage of the mono-fluoro product was determined by relative comparison between the doublet formed for the proton of the -CHF group and the singlet assigned to the CH_2 initial group of the starting material.

Table 30** Fluorination of Methyl-4-(2-methyl-1,3-dioxolan-2-yl)-3-oxobutanoate **327



327 **328**

Entry	Time [min]	Eff. time [min][a]	Flow rate [mL/min]	Vol. F_2/N_2 [mL]	F_2 [μmol]	F_2 [eq.]	Monofluoro [^{1}H-NMR %]
1	10	10	3.2	32.00	130.80	0.13080	0
2	20	19.5	3.15	61.92	253.12	0.25312	0
3	30	29	3.13	91.66	374.66	0.37466	0
4	40	38.5	3.13	121.39	496.20	0.49620	1
5	50	47	3.12	147.91	604.60	0.60460	3
6	60	56.5	3.11	177.46	725.37	0.72537	9
7	70	66	3.12	207.10	846.52	0.84652	25
8	80	75.5	3.12	236.74	967.67	0.96767	58
9	90	85	3.13	266.47	1089.22	1.08922	75
10	100	94.5	3.12	296.11	1210.37	1.21037	84

[a] Effective time = reaction time – sampling time (0.5 min) (sampling the reaction mixture done under N_2 flow)

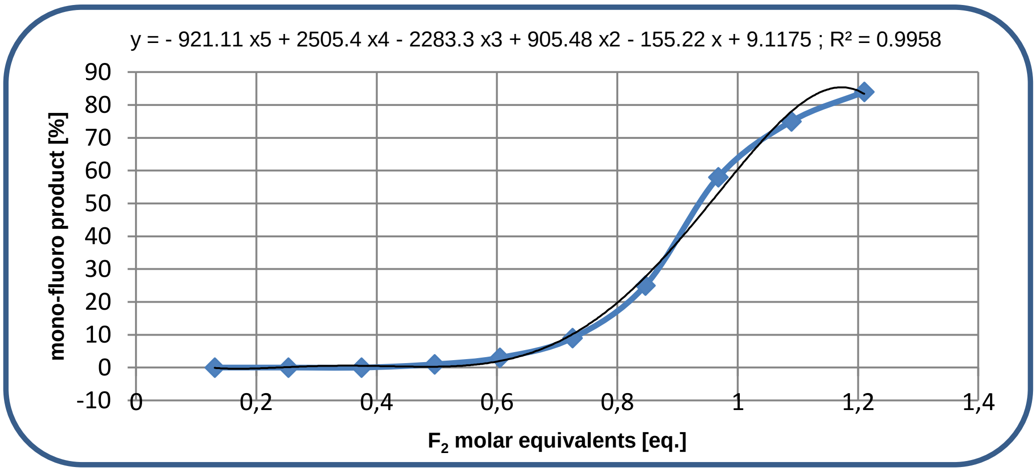


Figure 46** ^{1}H-NMR spectroscopic follow-up of the mono-fluorination of protected tricarbonyl ester **327

By plotting percentage of monofluoro-product versus time (Figure 46), we can observe the amount of mono-fluorinated product formed up to one molar equivalent of F_2. After that point, di-fluorinated molecule started to form under batch conditions, so the fluorination was stopped to avoid any type of further fluorination.

The Figures 47 and 48 show the resulting ^{19}F-NMR and ^{13}C-NMR spectroscopic data obtained from the crude fluorination product, revealing that the main product is the mono-fluorinated product. Further purification was not possible due to the end of the project period but this methodology indicates that using fluorinated tricarbonyl systems, if suitably deprotected, can be further developed.

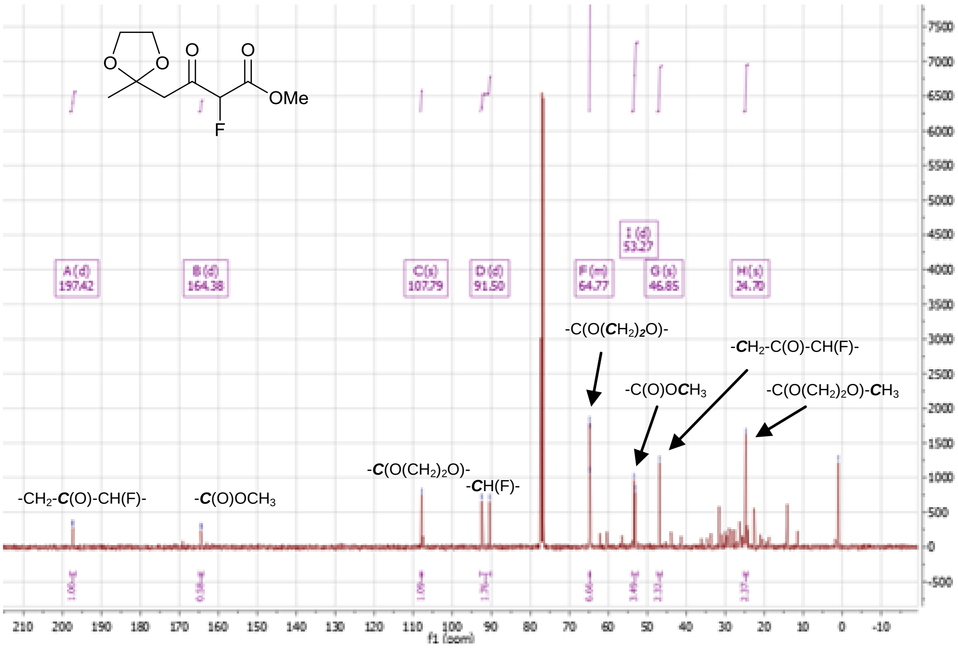


Figure 47 *^{13}C-NMR spectrum of crude fluorinated methyl 4-(2-methyl-1,3-dioxolan-2-yl)-3-oxobutanoate* ***328***

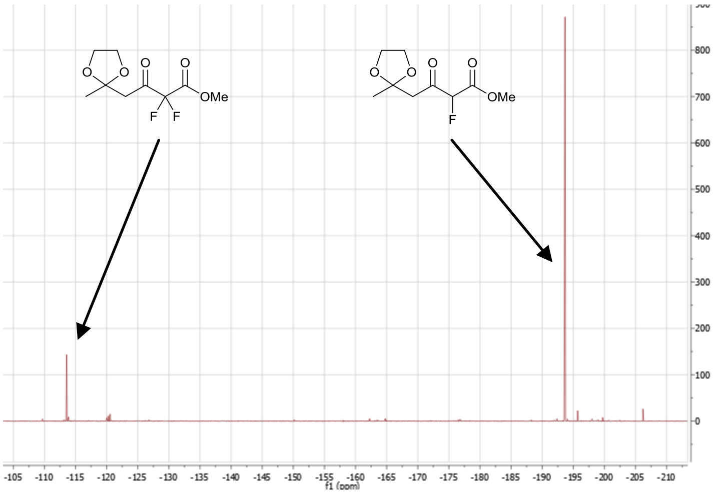


Figure 48 *^{19}F-NMR spectrum of crude fluorinated methyl 4-(2-methyl-1,3-dioxolan-2-yl)-3-oxobutanoate* ***328***

3. Nucleophilic substitutions using 2-fluoro-1,3-dicarbonyl substrates

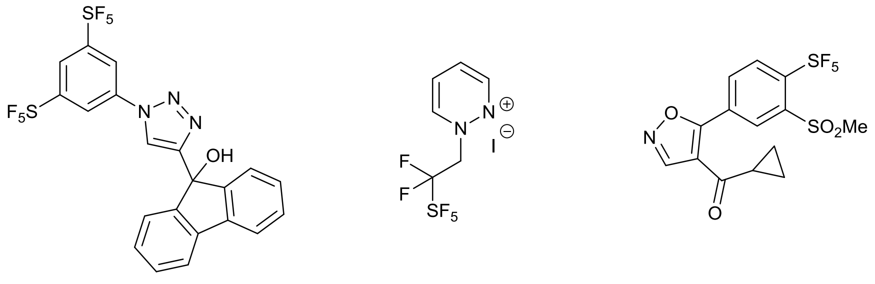
This chapter part is dedicated to the synthesis of SF_5-containing aromatics, their properties and applications, and our investigations around nucleophilic aromatic substitutions (S_NAr) and vicarious nucleophilic substitutions (VNS) using 2-fluoro-1,3-dicarbonyl starting material. This part of the project was carried out with collaborators at UOCHB Prague as part of the EU ITN Fluor21.

3.1. Preparation and utility of organic pentafluorosulfanyl-containing compounds

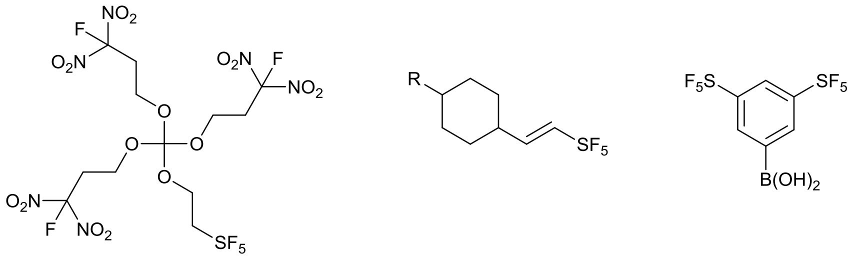
Organic compounds containing a SF_5 functional group possess a unique set of physicochemical properties and any SF_5-containing molecule represents an increasingly interesting structural shape for the design of bioactive compounds. However, we noticed a clear lack of synthetic methodologies for the synthesis of SF_5 basic building blocks, especially with low molecular weight. The synthesis of new Ar-SF_5 by derivatization of 1-fluoro-3-nitro-5-(pentafluorosulfanyl)benzene has already been reported by the group of Dr. P. Beier.[168,169]

Properties of aromatic SF_5 compounds have been largely showcased recently. Among all the different properties that can be enhanced, there are lipophilicity, with an increase on a drug’s bioavailability, electronegativity, as such molecules possess a stronger -I effect , higher molecular dipole and electronegativity compared to their CF_3 analogues, and chemical stability. Indeed aromatic-SF_5 compounds are resistant to hydrolysis and acid attack, and are thermally stable up to 300°C.

Aromatic SF_5 molecules may potentially be used in various fields, such as pharmaceuticals, ionic liquids, agrochemicals, explosives, liquid crystals and catalysts (Figure 47). In this project, we were particularly interested in the fluorinated nitro(pentafluorosulfanyl)benzene scaffold, as this molecular shape represents a widely available primary industrial product and good starting material for further synthesis of more complex SF_5-benzene derivatives.



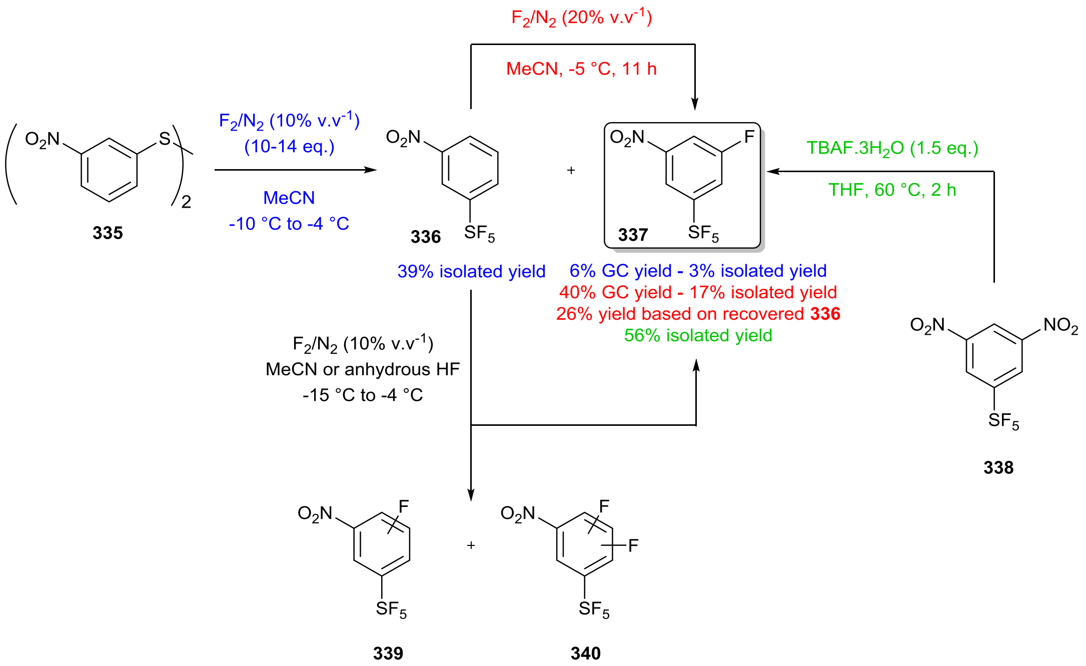
329, Anti-tumor cell activity **330** **331**, Herbicide



332 **333** **334**, Conia-Ene reaction catalyst

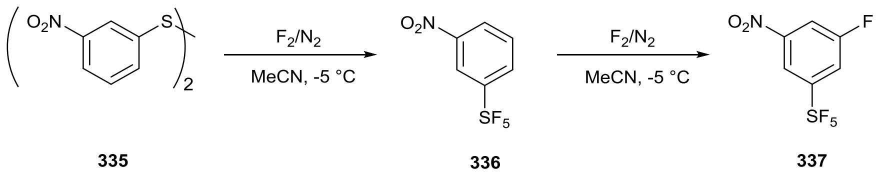
Figure 47 *Applications of aromatic-SF$_5$ substrates*

The direct fluorination of 1,2-bis(3-nitrophenyl)disulfane has been recently studied and is already applied to multi-kilogram scale by F_2 Chemicals Ltd. Indeed, there are three different pathways to obtain this target molecule in moderate yields, avoiding the formation of di-fluorinated by-products (Scheme 97).[170]



Scheme 97 *Synthesis of 5-fluoro-3-nitro-1-(pentafluorosulfanyl)benzene using different fluorination synthetic strategies (in blue: direct fluorination of 1,2-bis(3-nitrophenyl)disulfane; in red: preparative fluorination of 3-nitro-1-(pentafluorosulfanyl)benzene; in green: fluorodenitration method)*

Therefore, we directly fluorinate the 3-nitro-1-(pentafluorosulfanyl)benzene **336**, as it is commercially available, to gain the 5-fluoro-3-nitro-1-(pentafluorosulfanyl)benzene **337** (Scheme 98). This synthesis was realized in the laboratories of UOCHB in Prague using their fluorination facilities while on secondment as part of the Fluor21 Network.[170]



***Scheme 98** Full fluorination process of 1,2-bis(3-nitrophyl)disulfane*

Monitoring the process by GC-MS, this fluorination reaction is only able to provide 33% yield by GC-MS (Figure 48), which is characteristic from such a transformation, as it is important to avoid any formation of di-fluorinated products. Purification of the resulting crude mixture by column chromatography allowed us to isolate the 5-fluoro-3-nitro-1-(pentafluorosulfanyl)benzene **337** in 12% yield.

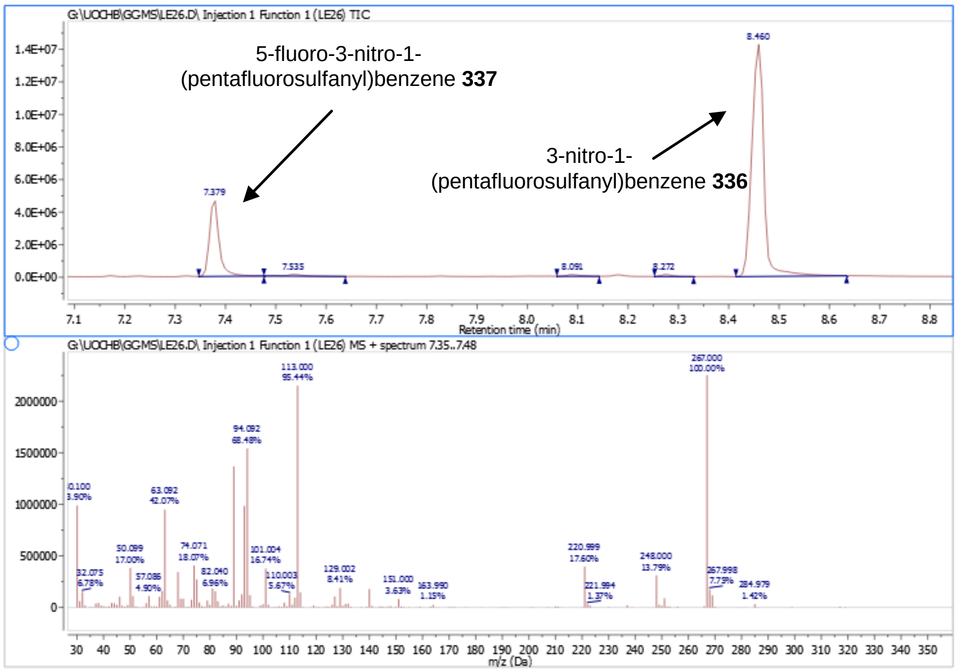


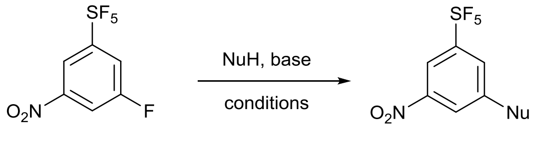
***Figure 48** GC-MS analysis of the resulting crude mixture from fluorination of* 3-nitro-1-(pentafluorosulfanyl)benzene **336**

After obtaining 5-fluoro-3-nitro-1-(pentafluorosulfanyl)benzene **337**, we then investigated the use of our previously synthesized fluorinated dicarbonyl molecules to act as nucleophiles to attempt to attach them to the SF_5-scaffold using different nucleophilic substitution conditions.

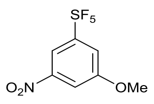
3.2. Comparison between nucleophilic aromatic substitutions and vicarious nucleophilic substitutions involving pentafluorosulfanyl benzene derivative

We based this part of our research on the ability of 2-fluoro-1,3-dimethylmalonate and 2-fluoro-ethylacetoacetate to act as potential nucleophiles using nucleophilic aromatic (S_NAr) substitutions and vicarious nucleophilic substitutions (VNS). As previously reported by Ajenjo et al., the use of 5-fluoro-3-nitro-1-(pentafluorosulfanyl)benzene and different nucleophiles under various basic conditions allowed the synthesis of diverse 5-nitro-1-(pentafluorosulfanyl)benzenes substituted in the fluoro-position using S_NAr processes (Table 30) and 3-fluoro-5-nitro-1-(pentafluorosulfanyl)benzenes substituted in position four using VNS (Table 31).[170]

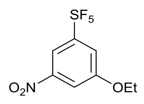
***Table 30** S_NAr reactions using 5-fluoro-3-nitro-1-(pentafluorosulfanyl)benzene and various nucleophiles by Ajenjo et al.*



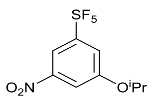
337 **341a-k**



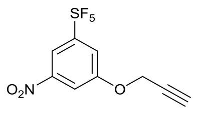
341a, 85%



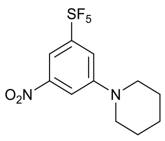
341b, 83%



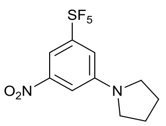
341c, 72%



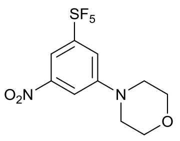
341d, 70%



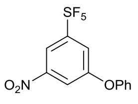
341e, 51%



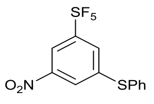
341f, 67%



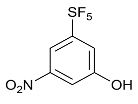
341g, 63%



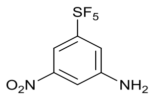
341h, 67%



341i, 46%

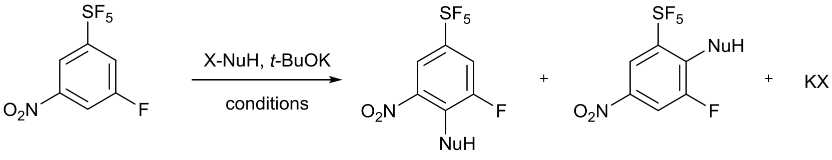


341j, 33%

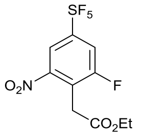
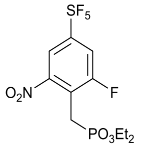
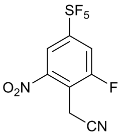
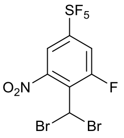
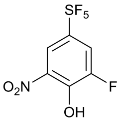
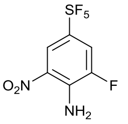


341k, 44%

Table 31 *VNS of 5-fluoro-3-nitro-1-(pentafluorosulfanyl)benzene with various nucleophiles*[a]



337 **342a-f** **343a-f**

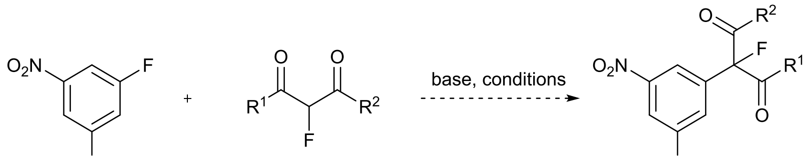
		
342a, 71% (97:3)	**342b**, 31% (97:3)	**342c**, 50% (87:13)
		
342d, 81% (>98:2)	**342e**, 60% (96:4)	**342f**, 85% (>98:2)

[a] Ratio of products determined by GC-MS under parentheses

We first focused our investigations on finding synthetic conditions to achieve similar processes. Using previously synthesized fluorinated malonates and ketoesters, Table 32 summarizes the different synthetic conditions and bases that were screened. Among all these tested conditions on both 2-fluoro-1,3-dimethylmalonate and 2-fluoro-ethylacetoacetate, no conversion of the starting substrates was observed in case of using K_2CO_3 in dry DMF (4 hours at room temperature), LiHMDS in dry toluene (2.5 hours at -78 °C), ^nBuLi in dry THF or dry Et_2O (4 hours at -78 °C), LDA in dry THF (at -78 °C for 2 hours using 2-fluoro-1,3-dimethylmalonate or 24 hours using 2-fluoro-ethylacetoacetate) and ^tBuOK in dry DMF (5 hours at -60 °C or at -78 °C).

The last conditions tested with ^tBuOK in dry DMF were realized at a higher temperature of -40 °C and we then clearly observe by GC-MS the formation of a new product. However, from GC-MS and NMR-spectroscopy analysis, it seemed that the same product was obtained in both cases, either starting from 1,3-dimethyl-2-fluoromalonate **62** or 2-fluoro-ethyl acetoacetate **19**.

Table 32 *Tested synthetic conditions for the attempted S_NAr of 5-fluoro-3-nitro-1-pentafluorosulfanylbenzene*



337

62, $R^1 = R^2 = OMe$
19, $R^1 = Me$ and $R^2 = OEt$

344

Entry[a]	Base [eq.]	62 or 19 [eq.]	Solvent[b]	Temp.	Reaction time [h]	Conversion [%][c]
1a	NaH [3.00]	4.2	THF	r.t.	20.0	7
1b						21
2a	K_2CO_3 [3.40]	1.8	DMF	r.t.	4.0	0
2b						
3a	LiHMDS [0.08]	0.8	toluene	-78 °C	2.5	0
3b						
4a	^{n}BuLi [0.08]	0.8	Et_2O	-78 °C	4.0	0
4b						
5a	^{n}BuLi [0.08]	0.8	THF	-78 °C	4.0	0
5b						
6a	LDA [0.40]	0.2	THF	-78 °C	2.0	0
6b					24.0	
7a	^{t}BuOK [3.00]	1.0	DMF	-40 °C	5.0	15
7b						22
8a				-60 °C		0
8b						
9a				-78 °C		0
9b						

[a] a: with 2-fluoro-1,3-dimethylmalonate, b: with 2-fluoro-ethyl acetoacetate; [b] Dry solvent; [c] By ^{19}F-NMR

To improve the conversion towards significant amount of product, synthetic conditions were modified with the addition of NaH in dry THF on a mixture of the starting SF_5-benzene derivative and 2-fluoro-ethylacetoacetate or 2-fluoro-1,3-dimethylmaonate, which was then allowed to stir over 19 hours at room temperature, then 3 hours at 50 °C followed by a further addition of NaH, to finally let the reaction mixture to stir over 20 hours at room temperature.

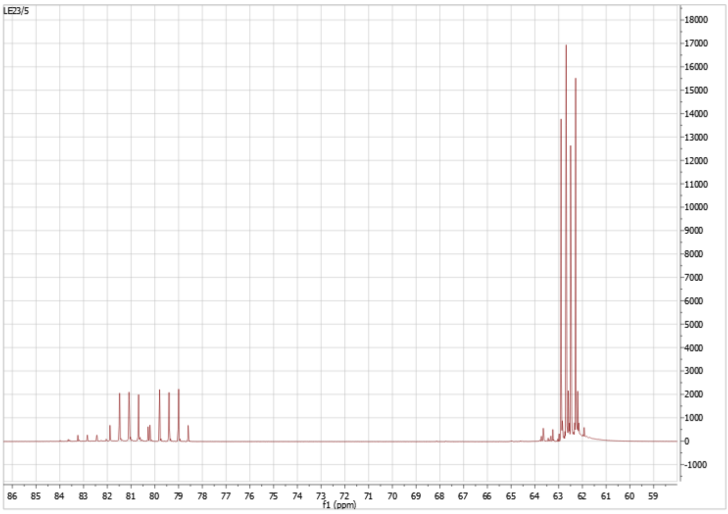


Figure 49 *^{19}F-NMR spectrum of the crude product of S_NAr between 2-fluoro-ethylacetoacetate and 5-fluoro-3-nitro-1-pentafluorosulfanylbenzene using NaH (59-86 ppm)*

The ^{19}F-NMR spectrum of the crude product of the reaction between 5-fluoro-3-nitro-1-pentafluorosulfanylbenzene and 2-fluoro-ethyl acetoacetate using NaH revealed the formation of a new SF_5 compound, as a new set of doublet + quintuplet in a ratio close to 1:1 compared to the ^{19}F-NMR shifts of the starting SF_5 benzene substrate appears (Figure 49). The absence of any ^{19}F-NMR shift corresponding to the starting 2-fluoro-ethylacetoacetate (around -190/-200 ppm) indicated full conversion of the starting fluorinated dicarbonyl compound. Purification by column chromatography using petroleum ether and diethylether as eluent system by a respective gradient from 9:1 to 7:3 allowed us to purify the product (Figures 50-51).

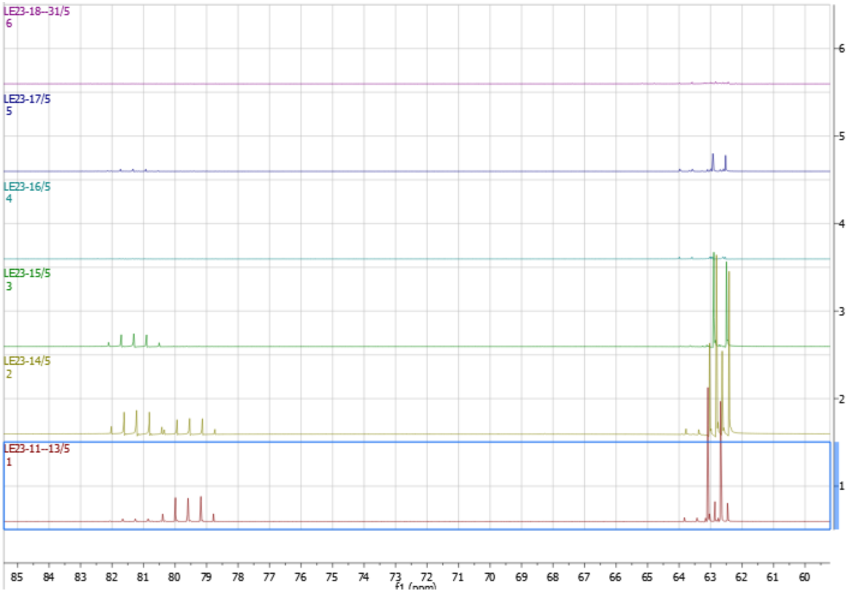


Figure 50 *^{19}F-NMR spectroscopy follow-up of the purification of crude product from S_NAr reaction between 2-fluoro-ethyl acetoacetate and 5-fluoro-3-nitro-1-pentafluorosulfanylbenzene*

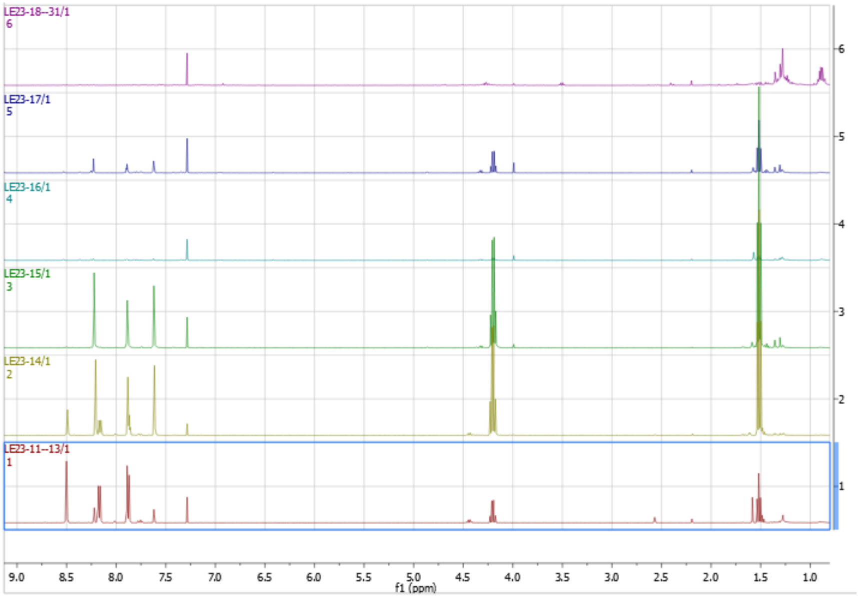
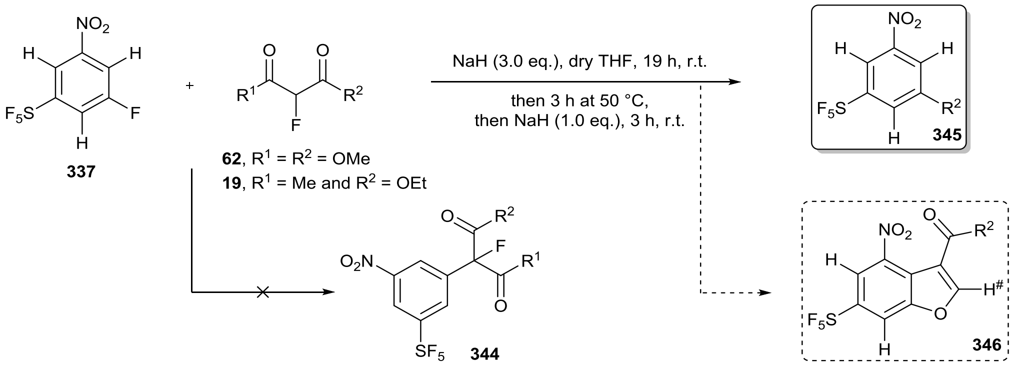


Figure 51 *^{1}H-NMR spectroscopy follow-up of the purification of crude product from S_NAr reaction between 2-fluoro-ethyl acetoacetate and 5-fluoro-3-nitro-1-pentafluorosulfanylbenzene*

A similar reaction using 2-fluoro-1,3-dimethylmalonate as nucleophile gave a similar product, which GC-MS analysis and ^{1}H-, ^{19}F- and ^{13}C-NMR spectroscopy showed was the methoxylated compound **345a** (48% yield) or ethoxylated compound **345b** (52% yield), respectively from 2-fluoro-1,3-dimethylmalonate or 2-fluoro-ethyl acetoacetate (Scheme 99).



Scheme 99 *Synthesis of 5-ethoxy-3-nitro-1-pentafluorosulfanylbenzene from 5-fluoro-3-nitro-1-pentafluorosulfanylbenzene, 2-fluoro-ethylacetoacetate and NaH*

We assume these products were formed by displacement of methoxide or ethoxide by base from 2-fluoro-1,3-dimethylmalonate **62** or 2-fluoro-ethyl acetoacetate **19** respectively and nucleophilic aromatic substitution. Since no VNS reactions were observed, no further research was carried out in this area.

4. Conclusion

Direct fluorination methodologies on substrates possessing a similar molecular scaffold as the previously studied 2-fluoro-1,3-dicarbonyl substrates still remains challenging despite all the conducted investigations, especially on the direct fluorination of the tricarbonyl systems. However, progress has been made towards a more selective strategy to achieve this fluorination pathway using a protection synthetic strategy. Unfortunately, using 2-fluoro-1,3-dicarbonyl substrates in S_NAr or VNS pathways appears to be unsuccessful, despite accessing fluorinated pentafluorosulfanyl benzene via an easy fluorination process. Finally, it seems that optimizing the purification process of the obtained crude products from direct fluorination of functionalized carbonyl systems appears problematic. However, few fluorinated products are obtained via this methodology and could entirely be used in further research.

Chapter 7 Flow process development and applications

A target of all our different fluorination projects was to develop first a chemical approach by using batch processes and then try to adapt optimized synthetic strategies to flow processes. This final chapter is dedicated to the many advantages of developing flow process methods, especially related to direct fluorination by F_2/N_2 (5-20% $v.v^{-1}$). Therefore, the key points of chemistry in flow, a few significant examples and our applications will be presented here.

1. Flow process strategies in chemistry

1.1. Key aspects of process and flow chemistry

Flow chemistry appears more and more to be a competitive alternative to batch chemistry for many reasons. The fact that reactions are run continuously by pumping and mixing of all inputs, typically in solution phase chemistry, using a choice of pumps, reactors, monitoring and quenching as part of the process, has many benefits.[171]

In fact, as a summary, the transition from batch to flow is like moving from a series of linked batch vessels to a stream within a flow tube, by choosing different flow regimes (laminar with N_{Re} < 2100, turbulent with N_{Re} > 4000), indicated by fluctuations in the values of the Reynolds numbers (N_{Re}: Reynolds number, D: pipe diameter, V: fluid velocity, ρ: fluid density, μ: fluid viscosity).

$$N_{Re} = \frac{D\,V\,\rho}{\mu}$$

Conventional batch chemistry presents many problems. Scalability, in terms of reactor size dependence, emptying and cleaning steps, efficiency, reaction kinetics, reliability, reproducibility, safety, dealing with hazardous chemicals, monitoring, typically done off-line (HPLC and NMR) with a delay between sampling and data analysis, cost, especially in case of high development and maintenance cost at process scale, and step-efficiency, with a desirable telescoping process, are all problems associated with batch chemistry.

In contrast to all those problems, flow chemistry showcases a better mixing via T-pieces, micro-chips and specific mixing elements, better heat transfer, better selectivity in many reported reactions, and the large advantage of being able to handle highly reactive species. Indeed, the use and generation of hazardous reagents can be highly restricted in batch processes. The small volumes of flow reactors mean that small quantities are generated at any given time. Many different examples have been already reported in recent reviews, such as formation of azides, diazo/diazonium synthesis, isocyanides formation, nitration and more interestingly in our case fluorination.[172]

In-line purification in flow has also already been developed, from using aqueous extraction to distillation, HPLC, crystallization or common scavenger resins. One of the main interests of flow process chemistry is the ability to realize a multistep synthesis in flow, such as sequential lithiation chemistry. Moreover, multistep synthesis in flow enables chemists to telescope individual steps to one single flow sequence, combining it with an in-line purification and analysis.

Conventional flow chemistry is mainly solution phase chemistry done using flow equipment such as syringe pump or HPLC-type piston pump (Figure 52), that allow various selected flow-rates.

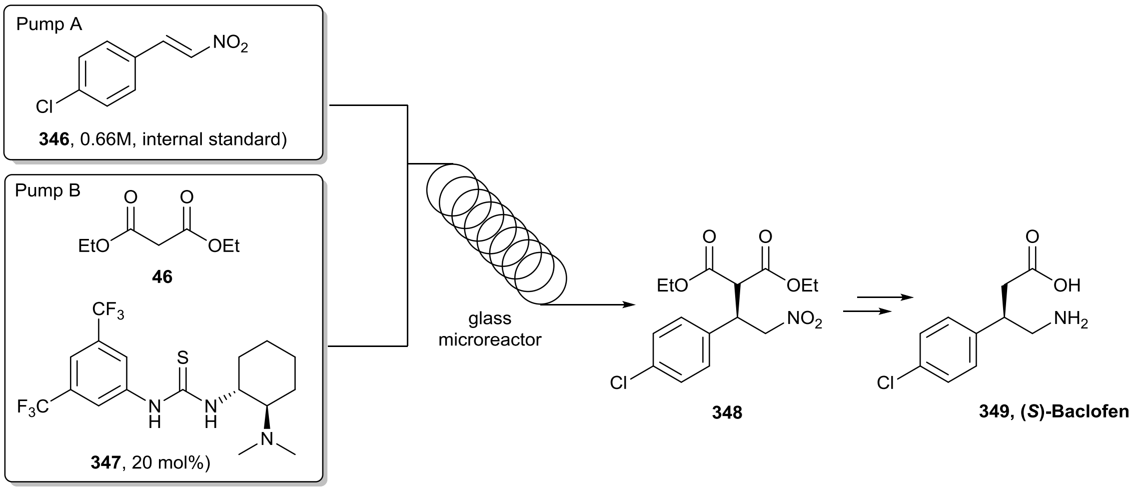
Figure 52 *HPLC-type piston pump (left) and syringe pump (right)*

Reactors such as micro-chip reactors, coiled reactors, such as the one presented in Figure 53, and oscillating reactors present different options, adapted to various reaction volumes and applications.

Figure 53 *Stainless steel coiled tube reactor*

1.2. Continuous flow process strategies

To exhibit different examples of various flow process strategies that have been recently reported, we discuss methods that are close to our related chemistry, previously developed in batch in chapter 2 to 6, *i.e*. reactions involving dicarbonyl scaffolds or Mannich-type processes.

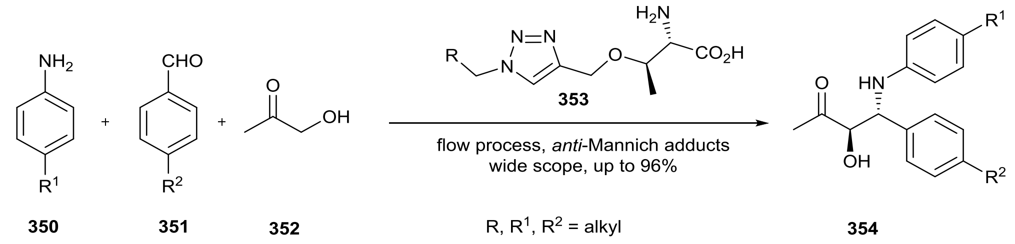


Scheme 100 *Flow process synthesis of (S)-Baclofen precursor*

Among all the different examples that have been reported on flow chemistry involving dicarbonyl systems, we were particularly interested in the (*S*)-Baclofen synthesis, as it involves derivatized olefins that were attached to the chosen dicarbonyl systems, which is a strategy related to Mannich-type chemistry method we developed earlier. The (*S*)-Baclofen precursor **348** was synthesized by stereoselective Michael addition of diethylmalonate to 4-chloro-β-styrene promoted by Takemoto catalyst under flow conditions. Reaction conditions have been screened and developed by Maggini and coworkers in a 10 µL glass microreactor and the scale-up was carried out in a 400 µL PTFE tubing (Scheme 100). The residence time was shown to be around 5 min for a temperature of 80 °C, affording the desired intermediate with 85% yield and 81% enantiomeric excess.[173]

For Mannich-type flow process reactions, in 2013, M. A. Pericàs et al. developed asymmetric anti-Mannich reactions in continuous flow using a packed bed reactor, a tubular reactor paced with solid catalyst particles based on a polystyrene-supported pyrrolidine-based catalyst. However, despite showing very high activity and excellent stereoselectivity, many disadvantages such as undesired thermal gradients, poor temperature control, channeling problems and difficult cleaning of the unit were discovered.[174]

Consequently, polymer-supported threonine and proline derivatives were reported to catalyze three component Mannich reaction in batch and also particularly in flow (Scheme 101).[175]



Scheme 101 *Continuous flow enantioselective three-component anti-Mannich reactions catalyzed by a polymer-supported threonine derivative*

The main interest of our research has been to conduct direct fluorination in flow and adapt it to the different projects that have previously been elaborated. Examples of fluorination in flow are outlined below.

2. Development of flow processes involving continuous flow fluorinations using F_2

2.1. Fluorination chemistry in flow

A basic micro-reactor has been developed at Durham University (Figure 54), allowing the control of the delivery of fluorine at one end of the reaction chamber by an accurate electronic mass-flow controller whereas reagents were delivered downstream by syringe pumping. Gas and liquid mixtures are thus flowing down the micro-channel in a laminar flow, improving the fluorination processes.[176]

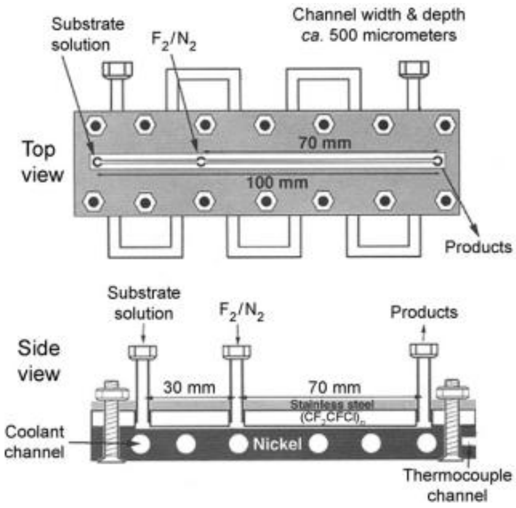


Figure 54 *Design of single channel reactor*

This micro-reactor was designed to achieve a variety of different fluorinations in flow. Scale-out of this micro-reactor was investigated. An efficient multi-channel micro-reactor system was designed, that can be used for larger scale uses, allowing the introduction of fluorine and substrate into many channels from one source and commercial systems for gas-liquid reactions are now available (Figure 55).[177]

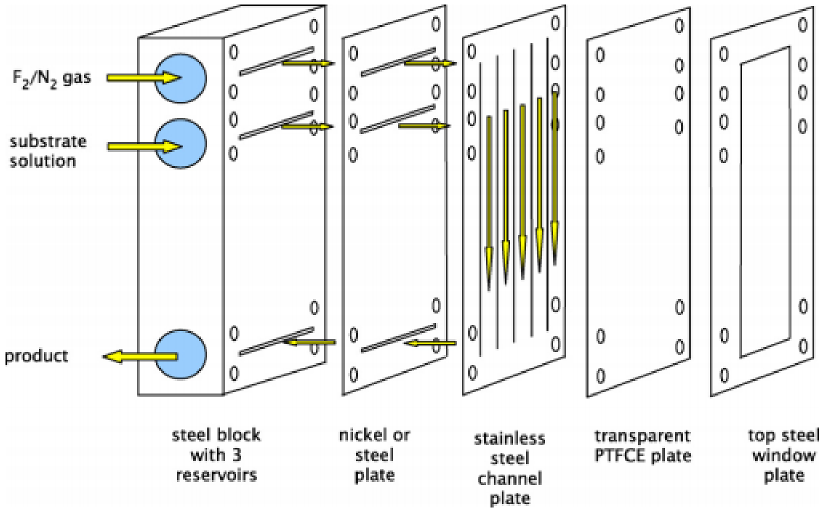
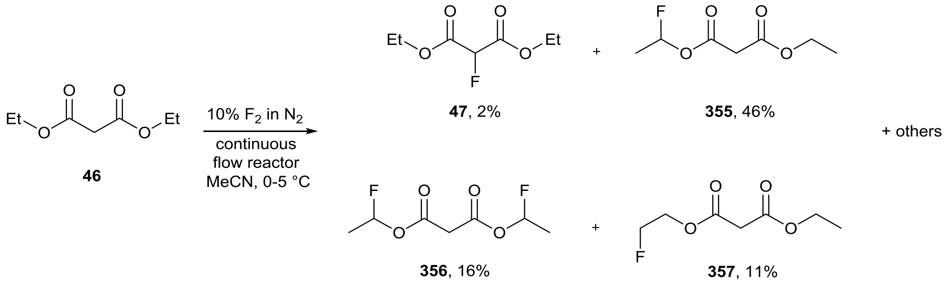
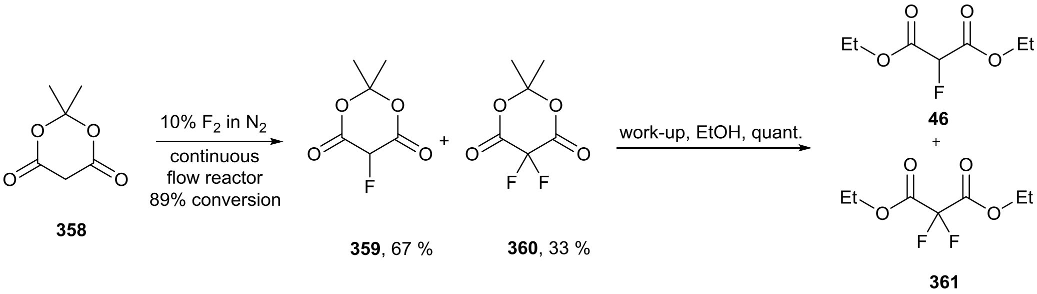


Figure 55 *Schematic representation of modular micro-reactor device*

A continuous flow approach has also been investigated from 1,3-diethylmalonate as starting substrates in acetonitrile, but gave poor selectivity between mono- and di-fluorinated products (Scheme 102).[178] But, choosing Meldrum's acid, also known as 2,2-dimethyl-1,3-dioxane-4,6-dione, as starting compound, allows a mixture of mono and di-fluorinated products to be obtained and separated after work-up (Scheme 103).[179]

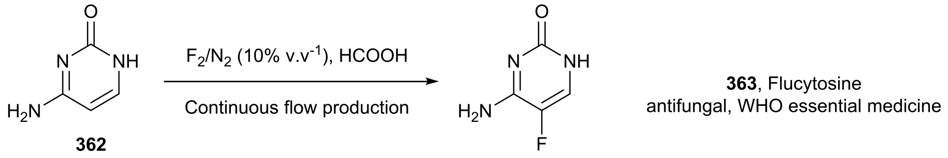


***Scheme 102** Results of direct fluorination of diethylmalonate*



***Scheme 103** Continuous flow fluorination of Meldrum's acid*

A one-step continuous flow process involving the reaction of inexpensive cytosine with fluorine gas has been recently reported by Harsanyi et al. showing various advantages, such as a one-step route, a continuous process, high yield, simple purification, API purity (Scheme 104). Last but not least, this process was using stainless steel tubular laboratory and pilot-scale silicon carbide reactor devices which is readily scalable to a manufacturing process with a low initial capital expenditure.[180]



***Scheme 104** One-step continuous flow synthesis of antifungal WHO essential medicine Flucytosine using fluorine*

Following the previously described chemical flow process, fluorination of diketones has been recently investigated, affording cyclization of the intermediate fluoro-diketone by reaction with hydrazine derivatives, added to the reagent stream by a T-piece, in a two-step sequential flow-process, giving access to new 4-fluoropyrazoles (Figure 56).[68]

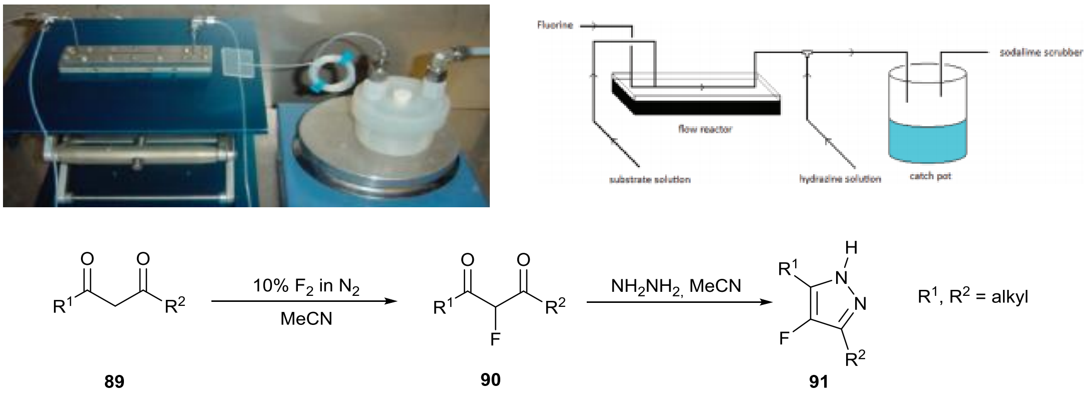


Figure 56 *Synthesis of 4-fluoro-3,5-dimethylpyrazole derivatives using designed flow reactor system*[68]

2.2. Synthetic flow process methodology on multi-carbonyl systems

In this research project, we attempted to develop previously optimized reactions discussed in chapters 2-6 to a flow process using helicoïdal stainless steel flow reactors and PTFE tubing reactors. The synthetic method presented in this study uses helicoïdal reactors with a retention time of 2 to 5 min depending on the flow rate and the length of reactors being used. Indeed our approach was to develop a shortly timed, non-heated and non-catalyzed option of the synthesis of Mannich-type products by a flow process able to involve a continuous flow fluorination step without impacting the efficiency of the multi-component reaction (Figure 57). We therefore designed our own two-step flow-process system to achieve such transformations.

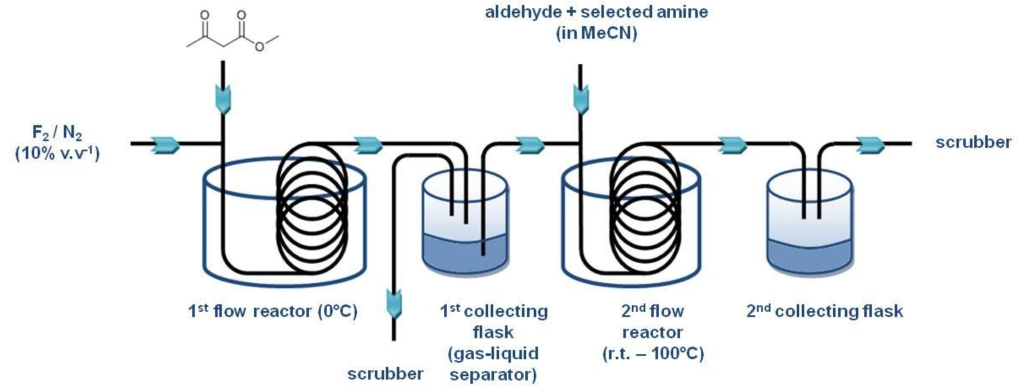


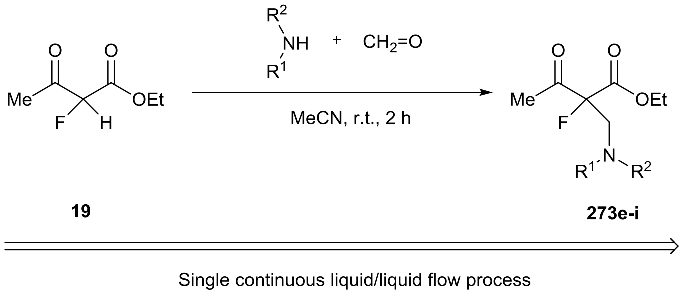
Figure 57 *Schematic flow process system applied to Mannich-type multicomponent reactions*

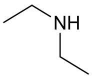
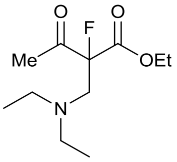
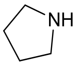
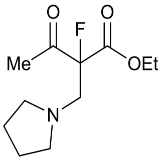
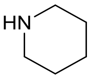
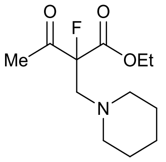
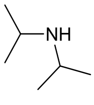
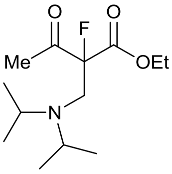
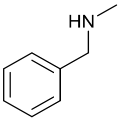
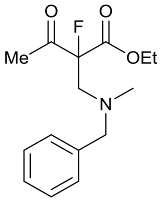
Unfortunately, the only limitations to this process have been proved to be the use of copper nitrate as a catalyst during the fluorination step of the 1,3-dimethymalonate, which was causing PTFE tubing blocks, meaning that the full two-steps process was only applied to the synthesis of β-fluoro(dicarbonyl)ethylamines from 2-fluoro-ethylacetoacetate.

Following optimization of continuous flow reactions of ethyl fluoro-ethylacetoacetate with amine/formaldehyde mixtures in a one-step liquid-liquid flow process (Table 33), we adapted our synthetic procedure described above to a two-step gas-liquid, liquid-liquid semi-continuous flow process using stainless steel coiled tube reactors (previously presented in Figure 53). A schematic diagram of the process is shown in Figure 57.

Fluorine gas in nitrogen was introduced into input 1 of the first coiled steel tube reactor and flowed along the tube concurrently with ethyl acetoacetate which was simultaneously added to the reactor system via inlet 2. The flow of the gaseous reactant stream was controlled by gas mass flow-meter and the liquid dicarbonyl reagent solution was introduced by HPLC pump so that the fluorine gas : dicarbonyl addition ratio was *ca.*1.3 : 1. The flow rate of each reagent was adjusted to ensure a retention time of 2 to 5 min of the substrate within the tubular reactor. The crude product mixture for the fluorination reaction was collected in a gas liquid separator flask where liquid is collected and gaseous waste passed through a scrubbing tower filled with soda-lime. The crude fluoro-dicarbonyl product mixture was then pumped without any work-up procedure directly into input 3 of the second continuous flow coiled steel tube reactor while, simultaneously, a solution containing the amine and aldehyde solution was added at a controlled flow rate. The crude product mixture for the two-step one continuous flow process was collected in Collection vessel 2 and, following work-up, allowed the Mannich products to be isolated in good yield and purity confirming the efficiency of this flow-process strategy (Table 34).

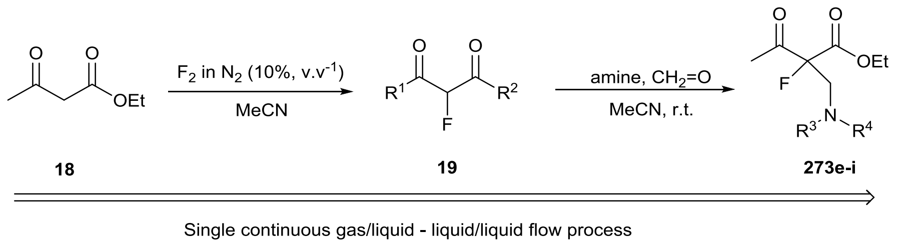
Table 33 *Three-component Mannich-type flow process reaction of 2-fluoro-ethyl acetoacetate, formaldehyde and a chosen amine*



Entry	Amine	Product	Yield [%][a]	Batch process yield [%][a]
1			**273e**, quant.	**98**
2			**273f**, 81	**98**
3			**273g**, 95	**98**
4			**273h**, 71	**90**
5			**273i**, 95	**95**

[a] Isolated

Table 34 *Synthesis of β-fluoro(dicarbonyl)alkylamines* ***273*** *from ethyl acetoacetate, amines* ***264*** *and formaldehyde by semi-continuous flow process*



Entry	R^3	R^4	Yield [%]^a
1	CH_2CH_3	CH_2CH_3	**273e**, 71
2	^{i}Pr	^{i}Pr	**273f**, 43
3	$-(CH_2)_4-$	-	**273g**, 55
4	$-(CH_2)_5-$	-	**273h**, 59
5	Bn	CH_3	**273i**, 67

^{a} Isolated

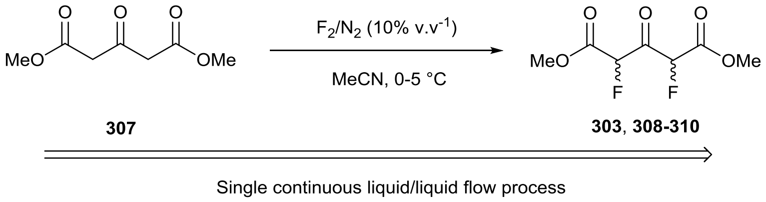
Combined gas-liquid/liquid-liquid sequential flow reaction using fluorine gas have not been well developed and only examples demonstrating the synthesis of fluoropyrazole derivatives have been recorded,[181] as previously mentioned, but the reasonable yields of Mannich products **273** obtained from fluorine, ketoester and aminal inputs in the two-step semi-continuous flow process offers further opportunities for process intensification of synthetic strategies using fluorine gas.

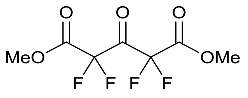
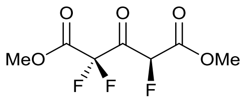
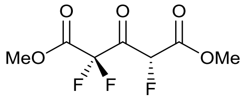
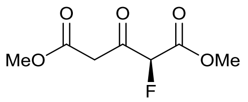
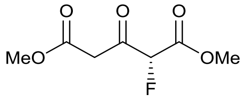
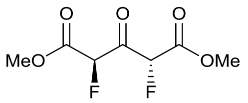
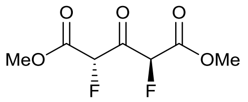
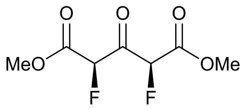
Using this flow-process set-up has been tested on the two other projects we developed earlier in this report, indeed the CAN-mediated addition of olefin on 2-fluoro-1,3-dicarbonyl systems and the synthesis of fluorinated functionalized pyrimidinones but none of these processes were successful due to the presence of residual catalyst preventing any significant flow in the first case and the low solubility of the amidines involved in these synthetic pathways in the second case.

2.3. Fluorination in flow of dimethylacetone-1,3-dicarboxylate

We also investigated the possibility of achieving the direct fluorination of tricarbonyl substrates, as we previously presented its fluorination in batch. Therefore, we were using a similar set-up as the first fluorination step of the combined MCR process but this time analyzing the different products formed inside the collecting flask by NMR spectroscopy. The Table 35 is presenting the various results obtained in different conditions of flow and percentages of F_2 in N_2.

***Table 35** Results of fluorination of dimethylacetone-1,3-dicarboxylate in flow using various conditions*



	Entry	1	2	3	4
	F_2/N_2 [%]	10	10	10	20
	Flow rate [mL/min]	20	30	40	20
	F_2:307 ratio	1.01	1.47	1.96	1.96
Products [^{19}F-NMR %]	 **303**	12	20	19	19
	 **310** 	3	8	8	8
	 **308** 	8	6	9	8
	 **309a** 	63	53	51	52
	 **309b**	14	13	13	13

These collected results showed that a better contact between the reactans inside the PTFE tubings provided a larger amount of *α,β*-bis-mono-fluorinated isomers

309a-b, but also a larger amount of the directly *α,β*-bis-di-fluorinated product **303**, where the batch processes were allowing us to gain access more easily to the *α*-mono-*β*-bis-di-fluorinated isomers **310**. Despite this larger amount of tetrafluoro products **303**, the major products were obtained in more than 60% ^{19}F-NMR ratio in all cases, showing that fluorination in flow still remains a better strategy compared to the batch process in this case.

3. Conclusion

The different advantages of a flow process synthetic strategy over the classic batch reactions have been showcased, especially in the case of handling toxic entities such as fluorine. Here, we exhibit that this method can perfectly be adapted to the direct fluorination of tricarbonyl substrates or multi-component processes, such as the Mannich-type reactions.

Chapter 8 Conclusions and future work

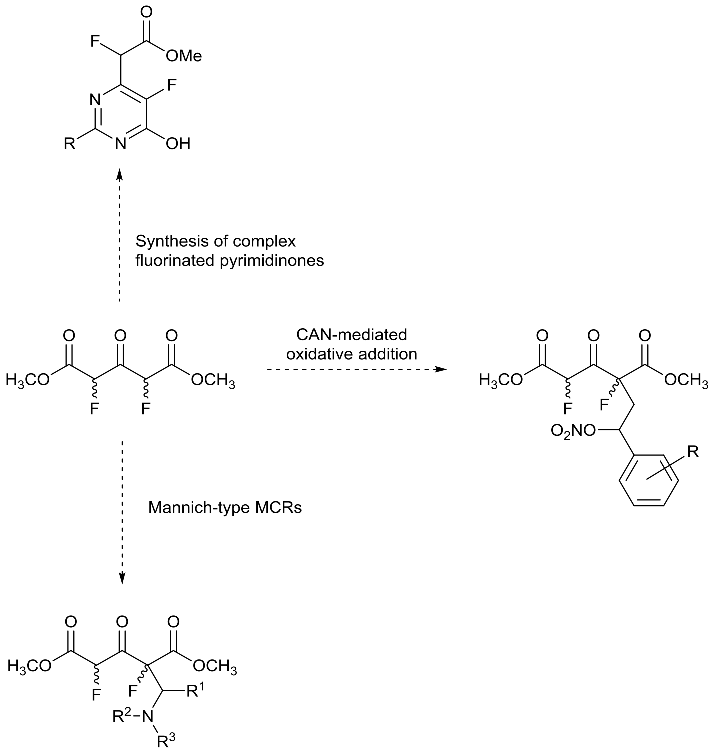
In this thesis, we presented the various advantages of organofluorine chemistry and its multiple applications and firstly described the synthesis of fluorinated dicarbonyl molecules using a direct fluorination strategy. Starting from these fluorinated 1,3-dicarbonyl substrates, we achieved the synthesis of various fluorinated heterocyclic systems such as fluoro-pyrimidinones, and, therefore, built a full library of fluorinated pyrimidine fragments with various functionalizations. Thanks to our research partners at both University of Vienna and UCD Dublin, we were able to study their potential activity against β-catenin and their role in biotransformation involving *C. elegans.*

Radical chemistry was then tested using different catalytic systems to achieve the oxidative addition of olefins to the 2-fluoro-1,3-dicarbonyl substrates. Among the different tested methodologies, $Mn(OAc)_3$- and CAN-mediated oxidative addition of olefins to 2-fluoro-ketoester provided the most successful results.

As part of the development of new synthetic methods towards fluorinated building-blocks, we then reported succesful multi-component strategies involving either 2-fluoroethylacetoacetate or 2-fluoro-1,3-dimethylmalonate as part of a Mannich-type reaction pathway using various amines and aldehydes.

The direct fluorination of various functionalized carbonyl compounds, including tricarbonyl systems was then performed and spectroscopic studies have been conducted to identify the different products formed. A synthetic methodology towards protected tricarbonyl substrates has been developed and we obtained first encouraging results by applying them to our direct fluorination process.

Last but not least, the development of a flow process system combined the fluorination step and further transformations, and this methodology proved to be more efficient than the usual batch strategy to synthesize Mannich-type reaction products in relatively convenient yields. Extension of flow process methodology to the use of various dialdehydes as part of MCR synthetic strategy, in addition to the potential use of fluorinated tricarbonyl systems, could allow the access of more sophisticated fluorinated compounds.



Scheme 105 *Potential synthetic options from fluorinated tricarbonyl molecules (synthetic pathways already developed in case of using 2-fluoro-1,3-dicarbonyl substrates)*

One of the area for potential future research is the further exploration of direct fluorination of various multi-carbonyl systems, potentially tested with other catalysts than copper, and the application of such fluorinated tricarbonyl substrates to the processes that have been previously developed with 2-fluoro-1,3-dicarbonyl molecules, either the synthesis of diverse fluorinated pyrimidinones, the radical oxidative addition of styrene-derivated olefins or any multicomponent reactions (Scheme 105).

Our work on radical chemistry has been largely focused on developing a convenient process using 1,3-dimethyl-2-fluoromalonate but most of our successful results have been obtained when simple fluorinated keto-esters were chosen as substrates. Therefore, it opens an area for future research on the development of oxidative addition of olefins on more complex fluorinated keto-esters using various radical initiators, potentially deriving from the previously described cerium(IV) reagent.

Aside of this work, developing other multicomponent reactions involving fluorinated dicarbonyl systems still remains an interesting challenge, firstly because this type of building-blocks often appears in such synthetic strategies but also because these synthetic pathways can be adapted in both batch and flow processes.

Chapter 9 Experimental

1. General experimental and instrumentation

NMR Spectroscopy

Proton, fluorine and carbon nuclear magnetic resonance spectra (^{1}H, ^{19}F, ^{13}C NMR) were obtained using a Bruker 400 Ultrashield spectrometer (^{1}H NMR at 400 MHz, ^{19}F NMR at 376 MHz and ^{13}C NMR at 101 MHz) and a Varian VNMRS-700 spectrometer (^{1}H NMR at 700 MHz; ^{13}C NMR at 176 MHz) using residual solvent peaks as the internal standard (^{1}H NMR; $CDCl_3$ at 7.26 ppm, ^{19}F NMR; $CFCl_3$ at 0.00 ppm and ^{13}C NMR; $CDCl_3$ at 77.16 ppm). NMR spectroscopic data are reported as follows: chemical shift (ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quarter, m = multiplet), coupling constant (Hz) and assignment.

Mass spectrometry

GC-MS data were obtained using a Shimadzu QP2010-Ultra equipped with a Rxi-17Sil MS column (0.15 µm x 10 m x 0.15 mm) under electron ionisation (EI) conditions at 70 eV using helium as a carrier gas. Liquid chromatography mass spectra (LC-MS) were obtained on a TQD mass spectrometer equipped with an Acquity UPLC BEH C18 1.7 µm column (2.1 mm x 50 mm). Accurate mass analysis was performed on a Xevo QtoF mass spectrometer (Waters Ltd, UK) with an accurate solids analysis probe (ASAP) or a TQD UPLC (Waters) instrument operating in electrospray ionization mode. Flash column chromatography purification was performed using Silicagel LC60A (40-63 micron).

IR Spectroscopy, Melting Points and Reagents

Infrared spectra were recorded on a Perkin Elmer Spectrum 2 FT-IR spectrometer at 25 °C and melting points were obtained using a Gallencamp melting point apparatus at atmospheric pressure. All the chemicals and solvents used were commercially purchased from Alfa Aesar, Apollo Scientific, Fluorochem or Sigma Aldrich and, unless otherwise stated, were used without any further purification.

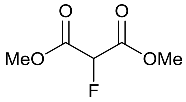
Fluorination set-up

Fluorinations were carried out in a glass fluorination reactor (100 mL, 250 mL or 500 mL) unless otherwise stated. The reactor was built from a standard glass bottle with

GL 45 thread joint and a PTFE screw cap or a glass flange head, equipped with a gas inlet/outlet head built of stainless steel, PTFE and FEP Swagelok components. Vacuum distillations were carried out using Fisher® micro Spaltrohr®-column MMS 255 with manual fraction collection. Brooks instruments®- gas mass flow controllers were used to control the various flow rates of the corresponding fluorination processes.

2. Experimental to chapter 2

2-Fluoro-1,3-dimethylmalonate, 62



$Cu(NO_3)_2 \cdot 2.5H_2O$ (10.16 g, 43.7 mmol) was added to a solution of acetonitrile (550 mL) and 1,3-dimethyl malonate (57.73 g, 437 mmol) and added to a glass reaction vessel with a PTFE-coated mechanical stirrer bar. The reaction vessel was purged with nitrogen for five minutes and cooled to 5 °C, before F_2 (20% F_2/N_2 $v.v^{-1}$, 220 mmol) was passed through the reaction solution at a flow rate of 44 mmol/h for 5 hours. After the reaction had progressed to completion, checked by ^{19}F-NMR spectroscopy, the fluorine supply was switched off and the reaction vessel was purged with nitrogen for five minutes. The reaction mixture was then concentrated in vacuo, dissolved in ethyl acetate (20 mL), washed with water (3 x 20 mL) and brine (3 x 20 mL) and dried with anhydrous magnesium sulfate. The filtrate was again concentrated in vacuo and distilled under reduced pressure (4 mbar, 66 °C) yielding 2-fluoro-1,3-dimethylmalonate **62** (85%, >98% purity) as a clear oil. ^1H NMR (400 MHz, *$CDCl_3$*) δ_H 5.31 (1H, d, *J* = 48.0 Hz, -C(F)***H***-), 3.85 (6H, s, 2 x OC***H₃***). ^{19}F NMR (376 MHz, *$CDCl_3$*) δ_F -195.4 (1F, d, *J* = 48.0 Hz, -C(***F***)-). ^{13}C NMR (101 MHz, *$CDCl_3$*) δ_C 164.3 (d, *J* = 24.3 Hz, 2 x -***C***(O)OCH₃), 85.1 (d, *J* = 196.5 Hz, -***C***(F)-), 53.3 (s, 2 x –O***C***H₃). MS (ESI) m/z 151 ($[M+H]^+$, 100%). HRMS (ESI) calcd for $[M+H]^+$ $C_5H_8O_4F$ 151.0407; found 151.0388. The spectroscopic data is in agreement with assignments reported in the literature.[57]

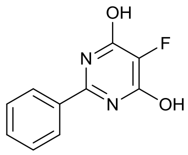
3. Experimental to chapter 3

3.1. Synthesis of fluorinated pyrimidines from 2-fluoro-1,3-dimethylmalonate

General Procedure

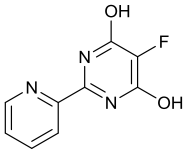
Sodium (0.92 g, 40 mmol) was dissolved in MeOH (100 mL) in a two-necked 250 mL flask, and amidine hydrochloride and a solution of 2-fluoro-1,3-dimethylmalonate **62** in acetonitrile (30 mL) were added. The resulting mixture was stirred at 80 ^{o}C for 16 h and cooled to rt before the addition of dilute aqueous HCl (4 mL, 6 M, 24 mmol). The mixture was filtered and the filtrate was concentrated *in vacuo* and washed with ethanol. The resulting solution was filtered, the filtrate was concentrated for a second time, washed with ethanol and filtered again to yield the desired fluorinated pyrimidine.

5-Fluoro-2-phenylpyrimidine-4,6-diol, 111d



2-Fluoro-1,3-dimethylmalonate **62** (3.03 g, 20 mmol) and benzamidine hydrochloride (3.12 g, 20 mmol) gave *5-fluoro-2-phenylpyrimidine-4,6-diol* (3.64 g, 88%) as a yellow powder; mp > 250 °C. ^{1}H NMR (400 MHz, *DMSO-d^{6}*) δ_H 8.03 – 7.94 (2H, m, 2 x ***H$_{ortho}$***), 7.50 – 7.32 (3H, m, 2 x ***H$_{meta}$*** + ***H$_{para}$***), 3.80 – 3.20 (2H, br s, OH). ^{19}F NMR (376 MHz, *DMSO-d^{6}*) δ_F -180.7 (s, -C(***F***)-). ^{13}C NMR (101 MHz, *DMSO-d^{6}*) δ_C 157.3 (d, *J* = 15.5 Hz, -***C***(OH)-), 151.5 (d, *J* = 6.9 Hz, -***C***-C(CH)$_5$-), 132.5 (d, *J* = 235.3 Hz, -***C***(F)-), 132.2 (-C-***C***(CH)$_5$-), 131.8 (***C$_{para}$***), 129.0 (***C$_{meta}$***), 128.1 (***C$_{ortho}$***). MS (ASAP) m/z 207 ([M+H]$^{+}$, 100%), 208 ([M+2H]$^{+}$, 15.6%). HRMS (ASAP) calcd for [M]$^{+}$ $C_{10}H_7N_2O_2F$ 206.0492; found 206.0495. IR (neat, cm^{-1}) 2637, 1626, 1581, 1511, 1445, 1322.

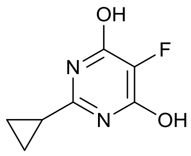
5-Fluoro-2-(pyridin-2-yl)pyrimidine-4,6-diol, 111c



2-Fluoro-1,3-dimethylmalonate **62** (2.27 g, 15 mmol) and pyridine-2-carboxamidine hydrochloride (2.36 g, 15 mmol) gave *5-fluoro-2-(pyridin-2-yl)pyrimidine-4,6-diol* (1.95 g, 63%) as a yellow powder; mp > 250 °C. ^{1}H NMR (600 MHz, *D$_2$O*) δ_H 8.38 (1H, ddd, *J* = 4.9, 1.8, 0.9 Hz, -C-CHCHCHC***H***-N-), 7.79 (1H, dt, *J* = 8.0, 1.2 Hz, -C-C***H***CHCHCH-N-), 7.74 (1H, td, *J* = 8.0, 1.8 Hz, -C-CHC***H***CHCH-N-), 7.28 (1H, ddd, *J* = 7.7, 4.9, 1.2 Hz, -C-CHCHC***H***CH-N-). ^{19}F NMR (376 MHz, *D$_2$O*) δ_F -181.0 (s, -C(***F***)-). ^{13}C NMR

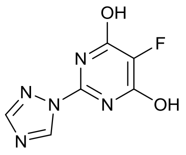
(176 MHz, *D_2O*) δ_C 164.4 (d, *J* = 12.5 Hz, 2 x –***C***(OH)-), 157.0 (d, *J* = 9.6 Hz, -***C***-C-(CH)$_4$-N-), 155.0 (-C-***C***-(CH)$_4$-N-), 148.4 (-C-CHCHCH***C***H-N-), 137.9 (-C-CH***C***HCHCH-N-), 137.0 (d, *J* = 230.3 Hz, -***C***(F)-), 124.3 (-C-CHCH***C***HCH-N-), 123.13 (-C-***C***HCHCH***C***H-N-). MS (ASAP) 208 ([M+H]$^+$, 100%), 209 ([M+2H]$^+$, 27%). HRMS (ASAP) m/z calcd for [M]$^+$ $C_9H_6N_3O_2F$ 207.0444; found 207.0431. IR (neat, cm^{-1}) 3282, 2521, 1640, 1604, 1327, 1283.

2-Cyclopropyl-5-fluoropyrimidine-4,6-diol, 111e



2-Fluoro-1,3-dimethylmalonate **62** (0.60 g, 4.0 mmol) and cyclopropyl-carboxamidine hydrochloride (0.48 g, 4.0 mmol) gave *2-cyclopropyl-5-fluoropyrimidine-4,6-diol* (0.55 g, 81%) as a pale yellow powder; mp > 250 °C. ^{1}H NMR (700 MHz, *D_2O*) δ_H 1.57 – 1.49 (1H, m, -C-C***H***(CH$_2$)$_2$-), 0.67 – 0.66 (4H, m, -C-CH(C***H$_2$***)***$_2$***-), 0.65 – 0.64 (2H, m, -C-CH(C***H$_2$***)***$_2$***-). ^{19}F NMR (376 MHz, *D_2O*) δ_F -185.0 (s, -C(***F***)-). ^{13}C NMR (176 MHz, *D_2O*) δ_C 164.4 (d, *J* = 9.3 Hz, -***C***-CH(CH$_2$)$_2$-), 164.3 (d, *J* = 12.3 Hz, 2 x -***C***(OH)-), 135.3 (d, *J* = 223.1 Hz, -***C***(F)-), 16.37 (-C-CH(***C***H$_2$)$_2$-), 7.27 (-C-***C***H(CH$_2$)$_2$-). MS (ASAP) m/z 171 ([M+H]$^+$, 100%). HRMS (ASAP) calcd for [M]$^+$ $C_7H_8N_2O_2F$ 171.0570; found 171.0567. IR (neat, cm^{-1}) 2621, 1621, 1536, 1325, 1283, 1176.

5-Fluoro-2-(1H-1,2,4-triazol-1-yl)pyrimidine-4,6-diol, 111f



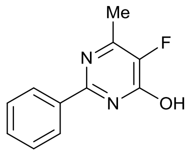
2-Fluoro-1,3-dimethylmalonate **62** (3.75 g, 25 mmol) and 1H-1,2,4-triazole-1-carboxamidine hydrochloride (3.69 g, 25 mmol) gave *5-fluoro-2-(1H-1,2,4-triazol-1-yl)pyrimidine-4,6-diol* (2.81 g, 57%) as a pale pink solid; mp > 250 ^{o}C. ^{1}H NMR (400 MHz, *D_2O*) δ_H 9.10 (1H, s, -N-C***H***-N-CH-N-), 8.26 (1H, s, -N-CH-N-C***H***-N-), 3.70-3.10 (2H, br s, 2 x O***H***). ^{19}F NMR (376 MHz, *DMSO-d^6*) δ_F -177.1 (s, -C(***F***)-). ^{13}C NMR (101 MHz, *DMSO-d^6)* δ_C 164.7 (d, *J* = 14.3 Hz, -***C***-N-CH-N-CH-N-), 151.7 (-N-CH-N-***C***H-N-), 151.3 (*J* = 29.8 Hz, 2 x -***C***(OH)-), 143.6 (-C-N-***C***H-N-CH-N-), 136.1 (d, *J* = 225.3 Hz, -***C***(F)-). MS (ASAP) m/z 197 ([M]$^+$, 21%), 198 ([M+H]$^+$, 100%). HRMS (ASAP) calcd for [M]$^+$ $C_6H_4N_5O_2F$ 197.0349; found 197.0341. IR (neat, cm^{-1}) 2981, 1561, 1508, 1445, 1116.

3.2. Synthesis of fluorinated pyrimidines from 2-fluoro-ethylacetoacetate

General Procedure

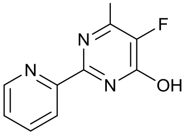
Sodium (0.92 g, 40 mmol) was dissolved in MeOH (100 mL) in a two-necked 250 mL flask and amidine hydrochloride and a solution of 2-fluoro-ethylacetoacetate **19** in acetonitrile (30 mL) were added. The resulting mixture was stirred at 80 ^{o}C for 16 h and cooled to r.t. before the addition of dilute aqueous HCl (4 mL, 6 M, 24 mmol). The mixture was filtered and the filtrate was concentrated *in vacuo* and washed with ethanol. The resulting solution was filtered, the filtrate was concentrated for a second time, washed with ethanol and filtered again to yield the desired fluorinated pyrimidine.

5-Fluoro-6-methyl-2-phenylpyrimidin-4-ol, 119d



2-Fluoro-ethylacetoacetate **19** (, 4.55 g, 30 mmol) and benzamidine hydrochloride (4.68 g, 30 mmol) gave *5-fluoro-6-methyl-2-phenylpyrimidin-4-ol* (5.51 g, 91%) as a white powder; mp 202 – 203 °C. ^{1}H NMR (400 MHz, D_2O) δ_H 7.87 – 7.82 (2H, m, 2 x $\boldsymbol{H}_{ortho}$), 7.46 – 7.40 (3H, m, 2 x $\boldsymbol{H}_{meta}$ + $\boldsymbol{H}_{para}$), 2.26 (3H, d, J = 3.0 Hz, -C$\boldsymbol{H}_3$). ^{19}F NMR (376 MHz, D_2O) δ_F -159.0 (q, J = 3.0 Hz, -C(***F***)-). ^{13}C NMR (101 MHz, D_2O) δ_C 165.3 (d, J = 14.3 Hz, -***C***(OH)-), 160.4 (d, J = 8.3 Hz, -***C***-C-(CH)$_5$-), 148.4 (d, J = 16.3 Hz, -***C***(CH$_3$)-), 146.8 (d, J = 247.5 Hz, -***C***(F)-), 137.8 (-C-***C***-(CH)$_5$-), 129.7 ($\boldsymbol{C}_{para}$), 128.4 ($\boldsymbol{C}_{meta}$), 127.8 ($\boldsymbol{C}_{ortho}$), 15.1 (-C(***C***H$_3$)-). MS (ASAP) m/z 204 ([M]$^+$, 15%), 205 ([M+H]$^+$, 100%), 206 ([M+2H]$^+$, 22%). HRMS (ASAP) m/z calcd for [M+H]$^+$ $C_{11}H_{10}N_2OF$ 205.0777; found 205.0782. IR (neat, cm^{-1}) 2962, 1652, 1614, 1543, 1313.

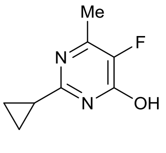
5-Fluoro-6-methyl-2-(pyridine-2-yl)pyrimidin-4-ol, 119c



2-Fluoro-ethylacetoacetate **19** (2.22 g, 15 mmol) and pyridine-2-carboxamidine hydrochloride (2.36 g, 15 mmol) gave *5-fluoro-6-methyl-2-(pyridine-2-yl)pyrimidin-4-ol* (2.81 g, 91%) as a dark yellow powder; mp 182 – 184 °C. ^{1}H NMR (400 MHz, D_2O) δ_H 8.45 (1H, ddd, J = 4.9, 1.7, 1.1 Hz, -C-CHCHCHC***H***-N-), 7.84 – 7.76 (2H, m, -C-C***H***C***H***CHCH-N-), 7.36 (1H, ddd, J = 6.4, 4.9, 2.6 Hz, -C-CHCHC***H***CH-N-), 2.20 (3H, d, J = 3.0 Hz, -C$\boldsymbol{H}_3$). ^{19}F NMR (376 MHz, D_2O) δ_F -157.1 (q, J = 3.0 Hz, -C(***F***)-). ^{13}C NMR (101 MHz, D_2O) δ_C 165.3 (d, J = 14.3 Hz, -***C***(OH)-), 158.3 (d, J = 8.5 Hz, -***C***-C-

CHCHC***HC***H-N-), 154.2 (-***C***-CHCHCHCH-N-), 148.7 (d, *J* = 14.1 Hz, -***C***(CH$_3$)-), 148.5 (-C-CHCHCH***C***H-N-), 147.4 (d, *J* = 220.2 Hz, -***C***(F)-), 138.0 (-C-CH***C***HCHCH-N-), 124.7 (-C-CHCH***C***HCH-N-), 123.3 (-C-***C***HCHCHCH-N-), 15.3 (-C(***C***H$_3$)-). MS (ASAP) m/z 206 ([M+H]$^+$, 100%), 207 ([M+2H]$^+$, 29%). HRMS (ASAP) m/z calcd for [M+H]$^+$ $C_{10}H_9N_3OF$ 206.0730; found 206.0730. IR (neat, cm^{-1}) 2981, 1665, 1615, 1459, 1426.

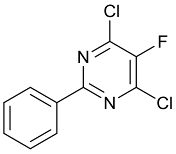
2-Cyclopropyl-5-fluoro-6-methylpyrimidin-4-ol, 119e



2-Fluoro-ethylacetoacetate **19** (0.74 g, 5.0 mmol) and cyclopropylcarboxamidine hydrochloride (0.60 g, 5.0 mmol) gave *2-cyclopropyl-5-fluoro-6-methylpyrimidin-4-ol* (0.82 g, 97%) as a white powder; mp > 250 °C. ^{1}H NMR (400 MHz, *D$_2$O*) δ_H 2.08 (3H, d, *J* = 3.0 Hz, -C(C***H$_3$***)-), 1.72 (1H, tt, *J* = 8.2, 5.0 Hz, -C-C***H***(CH$_2$)$_2$-), 0.84 – 0.69 (4H, m, -C-CH(C***H$_2$***)$_2$-). ^{19}F NMR (376 MHz, *D$_2$O*) δ_F -161.0 (q, *J* = 2.8 Hz, -C(***F***)-). ^{13}C NMR (176 MHz, *D$_2$O*) δ_C 166.1 (d, *J* = 8.0 Hz, -***C***-CH(CH$_2$)$_2$-), 165.3 (d, *J* = 14.3 Hz, -***C***(OH)-), 147.7 (d, *J* = 15.9 Hz, -***C***(CH$_3$)-), 146.1 (d, *J* = 243.8 Hz, -***C***(F)-), 16.5 (-C-***C***H(CH$_2$)$_2$-), 14.9 (d, *J* = 2.8 Hz, -C(***C***H$_3$)-), 8.0 (-C-CH(***C***H$_2$)$_2$-). MS (ASAP) m/z 169 ([M+H]$^+$, 100%). HRMS (ASAP) m/z calcd for [M+H]$^+$ $C_8H_{10}N_2OF$ 169.0777; found 169.0768. IR (neat, cm^{-1}) 2467, 1682, 1374, 1286, 1181.

3.3. Synthesis of chlorinated 5-fluoropyrimidines

4,6-Dichloro-5-fluoro-2-phenylpyrimidine, 104d



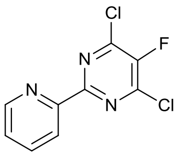
5-Fluoro-2-phenylpyrimidine-4,6-diol **111d** (0.41 g, 2.0 mmol) was added to a stirred solution of POCl$_3$ (4.60 g, 30 mmol) and *N*,*N*-dimethylaniline (0.24 g, 2.0 mmol) and heated at reflux temperature for 3 h. The reaction mixture was cooled to r.t. and added dropwise to a vigorously stirred bath of ice and brine. The mixture was filtered and the filtrate was extracted with EtOAc (3 x 30 mL), washed with brine (3 x 30 mL) and dried with anhydrous magnesium chloride. The solvent was evaporated under reduced pressure and the residue was recrystallised in water/acetone to yield *4,6-dichloro-5-fluoro-2-phenylpyrimidine* (0.15 g, 31%) as a yellow solid. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ_H 7.39 – 7.28 (2H, m, 2 x ***H$_{ortho}$***), 6.89 – 6.80 (3H, m, 2 x ***H$_{meta}$*** + ***H$_{para}$***). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ_F -129.9 (s). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ_C 159.8 (d, *J* = 10.1 Hz, -***C***-C-(CH)$_5$-), 148.5 (d, *J* = 18.1 Hz, -***C***(Cl)-), 148.4 (d, *J* = 271.7 Hz, -***C***(F)-), 134.3 (-***C***-(CH)$_5$-), 131.9 (***C$_{para}$***), 128.8 (***C$_{meta}$***), 128.7 (***C$_{ortho}$***). MS (ASAP) m/z 243

([M+H]$^+$, 100.0%), 242 ([M]$^+$, 36.1%). HRMS (ASAP) m/z calcd for [M$^+$] $C_{10}H_5N_2FCl_2$ 241.9814; found 241.9823.

General procedure for compounds 104c to 123e

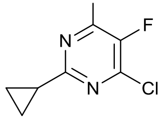
5-Fluoropyrimidine-4,6-diol or 5-fluoro-6-methylpyrimidin-4-ol (for amounts, see compound experimentals) was added to a solution of $POCl_3$ (10 – 20 eq.) and stirred at r.t. for 15 min under argon. The solution was then heated to 80 ^{o}C and triethylamine (1.1 eq. per -OH group) was added dropwise over 45 min. The reaction mixture was then stirred at 80 °C for a further 45 minutes before being cooled to rt and added slowly to a vigorously stirred bath of brine and ice. The mixture was filtered and the filtrate was extracted with EtOAc (3 x 30 mL), washed with brine (3 x 30 mL) and dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the resulting solid was purified by recrystallization in hexane/$CHCl_3$ to yield the desired chlorinated 5-fluoropyrimidine product.

4,6-Dichloro-5-fluoro-2-(pyridine-2-yl)pyrimidine, 104c



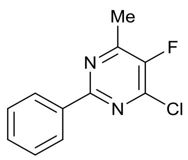
5-Fluoro-2-(pyridine-2-yl)pyrimidine-4,6-diol **111c** (1.45 g, 7.0 mmol), $POCl_3$ (9.8 mL, 16.10 g, 105 mmol), benzyltriethylammonium chloride (3.64 g, 16 mmol) and triethylamine (2.23 mL, 1.62 g, 16 mmol) gave *4,6-dichloro-5-fluoro-2-(pyridine-2-yl)pyrimidine* (0.46 g, 27%) as a yellow crystalline solid; mp 87 – 89 °C. ^{1}H NMR (400 MHz, *$CDCl_3$)* δ_H 8.83 (1H, ddd, *J* = 4.8, 1.8, 0.9 Hz, -C-CHCHCHC***H***-N-), 8.42 (1H, dt, *J* = 8.0, 1.1 Hz, -C-C***H***CHCHCH-N-), 7.85 (1H, td, *J* = 7.8, 1.8 Hz, -C-CHC***H***CHCH-N-), 7.43 (1H, ddd, *J* = 7.6, 4.8, 1.2 Hz, -C-CHCHC***H***CH-N-). ^{19}F NMR (376 MHz, *$CDCl_3$)* δ_F -126.9 (s, -C(***F***)-). ^{13}C NMR (101 MHz, *$CDCl_3$)* δ_C 158.3 (d, *J* = 9.9 Hz, -***C***-C-CHCHC***HC***H-N-), 151.5 (-***C***-CHCHCHCH-N-), 150.4 (-C-CHCHCH***C***H-N-), 149.5 (d, *J* = 276.7 Hz, -***C***(F)-), 149.2 (d, *J* = 18.0 Hz, -***C***(Cl)-), 137.2 (-C-CH***C***HCHCH-N-), 125.7 (-C-CHCH***C***HCH-N-), 124.2 (-C-***C***HCHCHCH-N-). MS (EI) m/z 243 ([M]$^+$, 100%), 208 ([M-Cl]$^+$, 84%), 78 ([C_6H_6]$^+$, 91%). HRMS (ASAP) m/z calcd for [M+H]$^+$ $C_9H_5N_3FCl_2$ 243.9845; found 243.9836. IR (neat, cm^{-1}) 3056, 1582, 1524, 1405, 1344, 995.

4,6-Dichloro-2-cyclopropyl-5-fluoropyrimidine, 104e



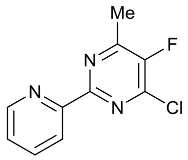
2-Cyclopropyl-5-fluoropyrimidine-4,6-diol **111e** (0.43 g, 2.5 mmol), $POCl_3$ (4.66 mL, 3.83 g, 50 mmol) and triethylamine (0.77 mL, 0.56 g, 5.5 mmol) gave *4,6-dichloro-2-cyclopropyl-5-fluoropyrimidine* as a white crystalline solid (0.19 g, 37%); mp 37 – 38 ^{o}C. ^{1}H NMR (400 MHz, *$CDCl_3$*) δ_H 2.21 – 2.18 (1H, m, -C-C***H***(CH$_2$)$_2$-), 1.19 – 1.08 (4H, m, -C-CH(C***H***$_2$)$_2$-). ^{19}F NMR (376 MHz, *$CDCl_3$*) δ_F -132.6 (s, -C(***F***)-). ^{13}C NMR (101 MHz, *$CDCl_3$*) δ_C 167.9 (d, *J* = 9.6 Hz, -***C***-CH(CH$_2$)$_2$-), 147.9 (d, *J* = 17.6 Hz, -***C***(Cl)-), 147.8 (d, *J* = 267.7 Hz, -***C***(F)-) 17.7 (-C-***C***H(CH$_2$)$_2$-), 11.9 (-C-CH(***C***H$_2$)$_2$-). MS (EI) m/z 206 ([M]$^+$, 23%), 170 ([M-HCl]$^+$, 11%). HRMS (ESI) m/z calcd for [M+H]$^+$ $C_7H_6N_2FCl_2$ 206.9892; found 206.9887. IR (neat, cm^{-1}) 3012, 1524, 1437, 1376, 1337, 932, 813.

4-Chloro-5-fluoro-6-methyl-2-phenylpyrimidine, 123d



5-Fluoro-4-hydroxy-6-methyl-2-phenylpyrimidine **119d** (2.04 g, 10 mmol), $POCl_3$ (14.0 mL, 23.00 g, 150 mmol) and triethylamine (1.47 mL, 1.06 g, 10.5 mmol) yielded *4-chloro-5-fluoro-6-methyl-2-phenylpyrimidine* (1.25 g, 56%) as a white crystalline solid; mp 78 – 79 ^{o}C. R$_f$ (19:1, hexane:EtOAc) 0.80. ^{1}H NMR (400 MHz, *$CDCl_3$*) δ_H 8.44 – 8.34 (2H, m, 2 x ***H$_{ortho}$***), 7.55 – 7.44 (3H, m, 2 x ***H$_{meta}$*** + ***H$_{para}$***), 2.63 (3H, d, *J* = 2.7 Hz, -C(C***H***$_3$)-). ^{19}F NMR (376 MHz, *$CDCl_3$*) δ_F -136.2 (q, *J* = 2.7 Hz, -C(***F***)-). ^{13}C NMR (101 MHz, *$CDCl_3$*) δ_C 159.5 (d, *J* = 9.3 Hz, -***C***-C-(CH)$_5$-), 155.9 (d, *J* = 15.5 Hz, -***C***(Cl)-), 151.1 (d, *J* = 265.4, -***C***(F)-), 147.2 (d, *J* = 18.3 Hz, -***C***(CH$_3$)-), 135.7 (-***C***-(CH)$_5$-), 131.0 (***C$_{para}$***), 128.6 (***C$_{meta}$***), 128.3 (***C$_{ortho}$***), 18.1 (d, *J* = 1.6 Hz, -C(***C***H$_3$)-). MS (EI) m/z 222 ([M]$^+$, 87%), 187 ([M-Cl]$^+$, 100%). HRMS (ASAP) m/z calcd for [M+H]$^+$ $C_{11}H_9N_2FCl$ 223.0438; found 223.0422. IR (neat, cm^{-1}) 1574, 1549, 1397, 1341, 1187, 849, 745. Single crystals for X-ray diffraction were grown by slow evaporation from acetone.

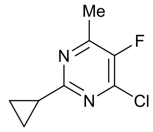
4-Chloro-5-fluoro-6-methyl-2-(pyridin-2-yl)pyrimidine, 123c



5-Fluoro-6-hydroxy-4-methyl-2-(pyridin-2-yl)pyrimidine **119c** (2.05 g, 10 mmol), $POCl_3$ (9.32 mL, 15.33 g, 100 mmol) and triethylamine (1.53 mL, 1.11 g, 11.0 mmol) gave *4-chloro-5-fluoro-6-methyl-2-(pyridin-2-yl)pyrimidine* (0.10 g, 5%) as a white crystalline solid; mp 93 – 94 °C. ^{1}H NMR (400 MHz, *$CDCl_3$*) δ_H 8.86 (1H, ddd, *J* = 4.8, 1.8, 0.9 Hz, -C-CHCHCHC***H***-N-), 8.47 (1H, dt, *J* = 8.0, 1.1 Hz, -C-C***H***CHCHCH-N-), 7.87 (1H, td, *J* = 7.8, 1.8 Hz, -C-CHC***H***CHCH-N-), 7.43 (1H, ddd, *J* = 7.6, 4.8, 1.2 Hz, -C-CHCHC***H***CH-N-), 2.71 (3H, d, *J* = 2.8 Hz, -C(C***H***$_3$)-). ^{19}F NMR (376 MHz, *$CDCl_3$*) δ_F -133.1 (q, *J* = 2.8 Hz, -C(***F***)-). ^{13}C NMR (101 MHz, *$CDCl_3$*) δ_C 158.2 (d, *J* = 9.2 Hz, -***C***-C-CHCHC***HC***H-N-), 156.6 (d, *J* = 15.9 Hz, -***C***(Cl)-), 152.8 (-***C***-CHCHCHCH-N-), 151.9 (d, *J* = 268.7 Hz, -***C***(F)-), 150.2 (-C-CHCHCH***C***H-N-), 147.7 (d, *J* = 18.5 Hz, -***C***(CH$_3$)-), 137.0 (-C-CH***C***HCHCH-N-), 125.0 (-C-CHCH***C***HCH-N-), 123.8 (-C-

CHCHCHCH-N-), 18.2 (d, *J* = 1.5 Hz, -C(***C***H$_3$)-). MS (ASAP) m/z 224 ([M]$^+$, 100%). HRMS (ASAP) m/z calcd for $C_{10}H_8N_3FCl$ [M+H]$^+$ 224.0391; found 224.0374. IR (neat, cm^{-1}) 3061, 1552, 1408, 1342, 758. Single crystals suitable for X-ray diffraction were grown by slow evaporation from acetone.

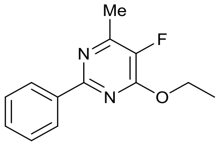
4-Chloro-2-cyclopropyl-5-fluoro-6-methylpyrimidine, 123e



2-Cyclopropyl-5-fluoro-6-hydroxy-4-methylpyrimidine **119e** (0.48 g, 2.8 mmol), POCl$_3$ (3.73 mL, 6.13 g, 40 mmol) and triethylamine (0.42 mL, 0.30 g, 3.0 mmol) gave *4-chloro-2-cyclopropyl-5-fluoro-6-methylpyrimidine* (0.22 g, 41 %) as a white crystalline solid; mp 38 – 39 °C. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ$_H$ 2.48 (3H, d, *J* = 2.7 Hz, -C***H$_3$***), 2.18 (1H, tt, *J* = 8.0, 4.9 Hz, -C***H***(CH$_2$)$_2$-), 1.12 – 1.08 (2H, m, -CH(C***H$_2$***)$_2$-), 1.07 – 1.02 (2H, m, -CH(C***H$_2$***)$_2$-). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ$_F$ -138.9 (q, *J* = 2.7 Hz, -C(***F***)-). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ$_C$ 167.1 (d, *J* = 9.1 Hz, -***C***-CH(CH$_2$)$_2$-), 155.3 (d, *J* = 15.3 Hz, -***C***(Cl)-), 150.5 (d, *J* = 261.6 Hz, -***C***(F)-), 146.7 (d, *J* = 18.0 Hz, -***C***(CH$_3$)-), 17.9 (d, *J* = 1.5 Hz, -***C***H(CH$_2$)$_2$-), 17.5 (d, *J* = 1.6, -C(***C***H$_3$)-), 11.0 (-CH(***C***H$_2$)$_2$-). MS (ASAP) *m/z* 187 ([M+H]$^+$, 100%). HRMS (ASAP) *m/z* calcd for $C_8H_9N_2FCl$ [M+H]$^+$ 187.0438; found 187.0434. IR (neat, cm^{-1}) 3010, 1547, 1440, 1379, 1183, 1028, 894.

3.4. Nucleophilic substitution of chlorinated 5-fluoropyrimidines

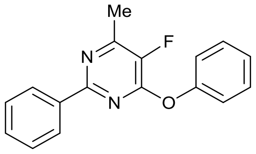
4-Ethoxy-5-fluoro-6-methyl-2-phenylpyrimidine, 124a



K$_2$CO$_3$ (0.28 g, 2.0 mmol) was added to a solution of 4-chloro-5-fluoro-6-methyl-2-phenylpyrimidine **123d** (0.11 g, 0.5 mmol) and ethanol (20 mL) and stirred at reflux for 19 h. Completion of the reaction was checked by GC analysis. The solvent was removed *in vacuo*, the residue was dissolved in 5% sodium bicarbonate solution (30 mL) and extracted with DCM (5 x 20 mL). The organic phase was washed with brine (3 x 20 mL), dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure to yield *4-ethoxy-5-fluoro-6-methyl-2-phenylpyrimidine* (0.88 g, 76%) as a white crystalline solid; mp 42–44 °C. ^{1}H NMR (700 MHz, *CDCl$_3$*) δ$_H$ 8.38 – 8.32 (2H, m, 2 x ***H$_{ortho}$***), 7.48 – 7.41 (3H, m, 2 x ***H$_{meta}$*** + ***H$_{para}$***), 4.61 (2H, q, *J* = 7.1 Hz, -OC***H$_2$***CH$_3$), 2.50 (3H, d, *J* = 3.0 Hz, -C(C***H$_3$***)-), 1.49 (3H, t, *J* = 7.1 Hz, -OCH$_2$C***H$_3$***). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ$_F$ -158.2 (q, *J* = 3.0 Hz, -C(***F***)-). ^{13}C NMR (176 MHz, *CDCl$_3$*) δ$_C$ 157.7 (d, *J* = 9.4 Hz, -***C***-C-(CH)$_5$-), 157.5 (d, *J* = 10.6 Hz, -***C***(OEt)-), 152.4 (d, *J* = 12.8 Hz, -***C***(CH$_3$)-), 143.6 (d, *J* = 260.5 Hz, -***C***(F)-), 137.1 (-***C***-(CH)$_5$-), 130.1

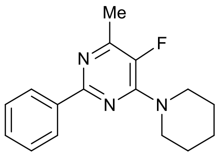
(***C**para*), 128.3 (***C**meta*) , 128.0 (***C**ortho*), 63.0 (-O**C**H_2CH_3), 17.3 (-C(**C**H_3)-), 14.4 (-OCH_2**C**H_3). MS (EI) m/z 232 ($[M]^+$, 62%), 217 ($[M-CH_3]^+$, 100%), 204 ($[M-CHCH_3]^+$, 80%), 77 ($[C_6H_5]^+$, 23%). HRMS (ASAP) m/z calcd for $[M+H]^+$ $C_{13}H_{14}N_2OF$ 233.1090; found 233.1096. IR (neat, cm^{-1}) 2990, 1602, 1578, 1451, 1384, 1349, 1216, 1079.

5-Fluoro-4-methyl-6-phenoxy-2-phenylpyrimidine, 124b



4-Chloro-5-fluoro-6-methyl-2-phenylpyrimidine **123d** (0.11 g, 0.5 mmol) was heated in acetonitrile (25 mL) at 75 °C for 16 h in the presence of phenol (0.28 g, 3.0 mmol) and Cs_2CO_3 (1.95 g, 6.0 mmol). The reaction was monitored by GC analysis and, after it had progressed to completion, the solvent was removed under reduced pressure. The resulting residue was dissolved in DCM (20 mL) and washed with 10% NaOH (3 x 20 mL), brine (3 x 20 mL) and dried with anhydrous magnesium sulfate. After filtration, removal of the solvent *in vacuo* and recrystallization in hexane/$CHCl_3$ yielded *5-fluoro-4-methyl-6-phenoxy-2-phenylpyrimidine* (0.061 g, 44%) as a white crystalline solid; mp 118–120 °C. ^1H NMR (400 MHz, *$CDCl_3$*) δ_H 8.20 – 8.12 (2H, m, 2 x ***H**ortho*), 7.56 – 7.24 (8H, m, ***H**aromatic*), 2.62 (3H, d, *J* = 2.9 Hz, -C(C***H₃***)-). ^{19}F NMR (376 MHz, *$CDCl_3$*) δ_F -156.5 (q, *J* = 2.9 Hz, -C(***F***)-). ^{13}C NMR (101 MHz, *$CDCl_3$*) δ_C 157.8 (d, *J* = 9.7 Hz, -**C**-C-$(CH)_5$-), 156.9 (d, *J* = 10.7 Hz, -**C**(OPh)-), 154.6 (d, *J* = 13.0 Hz, -**C**(CH_3)-), 152.2 (-O-**C**-$(CH)_5$-), 143.6 (d, *J* = 262.6 Hz, -**C**(F)-), 136.5 (-C-**C**-$(CH)_5$-), 130.4 (***C**para*), 129.4 (***C**meta*(phenol)), 128.4 (***C**meta*), 128.0 (***C**ortho*), 125.5 (***C**para*(phenol)), 121.6 (s, ***C**ortho*(phenol)), 17.6 (-C(**C**H_3)-). MS (ASAP) m/z 281 ($[M+H]^+$, 100%). HRMS (ASAP) m/z calcd for $[M+H]^+$ $C_{17}H_{14}N_2OF$ 281.1090; found 281.1085. IR (neat, cm^{-1}) 2963, 1575, 1428, 1387, 1220, 1196, 1024. Single crystals suitable for X-ray diffraction were grown by slow evaporation from acetone.

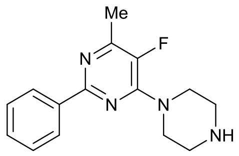
5-Fluoro-4-methyl-2-phenyl-6-(piperidin-1-yl)pyrimidine, 124c



Piperidine (0.13 g, 0.15 mL, 1.5 mmol) was added to a solution of 4-chloro-5-fluoro-6-methyl-2-phenylpyrimidine **123d** (0.11 g, 0.5 mmol) and Cs_2CO_3 (0.49 g, 1.5 mmol) in DMF (15 mL) and stirred at 50 °C for 16 h. The reaction mixture was quenched with dilute aqueous HCl (1M, 3 mL), diluted with water (100 mL) and extracted with diethyl ether (5 x 20 mL). The organic fractions were combined, washed with brine (3 x 30 mL) and dried with anhydrous magnesium sulfate. After filtration, the solvent of the filtrate was removed under reduced pressure to yield *5-fluoro-4-methyl-2-*

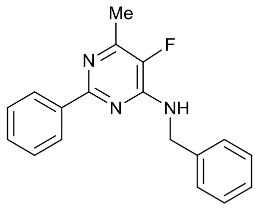
phenyl-6-(piperidin-1-yl)pyrimidine (0.097 g, 71%) as a white crystalline solid; mp 84 – 86 °C. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ_H 8.39 – 8.27 (2H, m, 2 x $\boldsymbol{H_{ortho}}$), 7.53 – 7.36 (3H, m, 2 x $\boldsymbol{H_{meta}}$ + $\boldsymbol{H_{para}}$), 3.84 – 3.78 (4H, m, -NC$\boldsymbol{H_2}$(CH$_2$)$_3$C$\boldsymbol{H_2}$-), 2.46 (3H, d, *J* = 3.7 Hz, -C(C$\boldsymbol{H_3}$)-), 1.77 – 1.67 (6H, m, -NCH$_2$(C$\boldsymbol{H_2}$)$_3$CH$_2$-). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ_F -148.2 (q, *J* = 3.7 Hz, -C(***F***)-). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ_C 157.8 (d, *J* = 8.1 Hz, -***C***-C-(CH)$_5$-), 151.7 (d, *J* = 17.4 Hz, -***C***(N-)-), 151.3 (d, *J* = 5.7 Hz, -***C***(CH$_3$)-), 144.3 (d, *J* = 255.8 Hz, -***C***(F)-), 138.0 (-***C***-(CH)$_5$-), 129.6 ($\boldsymbol{C_{para}}$), 128.2 ($\boldsymbol{C_{meta}}$), 128.0 ($\boldsymbol{C_{ortho}}$), 47.5 (d, *J* = 7.7 Hz, -N***C***H$_2$CH$_2$CH$_2$CH$_2$***C***H$_2$-), 26.0 (-NCH$_2$***C***H$_2$CH$_2$***C***H$_2$CH$_2$-), 24.9 (-NCH$_2$CH$_2$***C***H$_2$CH$_2$CH$_2$-), 17.5 (d, *J* = 1.2 Hz, -C(***C***H$_3$)-). MS (EI) m/z 271 ([M]$^+$, 100%), 84 ([C$_5$H$_{10}$N]$^+$, 62%). HRMS (ASAP) m/z calcd for [M+H]$^+$ $C_{16}H_{19}N_3F$ 272.1563; found 272.1550. IR (neat, cm^{-1}) 2930, 2849, 1597, 1405, 1211, 751, 697. Single crystals suitable for X-ray diffraction were grown by slow evaporation from acetone.

5-Fluoro-4-methyl-2-phenyl-6-(piperazin-1-yl)pyrimidine, 124d



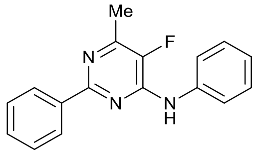
4-Chloro-5-fluoro-6-methyl-2-phenylpyrimidine **123d** (0.011 g, 0.5 mmol) was added to a boiling solution of piperazine (0.22 g, 2.5 mmol) in ethanol (20 mL) and stirred under reflux conditions for 16 h. After the reaction had progressed to completion by monitoring of LC-MS spectra, the reaction mixture was allowed to cool and the solvent was removed under reduced pressure. The residue was suspended in water and extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL) and dried with anhydrous magnesium sulfate, before evaporation of the filtrate under reduced pressure yielded *5-fluoro-4-methyl-2-phenyl-6-(piperazin-1-yl)pyrimidine* (0.12 g, 91%) as a white solid; mp 89 – 90 °C. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ_H 8.35 – 8.25 (2H, m, 2 x $\boldsymbol{H_{ortho}}$), 7.46 – 7.36 (3H, m, 2 x $\boldsymbol{H_{meta}}$ + $\boldsymbol{H_{para}}$), 3.86 – 3.72 (4H, m, 2 x –NC$\boldsymbol{H_2}$CH$_2$N(H)CH$_2$C$\boldsymbol{H_2}$-), 3.00 – 2.94 (4H, m, 2 x -NCH$_2$C$\boldsymbol{H_2}$N(H)C$\boldsymbol{H_2}$CH$_2$-), 2.43 (3H, d, *J* = 3.6 Hz, -C(C$\boldsymbol{H_3}$)-), 1.82 (1H, s, NH). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ_F -148.3 (q, *J* = 3.6 Hz, -C(***F***)-). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ_C 157.8 (d, *J* = 8.2 Hz, -***C***-C-(CH)$_5$-), 152.1 (d, *J* = 17.2 Hz, -***C***(N-)-), 151.2 (d, *J* = 5.3 Hz, -***C***(CH$_3$)-), 144.3 (d, *J* = 256.1 Hz, -***C***(F)-), 137.9 (-***C***-(CH)$_5$-), 129.7 ($\boldsymbol{C_{para}}$), 128.2 ($\boldsymbol{C_{meta}}$), 128.0 ($\boldsymbol{C_{ortho}}$), 47.5 (d, *J* = 7.5 Hz, -N***C***H$_2$CH$_2$N(H)CH$_2$***C***H$_2$-), 46.2 (-NCH$_2$***C***H$_2$N(H)***C***H$_2$CH$_2$-)), 17.5 (-C(***C***H$_3$)-). MS (ASAP) m/z 273 ([M+H]$^+$, 100%), 230 ([M-C$_2$H$_4$N]$^+$, 4%). HRMS (ASAP) m/z calcd for [M+H]$^+$ $C_{15}H_{18}N_4F$ 273.1516; found 273.1523. IR (neat, cm^{-1}) 3198, 2846, 1596, 1576, 1487, 1212, 746, 692.

N-Benzyl-5-Fluoro-6-methyl-2-phenylpyrimidin-4-amine, 124e



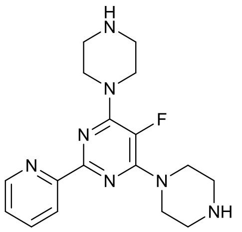
A solution of benzylamine (0.27 g, 0.28 mL, 2.5 mmol), 4-chloro-5-fluoro-6-methyl-2-phenylpyrimidine **123d** (0.11 g, 0.5 mmol) and triethylamine (.25 g, 0.35 mL, 2.5 mmol) in acetonitrile (10 mL) was stirred for 16 h at room temperature. The reaction mixture was monitored by LC-MS analysis and, on completion, the solvent was removed in vacuo prior to dissolution of the residue in ethyl acetate (20 mL). The organic phase was washed with water (3 x 20 mL) and brine (3 x 20 mL) and dried with anhydrous magnesium sulfate. Following filtration, the solvent was removed under reduced pressure and the crude product was recrystallised in hexane/CHCl$_3$ to yield *N-benzyl-5-fluoro-6-methyl-2-phenylpyrimidin-4-amine* (0.12 g, 84%) as a brown crystalline solid; mp 90 – 91 °C. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ_H 8.42 – 8.32 (2H, m, 2 x $\boldsymbol{H_{ortho}}$), 7.51 – 7.27 (8H, m, $\boldsymbol{H_{aromatic}}$), 5.29 (1H, t, *J* = 5.8 Hz, NH), 4.83 (2H, d, *J* = 5.8 Hz, -N(H)C$\boldsymbol{H_2}$-), 2.45 (d, *J* = 2.9 Hz, -C(C$\boldsymbol{H_3}$)-). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ_F -161.1 (q, *J* = 2.9 Hz, -C(***F***)-). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ_C 158.5 (d, *J* = 8.8 Hz, -***C***-C-(CH)$_5$-), 151.6 (d, *J* = 11.5 Hz, -***C***(N(H)-)-), 148.2 (d, *J* = 12.3 Hz, -***C***(CH$_3$)-), 143.4 (d, *J* = 253.5 Hz, -***C***(F)-), 138.7 (-N(H)CH$_2$-***C***-), 137.9 (-***C***-(CH)$_5$-), 129.8 ($\boldsymbol{C_{para}}$), 128.8 ($\boldsymbol{C_{meta}}$(benzyl)), 128.3 ($\boldsymbol{C_{meta}}$), 128.0 ($\boldsymbol{C_{ortho}}$), 127.9 ($\boldsymbol{C_{ortho}}$(benzyl)), 127.6 ($\boldsymbol{C_{para}}$(benzyl)), 44.6 (-N(H)***C***H$_2$-), 17.0 (-C(***C***H$_3$)-). MS (ESI) m/z 294 ([M+H]$^+$, 100%), 124 ([C$_7$H$_7$NF]$^+$, 32%). HRMS (ESI) m/z calcd for [M+H]$^+$ C$_{18}$H$_{17}$N$_3$F 294.1407; found 294.1409. IR (neat, cm^{-1}) 3419, 2928, 1210, 1386, 750, 693.

5-Fluoro-6-methyl-N,2-diphenylpyrimidin-4-amine, 124f



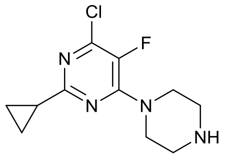
Aniline (0.27 g, 0.27 mL, 3.0 mmol) was added to a solution of 4-chloro-5-fluoro-6-methyl-2-phenylpyrimidine **123d** (0.11 g, 0.5 mmol) in ethanol (15 mL) and stirred at reflux for 30 h. The reaction was monitored by LC-MS analysis and, upon completion, the mixture was cooled to r.t. and the solvent was removed under reduced pressure. The residue was suspended in water and extracted with dichloromethane (3 x 15 mL). The combined organic fractions were washed with dilute aqueous HCl (1M, 3 x 20 mL), brine (3 x 20 mL) and dried with anhydrous magnesium sulfate. After filtration, the organic phase of the filtrate was removed *in vacuo* and the crude product was recrystallised in hexane/CHCl$_3$ to yield *5-fluoro-6-methyl-N,2-diphenylpyrimidin-4-amine* (0.10 g, 69%) as a white crystalline solid; mp 154 – 155°C. ^{1}H NMR (700 MHz, *CDCl$_3$*) δ_H 8.37 (2H, dt, *J* = 6.0, 1.5 Hz, 2 x $\boldsymbol{H_{ortho}}$), 7.80 – 7.76 (2H, m, 2 x $\boldsymbol{H}_{\boldsymbol{ortho}}$(aniline)), 7.50 – 7.43 (3H, m, 2 x $\boldsymbol{H}_{\boldsymbol{meta}}$ + $\boldsymbol{H}_{\boldsymbol{para}}$), 7.45 – 7.40 (2H, m, 2 x $\boldsymbol{H}_{\boldsymbol{meta}}$(aniline)), 7.15 (1H, tt, *J* = 7.7, 2.8 Hz, $\boldsymbol{H}_{\boldsymbol{para}}$(aniline)), 6.86 (1H, br s, NH), 2.52 (3H, d, *J* = 2.8 Hz, -C(C$\boldsymbol{H_3}$)-). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ_F -158.6 (s, -C(***F***)-). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ_C 158.4 (d, *J* = 9.2 Hz, -***C***-C-$(CH)_5$-), 149.4 (d, *J* = 13.1 Hz, -***C***(N(H)-)-), 149.1 (d, *J* = 9.4 Hz, -***C***(CH_3)-), 143.0 (d, *J* = 256.1 Hz, -***C***(F)-), 138.3 (-N(H)-***C***-), 137.5 (-***C***-$(CH)_5$-), 130.1 ($\boldsymbol{C}_{\boldsymbol{para}}$), 129.0 ($\boldsymbol{C}_{\boldsymbol{meta}}$(aniline)), 128.4 ($\boldsymbol{C}_{\boldsymbol{meta}}$), 128.1 ($\boldsymbol{C}_{\boldsymbol{ortho}}$), 123.6 ($\boldsymbol{C}_{\boldsymbol{para}}$(aniline)), 120.1 ($\boldsymbol{C}_{\boldsymbol{ortho}}$(aniline)), 17.2 (-C(***C***H_3)-). MS (ESI) m/z 280 ([M+H]$^+$, 100%). HRMS (ESI) m/z calcd for [M+H]$^+$ $C_{17}H_{15}N_3F$ 280.1250; found 280.1249. IR (neat, cm^{-1}) 3386, 1576, 1451, 1386, 752, 697. Single crystals suitable for X-ray diffraction were grown by slow evaporation from DCM.

5-Fluoro-4,6-bis(piperazin-1-yl)-2-(pyridin-2-yl)pyrimidine, 125



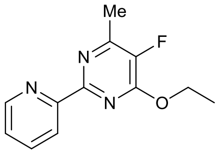
4,6-Dichloro-5-fluoro-2-(pyridin-2-yl)pyrimidine **104d** (0.24 g, 1.0 mmol) was added to a boiling solution of piperazine (0.44 g, 5.0 mmol) in ethanol (30 mL) and stirred under reflux conditions for 72 h after which the reaction was complete, confirmed by ^{19}F NMR spectral analysis. The reaction mixture was allowed to cool and the solvent was removed under reduced pressure. The residue was suspended in water and extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL) and dried with anhydrous magnesium sulfate, before evaporation of the filtrate under reduced pressure to yield *5-fluoro-4,6-bis(piperazin-1-yl)-2-(pyridin-2-yl)pyrimidine* (0.25 g, 74%) as a waxy yellow solid; mp > 250 °C. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ_H 8.71 – 8.61 (1H, m, -C-CHCHCHC***H***-N-), 8.29 – 8.12 (1H, m, -C-C***H***CHCHCH-N-), 7.73 – 7.57 (1H, m, -C-CHC***H***CHCH-N-), 7.32 – 7.16 (1H, m, -C-CHCHC***H***CH-N-), 3.74 – 3.51 (8H, m, 2 x –NC$\boldsymbol{H_2}$$CH_2N(H)CH_2C\boldsymbol{H_2}$-), 2.99 – 2.84 (8H, m, 2 x –NCH_2C$\boldsymbol{H_2}$N(H)C$\boldsymbol{H_2}$$CH_2$-), 1.84 (2H, s, NH). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ_F -156.3 (s, -C(***F***)-). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ_C 155.7 (d, *J* = 8.1 Hz, -***C***-C-CHCHCHCH-N-), 155.6 (-C-CHCHCH***C***H-N-), 153.0 (d, *J* = 7.0 Hz, -***C***(N-)-), 152.8 (d, *J* = 7.1 Hz, -***C***(N-)-), 149.6 (-***C***-CHCHCHCH-N-), 136.4 (-C-CH***C***HCHCH-N-), 134.9 (d, *J* = 254.5 Hz, -***C***(F)-), 123.8 (-C-CHCH***C***HCH-N-), 123.6 (-C-***C***HCHCHCH-N-), 51.7 (-N***C***$H_2CH_2N(H)CH_2$***C***H_2-), 48.2 (d, *J* = 6.7 Hz, -N***C***$H_2CH_2N(H)CH_2$***C***H_2-), 47.0 (-NCH_2***C***H_2N(H)***C***H_2CH_2-), 46.2 (-NCH_2***C***H_2N(H)***C***H_2CH_2-). MS (ASAP) m/z 344 ([M+H]$^+$, 100%). HRMS (ASAP) m/z calcd for [M+H]$^+$ $C_{17}H_{23}N_7F$ 344.1999; found 344.1990. IR (neat, cm^{-1}) 3275, 2835, 1580, 1444, 1390, 1001, 735.

4-Chloro-2-cyclopropyl-5-fluoro-6-(piperazin-1-yl)pyrimidine, 126



4,6-Dichloro-2-cyclopropyl-5-fluoropyrimidine **104e** (0.075 g, 0.36 mmol) was added to a boiling solution of piperazine (0.22 g, 2.5 mmol) in ethanol (20 mL) and stirred under reflux conditions for 16 h. The reaction mixture was allowed to cool and the solvent was removed under reduced pressure. The residue was suspended in water and extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL) and dried with anhydrous magnesium sulfate, before evaporation of the filtrate under reduced pressure. The crude product was purified by column chromatography on silica gel using a gradient of dichloromethane/methanol (0–6% methanol) as the eluent to yield *4-chloro-2-cyclopropyl-5-fluoro-6-(piperazin-1-yl)pyrimidine* (0.066 g, 71%) as a white solid; mp 89 – 90 °C. R$_f$ (19:1, DCM:MeOH) 0.35. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ$_H$ 3.83 – 3.64 (4H, m, 2 x –NC***H***$_2$CH$_2$N(H)CH$_2$C***H***$_2$-), 3.02 – 2.85 (4H, m, 2 x –NCH$_2$C***H***$_2$N(H)C***H***$_2$CH$_2$-), 2.00 (1H, tt, *J* = 8.0, 5.0 Hz, -C***H***(CH$_2$)$_2$-), 1.77 (1H, br s, NH), 0.98 (2H, dt, *J* = 5.0, 2.7 Hz, -CH(C***H***$_2$)$_2$-), 0.94 (2H, dt, *J* = 8.0, 2.7 Hz, -CH(C***H***$_2$)$_2$-). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ$_F$ -146.1 (s, -C(***F***)-). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ$_C$ 165.5 (d, *J* = 8.6 Hz, -***C***-CH(CH$_2$)$_2$-), 151.7 (d, *J* = 4.6 Hz, -***C***(Cl)-), 145.6 (d, *J* =18.8 Hz, -***C***(N-)-), 139.7 (d, *J* = 258.0 Hz, -***C***(F)-), 47.4 (d, *J* = 7.5 Hz, -N***C***H$_2$CH$_2$N(H)CH$_2$***C***H$_2$-), 46.1 (-NCH$_2$***C***H$_2$N(H)***C***H$_2$CH$_2$-), 17.5 (d, *J* = 1.6 Hz, -***C***H(CH$_2$)$_2$-), 10.2 (-CH(***C***H$_2$)$_2$-). MS (ASAP) m/z 257 ([M+H]$^+$, 100%). HRMS (ASAP) m/z calcd for [M+H]$^+$ $C_{11}H_{15}N_4FCl$ 257.0969; found 257.0963. IR (neat, cm^{-1}) 3312, 2916, 1575, 1435, 1227, 990, 792. Single crystals suitable for X-ray diffraction were grown by slow evaporation from toluene.

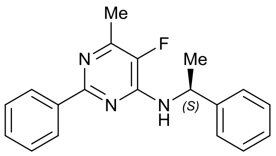
4-Ethoxy-5-fluoro-6-methyl-2-(pyridin-2-yl)pyrimidine, 127



4-Chloro-5-fluoro-6-methyl-2-(pyridin-2-yl)pyrimidine **123c** (0.067 g, 0.30 mmol) was added to a boiling solution of piperazine (0.13 g, 1.5 mmol) in ethanol (15 mL) and stirred under reflux conditions for 72 h, after which Cs_2CO_3 (0.49 g, 1.5 mmol) was added. The reaction mixture was stirred for a further 24 h followed by cooling to rt and removal of the solvent under reduced pressure. The residue was suspended in water and extracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine (3 x 20 mL) and dried with anhydrous magnesium sulfate, before evaporation of the filtrate under reduced pressure yielded *4-ethoxy-5-fluoro-6-methyl-2-(pyridin-2-yl)pyrimidine* (0.031 g, 38%) as a white solid; mp 76 – 77 °C.

^{1}H NMR (400 MHz, *$CDCl_3$*) δ_H 8.80 (1H, ddd, *J* = 4.8, 1.8, 0.9 Hz, -C-CHCHCHC***H***-N-), 8.36 (1H, dt, *J* = 7.9, 1.1 Hz, -C-C***H***CHCHCH-N-), 7.80 (1H, td, *J* = 7.9, 1.8 Hz, -C-CHC***H***CHCH-N-), 7.35 (1H, ddd, *J* = 7.6, 4.8, 1.1 Hz, -C-CHCHC***H***CH-N-), 4.63 (2H, q, *J* = 7.1 Hz, -OC$\boldsymbol{H_2}$$CH_3$), 2.58 (3H, d, *J* = 3.0 Hz, -C(C$\boldsymbol{H_3}$)-), 1.48 (3H, t, *J* = 7.1 Hz, -OCH_2C$\boldsymbol{H_3}$). ^{19}F NMR (376 MHz, *$CDCl_3$*) δ_F -155.3 (q, *J* = 3.1 Hz, -C(***F***)-). ^{13}C NMR (101 MHz, *$CDCl_3$*) δ_C 157.8 (d, *J* = 10.9 Hz, -***C***(OEt)-), 156.7 (d, *J* = 9.4 Hz, -***C***-C-CHCHCH***C***H-N-), 154.2 (-***C***-CHCHCHCH-N-), 153.4 (d, *J* = 13.2 Hz, -***C***(CH_3)-), 150.0 (-C-CHCHCH***C***H-N-), 144.4 (d, *J* = 262.6 Hz, -***C***(F)-), 136.8 (-C-CH***C***HCHCH-N-), 124.4 (-C-CHCH***C***HCH-N-), 123.5 (-C-***C***HCHCHCH-N-), 63.3 (-O***C***H_2CH_3), 17.5 (-C(***C***H_3)-), 14.4 (-OCH_2***C***H_3). MS (ASAP) m/z 234 ($[M+H]^+$, 100%). HRMS (ASAP) m/z calcd for $[M+H]^+$ $C_{12}H_{13}N_3OF$ 234.1043; found 234.1045. IR (neat, cm^{-1}) 2978, 1602, 1454, 1384, 1349.

5-Fluoro-6-methyl-N-[(1*S*)-1-phenylethyl]-2-phenylpyrimidin-4-amine, 128



4-Chloro-5-fluoro-6-methyl-2-phenylpyrimidine **123d** (0.11 g, 0.5 mmol) was added to a solution of (*S*)-(-)-1-phenylethylamine (0.30 g, 2.5 mmol) in acetonitrile (15 mL) and stirred at 80 ^oC for 24 h. Following the addition of triethylamine (0.14 mL, 1.0 mmol), the solution was stirred at 80 ^oC for a further 12 h before cooling to r.t. and removal of the solvent *in vacuo.* The resulting residue was dissolved in EtOAc and washed with water (3 x 25 mL), dilute aqueous HCl (1M, 2 x 20 mL), brine (3 x 25 mL) and dried with anhydrous magnesium sulfate. The filtrate was exaporated under reduced pressure and the crude product was purified by column chromatography on silica gel using hexane/ethyl acetate (8% ethyl acetate) to yield *5-fluoro-6-methyl-N-[(1S)-1-phenylethyl]-2-phenylpyrimidin-4-amine* (0.066 g, 43%) as a pale yellow oil. R_f (19:1, hexane:EtOAc) 0.30. ^{1}H NMR (400 MHz, *$CDCl_3$*) δ_H 8.36 – 8.23 (2H, m, 2 x $\boldsymbol{H_{ortho}}$), 7.59 – 7.28 (8H, m, $\boldsymbol{H_{aromatic}}$), 5.50 (1H, p, *J* = 7.0 Hz, -N(H)C***H***(CH_3)-), 5.27 – 5.17 (1H, m, NH), 2.44 (3H, d, *J* = 2.9 Hz, -C(C$\boldsymbol{H_3}$)-), 1.69 (3H, d, *J* = 7.0 Hz, -N(H)CH(C$\boldsymbol{H_3}$)-). ^{19}F NMR (376 MHz, *$CDCl_3$*) δ_F -160.9 (s, -C(***F***)-). ^{13}C NMR (101 MHz, *$CDCl_3$*) δ_C 158.4 (d, *J* = 8.8 Hz, -***C***-C-$(CH)_5$-), 150.9 (d, *J* = 11.4 Hz, -***C***(N(H)-)-), 148.1 (d, *J* = 12.4 Hz, -***C***(CH_3)-), 143.9 (s, -N(H)CH(CH_3)-***C***-), 143.3 (d, *J* = 255.5 Hz, -***C***(F)-), 138.0 (-***C***-$(CH)_5$)-), 129.7 ($\boldsymbol{C_{para}}$), 128.7 ($\boldsymbol{C_{meta}}$(α-methylbenzyl)), 128.2 ($\boldsymbol{C_{meta}}$), 128.0 ($\boldsymbol{C_{ortho}}$), 127.4 ($\boldsymbol{C_{para}}$(α-methylbenzyl)), 126.2 ($\boldsymbol{C_{ortho}}$(α-methylbenzyl)), 50.1 (-N(H)***C***H(CH_3)-), 22.4 (-N(H)CH(***C***H_3)-), 17.0 (-C(***C***H_3)-). MS (ESI) *m/z* 308 ($[M+H]^+$, 100%), 309 ($[M+2H]^+$, 49%). HRMS (ESI) *m/z* calcd for $[M+H]^+$ $C_{19}H_{19}FN_3$ 308.1563; found 308.1578. IR (neat, cm^{-1}) 3426, 2925, 1610, 1503, 1388, 754, 697.

4. Experimental to chapter 4

4.1. Mn(III)-induced oxidative addition of olefins to 2-fluoro-1,3-dimethylmalonate

General procedure

In a Schlenk tube were added manganese catalyst (see table 36), 1,3-dimethyl-2-fluoromalonate **62** (1.5 g, 10 mmol or 0.75 g, 5 mmol) in acetic acid (20 mL). Then the mixture was warmed up to 100 °C under inert atmosphere and olefin (see table 36) was added to the reaction mixture. The resulting mixture was allowed to stir and then, after a certain reaction time, cooled down to room temperature. Then water (50 mL) was added and the product was extracted with dichloromethane (50 mL), washed twice with sat. $NaHCO_3$ solution (50 mL), with water (50 mL), dried over anhydrous sodium sulfate and dichloromethane was removed under reduced pressure to give a crude product mixture, which was analyzed by NMR spectroscopy.

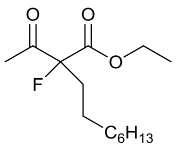
Table 36 *Addition of olefin to 1,3-dimethyl-2-fluoromalonate* ***62*** *using* $Mn(OAc)_3$

Entry	62 [mmol]	Olefin [5 mmol]		Catalyst [5 mmol]		Time [h]	Yield [%][a]
1	10	1-Octene	0.78 mL	$Mn(OAc)_3$	1.34 g	5	-
2	10					20	17
3[b]	10					20	18
4	10	Cyclo-hexene	0.5 mL	$Mn(OAc)_3$	1.34 g	24	7
5[b]	10					24	10
6	5	1-Octene	0.78 mL	Mn_2O_3	0.79 g	72	-
7	5			$Mn(acac)_3$	1.76 g	72	-
8	5			$Mn(OAc)_3$	1.34 g	120	48

[a] By ^{19}F-NMR; [b] With $Cu(OAc)_2$ (10 mol%)

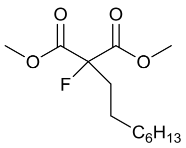
4.2. Mn(OAc)$_3$-induced oxidative addition of 1-octene to 2-fluoro-1,3-dicarbonyl substrates

Ethyl 2-octyl-2-fluoro-3-oxobutanoate, 139a



In a Schlenk tube were added manganese acetate dihydrate (2.68 g, 10 mmol), 2-fluoro-ethylacetoacetate **19** (1.5 mL, 10 mmol) in acetic acid (20 mL). Then the mixture was warmed up to 100 °C under inert atmosphere and 1-octene (1.57 mL, 10 mmol) was added to the reaction mixture. The resulting mixture was allowed to stir and then, after a certain reaction time, cooled down to room temperature. Then water (50 mL) was added and the product was extracted with dichloromethane (50 mL), washed twice with sat. sodium hydrogencarbonate solution (50 mL), with water (50 mL), dried over anhydrous sodium sulfate and dichloromethane was removed under reduced pressure to give a crude product mixture, which was distilled via Kugelrohr distillation (10 mbar, 150 °C), and then purified by column chromatography using a gradient of ethyl acetate and hexane. ^{1}H NMR (400 MHz, *CDCl$_3$*) δ_H 0.75 – 0.98 (m, 3H, -C$\boldsymbol{H_3}$), 1.07 – 1.44 (m, 15H, -OCH$_2$C$\boldsymbol{H_3}$ + -C(F)CH$_2$(C$\boldsymbol{H_2}$)$_{\boldsymbol{6}}$CH$_3$), 1.89 – 2.19 (m, 2H, -C(F)C$\boldsymbol{H_2}$-), 2.26 - 2.34 (m, 3H, -C(O)C$\boldsymbol{H_3}$), 4.11 – 4.38 (m, 2H, -OC$\boldsymbol{H_2}$CH$_3$). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ_F -167.39 (ddq, *J* = 25.2, 22.3, 4.8 Hz, -C(***F***)-), -166.56 (tq, *J* = 24.3, 4.8 Hz, -C(***F***)-, trace from di-substituted compound). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ_C 13.97, 14.02 (-OCH$_2$***C***H$_3$ + -C(F)CH$_2$(CH$_2$)$_6$***C***H$_3$), 22.58, 25.75, 29.04, 29.14, 29.31, 31.74 (-C(F)CH$_2$(***C***H$_2$)$_{\boldsymbol{6}}$CH$_3$), 33.84 (d, *J* = 20.9 Hz, -C(F)C$\boldsymbol{H_2}$(CH$_2$)$_6$CH$_3$), 62.43 (-O***C***H$_2$CH$_3$), 100.49 (d, *J* = 197.3 Hz, -***C***(F)-), 166.30 (d, *J* = 25.8 Hz, -***C***(O)OCH$_2$CH$_3$), 202.17 (d, *J* = 27.6 Hz, -***C***(O)CH$_3$). MS (ESI) *m/z* 259 ([M-H]$^+$, 100%), 260 ([M]$^+$, 17%), 261 ([M+H]$^+$, 48%). HRMS (ESI) *m/z* calcd for [M+H]$^+$ $C_{14}H_{26}FO_3$ 261.1866; found 261.1876.

Dimethyl-2-fluoro-2-octylmalonate, 140a



In a Schlenk tube were added manganese acetate dihydrate, 1,3-dimethyl-2-fluoromalonate **62** (see Table 37) in acetic acid (20 mL). Then the mixture was warmed up to 100°C under inert atmosphere and 1-octene (1.57 mL, 10 mmol) was added to the reaction mixture. The resulting mixture was allowed to stir and then, after a certain reaction time, cooled down to room temperature. Then water (50 mL) was added and the product was extracted with dichloromethane (50 mL), washed twice with sat. sodium hydrogencarbonate solution (50 mL), with water (50 mL), dried over anhydrous sodium sulfate and dichloromethane was removed under reduced pressure to give a crude product mixture, which was distilled via Kugelrohr distillation (10 mbar, 150 °C), and then purified by column chromatography using a gradient of ethyl acetate and hexane. ^{1}H NMR (400 MHz, *$CDCl_3$*) δ_H 0.83-0.92 (m, 3H, $\text{--C(F)CH}_2\text{(CH}_2)_6\text{C}\boldsymbol{H_3}$), 1.13 – 1.44 (m, 12H, $\text{-C(F)CH}_2\text{(C}\boldsymbol{H_2})_{\boldsymbol{6}}\text{CH}_3$), 1.91 – 2.21 (m, 2H, $\text{-C(F)C}\boldsymbol{H_2}\text{(CH}_2)_6\text{CH}_3$), 3.78 – 3.88 (m, 6H, 2 x –OCH_3). ^{19}F NMR (376 MHz, *$CDCl_3$*) δ_F -167.22 (t, *J* = 23.9 Hz, -C(***F***)-), -166.45 (t, *J* = 24.2 Hz, -C(***F***)-, trace from di-substituted compound). ^{13}C NMR (101 MHz, *$CDCl_3$*) δ 14.03 $\text{C(F)CH}_2\text{(CH}_2)_6\text{C}\boldsymbol{H_3}$), 22.16 – 22.95 (m), 28.25 – 29.61 (m), 31.43 – 31.92 (m) ($\text{-C(F)CH}_2(\boldsymbol{C}\text{H}_2)_{\boldsymbol{6}}\text{CH}_3$), 33.98 – 35.00 (m) ($\text{-C(F)}\boldsymbol{C}\text{H}_2\text{(CH}_2)_6\text{CH}_3$), 53.18 ($\text{-O}\boldsymbol{C}\text{H}_3$), 53.23 ($\text{-O}\boldsymbol{C}\text{H}_3$), 94.68 (d, *J* = 199.5 Hz, -***C***(F)-), 94.98 (d, *J* = 198.7 Hz, -***C***(F)-), 166.32 (d, *J* = 25.6 Hz, $\text{-}\boldsymbol{C}\text{(O)OCH}_3$), 166.74 (d, *J* = 25.7 Hz, $\text{-}\boldsymbol{C}\text{(O)OCH}_3$). MS (ESI) *m/z* 261 ($[M-H]^+$, 100%), 262 ($[M]^+$, 19%), 263 ($[M+H]^+$, 10%). HRMS (ESI) *m/z* calcd for $[M+H]^+$ $C_{13}H_{24}FO_4$ 263.1659; found 263.1664.

Table 37 *Addition of 1-octene to 1,3-dimethyl-2-fluoromalonate using $Mn(OAc)_3$*

Entry	**Time [h]**	**62**		**$Mn(OAc)_3$**		**Yield [%][b]**
1	24	0.75 g	5 mmol	1.34 g	5 mmol	22
2	72	0.75 g	5 mmol	2.68 g	10 mmol	77
3	72	1.5 g	10 mmol	2.68 g	10 mmol	20
4	72	1.5 g	10 mmol	1.34 g	5 mmol	25
5	72	3.0 g	20 mmol	1.34 g	5 mmol	45
6[a]	72	7.5 g	50 mmol	1.34 g	5 mmol	39
7[a]	72	11.25 g	75 mmol	1.34 g	5 mmol	50
8[a]	72	15.0 g	100 mmol	2.68 g	10 mmol	93
9[a]	72	22.5 g	150 mmol	2.68 g	10 mmol	95
10[a]	72	30.0 g	200 mmol	2.68 g	10 mmol	quant.

[a] Without AcOH; [b] Isolated

4.3. Oxidative addition of 1-octene to 2-fluoro-1,3-dimethylmalonate using other Manganese-based initiators

General procedure using $Mn(OAc)_2$ initiator

A mixture of potassium acetate (0.875 g, 9 mmol), 2-fluoro-1,3-dimethylmalonate **62** (25 mmol), and acetic acid (9 mL) was heated to 75 °C under inert atmosphere. 1-Octene (0.39 mL, 2.5 mmol) and manganese(III) acetate dihydrate (1.34 g, 5 mmol) were added and the solution was stirred at 75 °C. The mixture was then cooled to room temperature, diluted with water (50 mL) and extracted with DCM (3 x 50 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (2 x 50 mL), water (50 mL), dried over Na_2SO_4 and concentrated. The excess of malonate was removed by distillation (100 °C, 10 mbar) and the crude product was analyzed by NMR spectroscopy, showing no significant conversion and many by-products, so no further purification was carried out.

General procedure using $Mn(OAc)_2$ initiator combined with $KMnO_4$

A mixture of potassium acetate (0.875 g, 9 mmol), a few crystals of manganese(II) acetate tetrahydrate (cat.), 2-fluoro-1,3-dimethylmalonate **62** (25 mmol) and acetic acid (9 mL) was heated to 75°C under inert atmosphere. After the addition of the 1-octene (0.39 mL, 2.5 mmol), solid potassium permanganate (0.16 g, 0.4 eq.) was added in very small portions at 75 °C over a period of 4-10 hours. The mixture was then cooled to room temperature, diluted with water (50 mL) and extracted with DCM (3 x 50 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (2 x 50 mL), water (50 mL), dried over Na_2SO_4 and concentrated. Due to the presence of many by-products observed on NMR spectroscopy, no further purification was carried out.

General procedure using Mn(II) / Co(II) / O_2

To a solution of 2-fluoro-1,3-dimethylmalonate **62** (3.75 g, 15 eq.), $Mn(OAc)_2$ (52 mg, 2 mol %) and $Co(OAc)_2$ (26 mg, 1 mol %) in a two-necked flask equipped with a balloon filled with an appropriate concentration of O_2 (0.5 bar of O_2 diluted in 3.5 bar of N_2) was added 1-octene (0.31 mL, 2 mmol), and the mixture was stirred at 90 °C for 3 hours. After evaporation of AcOH, the excess of 1,3-dimethyl-2-fluoromalonate was removed by distillation (100 °C, 10 mbar). NMR spectroscopy of the crude mixture did not show any conversion of the starting 2-fluoro-1,3-dimethylmalonate and many by-products, therefore no further purification was carried out.

4.4. Oxidative addition of olefins to 2-fluoro-1,3-dimethylmalonate using ditertbutylperoxide $(^tBuO)_2$

General procedure

In a 50 mL flask were added 1,3-dimethyl-2-fluoromalonate **62**, ditertbutylperoxide (55 µL, 0.3 mmol) and olefin (see table 38). This mixture was then allowed to stir over four days at 105 °C under inert atmosphere. Then, the resulting mixture was allowed to cool at room temperature and was distilled under reduced pressure (120 °C, 10 mbar), and then distilled again by Kugelrohr distillation (150 °C, 5 mbar) and the crude product was analyzed by NMR spectroscopy. No further purification was carried out due to the small scale of these reactions and the polymerized by-products that were obtained.

Table 38 *Addition of olefin to 1,3-dimethyl-2-fluoromalonate using (^{t}BuO)$_2$*

Entry	**62**		**Olefin**			**Yield [%]**[a]
1	9.0 g	60 mmol	1-octene	313 µL	2 mmol	66
2	4.5 g	30 mmol	styrene	344 µL	3 mmol	-
3	4.5 g	30 mmol	vinylcyclohexane	410 µL	3 mmol	-
4	4.5 g	30 mmol	cyclohexene	303 µL	3 mmol	-
5	4.5 g	30 mmol	4-methylstyrene	395 µL	3 mmol	-

[a] By ^{19}F-NMR

4.5. Oxidative addition of olefins to 2-fluoro-1,3-dimethylmalonate using Bu$_3$SnH / AIBN

General procedure

In a 50 mL flask were added 1,3-dimethyl-2-fluoromalonate **62**, 1-octene, tributyltin hydride and a few crystals of AIBN in toluene or benzene (see Table 39). This mixture was then allowed to stir over four days at 85 °C under inert atmosphere. Then, the resulting mixture was allowed to cool at room temperature and a few crystals of I_2 were added to convert $Bu_3SnSnBu_3$ and unreacted Bu_3SnH to Bu_3SnI. The mixture was then diluted with diethyl ether (50 mL), water was added (50 mL), aqueous layer was removed and the organic layer was washed 2-3 times with 1M aqueous solution of KF (50 mL). Bu_3SnF precipitate formed at organic/aqueous phase interface (solution was filtered through Celite in some cases). Then the mixture was washed with saturated brine solution (50 mL), washed with sodium sulfite saturated solution to remove unreacted I_2, dried over $MgSO_4$, and the solvent was removed under reduced pressure. NMR spectroscopy of the crude product indicates the formation of Bu_3SnF and no product was observed, therefore no further purification was carried out.

Table 39 *Addition of 1-octene to 1,3-dimethyl-2-fluoromalonate using Bu_3SnH / AIBN*

Entry	**62**		**1-octene**		**Bu_3SnH**		**Solvent**
1	0.26 g	1.71 mmol	0.26 mL	1.71 mmol	0.5 g	1.71 mmol	toluene
2					1.0 g	3.42 mmol	
3					1.5 g	5.13 mmol	
4					0.5 g	1.71 mmol	benzene
5	0.52 g	3.42 mmol	0.52 mL	3.42 mmol	2.0 g	6.84 mmol	toluene

4.6. Oxidative addition of olefins to 2-fluoro-ethylacetoacetate using $Co(OAc)_2$

General procedure

In a 50 mL flask were added $Co(OAc)_2$ (1.77 g, 10 mmol), acetic acid (20 mL), then 2-fluoroethylacetoacetate (1.25 mL, 10 mmol), and olefin (see Table 40). This mixture was then allowed to stir for a certain time. Then, the resulting mixture was allowed to cool at room temperature, acetic acid was removed under reduced pressure and the residue was taken into diethyl ether (20 mL), washed with $NaHCO_3$ saturated solution (50 mL). The organic phase was then washed with ammonium chloride saturated solution (50 mL), washed with distillated water and dried over anhydrous Na_2SO_4. Diethyl ether was then removed under reduced pressure. Purification via Kugelrohr distillation (10 mbar, 150 °C) and column chromatography column chromatography using a gradient of ethyl acetate and hexane was carried out when appropriate.

Table 40 *Addition of olefin to 2-fluoroethylacetoacetate using $Co(OAc)_2$*

Entry	**Olefin**			**Temp.**	**Reaction time**	**Yield [%]**[a]
1	1-octene	2.33 mL	15 mmol	r.t.	3 days	24
2	Styrene	2.33 mL	20 mmol			15[b]
3	1-octene	2.33 mL	15 mmol	90 °C	4 days	67

[a] Isolated; [b] By ^{19}F-NMR

4.7. Oxidative addition of olefins to 2-fluoro-1,3-dimethylmalonate using CAN / $Cu(OAc)_2$

General procedure

Olefin (2 mmol, see table 41) was added to a solution of 1,3-dimethyl-2-fluoromalonate (see Table 41) in 30 mL of solvent under inert atmosphere. Then CAN (2.2 g, 4.0 mmol) was added (plus $Cu(OAc)_2$ (0.4 g, 2 mmol) if the reaction was carried out in acetic acid) and the resulting mixture was stirred at room temperature for 3 days. Acetonitrile was evaporated under reduced pressure, water (100 mL) was added to the residue and the resulting mixture extracted with DCM (3 x 50 mL), the organic phase was then removed under vacuo and crude product was analyzed by NMR spectroscopy. For reactions carried out in acetic acid, the reaction mixture was poured into water (100 mL) and extracted with DCM. The organic phase was then washed with as saturated $NaHCO_3$ solution (3 x 50 mL), then water and finally dried with Na_2SO_4. The crude product was then analyzed by ^{19}F-NMR spectroscopy. No further purification was carried out due to the low yields.

Table 41 *Addition of 2-fluoro-1,3-dimethylmalonate to olefins using CAN / $Cu(OAc)_2$*

Entry	Olefin [2 mmol]		62		Solvent	Yield [%][a]
1	1-Octene	0.31 mL	5 mmol	0.76 g	MeCN	-
2[b]	1-Octene	0.31 mL	5 mmol	0.76 g	AcOH	11
3	Cyclohexene	0.23 mL	5 mmol	0.76 g	MeCN	-
4[b]	Cyclohexene	0.23 mL	5 mmol	0.76 g	AcOH	12
5	Cyclohexene	0.23 mL	2 mmol	0.30 g	MeCN	-
6[b]	Cyclohexene	0.23 mL	2 mmol	0.30 g	AcOH	10

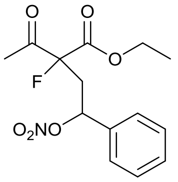
[a] By ^{19}F-NMR; [b] With $Cu(OAc)_2$ (2 mmol)

4.8. CAN-induced oxidative addition of olefins to 2-fluoroethylacetoacetate

General procedure

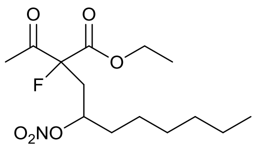
Olefin (2 mmol) was added to a solution of 2-fluoro-ethyl acetoacetate **19** (0.63 mL, 5.0 mmol) in 20 mL of acetonitrile under inert atmosphere. Then ceric ammonium nitrate (2.2 g, 4.0 mmol) was added and the resulting mixture was stirred at room temperature for 3 days. Acetonitrile was evaporated under reduced pressure, water (100 mL) was added to the residue and the resulting mixture extracted with dichloromethane (3 x 50 mL), the organic phase was then washed with brine (2 x 25 mL), dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude mixture was then purified by column chromatography eluting with dichloromethane to give the desired product as a pale yellow oil.

Ethyl-2-acetyl-2-fluoro-4-(nitrooxy)-4-phenylbutanoate, 219a (350 mg, 56%)



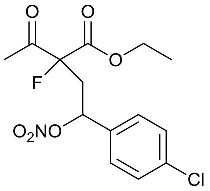
^{1}H NMR (400 MHz, *CDCl₃*) δ_H 1.26 (t, *J* = 7.1 Hz, 3H, $-OCH_2C\boldsymbol{H}_3$), 1.39 (td, *J* = 7.1, 5.3 Hz, 3H, $-OCH_2C\boldsymbol{H}_3$), 2.29 (d, *J* = 4.4 Hz, 3H, $-C(O)C\boldsymbol{H}_3$), 2.38 (d, *J* = 5.0 Hz, 3H, $-C(O)C\boldsymbol{H}_3$), 2.46 (ddd, *J* = 15.8, 11.3, 3.3 Hz, 1H, $-C(F)C\boldsymbol{H}_2-$), 2.69 (td, *J* = 15.4, 4.7 Hz, 1H, $-C(F)C\boldsymbol{H}_2-$), 2.83 – 2.96 (m, 1H, $-C(F)C\boldsymbol{H}_2-$), 2.95 – 3.09 (m, 1H, $-C(F)C\boldsymbol{H}_2-$), 4.05 – 4.24 (m, 2H, $-OC\boldsymbol{H}_2CH_3$), 4.27 – 4.48 (m, 2H, $-OC\boldsymbol{H}_2CH_3$), 5.99 – 6.15 (m, 2H, 2 x $-C(\boldsymbol{H})ONO_2$), 7.31 – 7.57 (m, 10H, 2 x 5$\boldsymbol{H}_{aromatic}$). ^{19}F NMR (376 MHz, *CDCl₃*) δ_F -167.78 (ddq, *J* = 22.4, 15.1, 4.9 Hz, $-C(\boldsymbol{F})-$), -166.92 (ddq, *J* = 29.1, 11.3, 4.4 Hz, $-C(\boldsymbol{F})-$). ^{13}C NMR (101 MHz, *CDCl₃*) δ_C 13.82 ($-C(O)\boldsymbol{C}H_3$), 13.93 ($-C(O)\boldsymbol{C}H_3$), 25.03 ($-OCH_2\boldsymbol{C}H_3$), 25.15 ($-OCH_2\boldsymbol{C}H_3$), 38.19 (d, *J* = 2.9 Hz, $-C(F)\boldsymbol{C}H_2-$), 38.39 (d, *J* = 2.4 Hz, $-C(F)\boldsymbol{C}H_2-$), 63.12 ($-O\boldsymbol{C}H_2CH_3$), 63.29 ($-O\boldsymbol{C}H_2CH_3$), 79.46 (d, *J* = 4.3 Hz, $-\boldsymbol{C}(H)ONO_2$), 80.02 (d, *J* = 4.9 Hz, $-\boldsymbol{C}(H)ONO_2$), 96.72 (d, *J* = 198.7 Hz, $-\boldsymbol{C}(F)-$), 97.31 (d, *J* = 201.1 Hz, $-\boldsymbol{C}(F)-$), 126.52, 126.69 (d, *J* = 2.3 Hz), 128.95, 129.01, 129.47, 129.48, 136.44, 136.78 (10C, $\boldsymbol{C}_{aromatic}$), 165.21 (d, *J* = 25.0 Hz, $-\boldsymbol{C}(O)CH_3$), 165.70 (d, *J* = 25.9 Hz, $-\boldsymbol{C}(O)CH_3$), 199.73 (d, *J* = 27.7 Hz, $-\boldsymbol{C}(O)OCH_2CH_3$), 201.23 (d, *J* = 28.6 Hz, $-\boldsymbol{C}(O)OCH_2CH_3$). IR (ATR) υ 2987 (m), 2173 (w), 2150 (w), 1754 (vs), 1736 (vs), 1636 (vs), 1587 (m), 1563 (m), 1530 (w), 1496 (m), 1457 (m), 1419 (w), 1359 (m), 1273 (vs), 1233 (m), 1194 (m), 1147 (m), 1105 (w), 1074 (w), 1057 (w), 1013 (s), 844 (vs), 753 (s), 698 (vs), 589 (m), 528 (s) cm^{-1}. m/z (EI$^+$) 251 (63%, $[M-ONO_2]^+$), 152 (100%, $[C_7H_6NO_3^{\bullet}]^+$). m/z (ASAP) 231 (100%, $[M-F-ONO_2^{\bullet}]^+$).

Ethyl-2-acetyl-2-fluoro-4-(nitrooxy)decanoate, 219b (225 mg, 35%)



^{1}H NMR (400 MHz, *CDCl₃*) δ_H 0.86 – 0.93 (m, 3H, $-C(H)ONO_2-CH_2(CH_2)_4C\boldsymbol{H}_3$), 1.21 – 1.52 (m, 11H, $-C(H)ONO_2-CH_2(C\boldsymbol{H}_2)_4CH_3 + -OCH_2C\boldsymbol{H}_3$), 1.58 – 1.97 (m, 2H, $-C(H)ONO_2-C\boldsymbol{H}_2(CH_2)_4CH_3$), 2.31 (d, *J* = 1.5 Hz, 3H, $-C(O)C\boldsymbol{H}_3$), 2.33 (d, *J* = 2.1 Hz, 3H, $-C(O)C\boldsymbol{H}_3$), 2.35 – 2.65 (m, 4H, 2 x $-C(F)C\boldsymbol{H}_2-$), 4.13 – 4.44 (m, 2H, $-OC\boldsymbol{H}_2CH_3$), 4.57 – 4.70 (m, 2H, $-OC\boldsymbol{H}_2CH_3$), 5.21 – 5.37 (m, 2H, 2 x $-C(\boldsymbol{H})ONO_2-$). ^{19}F NMR (376 MHz, *CDCl₃*) δ_F -167.42 (tq, *J* = 20.7, 4.8 Hz, $-C(\boldsymbol{F})-$), -166.97 (ddq, *J* = 28.1, 14.6, 4.4 Hz, $-C(\boldsymbol{F})-$). ^{13}C NMR (101 MHz, *CDCl₃*) δ 13.85, 13.87, 13.96, 13.98 (4C, 2 x $-OCH_2\boldsymbol{C}H_3 + -C(H)ONO_2-CH_2(CH_2)_4\boldsymbol{C}H_3$), 22.43, 22.46, 23.08, 24.54, 24.64, 24.69, 25.03, 25.06, 28.69, 28.73, 28.84, 30.47, 30.57, 31.42, 31.50, 33.32, 33.59, 34.35, 34.52 (12C, 2 x -C(O)***C***H$_3$ + 2 x -C(H)ONO$_2$-(***C***H$_2$)$_{\boldsymbol{5}}$CH$_3$), 35.86 (d, *J* = 10.7 Hz, -C(F)***C***H$_2$-), 36.07 (d, *J* = 10.4 Hz, -C(F)***C***H$_2$-), 63.18 (-O***C***H$_2$CH$_3$), 78.79 (d, *J* = 2.8 Hz, -***C***(H)ONO$_2$), 79.33 (d, *J* = 3.1 Hz, -***C***(H)ONO$_2$), 97.22 (d, *J* = 198.2 Hz, -***C***(F)-), 98.01 (d, *J* = 200.8 Hz, -***C***(F)-), 165.54 (d, *J* = 21.1 Hz, -***C***(O)CH$_3$), 165.79 (d, *J* = 22.3 Hz, -***C***(O)CH$_3$), 200.16 (d, *J* = 28.1 Hz, -***C***(O)OCH$_2$CH$_3$), 201.33 (d, *J* = 25.8 Hz, -***C***(O)OCH$_2$CH$_3$). IR (ATR) υ 2932 (m), 2861 (w), 1737 (s), 1631 (vs), 1558 (s), 1466 (w), 1358 (w), 1274 (vs), 1189 (w), 1154 (w), 1096 (w), 1014 (w), 844 (vs), 753 (m), 696 (m), 551 (w). m/z (EI$^+$) 43 (100%), 69 (46%), 81 (25%), 109 (19%).

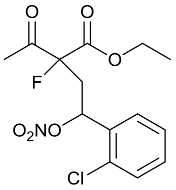
Ethyl-2-acetyl-2-fluoro-4-(nitrooxy)-4-4-chlorophenylbutanoate, 219d (390 mg, 56%)



^{1}H NMR (400 MHz, *CDCl$_3$*) δ$_H$ 1.27 (t, *J* = 7.1 Hz, 3H, -OCH$_2$C***H$_3$***), 1.37 (t, *J* = 7.2 Hz, 3H, -OCH$_2$C***H$_3$***), 2.30 (d, *J* = 4.4 Hz, 3H, -C(O)C***H$_3$***), 2.37 (d, *J* = 5.0 Hz, 3H, -C(O)C***H$_3$***), 2.42 (ddd, *J* = 15.8, 11.2, 3.3 Hz, 1H, -C(F)C***H$_2$***-), 2.65 (td, *J* = 15.2, 4.7 Hz, 1H, -C(F)C***H$_2$***-), 2.87 (ddd, *J* = 22.3, 15.5, 9.7 Hz, 1H, -C(F)C***H$_2$***-), 2.96 (ddd, *J* = 28.6, 15.6, 10.5 Hz, 1H, -C(F)C***H$_2$***-), 4.09 – 4.23 (m, 2H, -OC***H$_2$***CH$_3$), 4.27 – 4.46 (m, 2H, -OC***H$_2$***CH$_3$), 5.99 (dd, *J* = 9.1, 4.0 Hz, 1H, -C(***H***)ONO$_2$), 6.02 (dd, *J* = 10.1, 2.6 Hz, 1H, -C(***H***)ONO$_2$), 7.31 – 7.42 (m, 4H, ***H$_{aromatic}$***).^{19}F NMR (376 MHz, *CDCl$_3$*) δ$_F$ -167.75 (ddq, *J* = 22.3, 14.9, 4.9 Hz, -C(***F***)-), -166.81 (ddq, *J* = 29.0, 10.9, 4.3 Hz, -C(***F***)-).^{13}C NMR (101 MHz, *CDCl$_3$*) δ$_C$ 13.82 (-C(O)***C***H$_3$), 13.92 (-C(O)***C***H$_3$), 25.01 (-OCH$_2$***C***H$_3$), 25.12 (-OCH$_2$***C***H$_3$), 37.98 (d, *J* = 2.9 Hz, -C(F)***C***H$_2$-), 38.18 (d, *J* = 2.2 Hz, -C(F)***C***H$_2$-), 63.21 (-O***C***H$_2$CH$_3$), 63.35 (-O***C***H$_2$CH$_3$), 78.66 (d, *J* = 4.3 Hz, -***C***(H)ONO$_2$), 79.20 (d, *J* = 5.2 Hz, -***C***(H)ONO$_2$), 96.57 (d, *J* = 199.1 Hz, -***C***(F)-), 97.15 (d, *J* = 201.3 Hz, -***C***(F)-), 127.94 (-C-***C***(H)C(H)C(Cl)C(H)***C***(H)-), 128.13 (-C-***C***(H)C(H)C(Cl)C(H)***C***(H)-), 129.22 (-C-C(H)***C***(H)C(Cl)***C***(H)C(H)-), 129.28 (-C-C(H)***C***(H)C(Cl)***C***(H)C(H)-), 134.95 (-C-C(H)C(H)***C***(Cl)C(H)C(H)-), 135.30 (-C-C(H)C(H)***C***(Cl)C(H)C(H)-), 135.46 (-***C***-C(H)C(H)C(Cl)C(H)C(H)-), 135.50 (-***C***-C(H)C(H)C(Cl)C(H)C(H)-), 165.12 (d, *J* = 24.9 Hz, -***C***(O)CH$_3$), 165.58 (d, *J* = 25.9 Hz, -***C***(O)CH$_3$), 199.58 (d, *J* = 27.6 Hz, -***C***(O)OCH$_2$CH$_3$), 201.13 (d, *J* = 28.8 Hz, -***C***(O)OCH$_2$CH$_3$). IR (ATR) υ 2982 (m), 1754 (vs), 1735 (vs), 1637 (vs), 1598 (w), 1494 (s), 1416 (m), 1359 (m), 1272 (vs), 1233 (w), 1192 (m), 1148 (w), 1118 (w), 1092 (vs), 1058 (w), 1014 (vs), 963 (w), 836 (vs), 752 (m), 722 (w), 688 (m), 649 (w), 600 (w), 530 (s) cm^{-1}. m/z (EI$^+$) 285 (34%, [M-ONO$_2$]$^+$), 152 (100%,

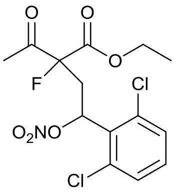
[$C_7H_5NO_3^{2\bullet}$]$^+$). Elemental analysis calcd for $C_{14}H_{15}ClFNO_6$, C: 48.36, H: 4.35, N: 4.03; found C: 47.96, H: 4.35, N: 3.94.

Ethyl-2-acetyl-2-fluoro-4-(nitrooxy)-4-2-chlorophenylbutanoate, 219e (390 mg, 57%)



^{1}H NMR (400 MHz, *CDCl$_3$*) δ_H 1.31 (t, *J* = 7.1 Hz, 3H, -OCH$_2$C***H$_3$***), 1.39 (t, *J* = 7.2 Hz, 3H, -OCH$_2$C***H$_3$***), 2.34 (d, *J* = 4.3 Hz, 3H, -C(O)C***H$_3$***), 2.40 (d, *J* = 5.0 Hz, 3H, -C(O)C***H$_3$***), 2.45 (dd, *J* = 9.2, 2.8 Hz, 1H, -C(F)C***H***$_2$-), 2.49 (dd, *J* = 9.2, 2.8 Hz, 1H, -C(F)C***H***$_2$-), 2.65 – 2.84 (m, 1H , -C(F)C***H***$_2$-), 2.82 – 2.96 (m, 1H, -C(F)C***H***$_2$-), 4.21 – 4.31 (m, 2H, -OC***H$_2$***CH$_3$), 4.30 – 4.47 (m, 2H, -OC***H$_2$***CH$_3$), 6.48 (dd, *J* = 10.3, 3.9 Hz, 1H, -C(***H***)ONO$_2$), 6.52 (dd, *J* = 11.0, 2.8 Hz, 1H, -C(***H***)ONO$_2$), 7.29 – 7.48 (m, 8H, ***H$_{aromatic}$***). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ_F -168.27 (ddq, *J* = 24.8, 13.2, 5.1 Hz, -C(***F***)-), -167.64 (ddq, *J* = 31.1, 8.9, 4.3 Hz, -C(***F***)-). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ_C 13.88 (-C(O)***C***H$_3$), 13.94 (-C(O)***C***H$_3$), 25.00 (-OCH$_2$***C***H$_3$), 25.19 (-OCH$_2$***C***H$_3$), 37.08 (d, *J* = 2.5 Hz, -C(F)***C***H$_2$-), 37.28 (d, *J* = 1.8 Hz, -C(F)***C***H$_2$-), 63.24 (-O***C***H$_2$CH$_3$), 63.30 (-O***C***H$_2$CH$_3$), 75.81 (d, *J* = 4.4 Hz, -***C***(H)ONO$_2$), 76.31 (d, *J* = 4.8 Hz, -***C***(H)ONO$_2$), 96.45 (d, *J* = 199.6 Hz, -***C***(F)-), 97.28 (d, *J* = 201.8 Hz, -***C***(F)-), 126.50, 126.72, 127.69, 127.73, 130.01 (d, *J* = 5.8 Hz), 130.27 (d, *J* = 4.3 Hz), 132.00, 132.17, 134.83, 135.03 (2 x 5C, ***C$_{aromatic}$***), 165.18 (d, *J* = 24.9 Hz, -***C***(O)CH$_3$), 165.68 (d, *J* = 26.0 Hz, -***C***(O)CH$_3$), 199.51 (d, *J* = 27.7 Hz, -***C***(O)OCH$_2$CH$_3$), 201.45 (d, *J* = 28.9 Hz, -***C***(O)OCH$_2$CH$_3$). IR (ATR) υ 2987 (m), 1755 (vs), 1735 (vs), 1641 (vs), 1594 (m), 1477 (m), 1444 (m), 1419 (w), 1359 (s), 1273 (vs), 1231 (m), 1192 (s), 1136 (m), 1102 (m), 1052 (m), 1037 (w), 1013 (m), 962 (w), 835 (vs), 756 (vs), 691 (s), 665 (w), 595 (m), 538 (s) cm^{-1}. m/z (EI$^+$) 285 (76%, [M-ONO$_2$]$^+$), 152 (100%, [$C_7H_5NO_3^{2\bullet}$]$^+$). m/z (ASAP) 265 (100%, [M-F-ONO$_2^\bullet$]$^+$). Elemental analysis calcd for $C_{14}H_{15}ClFNO_6$, C: 48.36, H: 4.35, N: 4.03; found C: 48.34, H: 4.35, N: 3.83.

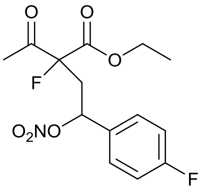
Ethyl-2-acetyl-2-fluoro-4-(nitrooxy)-4-2,6-dichlorophenylbutanoate, 219f (451 mg, 59%)



^{1}H NMR (400 MHz, *CDCl$_3$*) δ_H 1.30 (t, *J* = 7.1 Hz, 3H, -OCH$_2$C***H$_3$***), 1.39 (t, *J* = 7.1 Hz, 3H, -OCH$_2$C***H$_3$***), 2.34 (d, *J* = 4.4 Hz, 2H, -C(O)C***H$_3$***), 2.41 (d, *J* = 4.9 Hz, 3H, -C(O)C***H$_3$***), 2.47 (ddd, *J* = 15.9, 9.8, 3.5 Hz, 1H, -C(F)C***H***$_2$-), 2.78 (ddd, *J* = 15.5, 14.6, 4.6 Hz, 1H, -C(F)C***H***$_2$-), 3.37 (ddd, *J* = 24.4, 15.5, 10.0 Hz, 1H, -C(F)C***H***$_2$-), 3.50 (ddd, *J* = 30.9, 15.8, 10.8 Hz, 1H, -C(F)C***H***$_2$-), 4.18 – 4.51 (m, 3H, -OC***H$_2$***CH$_3$), 4.68

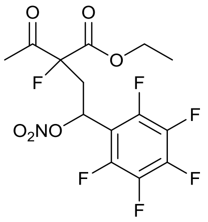
(ddd, *J* = 16.2, 12.9, 3.0 Hz, 1H, -OC$\boldsymbol{H_2}$CH$_3$), 5.38 (dd, *J* = 15.1, 10.0 Hz, 0.5H, -C($\boldsymbol{H}$)ONO$_2$), 5.92 (dd, *J* = 16.1, 8.8 Hz, 0.5H, -C($\boldsymbol{H}$)ONO$_2$), 6.80 (dd, *J* = 10.0, 4.6 Hz, 0.5H, -C($\boldsymbol{H}$)ONO$_2$), 6.86 (dd, *J* = 10.8, 3.4 Hz, 0.5H, -C($\boldsymbol{H}$)ONO$_2$), 7.18 – 7.56 (m, 2 x 3H, $\boldsymbol{H}_{\boldsymbol{aromatic}}$), 7.86 (d, *J* = 14.0 Hz, trace), 8.27 (d, *J* = 13.9 Hz, trace). ^{19}F NMR (376 MHz, Chloroform-*d*) δ$_\text{F}$ -168.58 (ddq, *J* = 24.4, 14.7, 4.9 Hz, -C($\boldsymbol{F}$)-), -167.97 (ddd, *J* = 30.8, 14.2, 4.4 Hz, -C($\boldsymbol{F}$)-). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ$_\text{C}$ 13.85 (-C(O)$\boldsymbol{C}$H$_3$), 13.94 (-C(O)$\boldsymbol{C}$H$_3$), 25.02 (-OCH$_2$$\boldsymbol{C}H_3$), 25.23 (-OCH$_2$$\boldsymbol{C}H_3$), 34.54 (d, *J* = 19.8 Hz, -C(F)$\boldsymbol{C}$H$_2$-), 34.64 (d, *J* = 20.3 Hz, -C(F)$\boldsymbol{C}$H$_2$-), 63.29 (-O$\boldsymbol{C}$H$_2$CH$_3$), 63.36 (-O$\boldsymbol{C}$H$_2$CH$_3$), 72.70, 72.82 (traces), 75.38 (d, *J* = 4.8 Hz, -$\boldsymbol{C}$(H)ONO$_2$), 75.64 (trace), 75.88 (d, *J* = 5.0 Hz, -$\boldsymbol{C}$(H)ONO$_2$), 80.27 (trace) , 96.67 (d, *J* = 199.1 Hz, -$\boldsymbol{C}$(F)-), 97.47 (d, *J* = 201.9 Hz, -$\boldsymbol{C}$(F)-), 129.27, 129.83, 130.76, 130.81, 130.88, 131.18, 131.61, 131.85, 132.04, 132.38 (2 x 5C, $\boldsymbol{C}_{\boldsymbol{aromatic}}$), 165.14 (d, *J* = 25.0 Hz, -$\boldsymbol{C}$(O)CH$_3$), 165.52 (d, *J* = 26.2 Hz, -$\boldsymbol{C}$(O)CH$_3$), 199.49 (d, *J* = 27.5 Hz, -$\boldsymbol{C}$(O)OCH$_2$CH$_3$), 201.01 (d, *J* = 28.4 Hz, -$\boldsymbol{C}$(O)OCH$_2$CH$_3$). IR (ATR) υ 2985 (m), 2023 (w), 1754 (vs), 1736 (vs), 1642 (vs), 1563 (vs), 1533 (m), 1438 (s), 1359 (w), 1341 (w), 1276 (vs), 1232 (w), 1208 (w), 1185 (s), 1153 (w), 1091 (m), 1059 (w), 1014 (m), 962 (m), 900 (w), 834 (vs), 774 (vs), 750 (w), 696 (m), 638 (w), 608 (w), 542 (s) cm^{-1}. m/z (EI$^+$) 319 (93%, [M-ONO$_2$]$^+$), 152 (100%, [C$_7$H$_4$NO$_3$$^{3\bullet}$]$^+$). m/z (ASAP) 299 (100%, [M-F-ONO$_2^\bullet$]$^+$).

Ethyl-2-acetyl-2-fluoro-4-(nitrooxy)-4-4-fluorophenylbutanoate, 219g (397 mg, 60%)



^{1}H NMR (400 MHz, *CDCl$_3$*) δ 1.26 (t, *J* = 7.1 Hz, 3H, -OCH$_2$C$\boldsymbol{H_3}$), 1.36 (t, *J* = 7.2 Hz, 3H, -OCH$_2$C$\boldsymbol{H_3}$), 2.28 (d, *J* = 4.4 Hz, 3H, -C(O)C$\boldsymbol{H_3}$), 2.36 (d, *J* = 4.9 Hz, 3H, -C(O)C$\boldsymbol{H_3}$), 2.43 (ddd, *J* = 15.8, 11.4, 3.4 Hz, 1H, -C(F)C$\boldsymbol{H}_2$-), 2.66 (td, *J* = 15.4, 4.8 Hz, 1H, -C(F)C$\boldsymbol{H}_2$-), 2.81 – 3.05 (m, 2H, -C(F)C$\boldsymbol{H}_2$-), 4.09 – 4.21 (m, 2H, -OC$\boldsymbol{H_2}$CH$_3$), 4.28 – 4.47 (m, 2H, -OC$\boldsymbol{H_2}$CH$_3$), 5.98 – 6.07 (m, 1H, -C($\boldsymbol{H}$)ONO$_2$), 7.09 (t, *J* = 8.6 Hz, 2H, 2 x $\boldsymbol{H}_{\boldsymbol{meta}}$), 7.35 – 7.42 (m, 2H, 2 x $\boldsymbol{H}_{\boldsymbol{ortho}}$). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ$_\text{F}$ -167.80 (ddq, *J* = 22.3, 15.1, 4.9 Hz, -C($\boldsymbol{F}$)-), -166.92 (ddq, *J* = 28.8, 11.4, 4.4 Hz, -C($\boldsymbol{F}$)-), -111.33 (dtt, *J* = 17.9, 8.4, 5.2 Hz, -C$\boldsymbol{F}_{\boldsymbol{para}}$). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ$_\text{C}$ 13.79 (-C(O)$\boldsymbol{C}$H$_3$), 13.89 (-C(O)$\boldsymbol{C}$H$_3$), 24.98 (-OCH$_2$$\boldsymbol{C}H_3$), 25.08 (-OCH$_2$$\boldsymbol{C}H_3$), 38.03 (d, *J* = 2.9 Hz, -C(F)$\boldsymbol{C}$H$_2$-), 38.23 (d, *J* = 2.3 Hz, -C(F)$\boldsymbol{C}$H$_2$-), 63.16 (-O$\boldsymbol{C}$H$_2$CH$_3$), 63.32 (-O$\boldsymbol{C}$H$_2$CH$_3$), 78.76 (d, *J* = 4.4 Hz, -$\boldsymbol{C}$(H)ONO$_2$), 79.30 (d, *J* = 5.2 Hz, -$\boldsymbol{C}$(H)ONO$_2$), 96.62 (d, *J* = 198.9 Hz, -$\boldsymbol{C}$(F)-), 97.19 (d, *J* = 201.2 Hz, -$\boldsymbol{C}$(F)-), 115.92 (d, *J* = 6.5 Hz, -C-C(H)$\boldsymbol{C}$(H)C(F)$\boldsymbol{C}$(H)C(H)-), 116.14 (d, *J* = 6.3 Hz, -C-C(H)$\boldsymbol{C}$(H)C(F)$\boldsymbol{C}$(H)C(H)-), 128.62 (d, *J* = 8.5 Hz, -C-***C***(H)C(H)C(F)C(H)***C***(H)-), 128.81 (d, *J* = 8.7 Hz, -C-***C***(H)C(H)C(F)C(H)***C***(H)-), 132.26 (d, *J* = 3.4 Hz, -C(H)(ONO$_2$)-***C***-), 132.62 (d, *J* = 3.3 Hz, -C(H)(ONO$_2$)-***C***-), 161.94 (d, *J* = 2.4 Hz, -C-C(H)C(H)***C***(F)C(H)C(H)-), 164.42 (d, *J* = 2.5 Hz, -C-C(H)C(H)***C***(F)C(H)C(H)-), 165.14 (d, *J* = 25.1 Hz, -***C***(O)CH$_3$), 165.61 (d, *J* = 25.9 Hz, -***C***(O)CH$_3$), 199.64 (d, *J* = 27.5 Hz, -***C***(O)OCH$_2$CH$_3$), 201.12 (d, *J* = 28.6 Hz, -***C***(O)OCH$_2$CH$_3$). IR (ATR) υ 2989 (m), 2036 (w), 1753 (vs), 1735 (vs), 1637 (vs), 1607 (m), 1563 (w), 1512 (vs), 1447 (w), 1420 (w), 1360 (m), 1274 (vs), 1227 (vs), 1192 (w), 1159 (m), 1113 (w), 1092 (m), 1057 (w), 1013 (m), 963 (w), 837 (vs), 753 (m), 725 (w), 696 (w), 665 (w), 606 (w), 568 (w), 531 (m) cm^{-1}. m/z (EI$^+$) 269 (97%, [M-ONO$_2$]$^+$), 152 (100%, [$C_7H_5NO_3^{2\bullet}$]$^+$). m/z (ASAP) 249 (100%, [M-F-ONO$_2^\bullet$]$^+$).

Ethyl-2-acetyl-2-fluoro-4-(nitrooxy)-4-2,3,4,5,6-pentafluorophenylbutanoate, 219h (500 mg, 62%)



^{1}H NMR (400 MHz, *CDCl$_3$*) δ_H 1.32 (t, *J* = 7.1 Hz, 3H, -OCH$_2$C***H$_3$***), 1.38 (t, *J* = 7.1 Hz, 3H, -OCH$_2$C***H$_3$***), 2.33 (d, *J* = 4.4 Hz, 3H, -C(O)C***H$_3$***), 2.38 (d, *J* = 4.8 Hz, 3H, -C(O)C***H$_3$***), 2.55 (ddd, *J* = 15.4, 10.7, 4.4 Hz, 1H, -C(F)C***H***$_2$-), 2.79 (td, *J* = 15.7, 5.3 Hz, 1H, -C(F)C***H***$_2$-), 3.14 (ddd, *J* = 22.0, 15.4, 8.9 Hz, 1H, -C(F)C***H***$_2$-), 3.25 (ddd, *J* = 29.3, 15.7, 9.8 Hz, 1H, -C(F)C***H***$_2$-), 4.25 – 4.47 (m, 4H, 2 x -OC***H$_2$***CH$_3$), 6.07 (d, *J* = 48.7 Hz, trace), 6.35 (dd, *J* = 9.0, 5.4 Hz, 1H, -C(***H***)ONO$_2$), 6.40 (dd, *J* = 9.8, 4.4 Hz, 1H, -C(***H***)ONO$_2$), 7.84 (d, *J* = 14.0 Hz, trace), 8.05 (d, *J* = 14.0 Hz, trace). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ_F -168.17 (ddq, *J* = 21.1, 15.4, 4.9 Hz, -C(***F***)-), -167.47 (ddq, *J* = 29.5, 9.0, 4.5 Hz, -C(***F***)-), -160.26 – -160.06 (m, 2F, -CF$_{meta}$), -150.43 (tdt, *J* = 20.9, 11.7, 3.1 Hz, 2F, -CF$_{para}$), -141.14 – -141.00 (m, 1F, -CF$_{ortho}$), -141.00 – -140.86 (m, 1F, -CF$_{ortho}$). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ_C 13.78 (-C(O)***C***H$_3$), 13.83 (-C(O)***C***H$_3$), 24.87 (-OCH$_2$***C***H$_3$), 25.06 (-OCH$_2$***C***H$_3$), 35.12 (d, *J* = 10.7 Hz, -C(F)***C***H$_2$-), 35.32 (d, *J* = 11.5 Hz, -C(F)***C***H$_2$-), 63.50 (-O***C***H$_2$CH$_3$), 63.56 (-O***C***H$_2$CH$_3$), 69.67 (br s, -***C***(H)ONO$_2$), 70.12 (br s, -***C***(H)ONO$_2$), 96.32 (d, *J* = 199.0 Hz, -***C***(F)-), 97.09 (d, *J* = 201.6 Hz, -***C***(F)-), 136.46, 138.98, 140.92, 143.48, 143.85, 146.37 (6 x m, 6C, ***C$_{aromatic}$***), 164.84 (d, *J* = 24.8 Hz, -***C***(O)CH$_3$), 165.13 (d, *J* = 26.0 Hz, -***C***(O)CH$_3$), 199.15 (d, *J* = 27.5 Hz, -***C***(O)OCH$_2$CH$_3$), 200.57 (d, *J* = 28.4 Hz, -***C***(O)OCH$_2$CH$_3$). IR (ATR) υ 2990 (m), 2073 (w), 1756 (vs), 1738 (vs), 1651 (vs), 1523 (s), 1507 (vs), 1427 (w), 1361 (m), 1309 (w), 1276 (s), 1224 (w), 1198 (w), 1151 (w), 1135 (m), 1109 (w), 1061 (w), 998 (s), 969 (w), 946 (w), 836 (vs), 750 (m), 683 (m), 625 (w), 575 (w), 534 (m) cm^{-1}. m/z (EI$^+$) 341 (93%, [M-ONO$_2$]$^+$), 152

(100%, [C$_7$HNO$_3^{6\bullet}$]$^+$). m/z (ASAP) 321 (100%, [M-F-ONO$_2^{\bullet}$]$^+$). Elemental analysis calcd for C$_{14}$H$_{11}$F$_6$NO$_6$, C: 41.70, H: 2.75, N: 3.47; found C: 41.43, H: 2.61, N: 3.57.

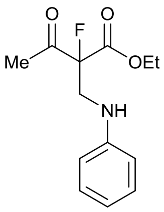
5. Experimental to chapter 5

General procedure

In a 50 mL two-necked flask containing dichloromethane (10 mL) were added the amine (17 mmol) followed by chosen aldehyde (15 mmol) and the resulting reaction mixture was allowed to stir at r.t. for 2 h., before the fluorinated dicarbonyl system was added (10 mmol). The reaction mixture was stirred at r.t. for 16 h, evaporated and the residue dissolved in dichloromethane (20 mL), washed with distilled water (2 x 20 mL), dried over magnesium sulfate and evaporated, to give the desired product. Further purification by distillation or column chromatography eluting from hexane/ethyl acetate was carried out when appropriate.

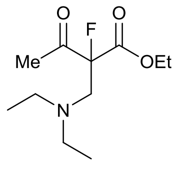
5.1. Mannich reactions of 2-fluoro-ethylacetoacetate and formaldehyde

Ethyl-2-((benzylamino)methyl)-2-fluoro-3-oxobutanoate, 273a



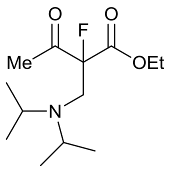
^{1}H NMR (400 MHz, *CDCl$_3$*) δ$_H$ 1.31 (t, *J* = 7.1 Hz, 3H, -OCH$_2$C***H*$_3$**), 1.97 (s, 1H, N***H***), 2.39 (d, *J* = 4.8 Hz, 3H, -C(O)C***H*$_3$**), 3.80 – 4.08 (m, 2H, -CF-C***H*$_2$**-NH-), 4.28 (q, *J* = 7.1 Hz, 2H, -OC***H*$_2$**CH$_3$), 6.63 – 6.95 (m, 3H, -NH-C-C***H***CHC***H***CHC***H***-), 7.12 – 7.24 (m, 2H, -NH-C-CHC***H***CHC***H***CH-). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ$_F$ -169.37 (tq, *J* = 22.4, 4.8 Hz, -C(***F***)-), -167.73 - -167.50 (m). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ$_C$ 13.97 (-OCH$_2$***C***H$_3$), 26.27 (-C(O)***C***H$_3$), 47.53 (d, *J* = 20.5 Hz, -CF-***C***H$_2$-N-), 62.96 (-O***C***H$_2$CH$_3$), 100.23 (d, *J* = 198.8 Hz, -***C***(F)-), 113.62 (-NH-C-***C***HCHCHCHCH-), 118.80 (-NH-C-CHCHCHCH***C***H-), 129.27 (-NH-C-CH***C***H***C***H***C***HCH-), 147.17 (-NH-***C***-CHCHCHCHCH-), 165.01 (d, *J* = 25.4 Hz, -***C***(O)OCH$_2$CH$_3$), 201.35 (d, *J* = 28.6 Hz, -***C***(O)CH$_3$). MS (ESI) m/z 115.02 (100%), 123.98 (68.4%), 224.12 (62.7%), 254.15 ([M+H]$^+$, 72.2%). HRMS (ESI) m/z calcd for [M+H]$^+$ C$_{13}$H$_{17}$FNO$_3$ 254.1200, found 254.1192.

Ethyl-2-((diethylamino)methyl)-2-fluoro-3-oxobutanoate, 273e



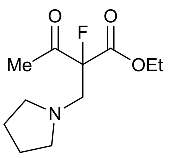
^{1}H NMR (400 MHz, *$CDCl_3$*) δ_H 0.87 (t, *J* = 7.1 Hz, 6H, 2 x –$NCH_2C\boldsymbol{H_3}$), 1.22 (t, *J* = 7.1 Hz, 3H, $-OCH_2C\boldsymbol{H_3}$), 2.23 (s, 1.5 H, $-C(O)C\boldsymbol{H_3}$), 2.24 (s, 1.5 H, $-C(O)C\boldsymbol{H_3}$), 2.51 (qd, *J* = 7.1, 1.0 Hz, 4H, 2 x –$NC\boldsymbol{H_2}CH_3$), 3.05 (s, 1H, $-CF-C\boldsymbol{H_2}-N-$), 3.12 (s, 1H, $-CF-C\boldsymbol{H_2}-N-$), 4.18 (q, *J* = 7.1 Hz, 2H, $-OC\boldsymbol{H_2}CH_3$). ^{19}F NMR (376 MHz, *$CDCl_3$*) δ_F -166.64 (tq, *J* = 26.1, 5.0 Hz, $-C(\boldsymbol{F})-$). ^{13}C NMR (101 MHz, *$CDCl_3$*) δ_C 11.45 (2 x –$NCH_2\boldsymbol{C}H_3$), 13.86 ($-OCH_2\boldsymbol{C}H_3$), 26.41 ($-C(O)\boldsymbol{C}H_3$), 47.89 (d, *J* = 2.5 Hz, 2 x –$N\boldsymbol{C}H_2CH_3$), 56.42 (d, *J* = 18.4 Hz, $-CF-\boldsymbol{C}H_2-N-$), 62.18 ($-O\boldsymbol{C}H_2CH_3$), 102.21 (d, *J* = 199.1 Hz, $-\boldsymbol{C}(F)-$), 165.39 (d, *J* = 26.0 Hz, $-\boldsymbol{C}(O)OCH_2CH_3$), 201.94 (d, *J* = 29.6 Hz, $-\boldsymbol{C}(O)CH_3$). MS (ESI) m/z 234.07 ($[M+H]^+$, 100%), 86.04 ($[M-C_6H_8FO_3]^+$, 95.3%), 266.10 (81.7%). HRMS (ESI) m/z calcd for $[M+H]^+$ $C_{11}H_{21}FNO_3$ 234.1505; found 234.1504.

Ethyl-2-((diisopropylamino)methyl)-2-fluoro-3-oxobutanoate, 273f



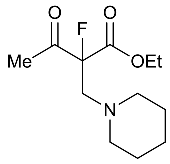
^{1}H NMR (400 MHz, *$CDCl_3$*) δ_H 0.97 (dd, *J* = 6.7, 3.9 Hz, 12H, 2 x $-N-CH-(C\boldsymbol{H_3})_2$), 1.21 (d, *J* = 6.2 Hz, $3H_B$, $-OCH_2C\boldsymbol{H_3}$), 1.32 (t, *J* = 7.1 Hz, $3H_A$, $-OCH_2C\boldsymbol{H_3}$), 2.32 (d, *J* = 5.1 Hz, $3H_A$, $-C(O)C\boldsymbol{H_3}$), 2.38 (d, *J* = 4.7 Hz, $3H_B$, $-C(O)C\boldsymbol{H_3}$), 3.08 (hept, *J* = 6.6 Hz, 2H, $-C(F)-C\boldsymbol{H_2}-N-$), 3.24 (dq, 2H, 2 x $-N-C\boldsymbol{H}-(CH_3)_2$), 4.13 – 4.39 (m, 2H, $-OC\boldsymbol{H_2}CH_3$).^{19}F NMR (376 MHz, *$CDCl_3$*) δ_F -163.81 (ddq, *J* = 22.3, 20.8, 4.7 Hz, $-C(\boldsymbol{F})-$). ^{13}C NMR (101 MHz, *$CDCl_3$*) δ_C 13.98 ($-OCH_2\boldsymbol{C}H_3$), 20.66 (d, *J* = 11.0 Hz, 2 x $-N-CH-(\boldsymbol{C}H_3)_2$), 26.87 ($-C(O)\boldsymbol{C}H_3$), 48.66 (d, *J* = 2.8 Hz, 2 x $-N-\boldsymbol{C}H-(CH_3)_2$), 49.45 (d, *J* = 18.7 Hz, $-C(F)-\boldsymbol{C}H_2-N-$), 62.29 ($-O\boldsymbol{C}H_2CH_3$), 102.78 (d, *J* = 198.7 Hz, $-\boldsymbol{C}(F)-$), 165.72 (d, *J* = 26.0 Hz, $-\boldsymbol{C}(O)OCH_2CH_3$), 202.63 (d, *J* = 30.3 Hz, $-\boldsymbol{C}(O)CH_3$). MS (ESI) m/z 102.10 ($[M-C_7H_{10}FO_3^{\bullet}]^+$, 100%), 114.10 ($[M-C_6H_8FO_3^{\bullet}]^+$, 77.9%), 262.13 ($[M+H]^+$, 74.3%), 294.2 (55.8%). HRMS (ESI) m/z calcd for $[M+H]^+$ $C_{13}H_{25}FNO_3$ 262.1818; found 262.1803.

Ethyl-2-(pyrrolidin-1-methyl)-2-fluoro-3-oxobutanoate, 273g



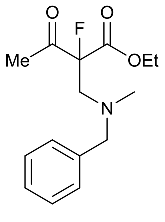
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.25 (tdd, *J* = 7.1, 2.1, 1.3 Hz, 3H, $-OCH_2C\boldsymbol{H_3}$), 1.66 (ddt, *J* = 6.9, 5.1, 2.6 Hz, 4H, $-NCH_2C\boldsymbol{H_2}C\boldsymbol{H_2}CH_2-$), 2.27 (s, 3H, $-C(O)C\boldsymbol{H_3}$), 2.49-2.65 (m, 4H, $-NC\boldsymbol{H_2}CH_2CH_2C\boldsymbol{H_2}-$), 3.06-3.31 (m, 2H, $-CF-C\boldsymbol{H_2}-N-$), 4.10-4.36 (m, 2H, $-OC\boldsymbol{H_2}CH_3$). ^{19}F NMR (376 MHz, *$CDCl_3$*) δ_F -166.84 (ddq, *J* = 29.7, 25.1, 4.8 Hz, $-C(\boldsymbol{F})-$). ^{13}C NMR (101 MHz, *$CDCl_3$*) δ_C 13.93 ($-OCH_2\boldsymbol{C}H_3$), 23.83 ($-NCH_2\boldsymbol{C}H_2\boldsymbol{C}H_2CH_2-$), 26.23 ($-C(O)\boldsymbol{C}H_3$), 55.28 ($-N\boldsymbol{C}H_2CH_2CH_2\boldsymbol{C}H_2-$), 58.41 (d, *J* = 19.4 Hz, $-CF-\boldsymbol{C}H_2-N-$), 62.34 ($-O\boldsymbol{C}H_2CH_3$), 101.62 (d, *J* = 199.2 Hz, $-\boldsymbol{C}(F)-$), 165.35 (d, *J* = 25.8 Hz, $-\boldsymbol{C}(O)OCH_2CH_3$), 201.39 (d, *J* = 28.6 Hz, -***C***(O)CH$_3$). MS (ESI) m/z 232.10 ([M+H]$^+$, 100%), 264.18 (56.4%), 84.01 ([M-C$_5$H$_6$FO$_4^{\bullet}$]$^+$, 49.3%). HRMS (ESI) m/z calcd for [M+H]$^+$ C$_{11}$H$_{19}$FNO$_3$ 232.1349; found 231.1350.

Ethyl-2-(piperidin-1-methyl)-2-fluoro-3-oxobutanoate, 273h



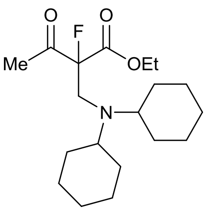
^{1}H NMR (400 MHz, *CDCl$_3$)* δ$_H$ 1.29 (t, *J* = 7.1 Hz, 3H, -OCH$_2$C***H$_3$***), 1.35 (q, *J* = 6.0 Hz, 2H, -NCH$_2$CH$_2$C***H$_2$***CH$_2$CH$_2$-), 1.48 (p, *J* = 5.5 Hz, 4H, -NCH$_2$C***H$_2$***CH$_2$C***H$_2$***CH$_2$-), 2.30 (d, *J* = 4.9 Hz, 3H, -C(O)C***H$_3$***), 2.49 (q, *J* = 5.9 Hz, 4H, -NC***H$_2$***CH$_2$CH$_2$CH$_2$C***H$_2$***-), 3.02 (d, *J* = 26.8 Hz, -CF-C***H$_2$***-N-), 4.09 – 4.43 (m, 2H, -OC***H$_2$***CH$_3$). ^{19}F NMR (376 MHz, *CDCl$_3$)* δ$_F$ -165.59 (tq, *J* = 26.6, 4.9 Hz, -C(***F***)-). ^{13}C NMR (101 MHz, *CDCl$_3$)* δ$_C$ 14.01 (-OCH$_2$***C***H$_3$), 23.84 (-NCH$_2$CH$_2$***C***H$_2$CH$_2$CH$_2$-), 26.18 (-NCH$_2$***C***H$_2$CH$_2$***C***H$_2$CH$_2$-), 26.40 (-C(O)***C***H$_3$), 55.82 (d, *J* = 2.5 Hz, -N***C***H$_2$CH$_2$CH$_2$CH$_2$***C***H$_2$-), 61.10 (d, *J* = 18.5 Hz, -CF-***C***H$_2$-N-), 62.30 (-O***C***H$_2$CH$_3$), 102.16 (d, *J* = 199.9 Hz, -***C***(F)-), 165.40 (d, *J* = 25.8 Hz, -***C***(O)OCH$_2$CH$_3$), 201.75 (d, *J* = 29.3 Hz, -***C***(O)CH$_3$). MS (ESI) m/z 246.31 ([M+H]$^+$, 100%). HRMS (ESI) m/z calcd for [M+H]$^+$ C$_{12}$H$_{21}$FNO$_3$ 246.1505; found 246.1508.

Ethyl-2-((benzylmethylamino)methyl)-2-fluoro-3-oxobutanoate, 273i



^{1}H NMR (400 MHz, *CDCl$_3$)* δ$_H$ 1.30 (t, *J* = 7.1 Hz, 3H, -OCH$_2$C***H$_3$***), 2.26 (d, *J* = 0.8 Hz, 3H, -C(O)C***H$_3$***), 2.34 (d, *J* = 4.7 Hz, 3H, -NC***H$_3$***), 3.24 (dq, *J* = 26.0, 14.7 Hz, 2H, -CF-C***H$_2$***-N-), 3.63 (d, *J* = 5.1 Hz, 2H, -N(CH$_3$)-C***H$_2$***-C-), 4.28 (q, *J* = 7.2 Hz, 2H, -OC***H$_2$***CH$_3$), 7.09 – 7.41 (m, 5H, ***H$_{aromatic}$***). ^{19}F NMR (376 MHz, *CDCl$_3$)* δ$_F$ -166.35 (tq, *J* = 25.8, 4.8 Hz, -C(***F***)-). ^{13}C NMR (101 MHz, *CDCl$_3$)* δ$_C$ 14.02 (-OCH$_2$***C***H$_3$), 26.27 (-C(O)***C***H$_3$), 43.40 (d, *J* = 3.2 Hz, -N***C***H$_3$), 59.84 (d, *J* = 18.4 Hz, -CF-***C***H$_2$-N-), 62.50 (-O***C***H$_2$CH$_3$), 63.51 (d, *J* = 2.5 Hz, -N(CH$_3$)-***C***H$_2$-C-), 102.16 (d, *J* = 199.5 Hz, -***C***(F)-), 127.12 (-CH$_2$-C-CHCH***C***HCHCH-), 128.22 (-CH$_2$-C-***C***HCHCHCH***C***H-), 128.90 (-CH$_2$-C-CH***C***HCH***C***HCH-), 138.59 (-CH$_2$-***C***-CHCHCHCHCH-), 165.36 (d, *J* = 26.0 Hz, -***C***(O)OCH$_2$CH$_3$), 201.13 (d, *J* = 28.8 Hz, -***C***(O)CH$_3$). MS (ESI) m/z 122.23 ([C$_8$H$_{10}$N$^{\bullet}$]$^+$, 100%), 282.23 ([M+H]$^+$, 90.5%), 300.36 (72.4%). HRMS (ESI) m/z calcd for [M+H]$^+$ C$_{15}$H$_{20}$FNO$_3$ 282.1505 ; found 282.1516.

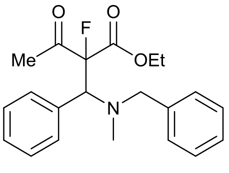
Ethyl-2-((dicyclohexylamino)methyl)-2-fluoro-3-oxobutanoate, 273j



^{1}H NMR (400 MHz, *CDCl$_3$*) δ_H 0.85 – 1.27 (m), 1.41 – 1.55 (m), 1.55 – 1.70 (m), 1.64 – 1.86 (m) (23H, 2 x -N-CH-(C$\boldsymbol{H_2}$)$_{\boldsymbol{5}}$- + -OCH$_2$C$\boldsymbol{H_3}$), 2.19 (d, *J* = 5.2 Hz, 3H$_A$, -C(O)C$\boldsymbol{H_3}$), 2.25 (d, *J* = 4.7 Hz, 3H$_B$, -C(O)C$\boldsymbol{H_3}$), 2.36 – 2.56 (m, 2H, 2 x –N-C$\boldsymbol{H}$-(CH$_2$)$_5$-), 3.14 - 3.35 (m, 2H, -C(F)-C$\boldsymbol{H_2}$-), 3.90 – 4.26 (m, 2H$_{A+B}$, -OC$\boldsymbol{H_2}$CH$_3$). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ_F -171.87 (ddq, *J* = 26.6, 21.8, 4.8 Hz, 1F$_B$, -C($\boldsymbol{F}$)-), -164.36 (tq, *J* = 26.5, 5.2 Hz, 1F$_A$, -C($\boldsymbol{F}$)-). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ_C 13.83 (-OCH2$\boldsymbol{C_A}$H3), 13.96 (-OCH$_2$$\boldsymbol{C_B}H_3$), 25.16, 25.92, 26.00, 26.42, 26.44 (-C(O)$\boldsymbol{C}$H$_3$ + 2 x -N-CH-CH$_2$($\boldsymbol{C}$H$_2$)$_{\boldsymbol{3}}$CH$_2$-), 26.57 (-C(O)$\boldsymbol{C_B}$H$_3$), 26.75 (-C(O)$\boldsymbol{C_A}$H$_3$), 31.74, 31.86, 33.80 (-N-CH-$\boldsymbol{C_{A+B}}$H$_2$(CH$_2$)$_3$$\boldsymbol{C_{A+B}}H_2$-), 50.28 (d, *J* = 18.5 Hz, -C(F)-$\boldsymbol{C_A}$H$_2$-), 52.92 (2 x -N-$\boldsymbol{C_A}$H-(CH$_2$)$_5$-), 58.89 (d, *J* = 2.4 Hz, 2 x -N-$\boldsymbol{C_B}$H-(CH$_2$)$_5$-), 62.07 (-O$\boldsymbol{C_A}$H$_2$CH$_3$), 62.35 (-O$\boldsymbol{C_B}$H$_2$CH$_3$), 63.04 (d, *J* = 20.7 Hz, -C(F)-$\boldsymbol{C_B}$H$_2$-), 100.78 (d, *J* = 199.6 Hz, -$\boldsymbol{C_B}$(F)-), 102.82 (d, *J* = 198.9 Hz, -$\boldsymbol{C_A}$(F)-), 164.77 (d, *J* = 25.2 Hz, -$\boldsymbol{C_B}$(O)OCH$_2$CH$_3$), 165.55 (d, *J* = 26.0 Hz, -$\boldsymbol{C_A}$(O)OCH$_2$CH$_3$), 201.46 (d, *J* = 28.5 Hz, -$\boldsymbol{C_B}$(O)CH$_3$), 202.48 (d, *J* = 30.3 Hz, -$\boldsymbol{C_A}$(O)CH$_3$). MS (ESI) m/z 182.2 ([C$_{12}$H$_{22}$N$^{\bullet}$+H]$^+$, 100%), 191.3 ([M-C$_6$H$_8$FO$_3$$^{\bullet}$]$^+$, 28.9%), 312.4 (38.5%), 342.4 ([M+H]$^+$, 31.5%), HRMS (ESI) m/z calcd for [M+H]$^+$ C$_{19}$H$_{33}$FNO$_3$ 342.2444, found 342.2445.

5.2. Mannich reactions of fluorinated dicarbonyl systems and benzaldehyde

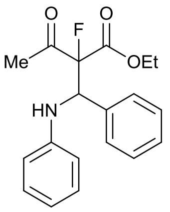
Ethyl-2-(phenyl(benzylmethylamino)methyl)-2-fluoro-3-oxobutanoate, 275a



^{1}H NMR (400 MHz, *CDCl$_3$*) δ_H 0.96 (t, *J* = 7.1 Hz, 3H$_A$, -OCH$_2$C$\boldsymbol{H_3}$), 1.36 (t, *J* = 7.1 Hz, 3H$_B$, -OCH$_2$C$\boldsymbol{H_3}$), 2.13 (d, *J* = 5.6 Hz, 3H$_A$, -C(O)C$\boldsymbol{H_3}$), 2.16 (s, 3H$_A$, -NC$\boldsymbol{H_3}$), 2.21 (s, 3H$_B$, -NC$\boldsymbol{H_3}$), 2.52 (d, *J* = 5.5 Hz, 3H$_B$, -C(O)C$\boldsymbol{H_3}$), 3.32 (d, *J* = 12.9 Hz, 1H, -N(CH$_3$)-C$\boldsymbol{H_2}$-), 3.46 (d, *J* = 13.0 Hz, 1H, -N(CH$_3$)-C$\boldsymbol{H_2}$), 3.67 (d, *J* = 12.9 Hz, 1H, -N(CH$_3$)-C$\boldsymbol{H_2}$), 3.78 (d, *J* = 8.4 Hz, 1H, -N(CH$_3$)-C$\boldsymbol{H_2}$), 3.96 – 4.13 (m, 2H$_A$, -OC$\boldsymbol{H_2}$CH$_3$), 4.41 (qd, *J* = 7.2, 1.5 Hz, 2H$_B$, -OC$\boldsymbol{H_2}$CH$_3$), 4.88 (dd, *J* = 35.0, 33.1 Hz, 1H, -C(F)-C$\boldsymbol{H}$-), 7.08 – 7.97 (m, 10H, $\boldsymbol{H_{aromatic}}$).^{19}F NMR (376 MHz, *CDCl$_3$*) δ_F -176.64 (dq, *J* = 34.6, 5.5 Hz, 1F$_A$, -C($\boldsymbol{F}$)-), -174.89 (dq, *J* = 35.1, 5.5 Hz, 1F$_B$, -C($\boldsymbol{F}$)-). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ_C 13.59 (-C(O)OCH$_2$$\boldsymbol{C_A}H_3$), 14.16 (-C(O)OCH$_2$$\boldsymbol{C_B}H_3$), 26.40 (-C(O)$\boldsymbol{C_B}H_3$), 26.99 (-C(O)$\boldsymbol{C_A}H_3$), 38.92 (d, *J* = 4.9 Hz, -N$\boldsymbol{C_A}$H$_3$), 39.23 (d, *J* = 4.2 Hz, -N$\boldsymbol{C_B}$H$_3$), 59.87 (d, *J* = 3.7 Hz, -N(CH$_3$)-$\boldsymbol{C_B}$H$_2$-C-), 61.00 (d, *J* = 3.0 Hz, -N(CH$_3$)-$\boldsymbol{C_A}$H$_2$-C-), 62.39 (-C(O)O$\boldsymbol{C_A}$H$_2$CH$_3$), 62.70 (-C(O)O$\boldsymbol{C_B}$H$_2$CH$_3$), 69.82 (d, *J* =

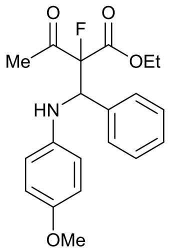
16.0 Hz, -C(F)-**C_B**H-), 70.79 (d, *J* = 15.8 Hz, -C(F)-**C_A**H-), 105.73 (d, *J* = 209.4 Hz, -**C_A**(F)-), 106.66 (d, *J* = 207.7 Hz, -**C_B**(F)-), 126.98, 127.08, 128.15, 128.19, 128.25, 128.41, 128.74, 129.00, 129.74 (**$C_{aromatic}$**), 130.25 (d, *J* = 3.5 Hz, -N(CH_3)-CH_2-**C_A**-), 130.71 (d, *J* = 3.7 Hz, -N(CH_3)-CH_2-**C_B**-), 131.64, 132.02, 134.44 (**$C_{aromatic}$**), 138.99 (-C(F)-CH_2-**C_A**-), 139.17 (-C(F)-CH_2-**C_B**-), 164.57 (d, *J* = 25.5 Hz, -**C_A**(O)OCH_2CH_3), 165.20 (d, *J* = 27.5 Hz, -**C_B**(O)OCH_2CH_3), 200.38 (d, *J* = 29.7 Hz, -**C_B**(O)CH_3), 201.85 (d, *J* = 30.6 Hz, -**C_A**(O)CH_3). MS (ESI) m/z 122.2 ([$C_8H_{10}N^{\bullet}$], 100%), 282.3 ([M-$C_6H_5^{\bullet}$+H]$^+$, 26.6%), 358.2 ([M+H]$^+$, 6.0%) HRMS (ESI) m/z calcd for [M+H]$^+$ $C_{21}H_{24}FNO_3$ 358.1818; found 358.1825.

Ethyl-2-(phenyl(phenylamino)methyl)-2-fluoro-3-oxobutanoate, 275b



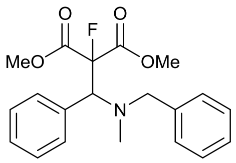
^{1}H NMR (400MHz, *$CDCl_3$*) δ_H 1.12 (t, *J* = 7.1 Hz, 3H, -OCH_2C**H_3**), 1.25 (t, *J* = 7.1 Hz, 3H, -OCH_2C**H_3**), 1.96 (d, *J* = 5.8 Hz, 3H, -OC**H_3**), 2.41 (d, *J* = 5.0 Hz, 3H, -OC**H_3**), 4.13 (qd, *J* = 7.1, 1.4 Hz, 2H, -OC**H_2**CH_3), 4.23 – 4.35 (m, 2H, -OC**H_2**CH_3), 5.47 (dd, *J* = 27.9, 7.0 Hz, 2H, 2 x -CF-C**H**-), 6.63 – 6.87 (m, 5H, **$H_{aromatic}$**), 7.23 – 7.48 (m, 4H, **$H_{aromatic}$**), 7.23 – 7.48 (m, 11H, **$H_{aromatic}$**), 7.48 – 7.56 (m, 2H, **$H_{aromatic}$**), 7.90 – 8.01 (m, 1H, **$H_{aromatic}$**), 8.50 (s, 1H, N**H**). ^{19}F NMR (376 MHz, *$CDCl_3$*) δ_F -179.28 (dq, *J* = 28.1, 5.9 Hz, -C(**F**)-), -178.69 (d, *J* = 24.6 Hz, -C(**F**)-), -109.51. ^{13}C NMR (101 MHz, *$CDCl_3$*) δ_C 13.80 (-OCH_2**C_B**H_3), 13.99 (-OCH_2**C_A**H_3), 26.65 (-C(O)**C_A**H_3), 26.81 (-C(O)**C_B**H_3), 60.51 (d, *J* = 18.3 Hz, -CF-**C_A**H-), 61.07 (d, *J* = 18.6 Hz, -CF-**C_B**H-), 62.80 (-O**C_B**H_2CH_3), 63.10 (-O**C_A**H_2CH_3), 102.32 (d, *J* = 206.2 Hz, -**C_B**(F)-), 103.03 (d, *J* = 204.7 Hz, -**C_A**(F)-), 114.47, 114.86, 115.10, 118.52, 118.93, 119.29 (2 x -NH-C-**C_{A+B}**HCHCHCH**C_{A+B}**H-), 120.89, 125.95, 128.20, 128.43, 128.48 – 128.66 (m), 128.81, 129.12 – 129.34 (m), 131.39 (**$C_{aromatic}$**), 135.47 (-C(F)-CH-**C_A**-), 136.05 (d, *J* = 39.8 Hz, -CF-CH-**C_B**-), 145.46 (-NH-**C_A**-CHCHCHCHCH-), 152.11 (-NH-**C_B**-CHCHCHCHCH-), 160.42 (-**C_B**(O)OCH_2CH_3), 164.61 (-**C_A**(O)OCH_2CH_3), 200.75 (-**C_B**(O)CH_3), 201.05 (-**C_A**(O)CH_3). MS (ESI) m/z 182.08 ([M- $C_6H_8FO_3^{\bullet}$]$^+$, 100%), 330.17 ([M+H]$^+$, 34.0%). HRMS (ESI) m/z calcd for [M+H]$^+$ $C_{19}H_{21}FNO_3$ 330.1505; found 330.1510.

Ethyl-2-(phenyl(4-methoxyphenylamino)methyl)-2-fluoro-3-oxobutanoate, 275c



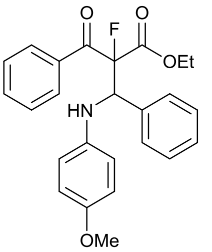
^{1}H NMR (400 MHz, *CDCl$_3$*) δ$_H$ 1.27 (t, *J* = 7.2 Hz, 3H, -OCH$_2$C***H***$_3$), 1.94 (d, *J* = 5.7 Hz, 3H, -C(O)C***H***$_3$), 3.70 (s, 3H, -OC***H***$_3$), 4.24-4.39 (m, 2H, -OC***H***$_2$CH$_3$), 5.34 (d, *J* = 28.2 Hz, 1H, -CF-C***H***-), 6.60-6.73 (m, 4H, -NH-C-(C***H***)$_2$-C(OMe)-(C***H***)$_2$-), 6.68-6.73 (m, 2H), 7.13-7.46 (m, 5H, -CH-C-(C***H***)$_5$-). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ$_F$ -179.57 (q, *J* = 5.8 Hz, -C(***F***)-), -179.49 (q, *J* = 5.8 Hz, -C(***F***)-). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ$_C$ 14.01 (-OCH$_2$***C***H$_3$), 26.63 (-C(O)***C***H$_3$), 55.55 (-O***C***H$_3$), 61.74 (d, *J* = 18.2 Hz, -CF-***C***H-), 63.01 (-O***C***H$_2$CH$_3$), 103.21 (d, *J* = 204.6 Hz, -***C***(F)-), 114.67 (-NH-C-CH***C***H-C(OMe)-***C***HCH-), 116.18 (-NH-C-***C***HCH-C(OMe)-CH***C***H-), 128.43 – 128.59 (m, ***C$_{aromatic}$***), 135.56 (-C(F)-CH-***C***-), 139.37 (-NH-***C***-CHCH-C(OMe)-CHCH-), 153.04 (-NH-CHCH-***C***(OMe)-CHCH-), 164.57 (d, *J* = 26.7 Hz, -***C***(O)OCH$_2$CH$_3$), 200.99 (d, *J* = 29.5 Hz, -***C***(O)CH$_3$). MS (ASAP) m/z 212.11 ([M-C$_6$H$_8$FO$_3^{\bullet}$]$^+$, 100%), 360.17 ([M+H]$^+$, 1.9%). HRMS (ASAP) m/z calcd for [M]$^+$ C$_{20}$H$_{22}$FNO$_4$ 359.1533; found 359.1538.

Dimethyl-2-(phenyl(benzylmethylamino)methyl)-2-fluoromalonate, 275d



^{1}H NMR (400MHz, *CDCl$_3$*) δ$_H$ 2.22 (s, 3H, -NC***H***$_3$), 3.40 (d, *J* = 13.0 Hz, 1H, -N(CH$_3$)-C***H***$_2$-), 3.60 (s, 3H, -C(O)OC***H***$_3$), 3.73 (d, *J* = 13.1 Hz, 1H, -N(CH$_3$)-C***H***$_2$-), 3.95 (s, 3H, -C(O)OC***H***$_3$), 4.87 (d, *J* = 33.8 Hz, 1H, -C(F)-C***H***-), 7.05 – 7.72 (m, 10H, ***H$_{aromatic}$***). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ$_F$ -176.52 (d, *J* = 33.7 Hz, -C(***F***)-). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ$_C$ 39.14 (d, *J* = 4.5 Hz, -N***C***H$_3$), 53.28 (-C(O)O***C***H$_3$), 53.43 (-C(O)O***C***H$_3$), 60.37 (d, *J* = 3.2 Hz, -N(CH$_3$)-***C***H$_2$-), 69.90 (d, *J* = 16.1 Hz, -C(F)-***C***H-), 100.63 (d, *J* = 211.5 Hz, -***C***(F)-), 127.07, 128.22, 128.23, 128.73, 129.02, 129.73, 130.51, 130.54 (***C$_{aromatic}$***), 134.46 (-N(CH$_3$)-CH$_2$-***C***-), 139.12 (-C(F)-CH-***C***-), 165.11 (d, *J* = 25.7 Hz, -***C***(O)OCH$_3$), 165.90 (d, *J* = 27.6 Hz, -***C***(O)OCH$_3$).MS (ESI) m/z 122.2 ([C$_8$H$_{10}$N$^{\bullet}$], 100%), 346.2 (10.3%), 360.4 ([M+H]$^+$, 7.2%) HRMS (ESI) m/z calcd for [M+H]$^+$ C$_{20}$H$_{22}$FNO$_4$ 360.1612; found 360.1611.

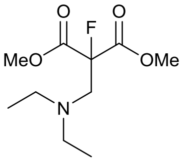
Ethyl-2-(phenyl(4-methoxyphenylamino)methyl)-2-fluoro-3-benzoylacetate, 275e



^{1}H NMR (400 MHz, *CDCl$_3$*) δ$_H$ 1.24 (t, *J* = 7.1 Hz, 3H, -OCH$_2$C***H***$_3$), 1.59 (s, 1H, N***H***), 3.71 (s, 3H, -OC***H***$_3$), 4.26 (dq, *J* = 10.7, 7.1 Hz, 2H, -OC***H***$_2$CH$_3$), 4.31 – 4.43 (m, 2H, -OC***H***$_2$CH$_3$), 5.68 (dd, *J* = 28.6, 11.8 Hz, 1H, -CF-C***H***-), 6.61 – 6.78 (m, 4H, -NH-C-(C***H***)$_2$-C(OMe)-(C***H***)$_2$-), 7.16 – 7.27 (m, 3H, -CF-CH-C-CHC***H***C***H***C***H***CH-), 7.34 – 7.46 (m, 4H, -CF-CH-C-C***H***CHCHCHC***H***- + -C(O)CHC***H***CHC***H***CH-), 7.47 – 7.58 (m, 1H, -C(O)CHCHC***H***CHCH-), 7.84 (ddd, *J* = 8.6, 2.1, 1.3 Hz, 2H, -C(O)C***H***CHCHCHC***H***-). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ$_F$ -173.71 (t, *J* = 2.0 Hz, -C(***F***)-), -173.64 (q, *J* = 2.0 Hz, -C(***F***)-). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ$_C$ 14.01 (-OCH$_2$***C***H$_3$), 55.57 (-O***C***H$_3$), 61.83 (d, *J* = 18.6 Hz, -CF-***C***H-), 63.13 (-O***C***H$_2$CH$_3$), 103.63 (d, *J* = 206.5 Hz, -***C***(F)-), 114.65 (-NH-C-CH***C***H-C(OMe)-***C***HCH-), 116.23 (-NH-C-***C***HCH-C(OMe)-CH***C***H-), 127.97, 128.24, 128.38, 128.99, 129.00, 129.45, 129.52 (***C$_{aromatic}$***), 133.68 (-CF-C(O)-***C***-), 136.20 (-CF-CH-***C***-), 139.63 (-NH-***C***-CHCH-C(OMe)-CHCH-), 153.01 (-NH-CHCH-***C***(OMe)-CHCH-), 165.72 (d, *J* = 27.1 Hz, -***C***(O)OCH$_2$CH$_3$), 191.74 (d, *J* = 26.5 Hz, -***C***(O)CH$_3$). MS (ASAP) m/z 212.11 ($[M-C_{11}H_{10}FO_3^{\bullet}]^+$, 100%), 421.19 ($[M]^+$, 1.9%). HRMS (ASAP) m/z calcd for $[M]^+$ $C_{25}H_{25}FNO_4$ 421.1689; found 421.1674.

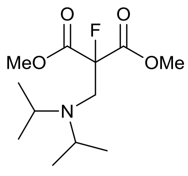
5.3. Mannich reactions of 2-fluoro-1,3-dimethymalonate and formaldehyde

Dimethyl-2-((diethylamino)methyl)-2-fluoromalonate, 274c



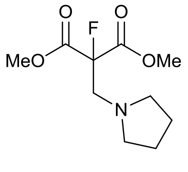
^{1}H NMR (400 MHz, *CDCl$_3$*) δ$_H$ 0.91 (t, *J* = 7.1 Hz, 6H, 2 x –CH$_2$C***H***$_3$), 2.57 (q, *J* = 7.1 Hz, 4H, 2 x C***H***$_2$CH$_3$), 3.17 (d, *J* = 26.2 Hz, 2H, -CF-C***H***$_2$-N-), 3.78 (s, 6H, 2 x -OC***H***$_3$). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ$_F$ -166.73 (t, 1F, *J* = 26.1 Hz, -C(***F***)-), -135.15 (tt, 1F, *J* = 26.8, 13.7 Hz). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ$_C$ 11.62 (-NCH$_2$***C***H$_3$), 11.74 (-NCH$_2$***C***H$_3$), 47.97 (d, *J* = 2.5 Hz, -N***C***H$_2$CH$_3$), 48.25 (d, *J* = 2.0 Hz, -N***C***H$_2$CH$_3$), 52.99 (2 x -O***C***H$_3$), , 56.38 (d, *J* = 18.7 Hz, -CF-***C***H$_2$-N-), 56.82 (d, *J* = 19.1 Hz, -CF-***C***H$_2$-N-), 97.27 (d, *J* = 200.0 Hz, -***C***(F)-), 165.82 (d, *J* = 26.3 Hz, 2 x -***C***(O)OCH$_3$). MS (ESI) m/z 236.14 ($[M+H]^+$, 100%), 178.08 ($[M-C_2H_3O_2^{\bullet}+2H]^+$, 64.1%), 122.04 (43.1%), 86.02 ($[M-C_5H_6FO_4^{\bullet}]^+$, 36.9%). HRMS (ESI) m/z calcd for $[M+H]^+$ $C_{10}H_{19}FNO_4$ 236.1298; found 236.1299.

Dimethyl-2-((diisopropylamino)methyl)-2-fluoromalonate, 274d



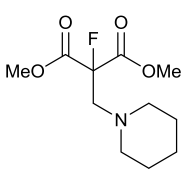
^{1}H NMR (400 MHz, *CDCl$_3$*) δ$_H$ 0.95 (d, *J* = 6.7 Hz, 12H$_A$, 2 x -N-CH-(C$\boldsymbol{H_3}$)$_2$), 1.25 (d, *J* = 6.7 Hz, 12H$_B$, 2 x -N-CH-(C$\boldsymbol{H_3}$)$_2$), 2.97 – 3.13 (m, 2H, -C(F)-C$\boldsymbol{H_2}$-N-), 3.29 (d, *J* = 26.8 Hz, 2H$_A$, 2 x -N-C$\boldsymbol{H}$-(CH$_3$)$_2$), 3.80 (s, 6H$_A$, 2 x -OC$\boldsymbol{H_3}$), 3.86 (s, 6H$_B$, 2 x -OC$\boldsymbol{H_3}$), 4.18 (d, *J* = 21.9 Hz, 2H$_B$, 2 x -N-C$\boldsymbol{H}$-(CH$_3$)$_2$).^{19}F NMR (376 MHz, *CDCl$_3$*) δ$_F$ -172.83 (t, *J* = 21.8 Hz, 1F$_B$, -C($\boldsymbol{F}$)-), -163.14 (t, *J* = 26.7 Hz, 1F$_A$, -C($\boldsymbol{F}$)-). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ$_C$ 20.62 (2 x -N-CH-($\boldsymbol{C_A}$H$_3$)$_2$), 21.13 (2 x -N-CH-($\boldsymbol{C_B}$H$_3$)$_2$), 48.42 (d, *J* = 3.0 Hz, 2 x -N-$\boldsymbol{C_A}$H-(CH$_3$)$_2$), 49.05 (d, *J* = 1.9 Hz, 2 x -N-$\boldsymbol{C_B}$H-(CH$_3$)$_2$), 49.51 (d, *J* = 19.1 Hz, -C(F)-$\boldsymbol{C_A}$H$_2$-N-), 50.48 (d, *J* = 19.3 Hz, -C(F)-$\boldsymbol{C_B}$H$_2$-N-), 52.96 (-C(O)O$\boldsymbol{C_A}$H$_3$), 53.49 (-C(O)O$\boldsymbol{C_B}$H$_3$), 94.87 (d, *J* = 199.6 Hz, -$\boldsymbol{C_B}$(F)-), 97.98 (d, *J* = 199.3 Hz, -$\boldsymbol{C_A}$(F)-), 165.10 (d, *J* = 25.4 Hz, -$\boldsymbol{C_B}$(O)OCH$_3$), 166.05 (d, *J* = 26.4 Hz, -$\boldsymbol{C_A}$(O)OCH$_3$). MS (ESI) m/z 102.26 ([M-C$_6$H$_8$FO$_4^{\bullet}$]$^+$, 100%), 114.10 ([M-C$_5$H$_6$FO$_4^{\bullet}$]$^+$, 49.6%), 264.29 ([M+H]$^+$, 68.5%). HRMS (ESI) m/z calcd for [M+H]$^+$ C$_{12}$H$_{23}$FNO$_4$ 264.1620; found 264.1611.

Dimethyl-2-(pyrrolidin-1-methyl)-2-fluoromalonate, 274e



^{1}H NMR (400 MHz, *CDCl$_3$*) δ$_H$ 1.63 – 1.74 (m, 4H, -NC$\boldsymbol{H_2}$CH$_2$CH$_2$C$\boldsymbol{H_2}$-), 2.54 – 2.66 (m, 4H, -NCH$_2$C$\boldsymbol{H_2}$C$\boldsymbol{H_2}$CH$_2$-), 3.24 (d, *J* = 26.6 Hz, 2H, -C(F)-C$\boldsymbol{H_2}$-N-), 3.81 (s, 6H, 2 x –C(O)OC$\boldsymbol{H_3}$). ^{19}F NMR (376 MHz, *CDCl$_3$*) δ$_F$ -166.92 (t, *J* = 26.7 Hz, -C($\boldsymbol{F}$)-). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ$_C$ 23.89 (-NCH$_2$$\boldsymbol{C}H_2$$\boldsymbol{C}H_2CH_2$-), 53.18 (2 x -C(O)O$\boldsymbol{C}H_3$), 55.26 (d, *J* = 1.8 Hz, -N$\boldsymbol{C}$H$_2$CH$_2$CH$_2$$\boldsymbol{C}H_2$-), 58.67 (d, *J* = 19.5 Hz, -CF-$\boldsymbol{C}$H$_2$-N-), 96.43 (d, *J* = 200.4 Hz, -$\boldsymbol{C}$(F)-), 165.81 (d, *J* = 25.9 Hz, -$\boldsymbol{C}$(O)OCH$_3$). MS (ESI) m/z 152.23 ([M-C$_5$H$_6$FO$_4^{\bullet}$]$^+$, 50.4%), 234.21 ([M+H]$^+$, 100%). HRMS (ESI) m/z calcd for [M+H]$^+$ C$_{10}$H$_{17}$FNO$_4$ 234.1142; found 234.1145.

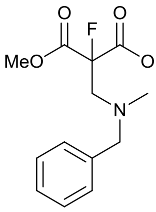
Dimethyl-2-(piperidin-1-methyl)-2-fluoromalonate, 274f



^{1}H NMR (400 MHz, *CDCl$_3$*) δ$_H$ 1.24-1.38 (m, 2H, -NCH$_2$CH$_2$C$\boldsymbol{H_2}$CH$_2$CH$_2$-), 1.44 (ddt, *J* = 24.9, 11.0, 5.6 Hz, 4H, -NCH$_2$C$\boldsymbol{H_2}$CH$_2$C$\boldsymbol{H_2}$CH$_2$-), 2.35 (d, *J* = 5.8 Hz, 2H, -NC$\boldsymbol{H_2}$CH$_2$CH$_2$CH$_2$C$\boldsymbol{H_2}$-), 2.44 (d, *J* = 5.3 Hz, 2H, -NC$\boldsymbol{H_2}$CH$_2$CH$_2$CH$_2$C$\boldsymbol{H_2}$-), 3.00 (d, *J* = 26.6 Hz, 2H, -C(F)-C$\boldsymbol{H_2}$-), 3.74 (s, 6H, 2 x -OC$\boldsymbol{H_3}$).^{19}F NMR (376 MHz, *CDCl$_3$*) δ$_F$ -165.65 (t, *J* = 26.6 Hz, -C($\boldsymbol{F}$)-). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ 23.79 (-NCH$_2$CH$_2$$\boldsymbol{C}H_2CH_2CH_2$-), 25.73, 26.17 (-NCH$_2$$\boldsymbol{C}H_2CH_2$$\boldsymbol{C}H_2CH_2$-, 52.88 (-C(O)O$\boldsymbol{C}H_3$), 52.98 (-C(O)O$\boldsymbol{C}H_3$), 55.60, 55.62 (-

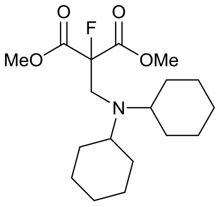
N***C***$H_2CH_2CH_2CH_2$***C***H_2-), 61.11 (d, *J* = 18.8 Hz, -CF-***C***H_2-N-), 97.11 (d, *J* = 200.9 Hz, -***C***(F)-), 165.71 (d, *J* = 26.1 Hz, 2 x -***C***(O)OCH_3). MS (ESI) m/z 85.85 ([M-$C_6H_8FO_4^{\bullet}$+H]$^+$, 100%), 190.10 ([M-$C_2H_3O_2^{\bullet}$+H]$^+$, 95.7%), 248.15 ([M+H]$^+$, 73.6%). HRMS (ESI) m/z calcd for [M+H]$^+$ $C_{11}H_{19}FNO_4$ 248.1298; found 248.1296.

Dimethyl-2-((benzylmethylamino)methyl)-2-fluoromalonate 274g



^{1}H NMR (400 MHz, *$CDCl_3$*) δ_H 2.31 (d, *J* = 21.2 Hz, 3H, -NC***H_3***), 3.31 (d, *J* = 25.9 Hz, 1H, -C(F)-C***H_2***-), 3.68 (d, *J* = 5.9 Hz, 2H, -N(CH_3)-C***H_2***-C-), 3.85 (s, 6H, 2 x -OC***H_3***), 7.11 – 7.55 (m, 5H, ***H**aromatic*). ^{19}F NMR (376 MHz, *$CDCl_3$*) δ_F -166.08 (t, *J* = 25.9 Hz, -C(***F***)-). ^{13}C NMR (101 MHz, *$CDCl_3$*) δ_C 40.48, 43.53 (d, *J* = 3.3 Hz, -N***C***H_3), 53.22 (-C(O)O***C***H_3), 59.48, 59.89 (d, *J* = 18.7 Hz, -CF-***C***H_2-N-), 63.46 (d, *J* = 2.3 Hz, -N(CH_3)-***C***H_2-C-), 97.03 (d, *J* = 200.2 Hz, -***C***(F)-), 126.76, 127.16, 128.18, 128.25, 128.90 (***C**aromatic*), 138.73, 139.62 (-N(CH_3)-CH_2-***C***-), 165.73 (d, *J* = 26.1 Hz, 2 x -***C***(O)OCH_3). MS (ESI) m/z 122.09 ([M-$C_6H_8FO_4^{\bullet}$+2H]$^+$, 100%), 90.98 ([M-$C_7H_{11}FNO_4^{\bullet}$]$^+$, 65.3%), 284.12 ([M+H]$^+$, 44.8%). HRMS (ESI) m/z calcd for [M+H]$^+$ $C_{14}H_{19}FNO_4$ 284.1298; found 284.1301.

Dimethyl-2-((dicyclohexylamino)methyl)-2-fluoromalonate, 274h



^{1}H NMR (400 MHz, *$CDCl_3$*) δ_H 0.96 – 1.33 (m), 1.42 – 1.98 (m) (22H, 2 x -N-CH-(C***H_2)$_5$***-), 2.42 – 2.70 (m, 2H, 2 x –N-C***H***-$(CH_2)_5$-), 3.39 (d, *J* = 26.4 Hz, 2H_A, -C(F)-C***H_2***-), 3.79 (s), 3.83 (s) (6H, 2 x -OC***H_3***), 4.14 (d, *J* = 23.6 Hz, 2H_B, -C(F)-C***H_2***-).^{19}F NMR (376 MHz, *$CDCl_3$*) δ_F -171.85 (t, *J* = 23.7 Hz, -C(***F***)-), -166.39 (dd, *J* = 21.9, 18.4 Hz, -C(***F***)-), -163.94 (t, *J* = 26.3 Hz, -C(***F***)-), -159.36 (dd, *J* = 32.0, 17.8 Hz, -C(***F***)-). ^{13}C NMR (101 MHz, *$CDCl_3$*) δ_C 25.23, 26.01, 26.51 (2 x -N-CH-CH_2(***C***H_2)$_3$$CH_2$-), 31.93 , 33.57 (2 x -N-CH-***C***$H_2$$(CH_2)_3$***C***$H_2$-), 50.64 (d, *J* = 18.9 Hz, -C(F)-***C***H_2-), 52.96 (d, *J* = 9.5 Hz, -N-***C***H-$(CH_2)_5$-), 58.77 (d, *J* = 2.5 Hz, -N-***C***H-$(CH_2)_5$-), 63.47 (d, *J* = 21.5 Hz, -C(F)-***C***H_2-), 95.59 (d, *J* = 199.9 Hz, -***C***(F)-), 98.02 (d, *J* = 200.0 Hz, -***C***(F)-), 165.28 (d, *J* = 25.5 Hz, -***C***(O)OCH_3), 166.09 (d, *J* = 26.4 Hz, -***C***(O)OCH_3). MS (ESI) m/z 182.31 ([$C_{12}H_{22}N^{\bullet}$+H]$^+$, 100%), 194.34 ([M-$C_5H_6FO_4^{\bullet}$]$^+$, 79.3%), 344.20 ([M+H]$^+$,15.8%). HRMS (ESI) m/z calcd for [M+H]$^+$ $C_{18}H_{31}FNO_4$ 344.2237, found 344.2247.

6. Experimental to chapter 6

6.1. Direct fluorination of functionalized carbonyl compounds

General procedure

In a 100 mL glass reaction vessel fitted with a PTFE coated mechanical stirrer, a FEP gas delivery tube and an exit tube to a scrubber filled with soda lime was charged with carbonyl compound, hydrated cupric nitrate, and acetonitrile (50 mL) before being cooled to 5-8 °C (see Table 42). The vessel was purged with nitrogen and then fluorine diluted to 10% v.v^{-1} with nitrogen was passed through the stirred solution at a rate of 40.0 mmol/h for 5 hours. When the fluorine supply has been turned off, the reaction vessel was purged with nitrogen. The reaction mixture was then evaporated under reduced pressure, washed two times with 100 mL of sat. NaCl solution, extracted with ethyl acetate (2 x 50 mL). Then anhydrous sodium sulfate was added and the mixture was filtered over Celite, and then concentrated under reduced pressure yielding a mixture of di-fluoro and mono-fluoro products, which was analyzed by NMR spectroscopy. Further purifications were carried out on the resulting mixture from fluorination with methylnitroacetate using multiple distillations under reduced pressure (5 mbar, 150 °C).

Table 42 *Direct fluorination of carbonyl compounds*

Entry	**Carbonyl compound**			**$Cu(NO_3)_2.2.5H_2O$**		**Yield [%]**[a]
1	Tertbutyl-cyanoacetate	4.3 mL	30 mmol	0.70 g	3.0 mmol	37
2	Trimethyl-phosphonoacetate	4.9 mL			3.0 mmol	48
3	Methyl-nitroacetate	2.75 mL			3.0 mmol	95
4	Ethyl-cyanoacetate	3.2 mL			3.0 mmol	35
5	Methyl-sulfonylacetate	3.3 mL	20 mmol	0.47 g	2.0 mmol	37

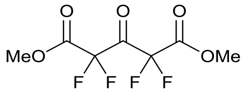
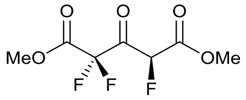
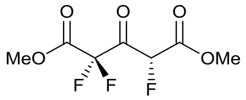
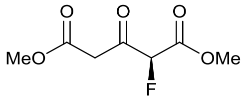
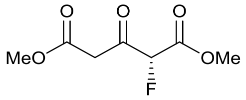
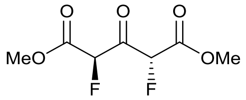
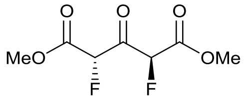
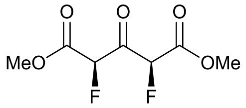
[a] By ^{19}F-NMR

6.2. Direct fluorination of tricarbonyl systems

General procedure

In a 100 mL glass reaction vessel fitted with a PTFE coated mechanical stirrer, a FEP gas delivery tube and an exit tube to a scrubber filled with soda lime was charged with tricarbonyl compound **307**, hydrated cupric nitrate (10 mol%), and acetonitrile (50 mL) before being cooled to 0-5 °C (see Table 44). The vessel was purged with nitrogen and then fluorine diluted with nitrogen was passed through the stirred solution at a chosen rate. When the fluorine supply has been turned off, the reaction vessel was purged with nitrogen. The reaction mixture was then evaporated under reduced pressure, washed two times with 100 mL of sat. NaCl solution, extracted with ethyl acetate (2 x 50 mL). Then anhydrous sodium sulfate was added and the mixture was filtered over Celite, and then concentrated under reduced pressure yielding a mixture of di-fluoro and mono-fluoro products, which was analyzed by NMR spectroscopy. ^{19}F-NMR data for each of these products is included in chapter 6 (Table 26).

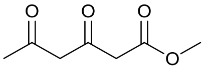
Table 44 *Fluorination of dimethylacetone-1,3-dicarboxylate in batch using various conditions*

	Entry	1[a]	2[a]	3[a]	4[b]	5[b]	6[b]
	F_2/N_2 [%]	10	10	10	20	20	10
	Flow rate [mL/min]	20	40	20	80	20	40
	Reaction time [min]	180	180	300	180	168	168
	F_2 [eq.]	0.49	0.98	0.80	4.69	1.10	1.10
Products [^{19}F-NMR %]	 **303**	6	8	9	39	29	1
	 **310** 	9	20	18	31	29	6
	 **308** 	15	17	24	7	14	8
	 **309a** 	60	47	35	20	21	65
	 **309b**	8	8	8	2	7	20

[a] Reaction achieved on 30 mmol scale; [b] Reaction achieved on 25 mmol scale

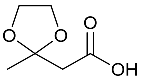
6.3. Synthesis of various tricarbonyl systems

Methyl 3,5-dioxohexanoate, 323



Magnesium turnings (2.6 g, 107 mmol) were dissolved in 500 mL methanol and dehydroacetic acid **322** (12 g, 70 mmol) in methanol (100 mL) was added. The reaction mixture was heated under reflux overnight, after which the solvent was removed under reduced pressure. The residue was taken up in ethyl acetate and acidified with aqueous 1M HCl (~ 200 mL) and extracted with ethyl acetate (5 x 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was then distilled under reduced pressure (110 °C / 15 mbar) to afford **323** as a colorless liquid (8.3 g, 75%). ^{1}H NMR spectrum indicated the presence of 72% of an enol form. ^{1}H NMR (400 MHz, *$CDCl_3$*) enol: δ_H 2.00 (s, 3H, -C(OH)C***H***$_3$), 3.26 (s, 2H, -C***H***$_2$-C(O)OCH$_3$), 3.66 (s, 3H, -C(O)OC***H***$_3$), 5.55 (s, 1H, ***H***$_{enol}$), ketone: δ_H 2.17 (s, 3H, -C(O)C***H***$_3$), 3.50 (s, 2H, -C***H***$_2$-C(O)OCH$_3$), 3.66 (s, 3H, -C(O)C***H***$_3$), 3.69 (s, 2H, -C***H***$_2$-C(O)CH$_3$). ^{13}C NMR (101 MHz, *$CDCl_3$*) enol: δ_C 24.19 (1C, -C(OH)***C***H$_3$), 44.78 (1C, -***C***H$_2$-C(O)OCH$_3$), 52.31 (1C, -C(O)O***C***H$_3$), 100.45 (1C, -***C***(H$_{enol}$)-, 167.89 (1C, -***C***(O)OCH$_3$), 187.11 (1C, -***C***(OH)CH$_3$), 190.04 (1C, -C(H$_{enol}$)-***C***(O)-CH$_2$-), ketone: 30.66 (1C, -C(O)***C***H$_3$), 49.07 (1C, -***C***H$_2$-C(O)OCH$_3$), 52.31 (1C, -C(O)O***C***H$_3$), 57.11 (1C, -***C***H$_2$--C(O)CH$_3$), 167.31 (1C, -***C***(O)OCH$_3$), 196.81 (1C, -***C***(O)CH$_3$), 201.70 (1C, -CH$_2$-***C***(O)-CH$_2$-). IR (ATR) 2983 (w), 1728 (vs), 1713 (vs), 1614 (vs), 1417 (w), 1373 (m), 1360 (m), 1239 (vs), 1157 (w), 1045 (s), 1003 (w), 939 (w), 913 (m), 847 (w), 780 (m), 629 (w), 606 (m), 530 (w), 510 (w), 480 (w), 446 (w), 404 (w). MS (EI, 70 eV): m/z (%) = 87 (100), 43 (47), 129 (13), 113 (8).

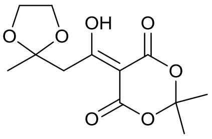
(2-Methyl-1,3-dioxolan-2-yl) acetic acid, 325



To a solution of ethyl 2-(2-methyl-1,3-dioxolan-2-yl) acetate (15.0 g, 86.1 mmol) in ethanol (75 mL) an aqueous solution of KOH (2M, 64.6 mL, 126.2 mmol) was added dropwise. After stirring the reaction mixture at room temperature for 1.5 h, ethanol was removed under reduced pressure. The aqueous phase was then washed with MTBE (2 x 25 mL), acidified to pH 3 using 2M HCl and extracted with ethyl acetate (5 x 50 mL). The combined organic fractions were dried over $MgSO_4$ and the solvent was then removed under reduced pressure giving a colorless oil (11.4 g, 91%). ^{1}H NMR (400 MHz, *$CDCl_3$*) δ_H 1.43 – 1.52 (m, 3H, -CH$_2$-C(O(CH$_2$)$_2$O-)-C***H***$_3$), 2.62 – 2.73 (m, 2H, -C***H***$_2$-C(O(CH$_2$)$_2$O-)-CH$_3$), 3.94 – 3.98 (m, 4H, -CH$_2$-C(O(C***H***$_2$)$_2$O-)-CH$_3$), 10.07 (br s, 1H, OH). ^{13}C NMR (101 MHz, *$CDCl_3$*) δ_C

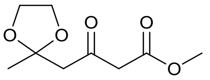
24.30 (1C, $-CH_2-C(O(CH_2)_2O-)-\boldsymbol{C}H_3$), 43.88 (1C, $-\boldsymbol{C}H_2-C(O(CH_2)_2O-)-CH_3$), 64.72 (2C, $-CH_2-C(O(\boldsymbol{C}H_2)_{\boldsymbol{2}}O-)-CH_3$), 107.42 (1C, $-CH_2-\boldsymbol{C}(O(CH_2)_2O-)-CH_3$), 174.78 (1C, -$\boldsymbol{C}$(O)OH). IR (ATR) 2981 (m), 2891 (m), 1711 (vs), 1379 (s), 1306 (w), 1184 (s), 1120 (w), 1093 (w), 1041 (vs), 950 (s), 855 (s), 838 (s), 799 (w), 746 (w), 645 (s), 594 (w), 511 (m), 395 (m). MS (EI, 70 eV): m/z (%) = 87 (100), 43 (61), 129 (10), 69 (3).

5-(1-hydroxy-2-(2-methyl-1,3-dioxolan-2-yl)ethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione, 326



Meldrum’s acid (4.53 g, 31.5 mmol), DCC (7.15 g, 34.6 mmol) and DMAP (4.23 g, 34.6 mmol) were dissolved in freshly distilled dichloromethane (50 mL). The solution was cooled to 0 °C and a solution of 2-(2-Methyl-1,3-dioxolan-2-yl) acetic acid **325** (4.6 g, 31.5 mmol) in anhydrous dichloromethane (20 mL) was added dropwise over an hour. The resulting solution was stirred in an ice bath over night (~ 18 hours), during which time crystals of dicyclohexylurea were formed. After filtration and evaporation of the solvent, water was added and the mixture was acidified with $KHSO_4$ to pH 2-3 and extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with 2% $KHSO_4$, water and dried over anhydrous magnesium sulfate. After filtration and evaporation of the solvent, the residual mixture was re-dissolved in hot petroleum ether and filtrated over celite. The clear solution was concentrated under reduced pressure affording **326** as a pale yellow oil (7.9 g, 93%). ^{1}H NMR (400 MHz, *$CDCl_3$*) δ_H 1.50 (s, 3H, $-CH_2-C(O(CH_2)_2O-)-C\boldsymbol{H_3}$), 1.74 (s, 6H, $-C(C\boldsymbol{H_3})_{\boldsymbol{2}}$), 3.54 (s, 2H, $-C\boldsymbol{H_2}-C(O(CH_2)_2O-)-CH_3$), 3.88 – 4.07 (m, 4H, $-CH_2-C(O(C\boldsymbol{H_2})_{\boldsymbol{2}}O-)-CH_3$). ^{13}C NMR (101 MHz, *$CDCl_3$*) δ_C 25.33 (1C, $-CH_2-C(O(CH_2)_2O-)-\boldsymbol{C}H_3$), 26.71 (2C, $-C(\boldsymbol{C}H_3)_{\boldsymbol{2}}$), 43.52 (1C, $-\boldsymbol{C}H_2-C(O(CH_2)_2O-)-CH_3$), 65.04 (2C, $-CH_2-C(O(\boldsymbol{C}H_2)_{\boldsymbol{2}}O-)CH_3$), 93.85 (1C, $-CH_2-C(OH)-\boldsymbol{C}-$), 104.77 (1C, $-\boldsymbol{C}(CH_3)_2$), 108.55 (1C, $-CH_2-\boldsymbol{C}(O(CH_2)_2O-)-CH_3$), 160.53, 170.35 (2C, 2 x $-C(OH)-C-(\boldsymbol{C}(O))_{\boldsymbol{2}}-$), 191.78 (1C, $-CH_2-\boldsymbol{C}(OH)-C-$). IR (ATR) 3661 (w), 2981 (m), 2890 (m), 2338 (w), 1737 (vs), 1661 (vs), 1574 (vs), 1403 (s), 1381 (s), 1292 (m), 1267 (s), 1201 (s), 1149 (s), 1105 (w), 1030 (vs), 970 (m), 950 (m), 929 (s), 893 (w), 841 (w), 810 (w), 790 (w), 746 (m), 727 (m), 680 (w), 642 (m), 608 (w), 547 (w), 506 (m), 464 (m), 407 (m), 383 (w). MS (EI, 70 eV): m/z (%) = 85 (100), 43 (71), 126 (40), 117 (23), 69 (21).

Methyl 4-(2-methyl-1,3-dioxolan-2-yl)-3-oxobutanoate, 327



5-(1-hydroxy-2-(2-methyl-1,3-dioxolan-2-yl)ethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione **326** (2.75 g, 20.2 mmol) was dissolved in toluene (25 mL) and methanol (1.86 mL, 45.6 mmol) was added. The mixture was then stirred at 90 °C for 3 hours and concentrated to afford quantitatively the desired product **327** as a pale yellow oil (4.0 g, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.41 (s, 3H, $-CH_2-C(O(CH_2)_2O-)-C\boldsymbol{H_3}$), 2.89 (s, 2H, $-C\boldsymbol{H_2}-C(O(CH_2)_2O-)-CH_3$), 3.59 (s, 2H, $-C\boldsymbol{H_2}-C(O)OCH_3$), 3.74 (s, 3H, $-CH_2-C(O)OC\boldsymbol{H_3}$), 3.96 – 4.01 (m, 4H, $-CH_2-C(O(C\boldsymbol{H_2})_{\boldsymbol{2}}O-)-CH_3$). Presence of the enol form (< 5%) δ_H 3.64 (s, 3H, $-CH_2-C(O)OC\boldsymbol{H_3}$)**,** 5.11 (s, 1H, $-C(\boldsymbol{H_{enol}})-$), 12.06 (s, 1H, OH). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C, keto: 24.48 (1C, $-CH_2-C(O(CH_2)_{\boldsymbol{2}}O-)-\boldsymbol{C}H_3$), 50.08 (1C, $-\boldsymbol{C}H_2-C(O)-$), 51.71 (1C, $-\boldsymbol{C}H_2-C(O)OCH_3$), 52.25 (1C, $-C(O)O\boldsymbol{C}H_3$), 64.65 (2C, $CH_2-C(O(\boldsymbol{C}H_2)_{\boldsymbol{2}}O-)-CH_3$), 107.75 (1C, $-CH_2-\boldsymbol{C}(O(CH_2)_{\boldsymbol{2}}O-)-CH_3$), 167.66 (1C, $-CH_2-\boldsymbol{C}(O)-CH_2-$), 199.89 (1C, $-\boldsymbol{C}(O)OCH_3$), enol: 24.27 (1C, $-CH_2-C(O(CH_2)_{\boldsymbol{2}}O-)-\boldsymbol{C}H_3$), 43.96, 44.64 (2C, $-CH_{enol}-C(OH)-CH_2-C(O)OCH_3$ or $-CH_2-C(O)-CH_{enol}-C(OH)OCH_3$), 51.16 (1C, $-C(O)O\boldsymbol{C}H_3$), 64.77 (2C, $CH_2-C(O(\boldsymbol{C}H_2)_{\boldsymbol{2}}O-)-CH_3$), 91.79 (1C, $-\boldsymbol{C}(H_{enol})$)), 108.34 (1C, $-CH_2-\boldsymbol{C}(O(CH_2)_{\boldsymbol{2}}O-)-CH_3$), 172.81 (1C, $-\boldsymbol{C}(OH)$)), 173.77 (1C, $-\boldsymbol{C}(OH)$)). IR (ATR) 2981 (m), 1745 (vs), 1713 (vs), 1657 (s), 1596 (w), 1438 (m), 1379 (m), 1326 (w), 1238 (w), 1206 (w), 1148 (m), 1042 (vs), 1014 (w), 970 (w), 950 (s), 895 (w), 840 (s), 789 (w), 761 (w), 732 (w), 630 (w), 583 (w), 524 (m), 462 (w), 405 (w), 385 (w). MS (EI, 70 eV) m/z (%) = 87 (100), 43 (60), 131 (46), 89 (33).

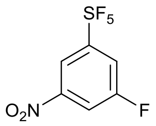
6.4. Direct fluorination of protected tricarbonyl ester

In a 100 mL glass reaction vessel fitted with a PTFE coated mechanical stirrer, a FEP gas delivery tube and an exit tube to a scrubber filled with soda lime was charged with tricarbonyl compound **327** (5.0 mmol, 1.0 g), hydrated cupric nitrate (115 mg, 10 mol%), and acetonitrile (20 mL) before being cooled to 0-5 °C. The vessel was purged with nitrogen and then fluorine diluted with nitrogen (1.1 eq., 10% v.v^{-1}) was passed through the stirred solution at 7 mL/min for 190 min. When the fluorine supply has been turned off, the reaction vessel was purged with nitrogen. The reaction mixture was then evaporated under reduced pressure, washed two times with 100 mL of sat. NaCl solution, extracted with ethyl acetate (2 x 50 mL). Then anhydrous sodium sulfate was added and the mixture was filtered over Celite, and then concentrated under reduced pressure yielding a mixture of di-fluoro and mono-fluoro products, which was analyzed by NMR spectroscopy, giving a 85:15

ratio of mono-fluorinated methyl-4-(2-methyl-1,3-dioxolan-2-yl)-3-oxobutanoate to di-fluorinated methyl-4-(2-methyl-1,3-dioxolan-2-yl)-3-oxobutanoate by ^{19}F-NMR. No further purification was carried out due to the end of the project period.

6.5. Synthesis of pentafluorosulfanyl benzene derivative

3-fluoro-5-nitro-1-(pentafluorosulfanyl)benzene, 337



A solution of 3-nitro-1-(pentafluorosulfanyl)benzene **336** (1.0 g, 4.0 mmol) in MeCN (25 mL) was added to a nitrogen flushed PFA reactor with a magnetic stirring bar. A mixture of 10% F_2/N_2 (v.v^{-1}) was bubbled for 1.38 h at a rate of 30 L/hour while maintaining the temperature of the bath at -3 ºC. The mixture was flushed with N_2 for 10 min. and solvent was removed under reduced pressure yielding residue containing 33% of 3-fluoro-5-nitro-1-(pentafluorosulfanyl)benzene **337** (by GC–MS). Purification by flash chromatography (Et$_2$O/petroleum ether, 10:90) afforded 3-fluoro-5-nitro-1-(pentafluorosulfanyl)benzene **337** (128 mg, 12% yield). ^{1}H NMR (400 MHz, *CDCl$_3$*) δ_H 8.48 (d, *J* = 1.4 Hz, 1H, -C(NO$_2$)-C(***H***)-C(SF$_5$)-), 8.15 (dt, *J* = 7.5, 2.3 Hz, 1H, -C(NO$_2$)-C(***H***)-C(F)-), 7.86 (dt, *J* = 7.8, 2.1 Hz, 1H, -C(F)-C(***H***)-C(SF$_5$)-). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ_C 161.68 (d, *J* = 256.3 Hz, -***C***(F)-), 154.78 (quintd, *J* = 21.3, 7.5 Hz, -***C***(SF$_5$)-), 148.81 (d, *J* = 7.0 Hz, -***C***(NO$_2$)-), 120.30 (dquint, *J* = 26.2, 4.6 Hz, -C(F)-***C***-C(SF$_5$)-), 117.84 (sextet, *J* = 4.9 Hz, -C(NO$_2$)-***C***-C(SF$_5$)-), 114.76 (d, *J* = 26.1 Hz, -C(NO$_2$)-***C***-C(F)-). ^{19}F NMR (377 MHz, *CDCl$_3$*) δ_F 80.03-78.27 (m, 1F, -S(F)$_4$***F***), 62.44 (d, *J* = 151.2 Hz, 4F, -S(***F***)$_4$F), -105.00 (s, 1F, -C(***F***)-). HRMS (EI) m/z calcd for $C_6H_3F_6NO_2S$ [M]$^+$ 266.9789, found 266.9788.

6.6. S$_N$Ar – VNS reactions

General procedure

In a Schlenk tube under inert atmosphere was added the selected base to a solution of 2-fluoro-1,3-dimethylmalonate **62** or 2-fluoro-ethylacetoacetate **19** in a selected solvent (see table 43). The reaction mixture was allowed to stir over one hour before the addition of 3-fluoro-5-nitro-1-(pentafluorosulfanyl)benzene (1 eq.). The reaction mixture was allowed to stir over a certain time at the chosen temperature (see Table 43). The reaction was then quenched when appropriate and water was added (10 mL). Then the organic layer was taken and the aqueous phase was washed with ethyl acetate. The combined organic layers were washed with brine (2 x 50 mL), water (50 mL), dried over $MgSO_4$ and solvent was removed under reduced pressure. The crude product was then analyzed by GC-MS spectrometry and NMR spectroscopy.

Table 43 *S_NAr – VNS of 5-fluoro-3-nitro-1-pentafluorosulfanylbenzene*

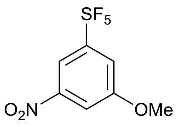
Entry[a]	Base	62 or 19	Solvent[b]	Temp.	Reaction time [h]	Conversion [%]
1a	NaH 1.41 mmol 57 mg 3.0 eq.	2 mmol 0.3 g 4.2 eq.	THF	r.t.	20.0	7
1b						21
2a	K_2CO_3 4.14 mmol 572 mg 3.4 eq.	2.2 mmol 330 mg 1.8 eq.	DMF	r.t.	4.0	0
2b						
3a	LiHMDS 0.3 mmol 50 mg 0.08 eq.	3 mmol 450 mg 0.8 eq.	toluene	-78 °C	2.5	0
3b						
4a	^{n}BuLi 0.3 mmol 187 µL (1.6M in Hexane) 0.08 eq.	3 mmol 450 mg 0.8 eq.	Et_2O	-78 °C	4.0	0
4b						
5a	^{n}BuLi 0.3 mmol 187 µL (1.6M in Hexane) 0.08 eq.	3 mmol 450 mg 0.8 eq.	THF	-78 °C	4.0	0
5b						
6a	LDA[c] 0.40 eq.	1.7 mmol 250 mg 0.2 eq.	THF	-78 °C	2.0	0
6b					24.0	
7a	^{t}BuOK 3.0 mmol 335 mg 3.0 eq.	1 mmol 150 mg 1.0 eq.	DMF	-40 °C	5.0	15
7b						22
8a				-60 °C		0
8b						
9a				-78 °C		0
9b						

[a] a: with 2-fluoro-1,3-dimethylmalonate, b: with 2-fluoro-ethyl acetoacetate; [b] Dry solvent; [c] LDA prepared by adding nBuLi (3.75 mmol, 2.34 mL, 1.6M in Hexane) to a solution of diisopropylamine (4.4 mmol, 0.61 mL) in dry THF at -78 °C, then stirred at 0 °C for 15 min

General procedure to access products 345

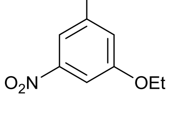
To a solution of 2-fluoro-1,3-dimethylmalonate **62** or 2-fluoro-ethylacetoacetate **19** (2 mmol, 0.3 g) in dry THF (10 mL) was added a solution of NaH (1.41 mmol, 57 mg, 3 eq.) in dry THF, then the reaction mixture was allowed to stir for 30 min, before 3-fluoro-5-nitro-1-(pentafluorosulfanyl)benzene (0.47 mmol, 126 mg) was added. The reaction mixture is then allowed to stir for 19 hours at room temperature, then 3 hours at 50 °C, then NaH (0.47 mmol, 190 mg) in dry THF was added and the obtained mixture was stirred for a further 20 hours at room temperature. Water was then added to the resulting mixture, a solution of NaOH (10 mL, 0.5M) was added and the product was extracted with Et_2O (4 x 20 mL) and the combined organic layers were washed with water (20 mL), brine (20 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was then purified by column chromatography using petroleum ether and diethyl ether (gradient 90:10 to 70:30) and the resulting product was analyzed by GC-MS spectrometry and NMR spectroscopy, allowing us to identify the corresponding products **345a** and **345b**, respectively from 2-fluoro-1,3-dimethylmalonate **62** and 2-fluoro-ethyl acetoacetate **19**, as their data are in agreement with assignments reported in the literature.[170]

3-methoxy-5-nitro-1-(pentafluorosulfanyl)benzene, 345a



^{1}H NMR (400 MHz, *CDCl$_3$*) δ_H 8.25 (t, *J* = 1.9 Hz, 1H, -C(NO_2)-C(***H***)-C(SF_5)-), 7.91 (t, *J* = 2.2 Hz, 1H, -C(SF_5)-C(***H***)-C(OMe)-), 7.63 (t, *J* = 2.1 Hz, 1H, -C(NO_2)-C(***H***)-C(OMe)-), 3.99 (s, 3H, -OC***H$_3$***). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ_C 160.25 (-***C***(OMe)-), 154.65 (quint, *J* = 19.7 Hz, -***C***(SF_5)-), 148.80 (-***C***(NO_2)-), 119.00 (quint, *J* = 4.7 Hz, -C(NO_2)-***C***-C(SF_5)-), 113.73 (quint, *J* = 4.9 Hz, -C(SF_5)-***C***-C(OMe)-), 111.06 (-C(NO_2)-***C***-C(OMe)-), 56.56 (-O***C***H_3). ^{19}F NMR (377 MHz, *CDCl$_3$*) δ_F 81.03 (quint, *J* = 149.0 Hz, 1F, -S(F)$_4$***F***), 62.76 (d, *J* = 151.2 Hz, 4F, -S(***F***)$_4$F). m/z (EI$^+$) 279 (100%, [M]$^+$), 63 (37%), 110 (33%), 125 (30%), 233 (23%).

3-ethoxy-5-nitro-1-(pentafluorosulfanyl)benzene, 345b



^{1}H NMR (400 MHz, *CDCl$_3$*) δ_H 8.23 (t, *J* = 1.9 Hz, 1H, -C(NO_2)-C(***H***)-C(SF_5)-), 7.89 (t, *J* = 2.1 Hz, 1H, -C(SF_5)-C(***H***)-C(OEt)-), 7.62 (t, *J* = 2.2 Hz, 1H, -C(NO_2)-C(***H***)-C(OEt)-), 4.20 (q, *J* = 7.0 Hz, 2H, -OC***H$_2$***CH_3), 1.52 (t, *J* = 7.0 Hz, 3H, -OCH_2C***H$_3$***). ^{13}C NMR (101 MHz, *CDCl$_3$*) δ_C 159.42 (-***C***(OEt)-), 154.64 (quint, *J* = 19.8 Hz, -***C***(SF_5)-), 148.77 (-***C***(NO_2)-), 119.38 (quint, *J* = 4.7 Hz, -C(NO_2)-***C***-C(SF_5)-), 113.50 (quint, *J* = 4.8 Hz, -C(SF_5)-***C***-C(OEt)-

), 111.44 (-C(NO_2)-***C***-C(OEt)-), 65.27 (-O***C***H_2CH_3), 14.40 (-OCH_2***C***H_3). ^{19}F NMR (377 MHz, *CDCl$_3$*) δ_F 82.45–79.75 (m, 1F, -S(F)$_4$***F***), 62.73 (d, *J* = 149.5 Hz, 4F, -S(***F***)$_4$F). m/z (EI$^+$) 264 (100%, [M-Et]$^+$), 293 (80%, [M]$^+$), 63 (26%), 111 (20%), 219 (23%).

7. Experimental to chapter 7

7.1. Mannich-type reaction by continuous flow one-step process

General procedure

After purging the continuous flow reactor apparatus with nitrogen, the 2-fluoro-ethylacetoacetate solution in acetonitrile (10 mL, 1 mmol/mL) was injected by a HPLC pump into the flow reactor channel at a prescribed flow rate through the first substrate Input (5 mL/h). A two-hours previously reacted mixture of formaldehyde and the chosen amine was then injected by a HPLC pump into the flow reactor channel at a prescribed flow rate through the second substrate Input. The molar ratio [1:1.5:1.7] was applied to the [2-fluoro-ethylacetoacetate:formaldehyde:amine] three-component system. The liquid flow stream was passed through the reactor and the product mixture was collected in a two-neck round-bottom flask. The collected mixture was then poured into water, extracted with dichloromethane (3 × 50 mL) and washed with brine (20 mL) and water (20 mL). The combined extracts were then dried ($MgSO_4$), filtered and the solvent evaporated to give a yellow oil, which was purified by micro-distillation or column chromatography on silica gel using hexane/ethyl acetate as eluent system when appropriate.

7.2. Mannich-type reaction by semi-continuous flow two-step process

General procedure

After purging the continuous flow reactor apparatus with nitrogen, a 10% mixture of fluorine in nitrogen (v.v^{-1}) (11 mmol, 1.1 eq.) was passed through the first flow reactor via Input 1 at a prescribed flow rate that was controlled by a gas mass flow controller (Brooks Instruments). The flow reactor was cooled by an external cryostat to 0-5 °C. The ethyl-acetoacetate solution in acetonitrile (10 mL, 1 mmol/mL) was injected by a HPLC pump into the flow reactor channel at a prescribed flow rate through Input 2 (5 mL/h). The gas-liquid flow stream was passed through the first reactor and the product mixture was collected in a three-neck round-bottomed flask.

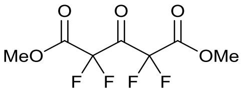
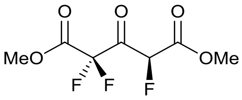
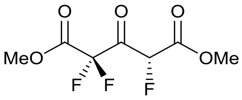
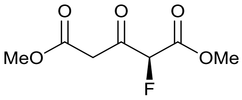
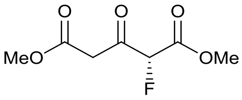
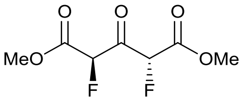
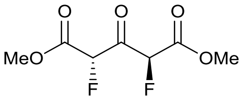
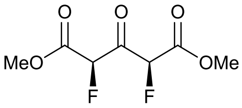
This collected mixture was directly injected by a HPLC pump into the second flow reactor at a prescribed flow rate (5 mL/h). Formaldehyde (15 mmol) and the amine 3 (17 mmol) were mixed together in acetonitrile for 2 h at rt and then injected by HPLC pump into the second flow reactor channel at a prescribed flow rate through the corresponding substrate Input via a T-piece. The molar ratio of fluorinated ethylacetoacetate:formaldehyde:amine was *ca.* 1:1.5:1.7. The liquid flow stream was passed through the second reactor and the product mixture was collected in a second two-neck round-bottomed flask. All flow streams were passed through the reactor and the product mixture was collected in a two-neck round-bottom flask. The collected mixture was then poured into water, extracted with dichloromethane (3 × 50 mL) and washed with brine (20 mL) and water (20 mL). The combined extracts were then dried ($MgSO_4$), filtered and the solvent evaporated to give a yellow oil, which was purified by micro-distillation or column chromatography on silica gel using hexane/ethyl acetate as eluent system when appropriate.

7.3. Fluorination in flow of dimethylacetone-1,3-dicarboxylate

General procedure

After purging the continuous flow reactor apparatus with nitrogen, a mixture of fluorine in nitrogen (see Table 45) was passed through the first flow reactor via Input 1 at a prescribed flow rate that was controlled by a gas mass flow controller (Brooks Instruments). The flow reactor was cooled by an external cryostat to 0-5 °C. The dimethylacetone-1,3-dicarboxylate solution in acetonitrile (10 mL, 1 mmol/mL) was injected by a HPLC pump into the flow reactor channel at a prescribed flow rate through Input 2 (5 mL/h). The gas-liquid flow stream was passed through the first reactor and the product mixture was collected in a three-neck round-bottomed flask. When the fluorine supply has been turned off, the reaction vessel was purged with nitrogen. The reaction mixture was then evaporated under reduced pressure, washed two times with 100 mL of sat. NaCl solution, extracted with ethyl acetate (2 x 50 mL). Then anhydrous sodium sulfate was added and the mixture was filtered over Celite, and then concentrated under reduced pressure yielding a mixture of di-fluoro and mono-fluoro products, which were analyzed by NMR spectroscopy (see Table 45). ^{19}F-NMR data for each of these products is included in chapter 6 (Table 26).

Table 45 *Fluorination of dimethylacetone-1,3-dicarboxylate in flow using various conditions*

Entry		**1**	**2**	**3**	**4**
F_2/N_2 [%]		10	10	10	20
Flow rate [mL/min]		20	30	40	20
F_2:307 ratio		1.01	1.47	1.96	1.96
Products [^{19}F-NMR %]	 **303**	12	20	19	19
	 **310** 	3	8	8	8
	 **308** 	8	6	9	8
	 **309a** 	63	53	51	52
	 **309b**	14	13	13	13

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