Application of Silver(II) Difluoride

in Organic Synthesis

BY

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THESIS

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This thesis is dedicated to my grandparents, Xuanjie Wu and Pingying Xiong, without whom it would never have been accomplished.

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NFSI   *N*-fluorobis(phenyl)sulfonimide

TADDOL   α,α,α',α'-tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5dimethanol

BINAP   2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

MTBE   Methyl tertbutyl ether

BQd   Benzoylquinidine

DFT   Density functional theory

18-Crown-6   1,4,7,10,13,16-hexaoxacyclooctadecane

TBAT   Tetrabutylammonium difluorotriphenylsilicate

TMAF   Tetramethylammonium fluoride

TBAF   Tetrabutylammonium fluoride

DAST   Diethylaminosulfur trifluoride

TREAT·HF   Triethylamine tris(hydrogen fluoride

PBSF   Perfluoro-1-butanesulfonyl fluoride

TFEDMA   1,1,2,2-Tetrafluoroethyl-*N*,*N*-dimethylamine

Deoxo-Fluor   Bis(2-methoxyethyl)aminosulfur trifluoride

XtalFluor-E   Diethylaminodifluorosulfinium tetrafluoroborate

NHPI   *N*-hydroxyphthalimide

SET   Single electron transfer

NDHPI   *N*,*N*-Dihydroxypyromellitimide

TCB   1,2,4,5- tetracyanobenzene

TBADT   Tetrabutylammonium salt of decatungstate

AQN   Anthraquinone

CAN   Ceric ammonium nitrate

BI-OH   1-hydroxy-1,2-benzodioxol-3-(1H)-one

TMS   Trimethylsilyl

NFOBS   *N*-fluoro-*O*-benzenedisulfonimide

LDA   Lithium diisopropylamide

PTFE   Polytetrafluoroethylene

DMSO   Dimethyl sulfoxide

DMF   Dimethylformamide

THF   Tetrahydrofuran

TMEDA   Tetramethylethylenediamine

TMP   Tetramethylpiperidide

NBS   *N*-Bromosuccinimide

NIS   *N*-Iodosuccinimide

Py   Pyridine

NMR   Nuclear magnetic resonance

IR   Infrared

GC   Gas chromatography

MS   Mass spectrum or spectrometry

TLC   Thin layer chromatography

R_f Retention factor

SUMMARY

Fluorinated compounds often possess valuable properties, such as increased metabolic stability, increased lipophilicity, and high oxidative stability. Therefore, chemists are seeking to master more synthesis methodology to access various fluorinated compounds.

Silver(II) difluoride is a unique fluorinating compound which has a relatively high oxidizing ability. It enables some difficult fluorinations on certain systems, such as benzene, pyridine, etc. However, due to its high reactivity, its chemoselectivity is low. Part of our research goal is to control the reaction condition so that the selectivity could be enhanced.

Gratifyingly, three different substrate categories were discovered to perform in a synthetically useful manner by our group. Cyclopropanols were fragmented to β-fluoroketones, alkyl tertiary bromides were transformed to alkyl tertiary fluorides, and benzofurans were converted to 2,3-difluoro-2,3-dihydrobenzofurans. In all the three cases, cryogenic conditions were applied in order to avoid side reactions. Synthetic applications were made to demonstrate the fluorinated products could participate in different synthetic routes.

Chapter I. General Fluorination Introduction

1. Introduction of Fluorine

Fluorine can bring many valuable properties to a molecule. For instance, fluorine can modulate the pK_a value of protons proximal to fluorine and increase membrane permeability at a physiological pH value.[1-2] Improved lipophilicity could be found in fluorinated arenes compared to their nonfluorinated counterparts,[2-6] which can be advantageous in drug development. Fluorine is regarded as an isostere for hydrogen in medicinal chemistry, for the van der Waals radii of fluorine and hydrogen are close (1.47 Å for fluorine and 1.20 Å for hydrogen),[7] and organism could, in many cases, recognize and accept fluorinated counterparts.[8] With all these features, fluorine chemistry has attracted significant interest.

As the most electronegative element, fluorine has a very strong Coulombic attraction with carbon through the polarized covalent bond.[9-10] The polarization leads to considerable interaction of the C−F fragment with hydrogen bond donors,[11-16] other fluorinated compounds, [17-20] polar functional groups such as carbonyl groups,[21-25] and hydrophobic moieties.[26-28] Likewise, this attraction also has a high opportunity to result in higher binding affinity to proteins.[21-26, 29-42] Unfortunately, this phenomenon is not universally applied in all the fluorinated compounds and could only be determined experimentally since fluorine atom is not always the dominating factor influencing binding affinity. Most fluorinated compounds, although not all, also exhibit increased metabolic stability by occupying potentially oxidizable sites to avoid further oxidation.[43-44]

High thermal stability
High oxidative stability
Weatherability

Low polarity
Weak intermolecular interactions
Small surface tension
Small refractive indices

High C-F bond strength

Perfluorocarbons (PFCs)

Mimicking enzyme substrates

Fluorine effects

Isoelectronic effects to O^- and OH

Blocking effect in metabolic transformations

Increased lipophilicity to enhance bioavailability

Figure 1. Fluorine Effects[45]

Most electrophilic fluorination reagents are synthesized with fluorine gas, the strongest

known elemental oxidant. Due to the high reactivity and high toxicity of the highly oxidizing

fluorinating reagents such as fluorine gas, hypofluorites,[46] and perchloryl fluoride,[47-48]

electrophilic fluorination reactions employing these reagents are difficult to perform, and special

caution and laboratory equipment are required. Xenon difluoride, XeF_2 was discovered in 1962

[49] and has been applied in fluorination reactions to solve partially this problem.[50] It is more

stable than the fluorinating reagents mentioned above, however, its high reactivity often provides

minimal selectivity, thus limiting its use. The development of crystalline, benchtop-stable

fluorinating reagents such as *N*-fluorobis(phenyl)sulfonimide (NFSI)[51] and related analogues,[51-57]

N-fluoropyridinium salts,[58-65] and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane

bis(tetrafluoroborate) (SelectFluor®, F-TEDA-BF_4)[66] enables selective, functional group-tolerant

fluorination methods. Although *N*-fluoro reagents perform formally as a source of fluoronium cations ("F$^+$"), the N−F bonds are polarized toward fluorine, with a partial negative charge on

NFSI	***N*-fluoropyridium salts**	**SelectFluor**®
−0.78 V	−0.73 V −0.47 V	−0.04 V

Increasing reduction potential
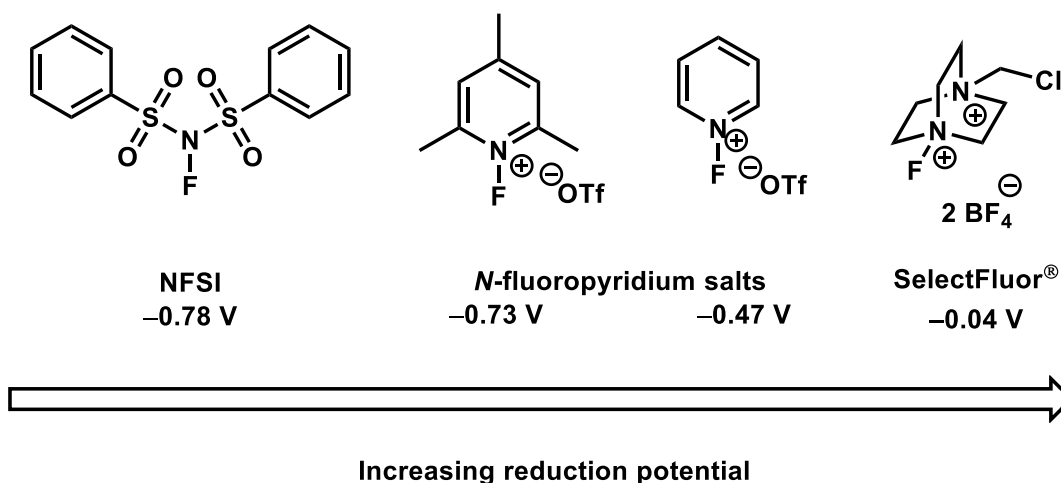
Figure 2. Reduction Potential of Common Fluorinating Reagents

fluorine. Since the σ*$_{N–F}$ orbitals are sterically inaccessible on the nitrogen atom for nucleophilic attack, the fluorine is instead attacked in an S$_N$2 fashion so that the fluorine transfer could be accomplished.

With a huge selection of fluorinating reagents, fluorine chemists were not satisfied with stoichiometric fluorination reactions. *sp*^{2} C−F bond formation research was giving fruitful results due to the readiness of oxidative addition on aryls. Sanford was one of the pioneers in the field of transition metal-catalyzed fluorination.[67] She described the first example of a Pd-catalyzed method for the formation of aromatic and benzylic C−F bonds in 2006 (Scheme 1). Taking advantage of nitrogen atom's directing ability, palladium was able to oxidatively add to a benzylic position or aromatic ring with high selectivity. SelectFluor® was chosen as the fluorinating reagent in this method and afforded the fluorinated compounds in 33−75%.
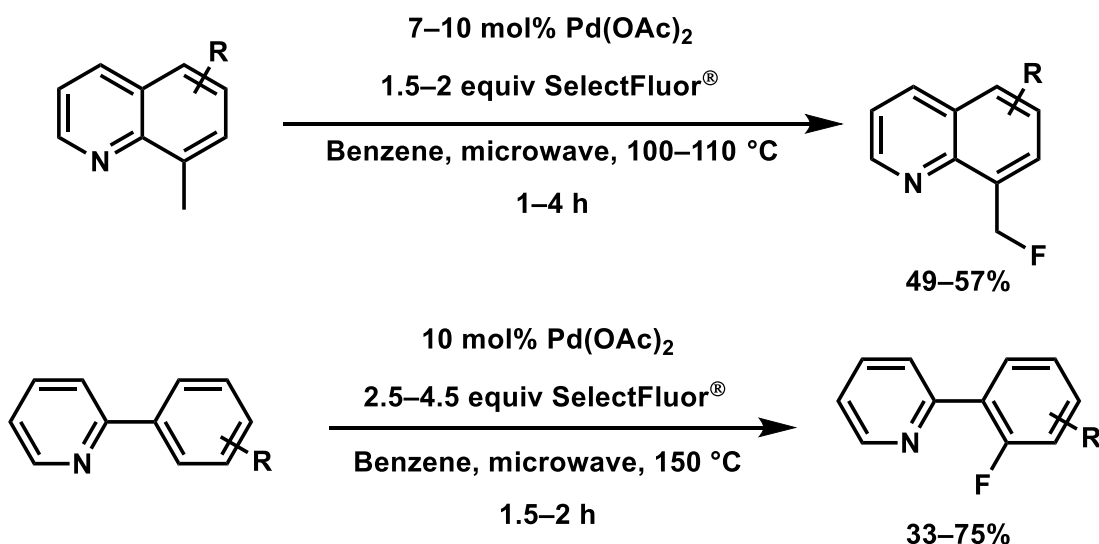
Scheme 1

Buchwald also reported a C−F bond formation method by catalytic triflate replacement

with fluoride (Scheme 2).[68] [LPd(II)Ar(F)] complexes were described, where L is a biaryl

monophosphine ligand and Ar is an aryl group, to undergo reductive elimination leading to Ar−F

bond. A catalytic amount of the complex could convert aryl bromides and aryl triflates into the

fluorinated arenes in excellent efficiency by using simple alkali metal fluoride salts.

6 mol% *t*BuBrettPhos

2 mol% [(cinnamyl)PdCl]$_2$

toluene, 80–130 °C, 12 h

57–84%

*t*BuBrettPhos =
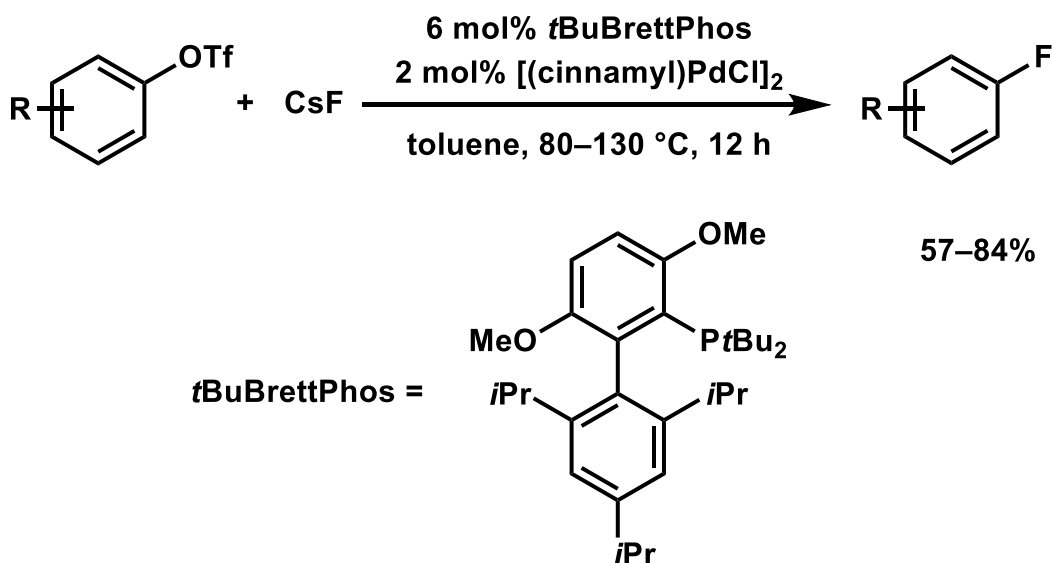
Scheme 2

It's noteworthy that not only both electron-rich and -deficient aryls, but also a variety of heterocyclic substrates such as flavones, indoles, and quinolines, could be converted to fluorinated compounds.

Fluorination could be applied on different chemical environments and every type is potentially useful. In the following text, sp^3 carbon fluorination is primarily discussed. To summarize, electrophilic, nucleophilic, and radical approaches are the three major classes of sp^3 fluorination methods that will be highlighted.

2. Electrophilic Fluorination for the Synthesis of Fluorinated sp^3 Carbon Centers

The α-fluorination of carbonyl, α'-ketocarbonyl, and related carbonyl derivatives with oxidizing fluorinating reagents including gaseous fluorine,[69-70] alkyl hypofluorite,[46] perchloryl fluoride,[71-74] fluoroxysulfate,[75] and XeF$_2$[76] usually show poor selectivity towards α-monofluorinated products since they frequently produce undesired α,α-difluorinated products as

well.[72, 76] Therefore, more selective and functional group tolerant electrophilic fluorinating reagents such as *N*-fluoropyridinium salts, NFSI, and SelectFluor® have been instead used for the selective α-monofluorination of carbonyl derivatives.[59, 61, 64-65, 72, 77-79] The asymmetric α-fluorination of carbonyl substrates was developed first with chiral electrophilic fluorinating reagents.[56-57, 80] Chiral catalysts which generate chiral enolate intermediates were found to be useful in similar transformations later.

Thanks to dicarbonyl compounds' two binding sites, they can chelate with chiral Lewis acid complexes. Additionally, considering their activated methylene or methine, dicarbonyl compounds are privileged to perform excellently in extensive enantioselective fluorination studies. The asymmetric fluorination of β-keto esters was achieved with titanium−TADDOLato-based catalysts by Togni and co-workers (Scheme 3),[81-85] Cu(II)−box complexes by Ma and Cahard (Scheme 4),[86] Ni(II)−box complexes by Shibata, Toru, and co-workers (Scheme 5 and 6),[87] chiral bis(imino)bis(phosphine)- ruthenium(II) complex by Togni and co-workers

Scheme 3

Scheme 4

R^1 = alkyl, Ar
R^2 = tBu, Bn
R^3 = alkyl

[Cu]* =

80–95%
62–90% *ee*
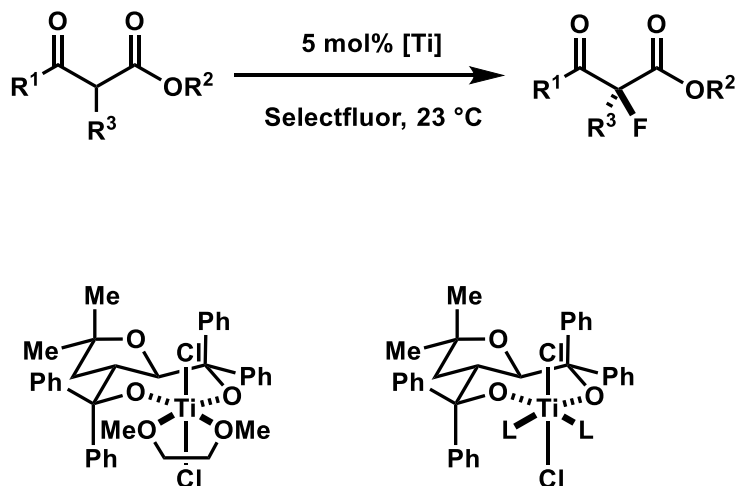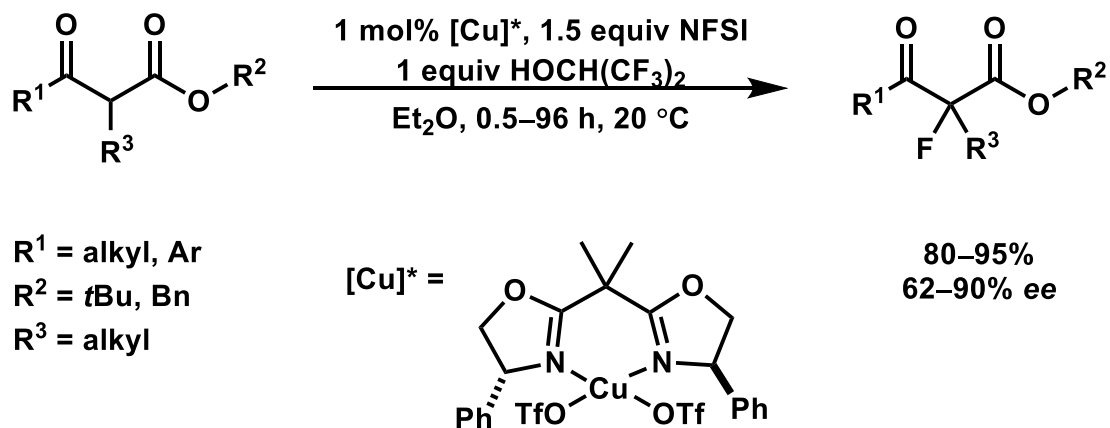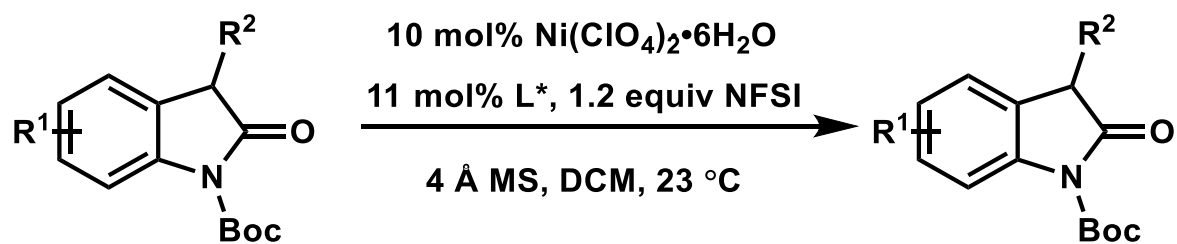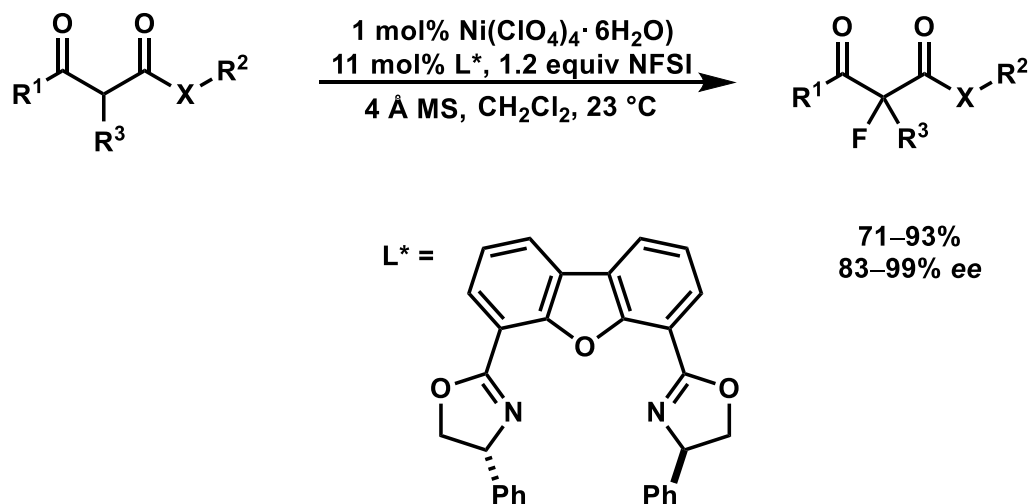
Scheme 5

Scheme 6

(Scheme 7),[88-89] and scandium binapthylphosphate complexes by Inanaga and co-workers

(Scheme 8).[90] The Ni-catalyzed reaction with 10 mol% catalyst is the method with the broadest

substrate scope so far, which allows the α-fluorination of a variety of β-keto esters and *N*-Boc-

protected amides in 71–93% yield and 83–99% *ee*, respectively.
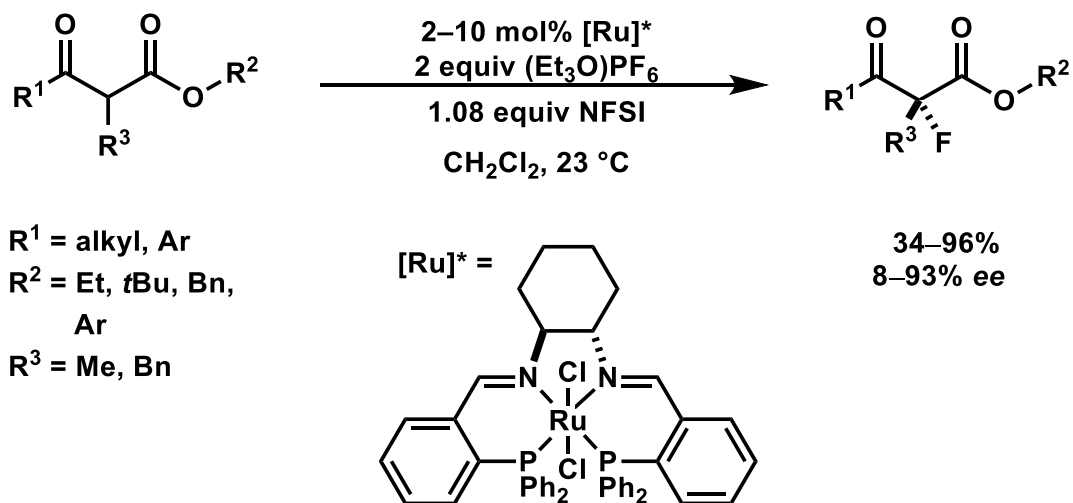
Scheme 7
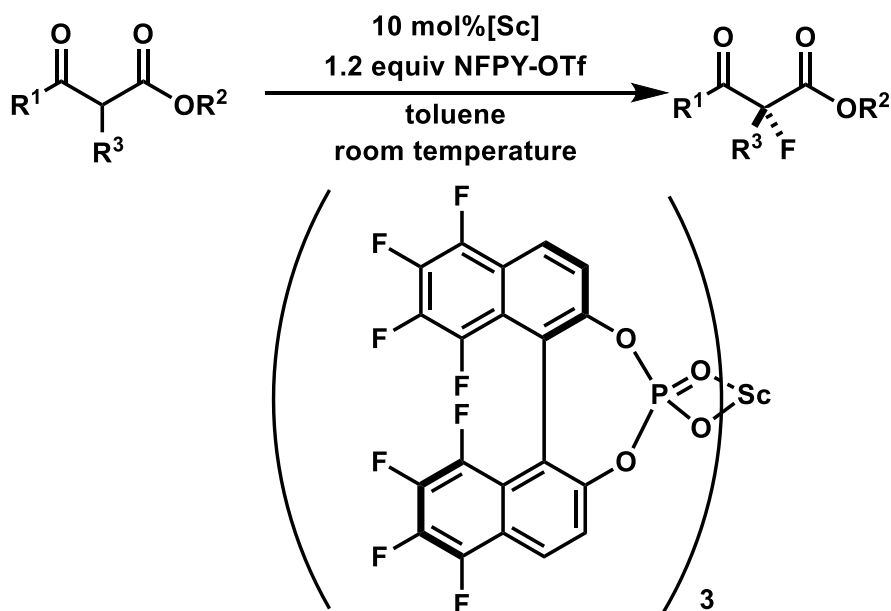
Scheme 8

Sodeoka and co-workers used chiral Pd−BINAP complexes to catalyze the enantioselective fluorination of α-keto esters,[91] β-keto esters,[92-93] β-keto phosphonates,[94-95] oxindoles,[96] and α-ester lactones/lactams (Scheme 9).[97] Chiral palladium complexes were especially efficient for the α-fluorination of acyclic α-keto esters, cyclic and acyclic tert-butyl β-keto ester as well as oxindoles α-substituted with a wide range of aryl and alkyl groups.[91-93, 96]
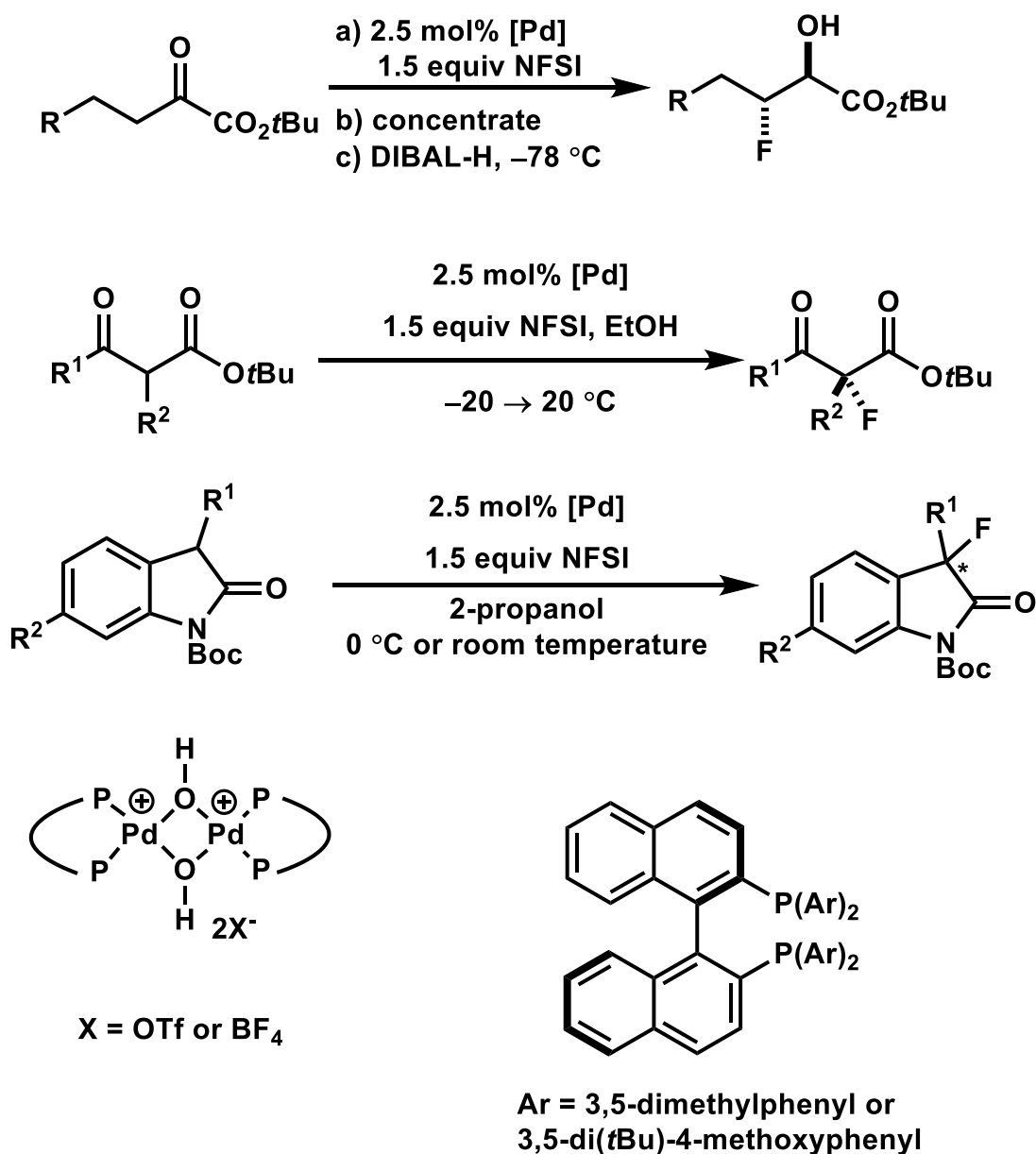
Scheme 9

In addition to transition metals, organic compounds have been applied to mediate

electrophilic fluorination. Cinchona alkaloids have been used to enantioselectively fluorinate

nucleophiles in the presence of an achiral fluorinating reagent. The enantioselective fluorination

of the activated methine groups in was accomplished by Takeuchi and co-workers, by using

stoichiometric amounts of cinchona alkaloid derivatives such as the cinchona alkaloid shown in

Scheme 10.[98]
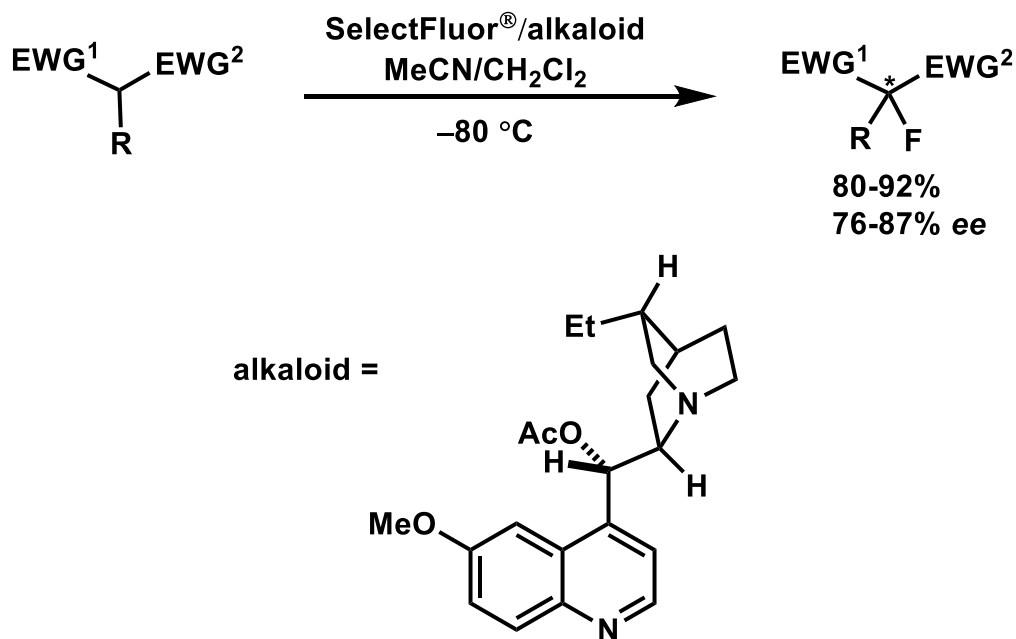
Scheme 10

Enantioselective α-fluorination mediated by cinchona alkaloids have also been used in

systems like silylenol ethers, α,α-cyanoester C−H acids, β-keto esters, and oxindoles.[99] The

method was applied to the synthesis of BMS-204352 (Scheme 11),[100] a potassium channel

opener, which has also been synthesized by utilizing chiral scandium Lewis acid catalysts.[101]

The enantioselective α-fluorination of β-keto esters can be accomplished by using cinchona

alkaloid-derived thiourea catalysts (Scheme 12).[102] Despite the reduced substrate scope currently

tolerated in enantioselective fluorinations with cinchona alkaloids when compared

BMS-204352

Scheme 11

1.1 equiv NFSI
10 mol% catalyst

1.0 equiv DMAP
MeOH
−60 °C

41–96%
0 → 99% ee
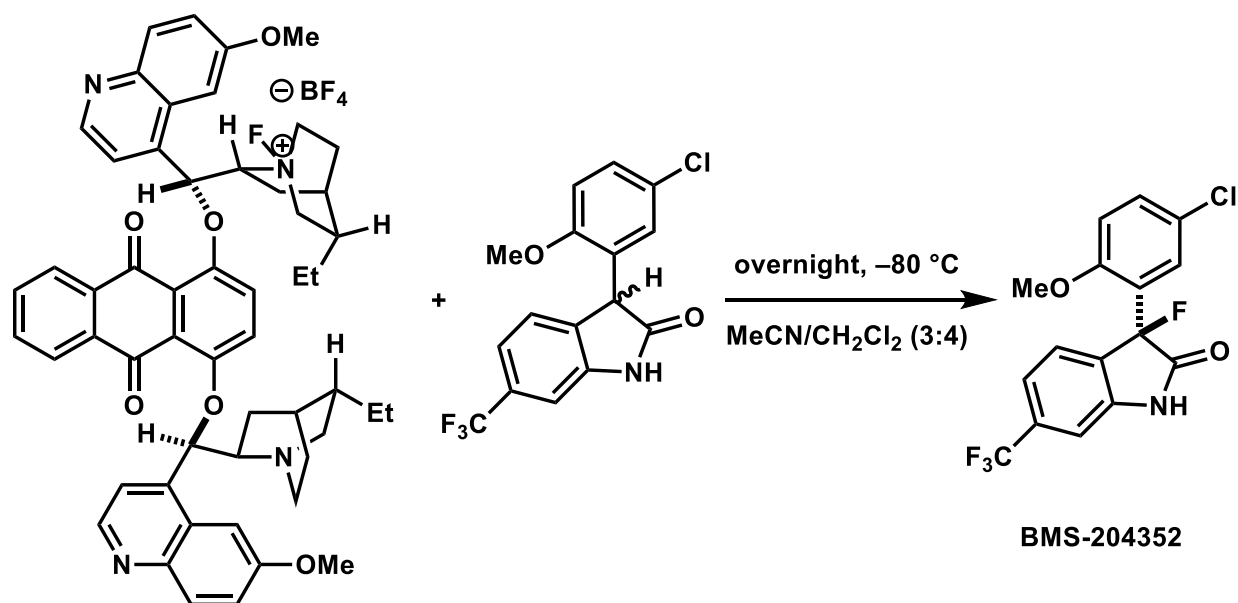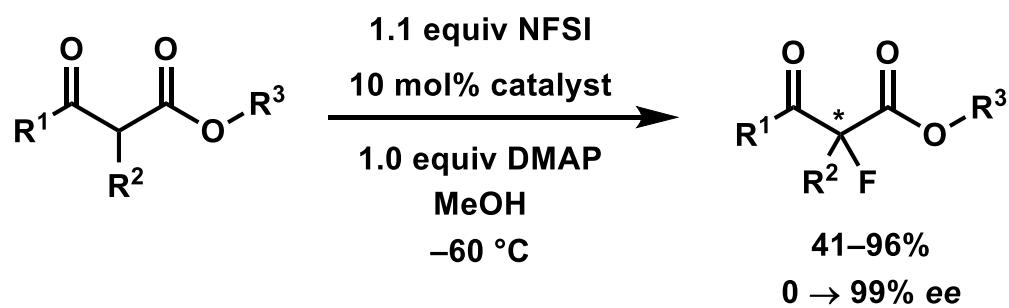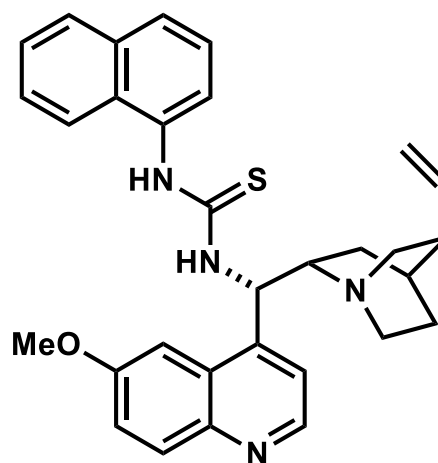
catalyst =

Scheme 12

to the Lewis acid catalyzed fluorinations of β-keto esters and oxindoles, substrates with only one

coordinating site can undergo the reaction smoothly and this area draws more and more attention.

Catalytic organocatalyzed fluorination is also being explored. By acting as chiral

fluorinating reagents or through reaction with the substrate, organocatalysts can generate chiral

nucleophiles.[103] The organocatalytic α-fluorination of aldehydes was accomplished

enantioselectively by Enders,[104] MacMillan (Scheme 13),[105] Jørgensen (Scheme 14),[106] and

Barbas (Scheme 15).[107] Similarly, enamine catalysis can achieve the enantioselective α-

fluorination of ketones.[108] The method for the α-fluorination of aldehydes described by
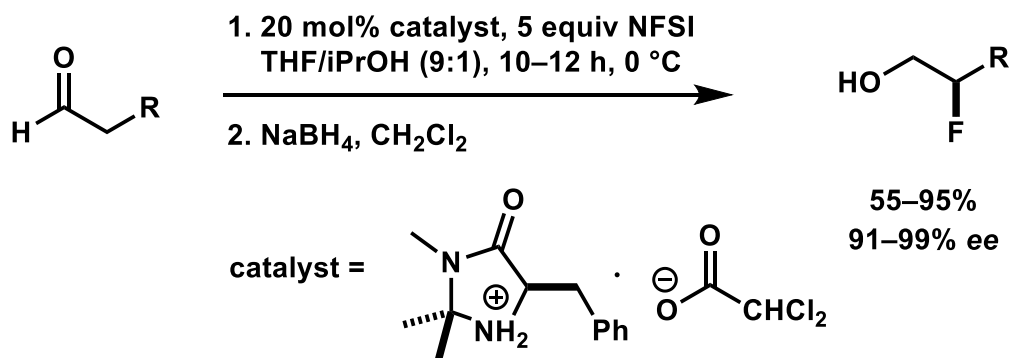
Scheme 13
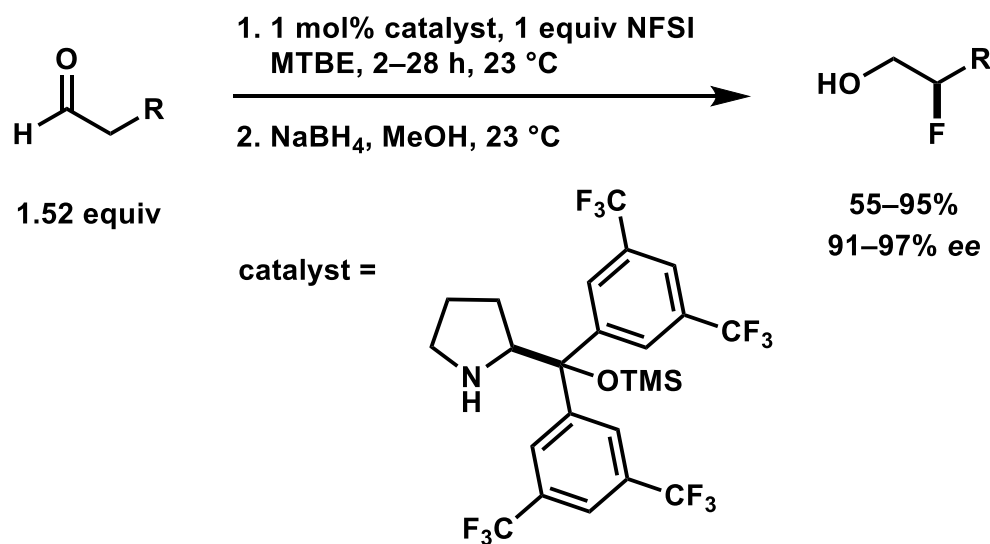
Scheme 14

MacMillan and co-workers presented a broad substrate scope, while Jørgensen and co-workers

reported a method using even lower loadings of catalyst and electrophilic fluorinating reagent.

Although α-branched aldehydes are difficult substrates for enantioselective α-fluorination,

Barbas and co-workers reported a method affording 98–99% yield and 45–66% *ee* for this class

of substrates. The fluorinated aldehyde products are especially useful for the synthesis of

enantiopure β-fluoroamines (Scheme 16),[109] which can arise from a chiral sulfinylimine

condensation and directed reduction sequence of the enantioenriched fluorinated aldehyde.
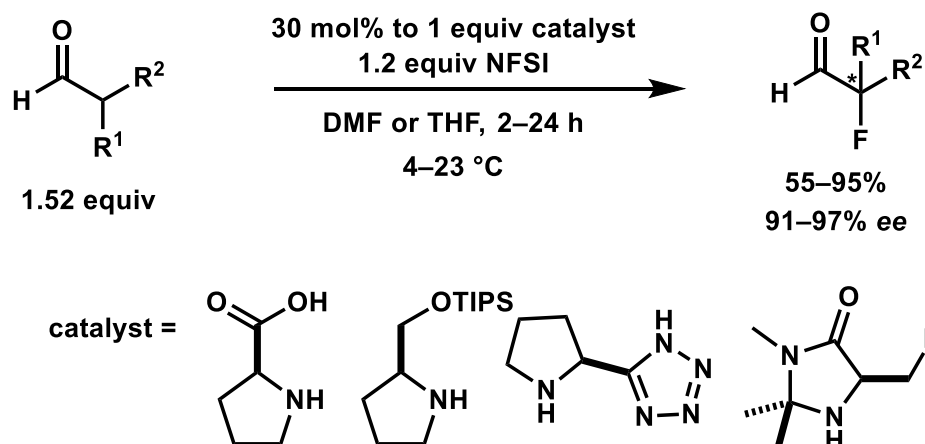
Scheme 15
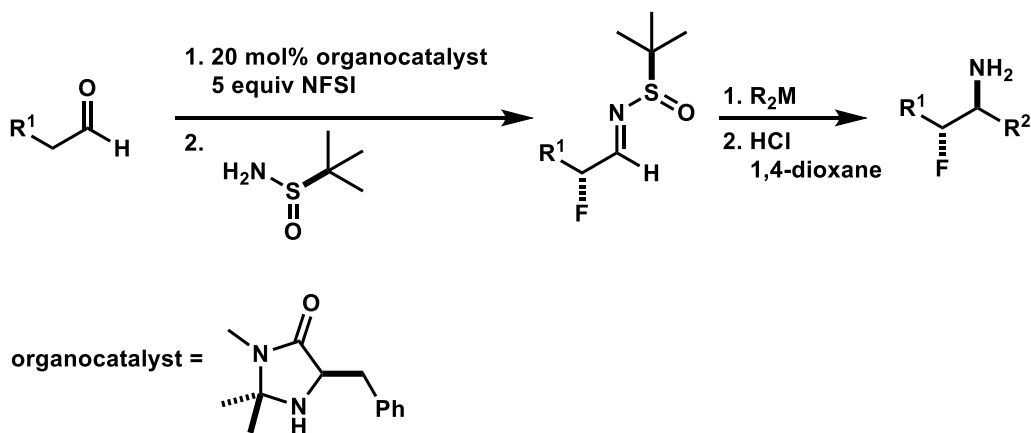
Scheme 16

The combination of a palladium catalyst, a chiral nucleophile, and an alkali metal has demonstrated its success in the enantioselective α-fluorination of acid chlorides reported by the Lectka research group (Scheme 17).[110-111] The cinchona alkaloid-based nucleophile reacts with the acid chloride to generate a chiral zwitterion BQd amide enolate intermediate. The palladium
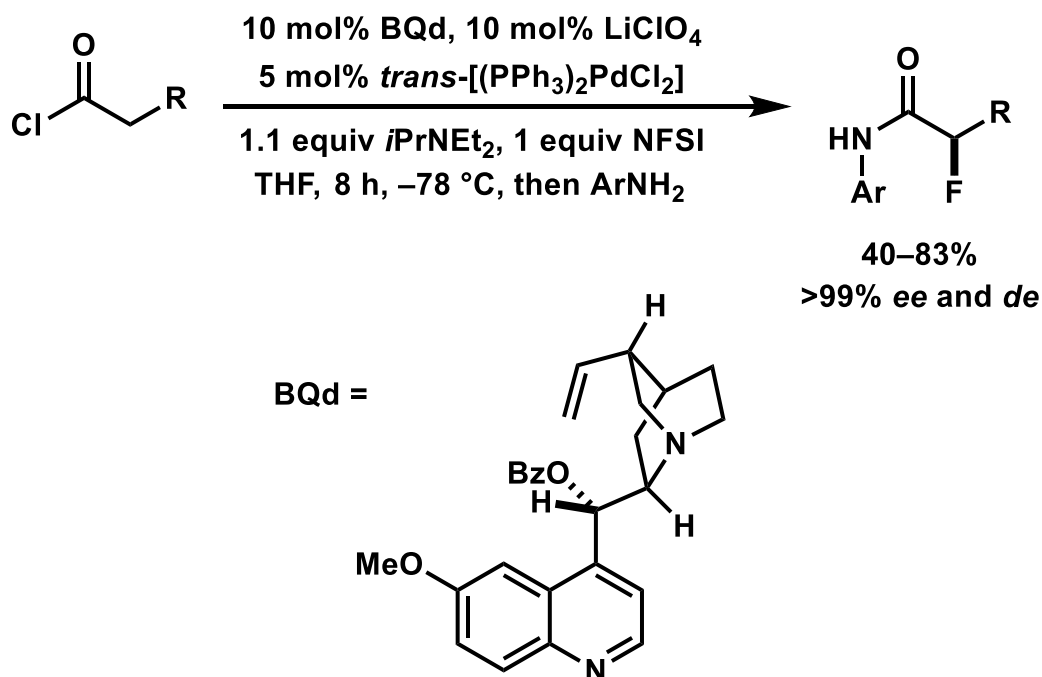
Scheme 17

catalysts then coordinate with the enolate oxygen atom to generate a chiral enolate for

fluorination based on DFT calculation. The authors hypothesized that the lithium cation

activated NFSI for nucleophilic attack by the chiral enolate through chelation of the sulfonyl

oxygen atoms.

3. Nucleophilic Fluorination for the Synthesis of Fluorinated sp^3 Carbon Centers

The challenge of nucleophilic fluorination is primarily attributable to the high

electronegativity of fluorine, which contributes to the high kinetic barriers in forming

carbon−fluorine bonds, despite the thermodynamic driving force of forming the strong C−F bond.

Moreover, the tendency of fluoride to form strong hydrogen bonds can decreases its

nucleophilicity. Although nucleophilicity of fluoride could be tuned with strict exclusion of

potential hydrogen-bond donors, the condition increases its basicity, which often leads to undesired side reactions.

The use of alkali metal fluoride salts is ideal due to their low cost, especially compared to electrophilic fluorinating reagents, as well as their stability under ambient condition.[112] The strong lattice energy of these salts results in their low nucleophilicity and poor solubility in organic solvents. Crown ethers such as 18-crown-6 can be used to improve the solubility of alkali fluoride salts, which often leads to an increase in the reactivity.[113-114] Aprotic solvents, especially polar aprotic solvents, are often favored for nucleophilic fluorination reactions since the nucleophilicity of fluoride anions would not influenced by hydrogen-bonding interactions to a significant extent, whereas the associated increase in the fluoride's basicity can result in elimination by-products.[113, 115] Tertiary alcohols such as *tert*-butanol have been proven to maintain the nucleophilicity of the fluoride while decreasing its basicity, thereby reducing the formation of undesired byproducts.[116-117] Tetrabutylammonium difluorotriphenylsilicate (TBAT), tetramethylammonium fluoride (TMAF), and tetrabutylammonium fluoride (TBAF) are some popular soluble fluoride sources.

Bertrand and co-worker reported a cyclic adduct synthesized by the activation of the para C−F bond of pentafluoropyridine by an ethynyl dithiocarbamate (Scheme 18).[118] The cyclic adduct is a reactive nucleophile to transfer fluoride to halides and pseudo-halides.

X = Cl, Br, I, OMs, OTs
R = alkyl, benzyl, aryl, acyl
Ar = 2,4,6-(*i*-Pr)$_3$-C$_6$H$_2$
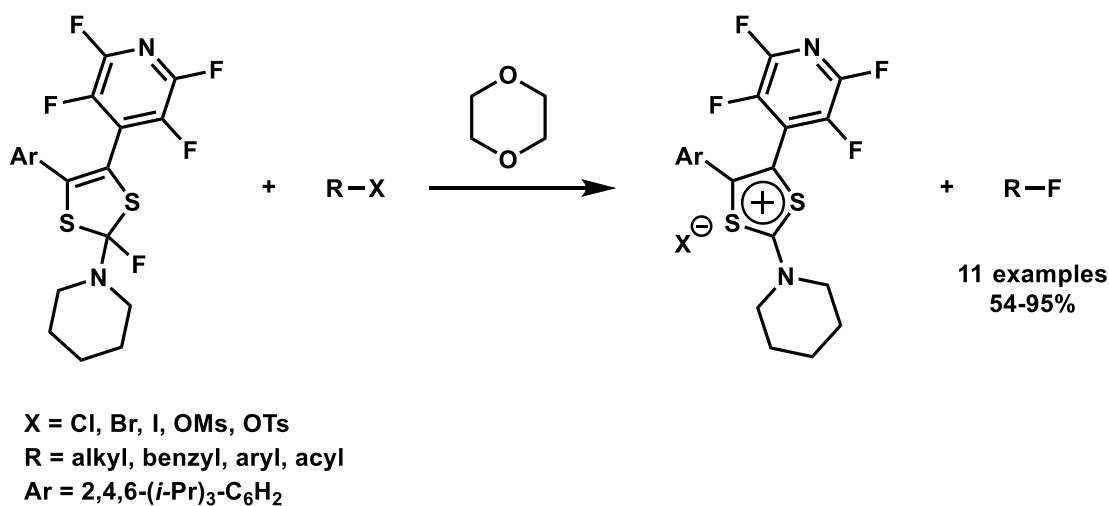
Scheme 18

A new copper(I) bifluoride complex incorporating a neocuproine ligand was described by Huang, Weng, and co-workers to react with pimary and secondary alkyl bromides in 2013 (Scheme 19).[119] This method showed a great tolerance with various functional groups, such as ethers, thioethers, amides, nitriles, alcohols, ketones, esters, and heterocycles.

R^1, R^2 = H, alkyl, aryl   40-90%
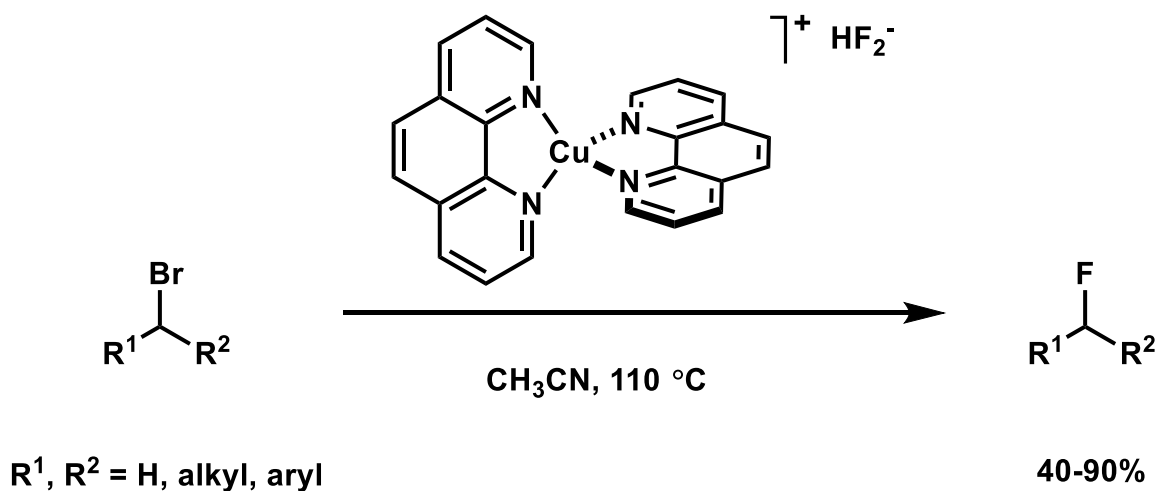
Scheme 19

Later in 2014, with the message that copper complex could be useful in fluorination reactions, Lalic and co-workers developed chemoselective catalytic fluorination of alkyl triflates

(Scheme 20).[120] With 10 mol % of (IPr)CuOTf, full conversion could be obtained in less than 10 min at 45 °C. This fluorination reaction has a broad scope with various functional groups, including alkyl tosylates and alkyl bromides.
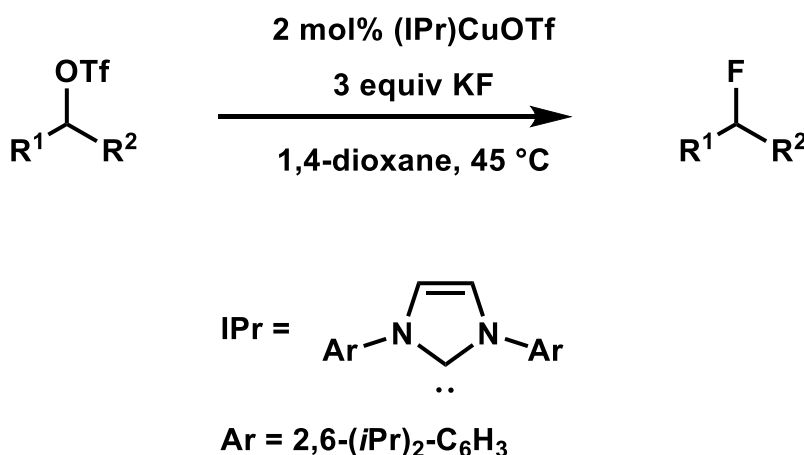
Scheme 20

Fluorodeoxygenation of carbon centers usually requires special fluorinating reagents that can accomplish oxygen activation/deoxygenation and in the meantime, provide a fluoride source. Various aryl and aminosulfur trifluorides and derivatives[121-129] as well as 2,2-difluoroimidazoline-type reagents[130-131] are employed in fluorodeoxygenation reactions. Several hydrogen fluoride-based reagents have been developed to facilitate the replacement of sulfur with fluoride in fluorodesulfurization reactions.[132-138]
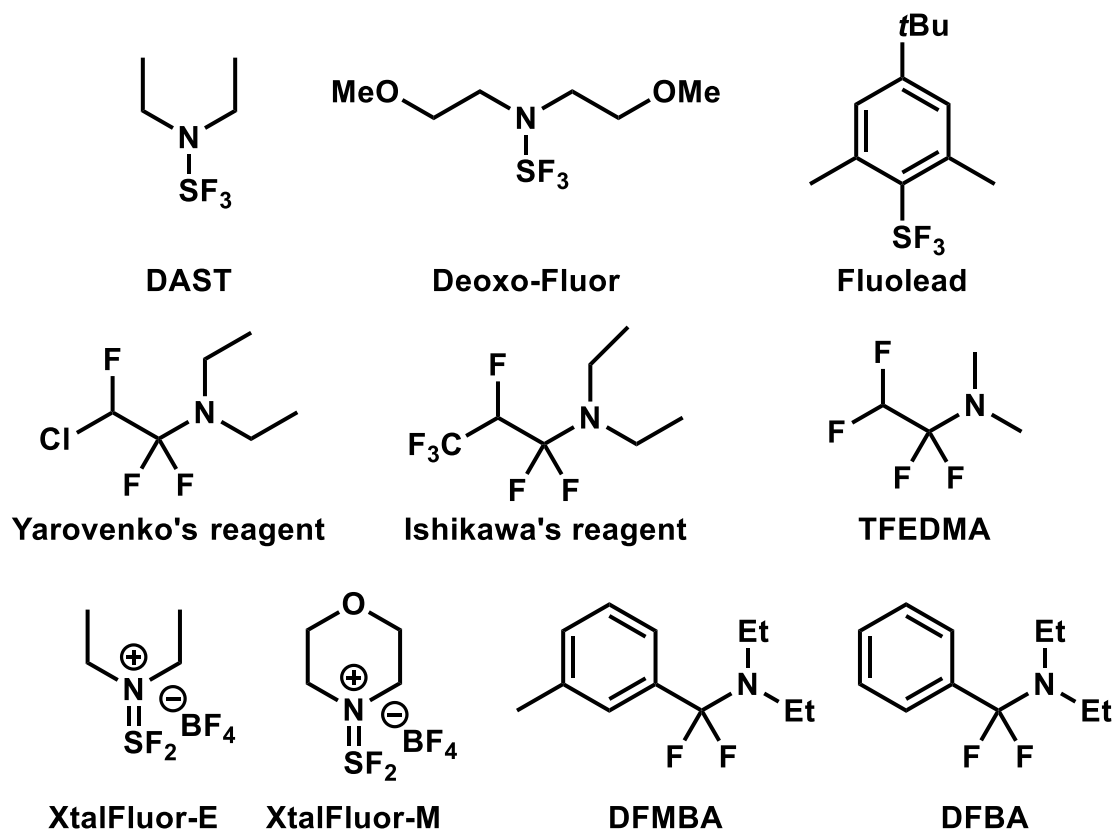
Figure 3. Common Deoxofluorinating Reagents

Nucleophilic fluorination at primary sp^3 carbon centers is well-established with appropriate selection of the fluoride source, leaving group, and solvent.[114, 139-143] Nucleophilic fluorination at a secondary or tertiary sp^3 carbon center is inherently more difficult, so general functional group tolerant method is still very challenging.

Carbonyl compounds were first converted into geminal difluoromethylene derivatives with sulfur tetrafluoride.[144-145] Chemistry of less volatile reagents such as aryl and aminosulfur trifluorides was studied to avoid the toxicity of volatile sulfur tetrafluoride.[121-129] Diethylaminosulfur trifluoride (DAST)[129] is one of the most famous reagents to fluorinate oxygenated (carbonyl, hydroxy) or sulfur-containing (thiocarbonyl, sulfide) substrates.[126, 146-160]

Nucleophilic attack of the alcohol substrate on the sulfur atom of DAST is proposed to form an alkoxyaminodifluorosulfane intermediate which is ready for S_N2 attack by fluoride.[161] In some cases, however, products in accordance to S_N1 mechanism were also discovered in DAST-mediated reactions.[153] DAST, in addition, suffers from moisture sensitivity as well as a tendency to explode upon heating.[124]

There are many other options for deoxyfluorination and dethiofluorination other than DAST: pyridinium poly(hydrogen fluoride) (Olah's reagent),[135, 137-138] nitrosonium tetrafluoroborate/pyridinium poly(hydrogen fluoride),[136] triethylamine tris(hydrogen fluoride) (TREAT·HF),[134] perfluoro-1-butanesulfonyl fluoride (PBSF),[162] sulfonyl fluoride/TREAT·HF mixture (Scheme 21),[163] Yarovenko's reagent (Figure 3),[164] Ishikawa's reagent (Figure 3),[165] TFEDMA (Figure 3),[166] *N,N*'-dimethyl-2,2,-difluroimidazolidine,[131] 4-morpholinosulfur
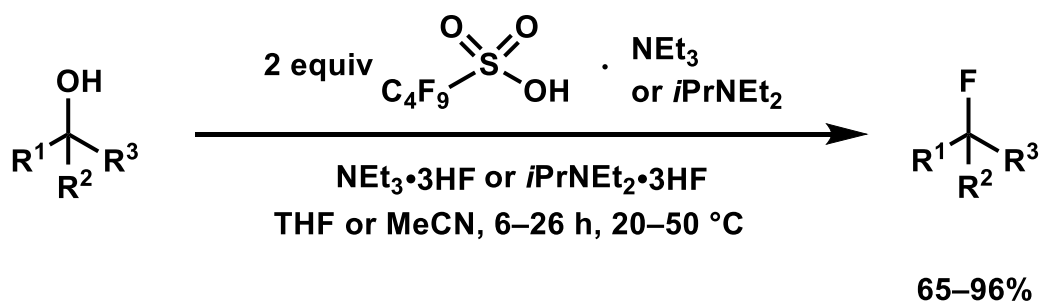
Scheme 21

trifluoride,[125, 167] Deoxo-Fluor,[123, 168-176] bromine trifluoride,[177-183] and 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride.[184] Deoxo-Fluor is currently the most popular reagent for fluorination reactions and is considered a safer, more thermally stable alternative to DAST, but is moisture sensitive and prone to decomposition to generate toxic HF as well. Similarly, Olah's

reagent is corrosive and toxic due to the presence of HF. TREAT·HF is considered to be a less hazardous alternative and is mild enough to be used in borosilicate glassware.

The development of the non-explosive, crystalline, less moisture-sensitive deoxyfluorinating reagent XtalFluor-E (diethylaminodifluorosulfinium tetrafluoroborate)[185] and related reagents[186] has resulted in fluorodeoxygenation with higher efficiency. Unlike DAST or Deoxo-Fluor, the fluorination with XtalFluor-type reagents requires the addition of an amine hydrogen fluoride such as triethylamine tris(hydrogen fluorine) as a fluoride source since the fluoride does not release after the addition of an alcohol to XtalFluor due to the fully protonated diethylamino group. Instead of adding an external fluoride source, deprotonation with DBU can also release the fluoride.

4. Radical Fluorination for the Synthesis of Fluorinated sp^3 Carbon Centers

The history of transition metal-catalyzed oxidative fluorination of aliphatic C−H bonds using fluoride starts late when in 2012 it was first reported by Sanford and co-workers (Scheme 22).[187] In presence of a hypervalent iodine oxidant and silver fluoride, the oxidative fluorination of functionalized 8-methylquinolinyl substrates was catalyzed by Pd(OAc)$_2$. High-valent palladium fluoride intermediates are postulated to occur tin this transformation which is also enabled by the strategic concurrent use of PhI(OPiv)$_2$ and AgF. The oxidative C−H fluorination of aliphatic substrates with a Mn(III) porphyrin catalyst in the presence of silver fluoride and

X = H or Br
Y = H, NO$_2$, CN
    CO$_2$Me, F, Br,
    I, OMe, Me, Ph

30–70%
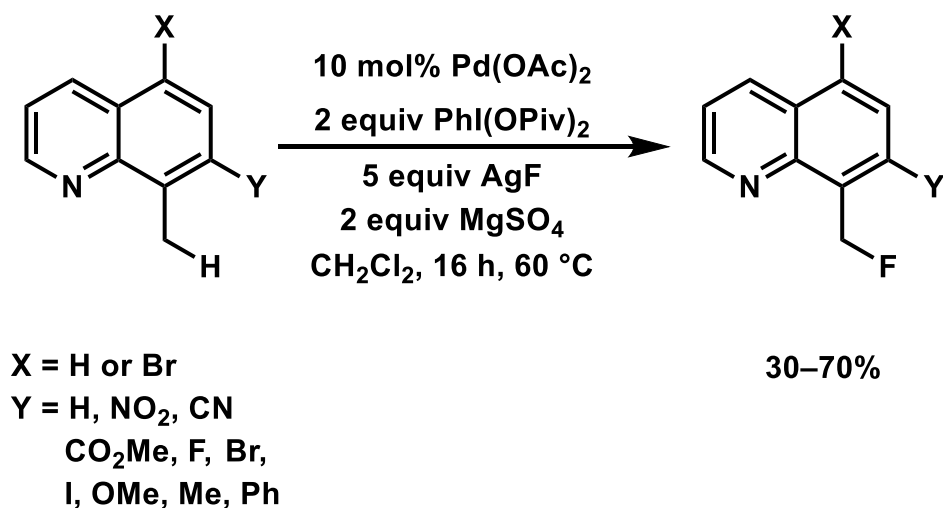
Scheme 22

iodosylbenzene was later discovered by Groves and co-workers (Scheme 23).[188] The authors

proposed an initial radical C−H bond cleavage by the Mn(V)-oxo intermediate, which results

from oxidation of the Mn(III) catalyst with PhIO. Radical recombination occurs between the

substrate and a Mn(IV)-difluoride complex generated from AgF and a Mn(IV)−hydroxide

complex. It is remarkable that the rate of the fluoride/hydroxide ligand exchange at the

manganese center exceeded that of the reaction between the alkyl radical and the Mn(IV)

complex. The authors found that F atom transfer from Mn(THP)F$_2$ to a cyclohexyl radical in the

equatorial configuration was calculated to occur with a surprisingly low activation barrier of 3

kcal/mol, similar to the barrier for reversed hydroxylation reaction catalyzed by oxomanganese

porphyrins. The reaction barrier for the F atom transfer in an axial configuration is slightly

higher (4.2 kcal/mol). Furthermore, the F transfer barrier was ~3 kcal/mol lower for the trans-

difluoro Mn(IV) species than for the hydroxy-fluoride counterpart, implying a much faster

reaction for the difluoride.   The transition state is calculated to be very early in the reaction

trajectory, consistent with the low F transfer barrier. Therefore, an excellent selectivity was

achieved for the fluorination over hydroxylation.

6–8 mol% [Mn(TMP)Cl]

3 equiv AgF, 0.3 equiv TBAF•3H$_2$O

R–H $\xrightarrow{\hspace{3cm}}$ R–F

6–8 equiv PhIO, MeCN/CH$_2$Cl$_2$ (3:1)

6–8 h, 50 °C

32–55%

[Mn(TMP)Cl]

49%

42%
$\alpha/\beta = 3.1$

57%

44%
d.r. = 8:1
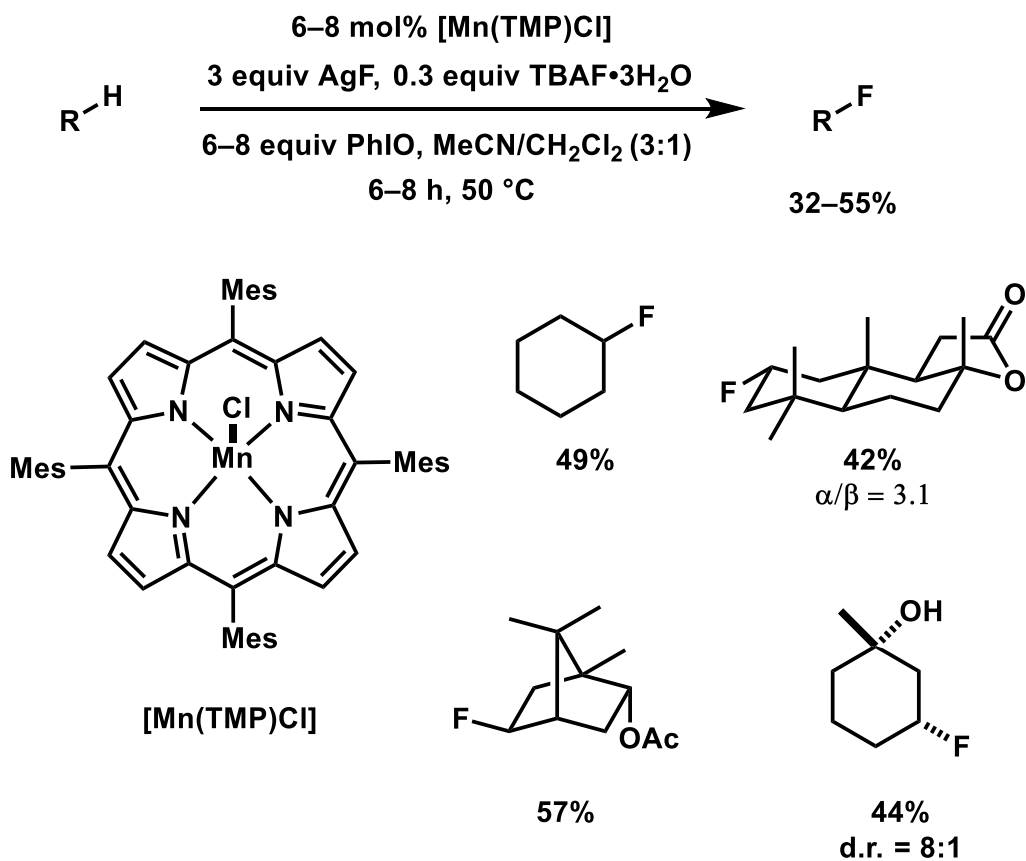
Scheme 23

Because of the advantage of the weak N−F bonds (*N*-fluorosultam bond dissociation

energy is 2.84 eV),[189] a variety of *tert*-butyl alkylperoxoates afforded the corresponding alkyl

5 equiv NFSI

$\xrightarrow{\hspace{3cm}}$

Benzene, 4 min–16 h, 110 °C

R–F

R = CH$_2$OPh,
(CH$_2$)$_2$CH$_2$Ph,
CHPhMe

24–98%
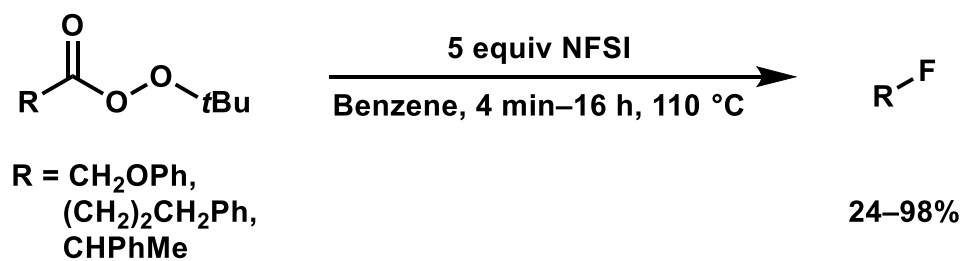
Scheme 24

fluorides upon treatment with NFSI under either photolysis or thermolysis conditions (Scheme 24).[190] The formation of primary alkyl fluorides was not efficient in accordance with the hypothetical radical mechanism.

Therefore, Lectka and co-workers utilized copper catalysis to facilitate the radical monofluorination of $C(sp^3)-H$ bonds (Scheme 25).[191-192] Their method was applied to various substrates, affording the desired products in moderate yields. Their catalytic system involves the use of SelectFluor®, the radical precursor N-hydroxyphthalimide (NHPI), an anionic phase-
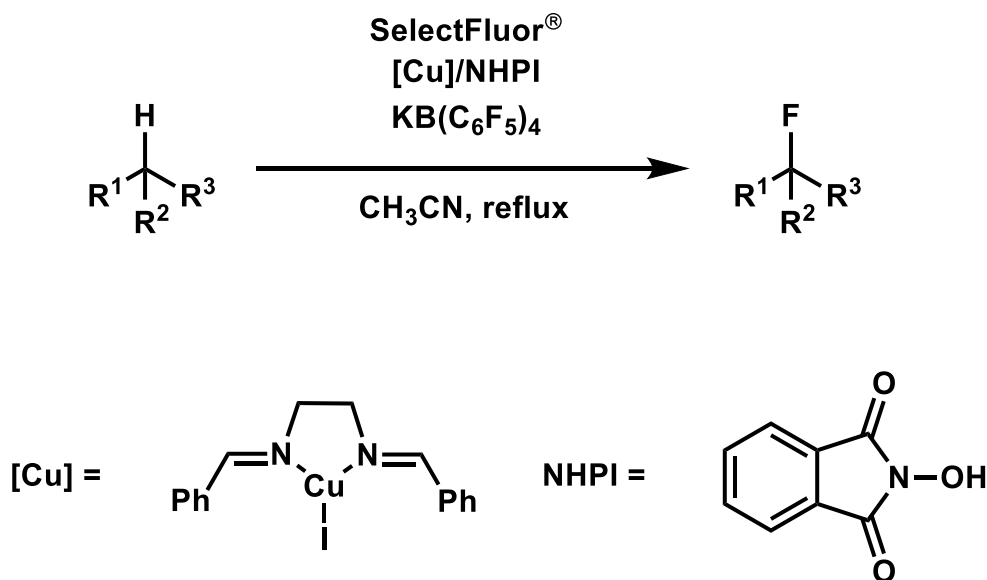
Scheme 25

transfer catalyst ($KB(C_6F_5)_4$) and a Cu(I) bis(imine) complex. An observed rearrangement of a radical clock experiment gave preliminary evidence that a radical chain mechanism initiated by an SET from Cu(I) to SelectFluor® was involved.

Vanadium(III) oxide was reported to catalyze $C(sp^3)-H$ fluorination by Chen and co-workers (Scheme 26).[193] This simple method allowed the fluorination of a wide range of

substrates in good yields. Despite of the low cost of vanadium catalyst, the method does not

differentiate secondary and tertiary reaction center, which might cause potential problem where

complex system is involved.

R^1, R^2, R^3 = H, alkyl, aryl

12–85%

85%   74%   73%
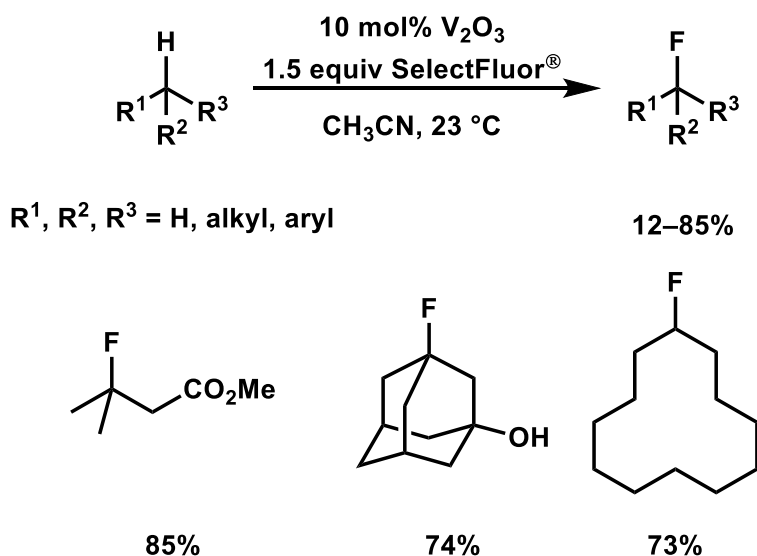
Scheme 26

A metal-free fluorination of sp^3 carbon center was described in 2013 by Inoue and co-

workers (Scheme 27).[194] *N,N*-Dihydroxypyromellitimide (NDHPI) was initiating the
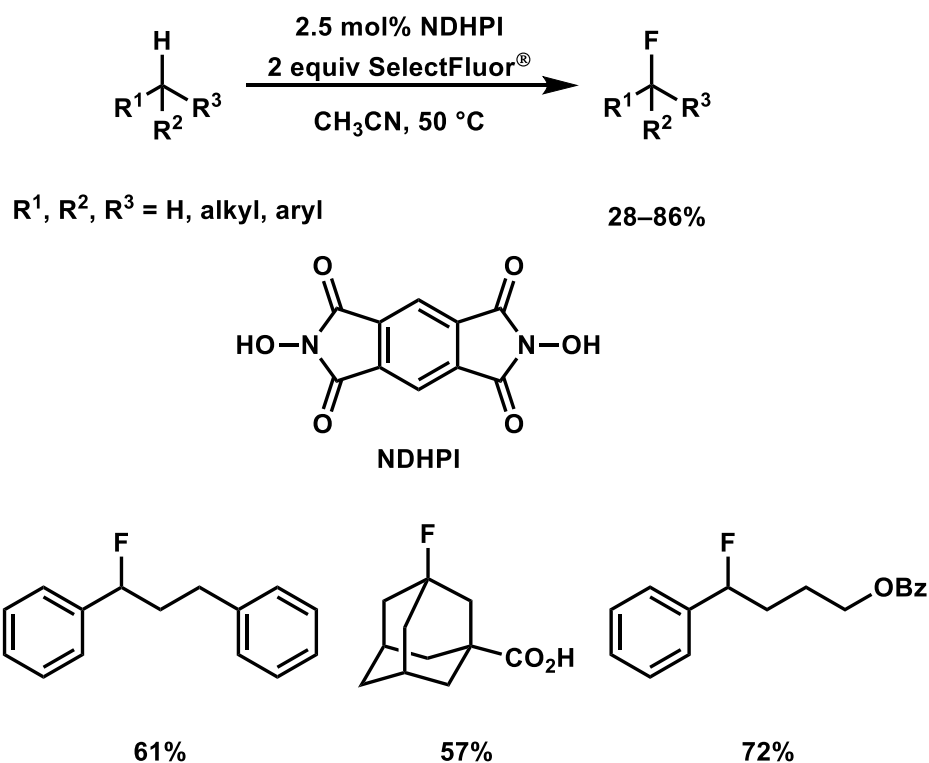
Scheme 27

fluorination by generating a *N*-oxyl radical to perform hydrogen abstraction at the electron-rich position.

The reaction is compatible with various functional groups, including benzoyl- and methanesulfonyl-protected alcohols, carboxylic acids, tertiary alcohols, cyanides, and bromides. Another metal-free C(sp^3) −H fluorination was reported by Lectka and co-workers in 2014. A substoichiometric amount of triethylborane in the presence of O_2 was hypothesized to initiate the radical chain reaction (Scheme 28).[195] This method is convenient and cheap, suffering low to modest yield in the same time.
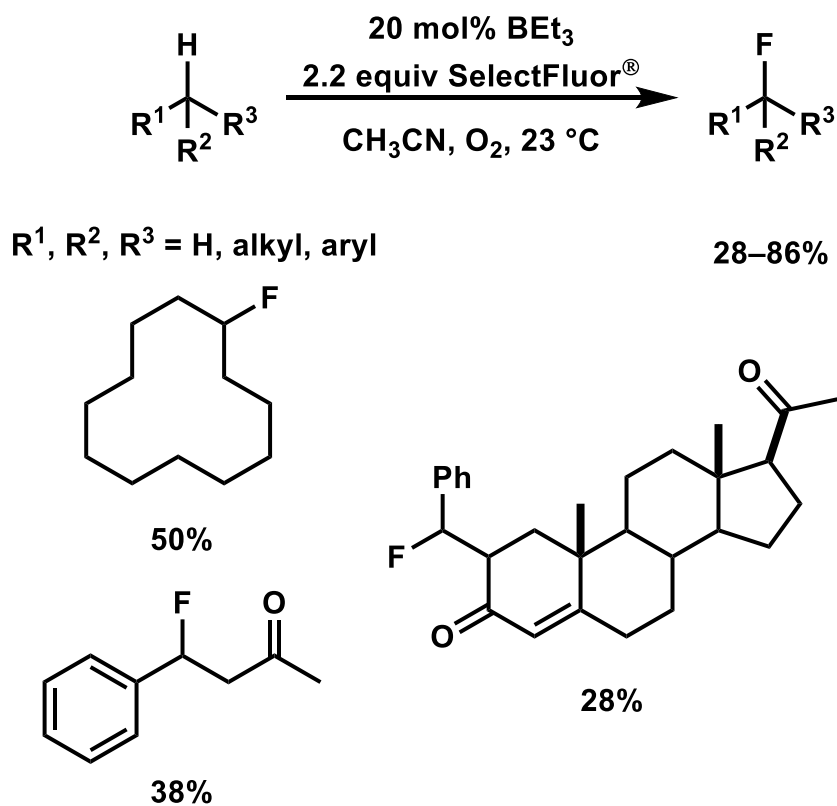
Scheme 28

Excitation of electrons by light to form radicals facilitates photocatalysis studies in fluorination reactions. Lectka and co-workers discovered a fluorination method with the use of ultraviolet light and 1,2,4,5- tetracyanobenzene (TCB) as photosensitizer in 2014 (Scheme 29).[196] Both simple hydrocarbons and complex natural products could be fluorinated in this study. In the same year, the fluorination of unactivated C−H bonds, reported by the Britton group, was accomplished by a decatungstate catalyst (TBADT, tetrabutylammonium salt of decatungstate) with good hydrogen-abstracting ability, in combination with NFSI (Scheme
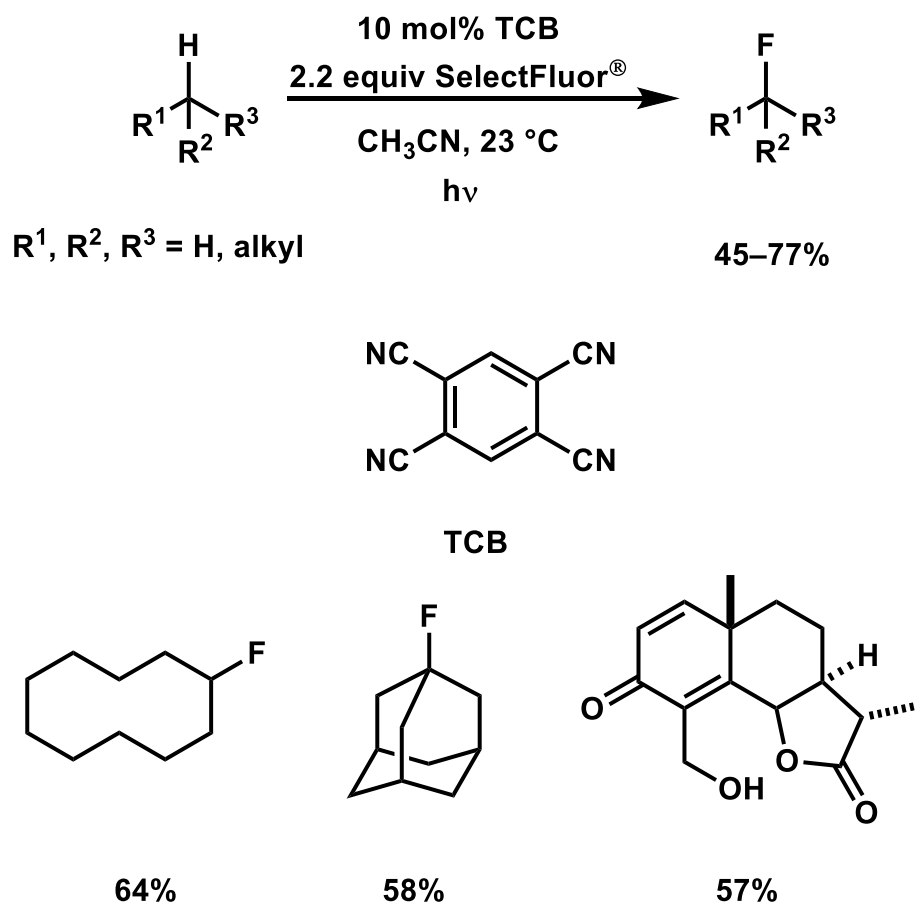
Scheme 29

30).[197] The scope of this method was also broad, which includes simple alkyl fluorides, natural

products, and fluorinated amino acid derivatives. A photocatalytic fluorination of inactivated

C(sp^3)−H bonds was also described by Tan and co-workers (Scheme 31).[198] Their method

suggested an energy transfer with anthraquinone(AQN) as a photocatalyst induced cationic *N*-

radicals from SelectFluor®. The reaction is scalable (25 mmol), and a variety of functional

groups are tolerated.

2 mol% TBADT

10 mol% NaHCO$_3$

1.5 equiv NFSI

CH$_3$CN, 23 °C

hν

R^1, R^2, R^3 = H, alkyl

13–58%

4X

TBADT

X = Bu$_4$N$^+$

45%

56%

58%, α/β = 4:1
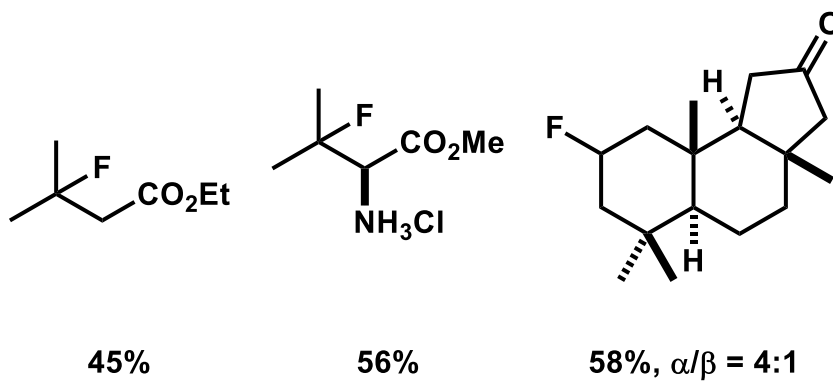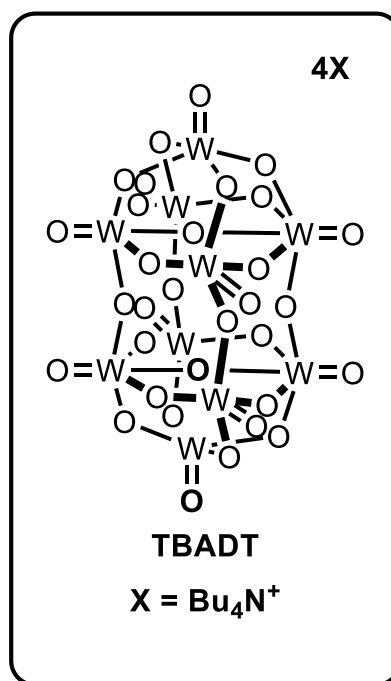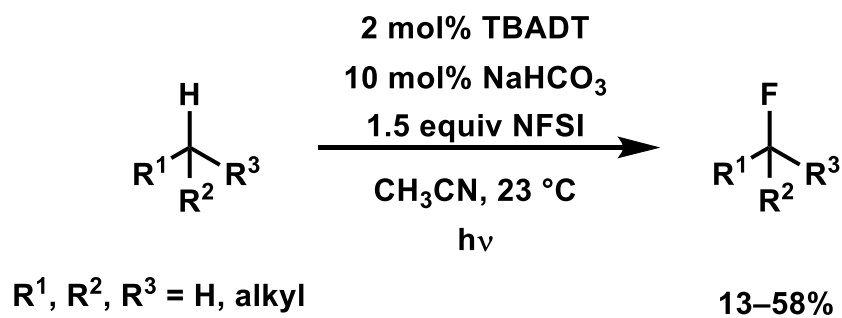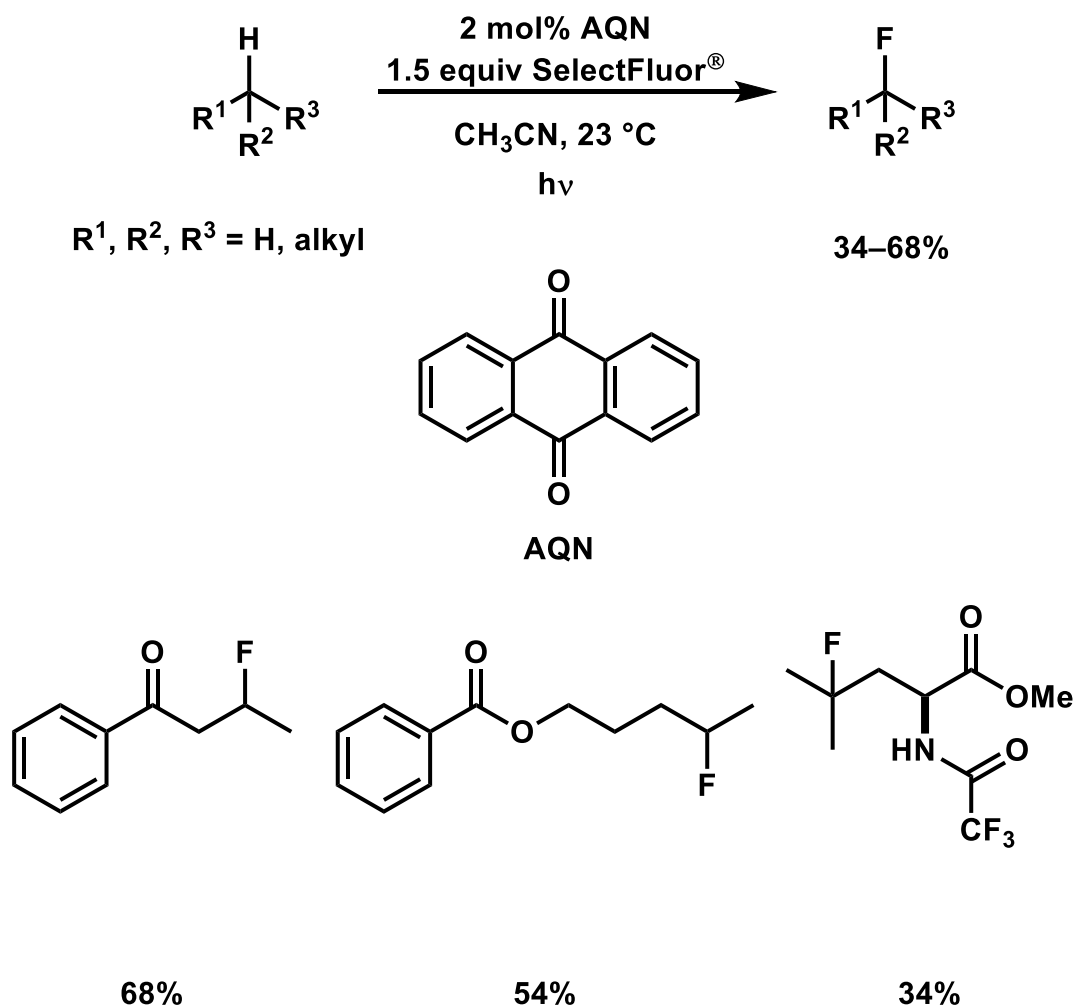
Scheme 30

Scheme 31

Decarboxylative fluorination, first discovered by Patrick and co-workers was recently

reported by Li and co-workers for secondary and tertiary aliphatic carboxylic acids with

SelectFluor® by silver catalysis (Scheme 32).[199] This approach is complementary to traditional

nucleophilic fluorination reactions with DAST-type reagents. The involvement of Ag-mediated

decarboxylation to form an alkyl radical during the reaction was demonstrated, but the detailed

mechanism for the formation of the key C−F bond remains undetermined. Meanwhile,

SelectFluor® is able to fluorinate deprotonated α-aryloxyacetic acids and α-aryloxy-α-
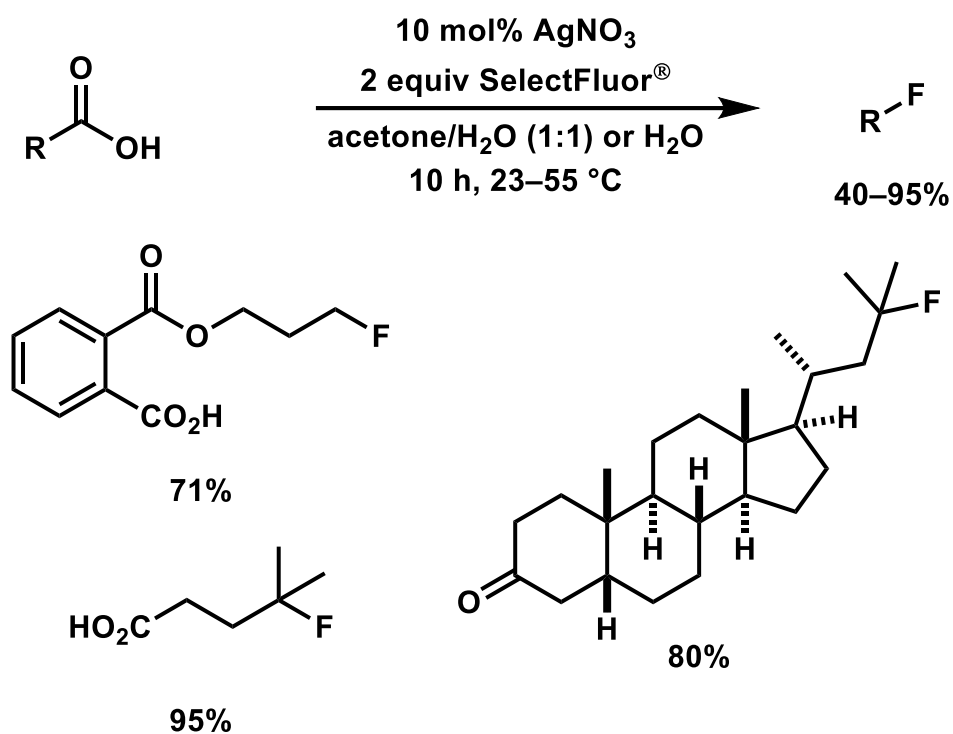
Scheme 32

fluoroacetic acids under photochemical condition to afford aryl fluoromethyl ethers or aryl

difluoromethyl ethers, respectively.[200]

5. Introduction of AgF_2

Silver naturally exists in its +1 oxidation state in compounds, but silver(II) fluoride is a rare member of silver(II) compound family. AgF_2 is a white crystalline powder, but commercial samples are usually black/brown due to impurities. The F/Ag ratio for most samples is less than 2, typically closed to 1.75 due to contamination with Ag, oxides, and carbon.[201] AgF_2 can be synthesized by fluorinating Ag_2O, AgF or AgCl with elemental fluorine, while AgF and AgCl will require heating to 200 °C.[202] As a strong fluorinating agent, AgF_2 should be stored in Teflon or a passivated metal container. Like many other silver salts, it is light sensitive at the same time.

Silver(II) difluoride's electrode potential is $+1.98V(Ag^{2+}+e^-\rightleftharpoons Ag^+)$[203] Compared to some common oxidizing reagents, this value is lower than that of $S_2O_8^{2-}$ (with an electrode potential +2.01 V) and higher than that of Cl_2 (with an electrode potential +1.36V), suggesting the oxidizing ability of Ag^{2+} is in between $S_2O_8^{2-}$ and Cl_2.

AgF_2 oxidizes xenon to xenon difluoride in anhydrous HF solutions.[204]

$$2\ AgF_2 + Xe \rightarrow 2\ AgF + XeF_2$$
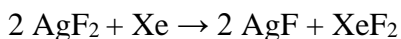
It also oxidizes carbon monoxide to carbonyl fluoride.

$$2\ AgF_2 + CO \rightarrow 2\ AgF + COF_2$$
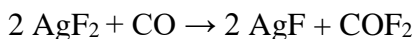
It reacts with water to form oxygen gas.

$$4\ AgF_2 + 4\ H_2O \rightarrow 2\ Ag_2O + 8\ HF + O_2$$
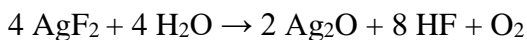
With the considerably high oxidizing ability, AgF_2 could also fluorinate aromatic

compounds, although selective monofluorinations are difficult. In 1980, Zweig and co-workers reported their discovery that on treatment of Silver(II) difluoride, fluorobenzene is obtained in 61% yield from a solution of benzene in *n*-hexane (Scheme 33).[205]
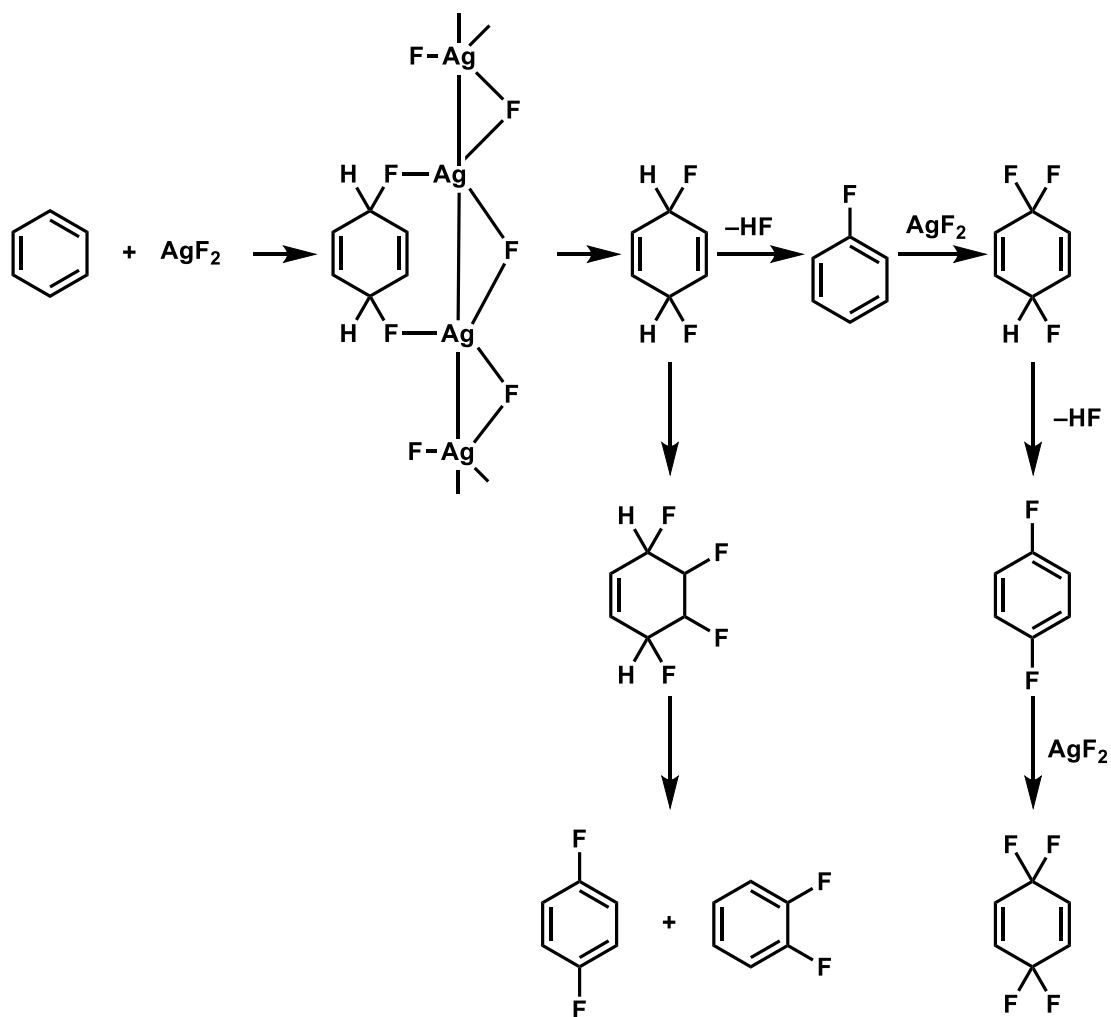
Scheme 33

Several other fluorinated compounds including *o*- and *p*-difluorobenzenes were also detected by ^{19}F NMR in the liquid product. Compounds where two or more fluorine atoms have added to the benzene ring were also found. Table 1 describes the results obtained in experiments involving reaction of benzene solutions with AgF_2. $CHCl_3$, CH_2Cl_2, and CCl_4 were picked as

solvents initially, but *n*-hexane afforded higher fluorobenzene yields and was thus more

extensively examined.[205] Other aliphatic alkanes such as cyclohexane behaved similarly.

Solvent, reaction temperature, and time influenced the yield and distribution of fluorinated

products as indicated in Table 1. The highest yield of fluorobenzene was 61%, based on AgF_2

charged. The benzene/AgF_2 ratio also affects the fluorobenzene yield. 26% yield of

solvent	solvent vol/mL	benzene equiv	Teperature/°C	PhF %yield
$CHCl_3$	25	1	62	19
$CHCl_3$	10	1	62	28
CCl_4	25	1	76	36
CCl_4	10	0.5	76	24
CH_2Cl_2	30	1	25	44
n-hexane	30	1	69	50
n-hexane	50	1	69	48
n-hexane	40	0.5	55	26
n-hexane	30	3.4	69	61
n-hexane	30	9.9	69	45
n-hexane	60	6.6	69	61
n-hexane	9.1	1	40	47

68 mmol AgF_2 was subjected in each reaction.
Yields were calculated based on the amount of AgF_2.

Table 1[205]

fluorobenzene is obtained by using 40 vol % of benzene in *n*-hexane. 2 equivalence of benzene

gives a 50% yield, while either 5 or 11 equivalences of benzene produces a 61% fluorobenzene

yield.

Since the three direct products shown in Scheme 34 below are difficult to separate, people oxidize the reaction mixture with potassium permanganate to obtain diols, which are robust to make further transformations. O'Hagan in 2012 unprecedentedly employed this route shown in Scheme 34[206] to obtain η-1,2,3,4,5,6-hexafluorocyclohexane, whose chloro-, bromo-analogues were synthesized by Faraday and Mitscherlich, respectively.
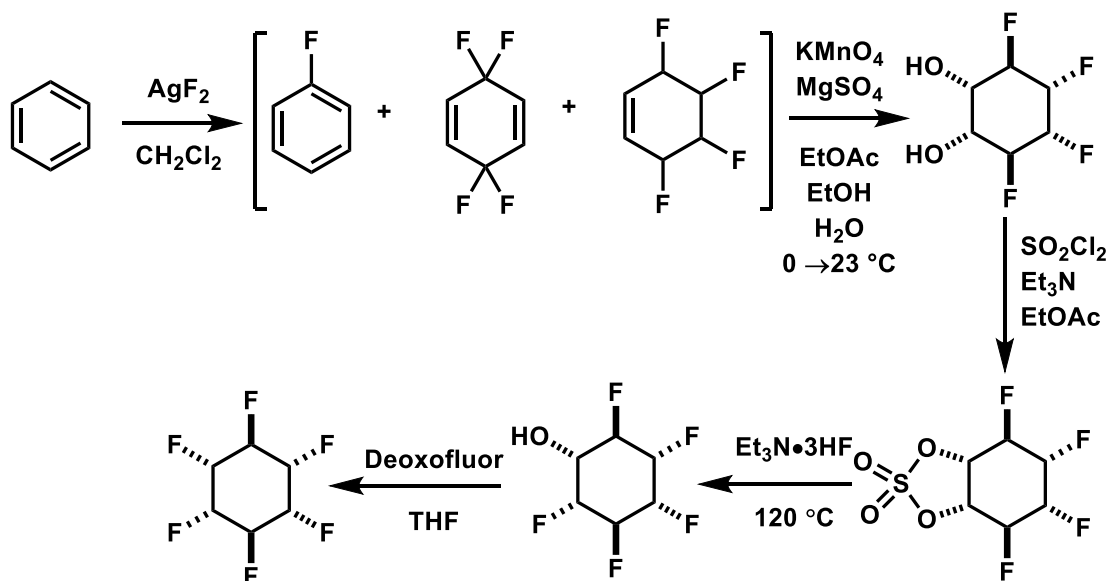
Scheme 34

The low chemo selectivity limits the use of AgF_2 in organic synthesis. Therefore, few studies have been carried out on this potentially useful fluorination reagent featuring both electrophilic nature and strong oxidizing ability at the same time.

Recently, AgF_2 was discovered to selectively fluorinate pyridine at the ortho position under mild condition by Hartwig and co-workers (Scheme 35).[207] The reaction is carried out at room temperature. A broad range of substituted pyridines were found to give corresponding ortho substituted pyridines in good yields. Both electron-donating and electron-withdrawing

groups at each position of the ring are tolerated. Pyridines containing ketones, esters, amides, acetals, protected alcohols and amines, nitriles, alkyl tosylates, and enolizable carbonyls are good substrates. Bromide and chloride substituents in the 2-position of the pyridine, which are ready to undergo nucleophilic displacement, remained intact during the reaction. Carboxylic acids and aldehydes were transformed to the corresponding acyl fluorides without forming 2-

AgF$_2$ (3 equiv)

MeCN

room temperature

R = Ph, 88%
R = Et, 94%
R = *t*Bu, 50%

X = OMe, 57%
X = Cl, 41%
X = Br, 43%

R = Ph, 59%
R = OEt, 73%
R = NEt$_2$, 83%

62%

96%

81%

X = F, 55%
X = Cl, 64%
X = Br, 72%
X = OMe, 70%

R = CF$_3$, 97%
R = CN, 53%

75%
5.3:1

77%
4.5:1

79%
2.3:1

86%
2.0:1

R = *t*Bu, 80%
R = OMe, 75%
R = Cl, 62%

R = NEt$_2$, 78%
R = OEt, 51%

74%

57%

| 75% | 44% | 63% | R = Me, 74% | 94% |

R = OBn, 99%

| 83% | 65% | 51% | 58% |

R = Me, 64%
R = Ph, 64%
R = H, 0%

| 76% | 78% | 35% |
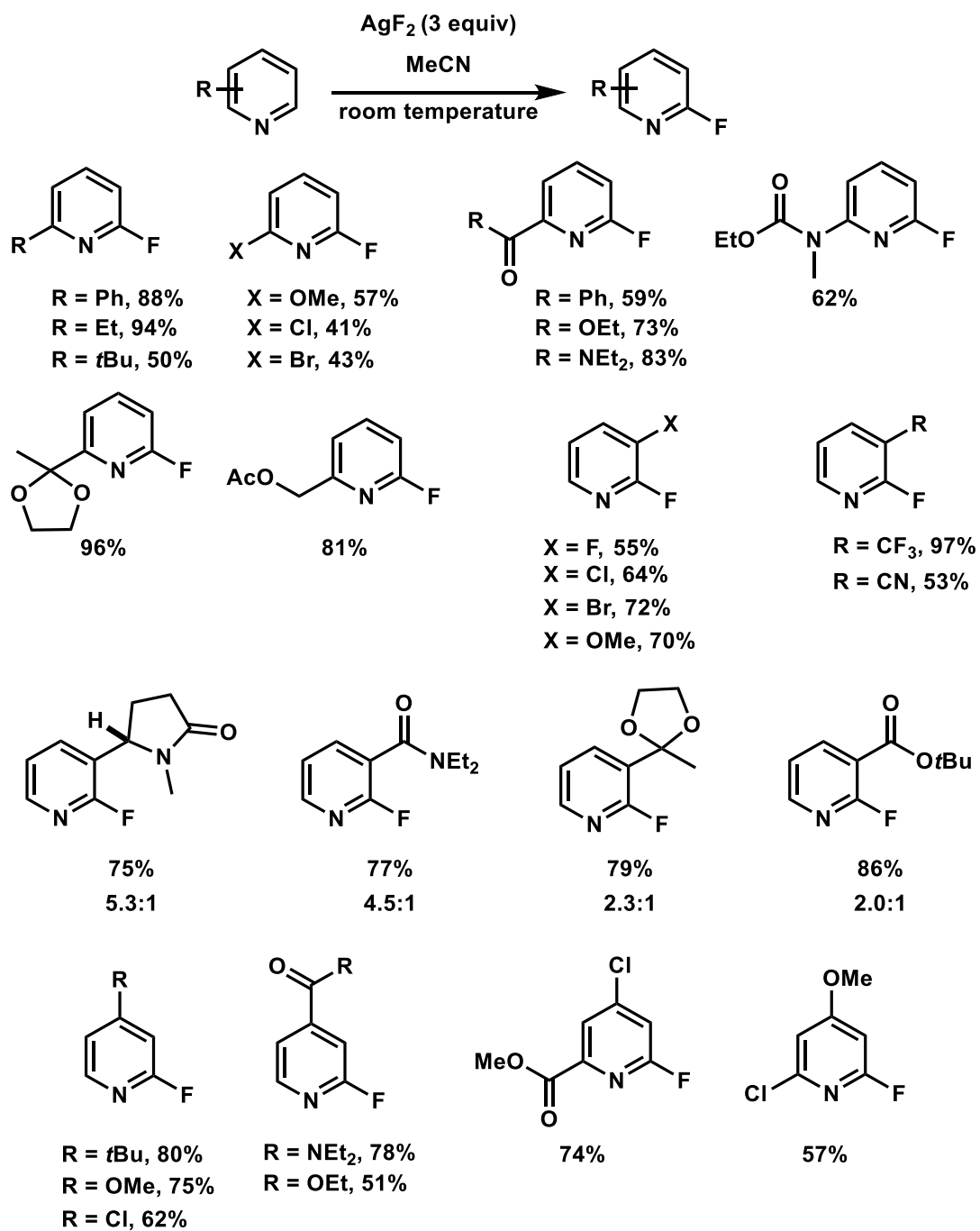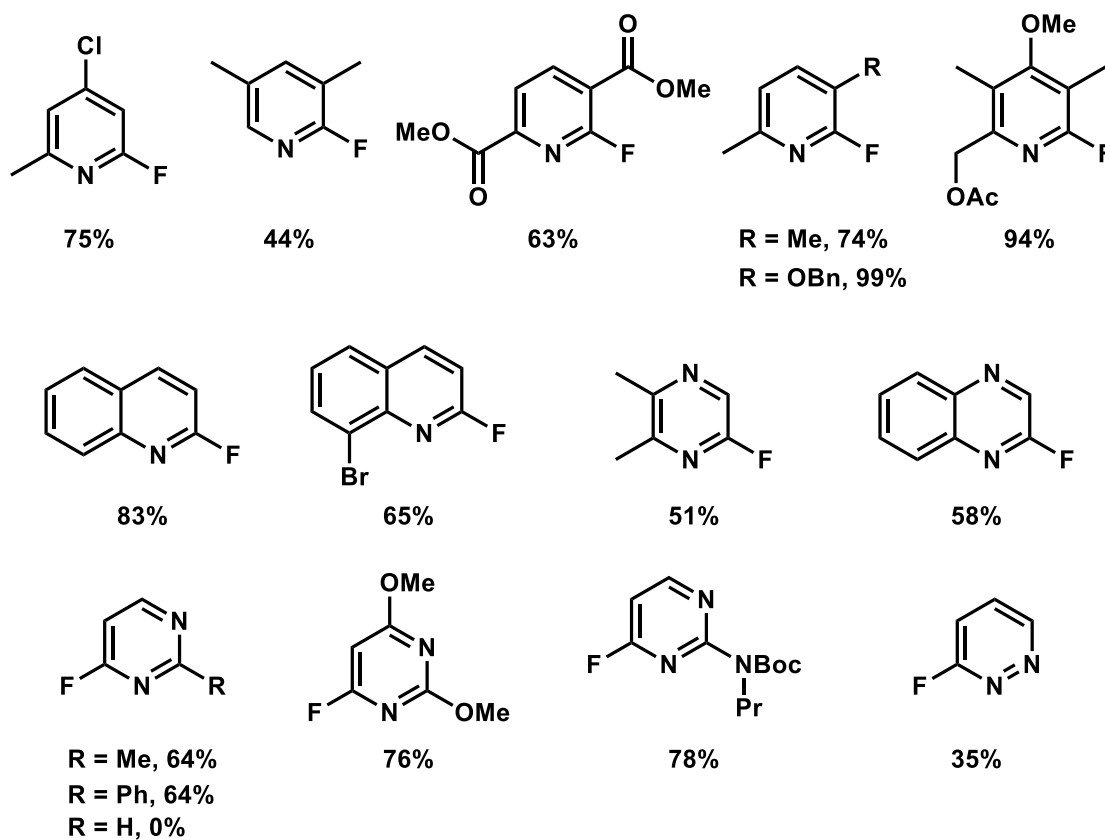
Scheme 35

fluoropyridine products. The reactions with pyridines containing functional groups in the 3-positions preferred to form the 2-fluoro-3-functionalized pyridine products. The fluorination also proceeded with several pyridines containing more than one substituent to form valuable trisubstituted fluoropyridines. Other six-membered nitrogen heterocycles, for example, quinolines, pyrazines, pyrimidines, and pyridazines, were also demonstrated to afford monofluorinated products under similar condition. Unlike most of examples, pyrimidines containing an alkyl, aryl, oxygen, or nitrogen group in the 2-position reacted to form the corresponding 4-fluoropyrimidines in good yield. However, AgF_2 reacted with the π-excessive five-membered aromatic heterocycles to form complex mixtures of products.

The authors proposed that the fluorination occurred by a mechanism similar to that of the Chichibabin reaction (Scheme 36).[207] This mechanism would initiate with coordination of AgF_2
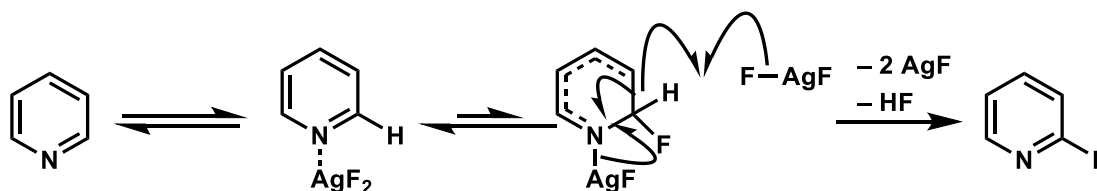
Scheme 36

to pyridine, followed by addition of the [Ag]−F bond across the π-system of the pyridine to form an amido-sliver(II)−fluoride complex. A second equivalent of AgF_2 would then abstract a hydrogen atom from the complex and form two equivalents of AgF and one equivalent of HF.

In 2016, Hartwig group published a facile fluorodecarboxylation induced by AgF_2 which transformed difluoro carboxylic acids to corresponding trifluoromethyl functional group (Scheme 37).[208] The reactions occur with either AgF_2 or a combination of AgF_2 and AgF under mild reaction conditions with a broad range of aryl groups. The reactivity of AgF_2 could be modulated by an electron-poor pyridine additive, 2,6-difluoropyridine, thus facilitating the synthesis of products with a broad substrate scope, including aliphatic alkyls, halides, cyanide, phenoxide, ketones and esters. The addition of AgF increased the yields, presumably, by serving as a source of ·F during the early stages of the reaction.

AgF$_2$ (3–5 equiv), AgF (0–2 equiv)

2,6-difluoropyridine (0–100 μL)

MeCN

86%

54%

80%

70%

74%

52%

51%

87%

98%

56%

80%

53%

44%

X = F:Br, 82%

41%

44%

65%

64%

78%

69%

83%
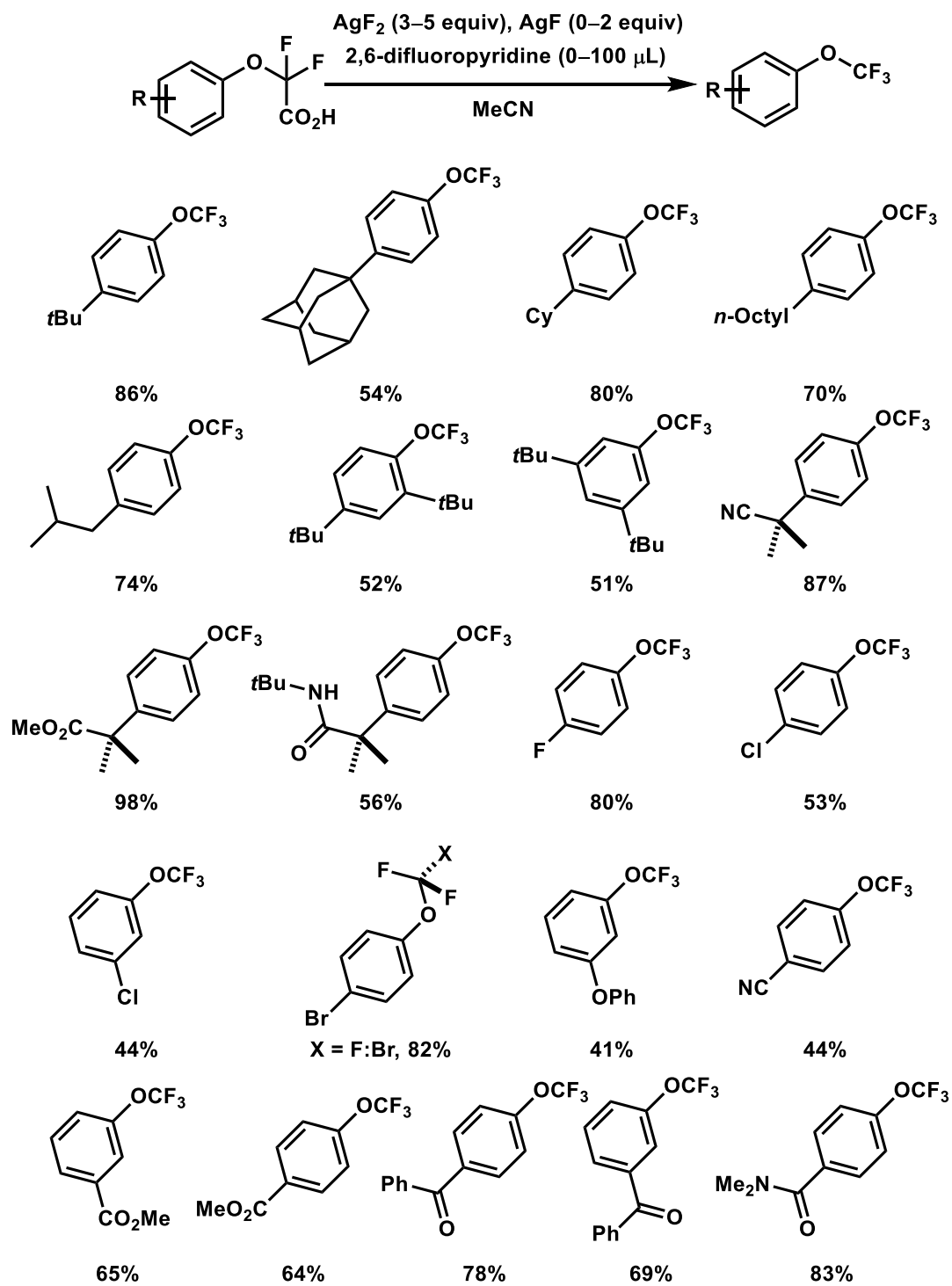
Scheme 37

AgF$_2$ can selectively exchange the iodine in 2-iodoalkylquinoline to afford fluoro quinoline (Scheme 38).[209] Substrates with alkyls, halides, alkoxides on different positions were examined. Substrates with alkoxides or bulky alkyl center adjacent to the reaction center were affording products in good yields, while 6-fluoro, 4-chloro, 8-chloro, and 6-bromo were found to be detrimental to the reaction. Also, if a bulky isopropyl is placed beside the reactive iodine atom,
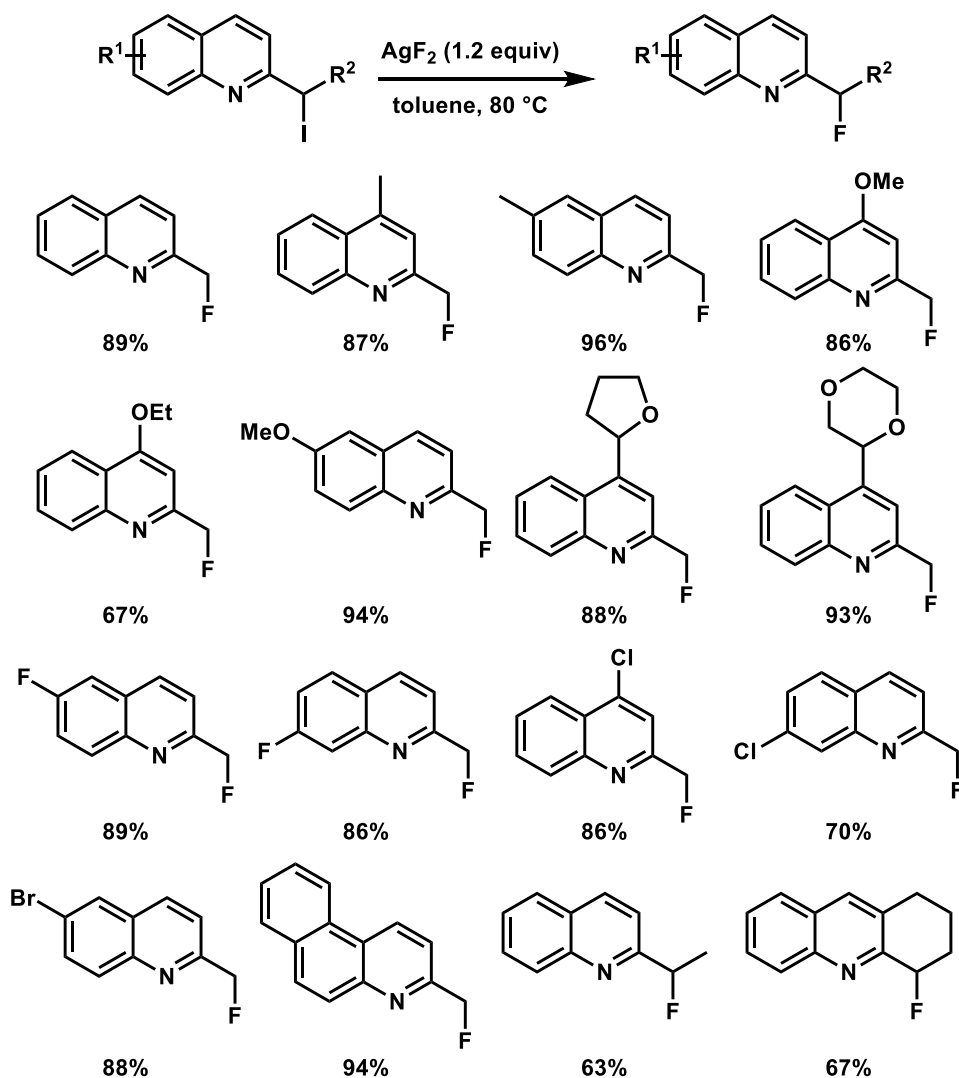
Scheme 38

the reaction efficiency decreased significantly. The authors proposed a mechanism in Scheme 39[209]: the substrate would coordinate with AgF_2 to produce the pyridine-AgF_2 complex. Then, the fluorine in the complex interacts with the carbon attached to iodine atom to form a transition state of 5-membered cyclic intermediate, affording the corresponding product via halide exchange.
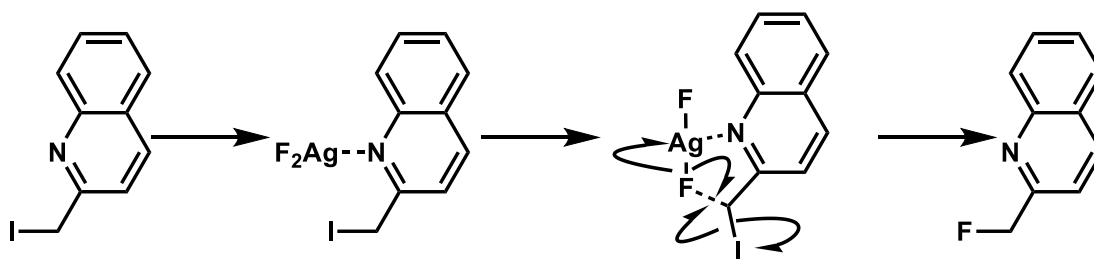
Scheme 39

Silver difluoride can oxidize disulfide to form sulfur trifluorides (Scheme 40),[210-211] usually useful difluorination reagents for aldehydes and ketones, and trifluorination reagents for carboxylic acids.[212]
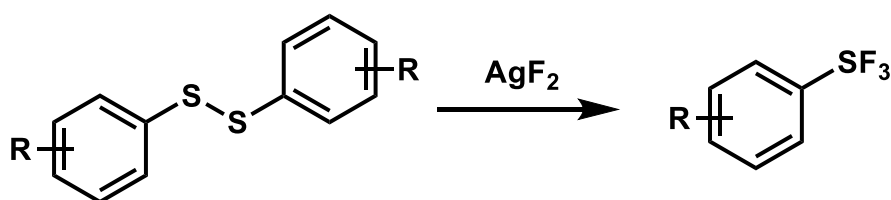
Scheme 40

In sum, although difficult to harness, once it's controlled, AgF_2 could be a fascinating fluorinating reagent. In order to obtain an insight to this potentially powerful reagent, this entire doctoral research was carried out.

Chapter II. Cyclopropanol to Beta Fluoro Ketone

1. Fluoro Ketone Synthesis

Fluoroketones are extremely valuable building blocks in medicinal and biological chemistry, and α-fluoroketones can be readily converted into chiral α-fluoroethylamines, α-fluoroethylhydroxys, and so on. As the α position of carbonyls is electron-deficient and therefore electronically activated, electrophilic fluorination on this position is relatively robust and a lot of studies were reported these years.

Generally, electrophilic fluorine sources are applied to install fluorine atom to the α position of carbonyls under basic conditions,[213-214] although electrophilic fluorinating reagents alone could induce fluorination reaction.[215] Cases of synthetic enolate equivalents, for instance, acetate[216] and silyl enolates,[213-215] reacting with electrophilic fluorine sources are also known. The optimal fluorine source varies depending on individual substrate, and therefore there is not a universally applicable fluorine source for all the reactions.

The proton of β-keto esters is more acidic than regular ketones, therefore, the reaction with fluorine sources is often even more robust than regular ketone counterparts. This strategy has been applied to facilitate various transformations when simple ketones are not reactive or selective enough. For example, enantioselective decarboxylative protonation can be a powerful tool to control the stereochemistry of the α alkyl substituents of ketones.[217] Likewise, Shimizu and his co-workers had utilized this feature to synthesize fluoro β-keto esters first and after subsequent palladium-catalyzed decarboxylation of β-keto carboxylates, regular fluoro ketones were afforded (Scheme 41).[218]
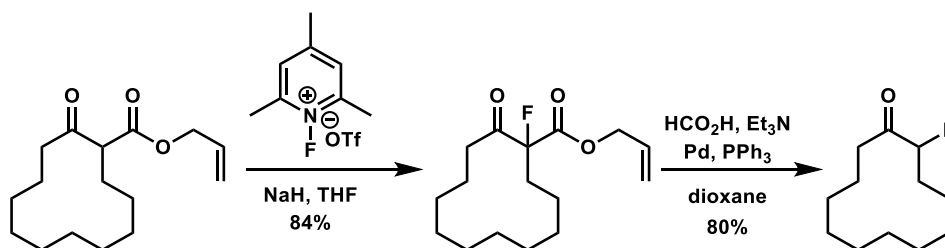
Scheme 41

α, β-epoxy sulfoxides could be employed in α-fluoroketone synthesis.[219] With a good leaving group, sulfoxide, and the activation of epoxide with Lewis acid, BF$_3$·OEt$_2$, α, β-epoxy sulfoxides were smoothly converted to α-fluoroketones with KHF$_2$ as the fluorinating reagent in 1990 by Yamakawa and his co-workers (Scheme 42).
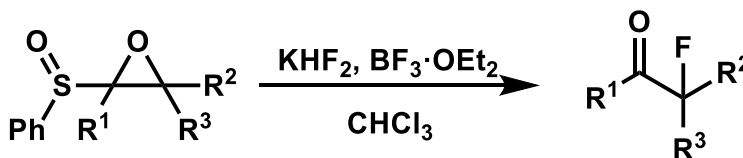
Scheme 42

Vinyl azides have been proved by Liu group in 2016 to react with SelectFluor® under a mild SET condition to afford α-fluoroketone (Scheme 43).[220] Over 20 examples were proven to perform efficiently in the reaction. The authors proposed a subsequent fluorine atom transfer process was also involved.
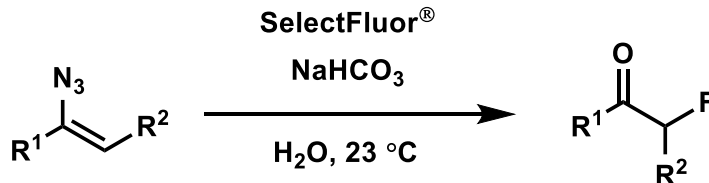
Scheme 43

MartÍn-Matute and his co-worker also reported a method using allylic alcohol to afford α-fluoroketone catalyzed by [IrCp*Cl$_2$]$_2$ (Scheme 44).[221]   This method is giving the best performance in aqueous media while the pH has to be carefully tuned.

R^1 = H, alkyl, phenyl
R^2 = H, methyl
R^3 = alkyl, phenyl

60-92%
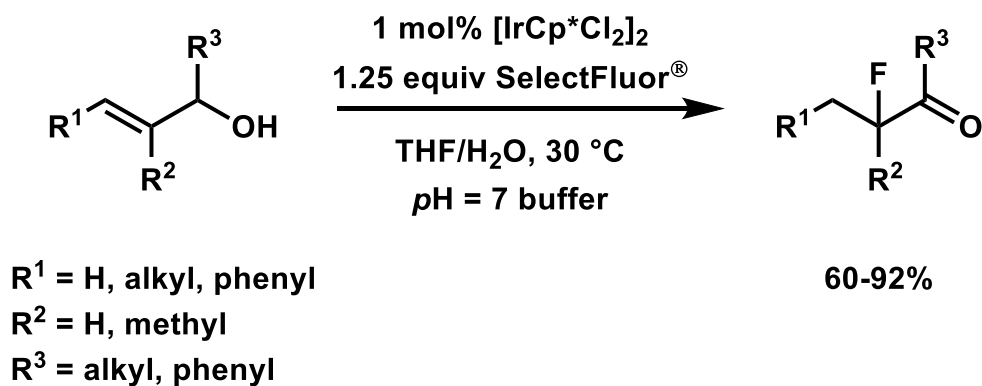
Scheme 44

Nucleophilic fluorination of α-bromoketones can be an efficient alternative of α-fluoroketones in water with TBAF·3H$_2$O as the fluorinating agent (Scheme 45).[222]   Primary and secondary centers are both feasible with this method.   However, the report did not show any positive result on tertiary bromide substrates, implying a potential limitation.
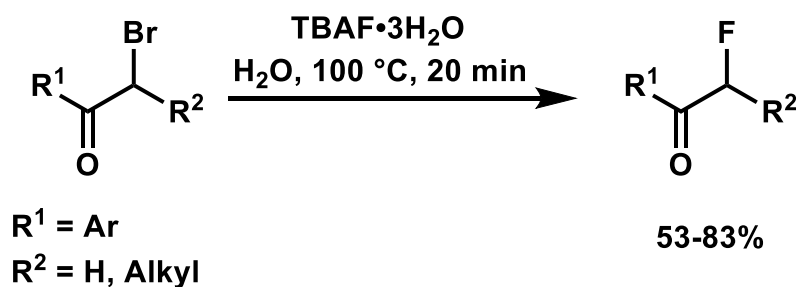
Scheme 45

Compared to the robustness of the α position of ketones, β position is relatively inert. However, more and more β-fluoroketones are synthesized recently via indirect methodologies. Zhu and his collaborators are pioneers in this regard. In 2015, they reported a novel methodology using cyclopropanols as substrates (Scheme 46).[223] Formal catalysis by silver(I) enabled the smooth conversion from cyclopropanols to β-fluoroketones. The reaction could tolerate electron- rich and electron neutral aryls, electron-rich and electron neutral benzyls, and
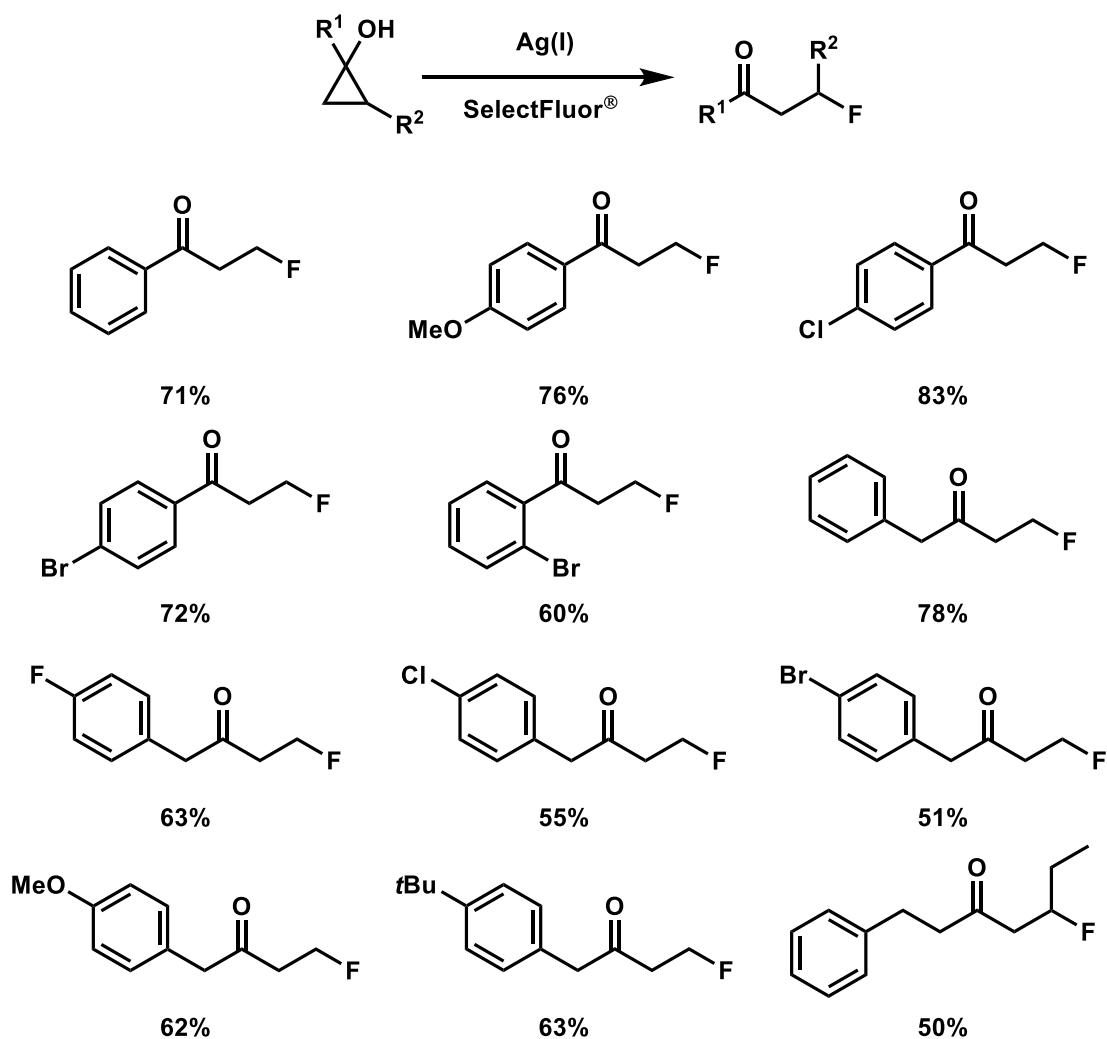
Scheme 46

alkyl as the group adjacent to the hydroxyl (R^1). On the other hand, selection of another

substituent on the cyclopropane ring (R^2) is relatively limited, for H and ethyl were the only

reported examples. In the same report, γ-fluoro ketones were also accomplished by applying

similar reaction protocol with cyclobutanols. The authors proposed a plausible mechanism

initiated by incorporation of a silver and cyclopropanol/cyclobutanol to generate a complex

(Scheme 47).[223] The complex then interacts with SelectFluor® to generate F−Ag(III) complex.

Homolysis of the Ag(III) complex produces an F−Ag(II) species and cyclopropyloxy/cyclobutyloxy radical, which fragments to form a linear secondary radical so
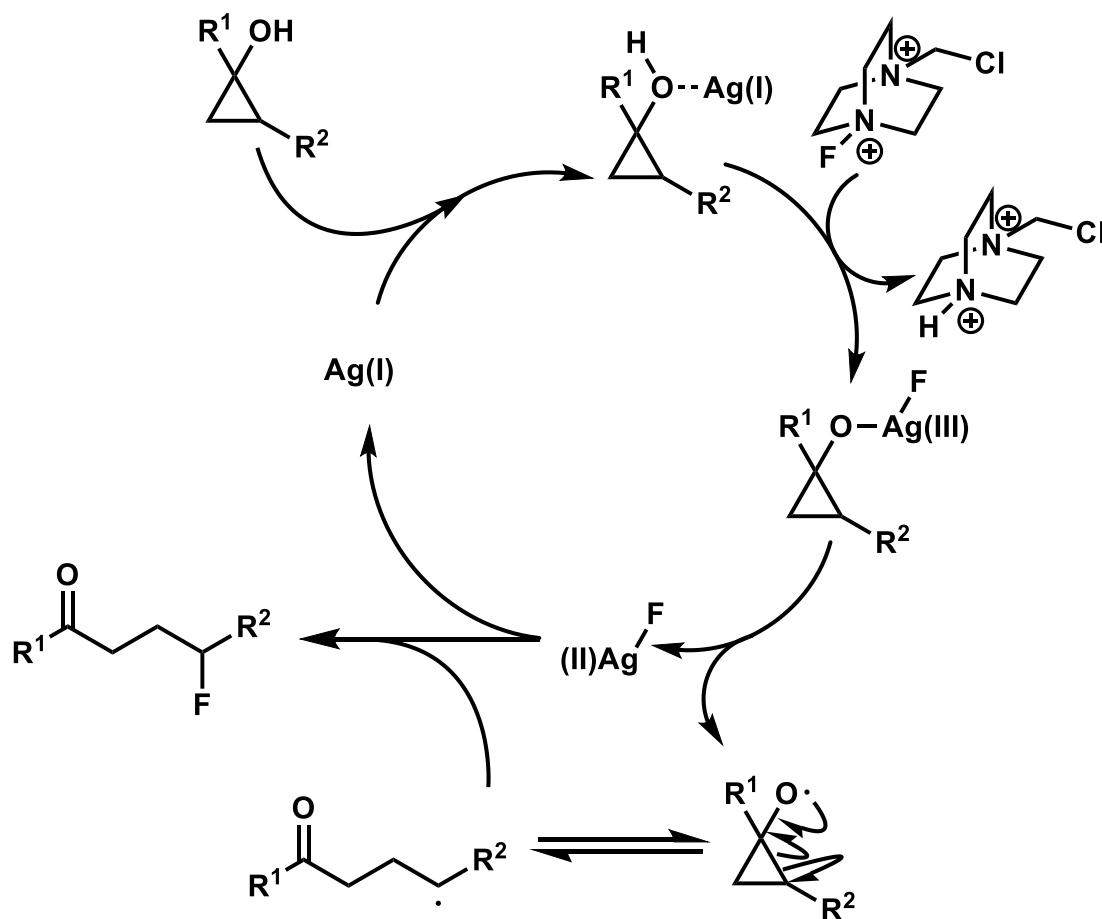
Scheme 47

that the ring strain can be released. This radical reacts with the Ag(II) complex to eventually afford the product β/γ-fluoroketones. Some other groups also published their similar reports to synthesize the β -fluoroketones and Fe(acac)₃ was proved to be an effective catalyst for this transformation.[224]

Later, Lectka applied a similar idea to synthesize β-fluoroketones (Scheme 48).[225] With

the help of a photosensitizer, 1,2,4,5-tetracyanobenzene, the authors were able to achieve the same result without the use of metal catalyst, which might be more economically amenable.
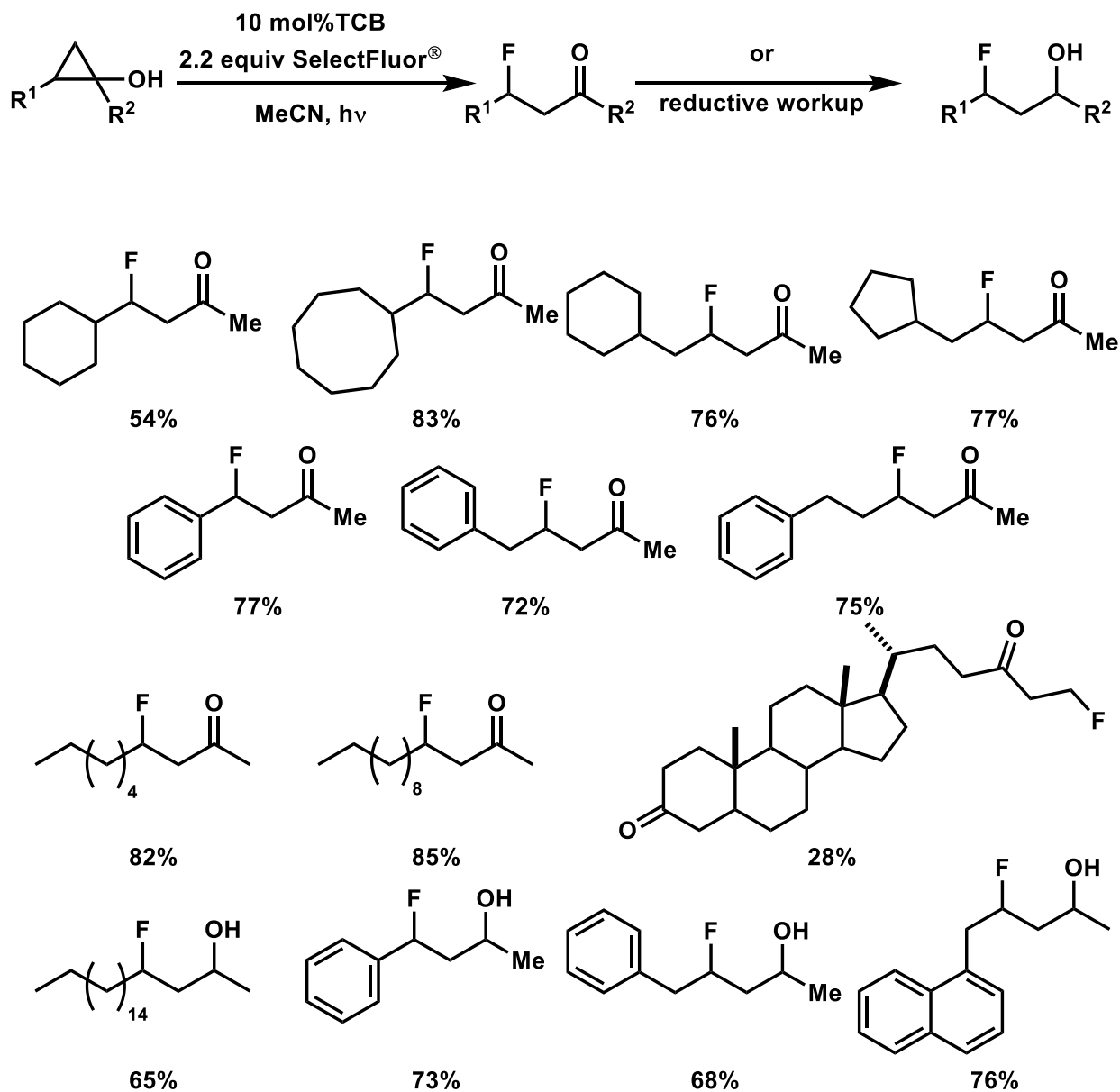
Scheme 48

2. Cyclopropane properties

A cyclopropane molecule consists of 3 equal length bonds, therefore geometrically the bonds angles have to be 60°. This is far less than the thermodynamically most stable angle of sp^3 C−C bonds, 109.5°, leading to significant ring strain (28 kcal/mol).[226-227] The eclipsed conformation of its hydrogen atoms also results in torsional strain. Therefore, the bonds between the carbon atoms are considerably weaker (65 kcal/mol) than in a typical alkane (80−85 kcal/mol),[228] where much higher reactivity arises. Even when substituents are attached and the bond lengths are no longer equal, this effect is not alleviated much.

Bonding between the carbon centers in cyclopropanes is generally described as bent bonds.[227] In this model, the carbon−carbon bonds are bent outwards so that the interorbital angle is 104°. This behavior reduces the bond strain and is achieved by distorting the sp^3 hybridization of carbon atoms to technically sp^5 (i.e. 1/6 s density and 5/6 p density)[229] so that π character is more than normal in the C−C bonds and the carbon-to-hydrogen bonds gain more s-character. This results in an unusual consequence that while the C−C bonds in cyclopropane are weaker than normal, the distance of 2 carbon atoms is less than in a regular alkane bond: 151 pm versus 153 pm (average alkene bond: 146 pm).[230]

These molecular features lead to special chemical properties compared to regular alkanes. Higher reactivity of cyclopropanes is often observed under free radical and thermal conditions.

3. Cyclopropanol synthesis

Cyclopropanation of enol derivatives, especially that of trialkylsily enol ethers, by carbene or carbenoid is the most straightforward and widely used method for the synthesis of

cyclopropanols and *O*-substituted cyclopropanols.[231-238] Cyclopropanation of carboxylic acid derivatives could also be an efficient alternative route to cyclopropanols.

3.1. Enol Derivatives

Cyclopropanation of metal enolates with zinc or samarium carbenoids is an efficient direct pathway to cyclopropanols.[239-245] Imamoto and co-workers discovered deprotonation of ketones with strong bases and treatment of the generated enolates with CH_2I_2-SmI_2 or CH_2I_2-Sm produced 1-substituted cyclopropanols effectively (Scheme 49).[242] The regioselectivity is quite high; therefore, 2-methylcyclohexan-1-one treated with LDA and then with CH_2I_2-SmI_2 gives
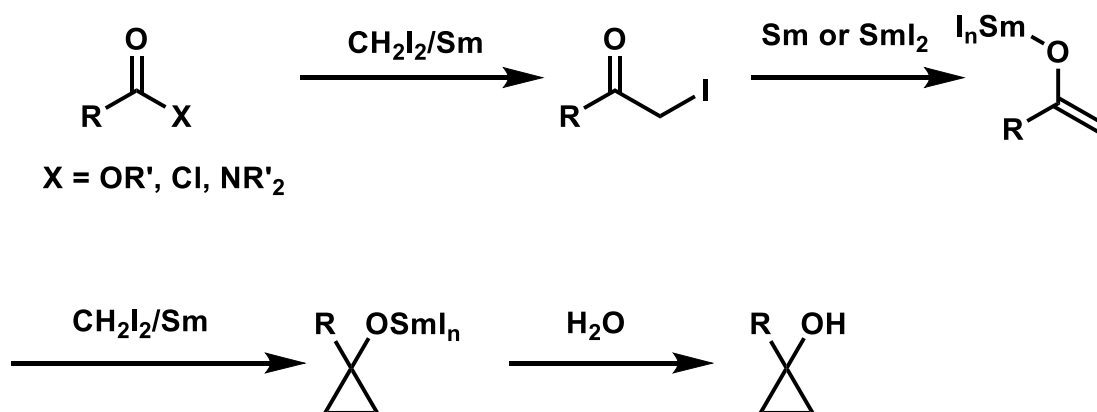
Scheme 49

rise to 2-methylbicyclo[4.1.0]heptan-1-ol in moderate yield.[240]

Similarly, α-halo ketones can be transformed to corresponding cyclopropanols in moderate to good yields by treatment with CH_2I_2 and Sm.[242] The key step of this reaction is also a Simmons-Smith cyclopropanation[246-247] of the corresponding samarium enolate.

3.2. Carboxylic Acid Derivatives

Kulinkovich and co-workers added esters to a mixture of 1 equiv of titanium(IV) isopropoxide and 3 equiv of ethylmagnesium bromide at low temperature to generate 1-alkylcyclopropanols in good to excellent yields.[248] A catalytic version is also available, with the order of reagents addition inverted: the organomagenesium compound was subjected to the mixture of ester and $Ti(OiPr)_4$ (Scheme 50).[249] In such condition, low temperature is no longer needed, and only 2 equiv of the Grignard reagent is required.

1. 2 equiv EtMgBr
5–10 mol% Ti(O*i*Pr)$_4$
Et$_2$O, 18–20 °C

2. 5 % H$_2$SO$_4$(aq), 5 °C
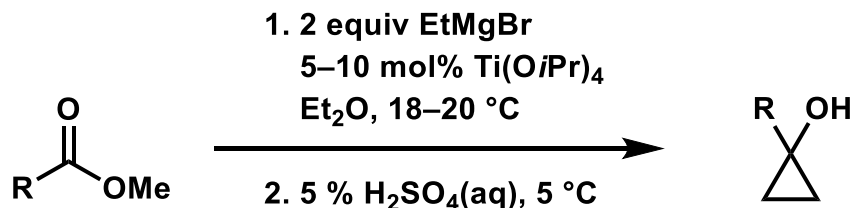
Scheme 50

The authors assumed the formation of the thermodynamically unstable diethyltitanium intermediate which would undergo rapid β-hydride elimination to give ethane and titanacyclopropane (Scheme 51).[248-249] The metallocycle behaves as a 1,2-dicarbanoionic equivalent in reaction with esters. Alkylation happens twice on alkoxycarbonyl to afford cyclopropanol as product.
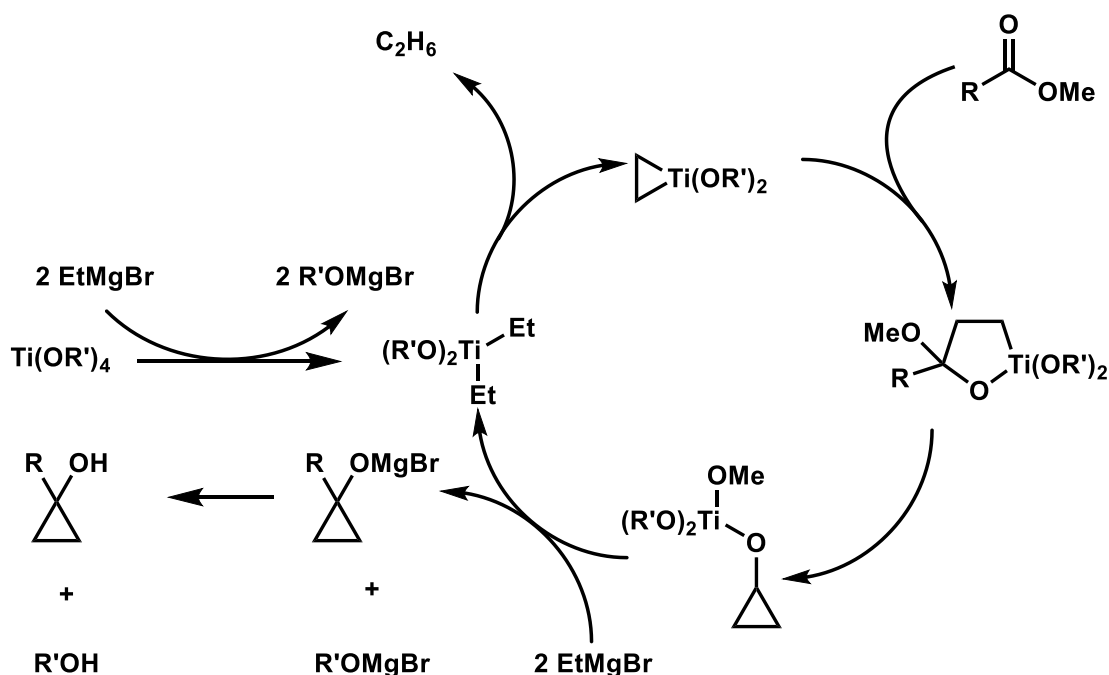
Scheme 51

Assuming a hypothetical ligand exchange process is involved, Sato[250] and Cha[251-253] groups proposed to use more sterically hindered titanacyclopropane intermediated generated from isopropyl,[250] *n*-butyl,[251] cyclohexyl,[252] or cyclopentylmagnesium bromide[253] to facilitate the ligand exchange process. These attempts allowed olefins to replace of Grignard reagents as substrates so that it is no longer necessary to synthesize Grignard reagents.

4. Cyclopropanol properties

Cyclopropanol has been studied a lot since it is a useful synthetic building block. Attributing to the weak C−C bond discussed above, polarization of hydroxyl group, and significantly increased ring strain caused by adjacent oxygen atom, cyclopropanol ring opening process is relatively facile. Therefore, it could be treated as a synthetic building block to achieve

β substituted ketone.

4.1. Reactions with Retention of the Ring

Reactions of cyclopropanols involving C−O bond cleavage are often accompanied by cleavage of the cyclopropane ring. However, when a strong electron-donor substituent attached to the same carbon atom as the hydroxyl group, nucleophilic displacement of the substituent usually proceeds more smoothly.[254-255]

Aminocyclopropane carboxylic acid[256-257] and some other methanoamino acids[258-260] could be synthesized by the corresponding 1-alkoxycyclopropanols. The Strecker reaction of hemiacetal with NaCN and (*S*)-α-phenylethylamine results in the (*S*, *R*)-aminonitrile as a mixture with its (*S*, *S*)-diastereomer (Scheme 52).[259]

d.r. = 6.7:1 to 9.0:1
77%–82%
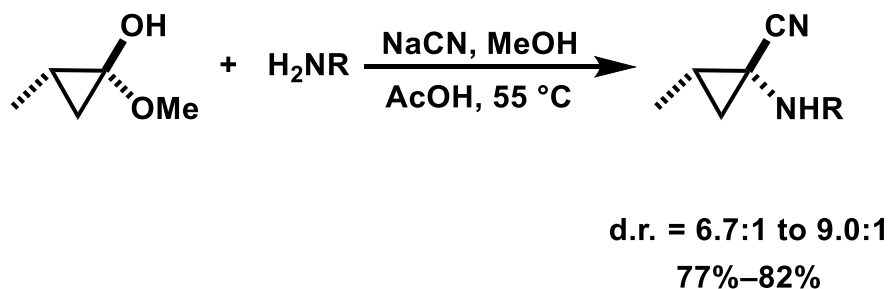
Scheme 52

Activation of the leaving group might be useful for nucleophilic displacement of the hydroxyl group in less reactive cyclopropanol derivatives (Scheme 52).[261-272] Salaün group discovered that 1-alkenyl cyclopropyl esters readily form π- or σ-ethyleneallylmetal complexes which lead to cyclopropane derivatives. The resulting allylmetal complex is readily substituted by nucleophiles to afford alkylidenecyclopropanes or cyclopropanes.[265, 273]
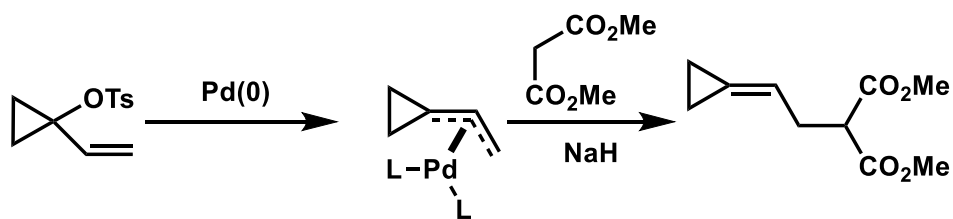
Scheme 53

When stabilized anions are involved, the nucleophilic substitution would be resulting in exclusive alkylidene cyclopropanes. By treating the respective substrates with appropriate 1,1-ethyleneallylpalladium complexes, regioselective *N*-allylation of amines (Scheme 53)[264, 274-275] and amino acids[266] could be accomplished.

R = H   81%
R = Me   95% *ee>98%*
R = CH$_2$Ph   77% *ee>98%*
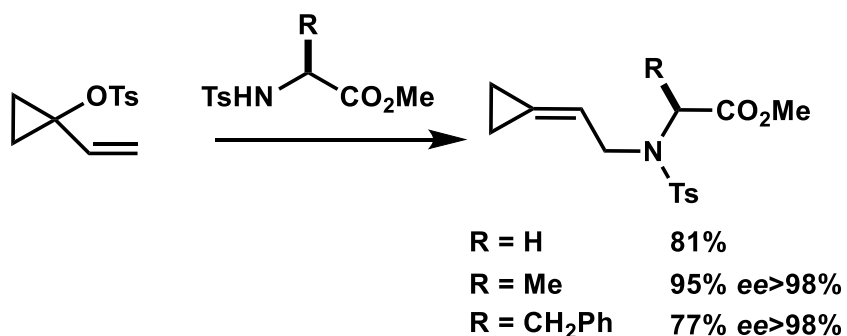
Scheme 54

As for non-stabilized nucleophiles (alkyl- and arylzinc chlorides,[270] metal hydrides,[268, 276] and azides),[269, 274-275] palladium-catalyzed nucleophilic substitution reactions of sulfonates of vinylcyclopropanols would produce 1-alkenyl-1-substituted cyclopropanes. Reaction of tosylate with phenylzinc chloride afforded exclusively 1-ethenyl-1-phenylcyclopropane (Scheme 55). π complex was assumed to transfer the phenyl group from zinc to palladium and palladium was closer to the cyclopropyl carbon at the allylic moiety to produce a σ complex, which undergoes a reductive elimination to give the product.[270] This is an interesting example of Pd catalyzed π-

allyl coupling with bond formation at the more substituted terminus of the allyl fragment.[277]
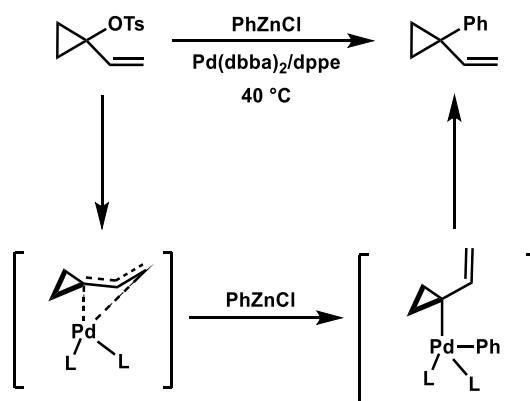
Scheme 55

The synthetic application of these transformations of 1-alkenylcyclopropanol derivatives was shown by several natural product syntheses. For example, coronamic acid[278] was prepared with a palladium(0)-catalyzed stereoselective azidation[269] of the corresponding mesylates as the key step (Scheme 56).
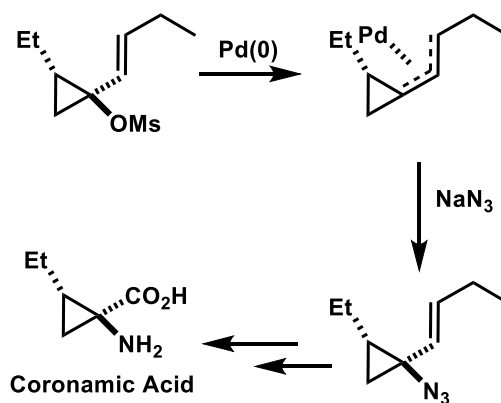
Scheme 56

4.2. Reactions with Ring Opening

Flowers and his collaborators found the oxidation of selected anions (N^{3-}, SCN^-, I^-, and Br^-) by ceric ammonium nitrate (CAN) in the presence of substituted cyclopropyl alcohols could lead to β-functionalized ketones in 2007 (Scheme 57).[279] Although the substrate scope was limited, the selected substrate can undergo azidation, thiocyanation, iodination, bromination

R = Ar   70-96%
X = N$_3$, SCN, I, Br,
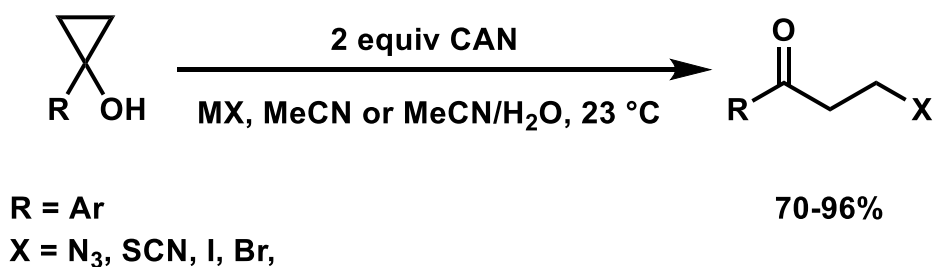
Scheme 57

smoothly in the specific system.

Copper(I)-catalyzed β-amination,[280] fluoroalkylation,[281] trifluoromethylation,[282] and thiotrifluoromethylation[282] was studied extensively by Dai group (Scheme 58). The mechanism of β-amination, trifluoromethylation, and thiotrifluoromethylation was proposed to form a Copper(III) species first and a simultaneous reductive elimination would occur to afford the corresponding products.
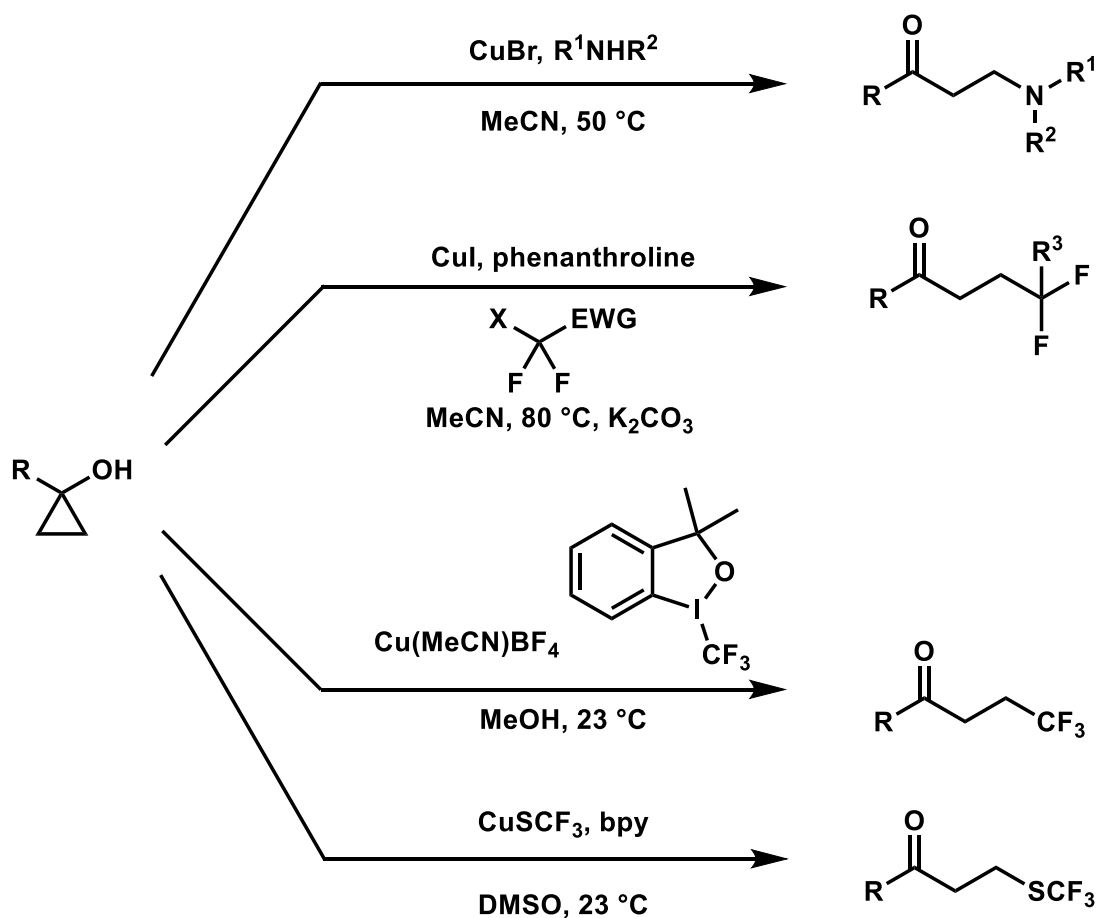
Scheme 58

Cyclobutanols could perform ring-opening reactions like cyclopropanols. Similar to their work on cyclobutanol/cyclopropanol fluorination,[223] Zhu group reported manganese-catalyzed oxidative azidation of cyclobutanols in 2015 (Scheme 59).[283] This methodology can afford primary, secondary, and tertiary alkyl azides products in synthetically useful yields and exclusive regioselectivity. Aside from linear alkyl azides, otherwise elusive medium-sized cyclic azides were also readily prepared. The authors suggested that the reaction likely proceeds by a radical mediated C−C bond cleavage/C−N$_3$ bond formation pathway (Scheme 60). Initially, Mn(OAc)$_3$, TMSN$_3$, and BI−OH generate the high-valent Mn(V) azide species, which reacts with
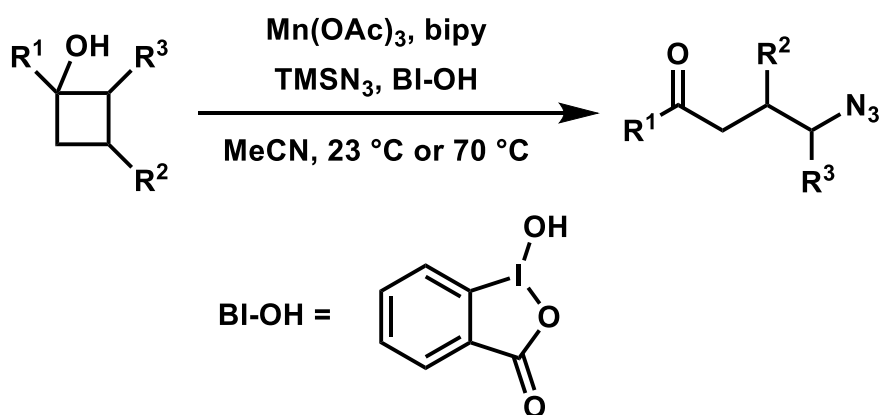
Scheme 59
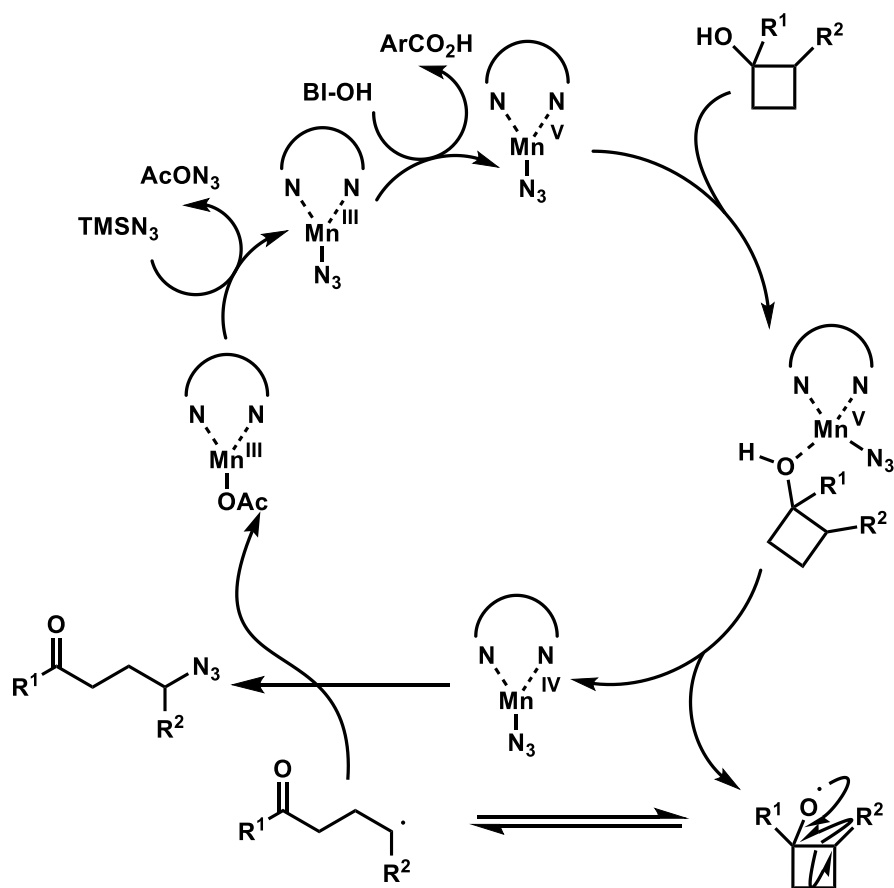
Scheme 60

cyclobutanol to coordinate with oxygen atom. The complex then undergoes simultaneous SET to

generate Mn(IV) azide species and cyclobutyloxy radical. The fragmented radical of cyclobutyloxy radical, is then trapped by the azidation reagent, eventually leading to alkyl azide product. It is likely that once formed, the cyclobutyloxy radical, the alkyl radical and the azidation reagent are confined within a solvent cage, which promotes the azidation. Otherwise, the free alkyl radical would instantly cyclize to generate 1-tetralone when R^1 group is an aryl.

Later in 2016, Zhu group reported a manganese-catalyzed oxidative ring-opening cyanation and ethynylation of cyclobutanols (Scheme 61).[284] Employing a similar idea with the
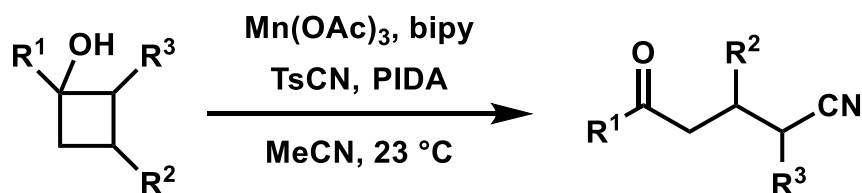
Scheme 61

method they reported in the previous year, cyano one-carbon unit and ethynyl two-carbon unit are regiospecifically introduced to the γ-position of ketones at room temperature, providing a mild yet powerful method for synthesizing aliphatic nitriles and alkynes. The initiation is postulated to be similar to their azidation (Scheme 62). After the γ alkyl radical is formed, the interaction of the intermediate and arylsulfone results in cleavage of the C−S bond, leading to cyanation product or alkynylation product, respectively. The chlorination of cyclobutanols, proceeding presumably in a similar way to cyanation and ethynylation of cyclobutanols, was also reported by Zhu group this year.[285]
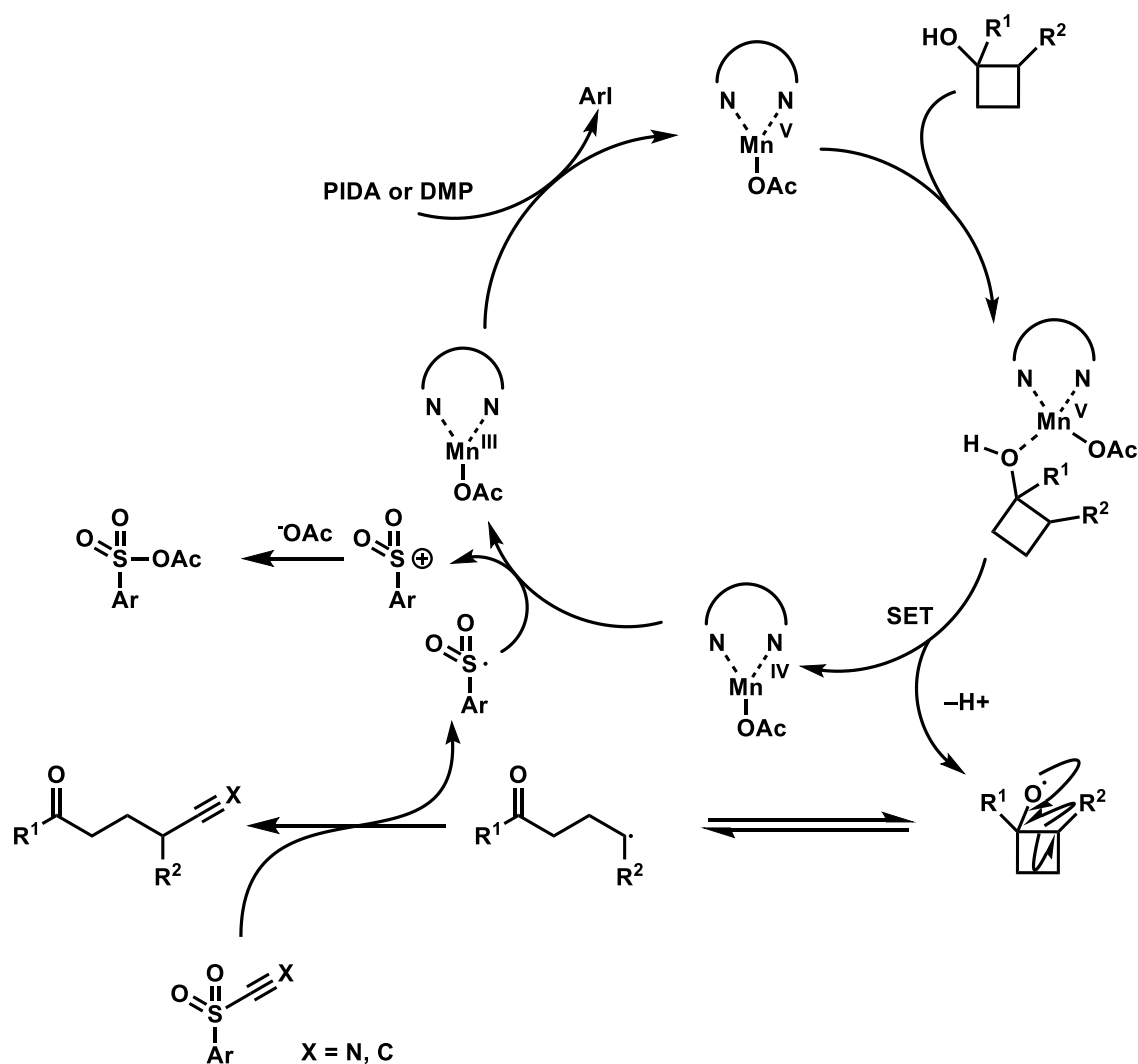
Scheme 62

In sum, cyclopropanols are powerful platforms to build β-substituted ketones under suitable conditions. Considering:1. Unit price of SelectFluor ($135 for 25 g = $1.91 per mmol, Alfa Aesar) and AgF_2 ($110 for 10 g = $1.60 per mmol, Alfa Aesar); 2. Oxidizing ability of AgF_2; 3. Scope limitation of Zhu methodology,[223] we pursue to develop a silver(II) difluoride mediated β fluorination.

5. Cyclopropanol Discussion

5.1. Discussion on Cyclopropanol Ring-Opening Fluorination

To our delight, the initial qualitative experiment of silver(II) difluoride and our model substrate, 1-methyl-2-phenylcyclopropan-1-ol produced product which showed ^{19}F NMR signal. After interpreting the structure, we began to find the optimal condition for the reaction.

All the yields were determined by ^{19}F NMR. The yields in parentheses are isolated yields.

5.1.1. Comparison of ClCH2CH2Cl stored in open air and anhydrous ClCH2CH2Cl

	%yield
ClCH$_2$CH$_2$Cl in air	25
ClCH$_2$CH$_2$Cl in N$_2$	43
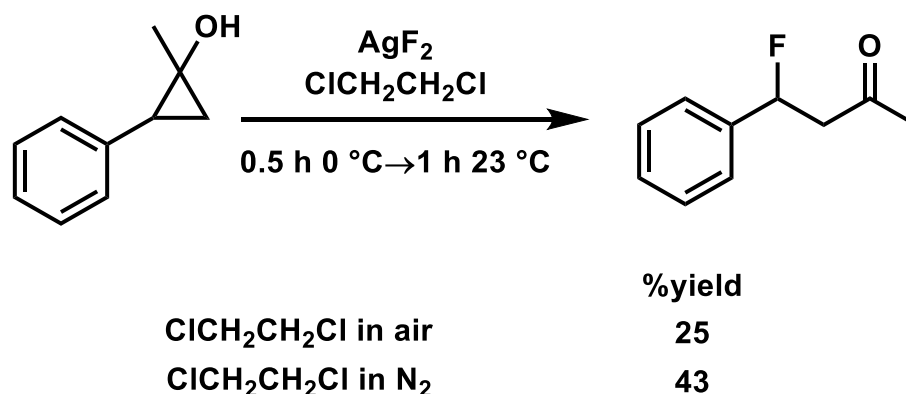
Table 2

The influence of moisture in open air and oxygen was tested with these control experiments. It was found that the efficiency of the fluorination reaction decreased when ClCH$_2$CH$_2$Cl stored in the open air was used, suggesting moisture and/or oxygen could be factor(s) impeding the reaction process. This result could be attributed to the fact that silver difluoride can react with water and oxygen, which might be more reactive than cyclopropanol in the reaction condition we used. Therefore, in the experiments carried out later, dry solvents were applied.

5.1.2. Influence of Temperature
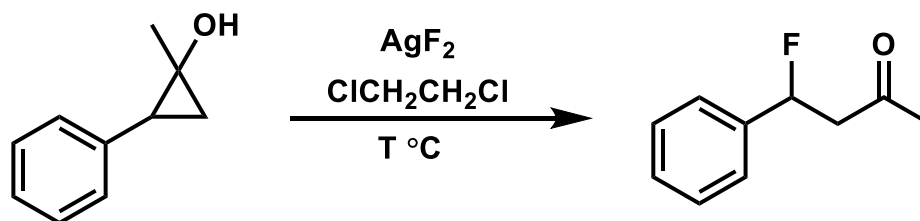
T	%yield
23	67
40	68
60	77

Table 3

The result showed as the reaction temperature rose, the reaction efficiency increased.   It is noteworthy that based on study later, this effect is only valid when the reaction scale is small. When the substrate amount scaled up, larger amount of solid silver difluoride (since it is insoluble in ClCH₂CH₂Cl, presumably the unit amount of silver difluoride in a certain area increased) tended to induce more byproduct, thus decreasing the yield of fluorination reaction. This series of experiments also implied a better reactivity (potentially resulting from stronger electrophilicity arising from the fragility of polarized cyclopropane) of cyclopropanol entity compared to aryl under the condition.

To find out the optimal temperature in cryogenic condition, a series of experiments were conducted as Table 4 listed. The results indicated at 0 °C the yield only dropped 17% compared to the highest yield obtained at 60 °C, whereas at –40 °C, the reaction almost terminated with a 9% yield of β fluoro ketone and 90% starting material remaining. A low reaction rate at –40 °C

can be the best explanation for this result.
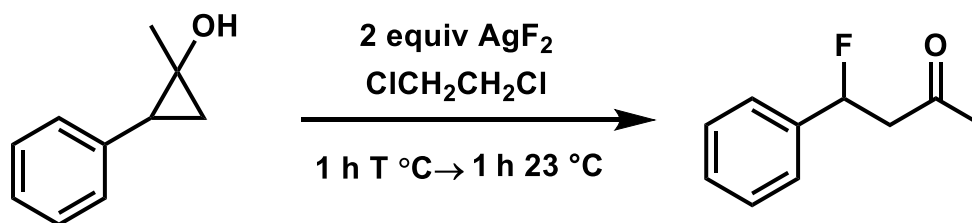
T	%yield
0	60
–40	9

Table 4

5.1.3. Influence of Solvent
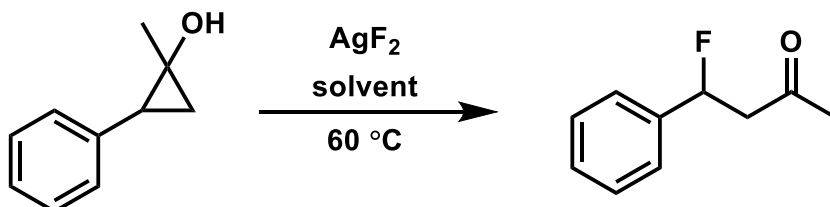
Solvent	%yield
$ClCH_2CH_2Cl$	43
CH_2Cl_2	30
$CHCl_3$	27
MeCN	10
THF	trace
1,4-dioxane	trace
heptane	N.R.
DMF	N.R.

Cyclopropanol (0.1mmol), and fluoride source (0.2mmol) in 2ml specified solvent at 60°C for 1 hour.

Table 5

It is noteworthy that the fluorination reaction in the examined halogenated solvents showed much better efficiency than the reaction performed in other solvents. Among chloroform, dichloromethane, and 1,2-dichloroethane, 1,2-dichloroethane was the best candidate.

5.1.4. Influence of Reaction Time
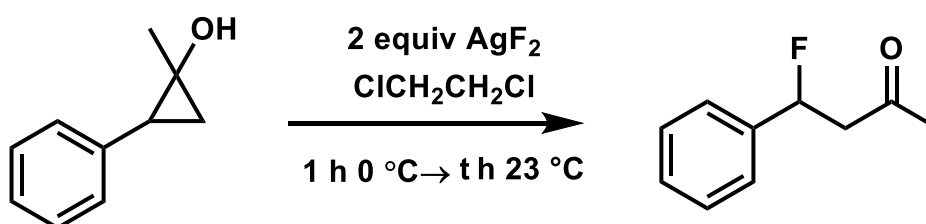
0.1 mmol, 2 mL DCE

t	%yield
1	60
4	60
6	64
8	57
17	42

Table 6

By allowing the reaction stirring at room temperature for 6 hours, optimal yield was achieved. In addition, after 1 hour, the yield was already reaching a relatively high level, indicating the reaction rate was fast in the beginning. After 6 hours, the substrate was almost consumed, and side reactions on the resulting β fluoro ketone began to dominate, thus the yield

decreased.

5.1.5. Final Check
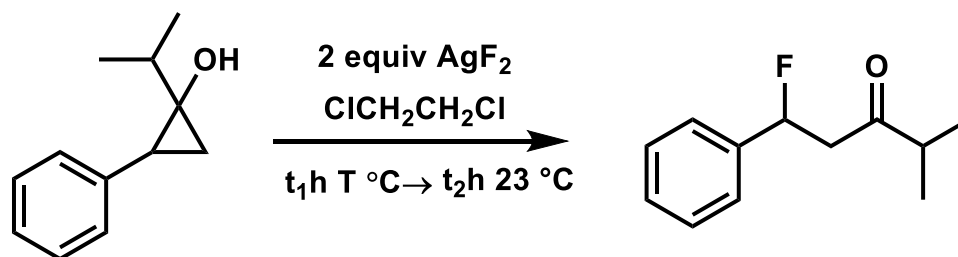
0.3 mmol, 6 mL ClCH$_2$CH$_2$Cl

T	t$_1$	t$_2$	%yield
0	1	1	58
0	2	2	62
0	2	1	48
−15	1	1	72

Table 7

As discussed in the section of influence of temperature, when large amount of substrate and silver difluoride is used, the condition needs to be modified to give the best performance. Therefore the experiments in the table above were conducted, and the optimal temperature in practical use was found to be –15 °C, which was controlled by a NaCl (solid) : crushed ice (1:2 volume ratio) cold bath.

5.2. Reaction Scope Study

A series of substrates were subjected to our optimized condition. To our delight, we found the reactions tolerated a few functional groups. Increasing the steric bulk adjacent to the hydroxyl group was not decreasing the reaction efficiency, but instead increasing the yields, when isopropyl gave a much higher yield and *tert*-butyl gave a slightly higher yield (entries 1–3) compared to methyl counterpart. An aromatic substituent attached to the carbinol increased reaction efficiency substantially (entry 4). This could be explained by presumable benzyl radical stabilization or possible acceleration caused by aryls. Substrates containing *p*-tolyl substituents (entries 5–7) led to exclusive mono-fluorinated products, suggesting that under the reaction conditions a simple benzylic fluorination mechanism is not likely and the regioselectivity of fluorination is dependent on the ring-opening process. Encouraged by this result we further examined substrates where fluorination would occur at a non-benzylic site (entries 9–10). Products of ring-opening/fluorination were observed in these cases without fluorination at other sites. Despite that the yields were somewhat reduced, it is noteworthy that the methodology does not require that the fluorination site be attached to an aryl group, thus the scope is not very limited. Compared to Zhu's methodology,[223] our chemistry features a broader collection of secondary fluorinated products as in Zhu's work, they only managed to show one example of secondary fluoride as their product.

HO R² → AgF₂ (2 equiv), ClCH₂CH₂Cl, −15 °C→23 °C → F O R²

Reaction: substrate (cyclopropanol with HO, R², R¹) converts under AgF₂ (2 equiv) in ClCH₂CH₂Cl at −15 °C→23 °C to give R¹–CHF–CH₂–C(O)–R² product.

Entry	Substrate	Product	Yield [%]
1	Ph-cyclopropanol, R²=Me	Ph-CHF-CH₂-C(O)-Me	53 (51)
2	Ph-cyclopropanol, R²=iPr	Ph-CHF-CH₂-C(O)-iPr	72 (69)
3	Ph-cyclopropanol, R²=tBu	Ph-CHF-CH₂-C(O)-tBu	59
4	Ph-cyclopropanol, R²=Ph	Ph-CHF-CH₂-C(O)-Ph	93
5	(4-Me-C₆H₄)-cyclopropanol, R²=Me	(4-Me-C₆H₄)-CHF-CH₂-C(O)-Me	47
6	(4-Me-C₆H₄)-cyclopropanol, R²=tBu	(4-Me-C₆H₄)-CHF-CH₂-C(O)-tBu	71 (55)
7	(4-Me-C₆H₄)-cyclopropanol, R²=CH₂Ph	(4-Me-C₆H₄)-CHF-CH₂-C(O)-CH₂Ph	67 (47)
8	(4-tBu-C₆H₄)-cyclopropanol, R²=tBu	(4-tBu-C₆H₄)-CHF-CH₂-C(O)-tBu	90
9	benzyl-cyclopropanol, R²=Ph	PhCH₂-CHF-CH₂-C(O)-Ph	60
10	(4-Et-C₆H₄)CH₂-cyclopropanol, R²=Ph	(4-Et-C₆H₄)CH₂-CHF-CH₂-C(O)-Ph	39 (42)

Yields are determined by 19F NMR. Yields in parentheses are isolated yields.

Table 8

5.3. Competition Experiments between 1-isopropyl-2-phenylcyclopropan-1-ol and 1,2-diphenylcyclopropan-1-ol

1 equiv AgF$_2$:	**5%**	**26%**
2 equiv AgF$_2$:	**15%**	**56%**
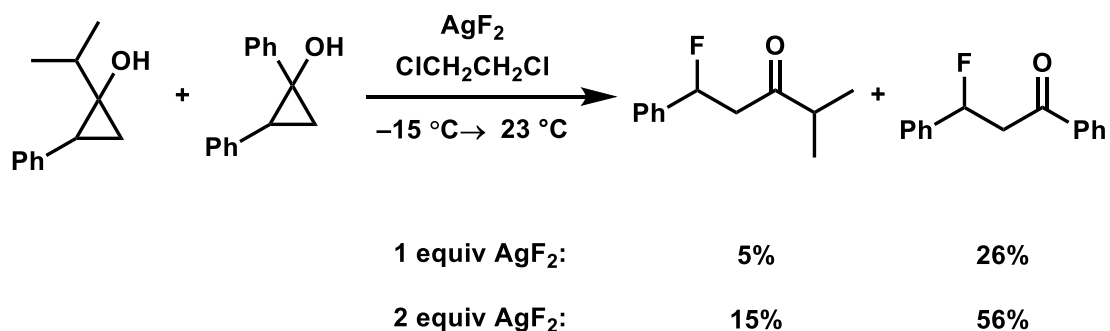
Table 9

Based on the experimental results, we noticed a phenomenon that reaction efficiency with aryl carbinols outcompetes that with aliphatic counterparts in general. In order to gain insight into the process, we conducted the competition experiment. In experiments with either 1 or 2 equiv of AgF$_2$, the yield of the benzylic alcohol reaction is ~4–5-fold over that of the aliphatic tertiary alcohol reaction. The effect is likely best explained through an influence at an early stage of the mechanism. The function of the aryl group proximal to the oxygen can be postulated to be accelerating a mechanism involving single electron intermediates that could arise from oxidation or bond fission instead of stabilizing a theoretical *O*-centered or benzylic radical. In addition, the Ag–O interaction might be intensified by the inductive effect of the aryl ring.

5.4. Mechanistic hypothesis
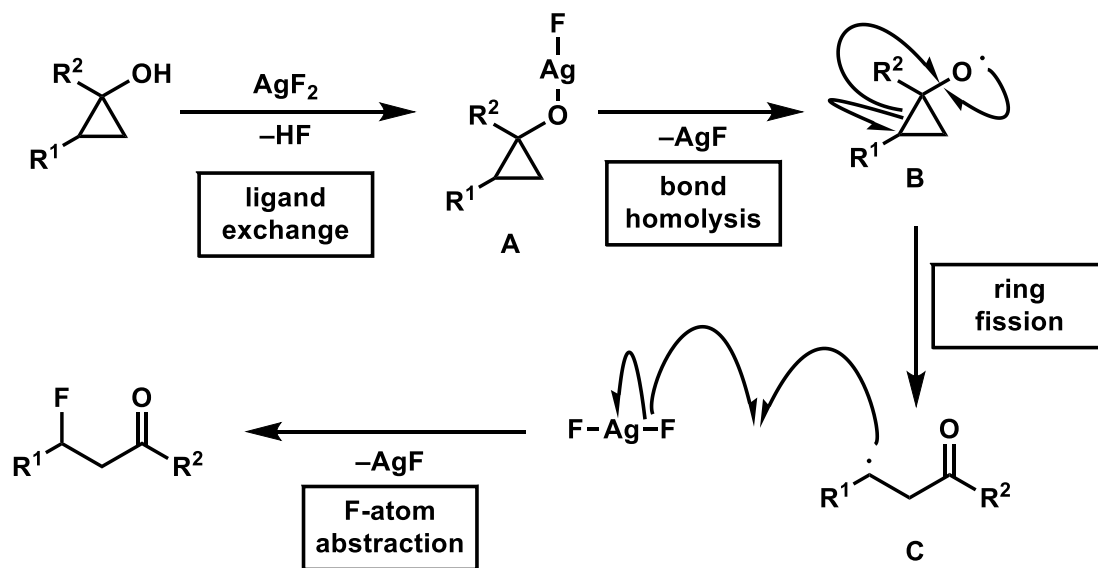
Scheme 63

A potential mechanism for the fragmentation is shown in Scheme 63. Although Ag(III) was claimed to be a key reactive intermediate in some related processes,[223-225, 288] we propose that Ag(II) may be a viable promoter of fragmentation. Thus, initial ligand exchange to form Ag–alkoxide complex A could be followed by single electron oxidation via Ag–O bond homolysis. Strain release in the cyclopropane system could lead the resulting alkoxy radical B to a bond fission and *C*-centered radical intermediate C is therefore formed. This is the key step explaining the regioselectivity in fragmentation arising from a preference for the secondary radical intermediate over primary intermediate. F-atom abstraction from a second molecule of AgF$_2$ would eventually afford the β- fluoroketone product. This is meanwhile our best rationale for the optimal reaction stoichiometry we found.

Although oxidation of the intermediate radical C to the corresponding carbocation could happen in the presence of Ag(II), deprotonation is more likely to be the major pathway since

undesired enone products were observed in some cases. The preference for opening at the secondary carbon site might rule out a homoenolate-type mechanism involving a carbanion intermediate as well as an electrophilic mechanism initiated by a formal F^+ interacting with the cyclopropanol.

6. Conclusion

We developed a useful method to access β-fluoro ketones. This is our first attempt to apply silver(II) difluoride in organic synthesis. Ten substrates were investigated and the yields range from 39% to 93%. The condition effectively prevents potential benzylic fluorination. In addition, sterically demanding environment in the substrate molecule did not become a big issue for the reaction. Compared to Zhu's methodology,[223] more secondary fluoride products were afforded in acceptable yields. Moreover, the cost of silver(II) difluoride is lower than that of SelectFluor®.

Appendix I. Experimental Part of Cyclopropanol

1. General Procedure for Preparation of Cyclopropanol Substrates

Cyclopropanol substrates were prepared according to Cha's work.[252]

To a solution of ester (10 mmol, 1 equiv) and alkene (10 mmol, 1 equiv) in 40 mL anhydrous THF was added Ti(O-iPr)$_4$ (10 mmol, 1 equiv). Cyclohexylmagnesium chloride (40 mmol, 31 mL 1.3M solution in toluene/THF) was added at 0 °C over 10 min. The reaction mixture was stirred for an additional 2 hours at 23 °C and was treated with 1 M hydrochloric acid to quench the reaction. The resulting mixture was vacuum filtered, and the resulting filtrate was extracted with ethyl acetate (3 x20 mL). The combined extracts were drided over MgSO$_4$. Filtration and evaporation in vacuo gave the crude product. Purification by column chromatography on silica gel afforded the pure product.

2. Optimization

2.1. Comparison of $ClCH_2CH_2Cl$ stored in open air and anhydrous $ClCH_2CH_2Cl$

	%yield
wet $ClCH_2CH_2Cl$	25
dry $ClCH_2CH_2Cl$	43

Table 10

An oven-dried 8 mL glass vial equipped with a magnetic stir bar, was evacuated and backfilled with nitrogen in a glovebox antechamber (three cycles). In the glovebox, solid AgF_2 (29.2 mg, 0.2 mmol, 2 equiv) was added and the vial was then sealed with a cap equipped with a rubber septum and transferred out of the glovebox. The vial was connected to a N_2-filled Schlenk line and then charged with anhydrous 1,2-dichloroethane (1 mL) or 1,2-dichloroethane (1 mL) stored in the open air. The mixture was cooled to 0 °C and stirred vigorously for 1 min. A solution of cyclopropanol (0.05 M solution in 1,2-dichloroethane, storage condition same as the solvent used to fill the vial first, 2 mL, 0.1 mmol, 1 equiv) was added in one portion and the resulting suspension was stirred for 0.5 h at 0 °C. The mixture was warmed to 23 °C, wrapped with aluminum foil, and stirred for 1 h. The reaction mixture was passed through a short silica plug to remove the solid residue, eluting with CH_2Cl_2 (2 x 1 mL). The vial was rinsed with CH_2Cl_2 (2 x 3 mL). The resulting organic solution was concentrated in vacuo. Neat α,α,α-trifluorotoluene (12.0 μL) was added to the residue as an internal standard and a ^{19}F NMR

spectrum was obtained to determine the yield. (The residue was purified by flash chromatography on silica gel to afford the desired product.)

2.2. Influence of Temperature

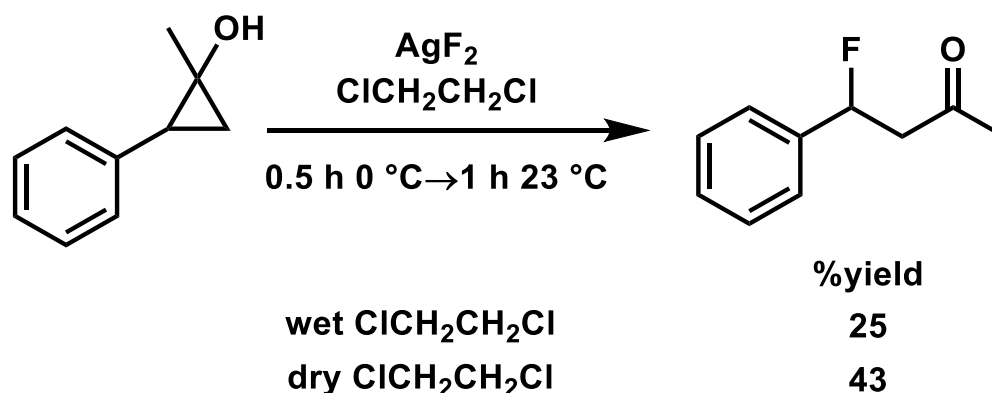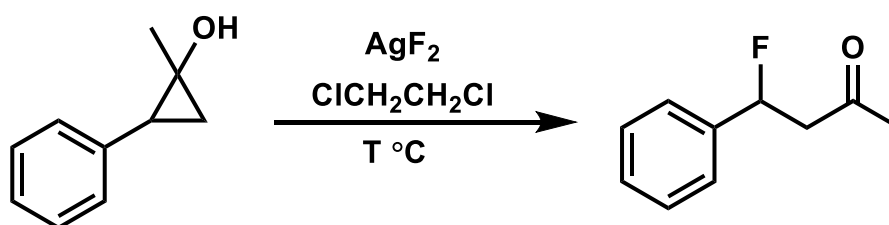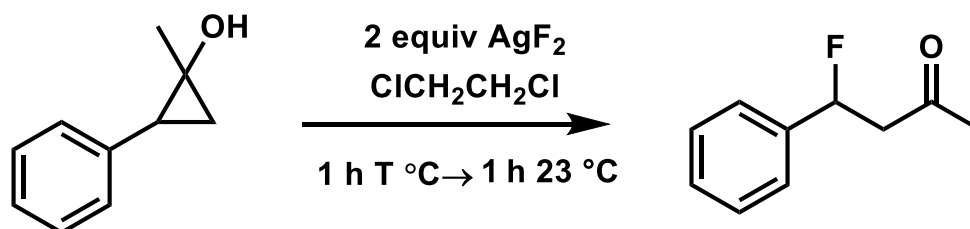| T	%yield
23	67
40	68
60	77

Table 11

An oven-dried 8 mL glass vial equipped with a magnetic stir bar, was evacuated and backfilled with nitrogen in a glovebox antechamber (three cycles). In the glovebox, solid AgF_2 (29.2 mg, 0.2 mmol, 2 equiv) was added and the vial was then sealed with a cap equipped with a rubber septum and transferred out of the glovebox. The vial was connected to a N_2-filled Schlenk line and then charged with anhydrous 1,2-dichloroethane (1 mL). A solution of cyclopropanol (0.05 M solution in 1,2-dichloroethane, 2 mL, 0.1 mmol, 1 equiv) was added in one portion and the resulting suspension, wrapped with aluminum foil, was stirred for 14 h at specified temperature. The reaction mixture was passed through a short silica plug to remove the solid residue, eluting with CH_2Cl_2 (2 x 1 mL). The vial was rinsed with CH_2Cl_2 (2 x 3 mL).

The resulting organic solution was concentrated in vacuo. Neat α,α,α-trifluorotoluene (12.0 µL) was added to the residue as an internal standard and a ^{19}F NMR spectrum was obtained to determine the yield. (The residue was purified by flash chromatography on silica gel to afford the desired product.)

T	%yield
0	60
–40	9

Table 12

2.3. Influence of Solvent
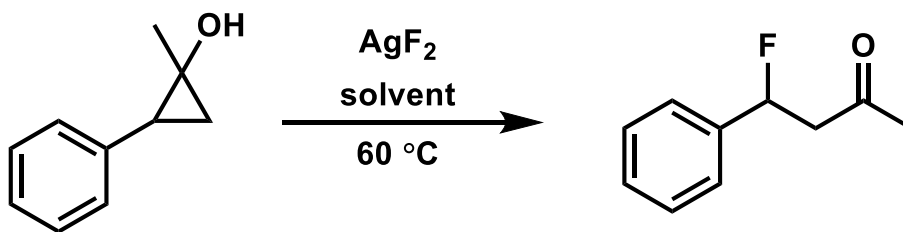
Solvent	%yield
ClCH$_2$CH$_2$Cl	43
CH$_2$Cl$_2$	30
CHCl$_3$	27
MeCN	10
THF	trace
1,4-dioxane	trace
heptane	N.R.
DMF	N.R.

Cyclopropanol (0.1mmol), and fluoride source (0.2mmol) in 2ml specified solvent at 60°C for 1 hour.

Table 13

An oven-dried 8 mL glass vial equipped with a magnetic stir bar, was evacuated and backfilled with nitrogen in a glovebox antechamber (three cycles). In the glovebox, solid AgF$_2$ (amount specified in the table) was added and the vial was then sealed with a cap equipped with a rubber septum and transferred out of the glovebox. The vial was connected to a N$_2$-filled Schlenk line and then charged with anhydrous 1,2-dichloroethane (1 mL). A solution of cyclopropanol (0.05 M solution in 1,2-dichloroethane, 2 mL, 0.1 mmol, 1 equiv) was added in one portion and the resulting suspension was stirred for 1 h at 60 °C. The reaction mixture was passed through a short silica plug to remove the solid residue, eluting with CH$_2$Cl$_2$ (2 x 1 mL). The vial was rinsed with CH$_2$Cl$_2$ (2 x 3 mL). The resulting organic solution was concentrated in vacuo. Neat α,α,α-trifluorotoluene (12.0 μL) was added to the residue as an internal standard

and a ^{19}F NMR spectrum was obtained to determine the yield. (The residue was purified by flash chromatography on silica gel to afford the desired product.)

2.4. Influence of the Amount of Silver Difluoride
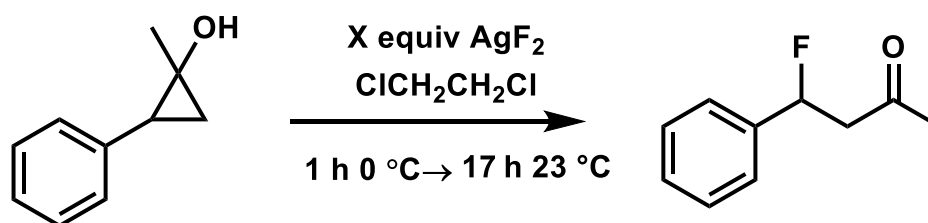
0.1 mmol, 2 mL DCE

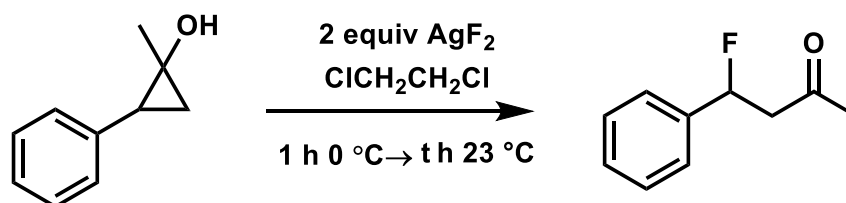| X	%yield
1	4
1.5	22
2	42
3	40

Table 14

An oven-dried 8 mL glass vial equipped with a magnetic stir bar, was evacuated and backfilled with nitrogen in a glovebox antechamber (three cycles). In the glovebox, solid AgF$_2$ (amount specified in the table) was added and the vial was then sealed with a cap equipped with a rubber septum and transferred out of the glovebox. The vial was connected to a N$_2$-filled Schlenk line and then charged with anhydrous 1,2-dichloroethane (1 mL). The mixture was cooled to 0 °C and stirred vigorously for 1 min. A solution of cyclopropanol (0.05 M solution in 1,2-dichloroethane, 2 mL, 0.1 mmol, 1 equiv) was added in one portion and the resulting

suspension was stirred for 1 h at 0 °C. The mixture was warmed to 23 °C, wrapped with aluminum foil, and stirred for 17 h. The reaction mixture was passed through a short silica plug to remove the solid residue, eluting with CH_2Cl_2 (2 x 1 mL). The vial was rinsed with CH_2Cl_2 (2 x 3 mL). The resulting organic solution was concentrated in vacuo. Neat α,α,α-trifluorotoluene (12.0 μL) was added to the residue as an internal standard and a ^{19}F NMR spectrum was obtained to determine the yield. (The residue was purified by flash chromatography on silica gel to afford the desired product.)

The fluorination reaction achieved a peak when 2 equivalence of silver difluoride was used.
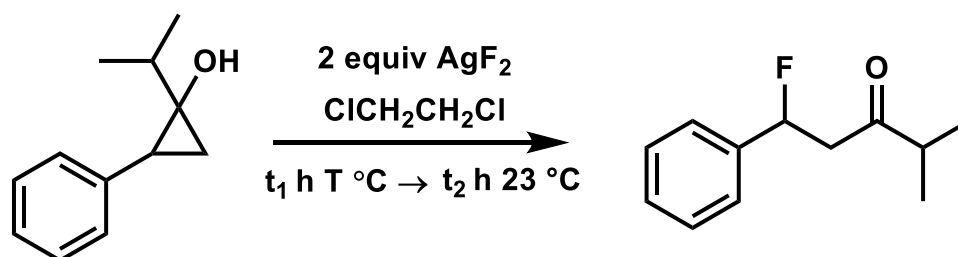
2.5. Influence of Reaction Time

0.1 mmol, 2 mL DCE

t	%yield
1	60
4	60
6	64
8	57
17	42

Table 15

An oven-dried 20 mL plastic vial equipped with a magnetic stir bar, was evacuated and backfilled with nitrogen in a glovebox antechamber (three cycles). In the glovebox, solid AgF_2 (29.2 mg, 0.2 mmol, 2 equiv) was added and the vial was then sealed with a rubber septum and transferred out of the glovebox. The vial was connected to a N_2-filled Schlenk line and then charged with anhydrous 1,2-dichloroethane (1 mL). The mixture was cooled to 0 °C and stirred vigorously for 1 min. A solution of cyclopropanol (0.05 M solution in 1,2-dichloroethane, 2 mL, 0.1 mmol, 1 equiv) was added in one portion and the resulting suspension was stirred for 1 h at 0 °C. The mixture was warmed to 23 °C, wrapped with aluminum foil, and stirred for specified time. The reaction mixture was passed through a short silica plug to remove the solid residue, eluting with CH_2Cl_2 (2 x 1 mL). The vial was rinsed with CH_2Cl_2 (2 x 3 mL). The resulting organic solution was concentrated in vacuo. Neat α,α,α-trifluorotoluene (12.0 μL) was added to the residue as an internal standard and a ^{19}F NMR spectrum was obtained to determine the yield. (The residue was purified by flash chromatography on silica gel to afford the desired product.)

2.6. Final Check

0.3 mmol, 6 mL ClCH$_2$CH$_2$Cl

T	t$_1$	t$_2$	%yield
0	1	1	58
0	2	2	62
0	2	1	48
−15	1	1	72

Table 16

An oven-dried 20 mL plastic vial equipped with a magnetic stir bar, was evacuated and backfilled with nitrogen in a glovebox antechamber (three cycles). In the glovebox, solid AgF$_2$ (87.6 mg, 0.6 mmol, 2 equiv) was added and the vial was then sealed with a rubber septum and transferred out of the glovebox. The vial was connected to a N$_2$-filled Schlenk line and then charged with anhydrous 1,2-dichloroethane (3 mL). The mixture was cooled to −15 °C and stirred vigorously for 1 min. A solution of cyclopropanol (0.05 M solution in 1,2-dichloroethane, 6 mL, 0.3 mmol, 1 equiv) was added in one portion and the resulting suspension was stirred for t$_1$ h at T °C. The mixture was warmed to 23 °C, wrapped with aluminum foil, and stirred for t$_2$ h. The reaction mixture was passed through a short silica plug to remove the solid residue, eluting with CH$_2$Cl$_2$ (2 x 1 mL). The vial was rinsed with CH$_2$Cl$_2$ (2 x 3 mL). The resulting organic solution was concentrated in vacuo. Neat α,α,α-trifluorotoluene (12.0 μL) was added to the

residue as an internal standard and a ^{19}F NMR spectrum was obtained to determine the yield. (The residue was purified by flash chromatography on silica gel to afford the desired product.) As discussed in the section of influence of temperature, when large amount of substrate and silver difluoride is used, the condition needs to be modified to give the best performance. Therefore the experiments in the table above were conducted, and the optimal temperature in practical use was found to be –15 °C, which was controlled by a NaCl:crushed ice (1:2 volume ratio) cold bath.

3. General Procedure for Ring-Opening Fluorination

An oven-dried 20 mL plastic vial equipped with a magnetic stir bar, was evacuated and backfilled with nitrogen in a glovebox antechamber (three cycles). In the glovebox, solid AgF$_2$ (87.6 mg, 0.6 mmol, 2 equiv) was added and the vial was then sealed with a rubber septum and transferred out of the glovebox. The vial was connected to a N$_2$-filled Schlenk line and then charged with anhydrous 1,2-dichloroethane (3 mL). The mixture was cooled to –15 °C and stirred vigorously for 1 min. A solution of cyclopropanol (0.05 M solution in 1,2-dichloroethane, 6 mL, 0.3 mmol, 1 equiv) was added in one portion and the resulting suspension was stirred for 1 h at –15 °C. The mixture was warmed to 23 °C, wrapped with aluminum foil, and stirred for 1 h. The reaction mixture was passed through a short silica plug to remove the solid residue, eluting with CH$_2$Cl$_2$ (2 x 1 mL). The vial was rinsed with CH$_2$Cl$_2$ (2 x 3 mL). The resulting organic solution was concentrated in vacuo. Neat α,α,α-trifluorotoluene (12.0 μL) was added to the residue as an internal standard and a ^{19}F NMR spectrum was obtained to determine the yield. (The residue was purified by flash chromatography on silica gel to afford the desired product.)

4. Procedure for Competition Experiments between 1-isopropyl-2-phenylcyclopropan-1-ol and 1,2-diphenylcyclopropan-1-ol

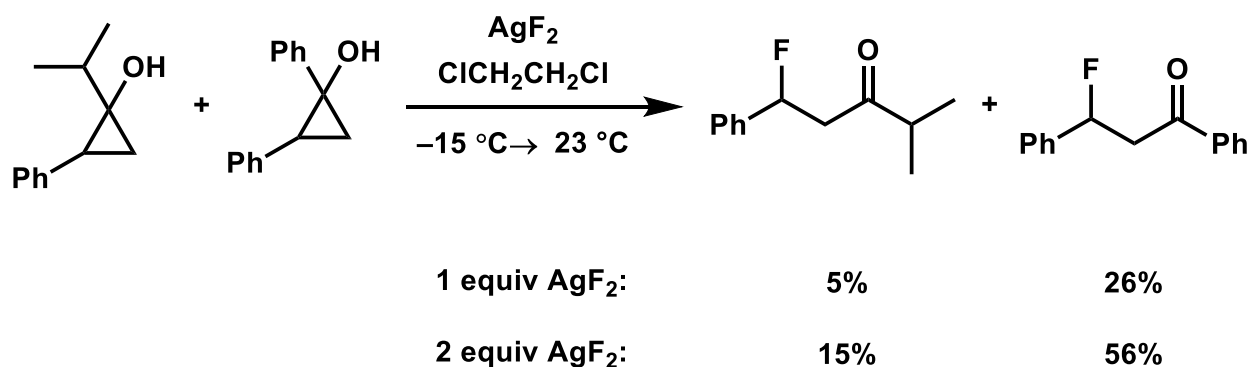|	5%	26%
1 equiv AgF$_2$:	5%	26%
2 equiv AgF$_2$:	15%	56%

Table 17

An oven-dried 20 mL plastic vial equipped with a magnetic stir bar, was evacuated and backfilled with nitrogen in a glovebox antechamber (three cycles). In the glovebox, solid AgF$_2$ (14.6 mg, 0.1 mmol, 1 equiv) was added and the vial was then sealed with a rubber septum and transferred out of the glovebox. The vial was connected to a N$_2$-filled Schlenk line and then charged with anhydrous 1,2-dichloroethane (3 mL) via syringe. The suspension was cooled to –15 °C and stirred vigorously for 1 min. A solution of 1-isopropyl-2-phenylcyclopropan-1-ol (17.6 mg, 0.1 mmol, 1 equiv) and 1,2-diphenylcyclopropan-1-ol (21.0 mg, 0.1 mmol, 1 equiv) dissolved in 1,2-dichloroethane (1 mL) was added at once and then the mixture was stirred for 1 h at –15 °C. The suspension was warmed to 23 °C, wrapped with aluminum foil, and stirred for 1 h. The reaction mixture was passed through a short plug of SiO$_2$ to remove the solid residue and eluted with CH$_2$Cl$_2$ (2 x 1 mL) and then the vial was washed with CH$_2$Cl$_2$ (2 x 3 mL). The combined solution was concentrated in vacuo. Neat α,α,α-trifluorotoluene (12.0 μL) was added into the residue as an internal standard and ^{19}F NMR spectrum was obtained to determine the

yield. (The residue was purified by flash chromatography on silica gel to afford the desired product.)
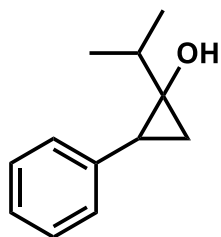
The experiment was also carried out with 0.2 mmol of AgF_2 (29.2 mg, 2 equiv) in a similar manner.

5. Characterization Data of Cyclopropanols
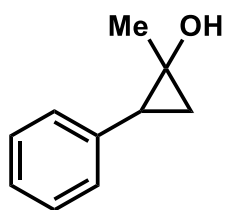
1-methyl-2-phenylcyclopropan-1-ol

Spectral data matches with the reported data.[286]

1-isopropyl-2-phenylcyclopropan-1-ol

The title compound was isolated as white powder.
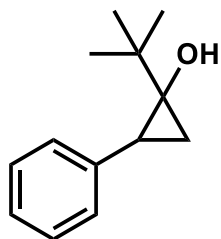
mp 60–62 °C

TLC (SiO$_2$) R_f = 0.33 in 5:1 hexanes/acetone, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.30–7.24 (m, 2H), 7.21–7.14 (m, 3H), 2,43 (dd, *J* = 9.5, 7.5 Hz, 1H), 1.24–1.11 (m, 3H), 1.03 (d, *J* = 6.5 Hz, 3H), 0.77 (d, *J* = 6.5 Hz, 3H)

^{13}C NMR (126 MHz, CDCl$_3$) δ 138.0, 128.3, 128.0, 125.8, 64.9, 31.9, 30.1, 18.5, 17.6, 16.7

IR (neat) 3369, 2968, 1600, 1450, 1216, 1047, 777, 702 cm^{-1}

GC/MS (*m/z*): 176.1 (16%), 131.0 (68%), 105.0 (100%), 91.0 (72%), 77.0 (32%)

1-(*tert*-butyl)-2-phenylcyclopropan-1-ol
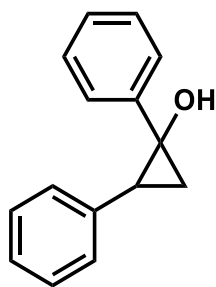
The title compound was isolated as white powder.

mp 58–59 °C

TLC (SiO$_2$) R_f = 0.37 in 5:1 hexanes/acetone, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.30–7.22 (m, 4H), 7.20–7.15 (m, 1H), 2.49 (dd, *J* = 10.0, 8.0 Hz, 1H), 1.33 (dd, *J* = 8.0, 6.0 Hz, 1H), 1.06 (dd, *J* = 10.0, 8.0 Hz, 1H), 0.80 (s, 9H)

^{13}C NMR (126 MHz, CDCl$_3$) δ 138.0, 128.3, 128.0, 125.8, 64.9, 31.9, 30.1, 18.5, 17.6, 16.7
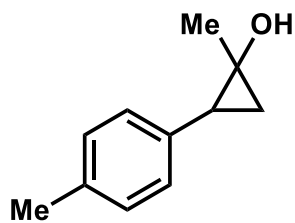
IR (neat) 3473, 3357, 2959, 1599, 1493, 1362, 1187, 1145, 774, 696, 608 cm^{-1}

GC/MS (*m/z*): 190.1 (6%), 133.0 (65%), 105.1 (100%), 91.0 (66%), 77.0 (19%), 57.1 (57%)
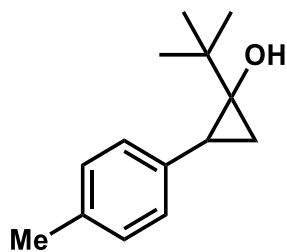
1,2-diphenylcyclopropan-1-ol

Spectral data matches with the reported data.[287]

1-methyl-2-(*p*-tolyl)cyclopropan-1-ol

Spectral data matches with the reported data.[286]

1-(*tert*-butyl)-2-(*p*-tolyl)cyclopropan-1-ol

The title compound was isolated as white powder.

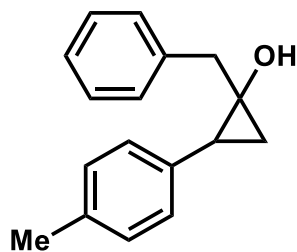**mp** 64–66 °C

TLC (SiO$_2$) R_f = 0.46 in 5:1 hexanes/acetone, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.16 (d, J = 7.5 Hz, 2H), 7.06 (d, J = 8 Hz, 2H), 2.44 (dd, J = 18.5, 8.5 Hz, 1H), 2.31 (s, 3H), 1.30 (dd, J = 7.5, 5.5 Hz, 1H), 1.03 (dd, J = 10.5, 6.0 Hz, 1H), 0.80 (s, 9H)

^{13}C NMR (126 MHz, CDCl$_3$) δ 135.5, 135.1, 129.5, 128.7, 66.4, 35.2, 31.7, 26.9, 21.1, 14.1

IR (neat) 3457, 2963, 2871, 1362, 1180, 1076, 907, 813, 550, 526 cm^{-1}

GC/MS (*m/z*): 204.1 (10%), 145.0 (41%), 119.1 (42%), 105.1 (100%), 91.0 (15%), 57.1 (44%)

1-benzyl-2-(*p*-tolyl)cyclopropan-1-ol

The title compound was isolated as clear colorless liquid.

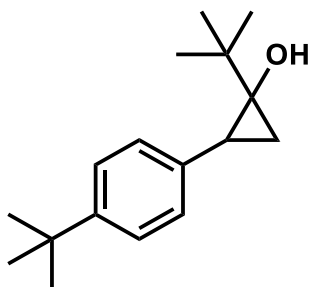**TLC** (SiO$_2$) R_f = 0.39 in 5:1 hexanes/acetone, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.37–6.96 (m, 9H), 2.86 (d, J = 14.5 Hz, 1H), 2.46 (dd, J = 9.5,

7.0 Hz, 2H), 2.36 (s, 3H), 1.32–1.23 (m, 2H)

¹³C NMR (126 MHz, CDCl₃) δ 138.4, 135.7, 135.1, 129.5, 129.0, 128.5, 128.3, 126.6, 125.6, 61.0, 39.4, 30.0, 21.1, 18.0

IR (neat) 3395, 3027, 2924, 2364, 2332, 1516, 1492, 1450, 1092, 813, 699, 530 cm^{-1}

GC/MS (*m/z*): 238.1 (5%), 147.0 (20%), 119.0 (27%), 105.0 (100%), 91.0 (24%)

1-(*tert*-butyl)-2-(4-(*tert*-butyl)phenyl)cyclopropan-1-ol

The title compound was isolated as white powder.

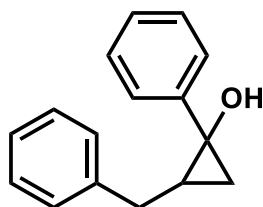**mp** 72–74 °C

TLC (SiO₂) R_f = 0.40 in 5:1 hexanes/acetone, *p*-anisaldehyde stain

¹H NMR (500 MHz, CDCl₃) δ 7.26 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 2.44 (dd, *J* = 10.5, 8.0 Hz, 1H), 1.30 (s, 10H), 1.03 (dd, *J* = 10.5, 6.0 Hz, 1H), 0.81 (s, 9H)

¹³C NMR (126 MHz, CDCl₃) δ 148.9, 135.0, 129.2, 124.8, 35.2, 31.7, 31.4, 31.3, 31.2, 26.9, 14.1

IR (neat) 3366, 2956, 2904, 2869, 1515, 1362, 820, 611, 526 cm^{-1}

GC/MS (*m/z*): 246.1 (30%), 189.0 (26%), 175.1 (19%), 147.1 (100%), 133.0 (96%), 117.0 (19%), 91.0 (17%), 57.0 (82 %)

2-benzyl-1-phenylcyclopropan-1-ol

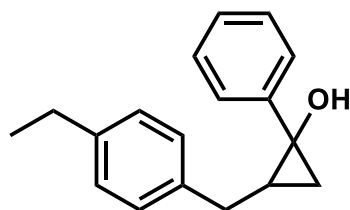The title compound was isolated as clear colorless liquid.

TLC (SiO$_2$) R_f = 0.43 in 5:1 hexanes/acetone, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.45 (d, *J* = 7.0 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.24 (t, *J* = 8.0 Hz, 2H), 7.16 (t, *J* = 7.0 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 2H), 2.53 (dd, *J* = 15.0, 2.5 Hz, 1H), 2.31 (s, 1H), 2.08 (dd, *J* = 15.0, 8.0 Hz, 1H), 1,82–1.75 (m, 1H), 1.25 (dd, *J* = 10.0, 6.0 Hz, 1H), 1.14 (app. t, *J* = 6.5 Hz, 1H)

^{13}C NMR (126 MHz, CDCl$_3$) δ 141.1, 140.0, 128.3, 128.2, 128.1, 127.6, 125.8, 61.8, 35.2, 27.8, 18.6

IR (neat) 3314, 3060, 3027, 2920, 2852, 1600, 1492, 1450, 1190, 1060, 764, 692 cm^{-1}

GC/MS (*m/z*): 224.1 (24%), 209.0 (4%), 133.0 (48%), 120.0 (46%), 105.0 (100%), 91.1 (30%), 77.0 (49%)

2-(4-ethylbenzyl)-1-phenylcyclopropan-1-ol

The title compound was isolated as clear colorless liquid.

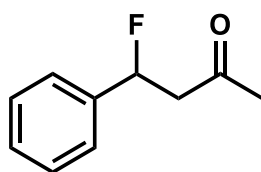**TLC** (SiO$_2$) R_f = 0.46 in 5:1 hexanes/acetone, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.45 (d, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 7.0 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.99 (d, *J* = 8.0 Hz, 2H), 2.60 (q, *J* = 8.0 Hz, 2H), 2.52 (dd, *J* = 15.0, 6.5 Hz, 1H), 2.02 (dd, *J* = 15.0, 8.0 Hz, 1H), 1.81–1.72 (m, 1H), 1.25 (app. t, *J* = 5.5 Hz, 1H), 1.22 (app. t, *J* = 7.5 Hz, 3H), 1.12 (app. t, *J* = 6.5 Hz, 1H)

^{13}C NMR (126 MHz, CDCl$_3$) δ 141.7, 140.1, 138.3, 128.3, 128.1, 128.1, 127.7, 127.6, 61.9, 34.8, 28.4, 28.0, 18.6, 15.6

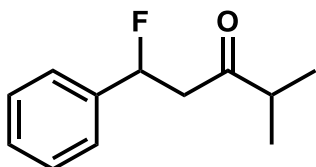**IR** (neat) 3336, 2963, 2930, 2859, 1682, 1512, 1447, 1190, 1060, 1024, 836, 758, 699 cm^{-1}

GC/MS (*m/z*): 252.1 (27%), 237.0 (11%), 132.1 (58%), 119.0 (44%), 105.0 (100%), 91.1 (23%), 77.0 (44%)

6. Characterization Data of β-fluoroketones

4-fluoro-4-phenylbutan-2-one

The title compound was prepared with a ^{19}F NMR yield of 53%, and was isolated (25.2 mg, 51%). Spectral data matches with the reported data.[225]

1-fluoro-4-methyl-1-phenylpentan-3-one

The title compound was prepared with a ^{19}F NMR yield of 72%, and was isolated as a pale yellow liquid (40.2 mg, 69%).

TLC (SiO$_2$) R_f = 0.52 in 5:1 hexanes/acetone, *p*-anisaldehyde stain
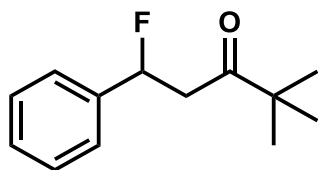
^{1}H NMR (500 MHz, CDCl$_3$) δ 7.42–7.31 (m, 5H), 5.99 (ddd, *J* = 46.5, 8.5, 4.0 Hz, 1H), 3.25 (ddd, *J* = 16.6, 14.5, 8.5 Hz, 1H), 2.81 (ddd, *J* = 31.5, 16.5, 4.0 Hz, 1H), 2.60 (sept, *J* = 6.5 Hz, 1H), 1.12 (d, *J* = 6.5 Hz, 3H), 1.08 (d, *J* = 6.5 Hz, 3H)

^{13}C NMR (126 MHz, CDCl$_3$) δ 210.5, 128.6, 125.5, 125.5, 100.1, 90.3 (d, *J* = 170.7 Hz), 47.6 (d, *J* = 26.3 Hz), 41.6, 17.7, 17.7

^{19}F NMR (376 MHz, CDCl$_3$) δ –174.9 (ddd, *J* = 46.4, 31.6, 13.9 Hz, 1F)

IR (neat) 2966, 2926, 2852, 1713, 1467, 1379, 1070, 1021, 985, 758, 699 cm^{-1}

GC/MS (*m/z*): 194.1 (2%), 174.0 (3%), 151.0 (19%), 131.0 (46%), 109.0 (100%), 77.0 (20%)

1-fluoro-4,4-dimethyl-1-phenylpentan-3-one

The title compound was prepared with a ^{19}F NMR yield of 59%, and was isolated as a white

solid.

mp 37–39 °C

TLC (SiO$_2$) R_f = 0.54 in 5:1 hexanes/acetone, *p*-anisaldehyde stain
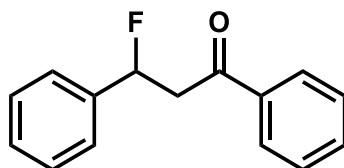
^{1}H NMR (500 MHz, CDCl$_3$) δ 7.42–7.31 (m, 5H), 6.02 (ddd, *J* = 46.5, 8.5, 4.5 Hz, 1H), 3.33

(ddd, *J* = 17.0, 14.0, 8.5 Hz, 1H), 2.77 (ddd, *J* = 31.5, 17.0, 4.5 Hz, 1H), 1.13 (s, 9H)

^{13}C NMR (126 MHz, CDCl$_3$) δ 211.6, 128.6, 128.5, 125.5, 125.5, 90.5 (d, *J* = 170.4 Hz), 44.2

(d, *J* = 26.5 Hz), 26.3, 25.8

^{19}F NMR (376 MHz, CDCl$_3$) δ –175.7 (ddd, *J* = 46.2, 31.6, 13.9 Hz, 1F)

IR (neat) 2972, 2930, 1694, 1609, 1473, 1369, 1086, 1028, 976, 855, 765, 699, 542 cm^{-1}

GC/MS (*m/z*): 208.1 (3%), 188.0 (2%), 131.0 (100%), 103.0 (38%), 57.0 (46%)

3-fluoro-1,3-diphenylpropan-1-one

The title compound was prepared with a ^{19}F NMR yield of 93%, and was isolated as a white

   solid.

mp 63–65 °C

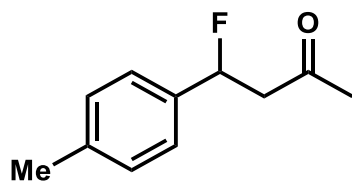**TLC** (SiO$_2$) R_f = 0.39 in 5:1 hexanes/acetone, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.97 (d, J = 8.0 Hz, 2H), 7.69–7.33 (m, 8H), 6.19 (ddd, J = 46.5,

   8.0, 4.0 Hz, 1H), 3.81 (app. dt, J = 15.0, 8.5 Hz, 1H), 3.33 (ddd, J = 29.5, 17.0, 4.0 Hz, 1H)

^{13}C NMR (126 MHz, CDCl$_3$) δ 196.1, 144.9, 139.6, 139.4, 136.7, 133.5, 132.8, 130.6, 129.0,

   128.7, 128.7, 128.5, 128.5, 128.2, 125.7, 125.6, 122.1, 90.3 (d, J = 171.2 Hz), 46.0 (d, J =

   26.2 Hz)

^{19}F NMR (376 MHz, CDCl$_3$) δ –174.5 (ddd, J = 46.0, 30.0, 14.9 Hz, 1F)

IR (neat) 3063, 3030, 2937, 1685, 1665, 1597, 1447, 1376, 1203, 995, 751, 687, 579, 547 cm^{-1}

GC/MS (*m/z*): 228.1 (16%), 207.1 (48%), 131.0 (20%), 105.0 (100%), 77.1 (78%)

4-fluoro-4-(*p*-tolyl)butan-2-one

The title compound was prepared with a ^{19}F NMR yield of 47%, and was isolated as a pale

yellow liquid.

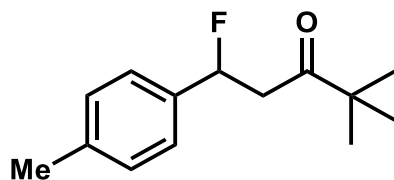**TLC** (SiO$_2$) R_f = 0.37 in 5:1 hexanes/acetone, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, CDCl$_3$) δ 7.23 (d, *J* = 11.0 Hz, 2H), 7.19 (d, *J* = 8.5, 2H), 5.91 (ddd, *J* = 47.0, 8.5, 4.5 Hz, 1H), 3.20 (ddd, *J* = 16.4, 14.8, 9.0 Hz, 1H), 2.81 (ddd, *J* = 32.0, 17.0, 4.0 Hz, 1H), 2.36 (s, 3H), 2.22 (s, 3H)

^{13}C NMR (126 MHz, CDCl$_3$) δ 204.9, 143.5, 138.6, 138.6, 129.3, 125.6, 125.6, 90.1 (d, *J* = 170.4 Hz), 50.6 (d, *J* = 26.5 Hz), 30.9, 29.7

^{19}F NMR (376 MHz, CDCl$_3$) δ –172.4 (ddd, *J* = 46.5, 31.9, 14.1 Hz, 1F)

IR (neat) 2959, 2923, 2855, 1720, 1668, 1609, 1457, 1366, 1258, 1180, 1044, 800 cm^{-1}

GC/MS (*m/z*): 180.1 (11%), 160.1 (15%), 145.0 (100%), 115.0 (42%), 91.0 (17%)

1-fluoro-4,4-dimethyl-1-(*p*-tolyl)pentan-3-one

The title compound was prepared with a ^{19}F NMR yield of 71%, and was isolated as a white solid (36.7 mg, 55%).

mp 34–36 °C

TLC (SiO$_2$) R_f = 0.22 in 20:1 hexanes/acetone, *p*-anisaldehyde stain

¹H NMR (500 MHz, CDCl₃) δ 7.25 (d, *J* = 7.0 Hz, 2H), 7.18 (d, *J* = 7.5 Hz, 2H), 5.98 (ddd, *J* = 46.5, 8.0, 4.0 Hz, 1H), 3.33 (ddd, *J* = 22, 13.5, 8.5 Hz, 1H), 2.76 (ddd, *J* = 31.0, 17.0, 4.0 Hz, 1H), 2.35 (s, 3H), 1.13 (s, 9H)

¹³C NMR (126 MHz, CDCl₃) δ 211.7, 142.9, 138.4, 136.7, 136.5, 129.6, 129.2, 128.3, 125.6, 125.5, 119.7, 90.5 (d, *J* = 169.6 Hz), 44.1 (d, *J* = 27.2 Hz), 26.4, 25.9, 21.2

¹⁹F NMR (376 MHz, CDCl₃) δ –173.8 (ddd, *J* = 46.1, 31.5, 13.6 Hz, 1F)

IR (neat) 2966, 2926, 2871, 1708, 1604, 1369, 1080, 1002, 979, 817, 728, 543 cm⁻¹

GC/MS (*m/z*): 222.1 (8%), 202.1 (6%), 145.1 (100%), 123.1 (34%), 115.1 (22%), 91.1 (11%)
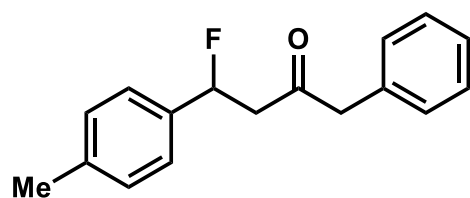
4-fluoro-1-phenyl-4-(*p*-tolyl)butan-2-one

The title compound was prepared with a ¹⁹F NMR yield of 67%, and was isolated as an off-white solid (36.3 mg, 47%).

mp 57–60 °C

TLC (SiO₂) *R_f* = 0.41 in 5:1 hexanes/acetone, *p*-anisaldehyde stain

¹H NMR (500 MHz, CDCl₃) δ 7.34 (t, *J* = 7.5 Hz, 3H), 7.29 (d, *J* = 7 Hz, 2H), 7.24–7.15 (m, 4H), 5.92 (ddd, *J* = 46.5, 8.5, 4.0 Hz, 1H), 3.75 (d, *J* = 5.0 Hz, 2H), 3.23 (ddd, *J* = 16.3,

14.8, 9.0 Hz, 1H), 2.82 (ddd, J = 31.0, 16.5, 3.0 Hz, 1H), 2.36 (s, 3H)

¹³C NMR (126 MHz, CDCl₃) δ 204.4, 197.4, 143.5, 141.1, 138.6, 136.1, 136.0, 134.6, 133.4, 131.7, 129.7, 129.5, 129.3, 128.8, 128.8, 128.4, 127.2, 127.1, 127.0, 125.7, 125.6, 124.3, 90.2 (d, J = 170.6 Hz), 51.0, 48.9 (d, J = 26.5 Hz), 48.3, 21.5, 21.2

¹⁹F NMR (376 MHz, CDCl₃) δ –172.5 (ddd, J = 46.2, 31.4, 13.9 Hz, 1F)

IR (neat) 3027, 2963, 2920, 1713, 1603, 1496, 1450, 1334, 1220, 1073, 1028, 817, 741, 696, 543 cm⁻¹

GC/MS (*m/z*): 256.1 (3%), 165.0 (18%), 145.0 (13%), 123.1 (100%), 91.0 (22%)
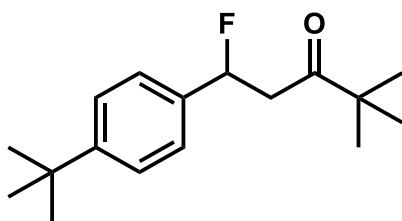
1-(4-(*tert*-butyl)phenyl)-1-fluoro-4,4-dimethylpentan-3-one

The title compound was prepared with a ¹⁹F NMR yield of 90%, and was isolated as a white solid.

mp 49–50 °C

TLC (SiO₂) R_f = 0.26 in 20:1 hexanes/acetone, *p*-anisaldehyde stain

¹H NMR (500 MHz, CDCl₃) δ 7.41 (d, J = 10.5 Hz, 2H), 7.30 (d, J = 9.5 Hz, 2H), 6.00 (ddd, J = 58.5, 11.0, 5.0 Hz, 1H), 3.36 (ddd, J = 21.1, 17.3, 11.0 Hz, 1H), 2.75 (ddd, J = 40.5, 21.5, 5.0 Hz, 1H), 1.32 (s, 9H), 1.14 (s, 9H)

¹³C NMR (126 MHz, CDCl₃) δ 211.7, 151.6, 136.6, 136.5, 125.5, 125.3, 125.3, 90.3 (d, J = 169.6 Hz),44.3,   44.0 (d, J = 27.0 Hz), 34.6, 31.3, 25.9

¹⁹F NMR (376 MHz, CDCl₃) δ –174.0 (ddd, J = 46.4, 32.5, 13.8 Hz, 1F)

IR (neat) 2960, 2928, 2905, 2868, 1704, 1476, 1364, 1082, 1002, 839, 582 cm⁻¹

GC/MS (*m/z*): 264.1 (4%), 249.1 (6%), 207.1 (6%), 187.1 (32%), 165.1 (31%), 131.0 (35%), 57.1 (100%)
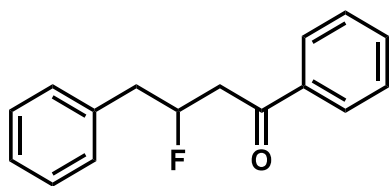
3-fluoro-1,4-diphenylbutan-1-one

The title compound was prepared with a ¹⁹F NMR yield of 60%, and was isolated as an off-white solid.

mp 55–56 °C

TLC (SiO₂) R_f = 0.43 in 5:1 hexanes/acetone, *p*-anisaldehyde stain

¹H NMR (500 MHz, CDCl₃) δ 7.91 (dd, J = 10.0, 1.0 Hz, 2H), 7.58 (app. tt, J = 9.0, 1.6 Hz, 1H), 7.46 (app. t, J = 10.0 Hz, 2H), 7.36–7.29 (m, 2H), 7.26 (app. d, J = 8.5 Hz, 3H), 5.40 (app. doublet of quintets, J = 59.0, 7.0 Hz, 1H), 3.45 (ddd, J = 21.3, 19.0, 9.0 Hz, 1H), 3.18–3.04 (m, 3H)

¹³C NMR (126 MHz, CDCl₃) δ 196.8, 136.8, 136.5, 133.4, 129.6, 128.7, 128.5, 128.1, 126.8, 90.4 (d, J = 171.7 Hz), 42.8 (d, J = 23.2 Hz), 41.2 (d, J = 21.0 Hz)

¹⁹F NMR (376 MHz, CDCl₃) δ –179.0 (app. ddt, J = 47.2, 23.1, 16.5 Hz, 1F)

IR (neat) 3031, 2959, 2930, 1682, 1597, 1447, 1379, 1213, 1083, 1009, 744, 686, 511 cm⁻¹

GC/MS (*m/z*): 222.1 (15%), 115.0 (18%), 105.0 (100%), 91.1 (9%), 77.0 (32%)
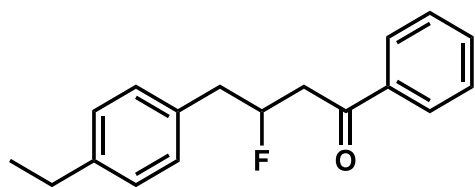
4-(4-ethylphenyl)-3-fluoro-1-phenylbutan-1-one

The title compound was prepared with a ¹⁹F NMR yield of 39%, and was isolated as a pale yellow liquid (33.9 mg, 42%).

TLC (SiO₂) R_f = 0.44 in 5:1 hexanes/acetone, *p*-anisaldehyde stain

¹H NMR (500 MHz, CDCl₃) δ 7.94–7.88 (m, 2H), 7.59–7.53 (m, 1H), 7.47–7.43 (m, 2H), 7.20–7.13 (m, 4H), 5.39 (app. doublet of quintet, J = 47.0, 6.0 Hz, 1H), 3.44 (ddd, J = 16.8, 15.5, 7.0 Hz, 1H), 3.17–3.02 (m, 3H), 2.64 (q, J = 7.5 Hz, 2H), 1.24 (t, J = 7.5 Hz, 3H)

¹³C NMR (126 MHz, CDCl₃) δ 196.9, 148.0, 142.8, 137.9, 136.8, 134.9, 133.6, 133.5, 133.4, 133.2, 132.6, 29.5, 128.8, 128.6, 128.5, 128.5, 128.2, 128.1, 128.0, 126.7, 90.5 (d, J = 171.7 Hz), 42.8 (d, J = 23.3 Hz), 40.8 (d, J = 21.2 Hz), 28.5, 15.6

¹⁹F NMR (376 MHz, CDCl$_3$) δ −178.7 (app. ddt, J = 47.7, 23.9, 15.8 Hz, 1F)

IR (neat) 2963, 2930, 2361, 2335, 1684, 1620, 1450, 1272, 1216, 1018, 983, 829, 754, 689 cm^{-1}

GC/MS (*m/z*): 250.1 (19%), 145.1 (12%), 117.1 (14%), 105.0 (100%), 91.1 (6%), 77.0 (29%)

Chapter III. Alkyl Tertiary Fluoride

1. Primary and Secondary Alkyl Fluoride Synthesis without Adjacent Electron-Withdrawing Group

Fluorides are weak nucleophiles under many typical conditions, so nucleophilic reactions are challenging with fluorides. The Finkelstein reaction is one of the conventional fluorination options.[289]

Classic Finkelstein reaction entails the conversion of an alkyl chloride or an alkyl bromide to an alkyl iodide by treatment with a solution of sodium iodide in acetone.[290] Scheme 64 shows a recent example published by Chi group, which takes advantage of ionic liquid to potentially improve the solubility of the alkali salt in order to enhance the reactivity of the fluorinating reagent. In Finkelstein reaction, alkyl bromide, iodide, mesylate, or tosylate is
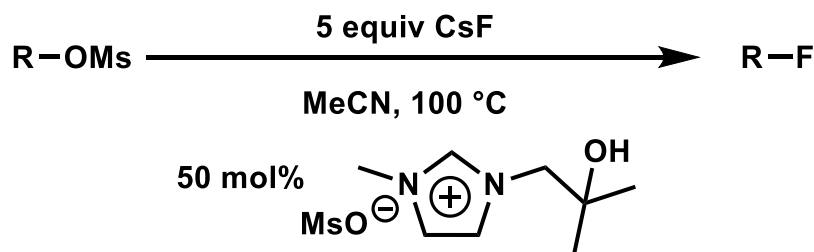
Scheme 64

an alkali fluoride MF (M=Li, Na, K, Rb, Cs) to afford alkyl fluoride.[291] Since the cost of alkali metal is generally low, the reaction itself is commonly used when the substrate is available. However, this method suffers from a practical problem that the required alkali fluoride is hygroscopic, and the fluorides are very likely to from hydrogen bonds with water to decrease the nucleophilicity of the fluoride ions, which is already weak. In addition, the solubility of alkali

fluoride salts in common organic solvents limits their application in organic synthesis. New

nucleophilic and electrophilic fluorinating reagents introduced in Chapter I, such as SelecFluor®,

NFSI, DAST, PyFluor, Phenofluor, Deoxo-Fluor, XtalFluor, and Fluolead, have been developed.

The fluorinating reagents mentioned above are also useful in modern catalytic reactions

and sometimes the catalysts could alter the fluorinating reagents' selectivity. For example, in

2013 Lectka and co-workers developed a radical fluorination procedure promoted by a Fe(II)

species in the presence of Selectfluor® (Scheme 65).[292-293] Even when there is an electron-
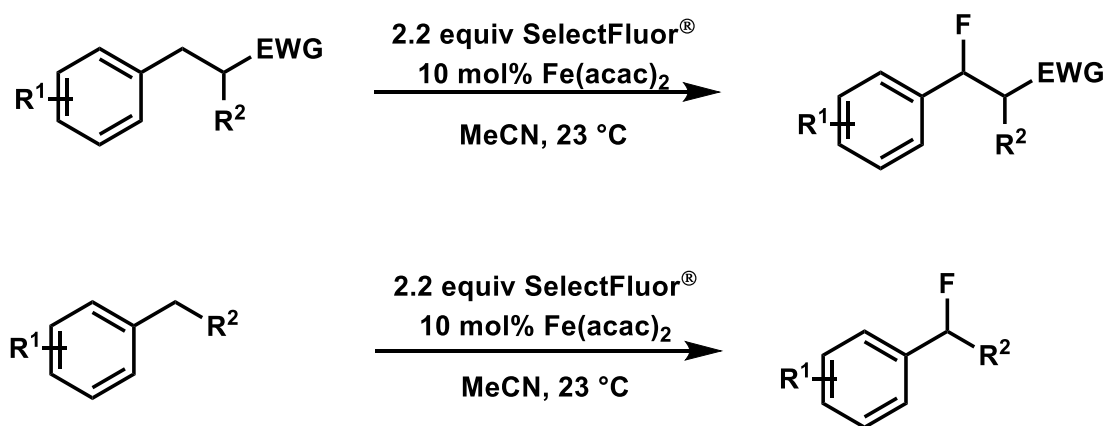
Scheme 65

withdrawing group (EWG) β to the benzylic position, benzylic fluorination was exclusive. This

is in sharp contrast to the traditional Selectfluor® reactivity in the presence of such EWG

(Selectfluor® alone would usually lead to α fluorination of EWG).[81-85, 98] Nitriles, sulfones, and

numerous derivatives of carbonyl groups, from carboxylic acids to aldehydes are all tolerated

under the condition. Simpler benzylic fluorides can also be synthesized in similar efficiency.

2. Tertiary Alkyl Fluoride Synthesis without Adjacent Electron-Withdrawing Group

Tertiary centers are suitable reaction centers for S_N1 and free radical reactions. Therefore, most syntheses of tertiary alkyl fluorides without adjacent electron-withdrawing group are accomplished with these two strategies.
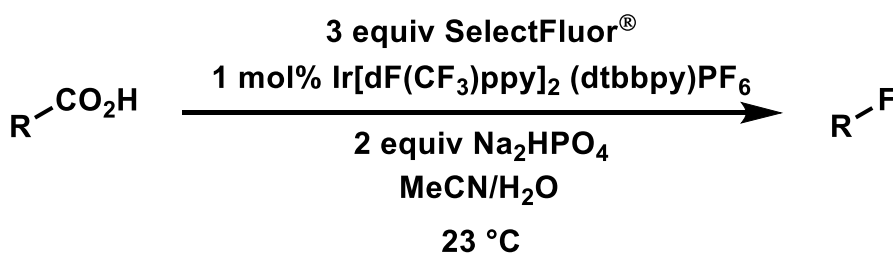
Tertiary alcohol is a popular category for S_N1 fluorination. With treatment of fluorinated aminosulfuranes, the hydroxyl is converted to a good leaving group by attacking sulfur and eliminating hydrogen fluoride.[294] The resulting alkoxyaminosulfur difluoride intermediate then dissociates and the resulting carbocation is attacked by nucleophilic fluoride, by an S_N1 pathway, leading to the tertiary fluoride product. As mentioned in Chapter 1, a lot of fluorinated aminosulfuranes have been developed to apply in various systems.

Despite the fact that adamantane is a very sterically demanding system, adamantyl bromide is very robust in fluorination. Early in 1965, Schleyer and his co-worker reported an example of adamantyl bromide fluorination with silver(I) fluoride.[295] Up to now, most of reports on alkyl tertiary bromide fluorination are on bromides of diamondoids.[296-299] The reason behind the limitation is likely to be that diamondoids tend to undergo an S_N1 pathway under the fluorination conditions and the relative stability of adamantal systems could potentially avoid side reactions like elimination. Also, Bollinger group discovered silver(I) fluoride could fluorinate 2-bromo-3- fluoro-2,3-dimethylbutane in 5% yield.[300]

A visible light-mediated benzylic fluorination was reported by Chen and co-workers.[301] The reaction uses 9-fluorenone as the light sensitive radical-initiating catalyst, which tolerates various functional groups on aromatic and alkyl chains. Electron rich substrate reaction rate is faster empirically. Moreover, the authors demonstrated that their transformation is viable in

gram-scale synthesis and generates secondary benzylic fluorides faster than primary or tertiary

ones.

   The direct conversion of aliphatic carboxylic acids to the corresponding alkyl fluorides

has been achieved via visible light-promoted photoredox catalysis by MacMillan group (Scheme

66).[302] This operationally simple fluorination method is applicable to a wide variety of

$$R\text{-}CO_2H \quad \xrightarrow[\substack{\textbf{2 equiv Na}_2\textbf{HPO}_4 \\ \textbf{MeCN/H}_2\textbf{O} \\ \textbf{23 °C}}]{\substack{\textbf{3 equiv SelectFluor}^® \\ \textbf{1 mol\% Ir[dF(CF}_3\textbf{)ppy]}_2 \textbf{ (dtbbpy)PF}_6}} \quad R\text{-}F$$

Scheme 66

carboxylic acids. Initial photon-induced oxidation of carboxylates leads to the formation of

carboxyl radicals, which upon rapid CO_2-extrusion and fluorine radical transfer from a

fluorinating reagent gives rise to the desired fluoroalkanes with high efficiency (Scheme 67).

Notably, this radical induction method is so versatile that it can generate primary, secondary, and

tertiary radicals, hence producing all three kinds of alkyl fluorides.
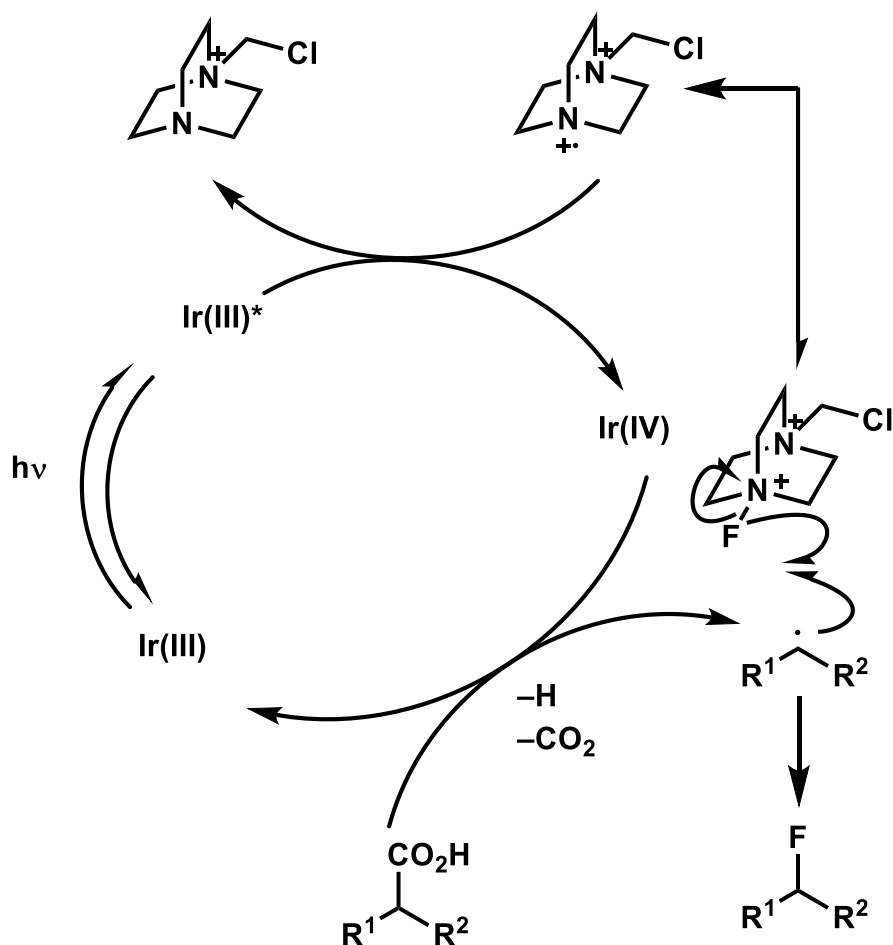
Scheme 67

3. Primary and Secondary Alkyl Fluoride Synthesis with Adjacent Electron-Withdrawing Group

α- fluorination of carbonyl compounds with electrophilic fluorine sources offers a solution to obtain carbonyl compounds with primary and secondary carbonyl compounds. A lot of examples were discussed in Chapter I. In general, carbonyl compounds with only a primary and secondary reaction center are excellent substrates for fluorination with enolates, either by

pre-making the enolate equivalents with silyl or acetate, etc., or preparing the enolate in situ followed by subsequent treatment of electrophilic fluorine sources.

4. Tertiary Alkyl Fluoride Synthesis with Adjacent Electron-Withdrawing Group

As discussed in Chapter I, β keto esters have been studied so extensively that enantioselective fluorination is already mature on many substrates in this category. However, blanks still exist in studies on fluorination of tertiary centers neighboring a single electron-withdrawing group. Known examples used small molecules such as $FOCl_3$,[47-48, 303] and AcOF.[304-305] Small molecule gaseous fluorine sources are potentially very toxic and require special fluorine tolerant lab equipment and special handling procedure. Common commercially available and widely used electrophilic fluorine sources such as SelectFluor®,[98] NFSI,[78, 107] NFOBS (N-fluoro-o-benzenedisulfonimide)[78] on the other hand, suffer from the problem that the tertiary centers are relatively sterically demanding and are rarely used as electrophilic fluorine sources for tertiary centers except the potentially activated benzylic centers.[306-307]

AgBF₄ was reported in 1979 to transform keto tertiary bromides to keto tertiary fluorides (Scheme 68).[308] This is the first example to fluorinate a tertiary bromide neighboring a ketone with stoichiometric silver(I) reagent. Primary bromide, as well as tertiary chloride, were found to be intact during the reaction process. Tertiary α-bromoaldehyde was also proven to be a good substrate with a 70% yield of tertiary α-fluoroaldehyde and only a 15% yield of the corresponding carboxylic acid.
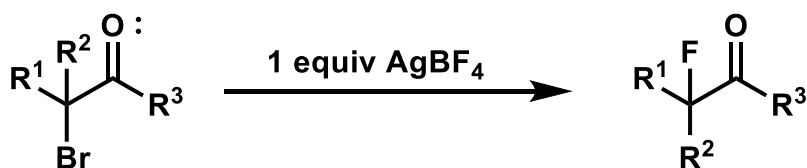
Scheme 68

α-Chloroesters have been demonstrated to convert to fluoroesters in cyclopropane system. Wang and co-workers reported the nucleophilic fluorination of α-chloroesters with retention of configuration (Scheme 69).[309] With an excess of KHF_2 (3 equiv) as the fluorinating agent, fluorinated compounds were afforded in high yields. An elimination-addition mechanism was proposed by the authors to explain the stereoselectivity.
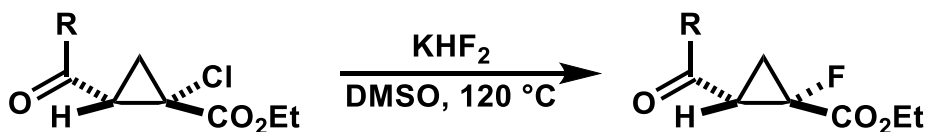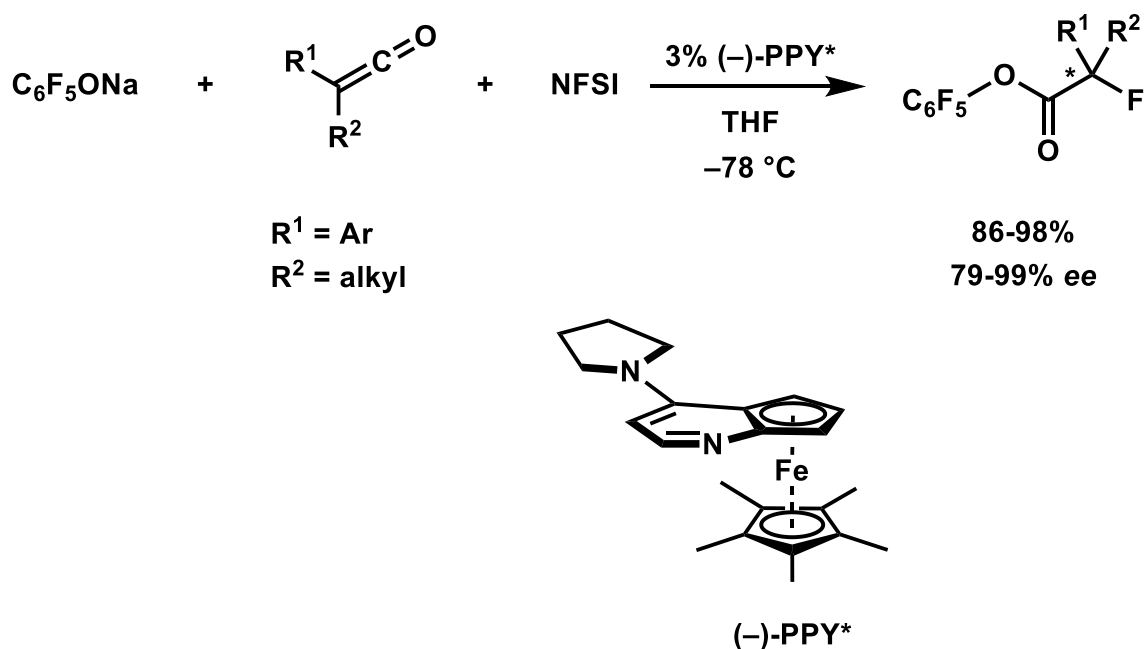

Scheme 69

In 2008, Hammond and co-workers reported the transformation of allenoates for the synthesis of α -fluorinated esters (Scheme 70).[310] They formed alkynyl enolates in situ with lithium diisopropylamide (LDA). With the addition of NFSI, they obtained the desired fluorinated compounds in moderate to good yields.
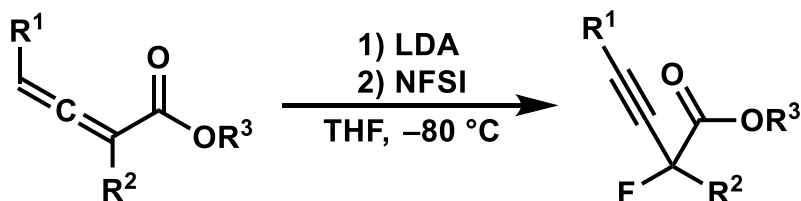
Scheme 70

Later, Fu utilized ketene to develop an enantioselective fluorination as an alternative in 2014 (Scheme 71).[311] This 3-component coupling, catalyzed by inexpensive iron catalyst renders tertiary α-fluoroesters asymmetrically in a catalytic fashion. Over 10 examples were

$R^1 = Ar$
$R^2 = alkyl$

86-98%
79-99% ee

(–)-PPY*

Scheme 71

shown. Mechanistic studies prove the addition of an external nucleophile (C_6F_5ONa) is critical for turnover, releasing the catalyst (PPY*) from an *N*-acylated intermediate (Scheme 72). Therefore, a "chiral enolate" pathway was suggested by the authors. Nucleophilic addition of PPY* to the ketene generates enolate, which is the resting state of the catalytic cycle. As the

reaction goes to turnover limiting step, the enolate is fluorinated by NFSI to provide

enantioenriched *N*-acylpyridinium salt. Aryl oxide then react with the intermediate to afford the

final product and reform the catalyst.
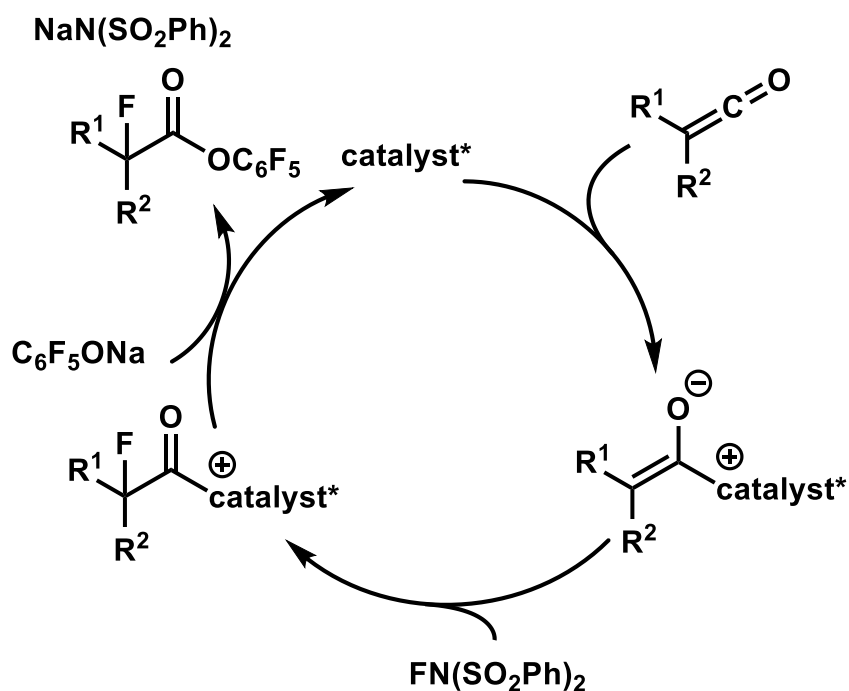
Scheme 72

In 2016, Nishikata and co-workers reported a copper catalyzed fluorination reaction of

tertiary bromide with neighboring amide (Scheme 73).[291] The method showed a good chemo

selectivity for primary and secondary alkyl bromide was kept intact under the reaction condition.

To note, this methodology proceeds well only with a neighboring amide. The catalytic cycle was

postulated to include at least, 1) a radical initiation and 2) a fluorination step involving the alkyl

radical generated from the bromo amide and copper fluoride (Scheme 74).[291] Fluoro amide

Scheme 73

66%

64%

43%

74%

73%

trace

trace

63%

80%

68%

73%

48%

51%

50%
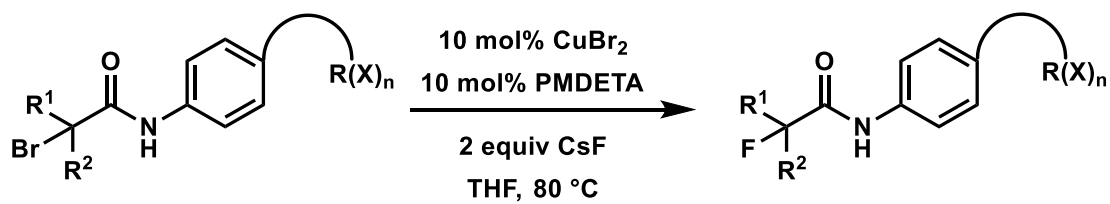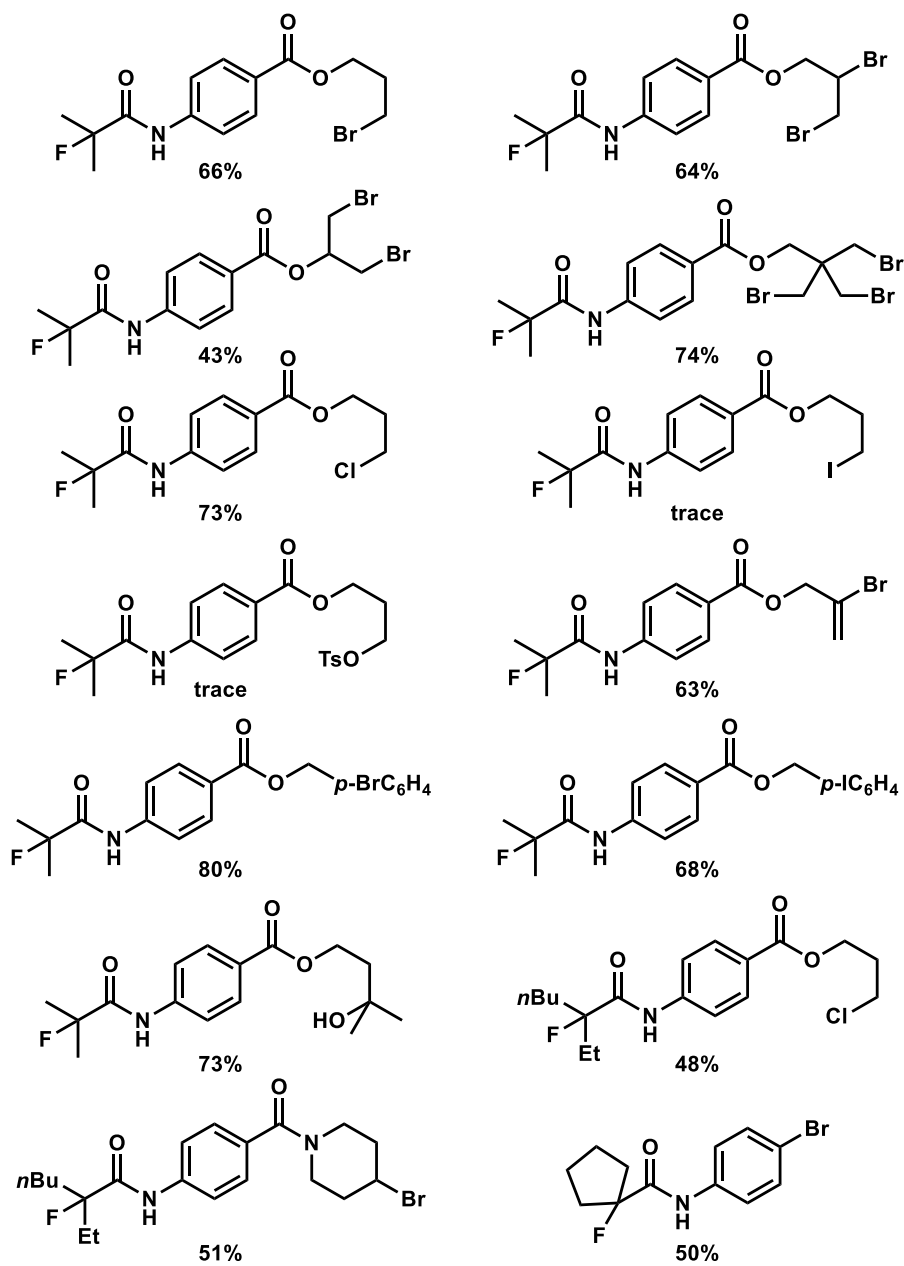
Table 18

could potentially be precursors to useful amino fluorides as well. The disadvantage of this

methodology, if any, is if an ester or a ketone is adjacent to the tertiary center, the reaction

produces trace amount of product.
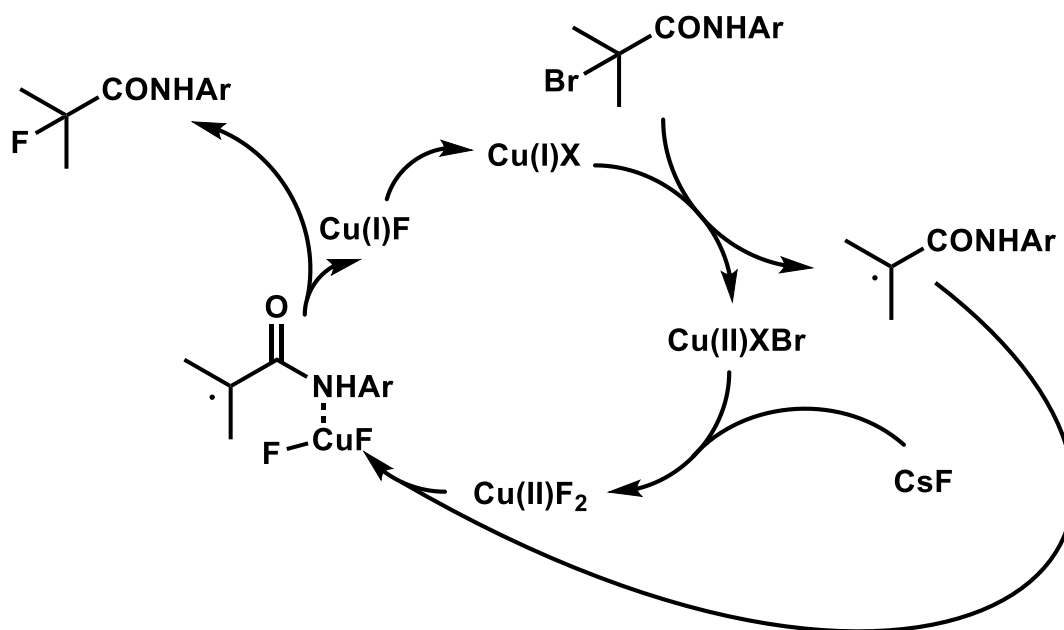
Scheme 74

In sum, bromides at tertiary centers are potential to be replaced by fluorides under

suitable conditions. Little is known on fluorination tertiary bromides adjacent to esters without

any other electron-withdrawing groups. Therefore, we want to take advantage of oxidizing

ability of silver(II) difluoride to synthesize tertiary bromides.

5. Tertiary Bromide Discussion

Based on the literature research we did, we found few reliable solutions to access tertiary α-fluoroketones and α-fluoroesters are known. We figured it is promising to achieve the fluorination of compounds with a relatively more accessible tertiary bromide via radical process.

Gratifyingly, our first attempt employing 2-bromoisobutyrophenone as our model afforded the desired product. When treated with 2 equiv of AgF_2 at 23 °C for 15 h, 0.1 mmol 2-bromoisobutyrophenones (0.05 M solution in 1,2-dichloroethane) was converted to its fluoro counterpart in 35% yield (Scheme 75). Low yield could be attributed to the side product, 2-methyl-1-phenylpropan-1-one, which derived from elimination reaction of the substrate.

All the yields were determined by ^{19}F NMR. The yields in parentheses are isolated yields.

5.1. Initial result
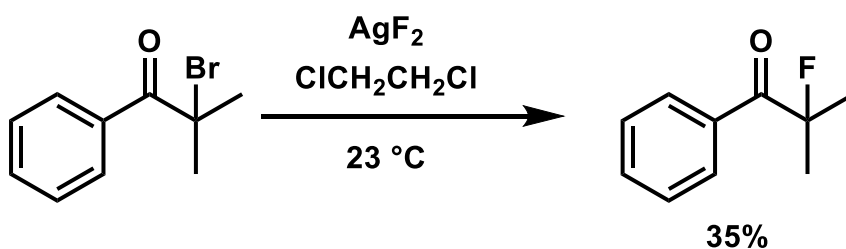
Bromide (0.1 mmol), and fluoride source (0.2 mmol) in 1,2-dichloroethane (2 mL) at 23 °C for 14 hours.

Scheme 75

Considering SelectFluor® can oxidize silver(I) in Zhu's report, it is worthwhile to test if the Zhu procedure is applicable in tertiary fluoride synthesis. An experiment using the optimized condition from Zhu's work was conducted. However, the catalytic condition was not yielding

any fluorinated compounds but recovered all the substrates (Scheme 76).
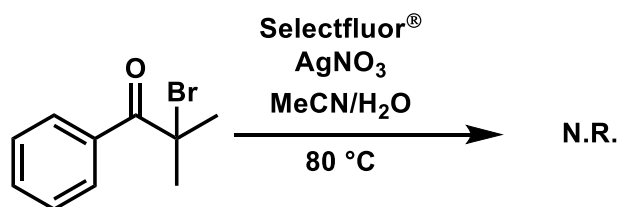
Bromide (0.119 mmol), silver nitrate (0.0238 mmol) and fluoride
source (0.238 mmol) in MeCN (2mL) and H_2O (2 mL) at 80 °C for 14 hours.

Scheme 76

Similar to what we found in cyclopropanol case, $ClCH_2CH_2Cl$ was the optimal choice of solvent.

5.2. Optimization

5.2.1. Influence of Solvent
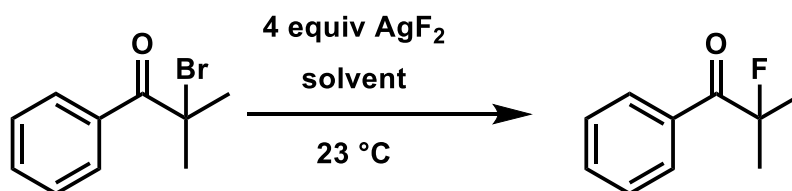
solvent	%yield
$ClCH_2CH_2Cl$	50
CH_2Cl_2	27
$CHCl_3$	25
MeCN	7
THF	trace
1,4-dioxane	trace
heptane	N.R.
DMF	N.R.

Bromide (0.119 mmol), and fluoride source (0.476 mmol) in 2 mL specified solvent at 23 °C for 14 h

Table 19

The reaction rate was relatively fast. After 1 hour of reaction time under 23 °C, the yield already achieved a relatively high level. 2-hour reaction time was the best under 23 °C. Even when the reaction was cooled in addition phase, 1-2 hour(s) total reaction time was enough to obtain the highest yields.

5.2.2. Influence of Reaction Time under Ambient Temperature
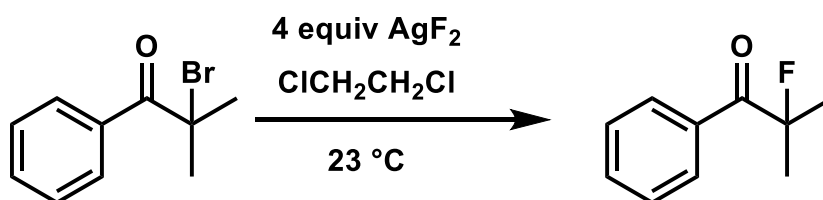
time (h)	%yield
1	43
2	45
4	41
6	43

Bromide (0.119 mmol), and fluoride source (0.476 mmol) in 1,2-dichloroethane (2 mL) at 23 °C for specified time

Table 20

5.2.3. Influence of Reaction Time under Low Temperature
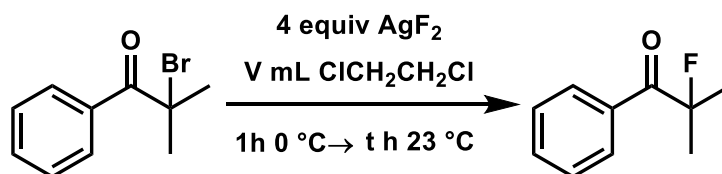
t	V	%yield
0	0.05	59
1	0.05	69
2	0.05	53
3	0.05	54
0	0.1	54
1	0.1	53
2	0.1	46
3	0.1	42

Bromide (0.119 mmol), and fluoride source (0.476 mmol) in V mL 1,2-dichloroethane at 0 °C for 1 h, then at 23 °C for t h

Table 21

We assumed that raising the concentration would result in the promotion of the fluorination route over the competitive elimination route as raising the concentration can potentially increase the fluorination rate. Later studies showed high concentration of fluorine source could suppress the amount of elimination product. Since the study in Table 19–21 was using a commercially available substrate with a known density, the solvent could be easily measured in small volume. Other substrates which were synthesized in our own hands would be relatively harder to apply this protocol. 0.476 M was found to be the most efficient concentration for this reaction with 0.238 mmol scale substrate.

5.2.4. Influence of Concentration (Tertiary α-Bromoketone As the Substrate)
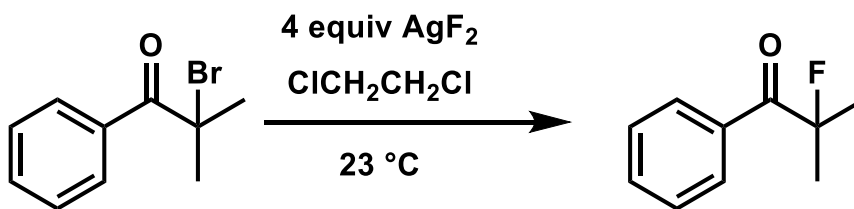
solvent volume (mL)	substrate concentration (M)	%yield
0.05	2.38	60
0.1	1.19	58
0.2	0.60	55
0.5	0.24	45
4	0.03	38
6	0.02	22

Bromide (0.119 mmol), and fluoride source (0.476 mmol) in 1,2-dichloroethane at 23 °C for 1 h

Table 22

5.2.5. Influence of Concentration (Tertiary α-Bromoester As the Substrate)
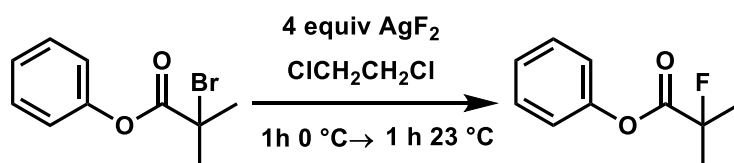
solvent volume (mL)	%yield
0.5	25
1	11
2	7
4	3

Bromide (0.238 mmol), and fluoride source (0.952 mmol) in specified volume of 1,2-dichloroethane at 0 °C for 1 h, then at 23 °C for 1 h

Table 23

In the reactions of esters, the reactions became more efficient as the concentration increased. Side product, phenyl methacrylate, is not observed in any of the reactions, and the only components in the reaction mixture are phenyl 2-fluoro-2-methylpropanoate and phenyl 2-bromo-2-methylpropanoate. Therefore, it can be postulated that it is either the reaction rate promotes as the concentration increases or the solvent can potentially react with silver(II) difluoride. Based on current information, we cannot rule out either of these possibilities.

In the end, with 0.238 mmol substrate, the optimal condition was determined as AgF$_2$ (0.952 mmol, 4 equiv) in 0.5 mL 1,2-dichloroethane at 0 °C for 1 hour, then at 23 °C for 2 hours.
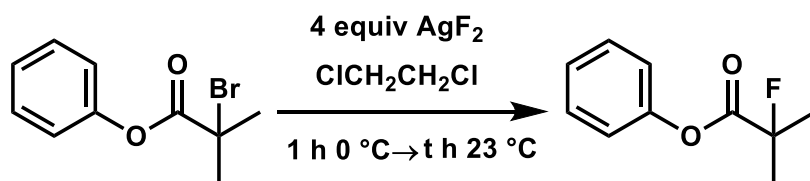
t	%yield
0.5	23
1	25
2	55
3	55
4	55

Bromide (0.238 mmol), and fluoride source (0.952 mmol) in 1,2-dichloroethane (0.5 ml) at 0 °C for 1 h, then at 23 °C for t h

Table 24

5.3. Reaction Scope Study

After establishing the optimal conditions, we then examined tertiary α-bromoketones' reactivity. Tertiary bromides (entry 1–6, Table 25) underwent smooth conversions into tertiary fluorides. In reactions of primary and secondary bromides (entry 7–8, Table 25), we failed to observe any fluoro products with ^{19}F NMR. Although tolyl substrate (entry 4, Table 25) was difluorinated, in (entry 5, Table 25) case, both the benzylic bromide and secondary benzylic proton were preserved. Therefore, the reaction is chemoselective to tertiary bromides in the presence of secondary bromide or secondary benzylic proton.

AgF$_2$

1,2-dichloroethane

0 °C → 23 °C

Examples	^{19}F NMR %yield (isolated yield)	Products
	63 (67)	
	47(44)	
	46(42)	
	55(48)	
	15(44)	
	41(45)	
	N.R.	
	N.R.	
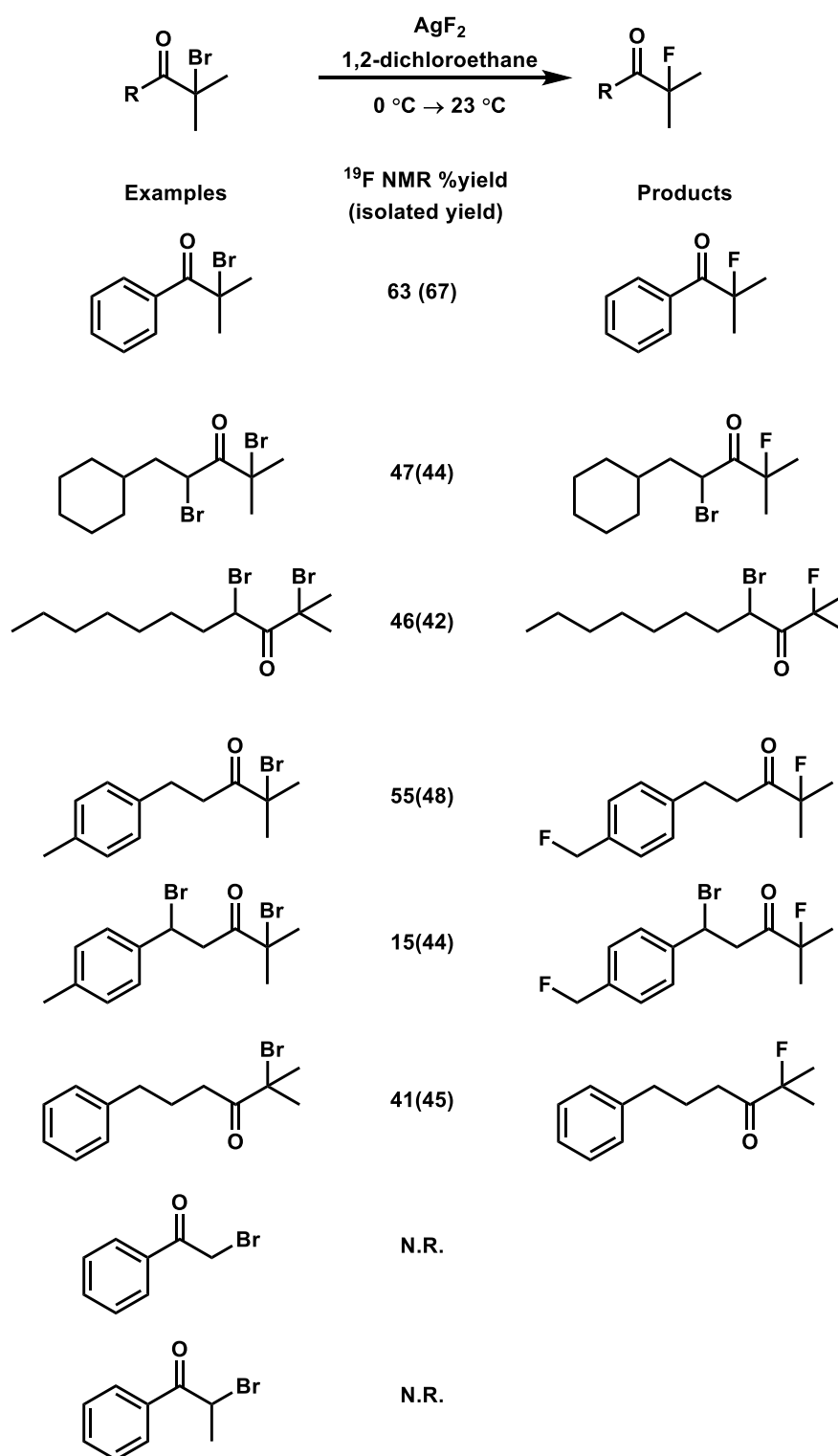
Table 25

In our studies on 2-bromo-2-methyl-1-phenylpropan-1-one, 2-methyl-1-phenylpropan-1-one was the major side product. Larger conjugation system in 2-methyl-1-phenylpropan-1-one can lower the potential energy. However, it was found later disrupting the large conjugation system reduced the elimination in the case of phenyl 2-bromo-2-methylpropanoate. We were pleased to observe there was no elimination product in the reaction of 2-bromo-2-methylpropionic acid phenyl ester under the condition of which the ketones were examined. A variety of esters were tested with our optimized condition. They show good reactivity. Aryls and alkyls on substrates did not have much difference in reactivity. On benzene ring, alkyl, fluoro, chloro, bromo, acetyl were tested, and compared to standard substrate (entry 1, Table 26), fluoro substrate (entry 4, Table 26) performed similarly, electron-rich system (entry 2, Table 26) and chloro, bromo compound (entry 3,6, Table 26) were less efficient, whereas electron-deficient system (entry 5, Table 26) was more effectively yielding the desired product. Unlike our previous studies on anisoles (when 2-(4-methoxyphenyl)-1-methylcyclopropan-1-ol is treated with our optimized condition, only 4-(4-methoxyphenyl)butan-2-one was observed), ethoxy on an alkyl chain (entry 8, Table 26) did not become a problem. Secondary alkyl alcohol derived ester (entry 10, Table 26) was demonstrated to perform less efficiently but in an acceptable range of fluorination reactions.

AgF$_2$
1,2-dichloroethane
0 °C → 23 °C
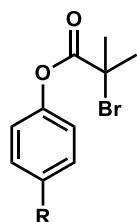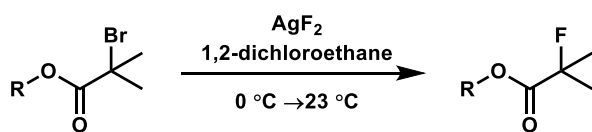
^{19}F NMR %yield
(isolated yield)

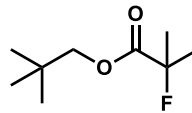R = H, 55(61)
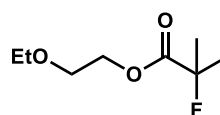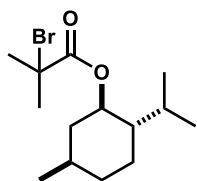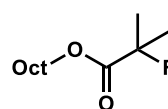R = tBu, 46(40)
R = Cl, 44(59)
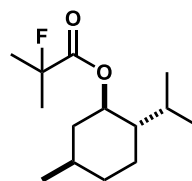R = F, 56(59)
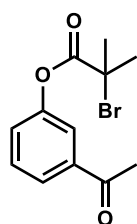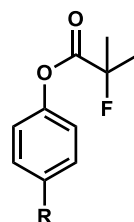
69
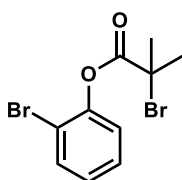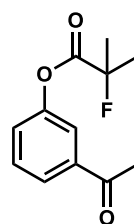
41
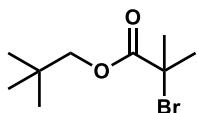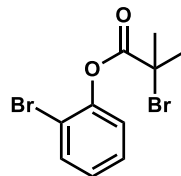
48
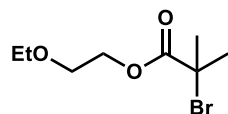
50
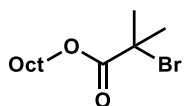
63 (51)

39

Table 26

Although tertiary alkyl bromides without electron withdrawing groups have been fluorinated previously, to test the versatility of our fluorination protocol, two examples were investigated. They showed excellent reaction efficiency, proving electron withdrawing groups are not essential for our reaction.
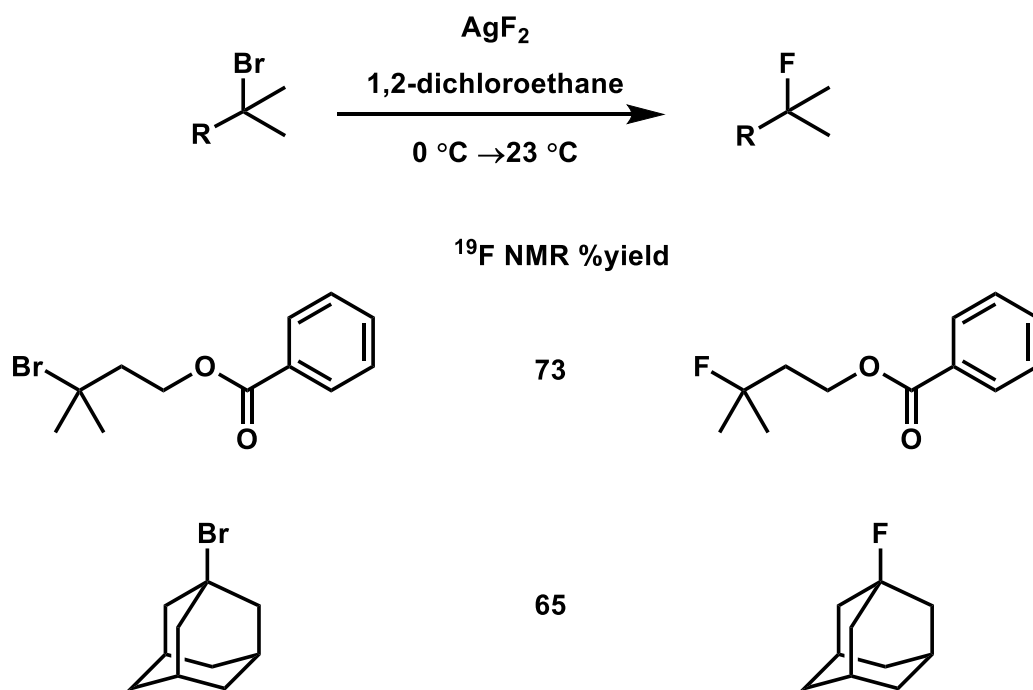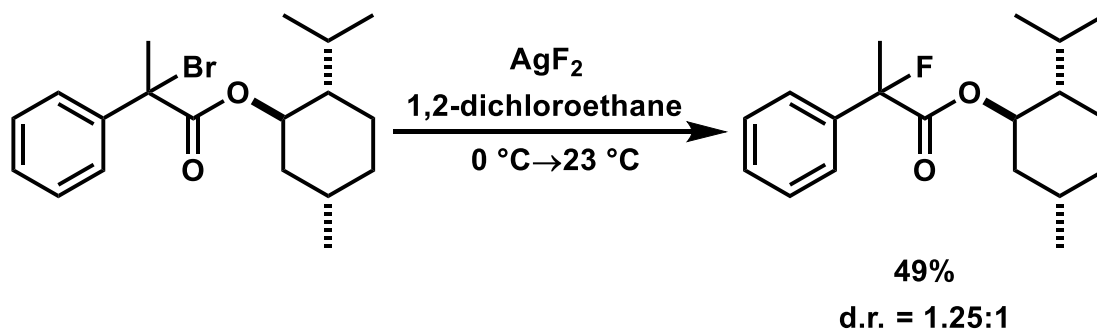

Table 27

5.4. Preliminary Diastereoselectivity Study

In the case of (1*R*,2*S*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-bromo-2-phenylpropanoate, we sought to examine the diastereoselectivity potential of our methodology (Scheme 77). To our delight, 1.25:1 d.r. was observed in ^{19}F NMR and 49% yield was obtained. The d.r. was not high,

but considering isopropyl in (L)-menthol moiety can be replaced with some even more steric demanding group, there is still potential for the selectivity to be improved. In the perspective of scope, it also demonstrates our methodology is not limited to tertiary bromide attached with three alkyls. Aryls is tolerated in the system too.

Scheme 77

5.5. Synthetic Application

Tertiary fluorides are also valuable synthetic building blocks (Table 28). Reactions of 2-fluoro-2-methylpropionic acid phenyl ester with pyrrolidine and geraniol successfully lead to corresponding amide and ester. To note, esters containing alkene and amides produce trace amount of fluorinated product in our condition. However, the transesterification and amidation solved this issue with 92% and 89% yield. Also, selective para iodination of the aromatic ring was also successfully providing a useful handle to make further potential transformation possible.
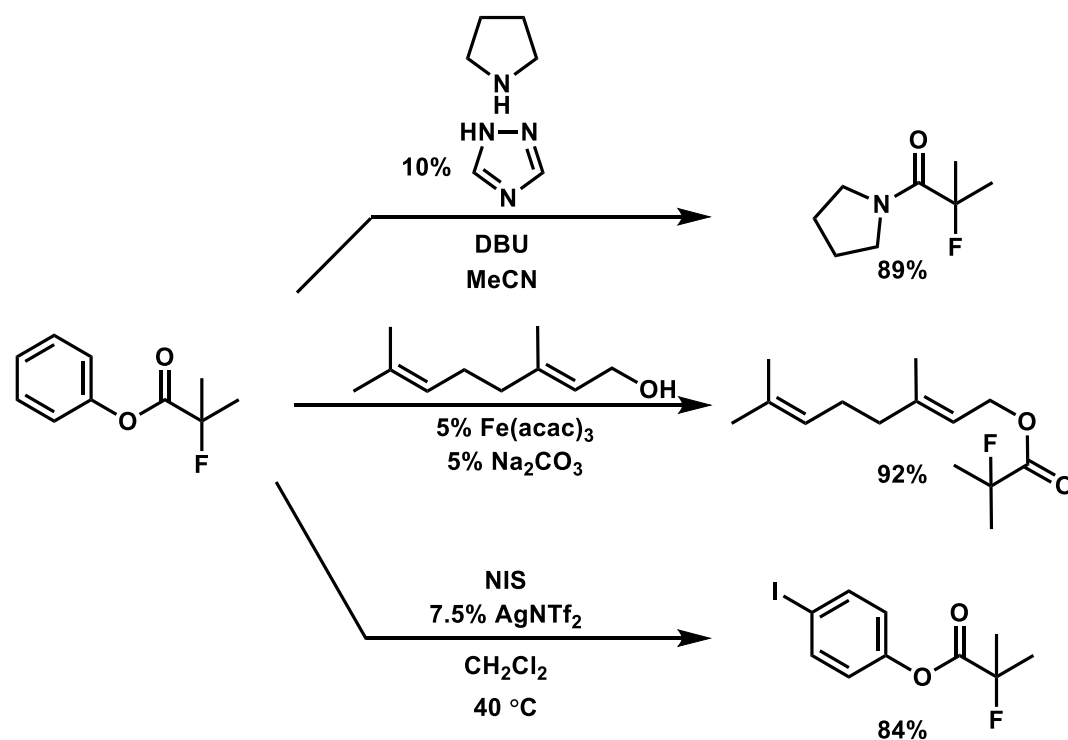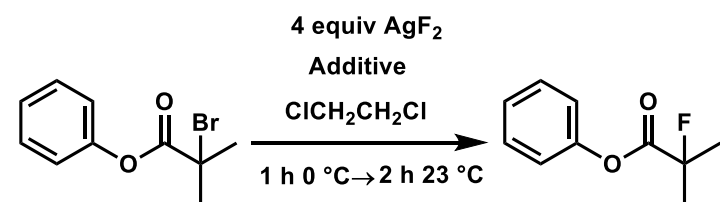
Table 28

5.6. Robustness Screen Experiments[319]

A series of additives were subjected into the reaction system to test adaptability. Alkyne, alkenes, primary bromide, ether, and amide (entry 1–3, 6–8, Table 29) could not be recovered in a high yield. But among them, alkene experiment was giving fluorinated compound in normal yield. Other additives were also hampering the fluoride–bromide exchange. Ketone and sulfoxide (entry 4–5, Table 29) were recovered in high yields, but sulfoxide obviously could not keep the original reaction integrity.

4 equiv AgF$_2$
Additive
ClCH$_2$CH$_2$Cl
1 h 0 °C→2 h 23 °C

Additive	%yield (α-fluoroketone)	%yield (additive)
	42	30
	67	24
	50	7
	42	85
	19	100
	42	0
	11	0
	27	0

Bromide (0.238 mmol) in 1,2-dichloroethane (0.5 ml) and specified additive (0.238 mmol) were injected into a vial containing fluoride source (0.952 mmol). The mixture were stirred at 0 °C for 1 h, then at 23 °C for 2 h.
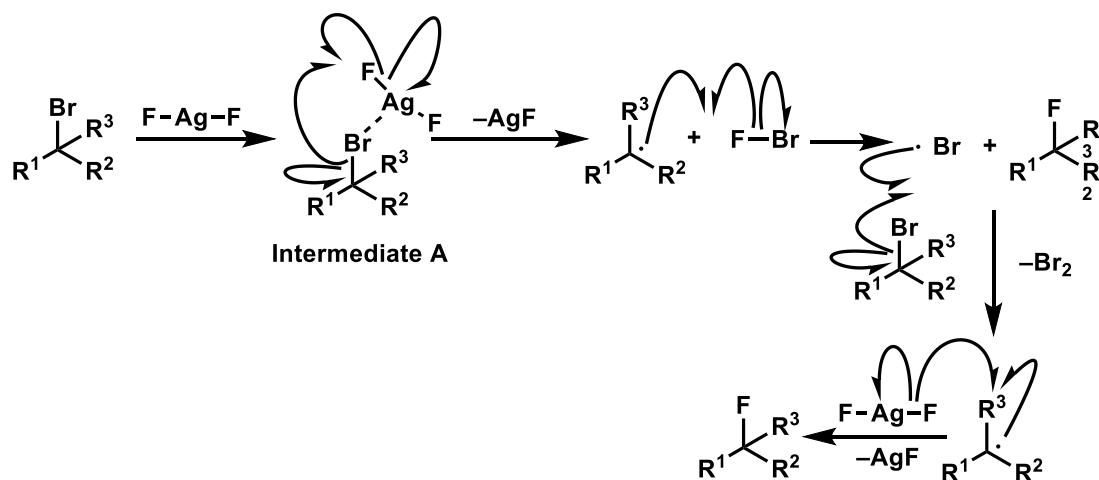
<div align="center">**Table 29**</div>

5.7. Mechanistic Discussion

Pathway 1
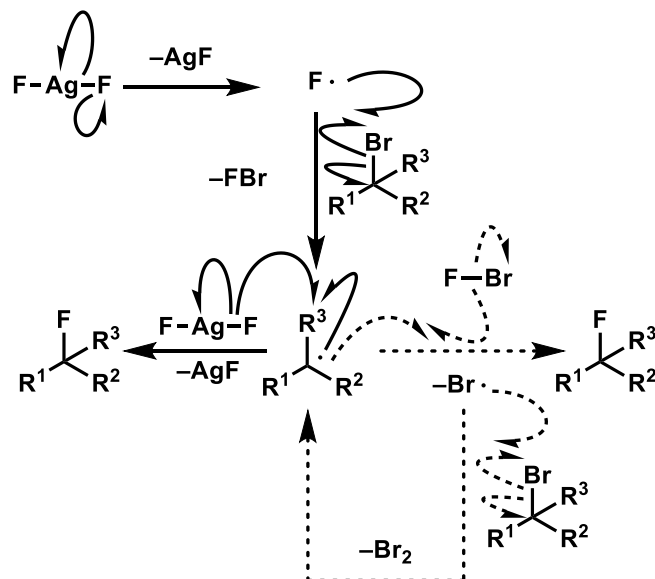
Pathway 2

<div align="center">**Scheme 78**</div>

Two plausible pathways for the Br–F replacement are shown in Scheme 78. Pathway 1

initiates by homolysis of silver(II) difluoride, leading to the formation of silver(I) fluoride radical and fluorine radical. Subsequent abstraction of bromine from the tertiary bromide substrate can produce the key intermediate, tertiary alkyl radical along with BrF. BrF is not a stable species but its high reactivity could lead to ready fluorination of the tertiary radical. Excess silver(II) difluoride or BrF can react with tertiary radical to form the fluorinated product. In pathway 2, the lone pair electrons on bromine atom have high affinity to electron-deficient silver(II). Although the huge energy barrier involving two sets of bonding electrons in intermediate A is concerning, the significant tendency for silver(II) to reduce to more stable lower valence might offset the energetic cost. With a facile single electron movement process, a tertiary radical and an unstable BrF could form. Bromine atom is then released and this could initiate the next chain process. Another tertiary radical is then formed and react with silver(II) difluoride to afford the fluorinated product. In the process of tertiary radical's formation, a molecule of bromine is hypothetically produced and its homolysis could also induce the initiation step of radical chain process.

6. Conclusion

In sum, we developed a methodology to synthesize α-fluoroketones, α-fluoroesters, and tertiary alkyl fluorides in synthetically useful yields. 19 examples were investigated and reasonable yields were obtained. The reaction on esters is so far unique for no extra activation in the substrates is required in our method. Unlike the chemoselectivity of Nishikata's method,[291] our method can be applied in various systems—esters, ketones, and alklys without any electron-withdrawing groups.

Preliminary diastereoselectivity study was conducted and a promising result was obtained. 2-fluoro-2-methylpropionic acid phenyl ester was converted to 2-fluoro-2-methyl-1-(pyrrolidin-1-yl)propan-1-one, (*E*)-3,7-dimethylocta-2,6-dien-1-yl 2-fluoro-2-methylpropanoate, and 4-iodophenyl 2-fluoro-2-methylpropanoate in good yields, which demonstrated the potential possibility to synthesize our products to some of other carbonyl derived compounds.

Appendix II. Experimental Part of Tertiary Bromide

1. General Procedure for Preparation of Isopropyl Ketone Substrates[312-313]
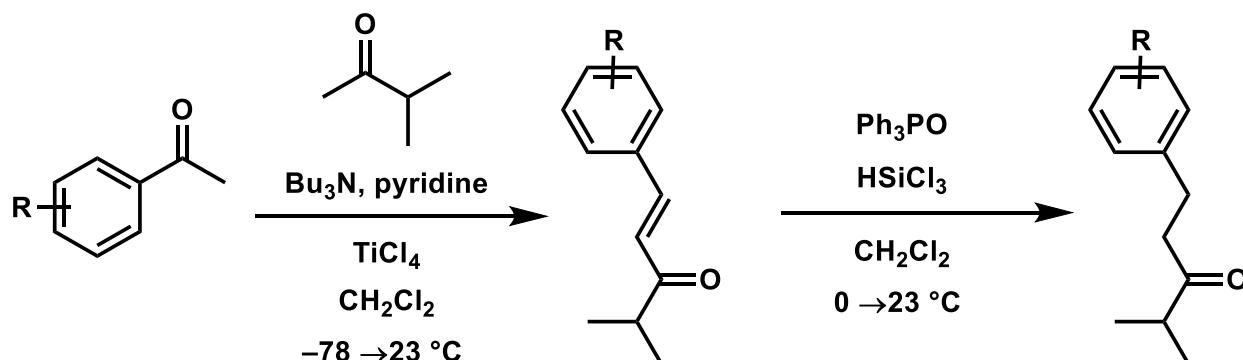
Bu$_3$N (1.2 mmol, 0.29 mL, 1.2 equiv) and TiCl$_4$ (1.1 mmol, 0.12 mL, 1.1 equiv) were successively added to a stirred solution of methyl isopropyl ketone (1.0 mmol, 0.11 mL, 1 equiv) in CH$_2$Cl$_2$ (2.0 mL) at −78 °C. After 30 min, acetophenone (1.0 mmol, 1 equiv) was added to the mixture at −78 °C. Then pyridine (5.0 mmol, 0.40 mL, 5 equiv) was added at −78 °C and the reaction mixture was warmed to room temperature. After being stirred for 5 h, the reaction mixture was diluted with Et$_2$O (5 mL) and hexane (5 mL). The mixture was filtered through a Celite pad and the filtrate was concentrated. The concentrated liquid was then dissolved in Et$_2$O (5 mL) and washed with 1M HCl solution (3×5 mL). The organic fraction was collected, dried over MgSO$_4$, and concentrated in vacuo. Triphenylphosphine oxide (1.0 mmol, 278.0 mg, 1 equiv) and the resulting aldol reaction mixture was added in a 20-mL glass vial. 4 mL CH$_2$ClCH$_2$Cl was used to dissolve the mixture. Then the solution was cooled to 0 °C, and HSiCl$_3$ (2.0 mmol, 0.2 mL, 2 equiv) was added in one portion. The vial was then closed by a cap. After 1 hour under 0 °C, the vial was removed from the ice bath and the reaction was allowed to stir for additional 4 hours. The reaction was quenched with saturated aqueous NaHCO$_3$ (3 mL). The organic fraction was dried over MgSO$_4$ and concentrated in vacuo. The desired product was

obtained by column chromatograph, using hexanes/ethyl acetate (from 20:1 to 10:1) as eluent.

2.   General Procedure for Preparation of α-bromoketone Substrates

α-Bromoketone substrates were prepared based on modified Gardner's work.[314]

To a solution of isopropyl ketone (1 mmol, 1 equiv) and in 3 mL acetic acid was added pyridinium perbromide (3 mmol, 960.0 mg, 3 equiv) at 23 °C in 3 batches. The reaction mixture was stirred for 14 hours at 23 °C. 3 mL toluene was added into the resulting reaction mixture and evaporated in vacuo. Purification by column chromatography on silica gel, using toluene/hexanes (1:10) as eluent, afforded the pure product.

3.   General Procedure for Preparation of Tertiary α-bromoesters Substrates

To a stirring solution of alcohol/phenol (5.7 mmol, 1.4 equiv) and pyridine (4 mmol, 0.32 mL, 1 equiv) under 0 °C in 8 mL CH_2Cl_2 in a 20-mL glass vial, α-bromoisobutyryl bromide (4 mmol, 0.5 mL, 1 equiv) was added dropwise. Upon completion of the addition, the vial was capped and removed from the ice bath. The reaction was allowed to stir for an additional 2 hours and was quenched with 5 mL 2 M NaOH aqueous solution. The aqueous solution was washed with Et_2O (2×3 mL), and the organic fractions were combined, dried over $MgSO_4$, and concentrated in vacuo. Purification by column chromatography on silica gel, using hexanes/ethyl acetate (from 20:1 to 10:1) as eluent, afforded the pure product.

4. Preparation of Substrate 3-bromo-3-methylbutyl benzoate

To a stirring solution of β-bromo-isovaleric acid (4.0 mmol, 729.1 mg, 1 equiv) under 0 °C in 8 mL tetrahydrofuran in a 20-mL glass vial, lithium aluminum hydride (4 mmol, 153.1 mg, 1 equiv) was added in three batches. The reaction was allowed to stir under 23 °C for 2 hours and was cooled to 0 °C again. 0.15 mL water was added first, followed by 0.15 mL 15 % aqueous sodium hydroxide and 0.45 mL water. The reaction mixture was then warmed to 23 °C and stir 15 min. The reaction mixture was then filtered through a Celite pad and the filtrate was dried over $MgSO_4$. The solution was concentrated in vacuo and dissolved in 2 mL CH_2Cl_2. Pyridine (6.0 mmol, 0.5 mL, 1.5 equiv) was added in the solution. With the solution stirred, benzoyl chloride (4.8 mmol, 0.55 mL, 1.2 equiv) was added dropwise. The reaction was stirred for additional 2 hours and was quenched with water. The organic fraction was collected, dried over $MgSO_4$, and concentrated in vacuo. Purification by column chromatography on silica gel, using hexanes/ethyl acetate (from 20:1 to 10:1) as eluent, afforded the pure product.

5. Preparation of Substrate (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-bromo-2-phenylpropanoate

5 g NH_4Cl was weighed in a 20-mL filtration flask equipped with a magnetic stirrer. The flask was sealed with a rubber septum and was connected with a syringe and a needle. 2-hydroxy-2-phenylpropanoic acid (1 mmol, 166 mg, 1 equiv) and (L)-menthol (3 mmol, 468 mg, 3 equiv) was weighed in a 20-mL vial equipped with a magnetic stirrer. 2 mL 1,4-dioxane was used to dissolve the solid mass. The vial was then sealed with a cap equipped with a rubber septum and a needle was placed through the septum. The filtration flask's needle was placed

through the vial's septum as well. With both stirrer stirring, 1 mL concentrated H_2SO_4 was measured in a syringe and needle and was subjected into the filtration flask (CAUTION: This operation has to be done in a well-ventilated hood). Vigorous gas evolving was observed. The gas was allowed to flow into the vial for 10 min and the outlet needle was removed first. After 30 seconds, the inlet needle was removed too. The vial was placed in a preheated 100 °C aluminum heating block and stirred for 16 hours. The resulting mixture was cooled to room temperature and poured into 5mL saturated aqueous $NaHCO_3$ solution, extracted with diethyl ether (2×3 mL). The organic fractions were combined and dried over $MgSO_4$. The solution was concentrated in vacuo and purified with a flash column, using hexanes/ethyl acetate (10:1) to afford the desired product, (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-hydroxy-2-phenylpropanoate. The product (0.29 mmol, 89 mg, 1 equiv) was treated with 32% HBr in AcOH (1.45 mmol, 0.27 mL, 5 equiv) and stirred for 16 hours. The resulting mixture was diluted with 2 mL toluene and concentrated in vacuo. After a flash column using hexanes/ethyl acetate (20:1), the desired product, (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-bromo-2-phenylpropanoate was obtained.

6. Synthesis of 2-fluoro-2-methyl-1-(pyrrolidin-1-yl)propan-1-one[315]

0.76 mL of freshly prepared stock solution of 1,2,4-triazole (0.19 mmol, 0.025 M solution, 0.1 equiv) and DBU (0.19 mmol, 0.025 M solution, 0.1 equiv) in acetonitrile was added to pyrrolidine (0.19 mmol, 15.6 µL, 1 equiv), followed by phenyl 2-fluoro-2-methylpropanoate (0.19 mmol, 34.7 mg, 1 equiv). After 15 h at room temperature, the solvent was removed under reduced pressure and the residue was diluted with Et_2O and passed through a plug of silica gel to

give pure product upon concentration.

7. Synthesis of (*E*)-3,7-dimethylocta-2,6-dien-1-yl 2-fluoro-2-methylpropanoate[316]

To a 20-mL vial was placed Fe(acac)$_3$ (0.01 mmol, 3.6 mg, 0.05 equiv), geraniol (0.2 mmol, 30.8 mg, 1 equiv), and Na$_2$CO$_3$ (0.01 mmol, 1.1 mg, 0.05 equiv) in 1 mL heptane at room temperature under nitrogen atmosphere. A solution of phenyl 2-fluoro-2-methylpropanoate (0.2 mmol, 36.4 mg, 1 equiv) in heptane (1 mL) was added via syringe. The resulting mixture was heated to 105 °C for 6 hours. The reaction mixture was then cooled to room temperature and quenched with saturated aqueous NH$_4$Cl solution (5 mL), then extracted with 2×3 mL ethyl acetate. The combined organic layer was dried over MgSO4, filtered, and evaporated to give a crude product that was purified by flash column on silica gel, using hexanes/ethyl acetate (40:1) to provide the desired product.

8. Synthesis of 4-iodophenyl 2-fluoro-2-methylpropanoate[317]

To a dry flask (10 mL) fitted with a magnetic stirrer were added phenyl 2-fluoro-2-methylpropanoate (0.2 mmol, 36.4 mg, 1 equiv), *N*-iodosuccinimide (0.22 mmol, 49.5 mmol, 1.1 equiv), silver triflimide (0.015 mmol, 5.8 mg, 0.075 equiv) and dichloromethane (4 mL) under an atmosphere of air. The reaction mixture was stirred in the dark at 40 °C. The reaction was allowed to stir at 40 °C for 15 hours. The reaction mixture was diluted with dichloromethane (15 mL) and washed with dilute aqueous solutions of sodium hydrogen carbonate (20 mL), sodium thiosulfate (20 mL), and sodium chloride (20 mL). The organic layer was dried over MgSO4 and

filtered. The solvent was removed under reduced pressure, and the product was purified by flash column, using hexanes/diethyl ether (4:1).

9. Optimization

9.1. Influence of the Amount of Silver Difluoride

	%yield
2 equiv	46
4 equiv	50
6 equiv	38
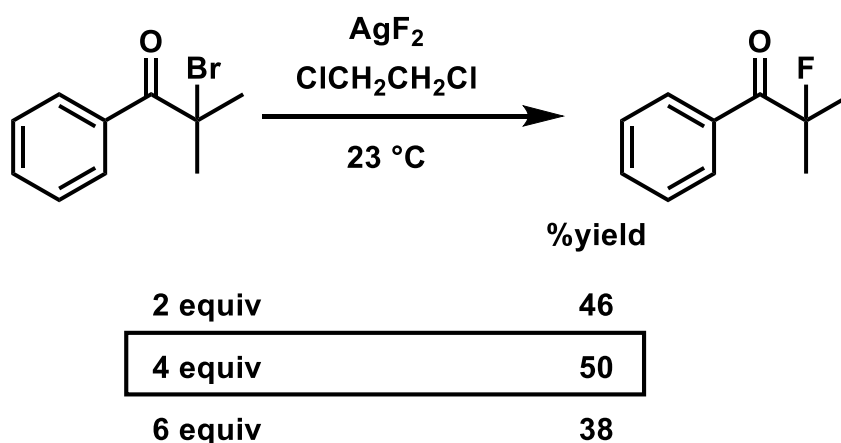
Bromide (0.119 mmol) in 1,2-dichloroethane (2 mL) at 23 °C for 14 hour.

Table 30

An oven-dried 8 mL glass vial equipped with a magnetic stirring bar, was evacuated and backfilled with nitrogen in a glovebox antechamber (three cycles). In the glovebox, specified amount of silver difluoride was added into the vial and the vial was sealed a cap equipped with a PTFE-lined rubber septum and transferred out of the glovebox. The vial was connected to a N_2-filled Schlenck line, and 2 mL 1,2-dichloroethane was added. 2-Bromoisobutyrophenone (0.119 mmol, 20.0 µL, 1 equiv) was added at once. The reaction was allowed to stir for 14 hours at 23 °C, wrapped with aluminum foil. The reaction mixture was passed through a short silica plug to remove the solid residue, and then 2×3 mL ethyl acetate was used to wash the vial

and 2×1 mL was used to wash the silica plug. The resulting solution was concentrated in vacuo. 12.0 μL α,α,α-trifluorotoluene was added into the residue as internal standard and ^{19}F NMR spectrum was taken to obtain the yield.

9.2. Influence of Solvent

solvent	%yield
ClCH$_2$CH$_2$Cl	50
CH$_2$Cl$_2$	27
CHCl$_3$	25
MeCN	7
THF	trace
1,4-dioxane	trace
heptane	N.R.
DMF	N.R.

Bromide (0.119 mmol), and fluoride source (0.476 mmol) in 2 mL specified solvent at 23 °C for 14 h
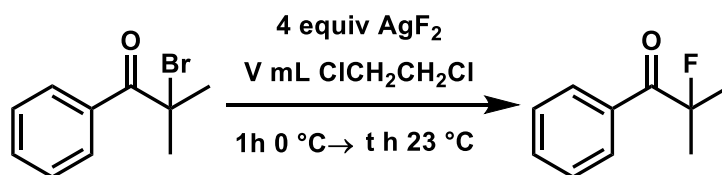
Table 31

An oven-dried 8 mL glass vial equipped with a magnetic stirring bar, was evacuated and backfilled with nitrogen in a glovebox antechamber (three cycles). In the glovebox, silver difluoride (0.476 mmol, 69.5 mg, 4 equiv) was added into the vial and the vial was sealed by a cap equipped with a PTFE-lined rubber septum and transferred out of the glovebox. The vial was connected to a N$_2$-filled Schlenck line, and 2 mL specified solvent was added. 2-

Bromoisobutyrophenone (0.119 mmol, 20.0 µL, 1 equiv) was added at once. The reaction was allowed to stir for 14 hours at 23 °C, wrapped with aluminum foil. The reaction mixture was passed through a short silica plug to remove the solid residue, and then 2×3 mL ethyl acetate was used to wash the vial and 2×1 mL was used to wash the silica plug. The resulting solution was concentrated in vacuo. 12.0 µL α,α,α-trifluorotoluene was added into the residue as internal standard and ^{19}F NMR spectrum was taken to obtain the yield.

9.3. Influence of Reaction Time under Ambient Temperature
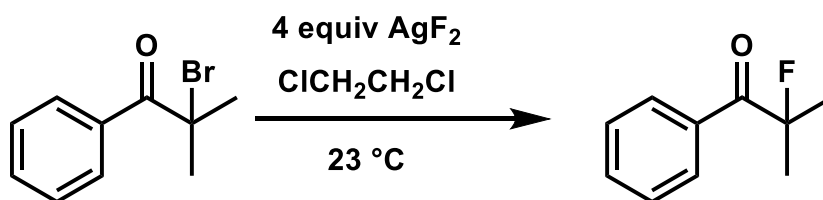
time (h)	%yield
1	43
2	45
4	41
6	43

Bromide (0.119 mmol), and fluoride source (0.476 mmol) in 1,2-dichloroethane (2 mL) at 23 °C for specified time

Table 32

An oven-dried 8 mL glass vial equipped with a magnetic stirring bar, was evacuated and backfilled with nitrogen in a glovebox antechamber (three cycles). In the glovebox, silver difluoride (0.476 mmol, 69.5 mg, 4 equiv) was added into the vial and the vial was sealed

by a cap equipped with a PTFE-lined rubber septum and transferred out of the glovebox. The vial was connected to a N$_2$-filled Schlenck line, and 2 mL 1,2-dichloroethane was added. 2-Bromoisobutyrophenone (0.119 mmol, 20.0 μL, 1 equiv) was added at once. The reaction was allowed to stir for specified time at 23 °C, wrapped with aluminum foil. The reaction mixture was passed through a short silica plug to remove the solid residue, and then 2×3 mL ethyl acetate was used to wash the vial and 2×1 mL was used to wash the silica plug. The resulting solution was concentrated in vacuo. 12.0 μL α,α,α-trifluorotoluene was added into the residue as internal standard and ^{19}F NMR spectrum was taken to obtain the yield.

9.4. Influence of Concentration (α-bromoketone As the Substrate)
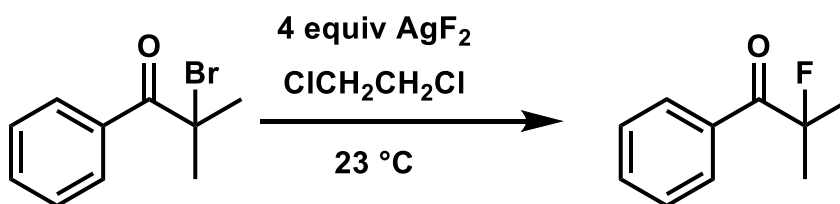
solvent volume (mL)	concentration (M)	%yield
0.05	2.38	60
0.1	1.19	58
0.2	0.60	55
0.5	0.24	45
4	0.03	38
6	0.02	22

Bromide (0.119 mmol), and fluoride source (0.476 mmol) in 1,2-dichloroethane at 23 °C for 1 h

Table 33

An oven-dried 8 mL glass vial equipped with a magnetic stirring bar, was evacuated and

backfilled with nitrogen in a glovebox antechamber (three cycles). In the glovebox, silver difluoride (0.476 mmol, 69.5 mg, 4 equiv) was added into the vial and the vial was sealed by a cap equipped with a PTFE-lined rubber septum and transferred out of the glovebox. The vial was connected to a N_2-filled Schlenck line, and specified amount of 1,2-dichloroethane was added. 2-Bromoisobutyrophenone (0.119 mmol, 20.0 μL, 1 equiv) was added at once. The reaction was allowed to stir for 1 hour at 23 °C, wrapped with aluminum foil. The reaction mixture was passed through a short silica plug to remove the solid residue, and then 2×3 mL ethyl acetate was used to wash the vial and 2×1 mL was used to wash the silica plug. The resulting solution was concentrated in vacuo. 12.0 μL α,α,α-trifluorotoluene was added into the residue as internal standard and ^{19}F NMR spectrum was taken to obtain the yield.

9.5. Influence of Reaction Time under Low Temperature

Since 0.05 mL and 0.1 mL experiments in Table 33 afforded similar yields of product, these 2 volumes were investigated in the following low temperature experiments.

t	V	%yield
0	0.05	59
1	0.05	69
2	0.05	53
3	0.05	54
0	0.1	54
1	0.1	53
2	0.1	46
3	0.1	42

Bromide (0.119 mmol), and fluoride source (0.476 mmol) in V mL 1,2-dichloroethane at 0 °C for 1 h, then at 23 °C for t h

Table 34

An oven-dried 8 mL glass vial equipped with a magnetic stirring bar, was evacuated and backfilled with nitrogen in a glovebox antechamber (three cycles). In the glovebox, silver difluoride (0.476 mmol, 69.5 mg, 4 equiv) was added into the vial and the vial was sealed a cap equipped with a PTFE-lined rubber septum and transferred out of the glovebox. The vial was connected to a N_2-filled Schlenck line. V mL 1,2-dichloroethane was added and was cooled to 0 °C for 1 min. 2-Bromoisobutyrophenone (0.119 mmol, 20.0 µL, 1 equiv) was added at once, followed by stirring for 1 hour at 0 °C. The suspension was warmed to 23 °C, wrapped with aluminum foil and stirred for additional specified time. The reaction mixture was passed through a short silica plug to remove the solid residue, and then 2×3 mL ethyl acetate was used to wash the vial and 2×1 mL was used to wash the silica plug. The resulting solution was

concentrated in vacuo. 12.0 µL α,α,α-trifluorotoluene was added into the residue as internal standard and ^{19}F NMR spectrum was taken to obtain the yield.

9.6. Influence of Concentration (Tertiary α-Bromoester As the Substrate)
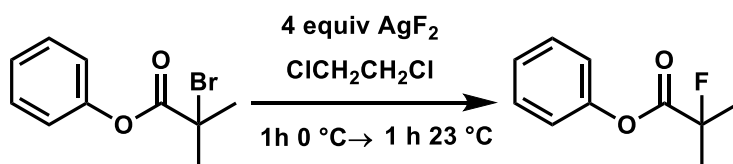
solvent volume (mL)	%yield
0.5	25
1	11
2	7
4	3

Bromide (0.238 mmol), and fluoride source (0.952 mmol) in specified volume of 1,2-dichloroethane at 0 °C for 1 h, then at 23 °C for 1 h

Table 35

An oven-dried 8 mL glass vial equipped with a magnetic stirring bar, was evacuated and backfilled with nitrogen in a glovebox antechamber (three cycles). In the glovebox, silver difluoride (139.0 mg, 0.952 mmol, 4 equiv) was added into the vial and the vial was sealed a cap equipped with a PTFE-lined rubber septum and transferred out of the glovebox. The vial was connected to a N$_2$-filled Schlenck line, and was cooled to 0 °C for 1 min. A solution of phenyl 2-bromo-2-methylpropanoate (solution in 1,2-dichloroethane, specified volume, 0.238 mmol, 1 equiv) was added at once, followed by stirring for 1 hour at 0 °C. The suspension was warmed to 23 °C, wrapped with aluminum foil and stirred for additional 1 hour. The reaction mixture was passed through a short silica plug to remove the solid residue, and then 2×3

mL ethyl acetate was used to wash the vial and 2×1 mL was used to wash the silica plug. The resulting solution was concentrated in vacuo. 12.0 μL α,α,α-trifluorotoluene was added into the residue as internal standard and ^{19}F NMR spectrum was taken to obtain the yield.

9.7. Influence of Reaction Time under Low Temperature (Tertiary α-Bromoester As the Substrate)
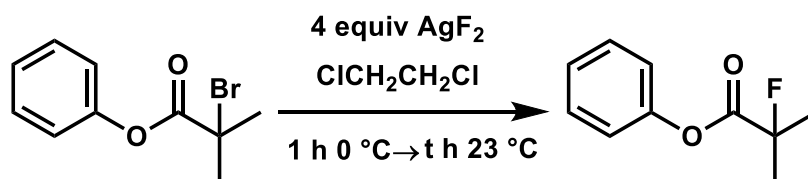
t	%yield
0.5	23
1	25
2	55
3	55
4	55

Bromide (0.238 mmol), and fluoride source (0.952 mmol) in 1,2-dichloroethane (0.5 mL) at 0 °C for 1 h, then at 23 °C for t h

Table 36

An oven-dried 8 mL glass vial equipped with a magnetic stirring bar, was evacuated and backfilled with nitrogen in a glovebox antechamber (three cycles). In the glovebox, silver difluoride (139.0 mg, 0.952 mmol, 4 equiv) was added into the vial and the vial was sealed a cap equipped with a PTFE-lined rubber septum and transferred out of the glovebox. The vial was connected to a N$_2$-filled Schlenck line, and was cooled to 0 °C for 1 min. A solution of phenyl 2-bromo-2-methylpropanoate (0.476M solution in 1,2-dichloroethane, 0.5 mL,

0.238 mmol, 1 equiv) was added at once, followed by stirring for 1 hour at 0 °C. The suspension was warmed to 23 °C, wrapped with aluminum foil and stirred for additional specified time. The reaction mixture was passed through a short silica plug to remove the solid residue, and then 2×3 mL ethyl acetate was used to wash the vial and 2×1 mL was used to wash the silica plug. The resulting solution was concentrated in vacuo. 12.0 μL α,α,α-trifluorotoluene was added into the residue as internal standard and ^{19}F NMR spectrum was taken to obtain the yield.

10. General Procedure for Fluorination of Tertiary Bromide

An oven-dried 8 mL glass vial equipped with a magnetic stirring bar, was evacuated and backfilled with nitrogen in a glovebox antechamber (three cycles). In the glovebox, silver difluoride (139.0 mg, 0.952 mmol, 4 equiv) was added into the vial and the vial was sealed a cap equipped with a PTFE-lined rubber septum and transferred out of the glovebox. The vial was connected to a N$_2$-filled Schlenck line, and was cooled to 0 °C for 1 min. A solution of tertiary bromide (0.476 M solution in 1,2-dichloroethane, 0.5 mL, 0.238 mmol, 1 equiv) was added at once, followed by stirring for 1 hour at 0 °C. The suspension was warmed to 23 °C, wrapped with aluminum foil and stirred for additional 2 hours. The reaction mixture was passed through a short silica plug to remove the solid residue, and then 2×3 mL ethyl acetate was used to wash the vial and 2×1 mL was used to wash the silica plug. The resulting solution was concentrated in vacuo. 12.0 μL α,α,α-trifluorotoluene was added into the residue as internal standard and ^{19}F NMR spectrum was taken to obtain the yield. (The residue was purified by flash chromatography on silica gel to afford the desired product.)

11. Robustness Screen Experiments

An oven-dried 8 mL glass vial equipped with a magnetic stirring bar, was evacuated and backfilled with nitrogen in a glovebox antechamber (three cycles). In the glovebox, silver difluoride (139.0 mg, 0.952 mmol, 4 equiv) was added into the vial and the vial was sealed a cap equipped with a PTFE-lined rubber septum and transferred out of the glovebox. The vial was connected to a N_2-filled Schlenck line, and was cooled to 0 °C for 1 min. A solution of tertiary bromide (0.476 M solution in 1,2-dichloroethane, 0.5 mL, 0.238 mmol, 1 equiv) and a solution of specified additive (0.476 M solution in 1,2-dichloroethane, 0.5 mL, 0.238 mmol, 1 equiv) was added at once, followed by stirring for 1 hour at 0 °C. The suspension was warmed to 23 °C, wrapped with aluminum foil and stirred for additional 2 hours. The reaction mixture was passed through a short silica plug to remove the solid residue, and then 2×3 mL ethyl acetate was used to wash the vial and 2×1 mL was used to wash the silica plug. The resulting solution was concentrated in vacuo. 12.0 μL α,α,α-trifluorotoluene and 7.0 μL CH_2Br_2 were added into the residue as internal standards. ^{1}H NMR spectrum was taken to obtain the additive recovery yield and ^{19}F NMR spectrum was taken to obtain the fluoride product yield.

4 equiv AgF$_2$

Additive

ClCH$_2$CH$_2$Cl

1 h 0 °C → 2 h 23 °C
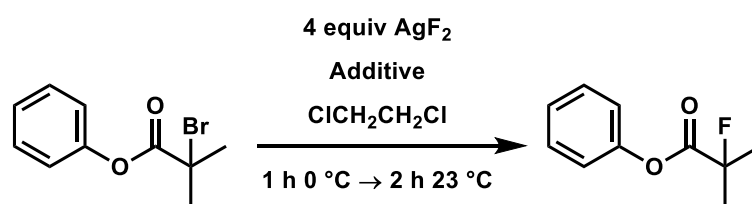
Additive	% yield	Additive recovery % yield
	42	30
	67	24
	50	7
	42	85
	19	100
	42	0
	11	0
	27	0

Bromide (0.238 mmol) in 1,2-dichloroethane (0.5 mL) and specified additive (0.238 mmol) were injected into a vial containing fluoride source (0.952 mmol). The mixture were stirred at 0 °C for 1 h, then at 23 °C for 2 h.

Table 37

12. Characterization Data of α-bromoketone
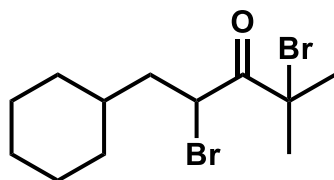
2,4-dibromo-1-cyclohexyl-4-methylpentan-3-one

The title compound was isolated as clear colorless liquid.

**TLC** (SiO$_2$) R_f = 0.41 in 4:1 hexanes/toluene, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.17 – 4.85 (m, 1H), 2.03 – 1.94 (m, 1H), 1.98 (d, *J* = 83.9 Hz, 6H), 1.84 – 1.77 (m, 3H), 1.77 – 1.60 (m, 4H), 1.50 (s, 1H), 1.34 – 1.12 (m, 4H), 1.07 – 0.82 (m, 2H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 198.21, 64.20, 43.84, 41.79, 35.19, 33.48, 32.25, 30.97, 29.23, 26.35, 26.00, 25.91.

IR (neat) 2921, 2851, 1717, 1448 cm^{-1}

GC/MS (*m/z*): 261.0 (7%), 243.9 (6%), 217.0 (21%), 199.0 (10%), 179.1 (48%), 109.1 (63%), 83.1 (90%), 55.1 (100%)
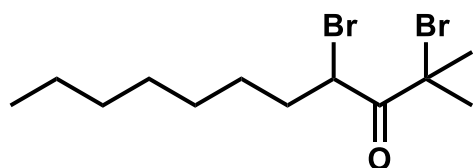
2,4-dibromo-2-methylundecan-3-one

The title compound was isolated as clear colorless liquid.

TLC (SiO$_2$) R_f = 0.40 in 4:1 hexanes/toluene, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, Chloroform-d) δ 4.95 (t, J = 7.2 Hz, 1H), 1.98 (d, J = 82.8 Hz, 6H), 1.55 –

1.17 (m, 9H), 0.88 (t, J = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-d) δ 198.04, 64.03, 45.69, 34.60, 31.70, 30.99, 29.19, 28.99,

27.31, 22.60, 14.07.

IR (neat) 2925, 2855, 1717, 1456, 1104 cm^{-1}

GC/MS (*m/z*): 263.0 (3%), 261.0 (3%), 243.9.0 (24%), 221.0 (18%), 121.0 (39%), 98.1 (60%),

84.1 (37%), 69.1 (100%),55.1 (55%)
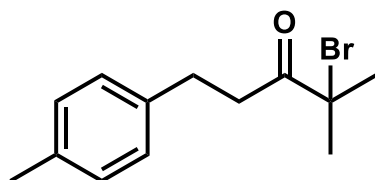
4-bromo-4-methyl-1-(p-tolyl)pentan-3-one

The title compound was isolated as clear colorless liquid.

TLC (SiO$_2$) R_f = 0.44 in 4:1 hexanes/toluene, *p*-anisaldehyde stain

¹H NMR (500 MHz, Chloroform-d) δ 7.10 (s, 4H), 3.11 (dd, J = 8.4, 6.9 Hz, 2H), 2.91 (t, J = 7.7 Hz, 2H), 2.32 (s, 3H), 1.81 (s, 6H).

¹³C NMR (126 MHz, Chloroform-d) δ 204.84, 137.75, 135.69, 129.15, 128.25, 63.81, 38.22, 30.33, 29.43, 20.99.

IR (neat) 2971, 2925, 1711, 1109, 1071, 809 cm^{-1}

GC/MS (*m/z*): 268.0 (1%), 119.1 (27%), 105.0 (100%)
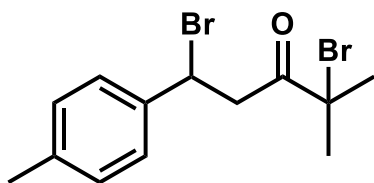
1,4-dibromo-4-methyl-1-(p-tolyl)pentan-3-one

The title compound was isolated as clear colorless liquid.

TLC (SiO$_2$) R_f = 0.41 in 4:1 hexanes/toluene, *p*-anisaldehyde stain

¹H NMR (500 MHz, Chloroform-d) δ 7.12 (d, J = 1.2 Hz, 4H), 5.08 (ddd, J = 7.9, 6.8, 1.1 Hz, 1H), 3.44 (dd, J = 14.2, 6.9 Hz, 1H), 3.27 (dd, J = 14.1, 7.8 Hz, 1H), 2.32 (d, J = 1.2 Hz, 3H), 1.99 (d, J = 1.2 Hz, 3H), 1.82 – 1.67 (m, 3H).

¹³C NMR (126 MHz, Chloroform-d) δ 198.16, 136.94, 133.73, 129.43, 129.23, 63.76, 45.81, 40.52, 28.91, 21.12.

IR (neat) 2970, 2927, 2359, 1716 cm^{-1}

GC/MS (*m/z*): 269.0 (46%), 267.0 (51%), 145.0 (46%), 117.0 (49%), 105.0 (100%)
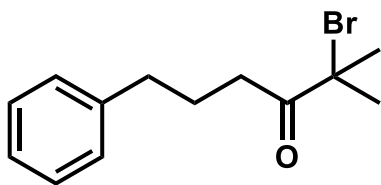
1,4-dibromo-4-methyl-1-(p-tolyl)pentan-3-one

The title compound was isolated as clear colorless liquid.

TLC (SiO$_2$) R_f = 0.43 in 4:1 hexanes/toluene, *p*-anisaldehyde stain

¹H NMR (500 MHz, Chloroform-d) δ 7.30 (t, J = 7.5 Hz, 2H), 7.21 (d, J = 7.4 Hz, 3H), 2.84 (t, J

= 7.2 Hz, 2H), 2.67 (t, J = 7.7 Hz, 2H), 2.08 – 1.93 (m, 2H), 1.85 (s, 6H).

¹³C NMR (126 MHz, Chloroform-d) δ 205.40, 141.57, 128.44, 128.37, 125.95, 63.91, 35.34,

34.97, 29.56, 26.02.

IR (neat) 3369, 2968, 1600, 1450, 1216, 1047, 777, 702 cm^{-1}

GC/MS (*m/z*): 176.1 (16%), 131.0 (68%), 105.0 (100%), 91.0 (72%), 77.0 (32%)

13. Characterization Data of α-bromoester
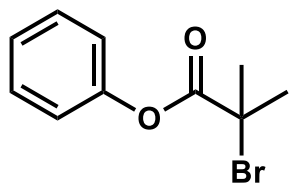
phenyl 2-bromo-2-methylpropanoate

Spectral data matches with the reported data. [318]
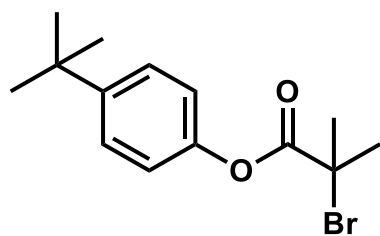
4-(tert-butyl)phenyl 2-bromo-2-methylpropanoate

The title compound was isolated as clear colorless liquid.

TLC (SiO$_2$) R_f = 0.37 in 20:1 hexanes/ethyl acetate, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, Chloroform-d) δ 7.47 – 7.33 (m, 2H), 7.10 – 6.98 (m, 2H), 2.07 (s, 6H), 1.32 (s, 9H).

^{13}C NMR (126 MHz, Chloroform-d) δ 170.38, 148.99, 148.39, 126.35, 120.27, 55.48, 34.50, 31.39, 30.65.

IR (neat) 2968, 2359, 1750, 1265, 1170, 1139, 1099 cm^{-1}

GC/MS (*m/z*): 300.0 (12%), 298.0 (12%), 285.0 (46%), 283.0 (46%), 135.1 (100%)
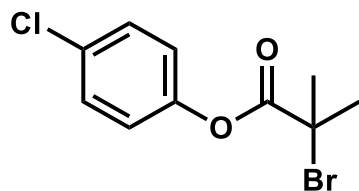
4-chlorophenyl 2-bromo-2-methylpropanoate

The title compound was isolated as clear colorless liquid.

TLC (SiO$_2$) R_f = 0.37 in 20:1 hexanes/ethyl acetate, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, Chloroform-d) δ 7.42 – 7.31 (m, 2H), 7.08 (dd, J = 8.4, 1.6 Hz, 2H), 2.06

(d, J = 1.2 Hz, 6H).

^{13}C NMR (126 MHz, Chloroform-d) δ 170.04, 149.19, 131.57, 129.56, 122.44, 55.10, 30.54.

IR (neat) 2970, 1750, 1403, 1228, 1085 cm^{-1}

GC/MS (*m/z*): 277.9 (15%), 275.9 (10%), 148.9 (22%), 128.0 (100%), 121.0 (52%)
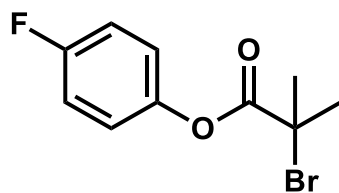
4-fluorophenyl 2-bromo-2-methylpropanoate

The title compound was isolated as clear colorless liquid.

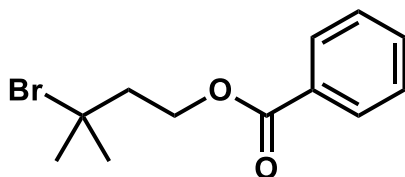**TLC** (SiO$_2$) R_f = 0.34 in 20:1 hexanes/ethyl acetate, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, Chloroform-d) δ 7.10 (s, 2H), 7.09 (d, J = 2.6 Hz, 2H), 2.06 (s, 6H).

¹³C NMR (126 MHz, Chloroform-d) δ 170.29, 161.37, 159.42, 146.53, 122.50, 122.44, 116.26, 116.07, 55.15, 30.56.

¹⁹F NMR (376 MHz, Chloroform-d) δ -116.93 (q, J = 6.4 Hz).

IR (neat) 2970, 2359, 1750, 1501, 1178, 1134, 1100 cm⁻¹

GC/MS (*m/z*): 262.0 (15%), 260.0 (15%), 151.0 (21%), 149.0 (21%), 123.0 (37%), 121.0 (37%), 112.1 (100%)
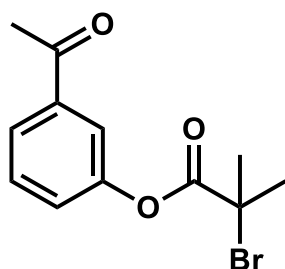
3-acetylphenyl 2-bromo-2-methylpropanoate

The title compound was isolated as clear colorless liquid.

TLC (SiO₂) *R_f* = 0.35 in 15:1 hexanes/ethyl acetate, *p*-anisaldehyde stain

¹H NMR (500 MHz, Chloroform-d) δ 7.86 (dq, J = 7.9, 1.4 Hz, 1H), 7.71 (q, J = 1.8 Hz, 1H), 7.52 (td, J = 7.9, 1.4 Hz, 1H), 7.35 (ddt, J = 8.2, 2.6, 1.2 Hz, 1H), 2.62 (d, J = 1.4 Hz, 3H), 2.08 (d, J = 1.4 Hz, 6H).

¹³C NMR (126 MHz, Chloroform-d) δ 196.84, 170.10, 150.96, 138.60, 129.76, 126.14, 125.86, 120.88, 55.03, 30.57, 26.70.

IR (neat) 2969, 2359, 1752, 1686, 1217, 1101 cm⁻¹

GC/MS (*m/z*): 286.0 (18%), 284.0 (18%), 150.9 (19%), 148.9 (19%), 121.0 (100%)
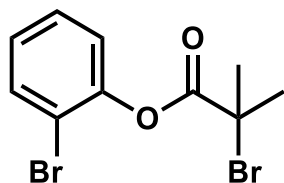
2-bromophenyl 2-bromo-2-methylpropanoate

The title compound was isolated as clear colorless liquid.

**TLC** (SiO$_2$) R_f = 0.41 in 20:1 hexanes/ethyl acetate, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, Chloroform-d) δ 7.62 (dt, J = 8.0, 1.3 Hz, 1H), 7.44 – 7.29 (m, 1H), 7.22 – 7.08 (m, 2H), 2.12 (d, J = 1.1 Hz, 6H).

^{13}C NMR (126 MHz, Chloroform-d) δ 169.31, 147.99, 133.46, 128.55, 127.63, 123.14, 115.87, 54.93, 30.81.

IR (neat) 2969, 2359, 1756, 1471, 1214, 1134, 1098 cm^{-1}

GC/MS (*m/z*): 322.0 (9%), 174.0 (100%), 172.0 (100%), 123.0 (52%), 121.0 (52%)
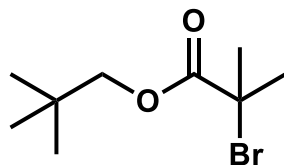
neopentyl 2-bromo-2-methylpropanoate

The title compound was isolated as clear colorless liquid.

TLC (SiO$_2$) R_f is unavailable, since it cannot be visualized on TLC plate.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.86 (s, 2H), 1.95 (s, 6H), 0.98 (s, 9H).

^{13}C NMR (126 MHz, Chloroform-d) δ 171.65, 75.09, 56.02, 31.70, 30.83, 26.35.

IR (neat) 2970, 2360, 1736, 1366, 1161 cm^{-1}

GC/MS (*m/z*): 236.9 (1%), 183.0 (34%), 181.0 (34%), 123.0 (33%), 121.0 (33%), 71.1 (84%), 57.1 (100%)
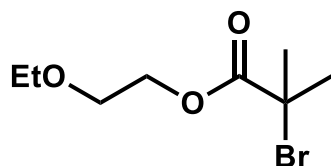
neopentyl 2-bromo-2-methylpropanoate

The title compound was isolated as clear colorless liquid.

TLC (SiO$_2$) R_f is unavailable, since it cannot be visualized on TLC plate.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.38 – 4.25 (m, 2H), 3.71 – 3.61 (m, 2H), 3.61 – 3.49 (m, 2H), 1.94 (s, 6H), 1.21 (td, *J* = 7.0, 1.4 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.65, 67.89, 66.67, 65.17, 55.70, 30.74, 15.12.

IR (neat) 2970, 2869, 2359, 1736, 1107 cm^{-1}

GC/MS (*m/z*): 238.9 (1%), 123.0 (12%), 121.0 (12%), 114.1 (30%), 72.1 (100%), 59.1 (54%)
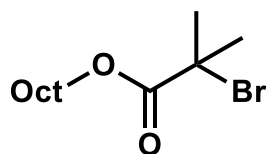
octyl 2-bromo-2-methylpropanoate

The title compound was isolated as clear colorless liquid.

TLC (SiO$_2$) R_f is unavailable, since it cannot be visualized on TLC plate.

^{1}H NMR (500 MHz, Chloroform-d) δ 4.17 (td, J = 6.6, 1.3 Hz, 2H), 1.93 (d, J = 1.3 Hz, 6H), 1.67 (q, J = 7.1 Hz, 2H), 1.45 – 1.16 (m, 10H), 0.99 – 0.81 (m, 3H).

^{13}C NMR (126 MHz, Chloroform-d) δ 171.72, 66.15, 55.98, 31.73, 30.77, 29.12, 28.33, 25.77, 22.61, 14.06.

IR (neat) 2926, 2360, 1736, 1161 cm^{-1}

GC/MS (*m/z*): 279.0 (1%), 169.0 (18%), 167.0 (18%), 123.0 (25%), 121.0 (25%), 112.1 (51%), 71.1 (93%), 57.1 (100%)
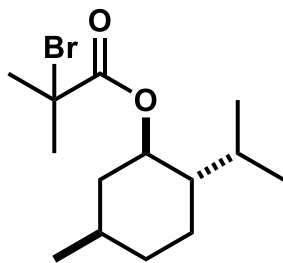
(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl 2-bromo-2-methylpropanoate

The title compound was isolated as clear colorless liquid.

TLC (SiO$_2$) R_f = 0.41 in 8:1 hexanes/ethyl acetate, *p*-anisaldehyde stain

¹H NMR (500 MHz, Chloroform-*d*) δ 4.70 (td, *J* = 10.9, 4.4 Hz, 1H), 2.08 – 1.96 (m, 2H), 1.92 (s, 6H), 1.70 (dt, *J* = 11.7, 2.9 Hz, 2H), 1.57 – 1.41 (m, 2H), 1.15 – 0.96 (m, 2H), 0.91 (dd, *J* = 6.8, 5.4 Hz, 6H), 0.77 (d, *J* = 6.9 Hz, 3H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 171.13, 75.98, 56.32, 46.99, 40.12, 34.20, 31.34, 30.77, 30.72, 26.10, 23.26, 21.98, 20.77, 16.10.

IR (neat) 2955, 2927, 2870, 1729, 1274, 1167 cm^{-1}

GC/MS (*m/z*): 156.0 (1%), 138.1 (21%), 83.1 (100%)
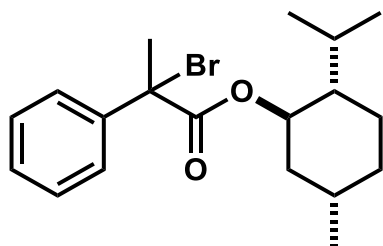
(1*R*,2*S*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-bromo-2-phenylpropanoate

The title compound was isolated as clear colorless liquid.

TLC (SiO$_2$) R_f = 0.37 in 8:1 hexanes/ethyl acetate, *p*-anisaldehyde stain

¹H NMR (500 MHz, Chloroform-*d*) δ 7.55 (dd, *J* = 7.8, 2.7 Hz, 1H), 7.38 – 7.26 (m, 4H), 4.72 (dtp, *J* = 21.2, 10.4, 5.4, 4.9 Hz, 1H), 2.29 (d, *J* = 5.2 Hz, 3H), 2.08 – 1.97 (m, 1H), 1.66 (ddt, *J* = 14.9, 11.8, 3.2 Hz, 3H), 1.11 – 0.92 (m, 2H), 0.90 (dt, *J* = 5.4, 2.7 Hz, 4H), 0.87 – 0.73 (m, 5H), 0.69 (dd, *J* = 21.5, 7.0 Hz, 3H).

13C NMR (126 MHz, Chloroform-*d*) δ 170.92, 170.40, 170.33, 141.31, 140.98, 136.84, 136.73, 75.47, 75.30, 62.64, 62.47, 54.92, 54.88, 47.09, 46.89, 46.78, 40.83, 40.26, 40.06, 39.84, 34.21, 34.13, 32.26, 32.09, 31.42, 31.38, 31.34, 31.27, 26.12, 25.74, 25.67, 23.25, 23.06, 21.99, 20.75, 20.71, 20.64, 20.52, 16.15, 15.88, 15.85.

IR (neat) 3369, 2968, 1600, 1450, 1216, 1047, 777, 702 cm^{-1}

GC/MS (*m/z*): 176.1 (16%), 131.0 (68%), 105.0 (100%), 91.0 (72%), 77.0 (32%)

14. Characterization Data of 3-bromo-3-methylbutyl benzoate

The title compound was isolated as clear colorless liquid.

TLC (SiO$_2$) R_f = 0.41 in 8:1 hexanes/ethyl acetate, *p*-anisaldehyde stain

1H NMR (500 MHz, Chloroform-*d*) δ 8.09 – 7.96 (m, 2H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 2H), 4.58 (t, *J* = 6.7 Hz, 2H), 2.31 (t, *J* = 6.7 Hz, 2H), 1.86 (s, 6H).

13C NMR (126 MHz, Chloroform-*d*) δ 166.42, 132.99, 130.10, 129.54, 128.38, 64.25, 63.08, 45.44, 34.73.

IR (neat) 2967, 1717, 1388, 1271, 1110 cm^{-1}

GC/MS (*m/z*): 206.9 (1%), 105.0 (100%), 77.1 (51%), 69.1 (60%)

15. Characterization Data of α-fluoroketone
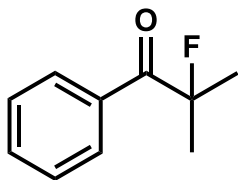
2-fluoro-2-methyl-1-phenylpropan-1-one

Spectral data matches with the reported data.
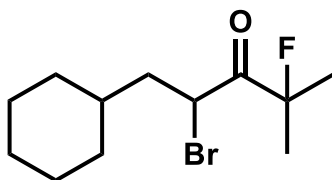
2-bromo-1-cyclohexyl-4-fluoro-4-methylpentan-3-one

The title compound was prepared with a ^{19}F NMR yield of 47%, and was isolated as clear colorless liquid (44%, 29.2 mg).

TLC (SiO$_2$) R_f = 0.35 in 4:1 hexanes/toluene, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.19 – 4.81 (m, 1H), 2.17 – 1.82 (m, 2H), 1.82 – 1.59 (m, 8H), 1.59 – 1.33 (m, 5H), 1.18 (d, *J* = 46.6 Hz, 4H), 1.07 – 0.71 (m, 2H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 205.59, 98.56 (d, *J* = 181.8 Hz), 42.83, 40.21, 35.61, 33.16, 32.45, 26.31, 25.99 (d, *J* = 16.9 Hz), 24.90, 24.71.

¹⁹F NMR (376 MHz, Chloroform-*d*) δ -149.80 – -150.08 (m, 1F).

IR (neat) 3369, 2968, 1600, 1450, 1216, 1047, 777, 702 cm⁻¹

GC/MS (*m/z*): 176.1 (16%), 131.0 (68%), 105.0 (100%), 91.0 (72%), 77.0 (32%)
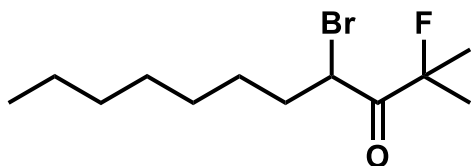
4-bromo-2-fluoro-2-methylundecan-3-one

The title compound was prepared with a ¹⁹F NMR yield of 46%, and was isolated as clear colorless liquid (42%, 28.1 mg).

**TLC** (SiO$_2$) R_f = 0.33 in 4:1 hexanes/toluene, *p*-anisaldehyde stain

¹H NMR (500 MHz, Chloroform-*d*) δ 4.84 (td, *J* = 7.3, 2.1 Hz, 1H), 2.14 – 1.87 (m, 2H), 1.68 (d, *J* = 21.5 Hz, 2H), 1.53 – 1.39 (m, 4H), 1.39 – 1.15 (m, 10H), 0.88 (t, *J* = 7.1 Hz, 3H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 205.50, 44.71, 33.01, 31.66, 28.97, 27.30, 26.27, 24.58, 22.57, 14.04.

¹⁹F NMR (376 MHz, Chloroform-*d*) δ -149.96 – -150.17 (m, 1F).

IR (neat) 3369, 2968, 1600, 1450, 1216, 1047, 777, 702 cm⁻¹

GC/MS (*m/z*): 176.1 (16%), 131.0 (68%), 105.0 (100%), 91.0 (72%), 77.0 (32%)
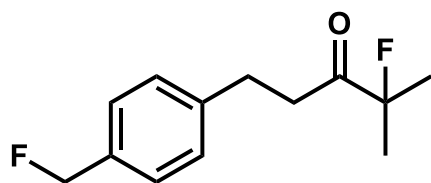
4-fluoro-1-(4-(fluoromethyl)phenyl)-4-methylpentan-3-one

The title compound was prepared with a 19F NMR yield of 55%, and was isolated as clear colorless liquid (48%, 25.8 mg).

**TLC** (SiO$_2$) R_f = 0.34 in 4:1 hexanes/toluene, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.36 – 7.27 (m, 2H), 7.23 (d, *J* = 7.8 Hz, 2H), 5.34 (d, *J* = 48.0 Hz, 2H), 3.08 – 2.87 (m, 4H), 1.42 (d, *J* = 21.3 Hz, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 211.33, 141.72, 134.07, 128.58, 127.91, 98.89 (d, *J* = 178.9 Hz), 84.47 (d, *J* = 165.5 Hz), 37.91, 28.70, 23.97, 15.26.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -137.77 – -169.55 (m, 1F), -205.36 (t, *J* = 47.9 Hz, 1F).

IR (neat) 3369, 2968, 1600, 1450, 1216, 1047, 777, 702 cm^{-1}

GC/MS (*m/z*): 176.1 (16%), 131.0 (68%), 105.0 (100%), 91.0 (72%), 77.0 (32%)
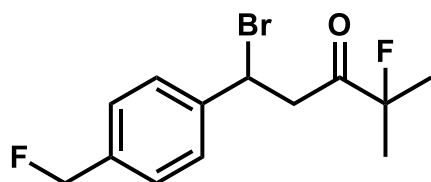
1-bromo-4-fluoro-1-(4-(fluoromethyl)phenyl)-4-methylpentan-3-one

The title compound was prepared with a ^{19}F NMR yield of 15%, and was isolated as clear colorless liquid (44%, 31.9 mg).

TLC (SiO$_2$) R_f = 0.31 in 4:1 hexanes/toluene, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.30 (d, *J* = 6.9 Hz, 2H), 7.28 – 7.14 (m, 2H), 5.33 (d, *J* = 47.8 Hz, 2H), 5.04 (d, *J* = 6.9 Hz, 1H), 3.67 – 3.00 (m, 4H), 1.62 (d, *J* = 21.5 Hz, 3H), 1.13 (d, *J* = 21.5 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 204.63, 137.60, 135.13, 129.66, 127.82, 98.37 (d, *J* = 181.7 Hz), 84.19 (d, *J* = 166.4 Hz), 42.80, 38.90, 26.15, 24.07.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -141.92 – -159.86 (m, 1F), -207.46 (m, 1F).

IR (neat) 3369, 2968, 1600, 1450, 1216, 1047, 777, 702 cm^{-1}

GC/MS (*m/z*): 176.1 (16%), 131.0 (68%), 105.0 (100%), 91.0 (72%), 77.0 (32%)
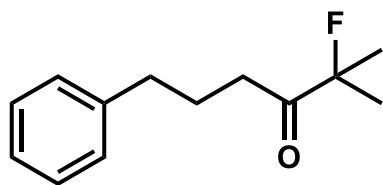
2-fluoro-2-methyl-6-phenylhexan-3-one

The title compound was prepared with a ^{19}F NMR yield of 41%, and was isolated as clear colorless liquid (45%, 22.3 mg).

TLC (SiO$_2$) R_f = 0.37 in 4:1 hexanes/toluene, *p*-anisaldehyde stain

¹H NMR (500 MHz, Chloroform-*d*) δ 8.03 (d, *J* = 7.9 Hz, 1H), 7.61 (t, *J* = 7.2 Hz, 1H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.39 (m, 2H), 3.61 – 2.89 (m, 2H), 1.59 (d, *J* = 7.4 Hz, 6H), 1.53 – 1.15 (m, 4H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 202.52, 133.18, 128.61, 128.05, 31.65, 30.58, 24.35, 24.16.

¹⁹F NMR (376 MHz, Chloroform-*d*) δ -149.51 (d, *J* = 21.8 Hz, 1F).

IR (neat) 3369, 2968, 1600, 1450, 1216, 1047, 777, 702 cm⁻¹

GC/MS (*m/z*): 176.1 (16%), 131.0 (68%), 105.0 (100%), 91.0 (72%), 77.0 (32%)

16. Characterization Data of α-fluoroester
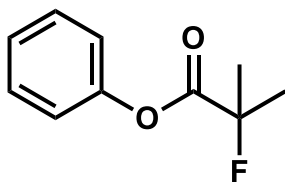
phenyl 2-fluoro-2-methylpropanoate

The title compound was prepared with a ¹⁹F NMR yield of 55%, and was isolated as clear colorless liquid (61%, 26.4 mg).

TLC (SiO₂) R_f = 0.30 in 4:1 hexanes/diethyl ether, *p*-anisaldehyde stain

¹H NMR (500 MHz, Chloroform-*d*) δ 7.45 – 7.33 (m, 2H), 7.29 – 7.24 (m, 1H), 7.18 – 7.02 (m, 2H), 1.75 (d, *J* = 21.1 Hz, 6H).

¹³C NMR (126 MHz, Chloroform-d) δ 170.69, 150.27, 129.52, 126.21, 121.17, 92.64 (d, J =

182.7 Hz), 24.88.

^{19}F NMR (376 MHz, Chloroform-d) δ -147.66 – -147.92 (m, 1F).

IR (neat) 2991, 2918, 2358, 1775, 1191, 1162, 1116 cm^{-1}

GC/MS (*m/z*): 182.0 (6%), 112.0 (5%), 94.0 (100%), 77.0 (5%), 61.0 (20%)
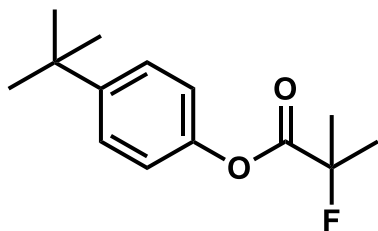
4-(tert-butyl)phenyl 2-fluoro-2-methylpropanoate

The title compound was prepared with a ^{19}F NMR yield of 46%, and was isolated as clear colorless liquid (40%, 22.7 mg).

TLC (SiO$_2$) R_f = 0.29 in 4:1 hexanes/diethyl ether, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, Chloroform-d) δ 7.40 (d, *J* = 8.7 Hz, 2H), 7.07 – 6.97 (m, 2H), 1.82 – 1.65 (m, 6H), 1.32 (s, 9H).

^{13}C NMR (126 MHz, Chloroform-d) δ 147.91, 126.40, 120.44, 92.65 (d, J = 182.4 Hz), 34.50, 31.37, 24.89.

^{19}F NMR (376 MHz, Chloroform-d) δ -140.47 – -159.35 (m, 1F).

IR (neat) 2962, 2870, 1778, 1206, 1106 cm^{-1}

GC/MS (*m/z*): 238.1 (8%), 223.1 (5%), 205.1 (2%), 150.1 (9%), 135.1 (100%), 107.0 (13%)
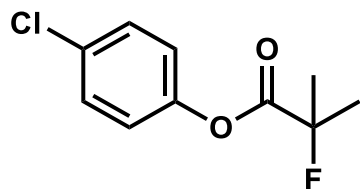
4-chlorophenyl 2-fluoro-2-methylpropanoate

The title compound was prepared with a ^{19}F NMR yield of 44%, and was isolated as clear colorless liquid (59%, 30.4 mg).

TLC (SiO$_2$) R_f = 0.28 in 4:1 hexanes/diethyl ether, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.37 (d, *J* = 8.9 Hz, 2H), 7.13 – 6.98 (m, 2H), 1.74 (dd, *J* = 21.1, 2.9 Hz, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.69, 148.71, 131.67, 129.60, 122.57, 92.61 (d, *J* = 183.2 Hz), 25.04.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -139.78 – -165.46 (m, 1F).

IR (neat) 2992, 2918, 2849, 2359, 1778, 1487, 1163, 1116, 1089 cm^{-1}

GC/MS (*m/z*): 216.0 (5%), 207.0 (2%), 128.0 (100%), 61.1 (24%)
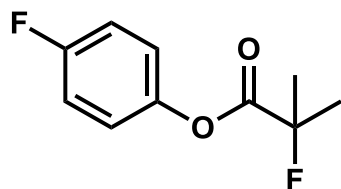
4-fluorophenyl 2-fluoro-2-methylpropanoate

The title compound was prepared with a 19F NMR yield of 55%, and was isolated as clear colorless liquid (59%, 28.1 mg).

TLC (SiO$_2$) R_f = 0.24 in 4:1 hexanes/diethyl ether, *p*-anisaldehyde stain

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.09 (d, *J* = 6.2 Hz, 4H), 1.74 (d, *J* = 21.1 Hz, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.72, 161.38, 159.44, 146.04, 122.59, 116.12, 93.34, 91.89, 24.85.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -116.78 (t, *J* = 6.5 Hz, 1F), -147.82 (p, *J* = 21.1 Hz, 1F).

IR (neat) 3083, 2992, 2917, 2358, 1777, 1502, 1179, 1152, 1114 cm^{-1}

GC/MS (*m/z*): 200.0 (5%), 112.0 (100%), 61.1 (18%)
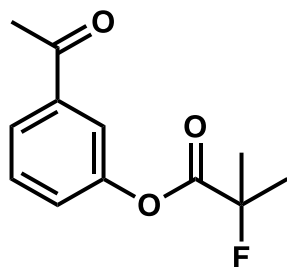
3-acetylphenyl 2-fluoro-2-methylpropanoate

The title compound was prepared with a ^{19}F NMR yield of 69%, and was isolated as pale yellow colorless liquid.

TLC (SiO$_2$) R_f = 0.20 in 4:1 hexanes/diethyl ether, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.86 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.70 (t, *J* = 2.0 Hz, 1H), 7.52 (t, *J* = 7.9 Hz, 1H), 7.34 (ddd, *J* = 8.1, 2.4, 1.0 Hz, 1H), 2.62 (s, 3H), 1.77 (d, *J* = 21.1 Hz, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 196.79, 170.75, 150.51, 138.63, 129.80, 126.01, 121.00, 92.62 (d, *J* = 183.2 Hz), 26.68, 24.87.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -147.80 (p, *J* = 20.9 Hz, 1F).

IR (neat) 2992, 2919, 1775, 1686, 1259, 1112 cm^{-1}

GC/MS (*m/z*): 224.0 (7%), 208.9 (1%), 136.0 (39%), 121.0 (100%), 66.1 (27%)
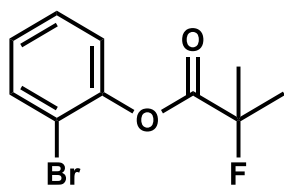
2-bromophenyl 2-bromo-2-methylpropanoate

The title compound was prepared with a ^{19}F NMR yield of 41%, and was isolated as clear colorless liquid.

TLC (SiO$_2$) R_f = 0.28 in 4:1 hexanes/diethyl ether, *p*-anisaldehyde stain

¹H NMR (500 MHz, Chloroform-*d*) δ 7.63 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.41 – 7.28 (m, 1H), 7.21 – 7.12 (m, 2H), 1.81 (d, *J* = 21.2 Hz, 6H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 169.87, 147.57, 133.54, 128.59, 127.74, 123.44, 92.78 (d, *J* = 182.8 Hz), 24.99.

¹⁹F NMR (376 MHz, Chloroform-*d*) δ -147.37 (p, *J* = 21.3 Hz, 1F).

IR (neat) 2991, 2941, 1783, 1470, 1209, 1123, 1103 cm⁻¹

GC/MS (*m/z*): 261.9 (4%), 259.9 (4%), 173.9 (95%), 171.9 (100%), 61.1 (30%)
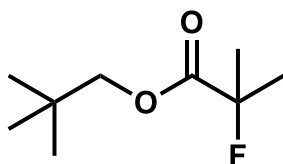
neopentyl 2-fluoro-2-methylpropanoate

The title compound was prepared with a ¹⁹F NMR yield of 48%, and was isolated as clear colorless liquid.

TLC (SiO₂) R_f is unavailable, since it cannot be visualized on TLC plate.

¹H NMR (500 MHz, Chloroform-*d*) δ 3.88 (s, 2H), 1.60 (dd, *J* = 21.1, 0.7 Hz, 6H), 0.96 (d, *J* = 0.7 Hz, 9H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 172.18, 92.66 (d, *J* = 180.7 Hz), 31.51, 26.30, 24.92.

¹⁹F NMR (376 MHz, Chloroform-*d*) δ -147.31 – -147.49 (m, 1F).

IR (neat) 2960, 2872, 1758, 1742, 1150 cm^{-1}

GC/MS (*m/z*): 161.1 (1%), 121.0 (14%), 71.1 (61%), 57.1 (100%)
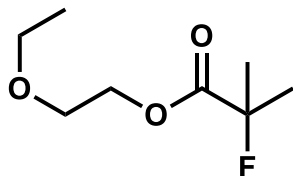
2-ethoxyethyl 2-fluoro-2-methylpropanoate

The title compound was prepared with a ^{19}F NMR yield of 50%, and was isolated as clear colorless liquid.

TLC (SiO$_2$) R_f is unavailable, since it cannot be visualized on TLC plate.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.56 – 4.17 (m, 2H), 3.66 (ddd, *J* = 6.1, 3.9, 1.6 Hz, 2H), 3.60 – 3.39 (m, 2H), 1.60 (dd, *J* = 21.2, 1.0 Hz, 6H), 1.27 – 0.70 (m, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 68.00, 66.62, 64.50, 25.07, 24.83, 15.08.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -147.81 (p, *J* = 21.2 Hz, 1F).

IR (neat) 2977, 2925, 2871, 2359, 1756, 1741, 1157 cm^{-1}

GC/MS (*m/z*): 133.0 (20%), 72.0 (76%), 60.1 (86%), 59.1 (100%)
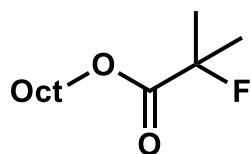
octyl 2-fluoro-2-methylpropanoate

The title compound was prepared with a ^{19}F NMR yield of 63%, and was isolated as clear colorless liquid (51%, 28.2 mg).

TLC (SiO$_2$) R_f is unavailable, since it cannot be visualized on TLC plate.

TLC (SiO$_2$) R_f = 0.41 in 4:1 hexanes/toluene, p-anisaldehyde stain

^{1}**H NMR** (400 MHz, Chloroform-d) δ 4.17 (t, J = 6.8 Hz, 2H), 1.78 – 1.64 (m, 3H), 1.58 (d, J = 21.2 Hz, 6H), 1.45 – 1.16 (m, 12H), 0.88 (t, J = 6.5 Hz, 3H).

^{13}**C NMR** (126 MHz, Chloroform-d) δ 172.51, 92.72 (d, J = 181.4 Hz), 65.66, 52.99, 31.73, 29.11, 28.47, 25.74, 24.88, 22.60, 14.05.

^{19}**F NMR** (376 MHz, Chloroform-d) δ -147.80 (p, J = 21.2, 20.7 Hz, 1F).

IR (neat) 2956, 2927, 2857, 2359, 1756, 1738, 1159 cm^{-1}

GC/MS (m/z): 157.1 (3%), 107.0 (23%), 84.1 (30%), 72.0 (85%), 57.1 (100%)
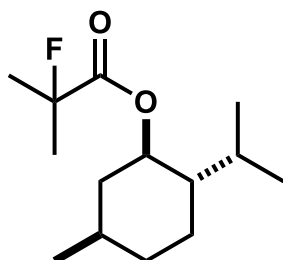
(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-fluoro-2-methylpropanoate

The title compound was prepared with a ^{19}F NMR yield of 39%, and was isolated as clear colorless liquid.

TLC (SiO$_2$) R_f = 0.20 in 4:1 hexanes/diethyl ether, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.75 (td, *J* = 11.0, 4.5 Hz, 1H), 2.06 – 1.79 (m, 2H), 1.78 – 1.65 (m, 2H), 1.58 (dt, *J* = 21.2, 3.1 Hz, 6H), 1.51 – 1.35 (m, 1H), 1.15 – 0.97 (m, 2H), 0.91 (t, *J* = 6.5 Hz, 6H), 0.76 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 171.81, 92.68 (d, *J* = 181.1 Hz), 46.89, 40.53, 34.15, 31.36, 26.23, 24.78, 23.29, 21.95, 20.72, 16.07.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -147.60 (p, *J* = 21.3 Hz, 1F).

IR (neat) 3369, 2968, 1600, 1450, 1216, 1047, 777, 702 cm^{-1}

GC/MS (*m/z*): 155.0 (1%), 138.1 (30%), 123.1 (25%), 109.1 (5%), 96.1 (60%), 83.1 (100%), 69.1 (38%), 55.1 (40%)
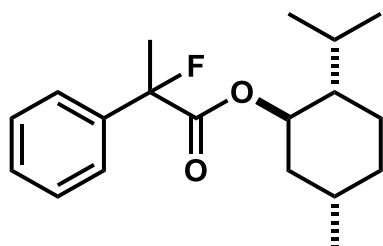
(1*R*,2*S*,5*S*)-2-isopropyl-5-methylcyclohexyl 2-bromo-2-phenylpropanoate

The title compound was prepared with a ^{19}F NMR yield of 49%, and was isolated as clear

colorless liquid. 1.25:1 d.r. was obtained, determined by ^{1}H NMR.

TLC (SiO$_2$) R_f = 0.20 in 4:1 hexanes/diethyl ether, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.56 – 7.46 (m, 2H), 7.36 (dt, *J* = 12.3, 7.1 Hz, 3H), 4.81 – 4.65 (m, 1H), 1.92 (dd, *J* = 22.2, 4.7 Hz, 6H), 1.65 (d, *J* = 12.2 Hz, 4H), 1.54 – 1.24 (m, 4H), 1.00 (d, *J* = 12.0 Hz, 1H), 0.97 – 0.82 (m, 6H), 0.76 (dd, *J* = 21.4, 7.0 Hz, 3H), 0.59 (dd, *J* = 14.9, 7.1 Hz, 3H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.58, 170.37, 139.32, 128.52, 128.42, 128.30, 128.13, 124.79, 124.73, 124.47, 124.40, 94.41 (d, *J* = 187.8 Hz), 46.95, 40.37, 40.26, 34.14, 31.35, 25.95, 25.82, 24.21, 24.03, 23.21, 21.93, 20.63, 20.58, 15.90.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -149.92 (d, *J* = 22.4 Hz), -152.15. (two diastereomers)

IR (neat) 2955, 2931, 2359, 1754, 1732, 1181, 1161 cm^{-1}

GC/MS (*m/z*): 176.1 (16%), 131.0 (68%), 105.0 (100%), 91.0 (72%), 77.0 (32%)

17. **Characterization Data of 3-fluoro-3-methylbutyl benzoate**
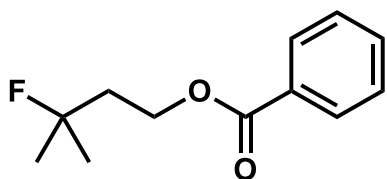
The title compound was prepared with a ^{19}F NMR yield of 73%, and was isolated as clear colorless liquid.

TLC (SiO$_2$) R_f = 0.34 in 8:1 hexanes/ethyl acetate, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.07 (dt, *J* = 7.9, 1.9 Hz, 2H), 7.69 – 7.56 (m, 1H), 7.56 – 7.41 (m, 2H), 4.80 – 4.44 (m, 2H), 2.16 (dtd, *J* = 19.4, 8.7, 7.6, 4.2 Hz, 2H), 1.63 – 1.41 (m, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 166.52, 132.97, 130.23, 129.55, 128.40, 94.28 (d, *J* = 165.7 Hz), 39.96, 27.21.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -138.52 (dq, *J* = 41.8, 20.7 Hz, 1F).

IR (neat) 3369, 2968, 1600, 1450, 1216, 1047, 777, 702 cm^{-1}

GC/MS (*m/z*): 176.1 (16%), 131.0 (68%), 105.0 (100%), 91.0 (72%), 77.0 (32%)

18. **Characterization Data of 2-fluoro-2-methyl-1-(pyrrolidin-1-yl)propan-1-one**
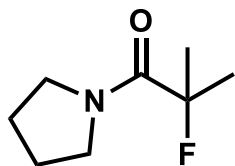
The title compound was isolated as clear colorless liquid (89%, 26.9 mg).

TLC (SiO$_2$) R_f is unavailable.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 3.82 – 3.04 (m, 4H), 1.86 (dt, *J* = 60.2, 6.8 Hz, 4H), 1.59 (d, *J* = 21.9 Hz, 6H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 170.90, 96.36 (d, *J* = 181.8 Hz), 47.69, 47.17, 36.62, 26.88, 25.39, 23.16.

¹⁹F NMR (376 MHz, Chloroform-*d*) δ -146.61 (p, *J* = 22.0 Hz, 1F).

IR (neat) 3369, 2968, 1600, 1450, 1216, 1047, 777, 702 cm⁻¹

GC/MS (*m/z*): 176.1 (16%), 131.0 (68%), 105.0 (100%), 91.0 (72%), 77.0 (32%)

19. **Characterization Data of (*E*)-3,7-dimethylocta-2,6-dien-1-yl 2-fluoro-2-methylpropanoate**
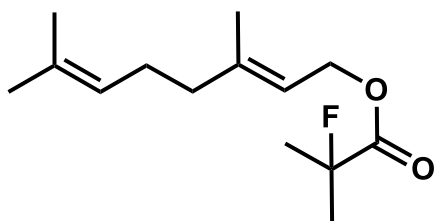
The title compound was isolated as clear colorless liquid (92%, 44.5 mg).

TLC (SiO₂) *R*ᶠ = 0.28 in 8:1 hexanes/ethyl acetate, *p*-anisaldehyde stain

¹H NMR (500 MHz, Chloroform-*d*) δ 5.53 – 5.21 (m, 1H), 5.18 – 4.97 (m, 1H), 4.69 (d, *J* = 7.1 Hz, 2H), 2.29 – 1.78 (m, 4H), 1.82 – 1.64 (m, 6H), 1.60 (s, 6H), 1.55 (s, 3H).

¹³C NMR (126 MHz, Chloroform-*d*) δ 172.24, 143.05, 131.84, 123.59, 117.67, 92.77 (d, *J* = 181.7 Hz), 62.36, 39.47, 26.19, 25.64, 24.86, 17.65, 16.47.

¹⁹F NMR (376 MHz, Chloroform-*d*) δ -147.76 (p, *J* = 21.2 Hz, 1F).

IR (neat) 2986, 2927, 2856, 1756, 1737, 1145 cm⁻¹

GC/MS (*m/z*): 242.1 (1%), 136.1 (10%), 93.1 (21%), 69.1 (100%)

20. **Characterization Data of 4-iodophenyl 2-fluoro-2-methylpropanoate**
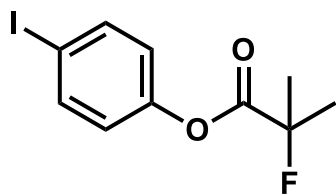
The title compound was isolated as clear colorless liquid (84%, 51.7 mg).

TLC (SiO$_2$) R_f = 0.26 in 4:1 hexanes/diethyl ether, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.71 (d, *J* = 8.3 Hz, 2H), 6.89 (d, *J* = 8.3 Hz, 2H), 1.73 (d, *J* = 21.1 Hz, 6H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 170.56, 150.12, 138.59, 123.37, 92.61 (d, *J* = 183.1 Hz), 90.31, 25.03.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -147.79 (p, *J* = 21.2 Hz, 1F).

IR (neat) 2991, 2918, 2358, 1775, 1191, 1162, 1116 cm^{-1}

GC/MS (*m/z*): 182.0 (6%), 112.0 (5%), 94.0 (100%), 77.0 (5%), 61.0 (20%)

Chapter IV. Synthesis of 2,3-Difluoro-2,3-dihydrobenzofuran

1. Property of Benzofuran

Benzofuran is the heterocyclic compound consisting of fused benzene and furan rings.

Many bioactive molecules as well as pharmaceuticals, molecular electronic and functional polymers consist of benzofuran as their cores.[320-321]

In spite of the significance of benzofurans in medicinal development, the functionalization of benzofurans remains undeveloped at some extent. Currently, known examples of benzofuran transformations focus on 2,3 functionalization[322-325] as well as 2-position deprotonation[326-329] and 3-position electrophilic aromatic substitution.[330-332] Records of benzofuran derived aryne also show another category of benzofuran reactivity.[333]

2. 2-Position Fuctionalization

This might be the most explored category of benzofuran chemistry. Conventionally, due to the relatively low pKa of 2-H (32.7 in DMSO at 25 °C),[334] people can relatively conveniently and selectively deprotonate that position and use proper electrophiles to make functionalization possible, by using alkyl lithiums with or without TMEDA, or using lithium amide bases. For example, tetracycle in Scheme 79 could be synthesized with a route started from benzofuran. The initial step was deprotonation of C2 on benzofuran with n-BuLi and treatment of DMF, forming benzofuran-2-carbaldehyde (Scheme 79).[326] In addition, the synthesis of 2-benzofuranylboronic acid could be accomplished with a similar manner, by treating benzofuran with nBuLi followed by triisopropyl borate.[327] The resulting boronic acid is a powerful handle to
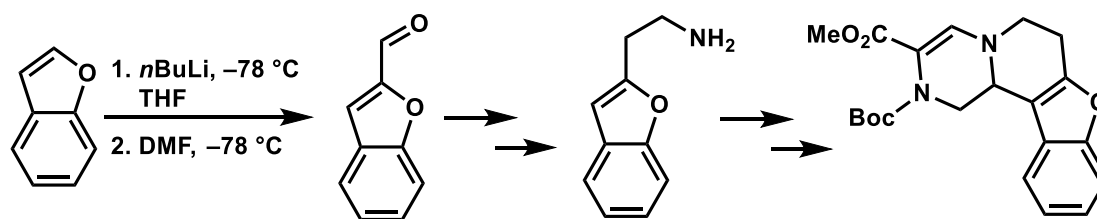
Scheme 79

obtain diversified functionality.[335-336]

Metalation of C2 on benzofuran followed by cross coupling or nucleophilic addition could also be useful tools for benzofuran 2-position functionalization. Zincation of benzofuran using ZnCl$_2$·TMEDA/LiTMP and subsequent cross coupling with aryl chloride was reported by Mongin and his co-workers (Scheme 80).[328] Zincate at the C2 position of benzofuran was
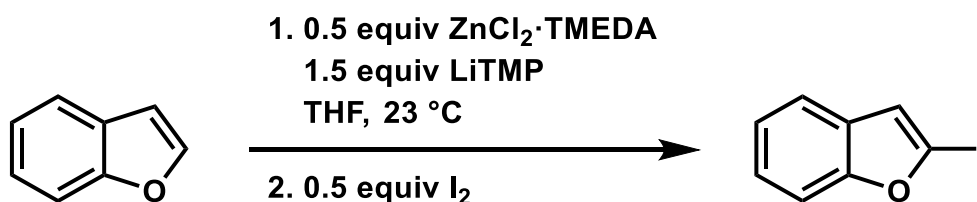
Scheme 80

prepared at room temperature by using a mixed base generated in situ from a 1:3 mixture of ZnCl$_2$·TMEDA/LiTMP. This sequence could readily install a variety of functionality on 2-position.

With the initial reaction occurring at the less electron-rich carbon atom, C2-selective cross-coupling of polybromobenzofuran is also feasible. 2,3-dibromobenzofuran could be sequentially functionalized at the C2 position and then the C3 position in a one-pot fashion in a (Ph$_3$P)$_4$Pd-catalyzed Suzuki–Miyaura coupling reaction using two different aryl boronic acids

(Scheme 81).[329] Negishi and Sonogashira couplings also occurred at the C2 position of 2,3,5-tribromobenzofuran first. However, it was more challenging to differentiate the C3 and C5
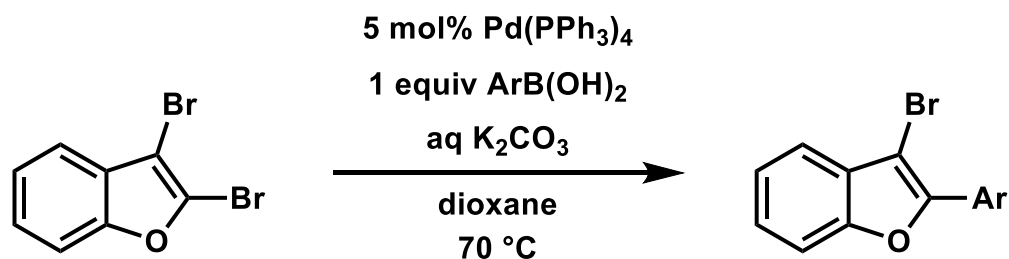
Scheme 81

positions by a palladium-catalyzed coupling. This was solved by a lithium–bromide exchange with *t*-BuLi that occurred selectively at the C3 position or by a nickel-catalyzed C5-selective Kumada coupling (Scheme 82).[337]
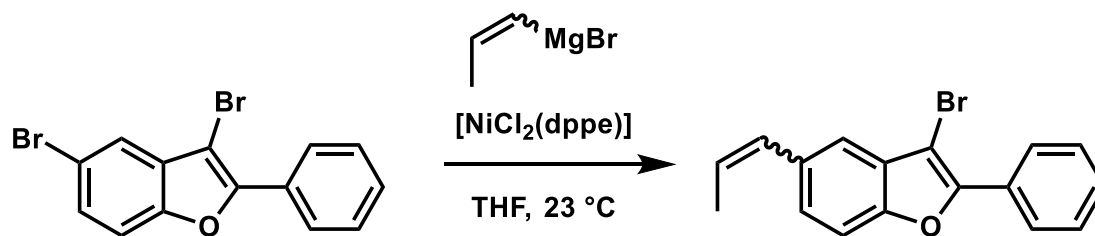
Scheme 82

3. 3-Position Electrophilic Aromatic Substitution

Friedel–Crafts aroylation of benzofuran derivatives with 4-methoxy benzoyl chloride in SnCl₄ afforded the corresponding methanones (Scheme 83).[330] This Friedel–Crafts aroylation
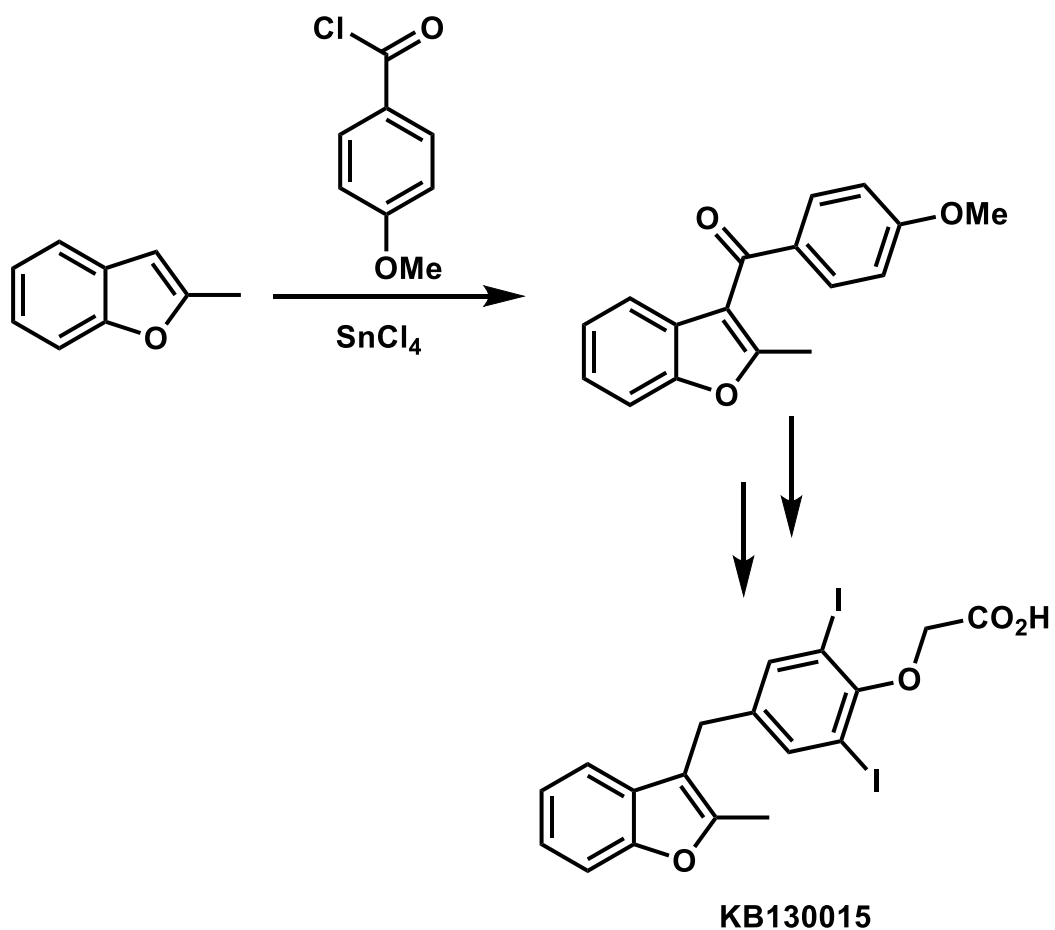
Scheme 83

was applied in initial steps of synthesis of a novel antiarrhythmic compound (KB130015). 2-position reaction site has to be blocked to improve the yield.

Similarly, a 3-position bromination was accomplished by blocking 2-position with a methyl group. Treated with NBS, 2-methyl benzofuran was converted to 3-bromo-2-methyl-benzofuran (Scheme 84).[331]
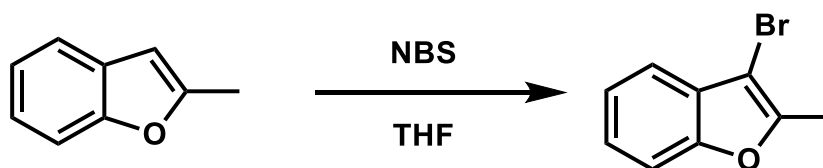
Scheme 84

Unlike the examples of Friedel–Crafts reaction[330] and bromination[331], the Yb-catalyzed electrophilic substitution of benzofuran introduced by Wang and his co-worker, did not require a substituent to block the 2 position (Scheme 85). The α-hydroxy ester was built in a regioselective manner.[332]
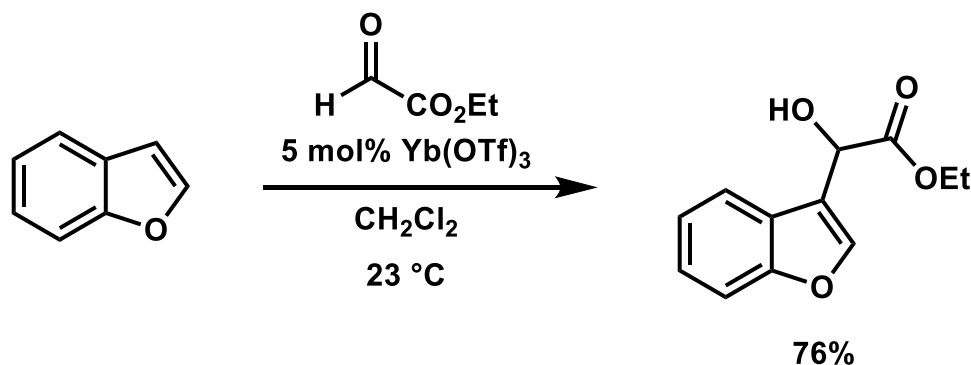
Scheme 85

4. 2,3-Benzofuryne

In 1902, Stoermer and Kahlert observed the formation of 2-ethoxybenzofuran on treatment of 3-bromobenzofuran with bases in ethanol and hypothesized the formation of *ortho-*didehydrobenzofuran (2,3-didehydrobenzofuran) as a reactive intermediate (Scheme 86).[333]
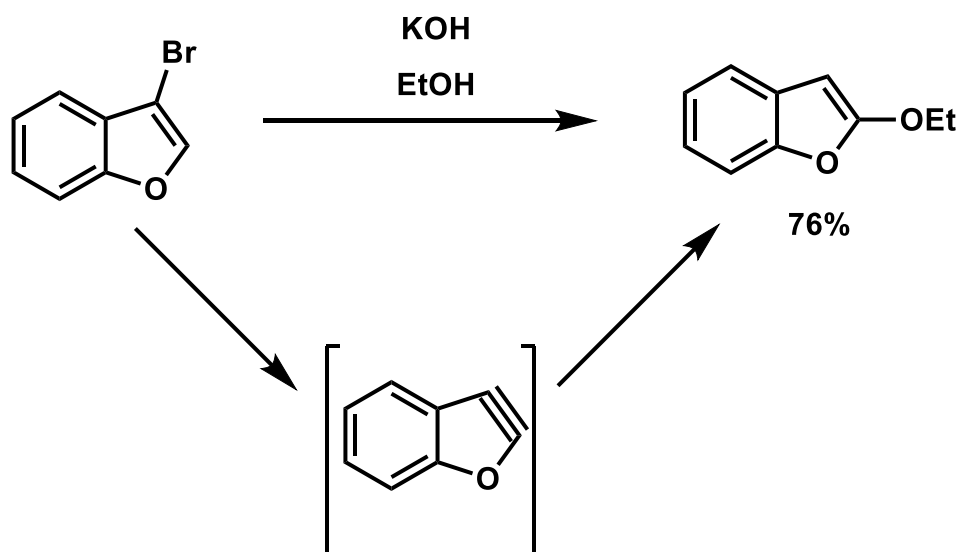
Scheme 86

Although it was the first proposal of an aryne in the literature, people seem to overlook this type of aryne and did not provide a solid evidence of 2,3-benzofuryne.

5. 2,3 Functionalization

Benzofuran is an aromatic system, however, its C=C double bond between 2- and 3-positions still inherits part of benzofuran's parent molecule, furan's chemical properties (since the degree of aromaticity of benzofuran is not very high, naphthalene (33.6) > benzothiophene (24.8) > indole (23.8) > benzofuran (20.3)).[338-339] For example, addition reaction can happen on benzofurans when treated with bromine. In their total synthesis of eupomatenoids 3, 4, 5, 6, and 15, Bach and his co-worker prepared their substrate 2,3-dibromo-2,3-dihydrobenzofuran from the reaction between bromine and benzofuran (Scheme 87).[322]
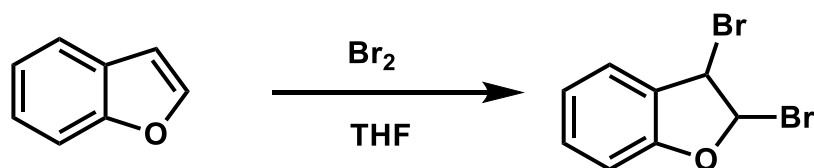
Scheme 87

Catalytic hydrogenation of benzofurans under most common conditions is accompanied by partial cleavage of the furan ring and formation of 2-ethylcyclohexanol and β-cyclohexylethyl alcohol. For example, in 1959, Oliver and their co-workers found that in liquid ammonia, 2-methylbenzofuran and the corresponding dihydro compound were reduced with a ring cleavage to afford *o*-propylphenol (Scheme 88).[323]
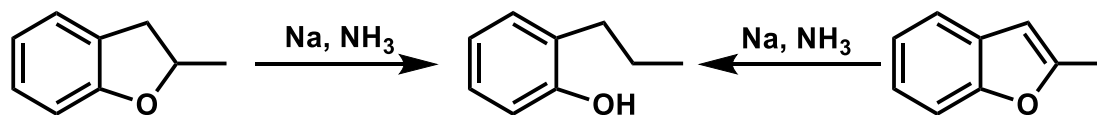
Scheme 88

Benzofurans can undergo facile reaction with ozone. Wacek and his co-workers discovered ozonlysis as a degradative solution in the benzofurans. Benzofuran can produce 25% salicyclic acid, 40% salicylaldehyde and 10% catechol under typical ozonlysis condition.[324]

It is viable to make cyclopropanes on benzofurans with carbenoids. In the synthesis of diazonamide A, Wood and his co-workers demonstrated after much experimentation cyclopropanation occurred with dirhodium(II) caprolactamate (Rh$_2$(cap)$_4$) in refluxing CH$_2$Cl$_2$ (Scheme 89).[325]
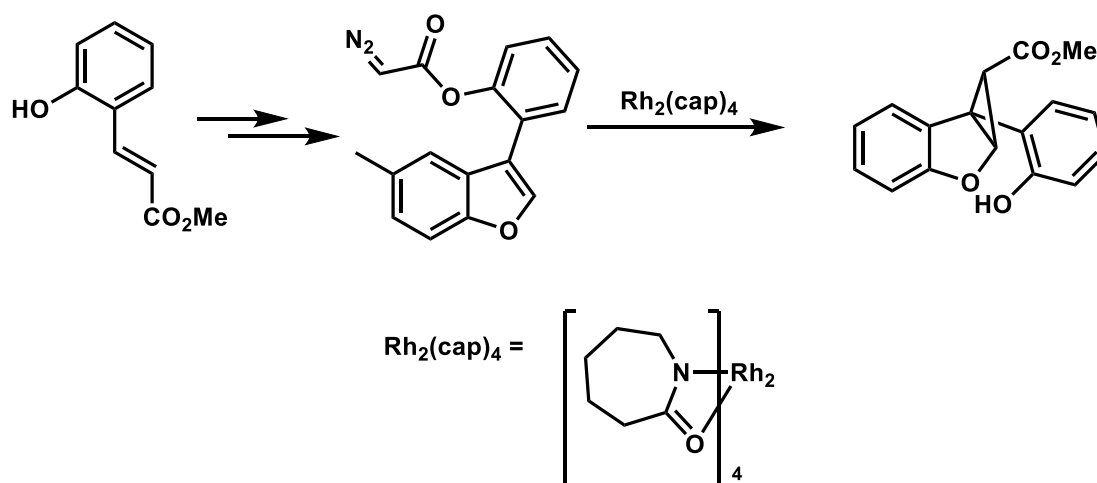
Scheme 89

6. Benzofuran Fluorination

The C(3)-position in 2-arylbenzofurans is usually a metabolic soft spot *in vivo*.[340] Therefore, introduction of F at this position may alter drug metabolism, thus improve pharmacokinetic properties. However, benzofuran fluorination is not well precedented. Very few examples of benzofuran fluorination exist. Sun and his co-workers developed a methodology to access 3-fluoro-2-hydroxy-2-substituted benzofurans with Selectfluor® as the fluorinating reagent in MeCN and water.[341] The methodology requires an aryl on C2 position potentially to stabilize the oxocarbenium ion formed in the process. By utilizing $SOCl_2$/Py as the
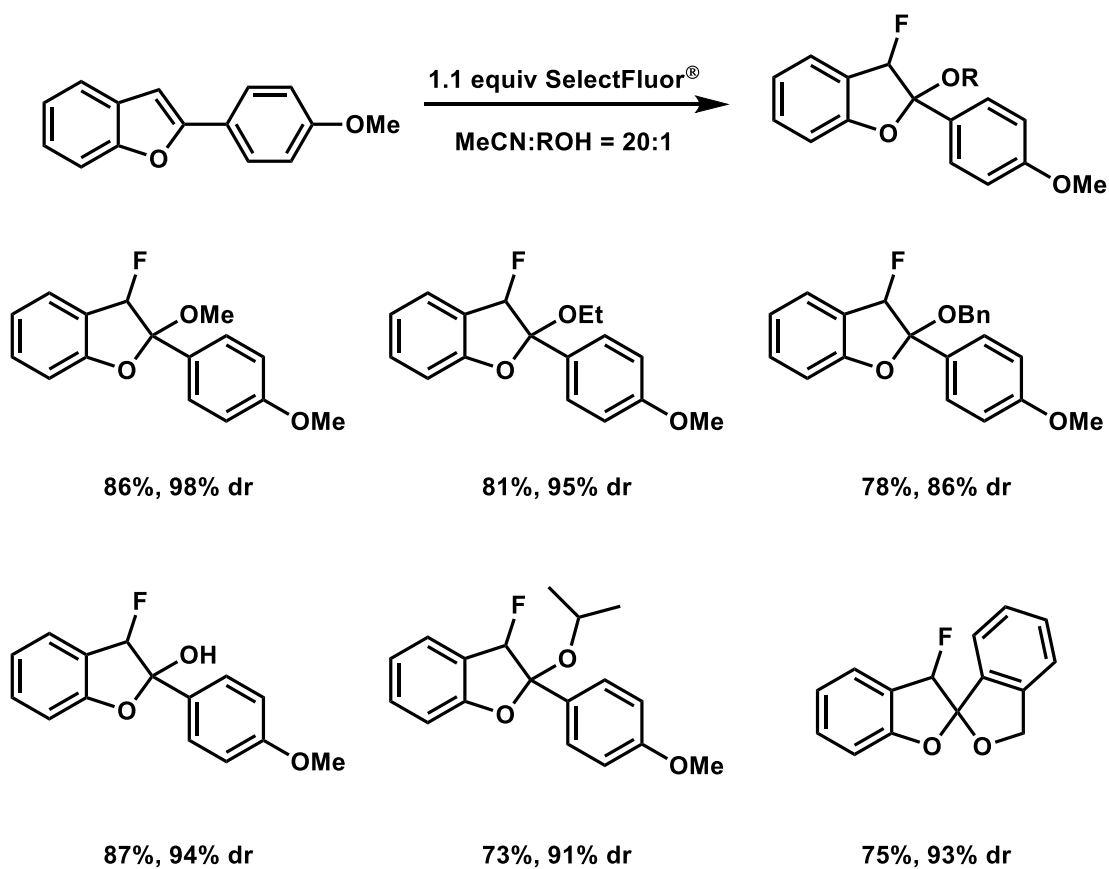
Table 38

dehydrating agent, the fluorinated compounds were readily converted to 3-fluorinated, 2-substituted benzofurans in high yields. The authors proposed Selectfluor® induces the oxygen to form oxocarbenium ion, which is then attacked by water to form an oxonium ion. After

1. SelectFluor®, MeCN/H$_2$O

2. SOCl$_2$/Pyridine
   dichloromethane

75%

71%

62%

70%

69%

58%

51%

61%

71%

43%

68%

70%

52%

78%

52%
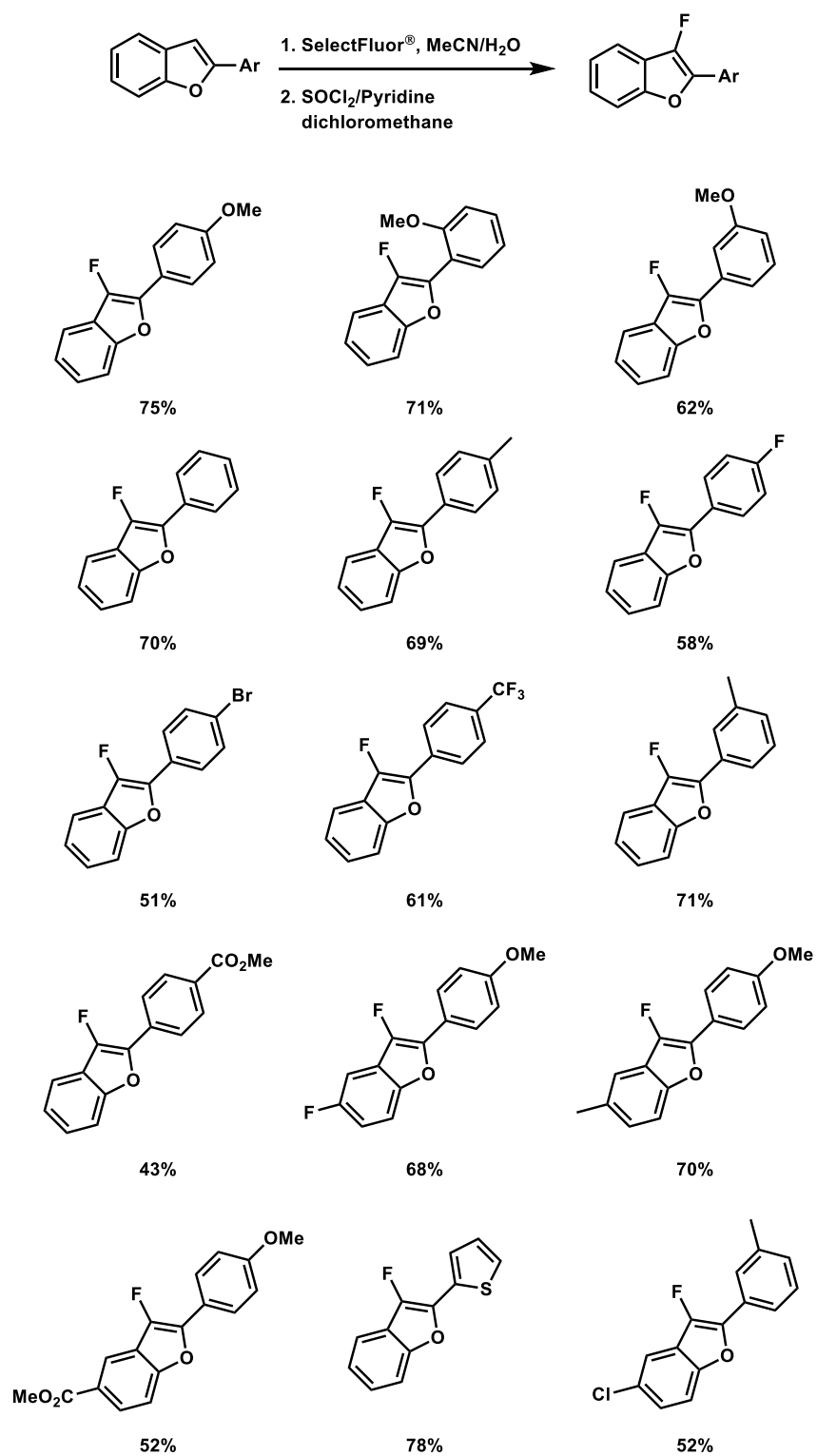
Table 39

deprotonation, the desired hydrofluorinated compound undergoes chlorination and elimination to give 3-fluoro benzofuran (Scheme 90).
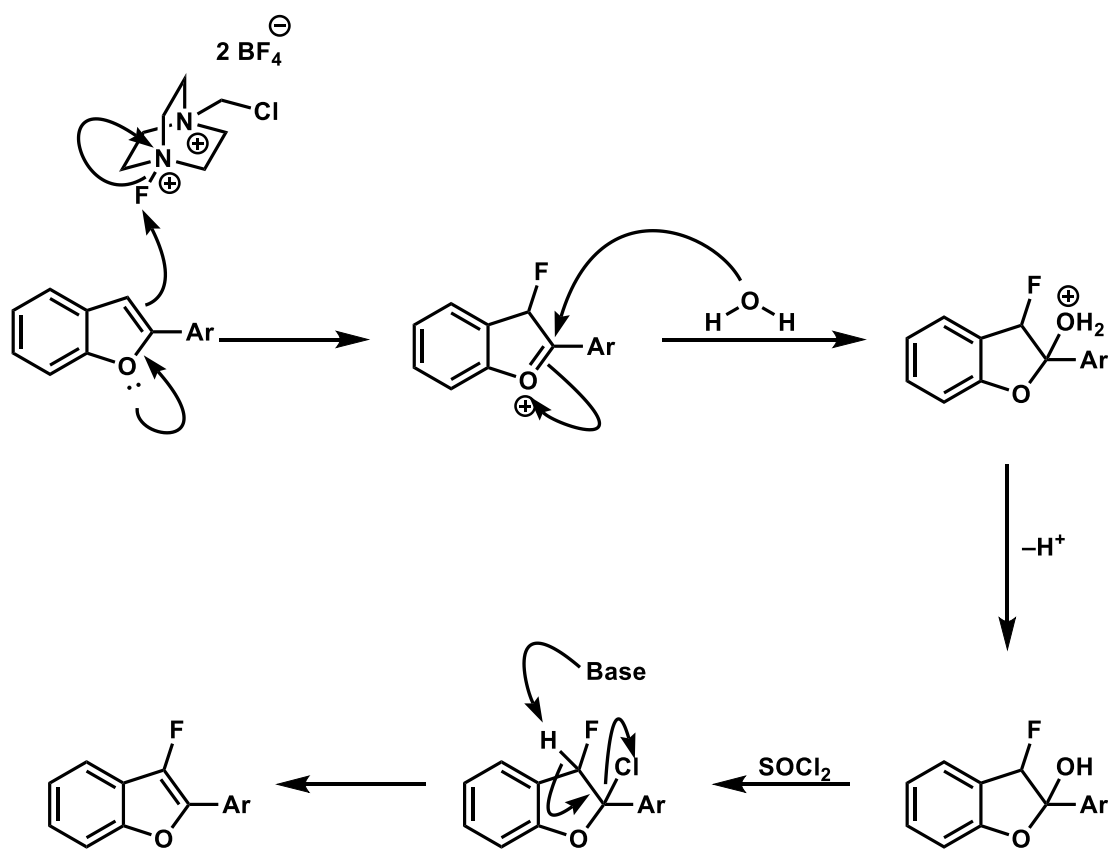
Scheme 90

In sum, 3-fluorobenzofuran is a subject that is very useful and undeveloped at some extent. Therefore, it is meaningful to invest some efforts to investigate this area of chemistry.

7. Benzofuran Discussion

All yields are isolated yields. Diastereomeric ratios were determined by ^{1}H NMR.

7.1. Initial result

Considering the potential dual role of AgF$_2$ (oxidizing reagent and electrophilic fluorine source), we figured treatment of AgF$_2$ may result in fluorination of benzofuran as well as further transformations.   Therefore, the first experiment was conducted to test the reactivity. Gratifyingly, a 50% yield of difluorinated product was obtained under the condition specified (2 equiv AgF$_2$, 0.1 mmol substrate, 0.05 M solution in 1,2-dichloroethane, 23 °C) (Scheme 91).
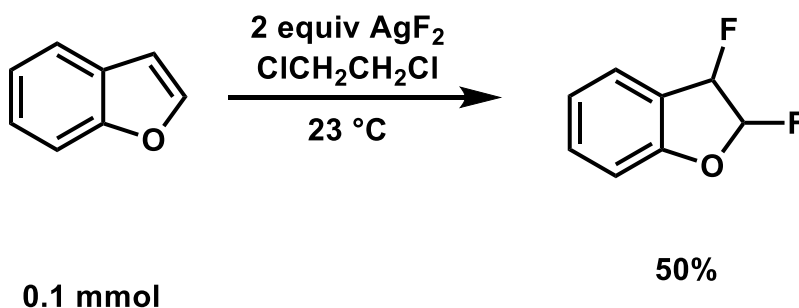
Scheme 91

The diastereomeric ratio (1:1) did not change dramatically throughout the optimization process described in the following text.

7.2. Optimization

7.2.1. Influence of Solvents
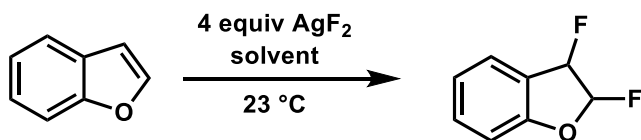
0.3 mmol, 18 h

solvent	%yield
ClCH$_2$CH$_2$Cl	24
CH$_2$Cl$_2$	16
CHCl$_3$	15
MeCN	7
THF	trace
1,4-dioxane	trace
heptane	N.R.
DMF	N.R.

Table 40

Similar to what we found in cyclopropanol and tertiary bromide cases, ClCH$_2$CH$_2$Cl was the optimal choice of solvent.

7.2.2. Influence of Temperature
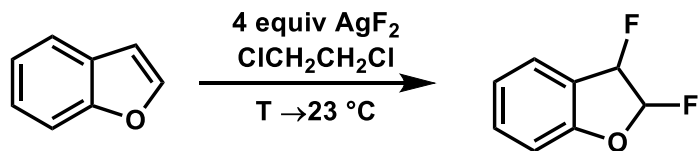
0.3 mmol, T °C 1 h, 23 °C 18 h

T	%yield
0	66
−20	53

Table 41

–20 °C and 0 °C conditions were tested, and 0 °C was the better condition.

7.2.3. Influence of Reaction Time
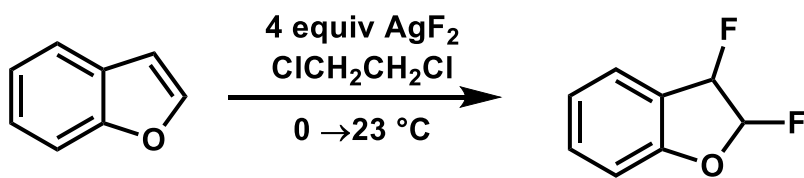
0.3 mmol	
1 h 0 °C	
t h 23 °C	

t	%yield
0	51
1	65
2	58
4	66
5	78
6	83
7	81
8	71

Table 42

The reaction rate was relatively slow. After 1 hour of reaction time at 0 °C, the reaction was allowed to warm up to ambient temperature. Although about 50% benzofuran were converted to difluorinated product right after the 0 °C condition, 6-hour reaction time at 23 °C after 0 °C treatment would give the highest yield.

7.2.4. Influence of Concentration

4 equiv AgF$_2$
ClCH$_2$CH$_2$Cl
0 →23 °C

0.3 mmol
1 h 0 °C
6 h 23 °C
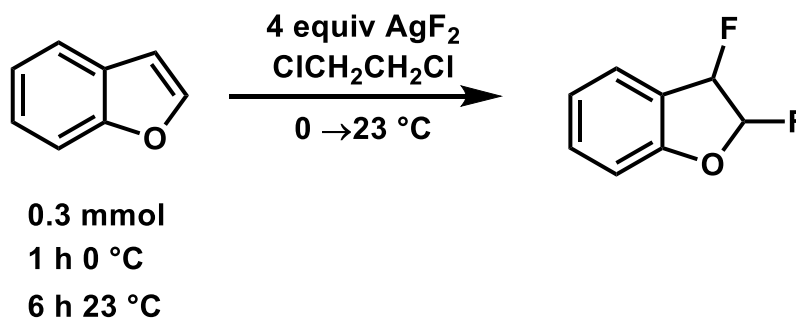
solvent volume (mL)	%yield
1.5	53
3	66
6	83
12	62
18	50

Table 43

A series of benzofuran solution volumes were examined to find the optimal concentration. 6 mL was affording the most fluorinated product. Too high concentration may lead to larger thermal change and more byproduct, whereas too low concentration will result in a low reaction rate. In addition, a reaction between AgF$_2$ and ClCH$_2$CH$_2$Cl is suspected, according to a color change of AgF$_2$ after the treatment of pure ClCH$_2$CH$_2$Cl as well as all other reactions we carried out using AgF$_2$ and ClCH$_2$CH$_2$Cl.

7.3. Reaction Scope Study

Various benzofuran substrates were examined to research the functional group tolerance.

The standard substrate, benzofuran (entry 1, Table 44), is performing the best among all the samples. Alkyl groups and aryl group, for example, 5-*t*Bu, and 7-phenyl(entry 2, 4, Table 44) were not decreasing the reactivity much. Similarly, halogens (entry 7–9, Table 44) except fluorine were not interfering the reaction significantly, either. Electron-withdrawing groups, including 5- and 7-fluoro, 5-ethyl ester, and 2-acetyl (entry 5, 6, 3, 10, Table 44), on the other hand, were causing much lower yields. Since not much byproduct was observed, electron-deficient system might result in less reactivity. The diastereoselectivity was not influenced much by halogens except fluorine on 7-position of benzofuran or carbonyl. Interestingly, 7-fluoro benzofuran showed a more significant diastereoselectivity than the chloro- and bromo-benzofuran. In addition, the reaction of ethyl benzofuran-5-carboxylate produced a single diastereomer.
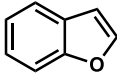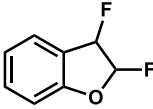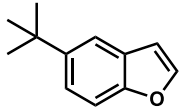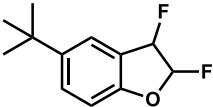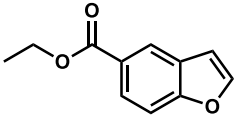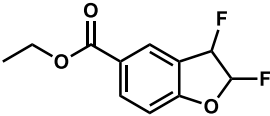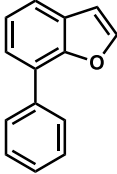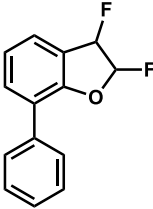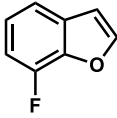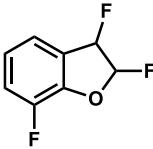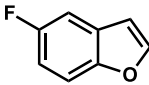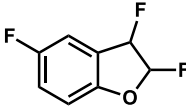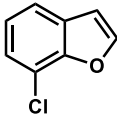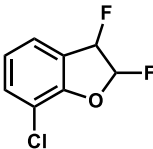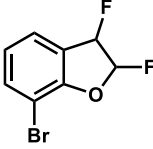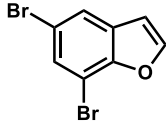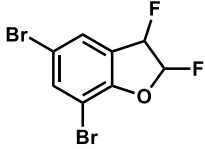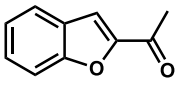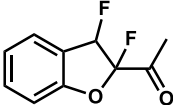
entry	Substrate	Product	%Yield	d.r.
1			83	1:1
2			53	1:1
3			33	single diastereomer
4			50	1:1
5			34	2:3
6			37	1:1
7			62	3:4
8			64	3:4
9			49	1:1
10			35	1:1

Table 44

7.4. Synthetic Application

	%yield
E = I	62
E = TMS	69
E = (OH, Ph group)	50
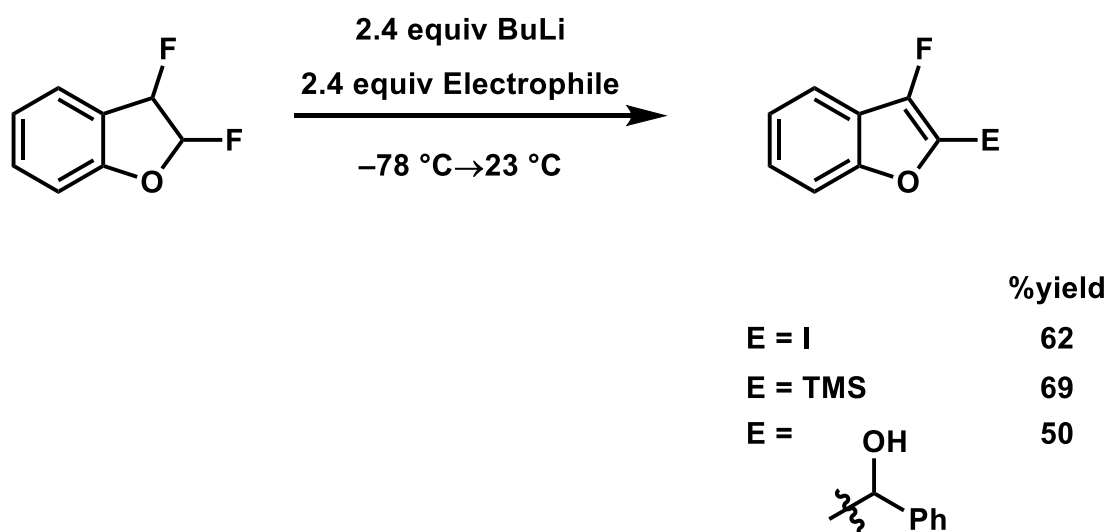
Table 45

2,3-difluoro-2,3-dihydrobenzofuran can be converted to 2-substuted, 3-fluorobenzofurans with the treatment of *n*BuLi and suitable electrophiles. This is a good solution to solve the problem of diastereomers (since often the diastereomers of 2,3-difluoro-2,3-dihydrobenzofurans are hard to isolate and cause substantial difficulty to interpret spectra). Moreover, this also offers access to diversify 3-fluorobenzofuran core in order to expand the library. As mentioned in benzofuran intro chapter, 3-position of benzofuran is a metabolic soft spot *in vivo*, therefore 3-fluorobenzofuran would be a very valuable synthetic core to start from.

7.5. Mechanistic Discussion
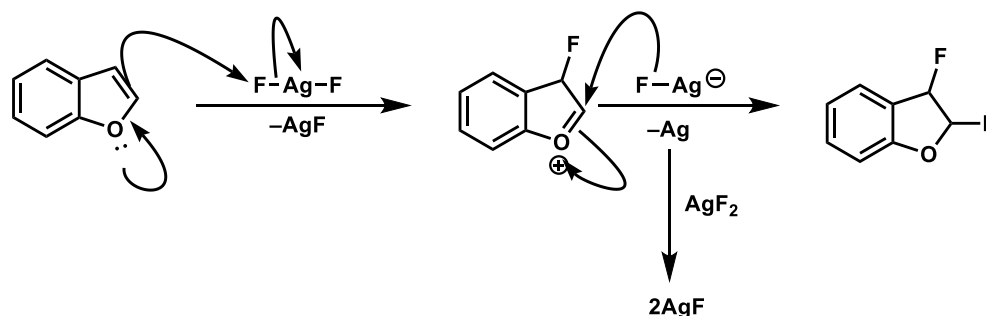
Scheme 92

As silver(II) difluoride is a good electrophilic fluorine source, electron-rich benzofuran can form oxocarbenium ion intermediate with the induction of silver(II) difluoride (Scheme 92). Subsequently, the oxocarbenium ion could be a better electrophile versus silver(II) difluoride, therefore the byproduct from last step, silver(0) fluoride attack on 2-carbon would result in the difluorinated product. The resulting elemental silver might be converted to silver(I) fluoride by a comproportionation with excess silver(II) difluoride. This mechanism can account for the phenomenon that whenever there is an electron-withdrawing group as a substituent of the aromatic system, the efficiency decreased significantly.

8. Conclusion

We developed a protocol to difluorinate benzofurans under mild condition. Ten examples were examined and the yields range from 33% to 83%. Electron-withdrawing groups can be harmful to the reaction whereas electron-donating groups might be less influencing. With treatment of *n*BuLi and suitable electrophiles, 2,3-difluoro-2,3-dihydrobenzofuran were converted to 2-substituted 3-fluoro benzofurans, which are potentially very useful due to the

blockage of potential oxidizable site. Compared to Sun's work,[341] our methodology is able to install heteroatoms on 2-position. In addition, aryl groups are not required on 2-position for our reaction to proceed.

Appendix III. Experimental Part of Benzofuran

1. General Procedure for Preparation of Benzofuran Substrates[342]

Most of the substrates except commercially available 2,3-benzofuran and 2-benzofuranyl methyl ketone and otherwise noted substrates were synthesized based on Huang's work.[342]

In a 100 mL round-bottom flask, NaH (30.5 mmol, 1.22 g, 1.1 equiv) was slowly added to stirred solution of phenol (27.74 mmol, 1 equiv) in N,N-dimethylformamide at room temperature. Then 2-bromo-1,1-diethoxyethane (33.8 mmol, 5.2 mL, 1.21 equiv) was added, and the reaction mixture was stirred at reflux for 24 h. The mixture was allowed to cool down to room temperature and was poured over ice-water. The aqeous phase was extracted with ethyl acetate (3×30 mL), and the combined ethyl acetate fractions were washed with 1 M NaOH solution and brine, dried over anhydrous Mg_2SO_4, filtered and concentrated in vacuo to give the desired product that was used without further purification. To a solution of the previous reaction mixture in toluene was added polyphosphoric acids (6 g, 59.8 mmol), and the mixture was stirred at reflux for 12 h. After which the mixture was allowed to cool down to room temperature and filtered through a plug of silica gel, eluted with petroleum ether. The filtrate was concentrated under reduced pressure to afforded the desired benzofuran product.

2. Preparation of 2-benzylbenzofuran

The preparation was a modified version of Pu's work.[343]

To a stirred anhydrous THF solution (100 mL) containing benzofuran (50 mmol, 5.5 mL, 1 equiv) was slowly added n-BuLi (55 mmol, 22 mL 2.5 M solution in hexane, 1.1 equiv) at

under nitrogen atmosphere, and the solution was stirred for 45 min. Then the benzyl bromide (60 mmol, 7.13 mL, 1.2 equiv) was added slowly to the reaction mixture, and the reaction mixture was warmed to room temperature, kept stirring for another 16 h. Then the reaction mixture was poured into concentrated sodium chloride solution and extracted with diethyl ether. The organic layer was dried, filtrated, and concentrated. The residue was purified by column chromatography using hexanes as eluent.

3. Optimization

3.1. Influence of Amount of Silver(II) Difluoride
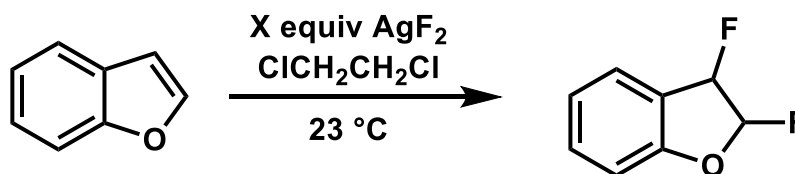
0.3 mmol, 18 h

X	%yield
2	13
4	24

Table 46

An oven-dried 20 mL plastic vial equipped with a magnetic stirring bar, was evacuated and backfilled with nitrogen in a glovebox antechamber (three cycles).   In the glovebox, specified amount of silver difluoride was added into the vial and the vial was sealed with a

rubber septum and transferred out of the glovebox. The vial was connected to a N$_2$-filled Schlenck line. 6 mL dry 1,2-dichloroethane was added and neat benzofuran (0.3 mmol, 33.0 μL, 1 equiv) was added at once, followed by stirring for 18 hour at 23 °C, with the vial wrapped with aluminum foil. The reaction mixture was passed through a short silica plug to remove the solid residue, and then 2×3 mL dichloromethane was used to wash the vial and 2×1 mL was used to wash the silica plug. The resulting solution was concentrated in vacuo. The residue was purified by flash chromatography on silica gel to afford the desired product.

3.2. Influence of Solvents
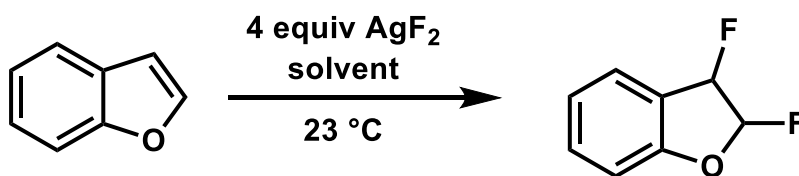
4 equiv AgF$_2$
solvent
23 °C

0.3 mmol, 18 h

solvent	%yield
ClCH$_2$CH$_2$Cl	24
CH$_2$Cl$_2$	16
CHCl$_3$	15
MeCN	7
THF	trace
1,4-dioxane	trace
heptane	N.R.
DMF	N.R.

Table 47

An oven-dried 20 mL plastic vial equipped with a magnetic stirring bar, was evacuated

and backfilled with nitrogen in a glovebox antechamber (three cycles). In the glovebox,

silver difluoride (175.2 mg, 1.2 mmol, 4 equiv) was added into the vial and the vial was sealed

with a rubber septum and transferred out of the glovebox. The vial was connected to a N_2-

filled Schlenck line. 6 mL dry specified solvent was added and neat benzofuran (0.3 mmol, 33.0

µL, 1 equiv) was added at once, followed by stirring for 18 hours at 23 °C, with the vial wrapped

with aluminum foil. The reaction mixture was passed through a short silica plug to remove the

solid residue, and then 2×3 mL dichloromethane was used to wash the vial and 2×1 mL was used

to wash the silica plug. The resulting solution was concentrated in vacuo. The residue was

purified by flash chromatography on silica gel to afford the desired product.

3.3. Influence of Temperature

4 equiv AgF$_2$
ClCH$_2$CH$_2$Cl
T →23 °C

0.3 mmol, T °C 1 h, 23 °C 18 h
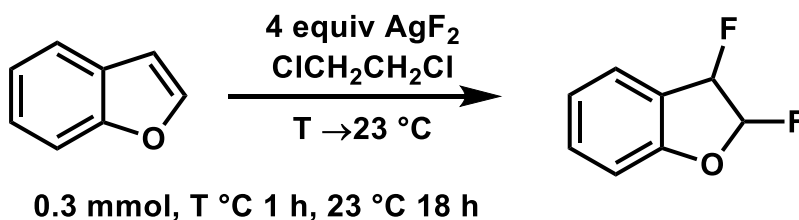
T	%yield
0	66
−20	53

Table 48

An oven-dried 20 mL plastic vial equipped with a magnetic stirring bar, was evacuated

and backfilled with nitrogen in a glovebox antechamber (three cycles). In the glovebox,

silver difluoride (175.2 mg, 1.2 mmol, 4 equiv) was added into the vial and the vial was sealed

with a rubber septum and transferred out of the glovebox. The vial was connected to a N$_2$-filled Schlenck line. Cooled to specified temperature, 3 mL dry 1,2-dichloroethane was added and the mixture was stirred vigorously for 1 min. A solution of benzofuran (0.05 M solution in 1,2-dichloroethane, 6 mL, 0.3 mmol, 1 equiv) was added at once, followed by stirring for 1 hour at specified temperature. The suspension was warmed to 23 °C, wrapped with aluminum foil and stirred for additional 18 hours. The reaction mixture was passed through a short silica plug to remove the solid residue, and then 2×3 mL dichloromethane was used to wash the vial and 2×1 mL was used to wash the silica plug. The resulting solution was concentrated in vacuo. The residue was purified by flash chromatography on silica gel to afford the desired product.

3.4. Influence of Reaction Time
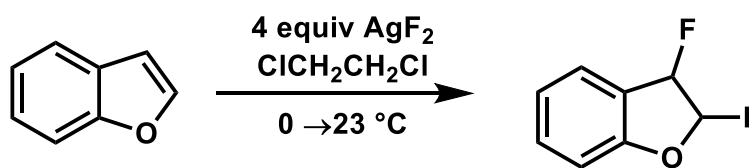
t	%yield
0	51
1	65
2	58
4	66
5	78
6	83
7	81
8	71

0.3 mmol, 1 h 0 °C, t h 23 °C

Table 49

An oven-dried 20 mL plastic vial equipped with a magnetic stirring bar, was evacuated and backfilled with nitrogen in a glovebox antechamber (three cycles). In the glovebox, silver difluoride (175.2 mg, 1.2 mmol, 4 equiv) was added into the vial and the vial was sealed with a rubber septum and transferred out of the glovebox. The vial was connected to a N_2-filled Schlenck line. Cooled to 0 °C, 3 mL dry 1,2-dichloroethane was added and the mixture was stirred vigorously for 1 min. A solution of benzofuran (0.05 M solution in 1,2-dichloroethane, 6 mL, 0.3 mmol, 1 equiv) was added at once, followed by stirring for 1 hour at 0 °C. The suspension was warmed to 23 °C, wrapped with aluminum foil and stirred for additional specified time. The reaction mixture was passed through a short silica plug to remove the solid residue, and then 2×3 mL dichloromethane was used to wash the vial and 2×1 mL was used to wash the silica plug. The resulting solution was concentrated in vacuo. The residue was purified by flash chromatography on silica gel to afford the desired product.

3.5. Influence of Concentration

0.3 mmol
1h 0 °C
6h 23 °C

Reaction scheme: benzofuran + 4 equiv AgF$_2$, ClCH$_2$CH$_2$Cl, 0 →23 °C → 2,3-difluoro-2,3-dihydrobenzofuran
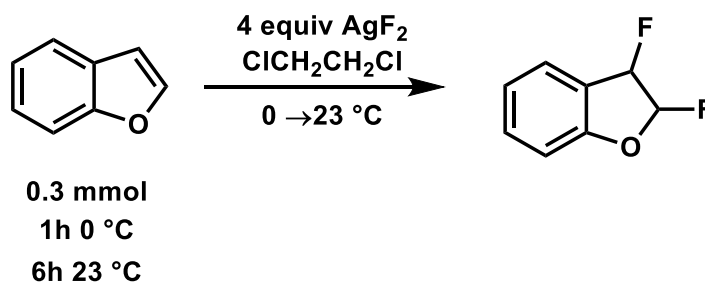
solvent volume (mL)	%yield
1.5	53
3	66
6	83
12	62
18	50

Table 50

An oven-dried 20 mL plastic vial equipped with a magnetic stirring bar, was evacuated and backfilled with nitrogen in a glovebox antechamber (three cycles). In the glovebox, silver difluoride (175.2 mg, 1.2 mmol, 4 equiv) was added into the vial and the vial was sealed with a rubber septum and transferred out of the glovebox. The vial was connected to a N$_2$-filled Schlenck line. Cooled to 0 °C, 3 mL dry 1,2-dichloroethane was added and stirred vigorously for 1 min. A solution of benzofuran in specified volume of 1,2-dichloroethane (0.3 mmol benzofuran, 1 equiv) was added at once, followed by stirring for 1 hour at 0 °C. The suspension was warmed to 23 °C, wrapped with aluminum foil and stirred for additional 6 hours. The reaction mixture was passed through a short silica plug to remove the solid residue, and then 2×3 mL dichloromethane was used to wash the vial and 2×1 mL was used to wash the silica plug.

The resulting solution was concentrated in vacuo. The residue was purified by flash chromatography on silica gel to afford the desired product.

4. General Procedure for Fluorination of Benzofurans

An oven-dried 20 mL plastic vial equipped with a magnetic stirring bar, was evacuated and backfilled with nitrogen in a glovebox antechamber (three cycles). In the glovebox, silver difluoride (175.2 mg, 1.2 mmol, 4 equiv) was added into the vial and the vial was sealed with a rubber septum and transferred out of the glovebox. The vial was connected to a N_2-filled Schlenck line. Cooled to 0 °C, 3 mL dry 1,2-dichloroethane was added and stirred vigorously for 1 min. A solution of benzofuran (0.05 M solution in 1,2-dichloroethane, 6 mL, 0.3 mmol, 1 equiv) was added at once, followed by stirring for 1 hour at 0 °C. The suspension was warmed to 23 °C, wrapped with aluminum foil and stirred for additional 6 hours. The reaction mixture was passed through a short silica plug to remove the solid residue, and then 2×3 mL dichloromethane was used to wash the vial and 2×1 mL was used to wash the silica plug. The resulting solution was concentrated in vacuo. The residue was purified by flash chromatography on silica gel to afford the desired product.

5. Reactions of 2,3-difluoro-2,3-dihydrobenzofuran and Iodine

In a 20-mL vial evacuated and backfilled with nitrogen for three cycles, *n*BuLi (0.48 mmol, 218 μL 2.5 M solution in hexane, 2.4 equiv) was subjected. The *n*BuLi was diluted with 2 mL THF and cooled to –78 °C and stirred vigorously for 1 min. 2,3-difluoro-2,3-

dihydrobenzofuran (0.2 mmol, 0.2M solution in THF, 1 equiv) was then injected into the vial and the reaction was stirred at –78 °C for 30 min, followed by addition of iodine (0.48 mmol, 0.2M solution in THF, 2.4 equiv). The reaction was allowed to warm up to 23 °C and kept stirring for 2 hours. The reaction was quenched with saturated aqueous NH$_4$Cl solution and extracted with diethyl ether (2×3 mL). The organic fractions were combined and dried over MgSO$_4$. The solution was then concentrated in vacuo and purified by flash column, using ethyl acetate/hexanes (1:40) to afford the desired product.

6. Reactions of 2,3-difluoro-2,3-dihydrobenzofuran and TMSCl

In a 20-mL vial evacuated and backfilled with nitrogen for three cycles, *n*BuLi (0.48 mmol, 218 µL 2.5 M solution in hexane, 2.4 equiv) was subjected. The *n*BuLi was diluted with 2 mL THF and cooled to –78 °C and stirred vigorously for 1 min. 2,3-difluoro-2,3-dihydrobenzofuran (0.2 mmol, 0.2M solution in THF, 1 equiv) was then injected into the vial and the reaction was stirred at –78 °C for 30 min, followed by addition of TMSCl (0.48 mmol, 0.2M solution in THF, 2.4 equiv). The reaction was allowed to warm up to 23 °C and kept stirring for 2 hours. The reaction was quenched with saturated aqueous NH$_4$Cl solution and extracted with diethyl ether (2×3 mL). The organic fractions were combined and dried over MgSO$_4$. The solution was then concentrated in vacuo and purified by flash column, using ethyl acetate/hexanes (1:40) to afford the desired product.

7. Reactions of 2,3-difluoro-2,3-dihydrobenzofuran and Benzaldehyde

In a 20-mL vial evacuated and backfilled with nitrogen for three cycles, *n*BuLi (0.48 mmol, 218 μL 2.5 M solution in hexane, 2.4 equiv) was subjected. The *n*BuLi was diluted with 2 mL THF and cooled to –78 °C and stirred vigorously for 1 min. 2,3-difluoro-2,3-dihydrobenzofuran (0.2 mmol, 0.2M solution in THF, 1 equiv) was then injected into the vial and the reaction was stirred at –78 °C for 30 min, followed by addition of benzaldehyde (0.48 mmol, 0.2M solution in THF, 2.4 equiv). The reaction was allowed to warm up to 23 °C and kept stirring for 2 hours. The reaction was quenched with saturated aqueous NH$_4$Cl solution and extracted with diethyl ether (2×3 mL). The organic fractions were combined and dried over MgSO$_4$. The solution was then concentrated in vacuo and purified by flash column, using ethyl acetate/hexanes (1:8) to afford the desired product.

All the substrates were prepared based on known procedures and the spectra match with the literatures.

8. Characterization Data of 2,3-difluoro-2,3-dihydrobenzofurans
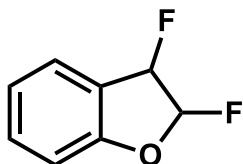
2,3-difluoro-2,3-dihydrobenzofuran

The title compound was isolated as clear colorless liquid (83%, 38.8 mg), inseparable diastereomers, d.r. ≈ 1:1.

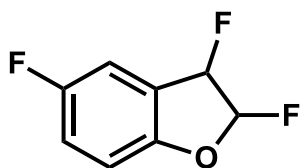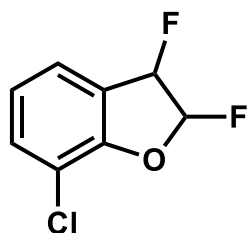**TLC** (SiO$_2$) R_f = 0.41 in 8:1 hexanes/toluene, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, Chloroform-d) δ 7.54 (dt, J = 7.6, 1.8 Hz, 2H), 7.50 – 7.42 (m, 5H), 7.38 (t, J = 7.8 Hz, 3H), 7.15 – 7.02 (m, 7H), 6.98 (d, J = 8.1 Hz, 3H), 6.32 (d, J = 11.5 Hz, 1H), 6.27 – 6.18 (m, 3H), 6.15 – 6.06 (m, 3H), 6.03 – 5.90 (m, 3H), 5.82 (d, J = 11.7 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-d) δ 160.52, 157.21, 132.94, 132.91, 132.02, 126.97, 125.98, 123.11, 123.07, 121.53, 121.37, 114.96, 114.63, 113.12, 112.80, 111.38, 111.15, 108.94, 108.83, 107.00, 106.88, 93.83 (dd, J = 184.0, 37.8 Hz), 89.16 (dd, J = 200.3, 16.4 Hz).

^{19}F NMR (376 MHz, Chloroform-d) δ -133.41 (dd, J = 58.4, 11.4 Hz, 1F), -146.11 (dt, J = 61.4, 15.9 Hz, 1F), -175.86 (d, J = 54.3 Hz, 1F), -200.18 (dd, J = 54.5, 17.0 Hz, 1F).

IR (neat) 2361, 1604, 1479, 1468,1024, 751 cm^{-1}

GC/MS (*m/z*): 174.0 (1%), 156.0 (50%), 108.0 (100%)
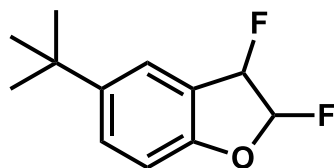
trans diastereomer 1

cis diastereomer 2

5-(tert-butyl)-2,3-difluoro-2,3-dihydrobenzofuran

The title compound was isolated as clear colorless liquid (53%, 33.7 mg), separable diastereomers, d.r. ≈ 1:1.

TLC (SiO$_2$) R_f (diastereomer 1) = 0.41 in 8:1 hexanes/toluene, *p*-anisaldehyde stain

R_f (diastereomer 2) = 0.32 in 8:1 hexanes/toluene, *p*-anisaldehyde stain

¹H NMR (500 MHz, Chloroform-d) (diastereomer 1) δ 7.55 (t, *J* = 2.3 Hz, 1H), 7.47 (dt, *J* = 8.5, 2.5 Hz, 1H), 7.04 – 6.86 (m, 1H), 6.25 (dd, *J* = 58.6, 11.4 Hz, 1H), 5.85 (dd, *J* = 55.0, 11.7 Hz, 1H), 1.33 (s, 9H).

¹H NMR (500 MHz, Chloroform-d) (diastereomer 2) δ 7.48 (s, 1H), 7.39 (dt, *J* = 8.6, 2.0 Hz, 1H), 6.89 (dd, *J* = 8.5, 1.7 Hz, 1H), 6.17 (ddd, *J* = 61.8, 4.6, 3.1 Hz, 1H), 6.09 – 5.94 (m, 1H), 1.32 (s, 9H).

¹³C NMR (126 MHz, Chloroform-d) (diastereomer 1) δ 146.39, 146.37, 130.13, 130.09, 123.59, 120.87, 114.18 (dd, *J* = 230.6, 41.6 Hz), 110.66, 94.22 (dd, *J* = 184.0, 37.8 Hz), 34.54, 31.53.

¹³C NMR (126 MHz, Chloroform-d) (diastereomer 2) δ 129.10, 122.68, 110.44, 108.19 (dd, *J* = 244.3, 14.6 Hz), 89.50 (dd, *J* = 199.4, 16.3 Hz), 77.24, 31.53.

¹⁹F NMR (376 MHz, Chloroform-d) (diastereomer 1) δ -132.98 (dt, J = 58.4, 11.5 Hz, 1F), -175.41 (d, J = 55.1 Hz, 1F).

¹⁹F NMR (376 MHz, Chloroform-d) (diastereomer 2) δ -145.80 (dt, J = 61.3, 15.7 Hz, 1F), -199.95 (dd, J = 55.1, 16.5 Hz, 1F).

IR (neat) (diastereomer 1) 2964, 2360, 1492, 1014 cm⁻¹

IR (neat) (diastereomer 2) 2963, 2360, 1492, 1031 cm⁻¹

GC/MS (*m/z*) (diastereomer 1): 212.0 (14%), 197.1 (100%), 169.0 (23%)

GC/MS (*m/z*) (diastereomer 2): 212.0 (14%), 197.1 (100%), 169.0 (19%)
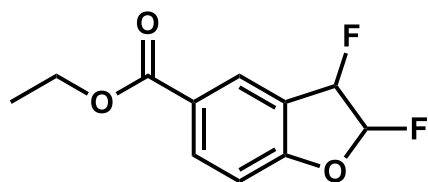
trans diastereomer

ethyl 2,3-difluoro-2,3-dihydrobenzofuran-5-carboxylate

The title compound was isolated as pale-yellow liquid (33%, 22.6 mg), single diastereomer.

TLC (SiO$_2$) R_f = 0.24 in 8:1 hexanes/toluene, *p*-anisaldehyde stain

¹H NMR (400 MHz, Chloroform-d) δ 8.25 (s, 1H), 8.18 (d, J = 8.5 Hz, 1H), 7.08 (d, J = 9.1 Hz, 1H), 6.32 (dd, J = 57.7, 12.1 Hz, 1H), 5.89 (dd, J = 54.4, 11.7 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H).

13C NMR (126 MHz, Chloroform-d) δ 165.38, 163.76, 146.13, 135.15, 129.02, 125.96, 123.62, 121.75, 114.40 (dd, J = 232.4, 40.9 Hz), 111.19, 107.07, 93.00 (dd, J = 184.4, 37.8 Hz), 61.14, 14.30.

19F NMR (376 MHz, Chloroform-d) δ -133.44 (dt, J = 57.6, 10.7 Hz), -176.89 (dt, J = 54.5, 10.4 Hz).

IR (neat) 2983, 1713, 1621, 1267 cm^{-1}

GC/MS (*m/z*): 228.1 (15%), 200.0 (29%), 183.0 (100%)
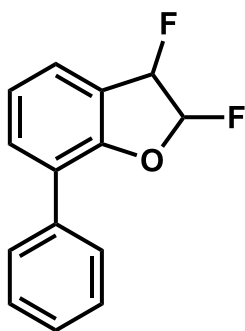
trans **diastereomer 1**
cis **diastereomer 2**

2,3-difluoro-7-phenyl-2,3-dihydrobenzofuran

The title compound was isolated as clear colorless liquid (50%, 34.8 mg), separable diastereomers, d.r. ≈ 1:1.

TLC (SiO$_2$) R_f (diastereomer 1) = 0.38 in 8:1 hexanes/toluene, *p*-anisaldehyde stain

R_f (diastereomer 2) = 0.30 in 8:1 hexanes/toluene, *p*-anisaldehyde stain

¹H NMR (500 MHz, Chloroform-d) (diastereomer 1) δ 7.70 (dt, J = 6.4, 1.3 Hz, 2H), 7.64 – 7.57 (m, 1H), 7.55 – 7.50 (m, 1H), 7.50 – 7.43 (m, 2H), 7.42 – 7.35 (m, 1H), 7.21 (t, J = 7.6 Hz, 1H), 6.32 (dd, J = 58.2, 11.5 Hz, 1H), 5.93 (dd, J = 54.8, 11.6 Hz, 1H).

¹H NMR (500 MHz, Chloroform-d) (diastereomer 2) δ 7.73 – 7.60 (m, 2H), 7.56 – 7.49 (m, 1H), 7.46 (t, J = 8.0 Hz, 3H), 7.41 – 7.33 (m, 1H), 7.19 (t, J = 7.6 Hz, 1H), 6.36 – 6.15 (m, 1H), 6.16 – 5.99 (m, 1H).

¹³C NMR (126 MHz, Chloroform-d) (diastereomer 1) δ 128.50 (d, J = 14.3 Hz), 113.60 (dd, J = 230.9, 40.5 Hz), 93.82 (dd, J = 183.3, 38.2 Hz).

¹³C NMR (126 MHz, Chloroform-d) δ 135.39, 128.54, 128.43, 127.84, 125.35, 124.84, 123.69, 122.13, 107.76 (d, J = 259.5 Hz), 89.27 (d, J = 198.9 Hz).

¹⁹F NMR (376 MHz, Chloroform-d) (diastereomer 1) δ -133.10 (dt, J = 58.3, 10.9 Hz, 1F), -175.87 (dt, J = 54.7, 11.1 Hz, 1F).

¹⁹F NMR (376 MHz, Chloroform-d) (diastereomer 2) δ -142.74 – -150.04 (m, 1F), -198.06 – -203.98 (m, 1F).

IR (neat) (diastereomer 1) 3037, 2359, 1428, 1016,757 cm^{-1}

IR (neat) (diastereomer 2) 2925, 2360, 1427, 1020, 756 cm^{-1}

GC/MS (*m/z*) (diastereomer 1): 232.1 (93%), 183.1 (100%)

GC/MS (*m/z*) (diastereomer 2): 232.1 (88%), 183.1 (100%)
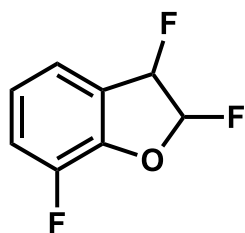
2,3,7-trifluoro-2,3-dihydrobenzofuran

The title compound was isolated as clear colorless liquid (34%, 17.7 mg), inseparable diastereomers, d.r. ≈ 2:3.

TLC (SiO$_2$) R_f = 0.32 in 8:1 hexanes/toluene, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, Chloroform-d) δ 7.25 (s, 1H), 7.16 (t, *J* = 9.3 Hz, 1H), 7.06 (dd, *J* = 8.0, 4.3 Hz, 1H), 6.24 (dt, *J* = 60.3, 3.7 Hz, 1H), 6.07 (ddd, *J* = 54.2, 14.2, 4.5 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-d) δ 119.14 (d, *J* = 16.5 Hz), 108.41 (dd, *J* = 247.9, 15.0 Hz), 88.84 (dd, *J* = 201.5, 16.1 Hz).

^{19}F NMR (376 MHz, Chloroform-d) δ -137.16 (s, 1F), -144.12 – -148.15 (m, 1F), -200.14 (dd, *J* = 53.7, 16.2 Hz, 1F).

IR (neat) 2918, 2360, 1493, 1024, 775, 730 cm^{-1}

GC/MS (*m/z*): 174.0 (50%), 126.0 (100%)

2,3,5-trifluoro-2,3-dihydrobenzofuran

The title compound was isolated as clear colorless liquid (37%, 19.3 mg), inseparable diastereomers, d.r. ≈ 1:1.

TLC (SiO$_2$) R_f = 0.33 in 8:1 hexanes/toluene, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, Chloroform-d) δ 7.24 (dt, *J* = 7.2, 2.5 Hz, 1H), 7.19 – 7.11 (m, 2H), 7.11 – 7.03 (m, 1H), 6.99 (ddd, *J* = 8.9, 3.9, 1.6 Hz, 1H), 6.94 – 6.87 (m, 1H), 6.26 (dd, *J* = 58.2, 11.5 Hz, 1H), 6.19 (ddd, *J* = 60, 4.4, 2.5 Hz, 1H), 6.12 (dt, *J* = 60.0, 3.0 Hz, 1H), 6.04 (ddd, *J* = 50.0, 15.3, 4.4 Hz, 1H), 5.83 (dd, *J* = 54.2, 11.6 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-d) δ 159.5, 157.5, 119.87, 119.68, 118.76, 118.57, 115.45, 115.13, 113.82, 113.62, 113.29, 113.01, 112.80, 112.16, 112.05, 111.98, 109.42, 109.30, 107.47, 107.35, 94.52, 94.21, 93.05, 93.63 (dd, *J* = 184.8, 38.4 Hz), 90.62 – 87.37 (m).

^{19}F NMR (376 MHz, Chloroform-d) δ -120.47 (s, 1F), -120.69 (s, 1F), -133.14 (dt, *J* = 58.3, 11.2 Hz, 1F), -145.56 (dt, *J* = 61.0, 15.6 Hz, 1F), -177.03 (dt, *J* = 54.3, 10.6 Hz, 1F), -201.79 (dd, *J* = 53.9, 15.9 Hz, 1F).

IR (neat) 2926, 2360, 1484, 1027 cm^{-1}

GC/MS (*m/z*): 174.0 (57%), 126.0 (100%)

***trans* diastereomer 1**

***cis* diastereomer 2**

7-chloro-2,3-difluoro-2,3-dihydrobenzofuran

The title compound was isolated as clear colorless liquid (62%, 35.4 mg), separable diastereomers, d.r. ≈ 3:4.

TLC (SiO$_2$) R_f (minor diastereomer 1) = 0.40 in 8:1 hexanes/toluene, *p*-anisaldehyde stain

R_f (major diastereomer 2) = 0.33 in 8:1 hexanes/toluene, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, Chloroform-d) (minor diastereomer 1) δ 7.44 (dt, *J* = 7.9, 2.4 Hz, 2H), 7.07 (td, *J* = 7.8, 1.0 Hz, 1H), 6.32 (dd, *J* = 57.5, 11.5 Hz, 1H), 5.91 (dd, *J* = 54.3, 11.7 Hz, 1H).

^{1}H NMR (500 MHz, Chloroform-d) (major diastereomer 2) δ 7.43 – 7.29 (m, 2H), 7.05 (t, *J* = 7.8 Hz, 1H), 6.39 – 6.16 (m, 1H), 6.07 (ddd, *J* = 54.2, 14.3, 4.4 Hz, 1H).

^{13}C NMR (126 MHz, Chloroform-d) (minor diastereomer 1) δ 133.12, 133.09, 125.21, 124.08, 124.06, 116.88, 113.81 (dd, *J* = 233.4, 40.6 Hz), 93.98 (dd, *J* = 185.1, 37.7 Hz).

^{13}C NMR (126 MHz, Chloroform-d) (major diastereomer 2) δ 132.27, 132.25, 124.24, 124.18, 123.12, 116.71, 107.89 (dd, *J* = 247.6, 14.9 Hz), 89.10 (dd, *J* = 201.5, 16.3 Hz).

^{19}F NMR (376 MHz, Chloroform-d) (minor diastereomer 1) δ -133.37 (dt, *J* = 57.5, 10.5 Hz, 1F), -176.37 (dt, *J* = 54.8, 10.5 Hz, 1F).

¹⁹F NMR (376 MHz, Chloroform-d) (major diastereomer 2) δ -145.75 (dt, J = 60.3, 15.3 Hz, 1F), -199.72 (dd, J = 54.1, 16.2 Hz, 1F).

IR (neat) (diastereomer 1) 2926, 2360, 1473, 1027 cm⁻¹

IR (neat) (diastereomer 2) 2924, 2360, 1470, 1018 cm⁻¹

GC/MS (*m/z*) (diastereomer 1): 192.0 (24%), 190.0 (68%), 142.0 (70%), 107.0 (100%)

GC/MS (*m/z*) (diastereomer 2): 192.0 (23%), 190.0 (71%), 142.0 (71%), 107.0 (100%)
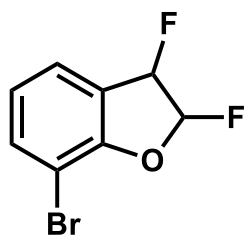
7-bromo-2,3-difluoro-2,3-dihydrobenzofuran

The title compound was isolated as clear colorless liquid (64%, 45.1 mg), inseparable diastereomers, d.r. ≈ 3:4.

TLC (SiO₂) R_f = 0.41 in 8:1 hexanes/toluene, *p*-anisaldehyde stain

¹H NMR (500 MHz, Chloroform-d) δ 7.78 – 7.53 (m, 1H), 7.48 (dt, J = 7.5, 1.6 Hz, 1H), 7.07 – 6.94 (m, 1H), 6.32 (dd, J = 57.6, 11.5 Hz, 1H), 5.94 (dd, J = 54.3, 11.7 Hz, 1H).

¹³C NMR (126 MHz, Chloroform-d) δ 135.97, 135.94, 125.89, 124.41, 122.59, 113.54 (dd, J = 233.6, 40.5 Hz), 104.08, 94.20 (dd, J = 185.1, 37.7 Hz).

¹⁹F NMR (376 MHz, Chloroform-d) δ -133.36 (dt, J = 57.3, 10.6 Hz, 1F), -175.97 – -176.29 (m, 1F).

IR (neat) 2924, 2360, 1469, 1021, 982 cm⁻¹

GC/MS (*m/z*): 235.9 (82%), 233.9 (85%), 187.9 (45%), 185.9 (45%), 107.0 (100%)
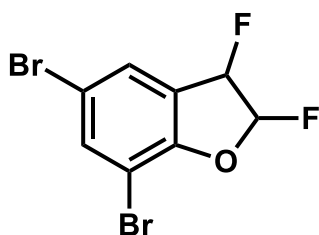
trans diastereomer 1
cis diastereomer 2

5,7-dibromo-2,3-difluoro-2,3-dihydrobenzofuran

The title compound was isolated as clear colorless liquid (49%, 46.1 mg), separable diastereomers, d.r. ≈ 1:1.

TLC (SiO₂) R_f (diastereomer 1) = 0.33 in 8:1 hexanes/toluene, *p*-anisaldehyde stain

R_f (diastereomer 2) = 0.28 in 8:1 hexanes/toluene, *p*-anisaldehyde stain

¹H NMR (500 MHz, Chloroform-d) (diastereomer 1) δ 7.74 (d, J = 2.1 Hz, 1H), 7.60 (d, J = 1.9 Hz, 1H), 6.31 (ddd, J = 57.2, 11.5, 1.3 Hz, 1H), 5.91 (dd, J = 53.8, 11.6 Hz, 1H).

¹H NMR (500 MHz, Chloroform-d) (diastereomer 2) δ 7.68 (d, J = 1.7 Hz, 1H), 7.53 (d, J = 1.9

Hz, 1H), 6.35 – 6.16 (m, 1H), 6.07 (ddd, J = 53.7, 14.7, 4.4 Hz, 1H).

¹³C NMR (126 MHz, Chloroform-d) (diastereomer 1) δ 138.16, 138.12, 128.91, 124.04, 115.42, 113.71 (dd, J = 234.9, 39.9 Hz), 105.05, 93.72 (dd, J = 187.1, 37.9 Hz).

¹³C NMR (126 MHz, Chloroform-d) (diastereomer 2) δ 153.92, 137.24, 127.95, 124.39, 115.60, 110.83 – 106.05 (m), 104.98, 88.88 (dd, J = 203.5, 16.5 Hz).

¹⁹F NMR (376 MHz, Chloroform-d) (diastereomer 1) δ -133.12 (dt, J = 57.2, 10.3 Hz, 1F), -176.97 (dt, J = 54.3, 10.6 Hz, 1F).

¹⁹F NMR (376 MHz, Chloroform-d) (diastereomer 2) δ -145.26 (dt, J = 59.8, 14.9 Hz, 1F), -200.34 (dd, J = 53.6, 15.6 Hz, 1F).

IR (neat) (diastereomer 1) 3079, 2361, 1451, 1150 cm^{-1}

IR (neat) (diastereomer 2) 2919, 2359, 1450, 1021 cm^{-1}

GC/MS (*m/z*) (diastereomer 1): 315.9 (50%), 313.9 (100%), 311.9 (50%), 265.8 (29%), 184.9 (30%)

GC/MS (*m/z*) (diastereomer 2): 315.9 (50%), 313.9 (100%), 311.9 (50%), 265.8 (29%), 184.9 (30%)
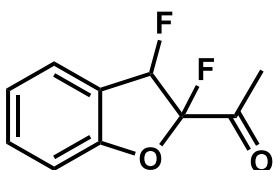
trans diastereomer 1
cis diastereomer 2

1-(2,3-difluoro-2,3-dihydrobenzofuran-2-yl)ethan-1-one

The title compound was isolated as clear colorless liquid (35%, 20.8 mg), separable diastereomers, d.r. ≈ 1:1.

TLC (SiO$_2$) R_f (diastereomer 1) = 0.27 in 8:1 hexanes/toluene, *p*-anisaldehyde stain
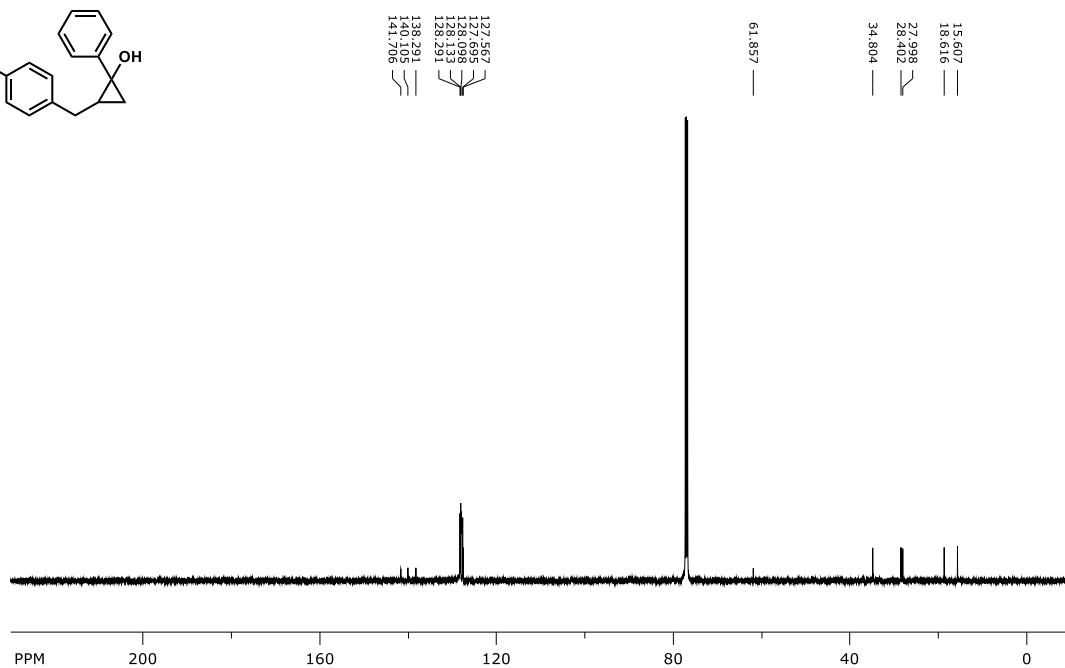
R_f (diastereomer 2) = 0.22 in 8:1 hexanes/toluene, *p*-anisaldehyde stain

¹H NMR (500 MHz, CDCl3) (diastereomer 1) δ 7.30–7.24 (m, 2H), 7.21–7.14 (m, 3H), 2,43 (dd, *J* = 9.5, 7.5 Hz, 1H), 1.24–1.11 (m, 3H), 1.03 (d, *J* = 6.5 Hz, 3H), 0.77 (d, *J* = 6.5 Hz, 3H).

¹H NMR (500 MHz, Chloroform-d) (diastereomer 2 mixed with diastereomer 1) δ 7.52 (d, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.46 (dd, *J* = 54.9, 11.3 Hz, 1H), 2.56 (s, 3H).

¹³C NMR (126 MHz, Chloroform-d) (diastereomer 1) δ 196.78, 160.53, 133.23, 127.04, 123.77, 120.58, 111.77, 94.71 (dd, *J* = 187.1, 43.1 Hz), 29.99 (d, *J* = 77.4 Hz), 26.81.

¹³C NMR (126 MHz, Chloroform-d) (diastereomer 2 mixed with diastereomer 1)

δ 198.08, 156.60, 132.29, 126.26, 123.80, 121.64, 111.24, 88.28 (d, *J* = 184.8 Hz).

¹⁹F NMR (376 MHz, Chloroform-d) (diastereomer 1) δ -119.48 (t, *J* = 10.3 Hz, 1F), -175.50 (d,

J = 55.7 Hz, 1F).

¹⁹F NMR (376 MHz, Chloroform-d) (diastereomer 2 mixed with diastereomer 1)

δ -130.91 (t, J = 14.9 Hz, 1F), -196.24 (dd, J = 54.9, 18.2 Hz, 1F).

IR (neat) (diastereomer 1) 2920, 2360, 1745, 1469, 960, 752 cm^{-1}

IR (neat) (diastereomer 2) 2921, 2860, 1739, 1468, 990, 751 cm^{-1}

GC/MS (*m/z*) (diastereomer 1): 198.0 (9%), 136.0 (100%), 108.0 (34%)

GC/MS (*m/z*) (diastereomer 2): 198.0 (17%), 136.0 (100%), 108.0 (38%)

9. Characterization Data of 3-fluoro-2-iodobenzofuran
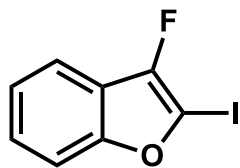
The title compound was isolated as clear colorless liquid.

TLC (SiO$_2$) R_f = 0.43 in 20:1 hexanes/toluene, *p*-anisaldehyde stain

¹H NMR (500 MHz, Chloroform-d) δ 7.59 – 7.49 (m, 1H), 7.46 – 7.37 (m, 1H), 7.31 – 7.22 (m, 1H).

¹³C NMR (126 MHz, Chloroform-d) δ 154.34, 152.30, 125.35, 123.35, 119.38 (d, J = 19.6 Hz), 116.74 (d, J = 3.3 Hz), 111.79, 80.03 (d, J = 37.4 Hz).

¹⁹F NMR (376 MHz, Chloroform-d) δ -165.57 (s, 1F).

IR (neat) 3100, 2921, 1614, 1445, 1369, 1126 cm^{-1}

GC/MS (*m/z*): 261.9 (100%), 107,0 (65%)

10. Characterization Data of (3-fluorobenzofuran-2-yl)trimethylsilane
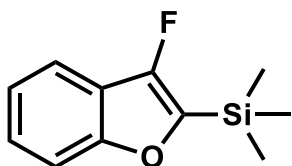
The title compound was isolated as clear colorless liquid.

TLC (SiO$_2$) R_f = 0.45 in 20:1 hexanes/toluene, *p*-anisaldehyde stain

^{1}H NMR (500 MHz, Chloroform-d) δ 7.57 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.43 (ddt, *J* = 8.3, 2.3, 0.9 Hz, 1H), 7.32 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.25 (ddd, *J* = 7.9, 7.1, 1.0 Hz, 1H), 0.41 (s, 9H).

^{13}C NMR (126 MHz, Chloroform-d) δ 158.74, 156.73, 155.92, 144.11 (d, *J* = 34.4 Hz), 125.34, 122.51, 119.35 (d, *J* = 21.2 Hz), 117.69 (d, *J* = 2.3 Hz), 111.97, -1.98.

^{19}F NMR (376 MHz, Chloroform-d) δ -169.72 (s, 1F).

IR (neat) 2959, 1569, 1371, 841 cm^{-1}

GC/MS (*m/z*): 208.1 (57%), 193.0 (100%), 115.0 (74%)

11. Characterization Data of (3-fluorobenzofuran-2-yl)(phenyl)methanol
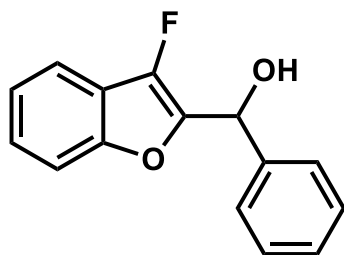
The title compound was isolated as clear colorless liquid.

TLC (SiO$_2$) R_f = 0.25 in 4:1 hexanes/toluene, *p*-anisaldehyde stain

^{1}H NMR (400 MHz, Chloroform-d) δ 7.70 – 7.47 (m, 2H), 7.47 – 7.00 (m, 5H), 6.12 (s, 1H), 2.88 – 2.47 (m, 1H).

^{13}C NMR (126 MHz, Chloroform-d) δ 128.63, 128.28, 126.44, 125.60, 123.16, 117.94, 112.13, 67.47.

^{19}F NMR (376 MHz, Chloroform-d) δ -174.71 (s, 1F).

IR (neat) 3357, 2359, 2234, 1452, 1128, 1034, 744 cm^{-1}

GC/MS (*m/z*): 242.0 (36%), 221.1 (100%), 165.0 (53%), 149.0 (32%), 105.0 (29%)

Appendix IV. Cyclopropanol Project NMR

1. NMR Spectra for Cyclopropanol
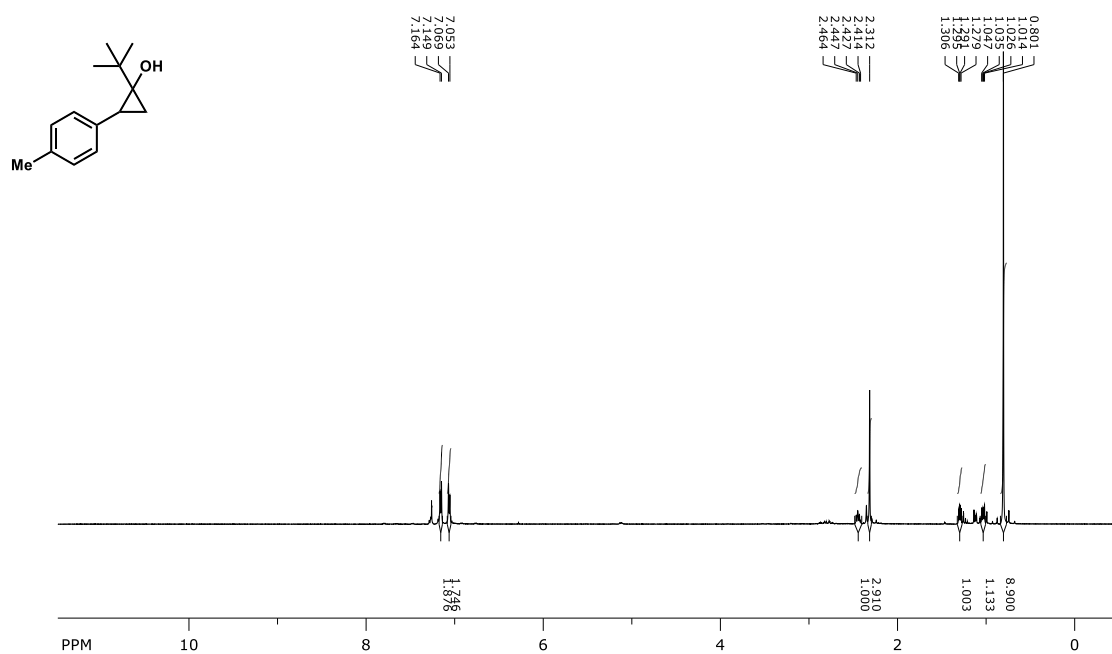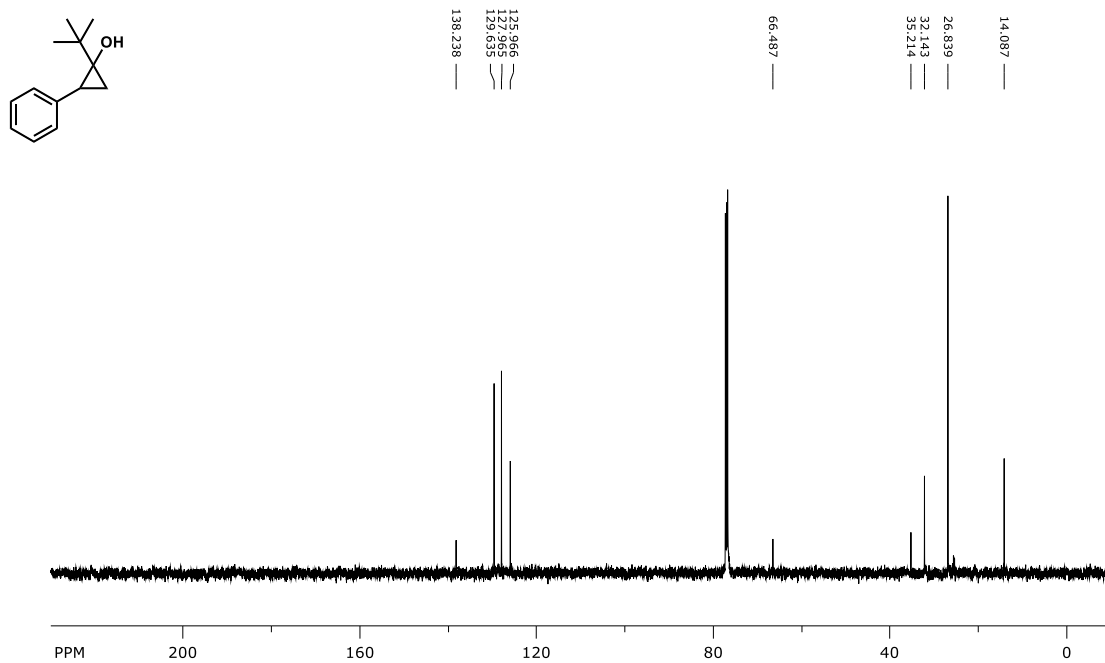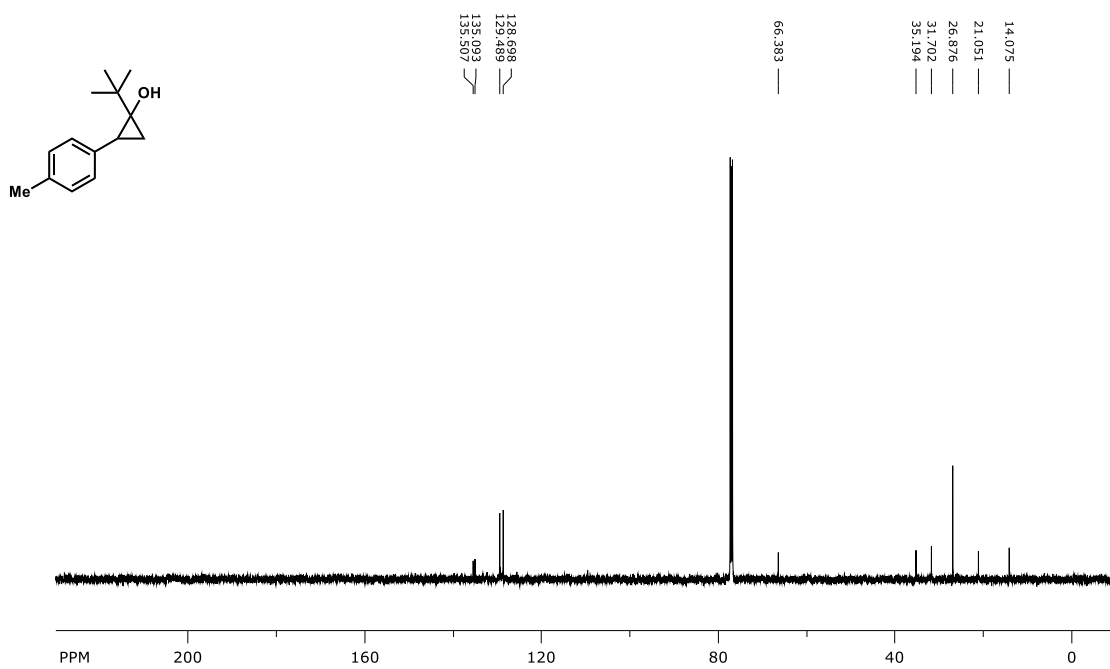
[1] H NMR (500 MHz, CDCl$_3$)

13C NMR (126 MHz, CDCl₃)

1 H NMR (500 MHz, CDCl₃)

138.238
125.966
127.965
129.635
66.487
32.143
35.214
26.839
14.087

¹³C NMR (126 MHz, CDCl₃)

7.053
7.069
7.149
7.164
2.312
2.414
2.427
2.447
2.464
1.281
1.291
1.306
1.014
1.026
1.035
1.047
1.279
0.801

1.746
1.876
2.910
1.000
1.003
1.133
8.900

¹ H NMR (500 MHz, CDCl₃)

¹³C NMR (126 MHz, CDCl₃)

^{1} **H NMR** (500 MHz, CDCl$_3$)

¹³C NMR (126 MHz, CDCl₃)

¹ H NMR (500 MHz, CDCl₃)

148.926

135.046
129.217
124.823

35.176
31.651
31.388
31.289
31.250
26.881

14.084

PPM   200   160   120   80   40   0

¹³C NMR (126 MHz, CDCl₃)

7.454
7.440
7.387
7.372
7.357

2.308

1.250
1.238
1.148
1.135
1.123

PPM   10   8   6   4   2   0

1.778
1.765

0.999
0.805
1.020
0.922
1.020
1.176
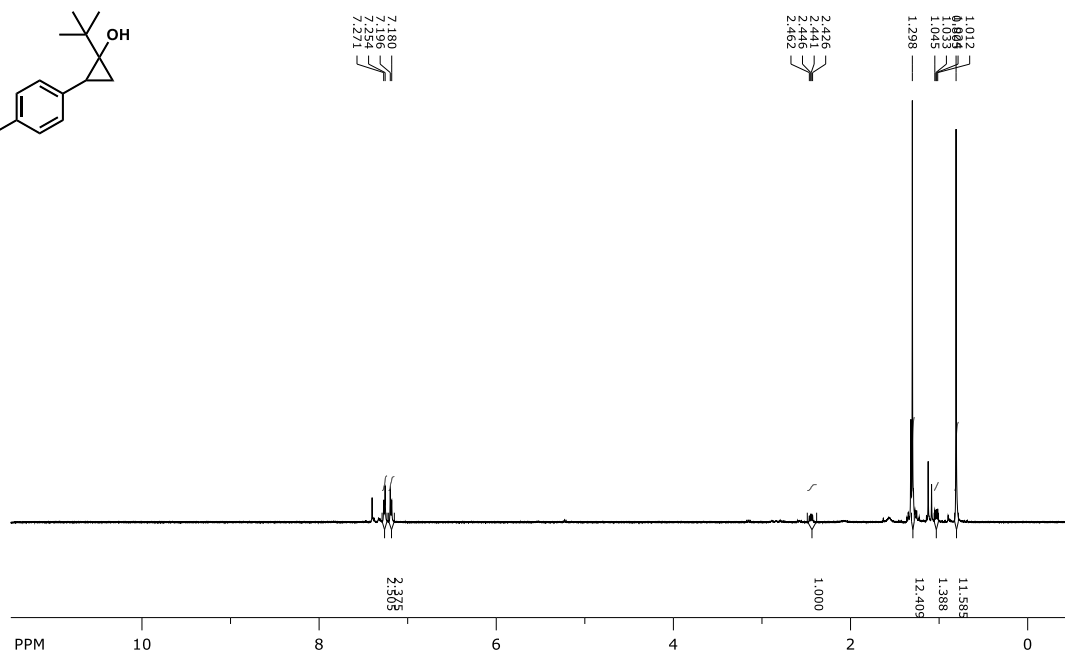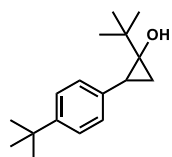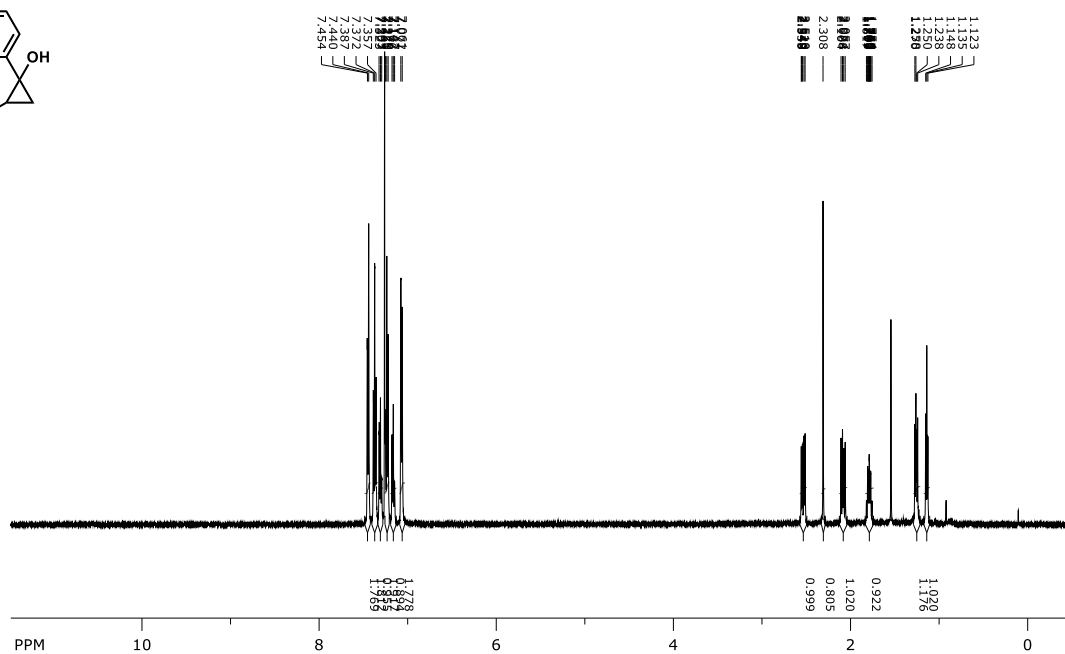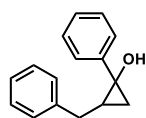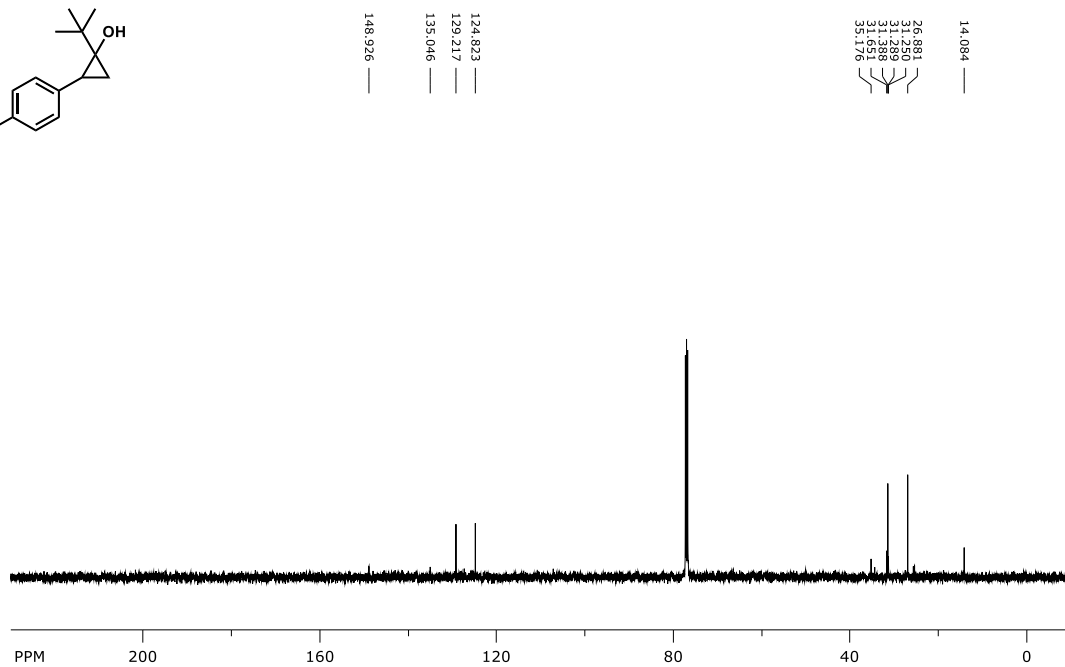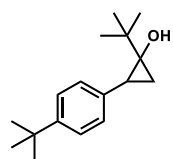
¹H NMR (500 MHz, CDCl₃)

¹³C NMR (126 MHz, CDCl₃)
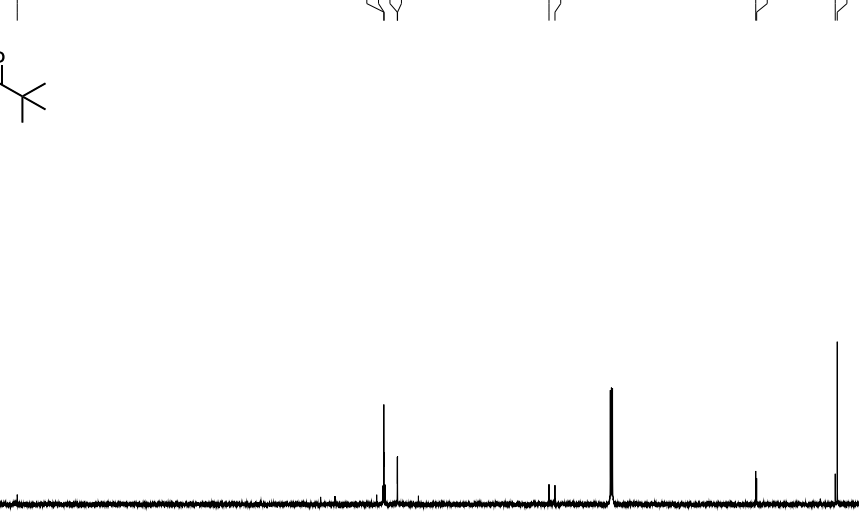
^{1} H NMR (500 MHz, CDCl$_3$)

13C NMR (126 MHz, CDCl₃)

2. MR Spectra for β-Fluoro Ketones

¹ H NMR (500 MHz, CDCl₃)

13C NMR (126 MHz, CDCl$_3$)

19F NMR (376 MHz, CDCl$_3$)

¹ H NMR (500 MHz, CDCl₃)

¹³C NMR (126 MHz, CDCl₃)

-175.797
-175.760
-175.714
-175.675
-175.636
-175.596
-175.553

¹⁹F NMR (376 MHz, CDCl₃)

^{1} **H NMR** (500 MHz, CDCl$_3$)
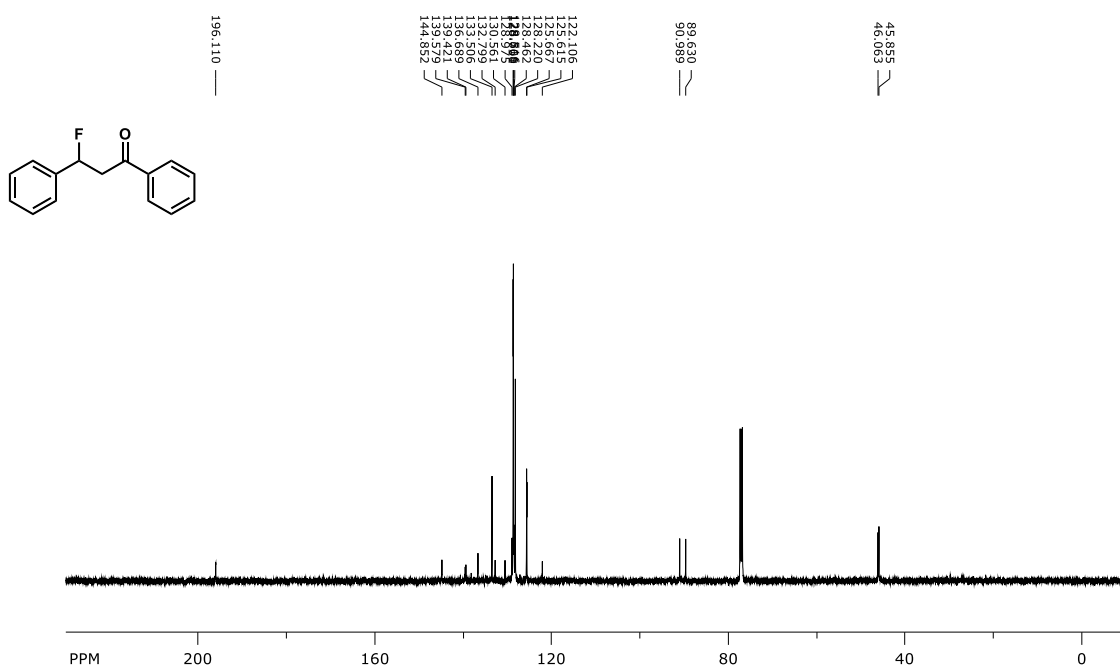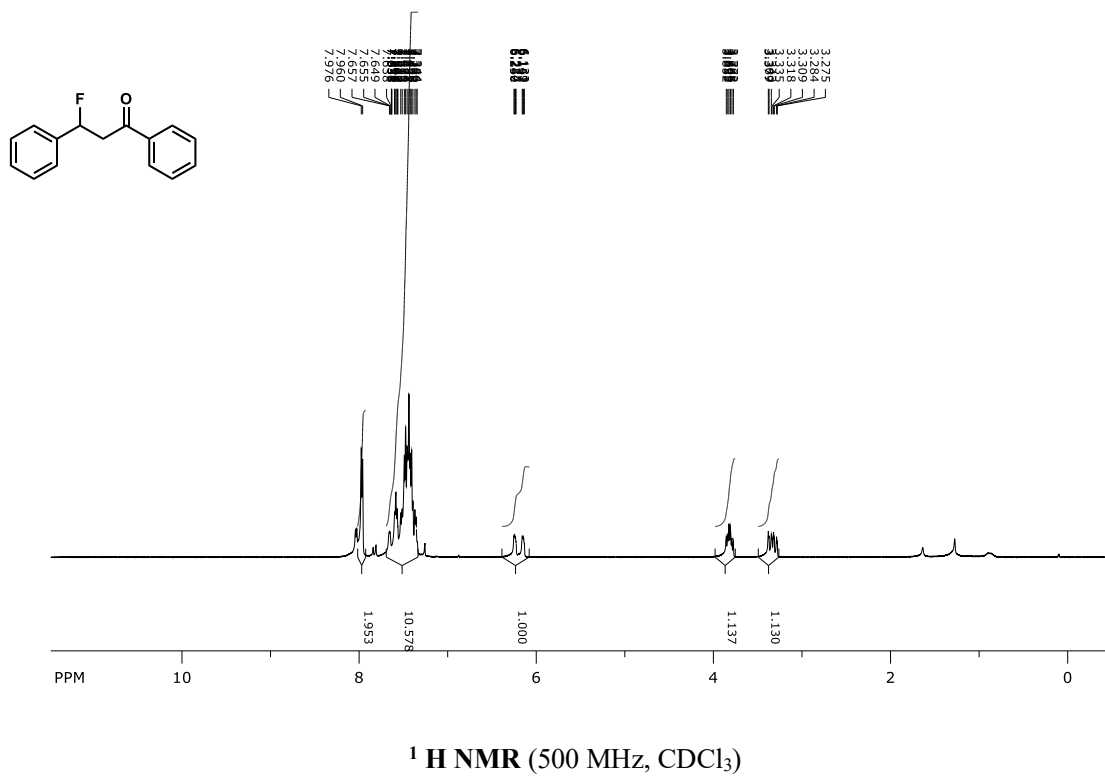
13C NMR (126 MHz, CDCl3)

-174.588
-174.549
-174.509
-174.467
-174.425
-174.386
-174.346

| PPM | -30 | -50 | -70 | -90 | -110 | -130 | -150 | -170 | -190 |

19F NMR (376 MHz, CDCl3)

^{1} **H NMR** (500 MHz, CDCl$_3$)

¹³C NMR (126 MHz, CDCl₃)

-172.561
-172.523
-172.476
-172.438
-172.398
-172.352
-172.315

¹⁹F NMR (376 MHz, CDCl₃)

PPM   -80   -100   -120   -140   -160   -180   -200   -220   -240

^{1} **H NMR** (500 MHz, CDCl$_3$)

¹³C NMR (126 MHz, CDCl₃)

-173.872
-173.835
-173.789
-173.750
-173.711
-173.665
-173.629

¹⁹F NMR (376 MHz, CDCl₃)

^{1} **H NMR** (500 MHz, CDCl$_3$)

¹³C NMR (126 MHz, CDCl₃)

-172.588
-172.551
-172.506
-172.466
-172.427
-172.381
-172.345

PPM   -80   -100   -120   -140   -160   -180   -200   -220   -240

¹⁹F NMR (376 MHz, CDCl₃)

¹ H NMR (500 MHz, CDCl₃)
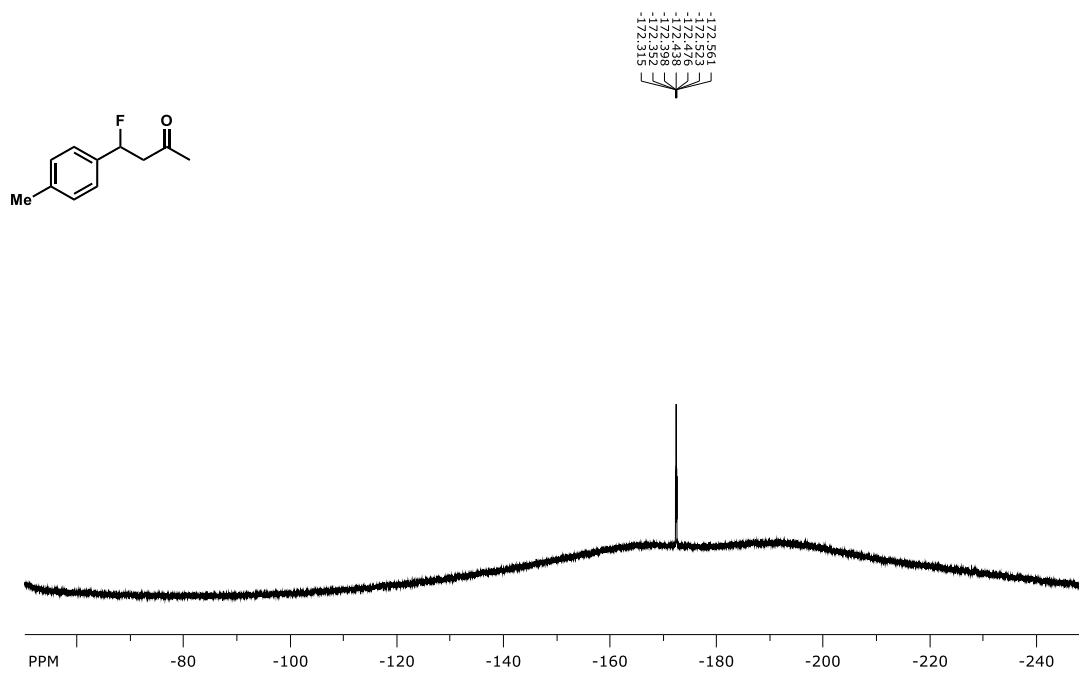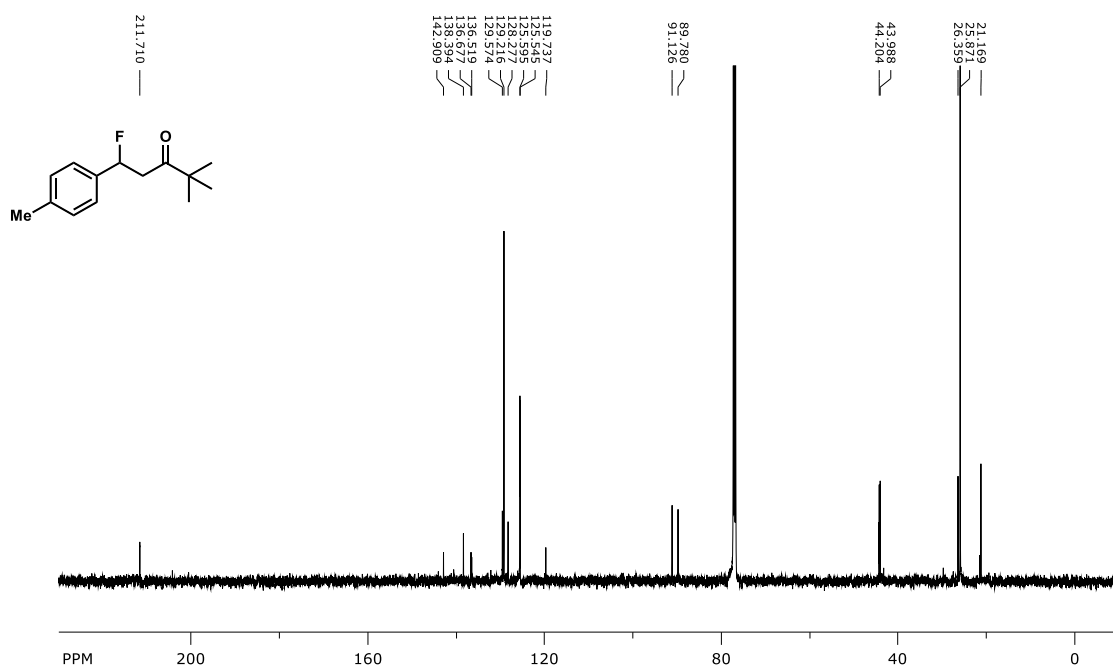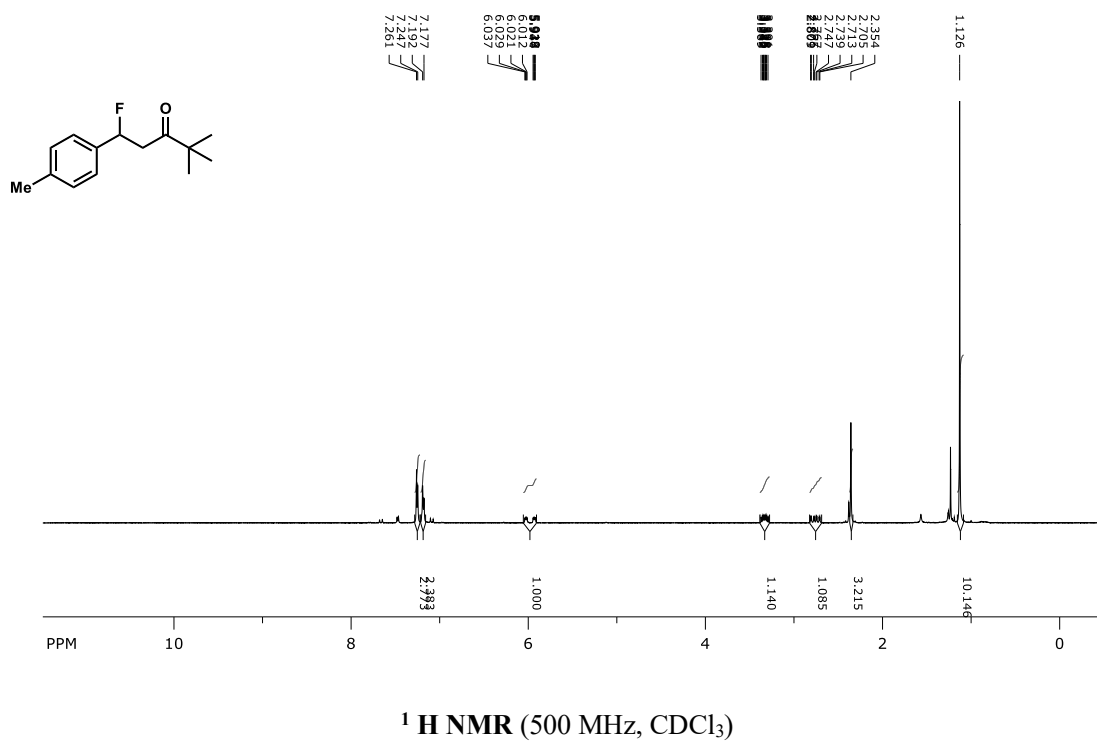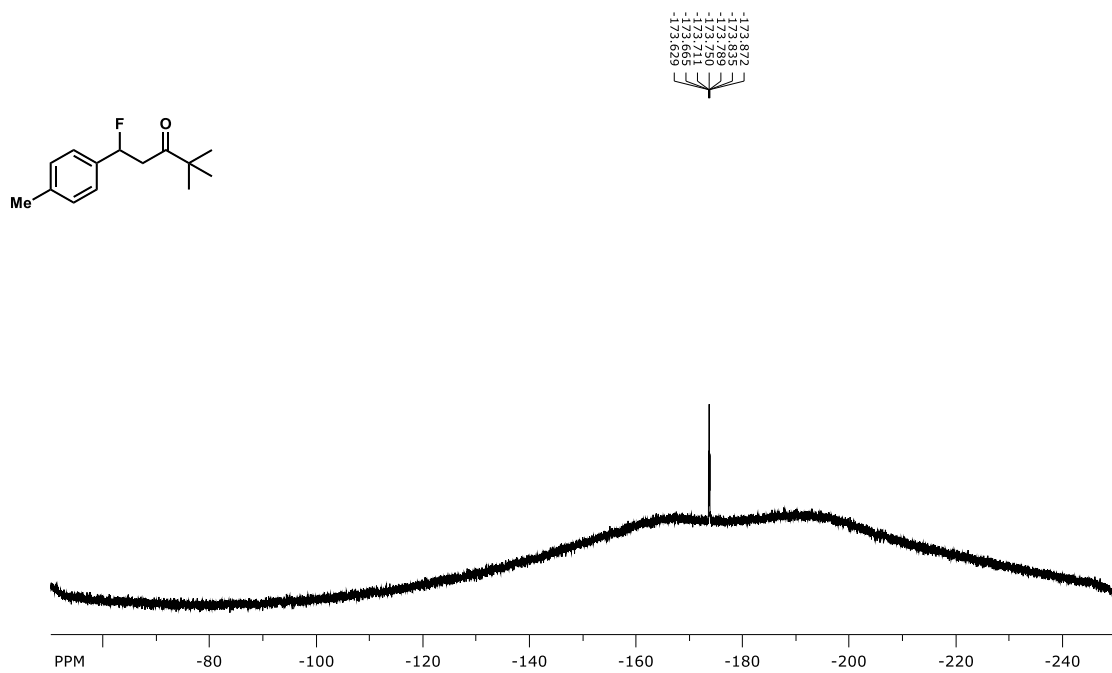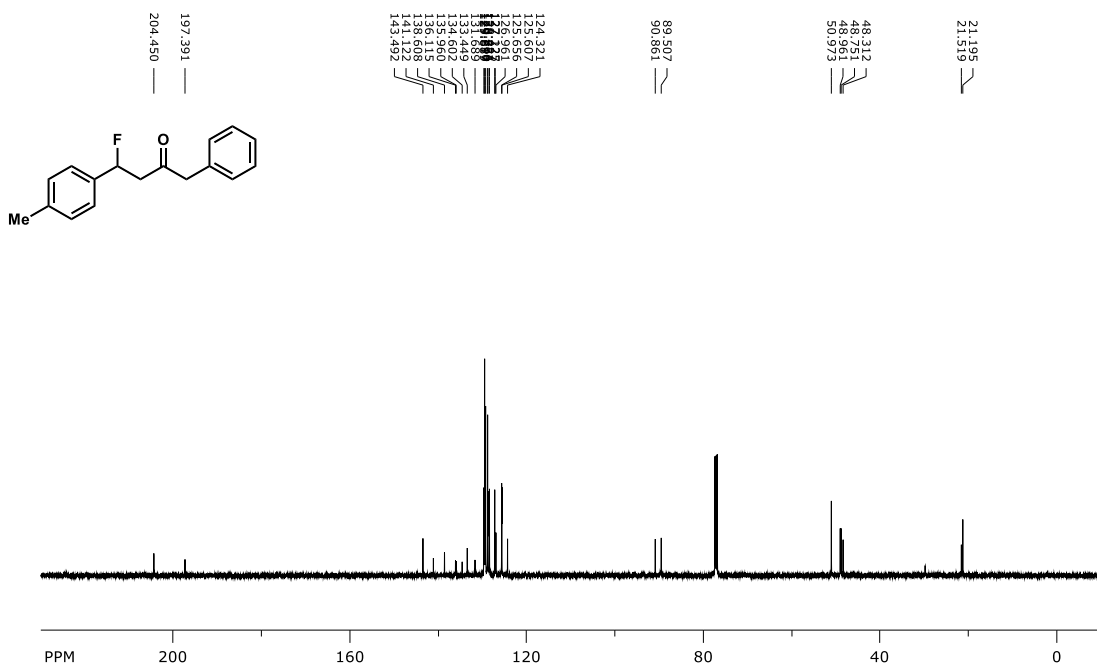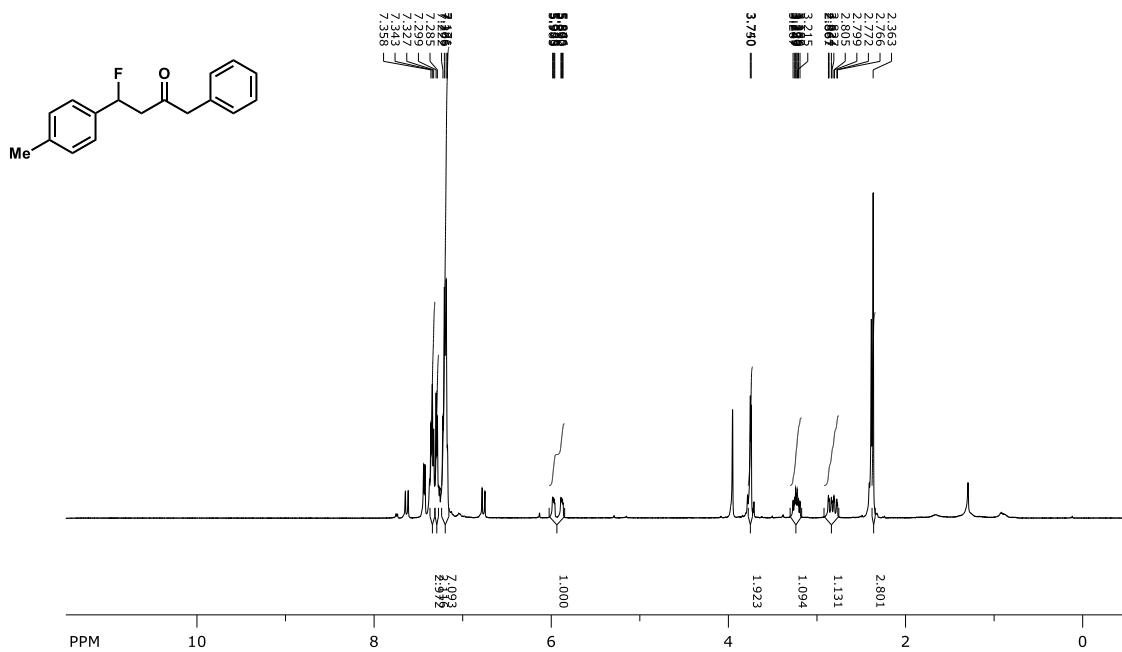
¹³C NMR (126 MHz, CDCl₃)

-174.085
-174.048
-173.969
-173.961
-173.924
-173.875
-173.838
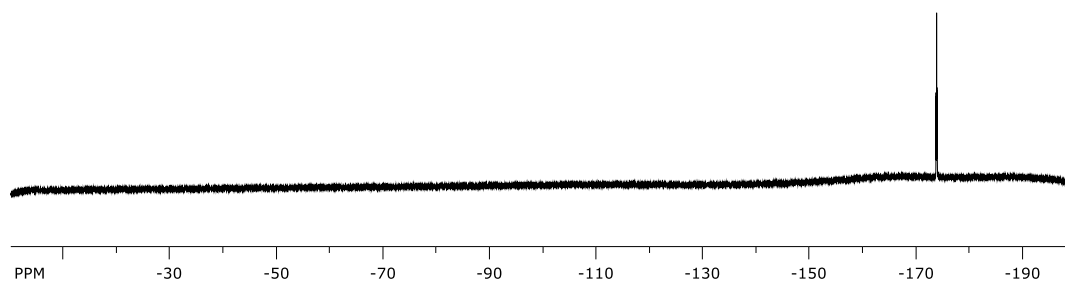
PPM   -30   -50   -70   -90   -110   -130   -150   -170   -190

¹⁹F NMR (376 MHz, CDCl₃)

¹ H NMR (500 MHz, CDCl₃)

¹³C NMR (126 MHz, CDCl₃)

¹⁹F NMR (376 MHz, CDCl₃)

^{1} **H NMR** (500 MHz, CDCl$_3$)

¹³C NMR (126 MHz, CDCl₃)

-178.925
-178.883
-178.862
-178.821
-178.672
-178.631
-178.609
-178.567

¹⁹F NMR (376 MHz, CDCl₃)

PPM   -80   -100   -120   -140   -160   -180   -200   -220   -240
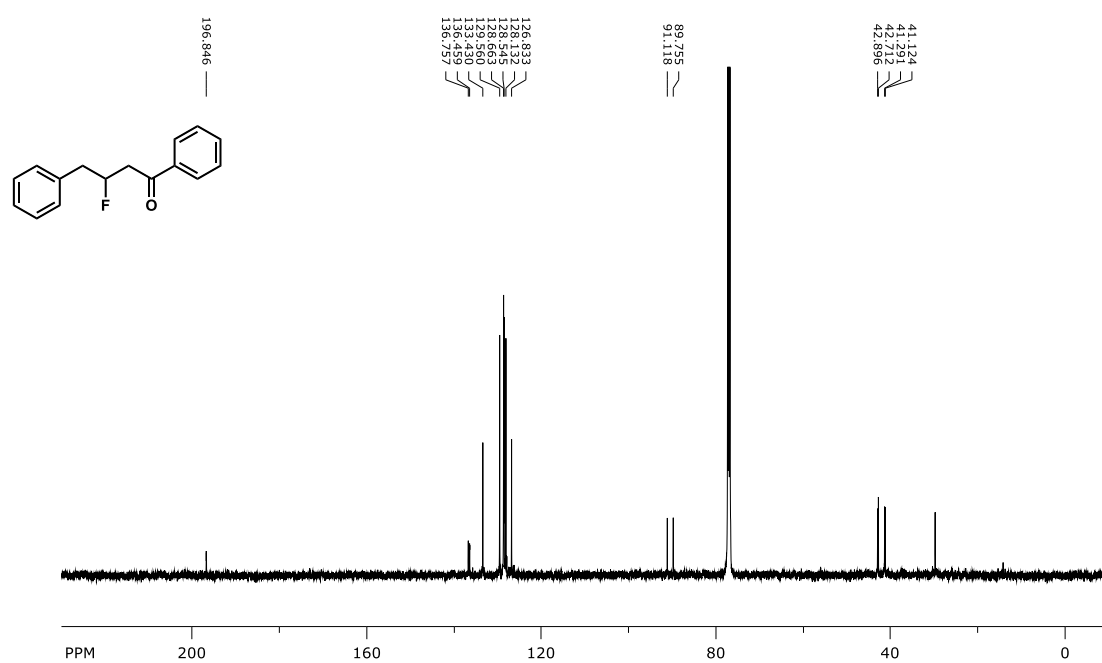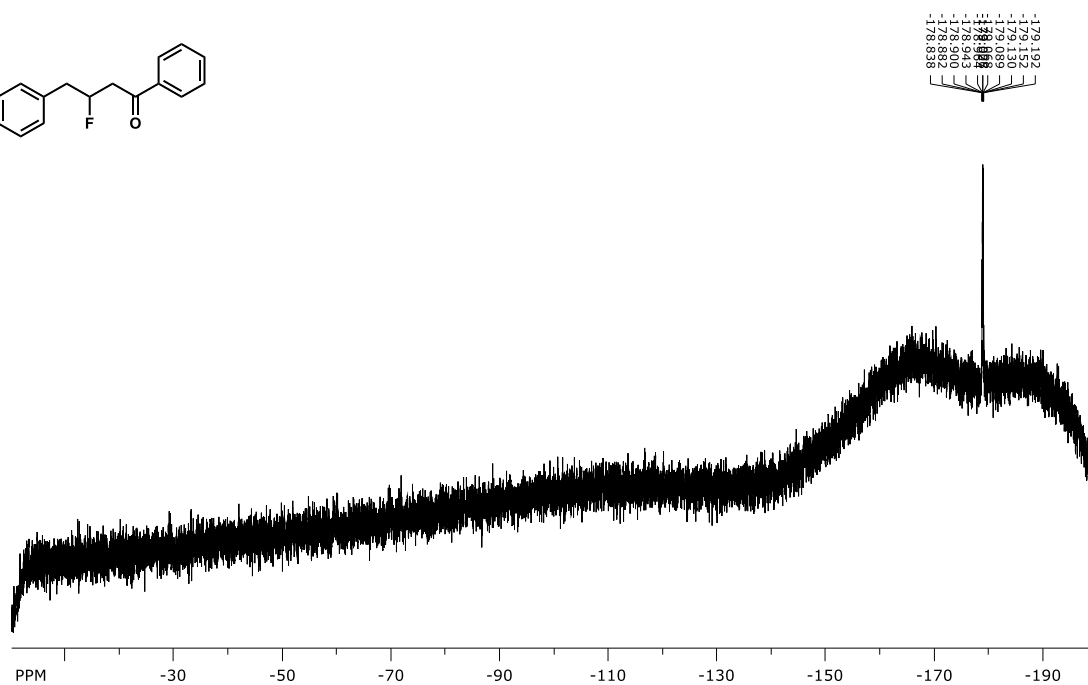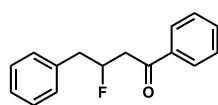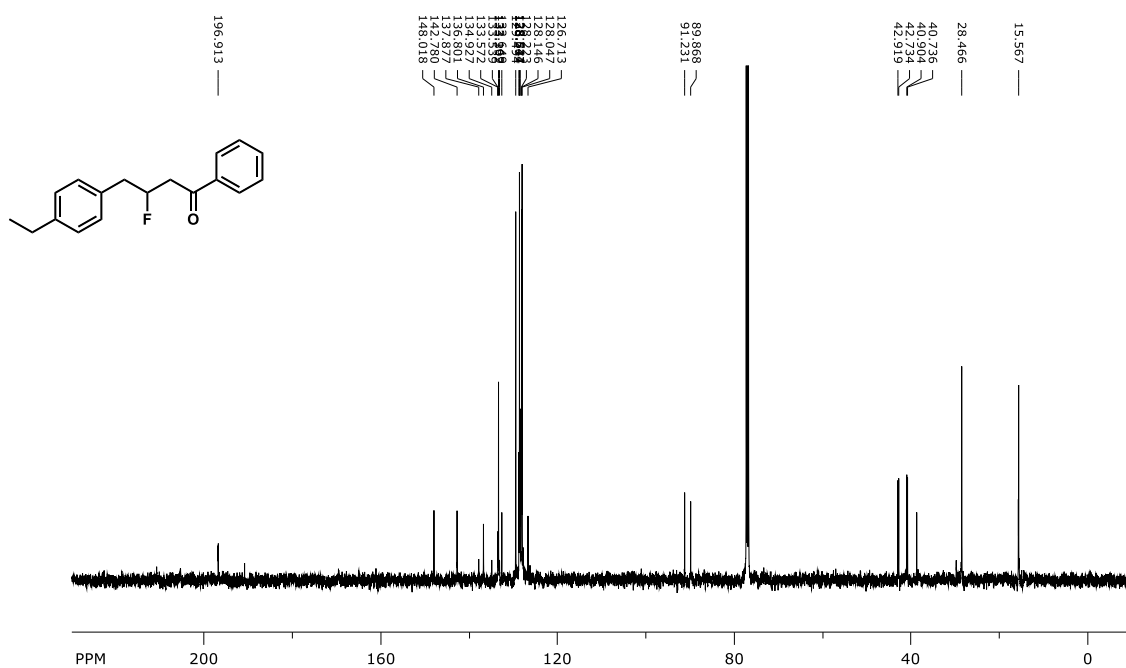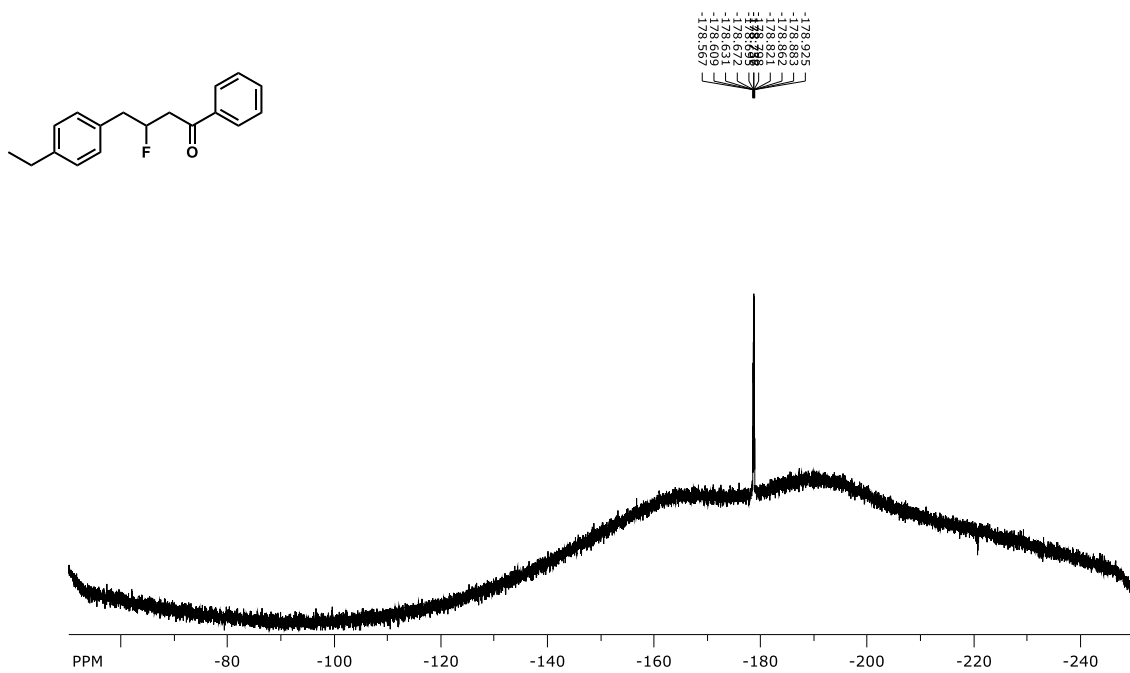
Appendix V. Tertiary Bromide Project NMR

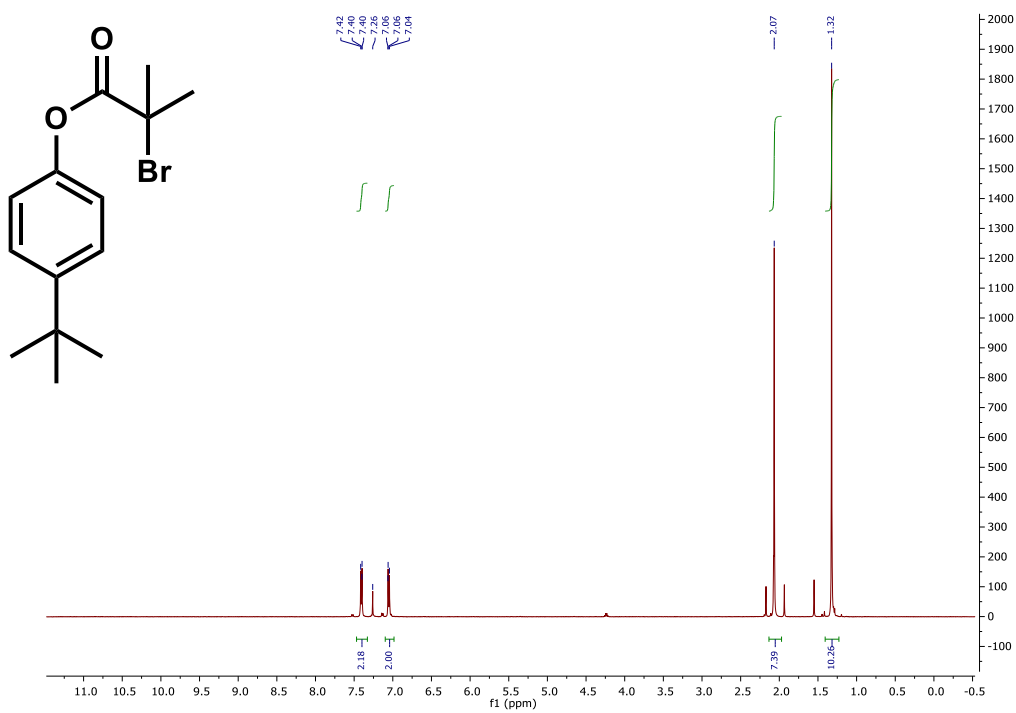## 1. NMR Spectra for α-Bromoketones

^{1}**H NMR** (500 MHz, Chloroform-*d*)

^{13}C NMR (126 MHz, Chloroform-*d*)

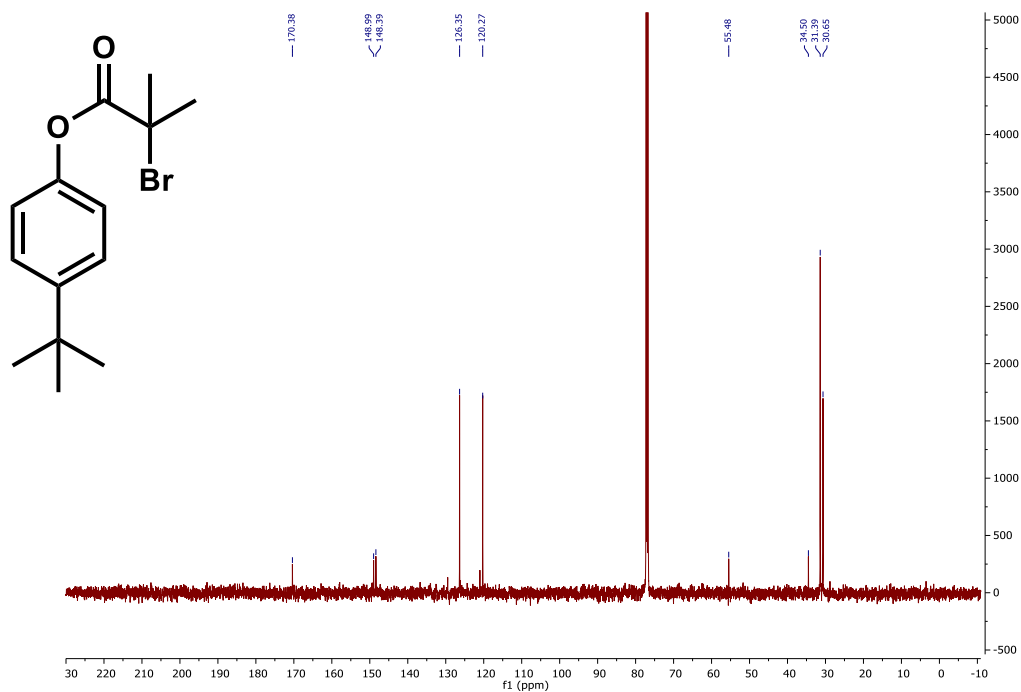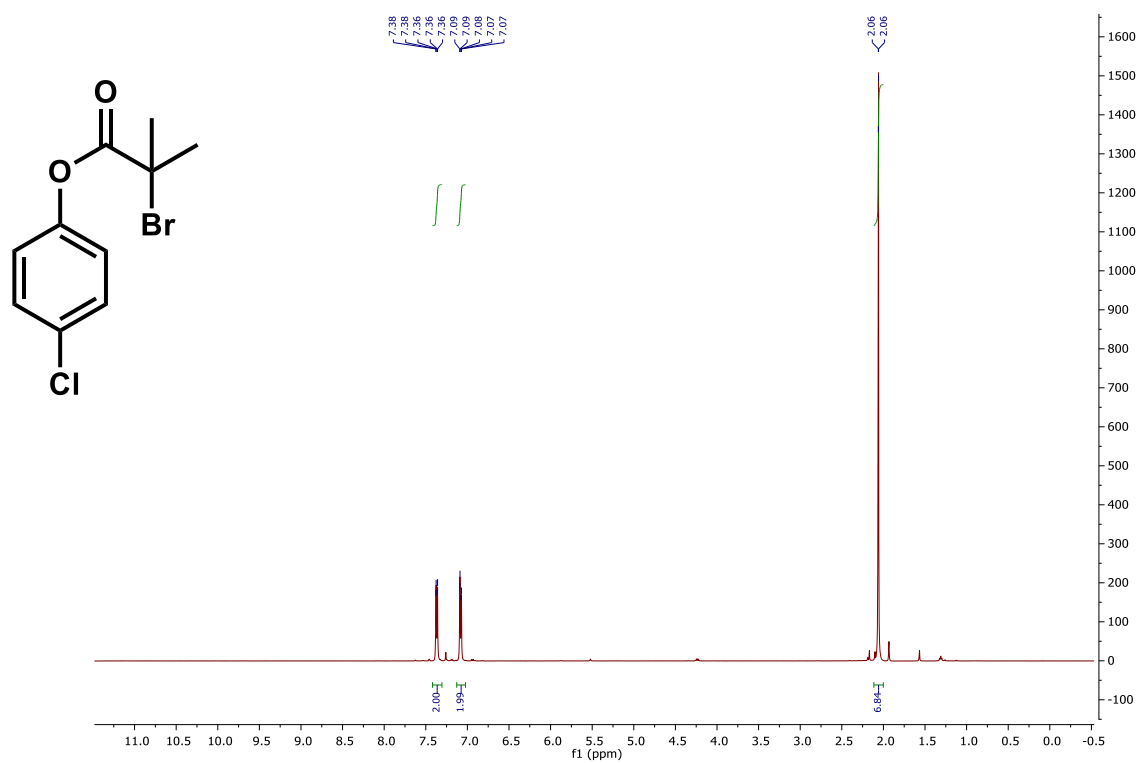**^{1}H NMR** (500 MHz, Chloroform-*d*)

¹³C NMR (126 MHz, Chloroform-*d*)

¹H NMR (500 MHz, Chloroform-*d*)

¹³C NMR (126 MHz, Chloroform-*d*)

¹H NMR (500 MHz, Chloroform-*d*)

¹³C NMR (126 MHz, Chloroform-*d*)
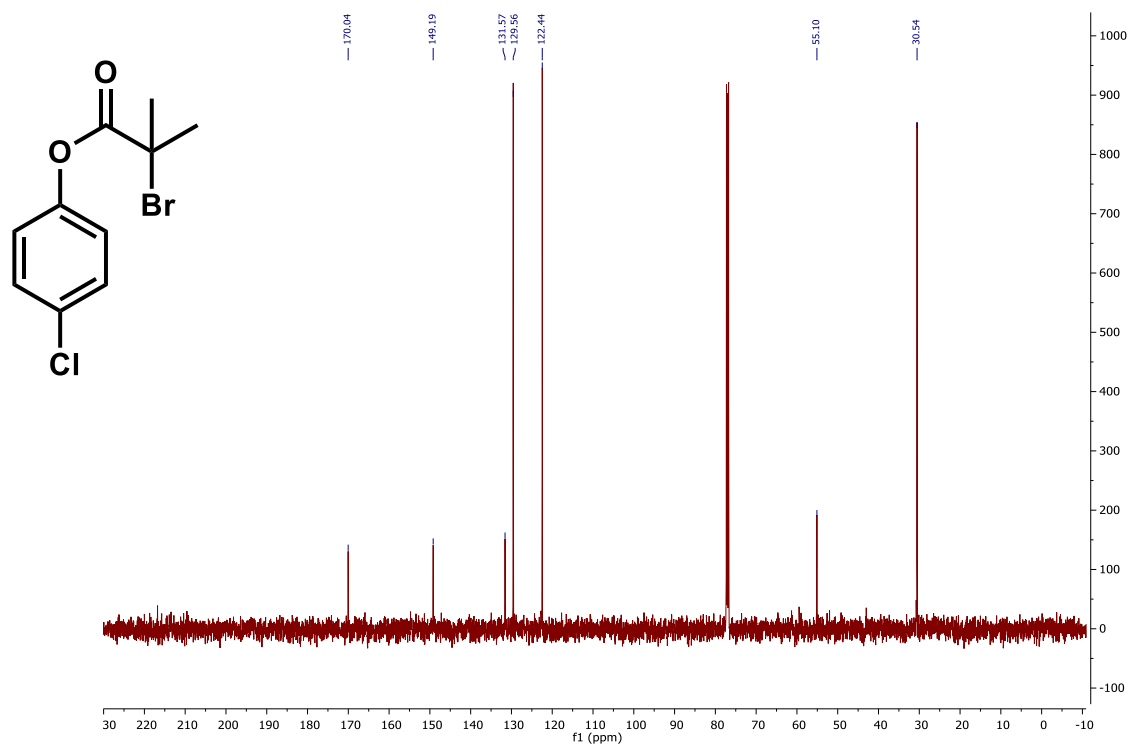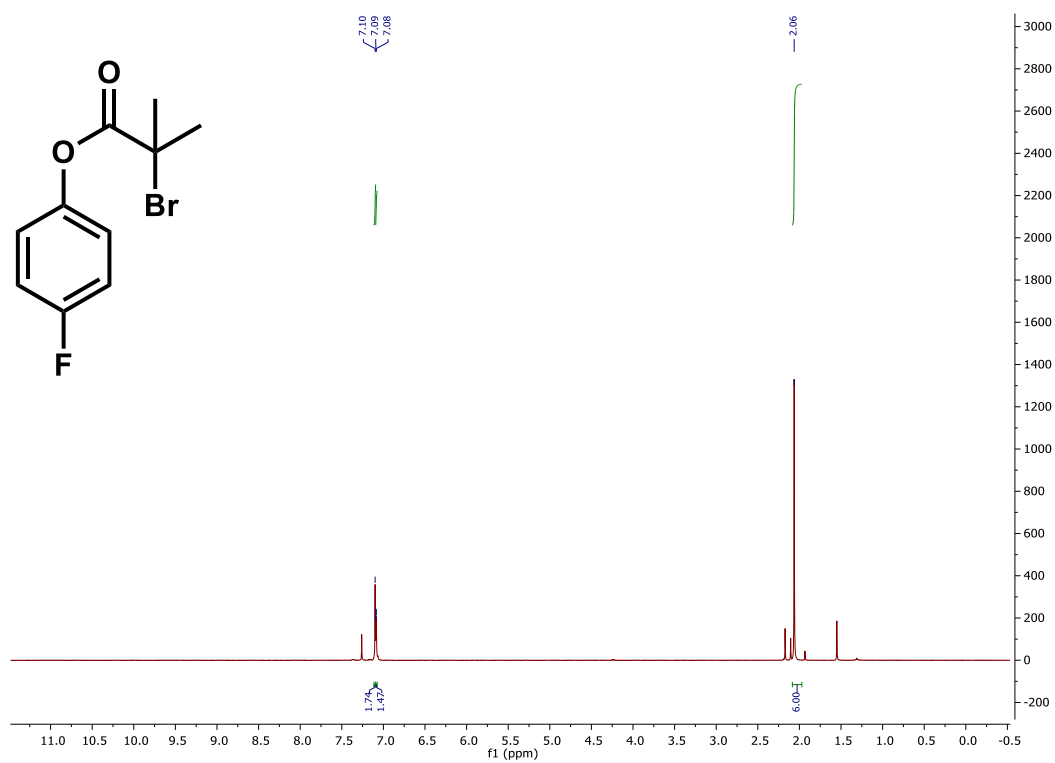

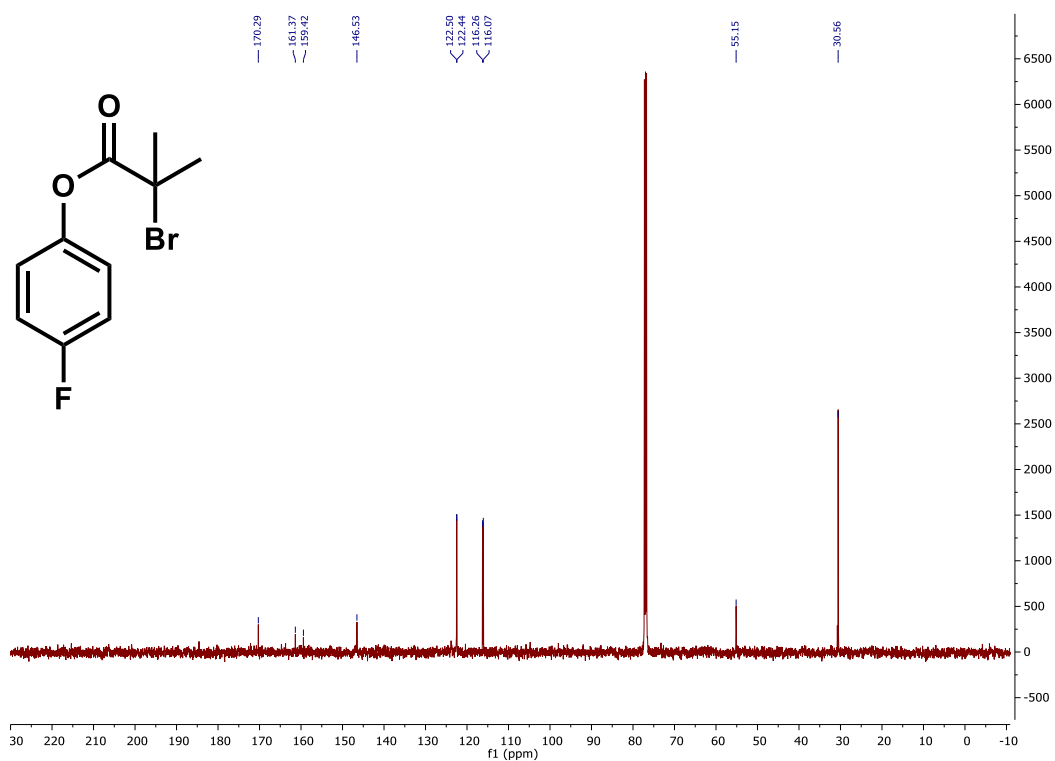
¹H NMR (500 MHz, Chloroform-*d*)

^{13}**C NMR** (126 MHz, Chloroform-*d*)

2. NMR Spectra for α-Bromoesters

¹H NMR (500 MHz, Chloroform-*d*)

¹³C NMR (126 MHz, Chloroform-*d*)

¹H NMR (500 MHz, Chloroform-*d*)

¹³C NMR (126 MHz, Chloroform-*d*)

¹H NMR (500 MHz, Chloroform-*d*)

¹³C NMR (126 MHz, Chloroform-*d*)

-116.90
-116.92
-116.94
-116.95

¹⁹F NMR (376 MHz, Chloroform-*d*)

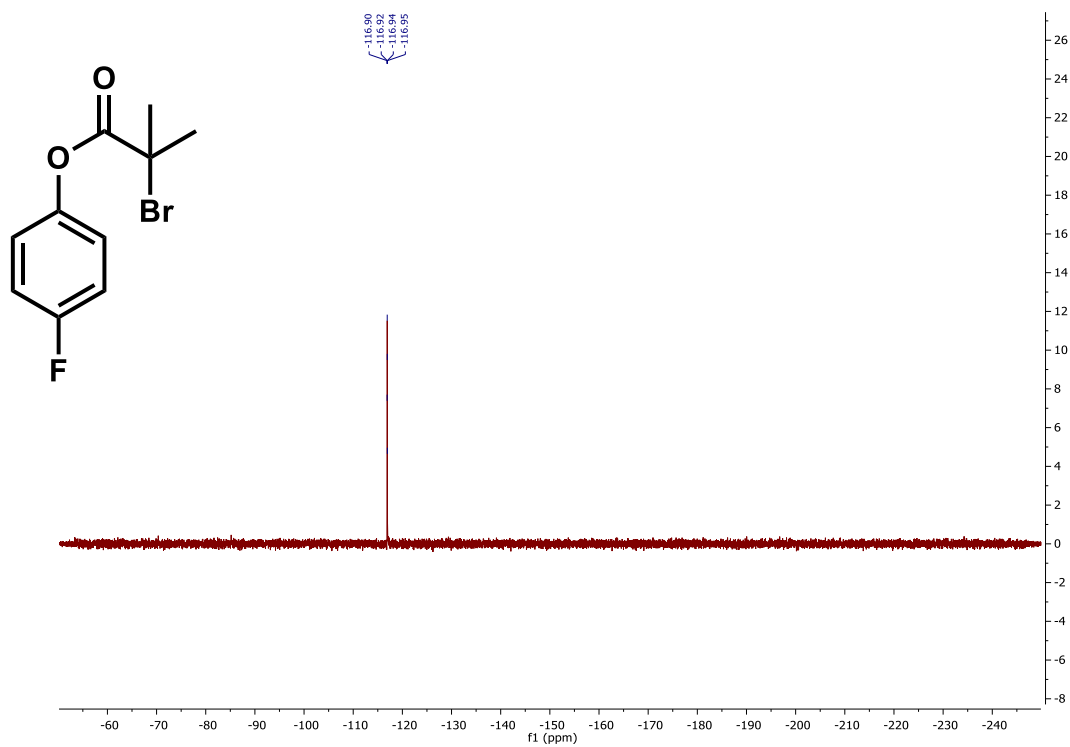**¹H NMR** (500 MHz, Chloroform-*d*)

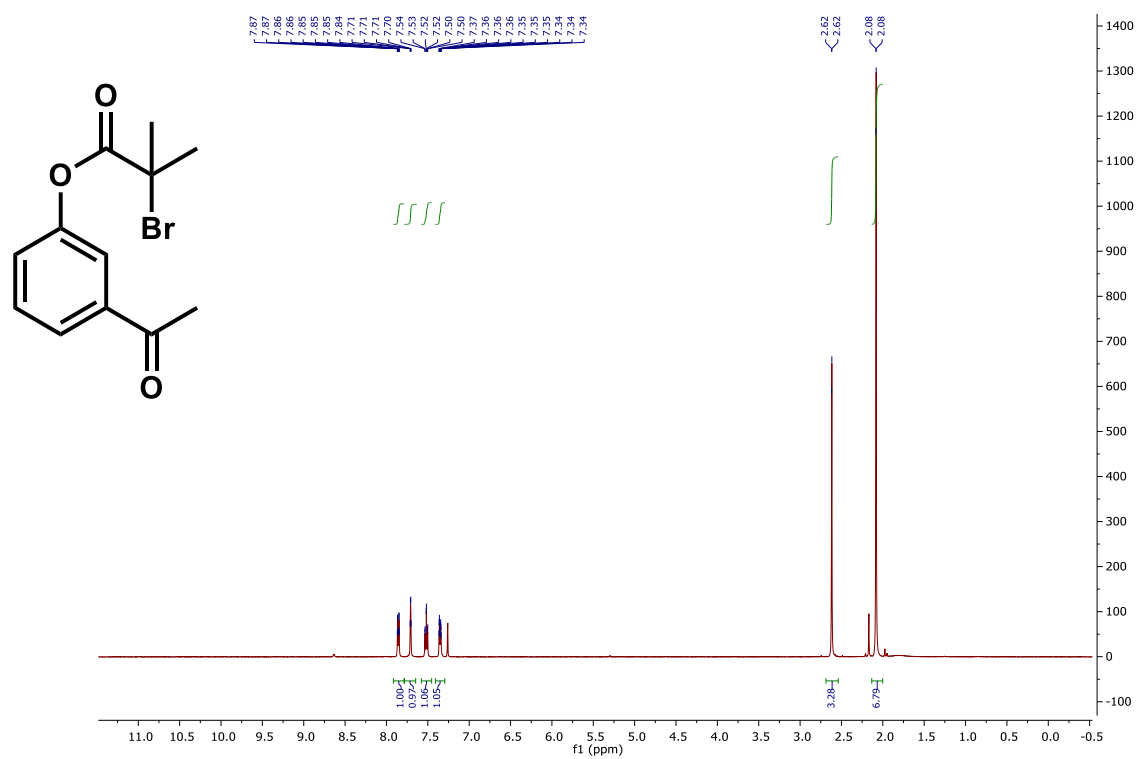**¹³C NMR** (126 MHz, Chloroform-*d*)

¹H NMR (500 MHz, Chloroform-*d*)

^{13}**C NMR** (126 MHz, Chloroform-d)

¹H NMR (500 MHz, Chloroform-*d*)

¹³C NMR (126 MHz, Chloroform-*d*)

¹H NMR (500 MHz, Chloroform-*d*)
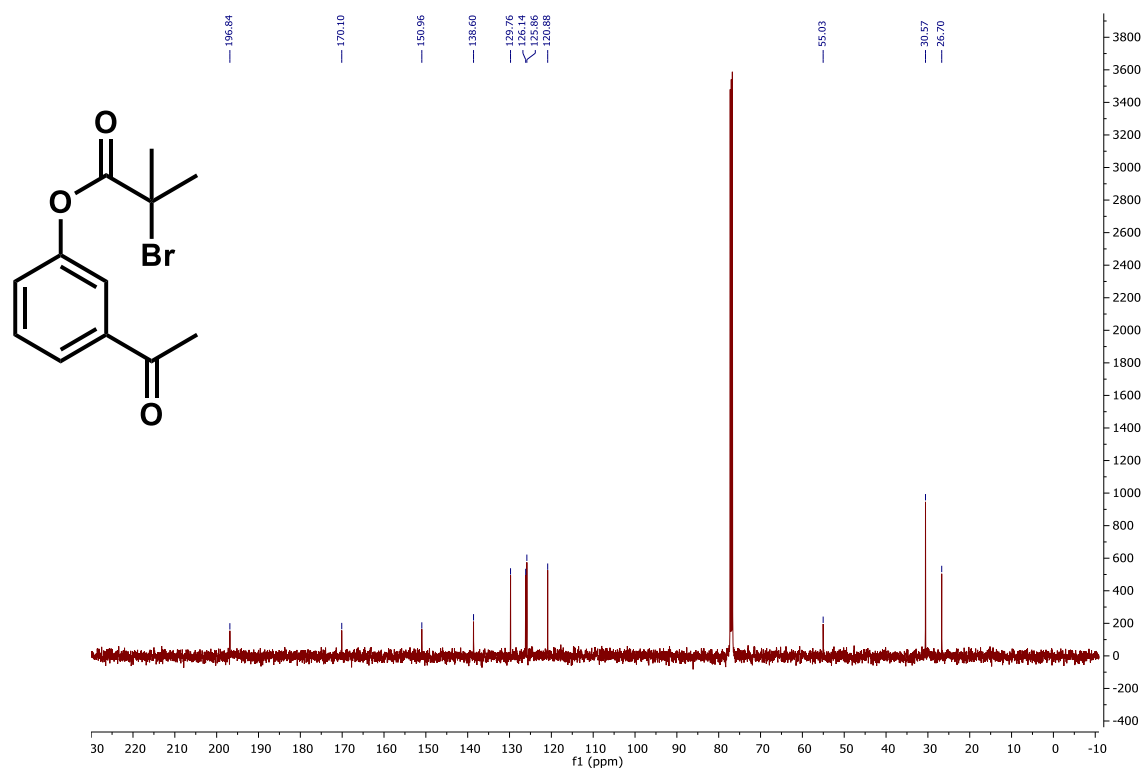
¹³C NMR (126 MHz, Chloroform-*d*)
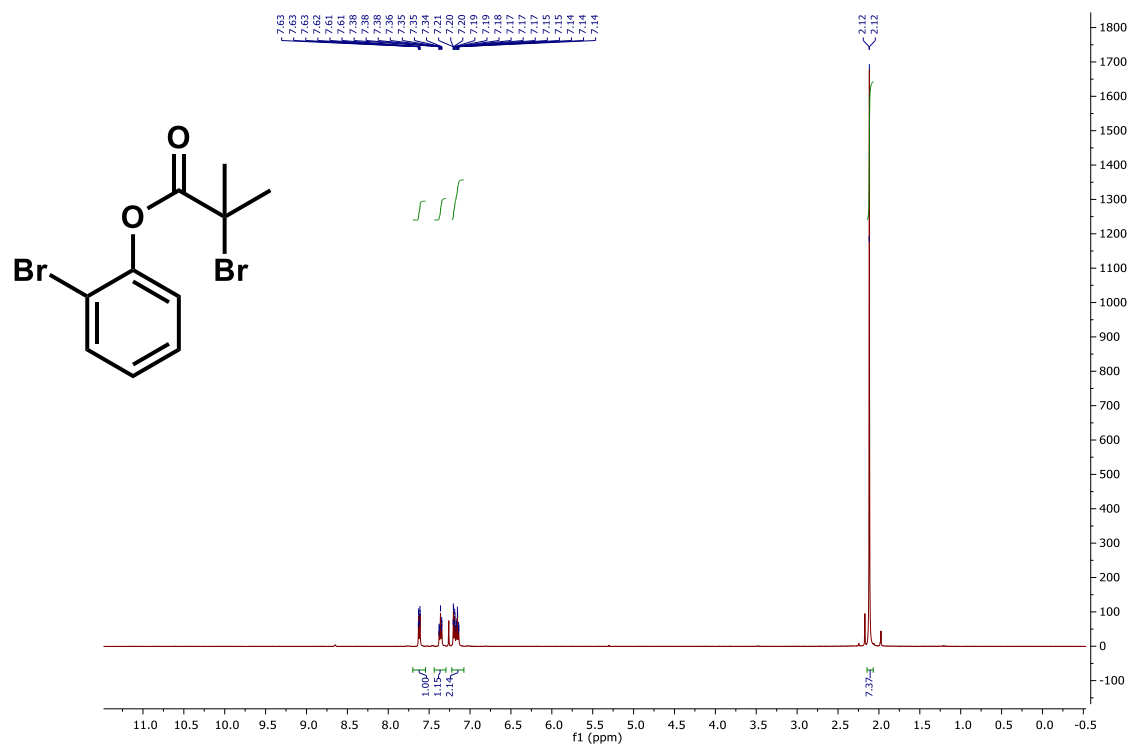
¹H NMR (500 MHz, Chloroform-*d*)

13C NMR (126 MHz, Chloroform-*d*)
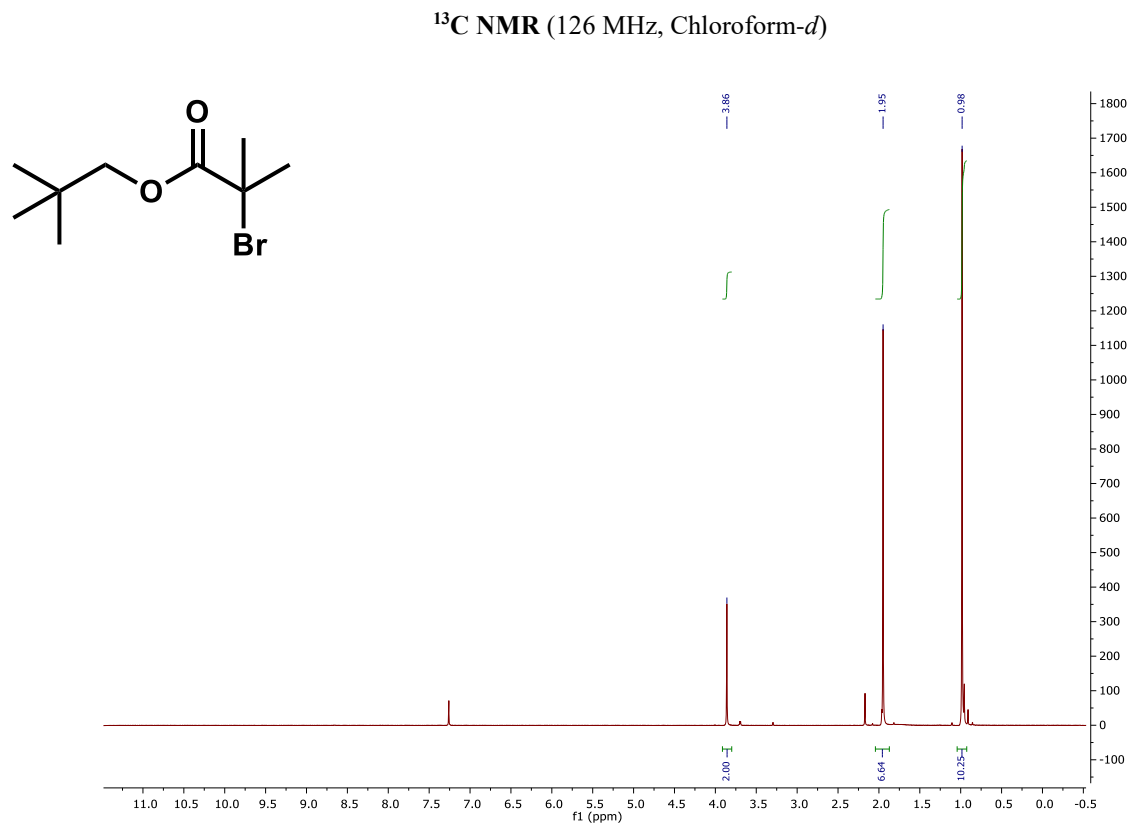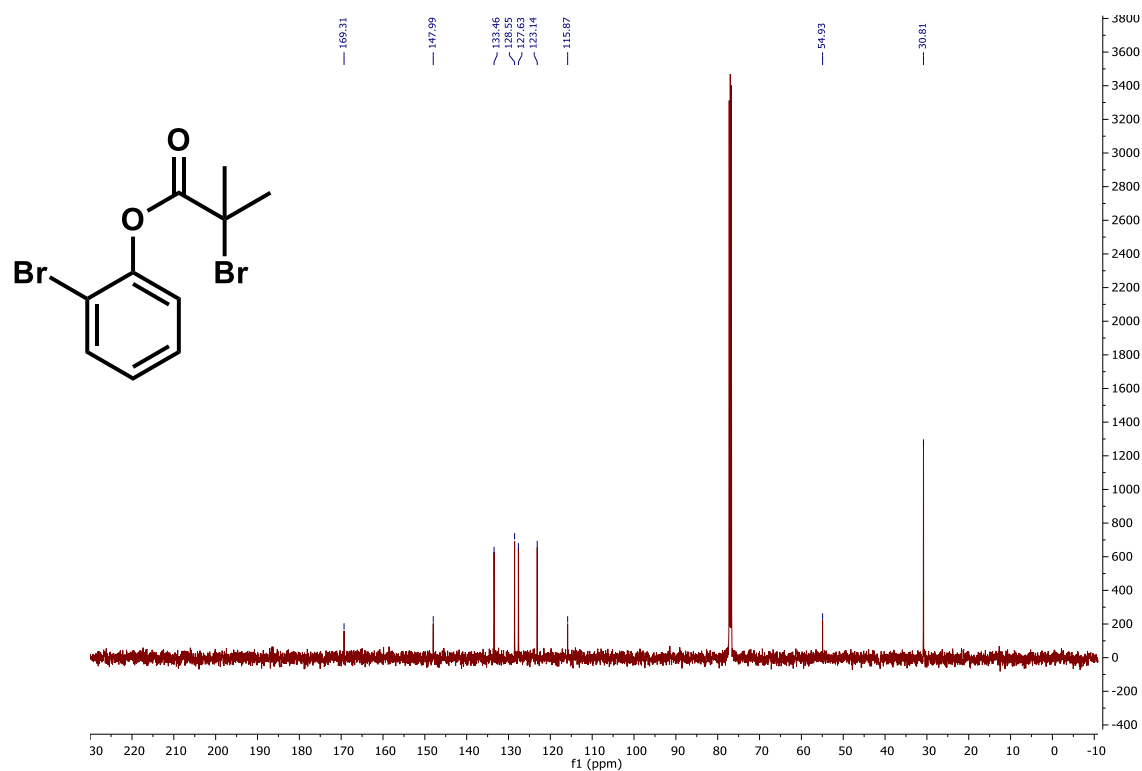
¹H NMR (500 MHz, Chloroform-*d*)

¹³C NMR (126 MHz, Chloroform-*d*)

¹H NMR (500 MHz, Chloroform-*d*)

¹³C NMR (126 MHz, Chloroform-*d*)

3. NMR Spectra for Alkyl Tertiary Bromide

^{1}**H NMR** (500 MHz, Chloroform-*d*)
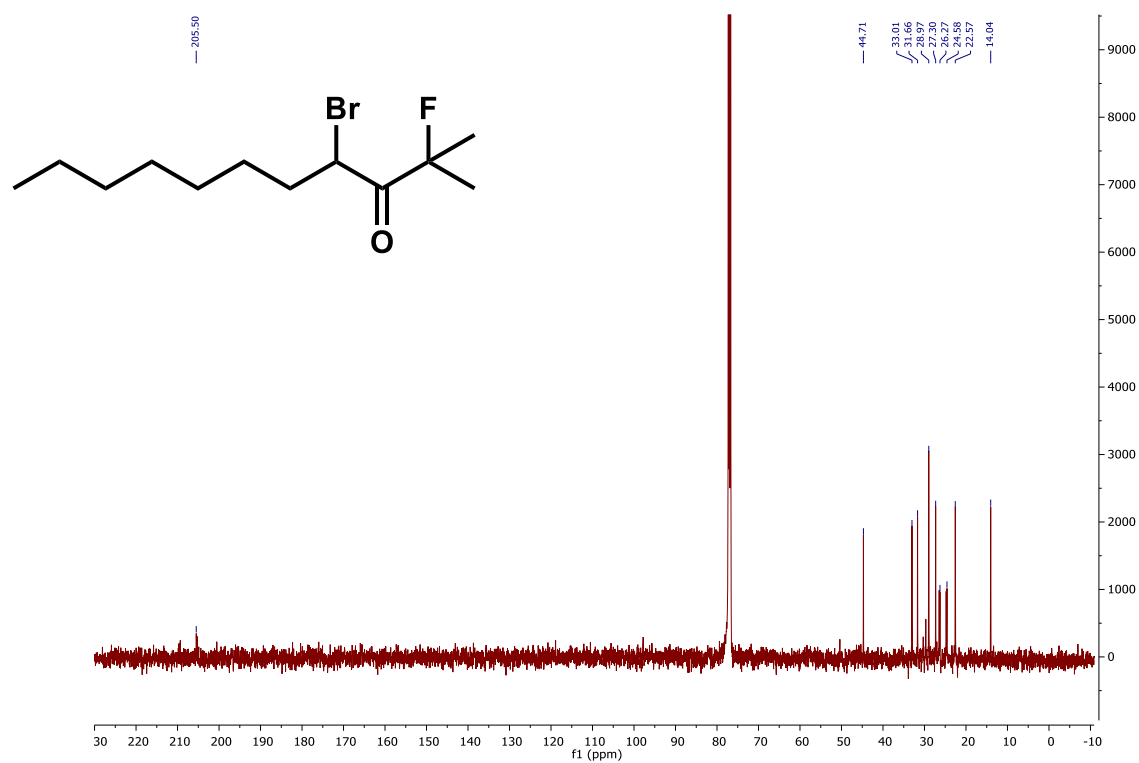
¹³C NMR (126 MHz, Chloroform-*d*)
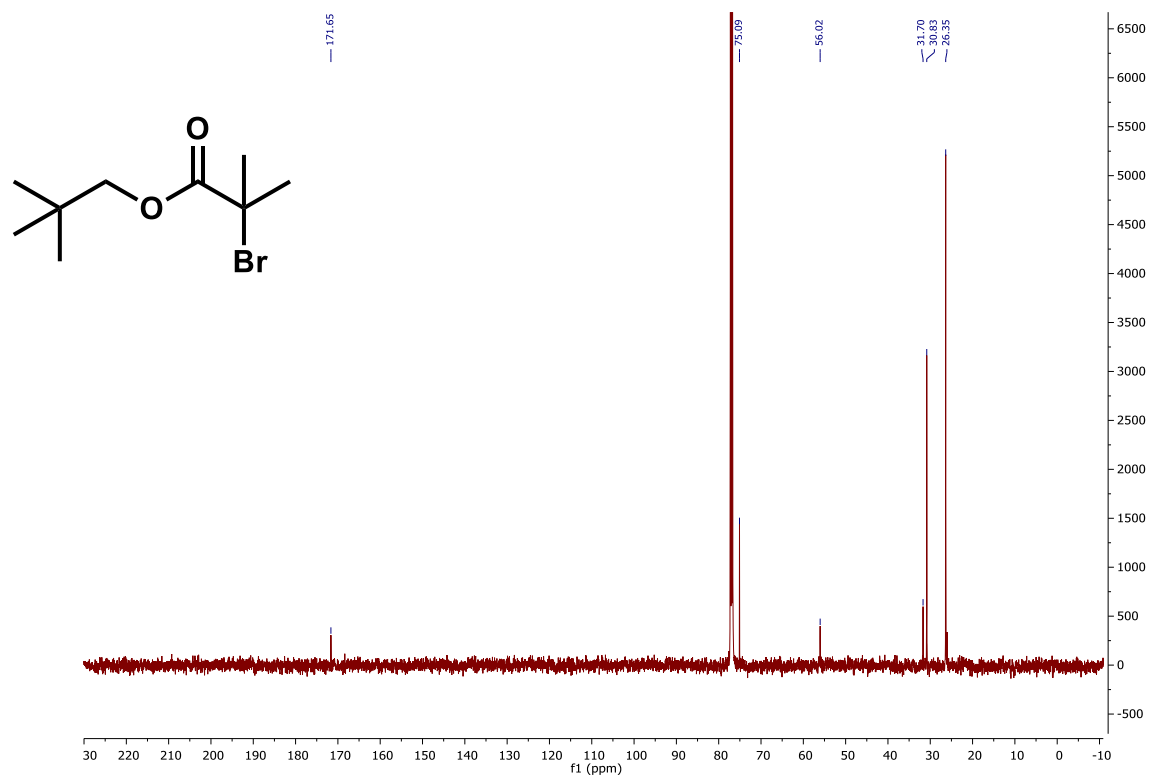
4. NMR Spectra for α-Fluoroketones

¹H NMR (500 MHz, Chloroform-*d*)

¹³C NMR (126 MHz, Chloroform-*d*)

¹⁹F NMR (376 MHz, Chloroform-*d*)

¹H NMR (500 MHz, Chloroform-*d*)

¹³C NMR (126 MHz, Chloroform-*d*)

¹⁹F NMR (376 MHz, Chloroform-*d*)
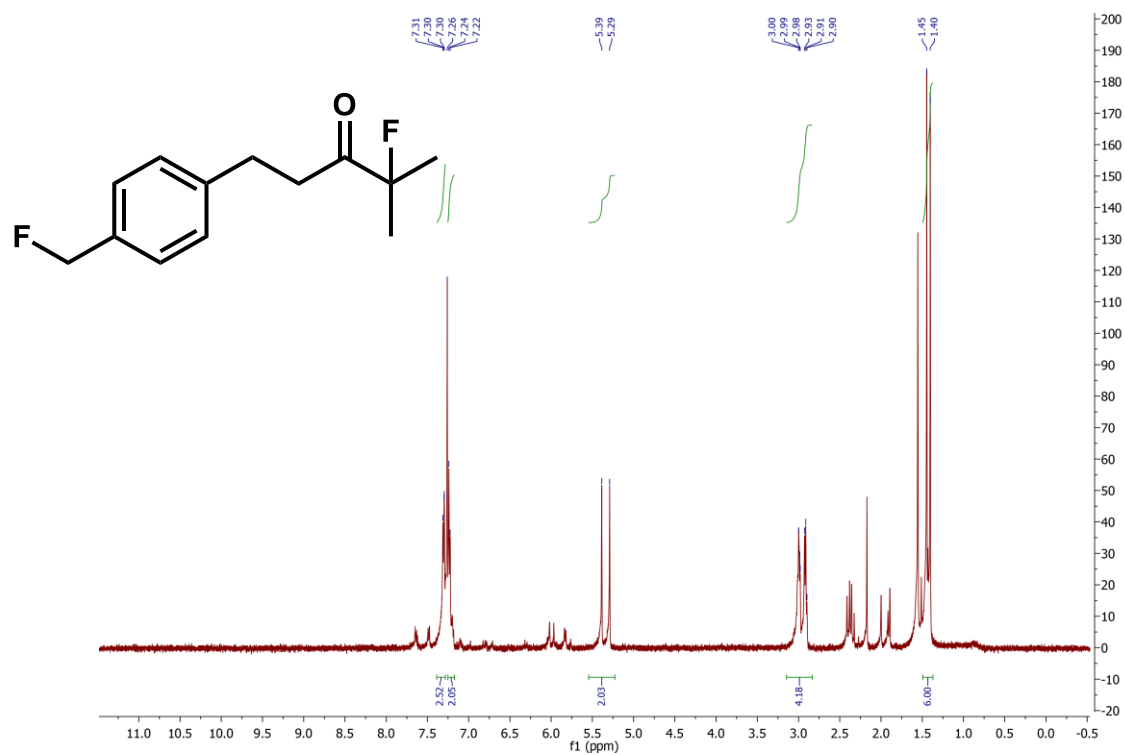
¹H NMR (500 MHz, Chloroform-*d*)
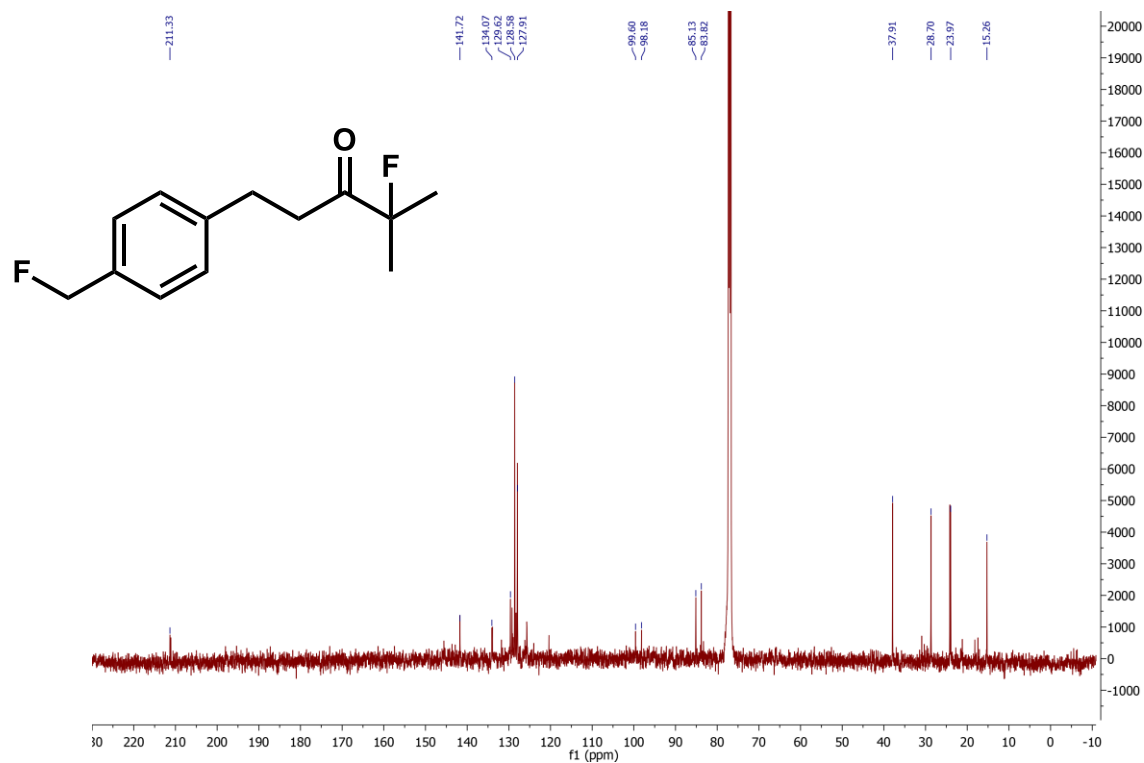
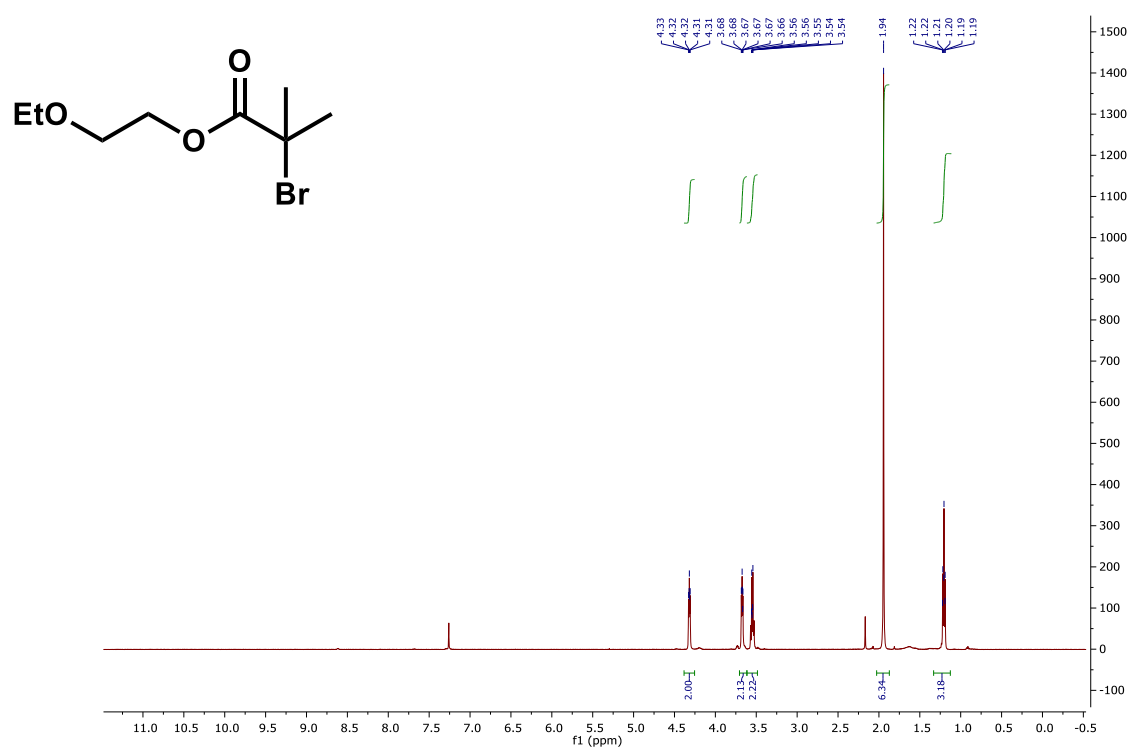**¹³C NMR** (126 MHz, Chloroform-*d*)

¹⁹F NMR (376 MHz, Chloroform-*d*)

¹H NMR (500 MHz, Chloroform-*d*)

¹³C NMR (126 MHz, Chloroform-*d*)
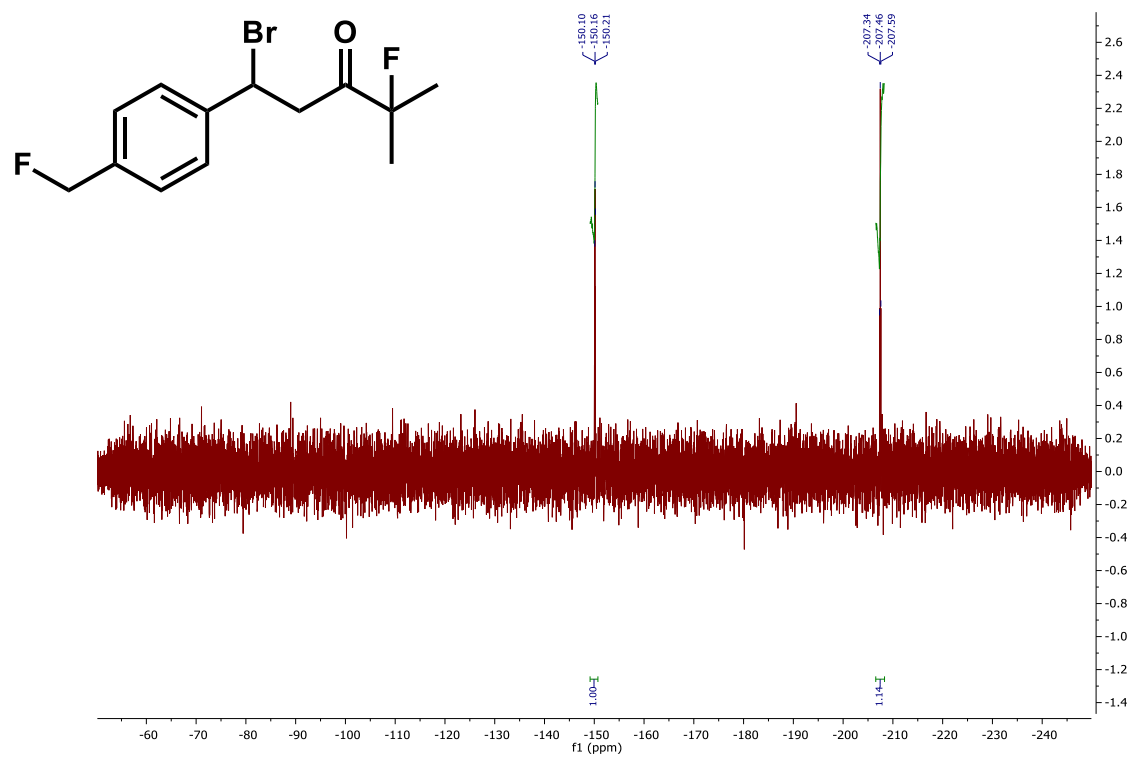
¹⁹F NMR (376 MHz, Chloroform-*d*)
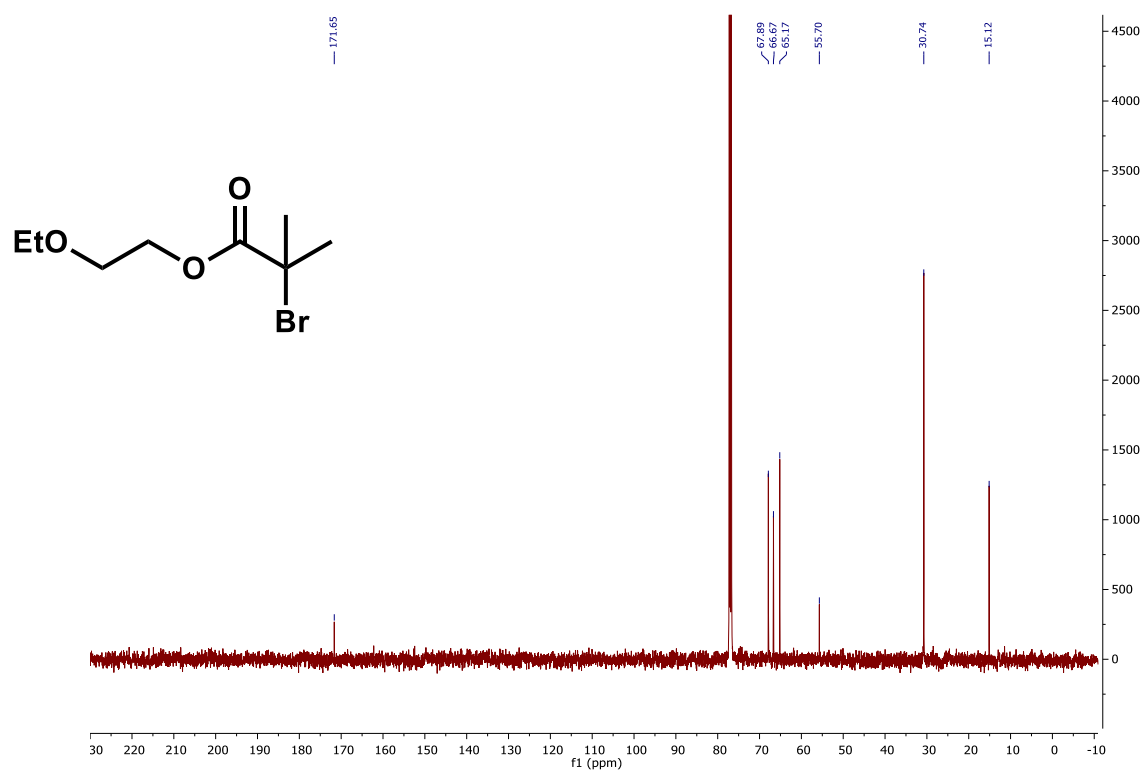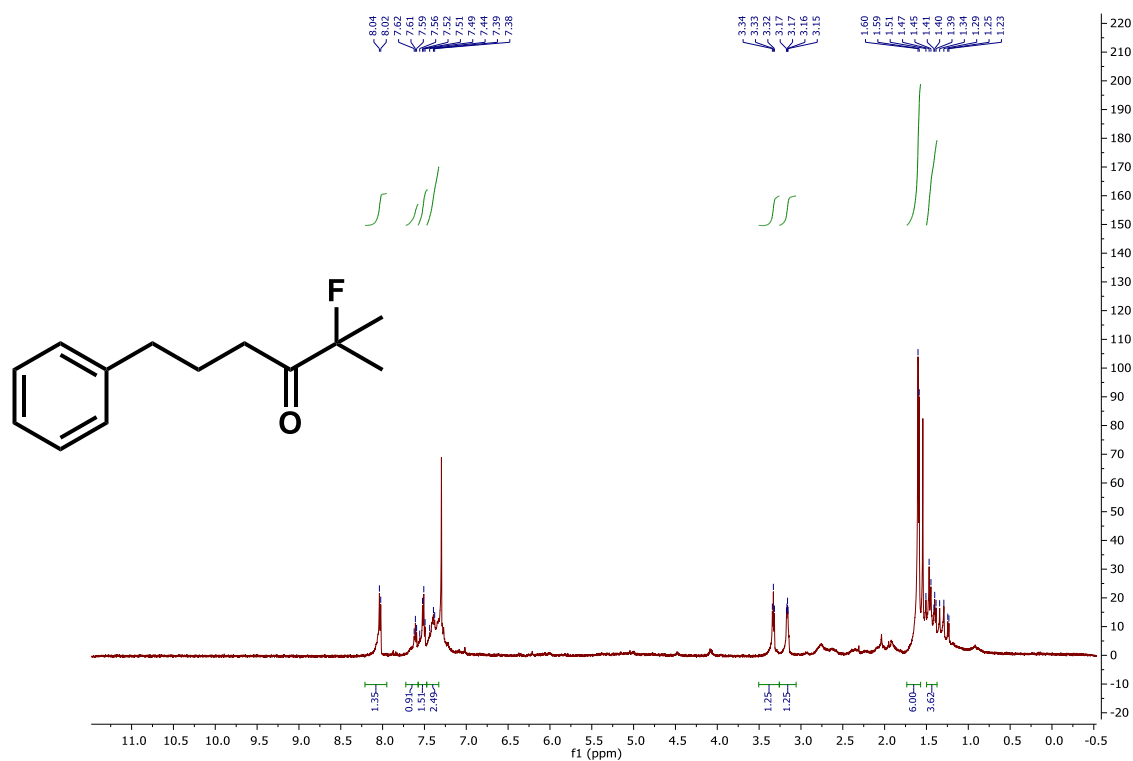
¹H NMR (500 MHz, Chloroform-*d*)
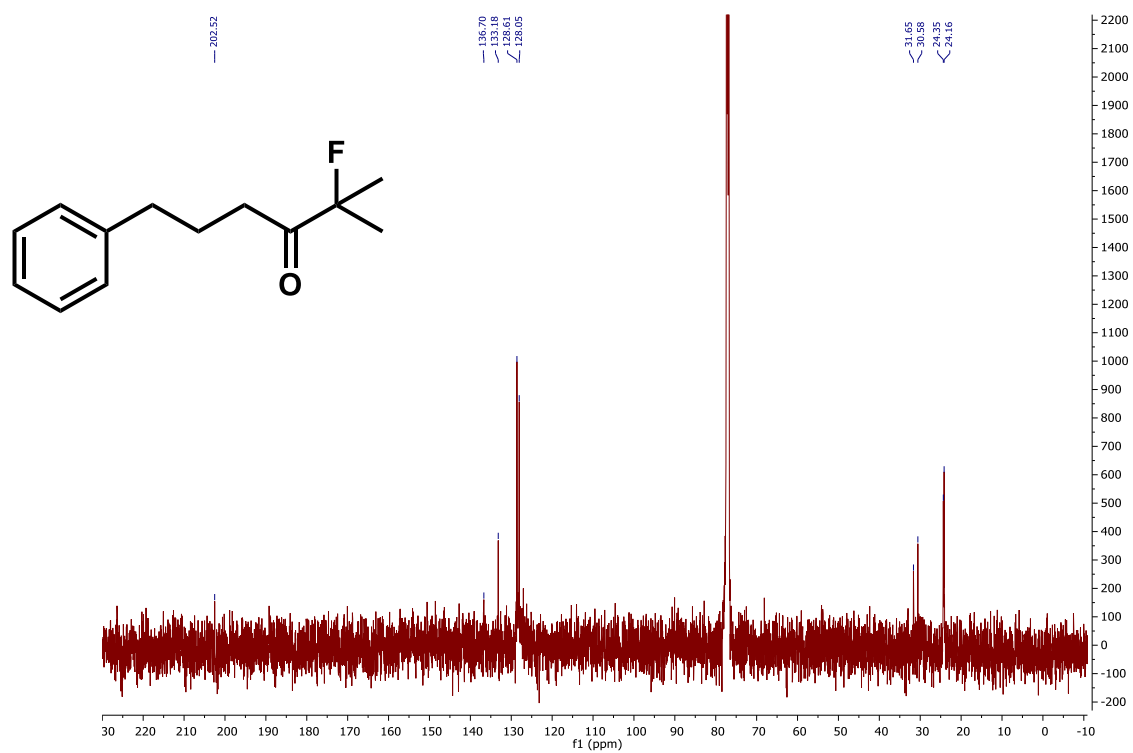
¹³C NMR (126 MHz, Chloroform-*d*)
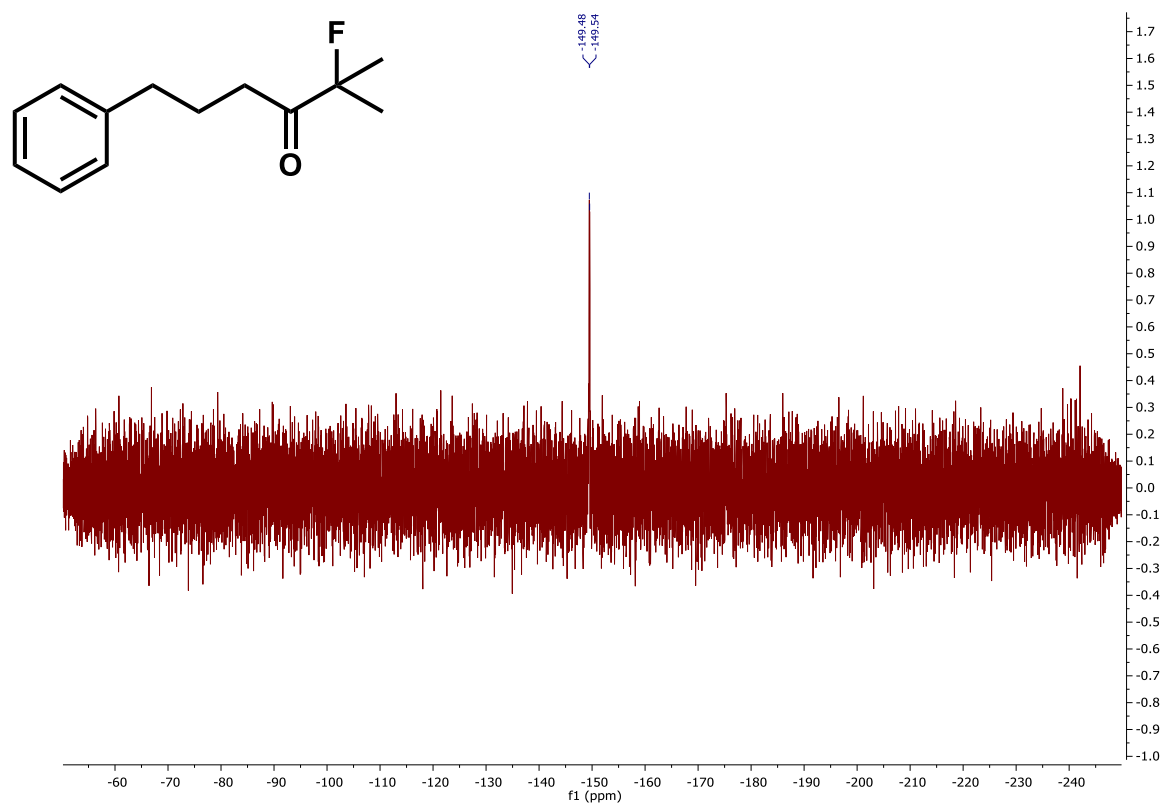
¹⁹F NMR (376 MHz, Chloroform-*d*)
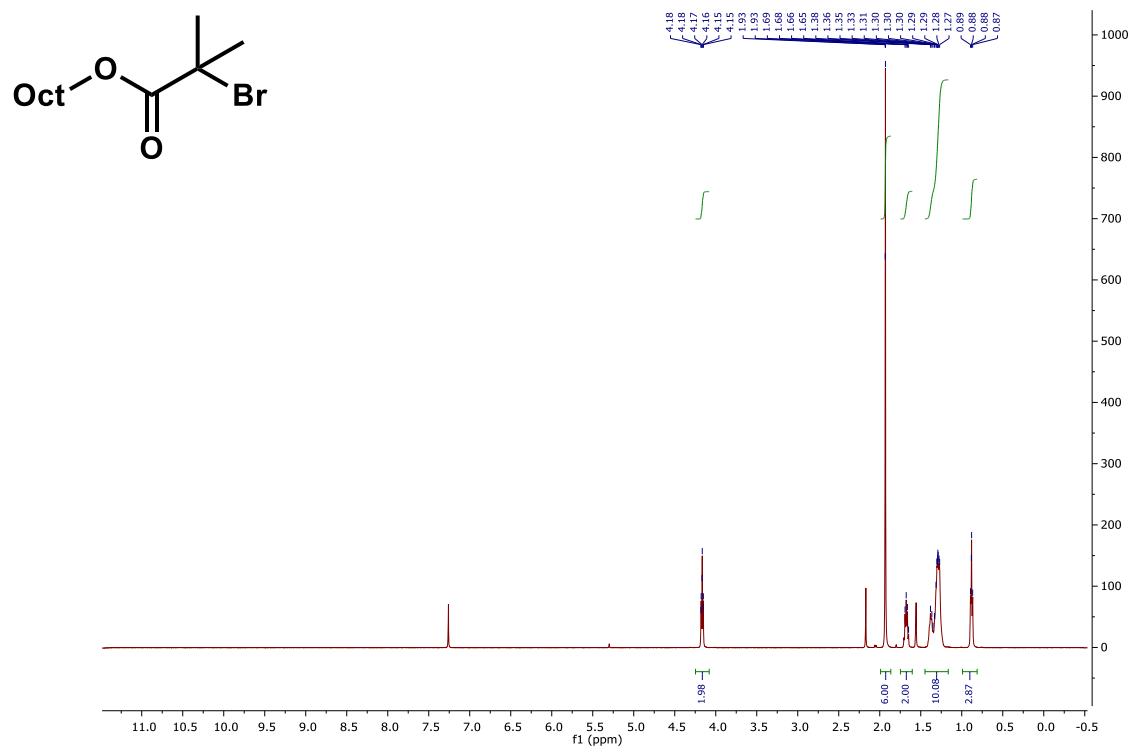
5. NMR Spectra for α-Fluoroesters

¹H NMR (500 MHz, Chloroform-*d*)

13C NMR (126 MHz, Chloroform-*d*)

19F NMR (376 MHz, Chloroform-*d*)

^{1}**H NMR** (500 MHz, Chloroform-*d*)

¹³C NMR (126 MHz, Chloroform-*d*)

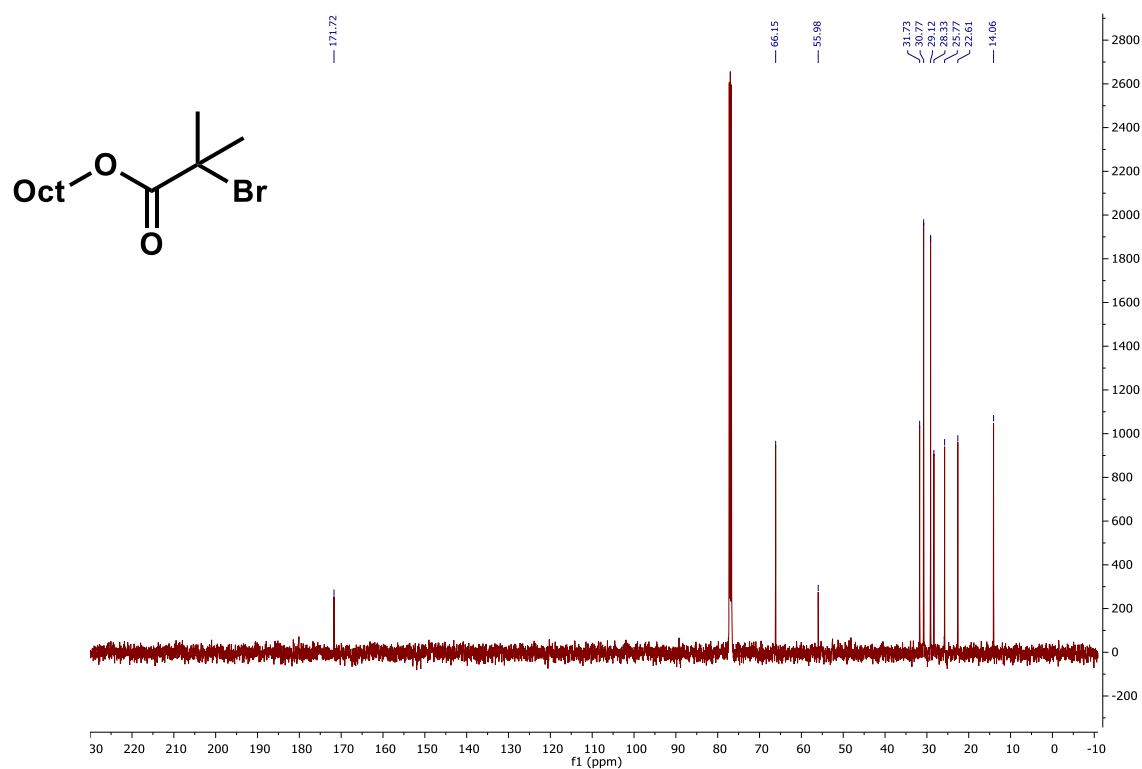
¹⁹F NMR (376 MHz, Chloroform-*d*)

¹H NMR (500 MHz, Chloroform-*d*)
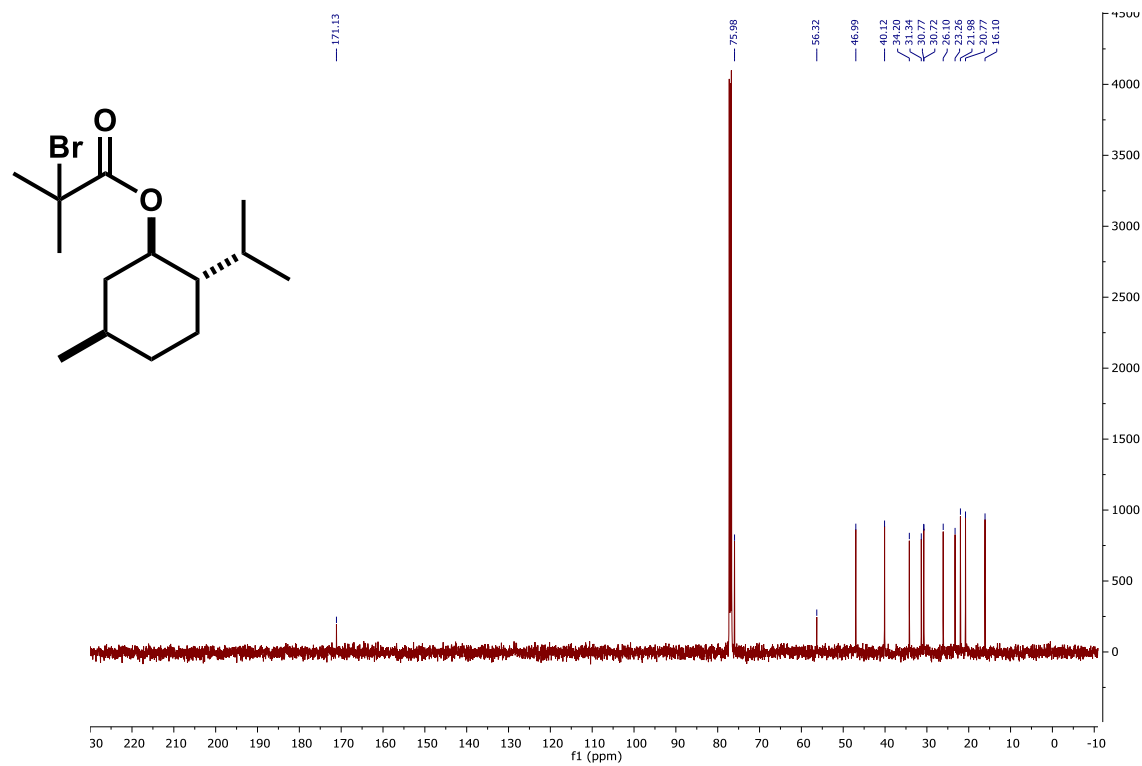

¹³C NMR (126 MHz, Chloroform-*d*)

−147.71
−147.76
−147.82
−147.87

¹⁹F NMR (376 MHz, Chloroform-*d*)

7.09
7.08

1.77
1.71

4.00

6.73

¹H NMR (400 MHz, Chloroform-*d*)

¹³C NMR (126 MHz, Chloroform-*d*)

-116.76
-116.78
-116.80

-147.71
-147.76
-147.82
-147.88
-147.93

1.00

0.98

19F NMR (376 MHz, Chloroform-*d*)

7.87
7.87
7.86
7.85
7.85
7.71
7.70
7.70
7.53
7.52
7.50
7.35
7.35
7.35
7.34
7.33
7.33
7.33

2.62

1.79
1.74

1.06
1.00
1.20
1.14

3.74

7.19

¹H NMR (500 MHz, Chloroform-*d*)

¹³C NMR (126 MHz, Chloroform-*d*)

-147.69
-147.74
-147.80
-147.86
-147.91

¹⁹F NMR (376 MHz, Chloroform-*d*)

7.64
7.64
7.62
7.38
7.37
7.36
7.36
7.34
7.34
7.18
7.17
7.17
7.16
7.16
7.16
7.15

1.83
1.79

1.00
1.10
2.10

7.34

¹H NMR (500 MHz, Chloroform-*d*)

¹³C NMR (126 MHz, Chloroform-*d*)

¹⁹F NMR (376 MHz, Chloroform-*d*)

¹H NMR (500 MHz, Chloroform-*d*)

¹³C NMR (126 MHz, Chloroform-*d*)

¹⁹F NMR (376 MHz, Chloroform-*d*)

¹H NMR (500 MHz, Chloroform-*d*)

¹³C NMR (126 MHz, Chloroform-*d*)

¹⁹F NMR (376 MHz, Chloroform-*d*)

¹H NMR (400 MHz, Chloroform-*d*)

¹³C NMR (126 MHz, Chloroform-*d*)

19F NMR (376 MHz, Chloroform-*d*)

¹H NMR (500 MHz, Chloroform-*d*)

¹³C NMR (126 MHz, Chloroform-*d*)

¹⁹F NMR (376 MHz, Chloroform-*d*)

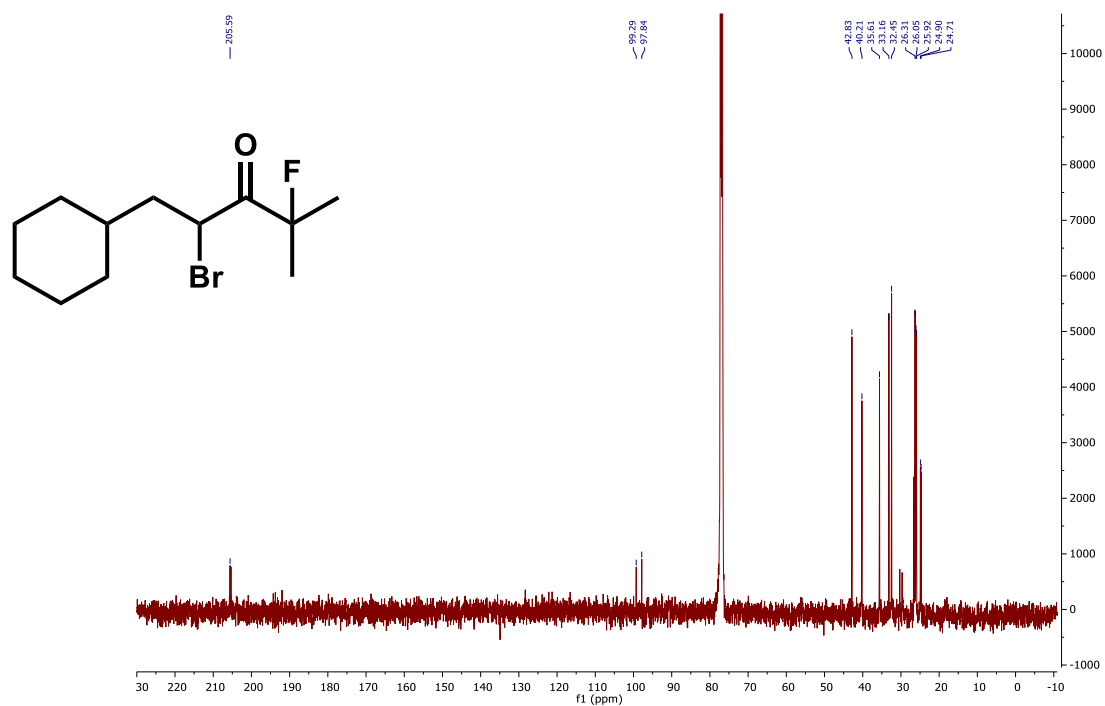**¹H NMR** (500 MHz, Chloroform-*d*)

13C NMR (126 MHz, Chloroform-*d*)
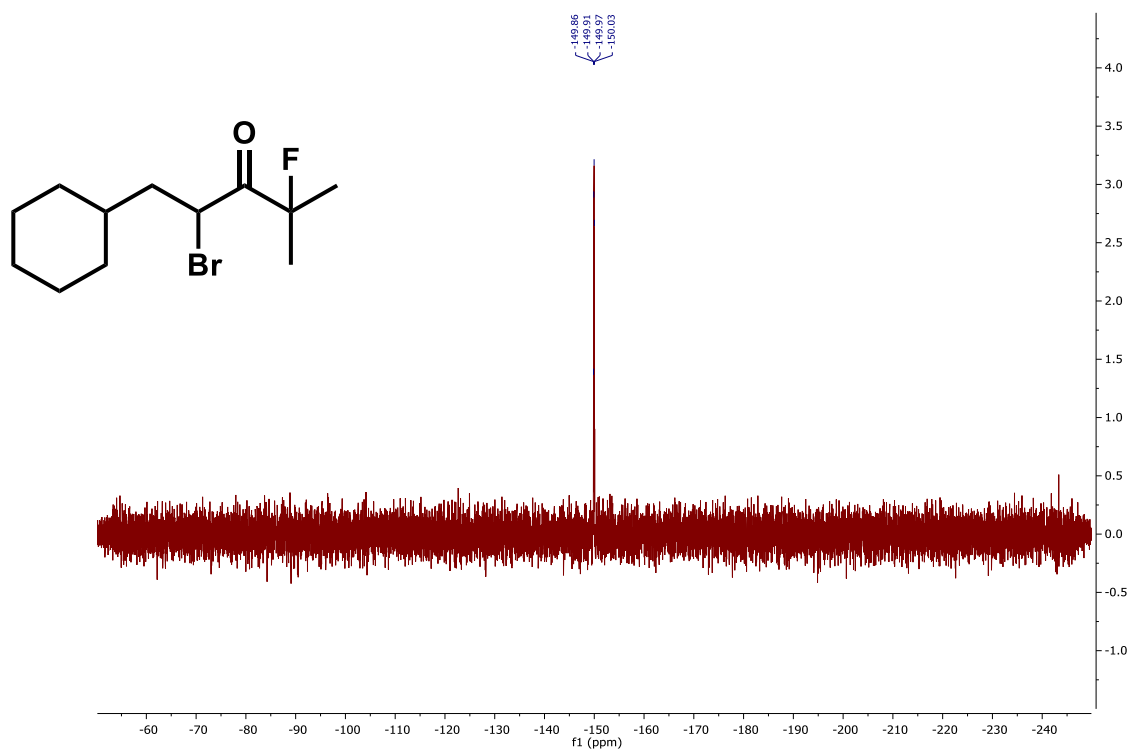
¹⁹F NMR (376 MHz, Chloroform-*d*)

6. NMR Spectra for Alkyl Tertiary Fluoride

¹H NMR (500 MHz, Chloroform-*d*)

¹³C NMR (126 MHz, Chloroform-*d*)

-138.38
-138.44
-138.49
-138.55
-138.60
-138.66
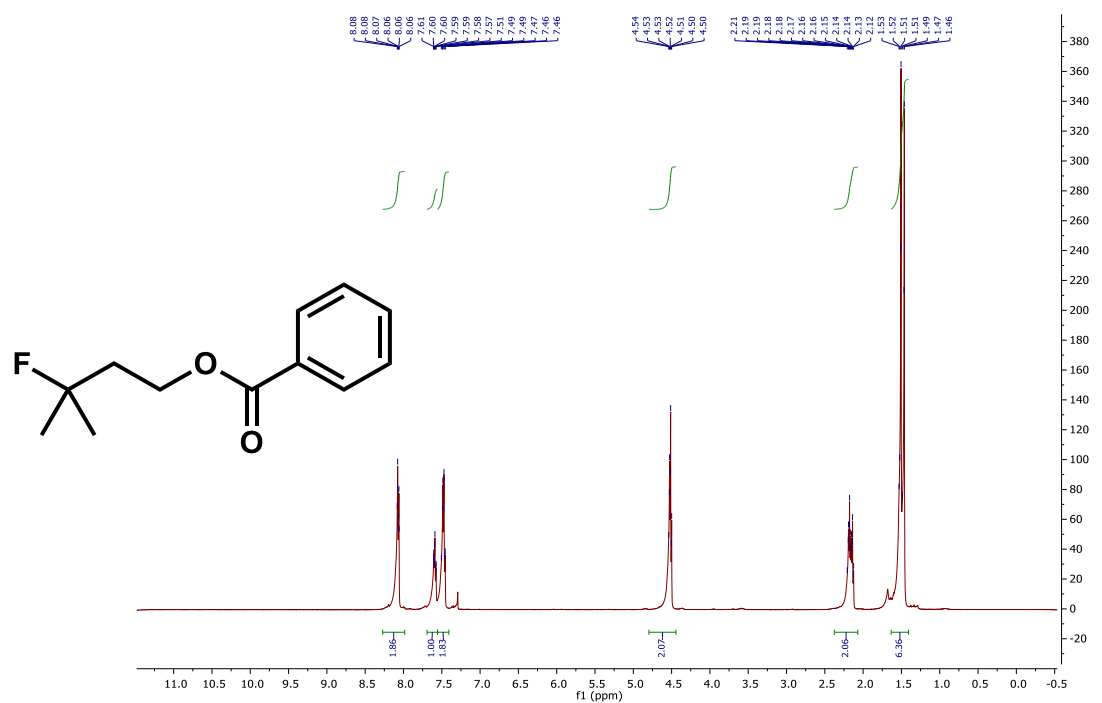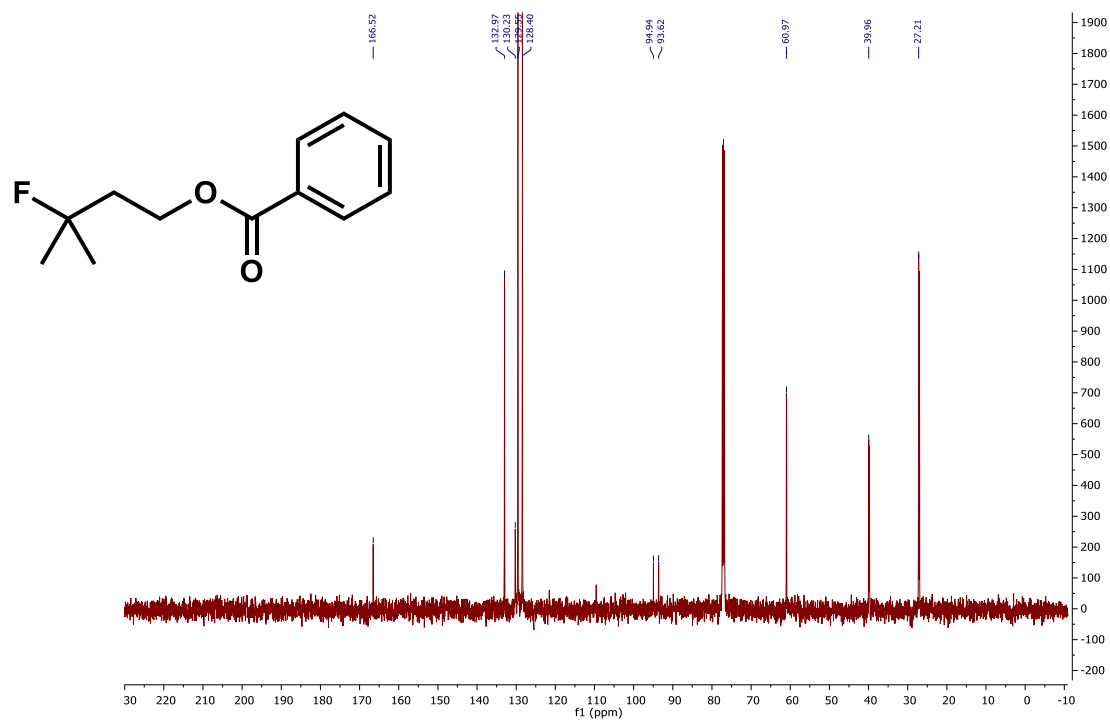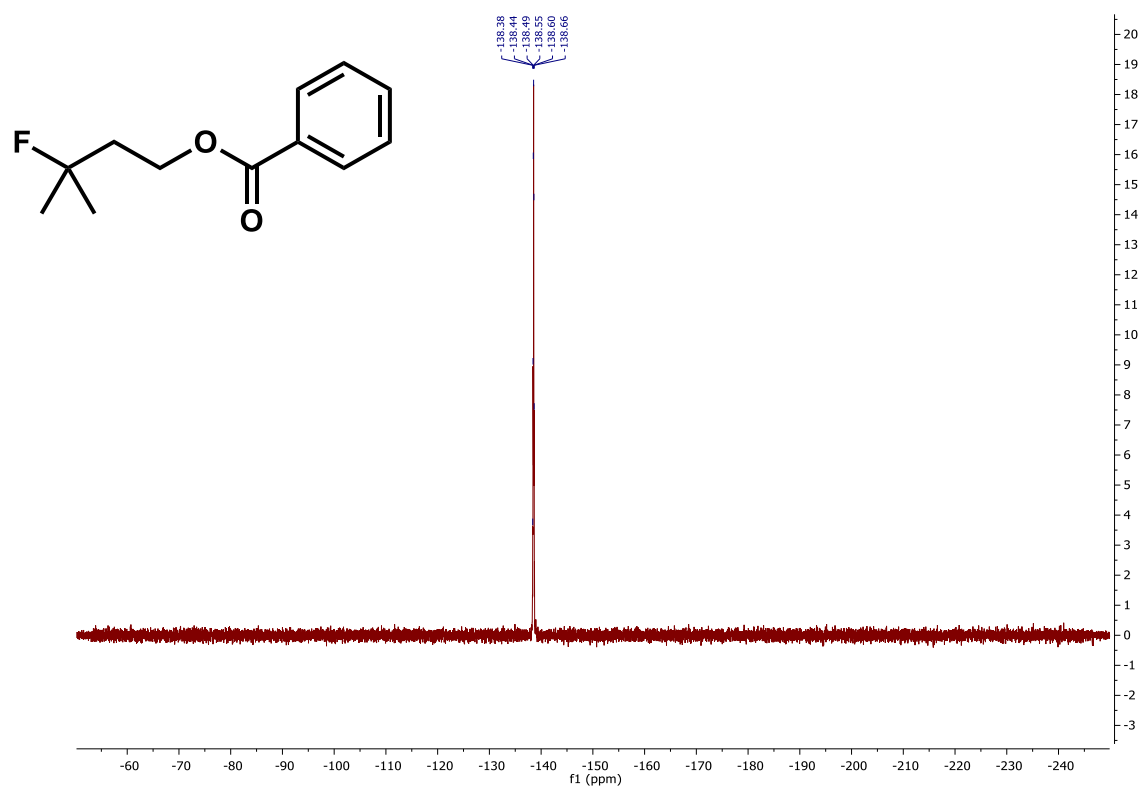
¹⁹F NMR (376 MHz, Chloroform-*d*)

7. NMR Spectra for 2-Fluoro-2-methyl-1-(pyrrolidin-1-yl)propan-1-one
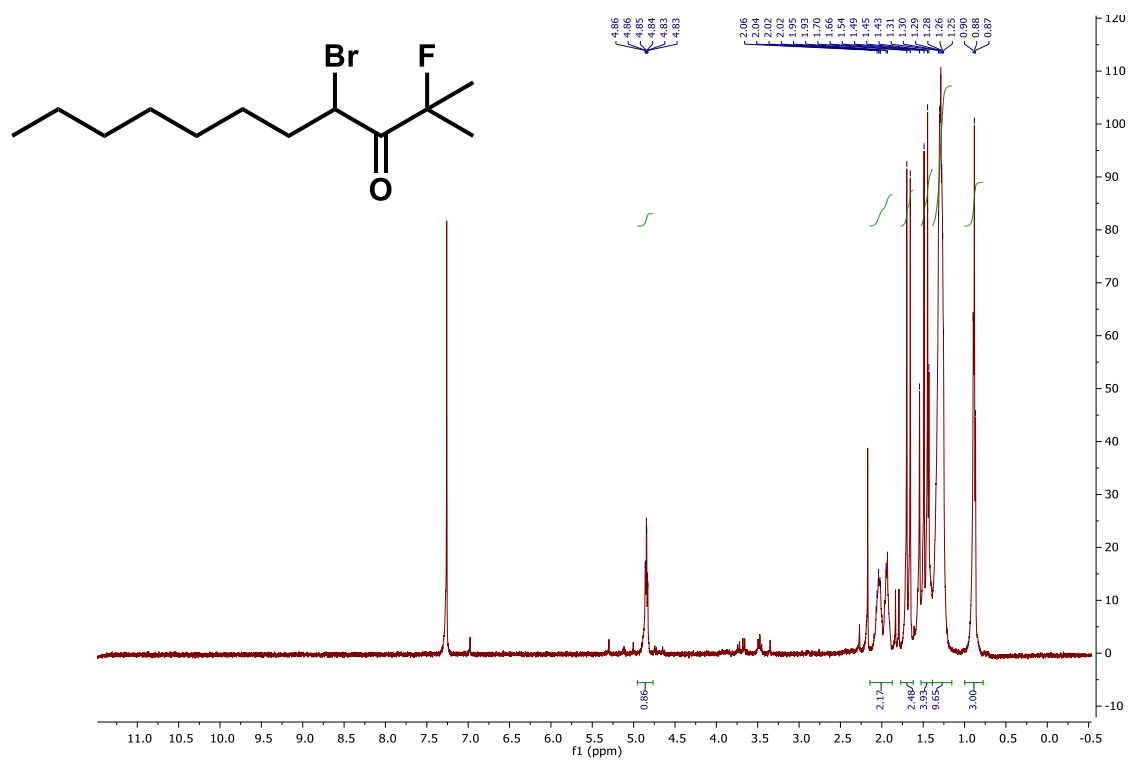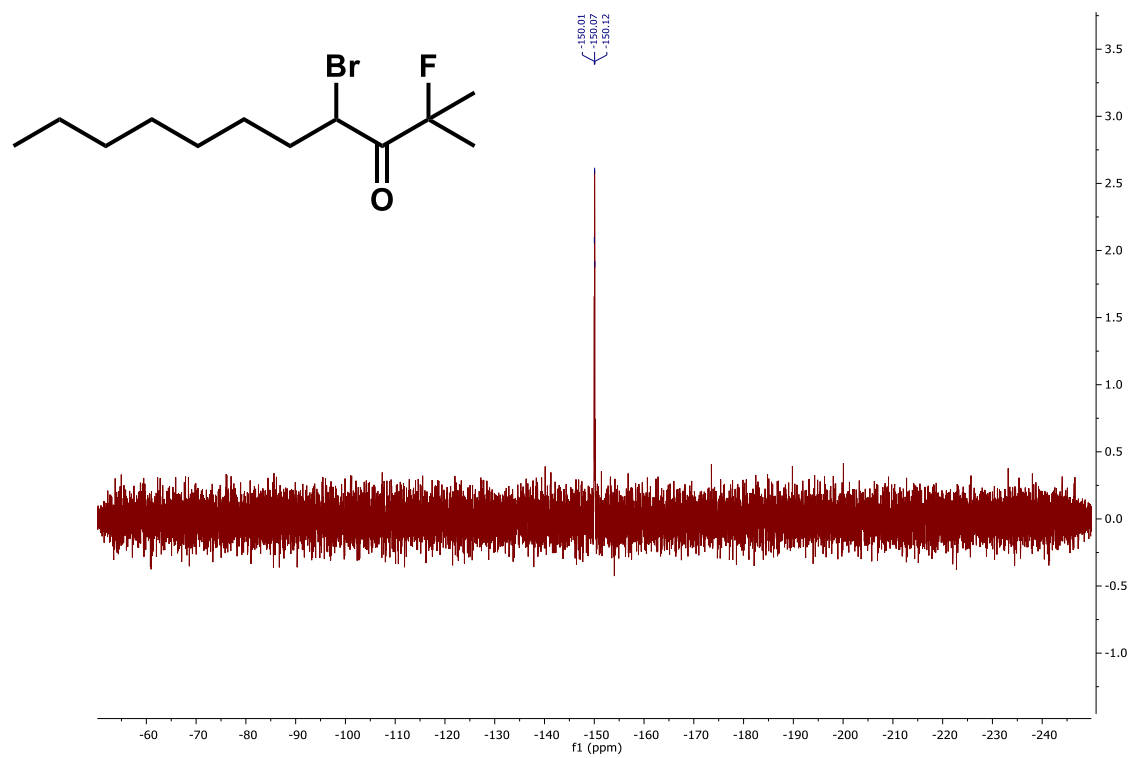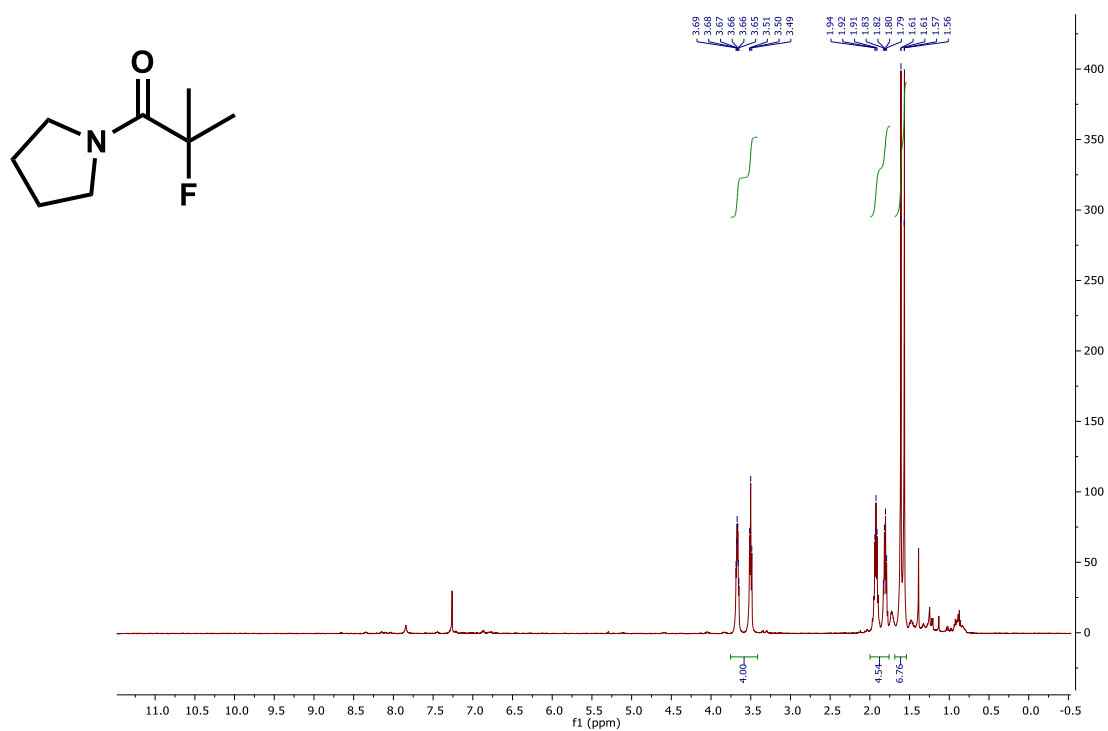

¹H NMR (500 MHz, Chloroform-*d*)
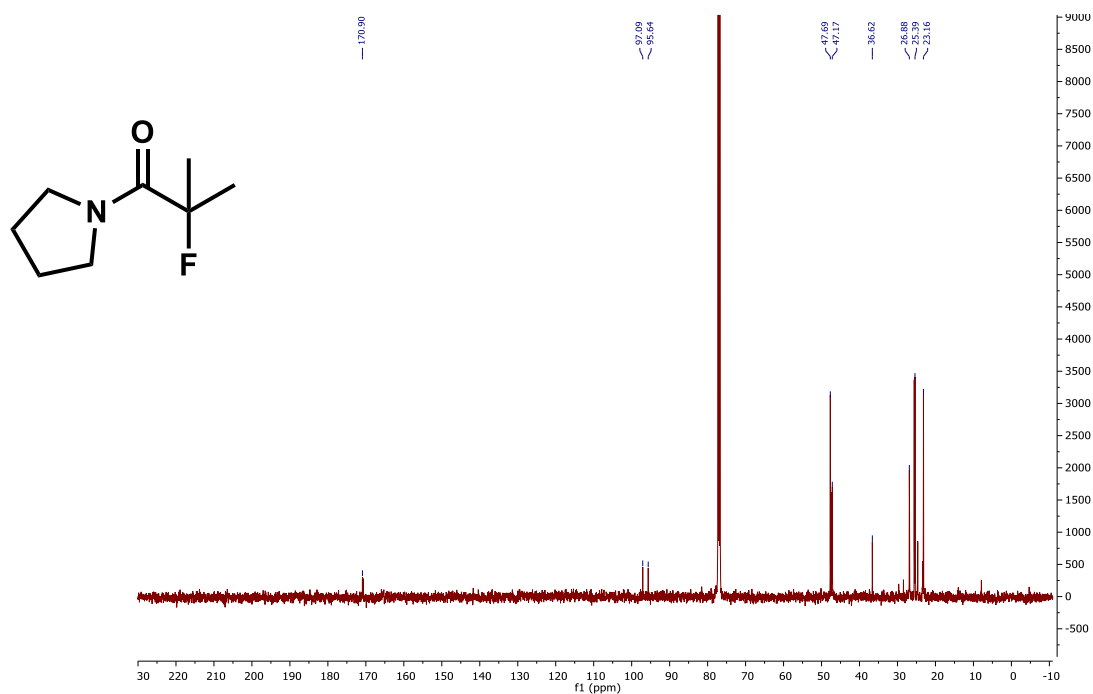
¹³C NMR (126 MHz, Chloroform-*d*)
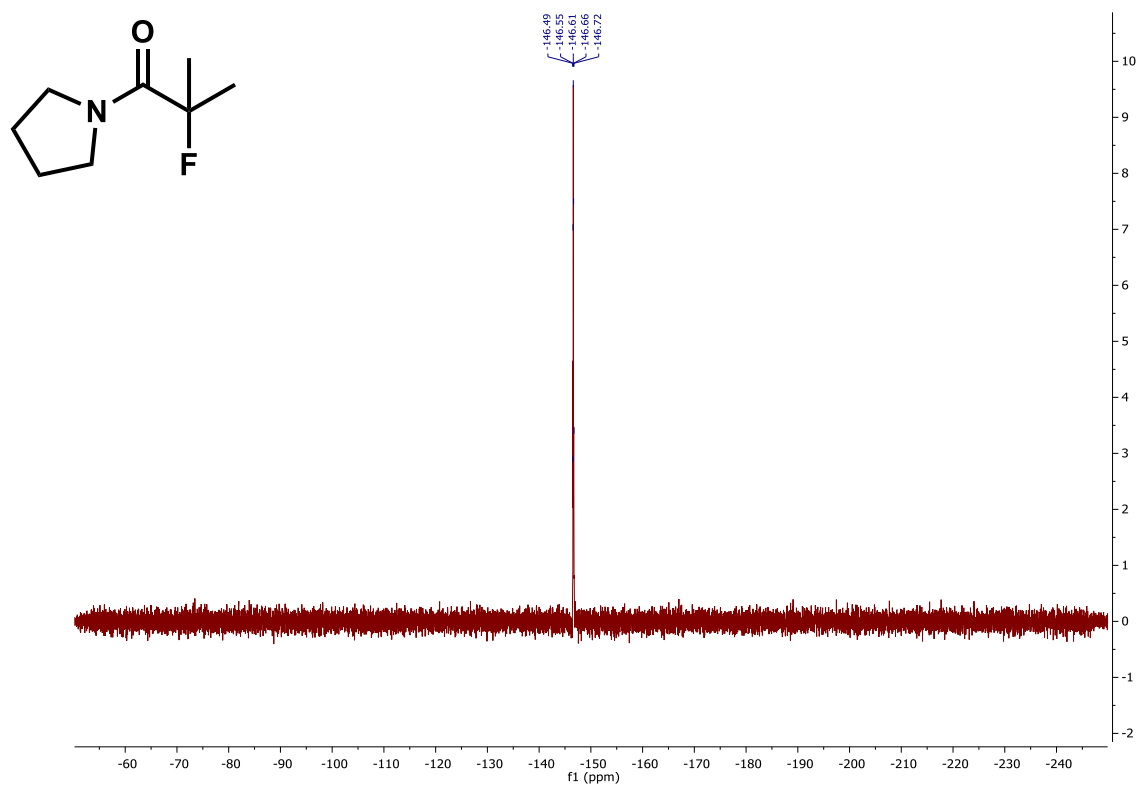
¹⁹F NMR (376 MHz, Chloroform-*d*)

8. NMR Spectra for (*E*)-3,7-dimethylocta-2,6-dien-1-yl 2-fluoro-2-methylpropanoate
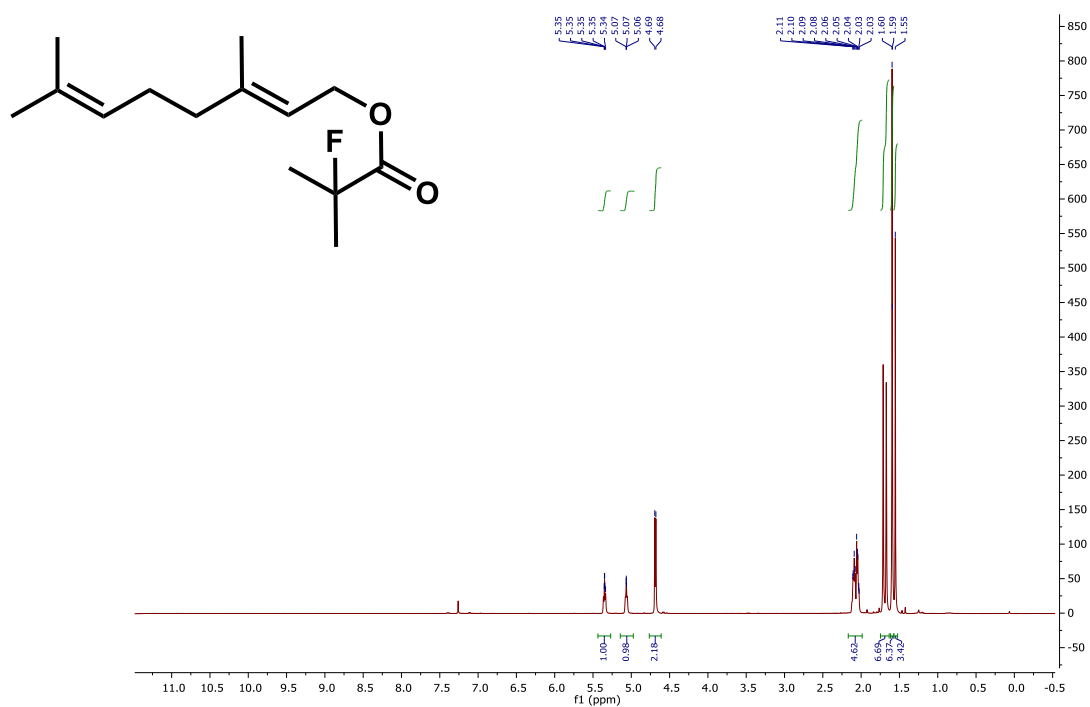
¹H NMR (500 MHz, Chloroform-*d*)
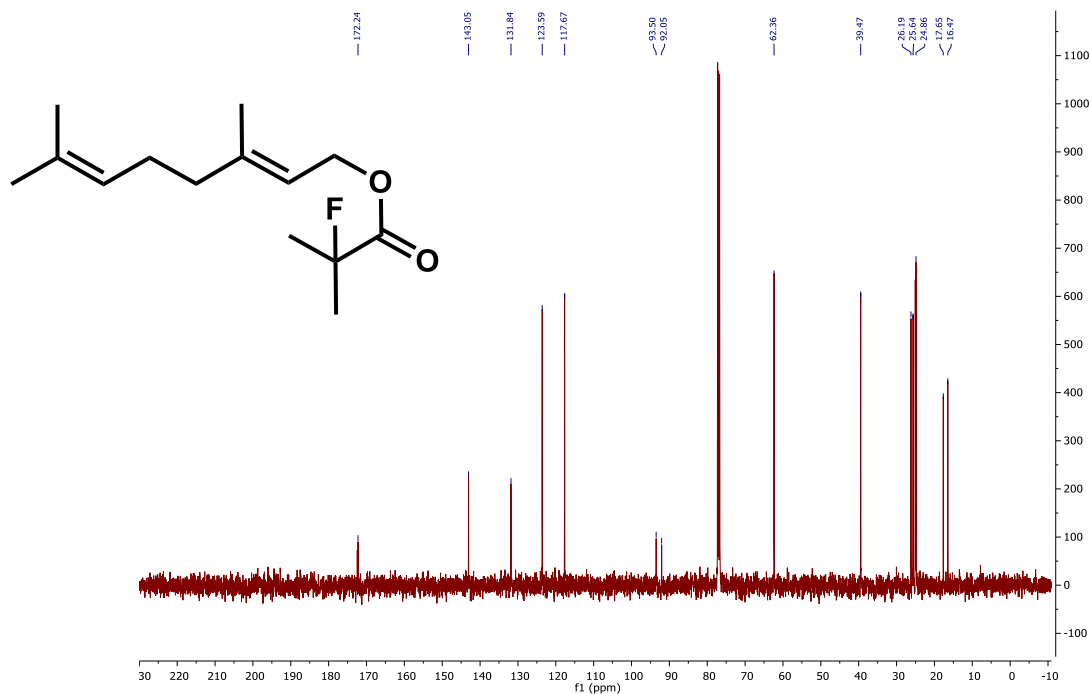
¹³C NMR (126 MHz, Chloroform-*d*)
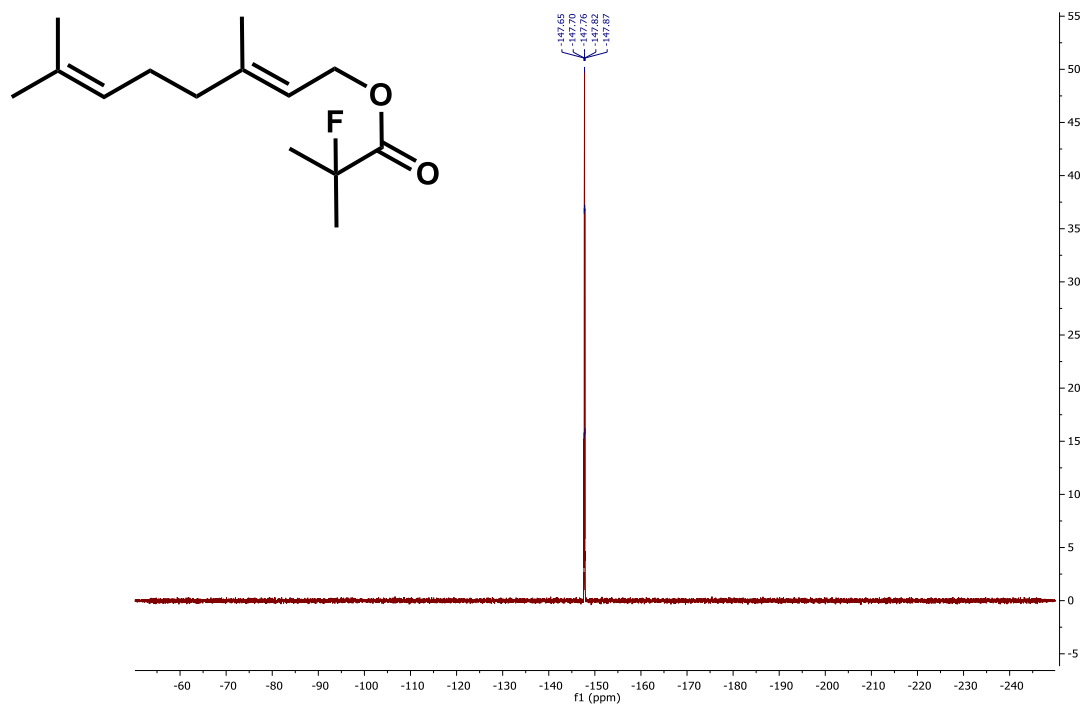
¹⁹F NMR (376 MHz, Chloroform-*d*)

9. **NMR Spectra for 4-Iodophenyl 2-fluoro-2-methylpropanoate**
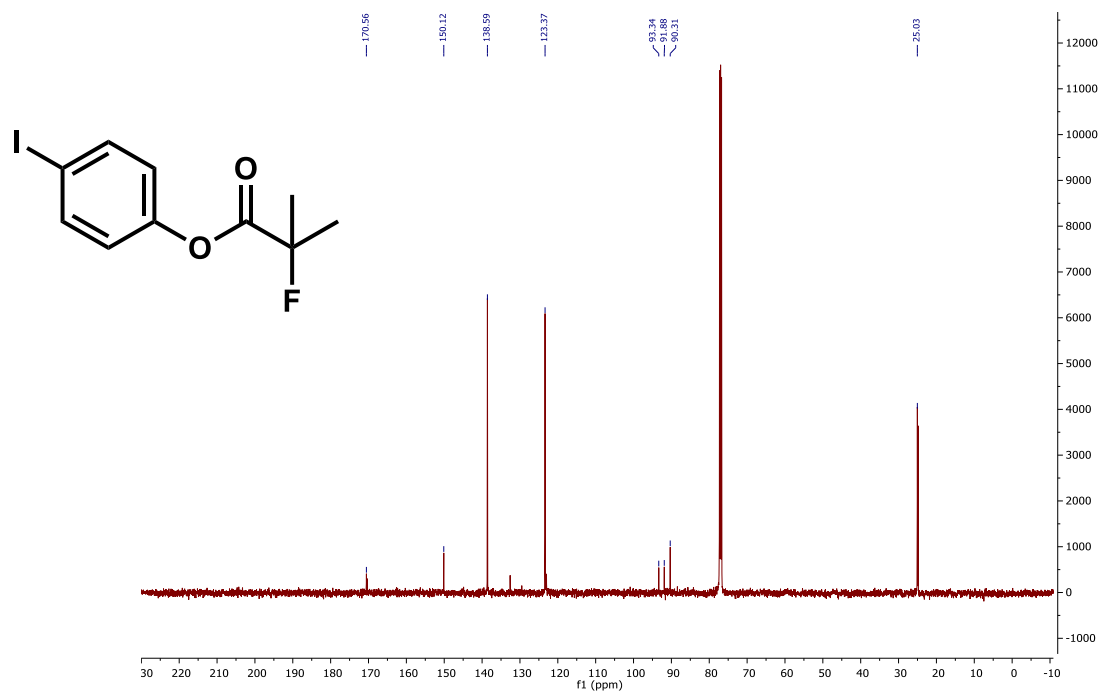
¹H NMR (500 MHz, Chloroform-*d*)

¹³C NMR (126 MHz, Chloroform-*d*)

¹⁹F NMR (376 MHz, Chloroform-*d*)

Appendix VI. Benzofuran Project NMR

1. NMR Spectra for 2,3-Difluoro-2,3-dihydrobenzofurans

¹H NMR (500 MHz, Chloroform-d)

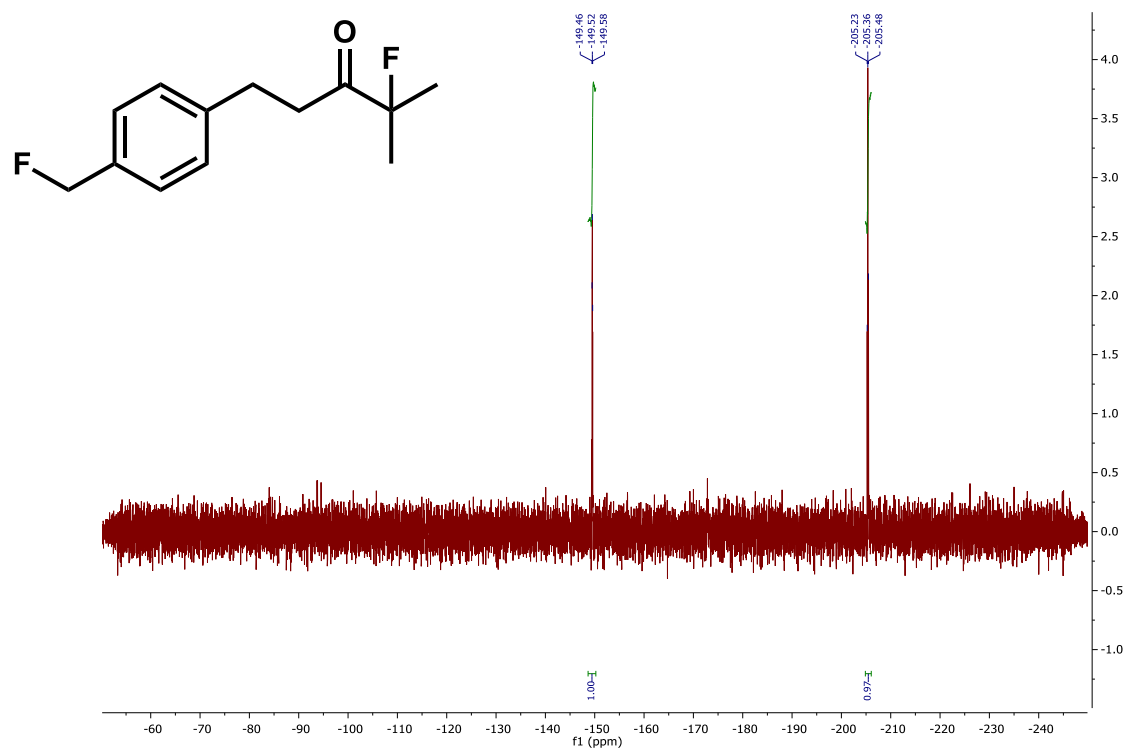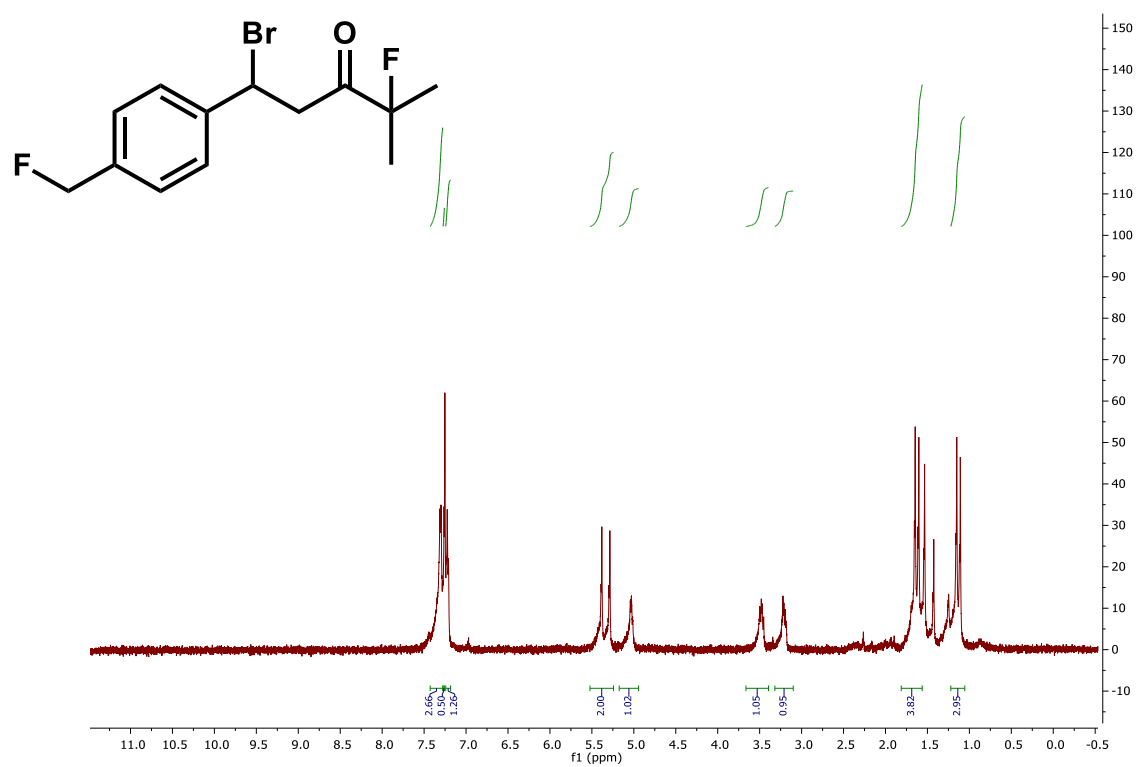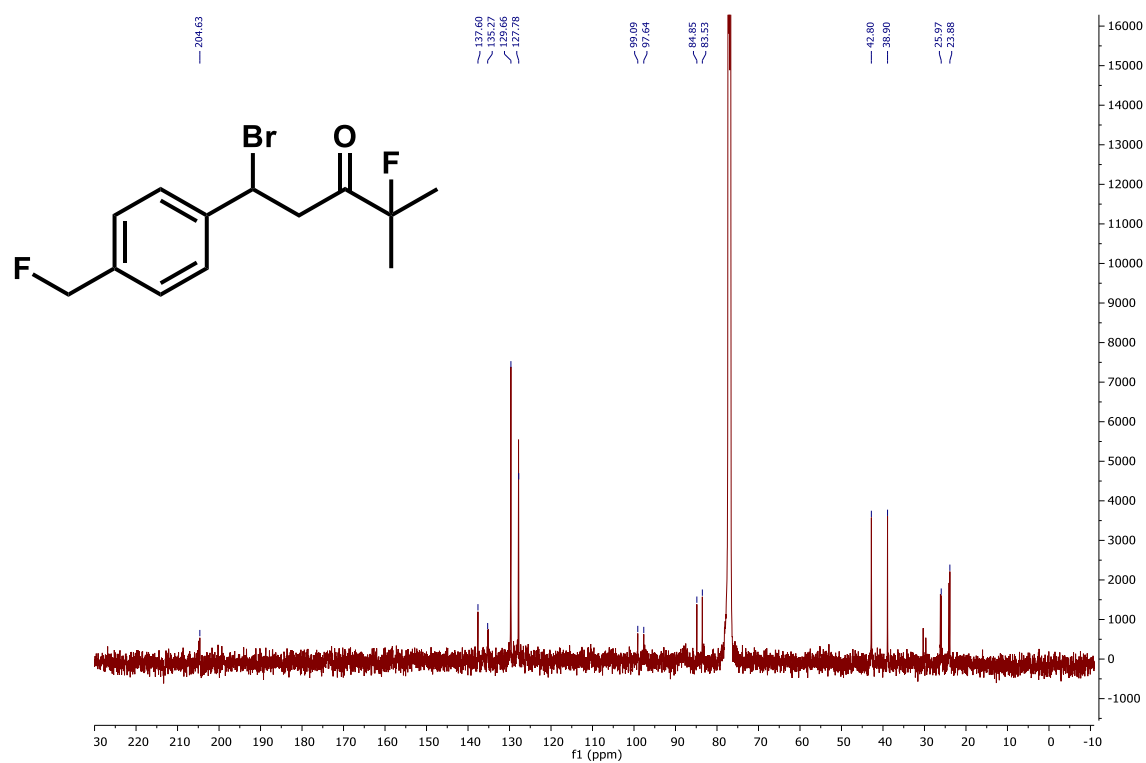**¹³C NMR** (126 MHz, Chloroform-d)

¹⁹F NMR (376 MHz, Chloroform-d)

7.55, 7.55, 7.54, 7.48, 7.48, 7.47, 7.46, 7.45, 6.98, 6.97, 6.96, 6.96, 6.32, 6.30, 6.20, 6.18, 5.92, 5.89, 5.81, 5.78

1.33

1.11, 1.07, 1.07, 1.00, 1.05, 11.04

¹H NMR (500 MHz, Chloroform-d)

158.38, 146.39, 146.37, 130.13, 130.09, 123.59, 120.87, 115.26, 114.93, 113.43, 113.11, 110.66, 95.10, 94.80, 93.64, 93.34, 34.54, 31.53, 31.43
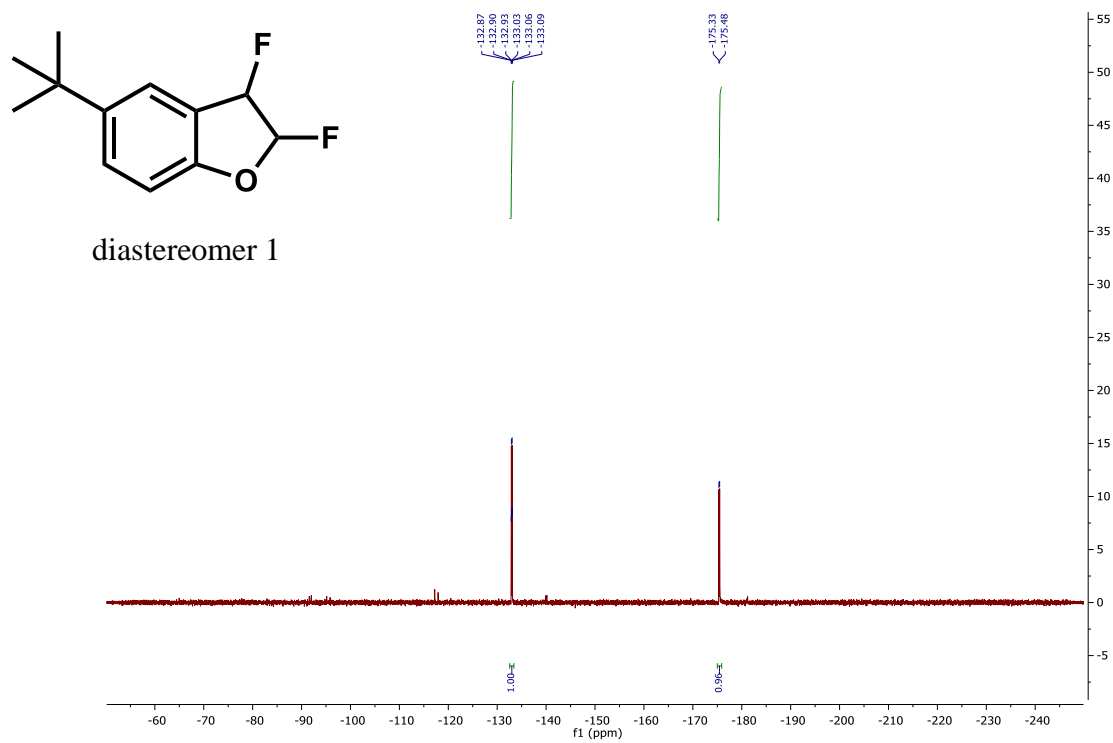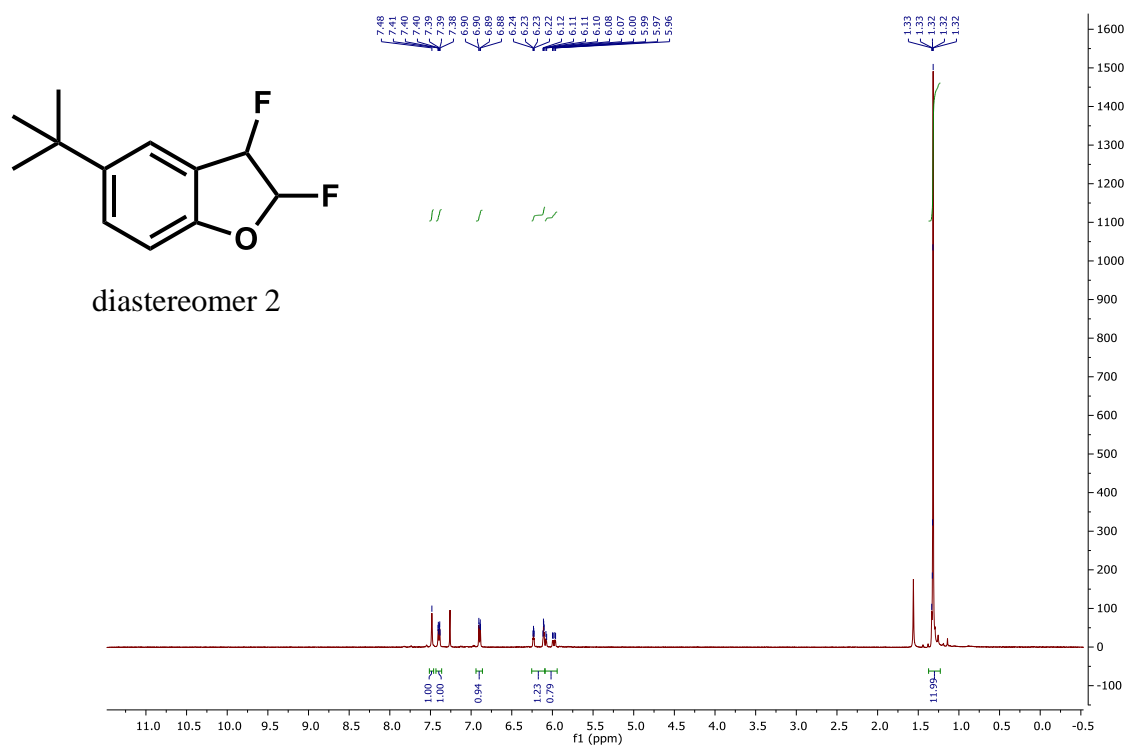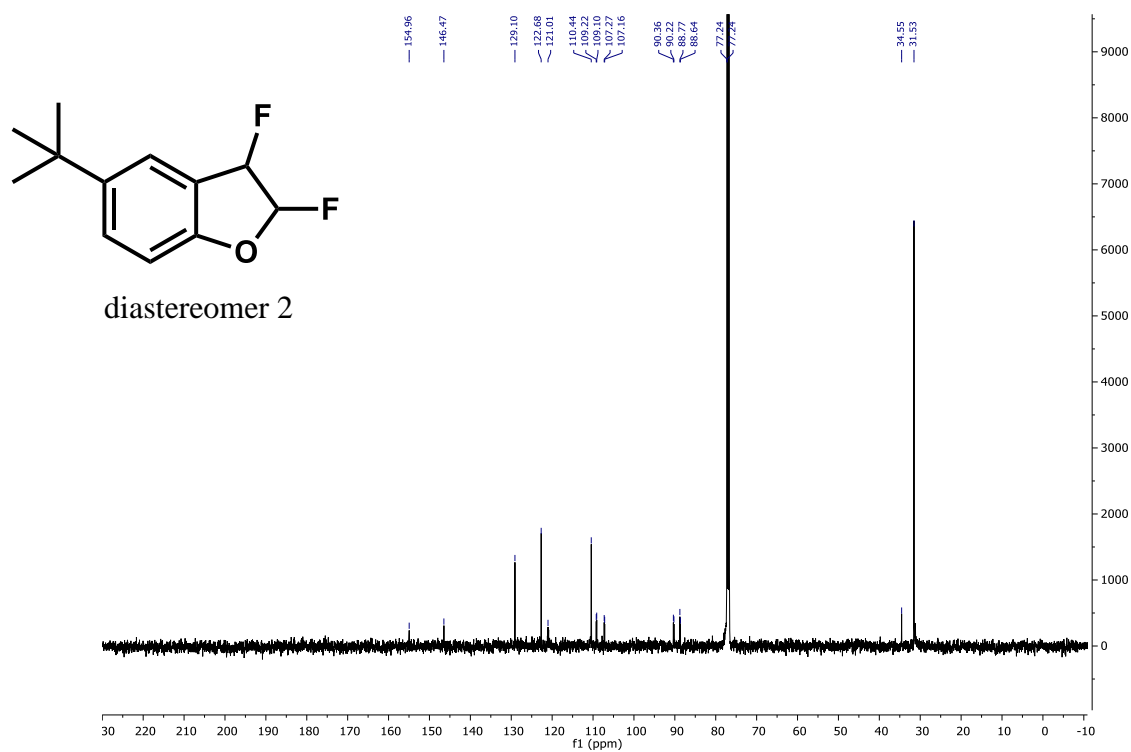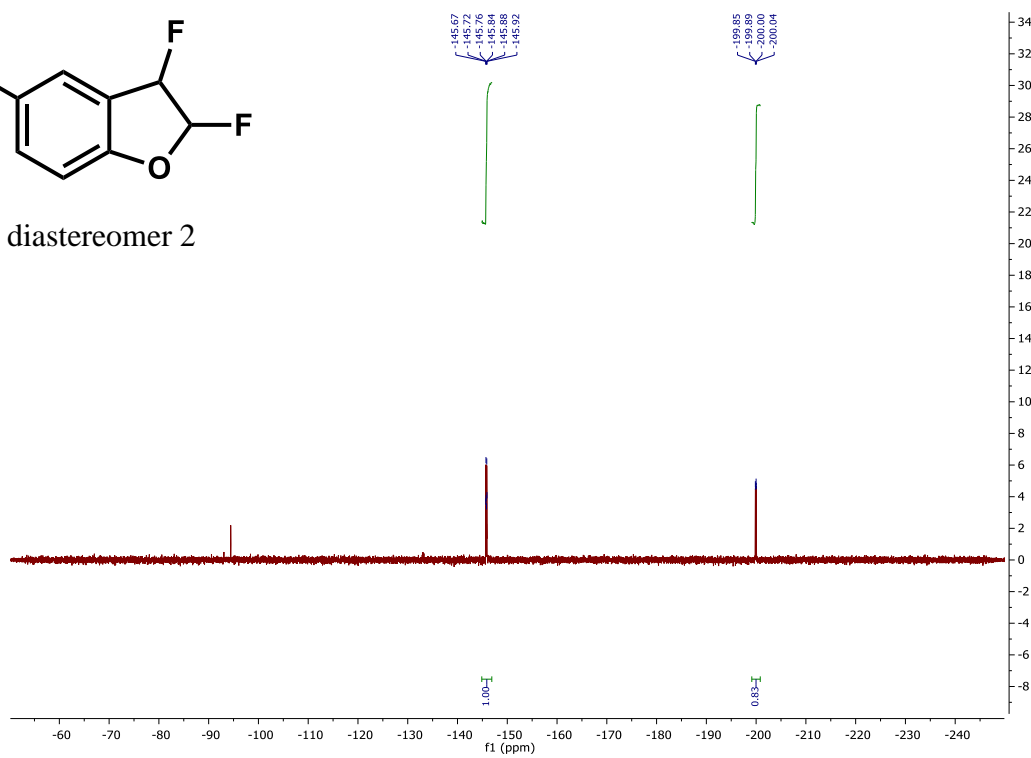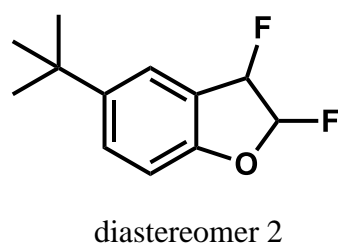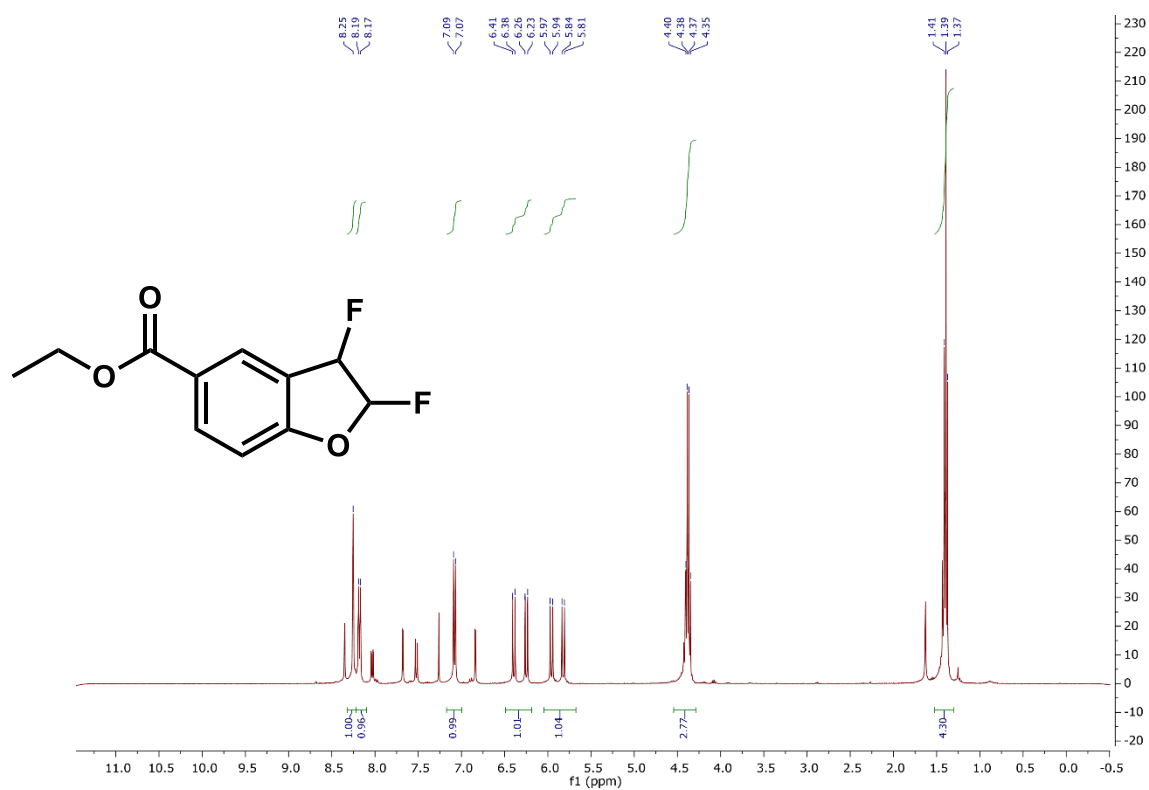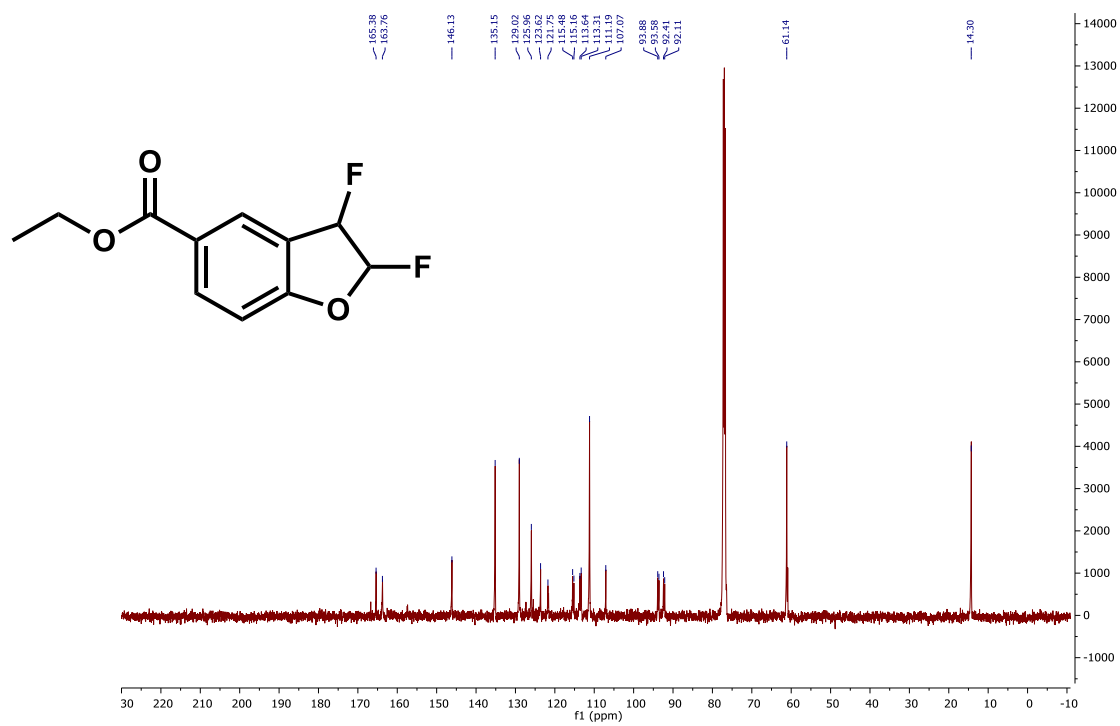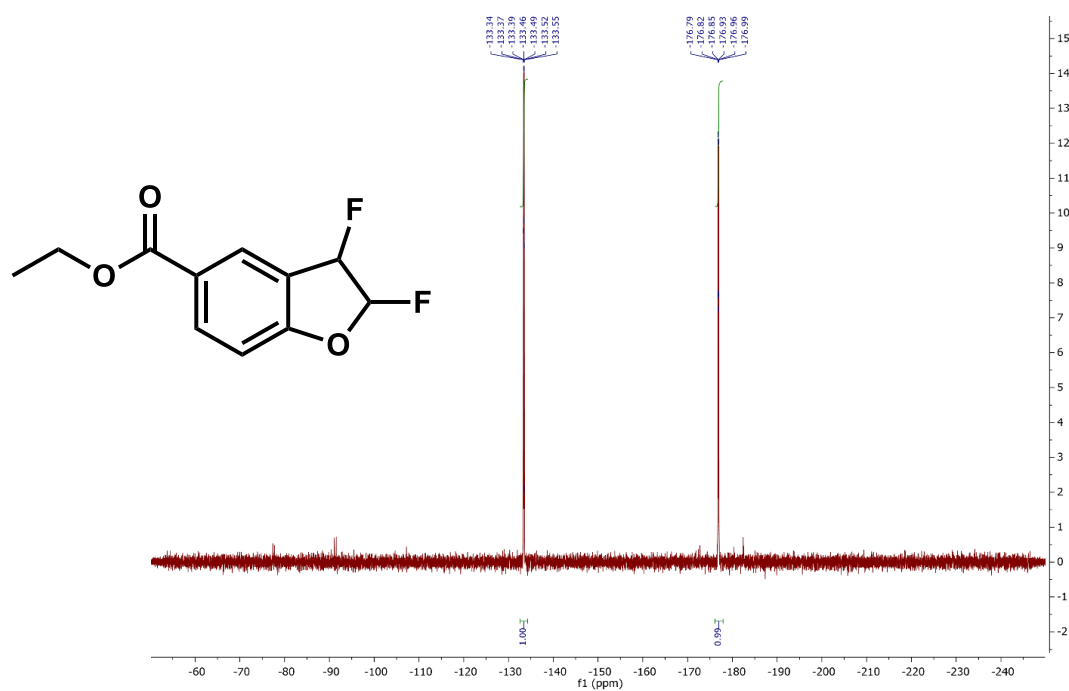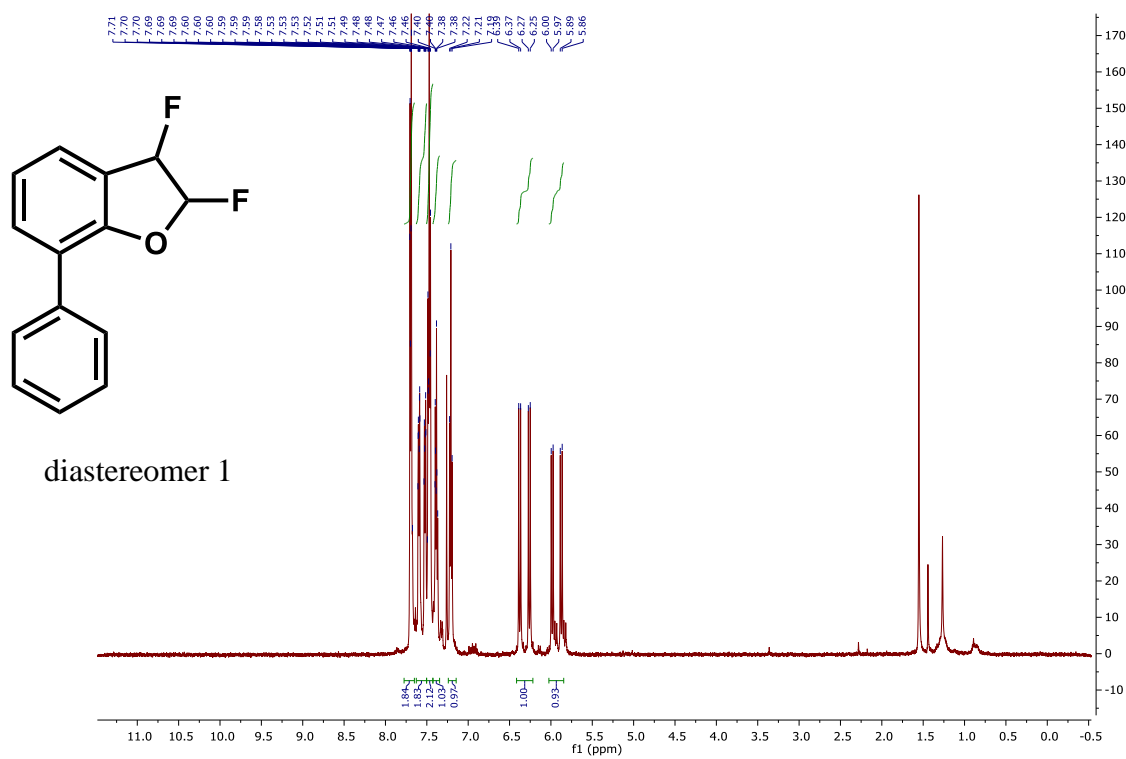
diastereomer 1

diastereomer 1

¹³C NMR (126 MHz, Chloroform-d)

diastereomer 1

-132.87
-132.90
-132.93
-133.03
-133.06
-133.09

-175.33
-175.48

1.00=

0.96=

¹⁹F NMR (376 MHz, Chloroform-d)

diastereomer 2

¹H NMR (500 MHz, Chloroform-d)

diastereomer 2

¹³C NMR (126 MHz, Chloroform-d)

diastereomer 2

-145.67
-145.72
-145.76
-145.84
-145.88
-145.92

-199.85
-199.89
-200.00
-200.04

¹⁹F NMR (376 MHz, Chloroform-d)

¹H NMR (400 MHz, Chloroform-d)

13C NMR (126 MHz, Chloroform-d)

19F NMR (376 MHz, Chloroform-d)


diastereomer 1

¹H NMR (500 MHz, Chloroform-d)

diastereomer 1

135.46
132.63
132.60
128.69
128.56
128.44
128.33
127.88
125.86
125.62
123.62
122.07
121.93
114.68
114.36
112.85
112.52
94.70
94.40
93.25
92.94

¹³C NMR (126 MHz, Chloroform-d)

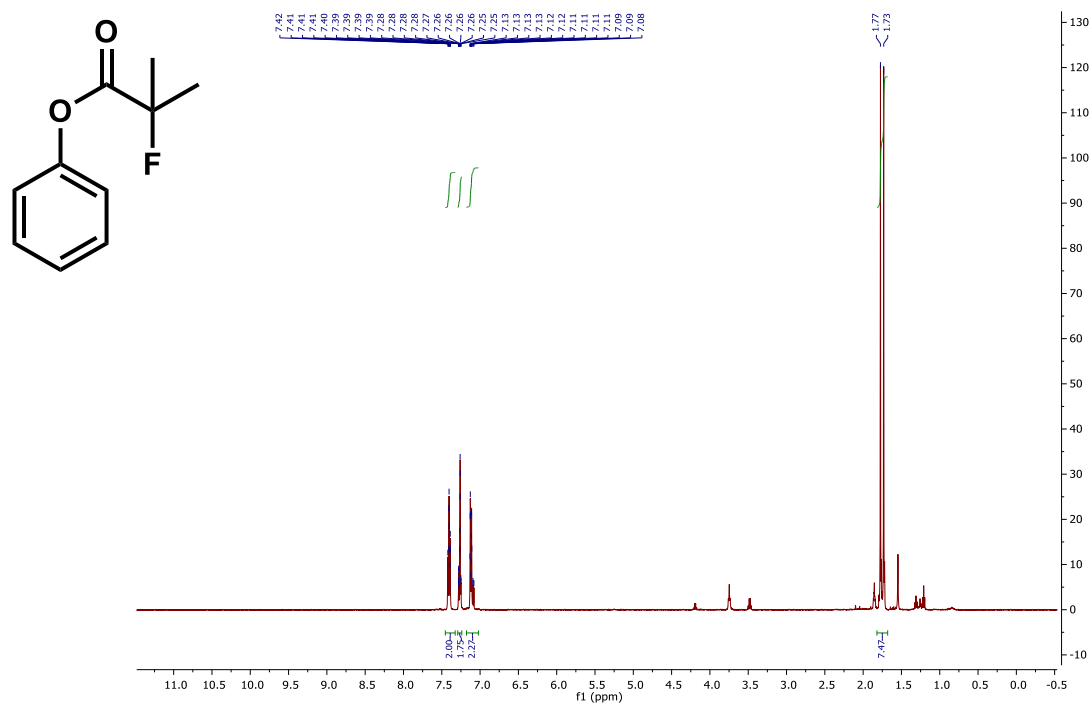**¹⁹F NMR** (376 MHz, Chloroform-d)

¹H NMR (500 MHz, Chloroform-d)

diastereomer 2

¹³C NMR (126 MHz, Chloroform-d)

^{19}**F NMR** (376 MHz, Chloroform-d)

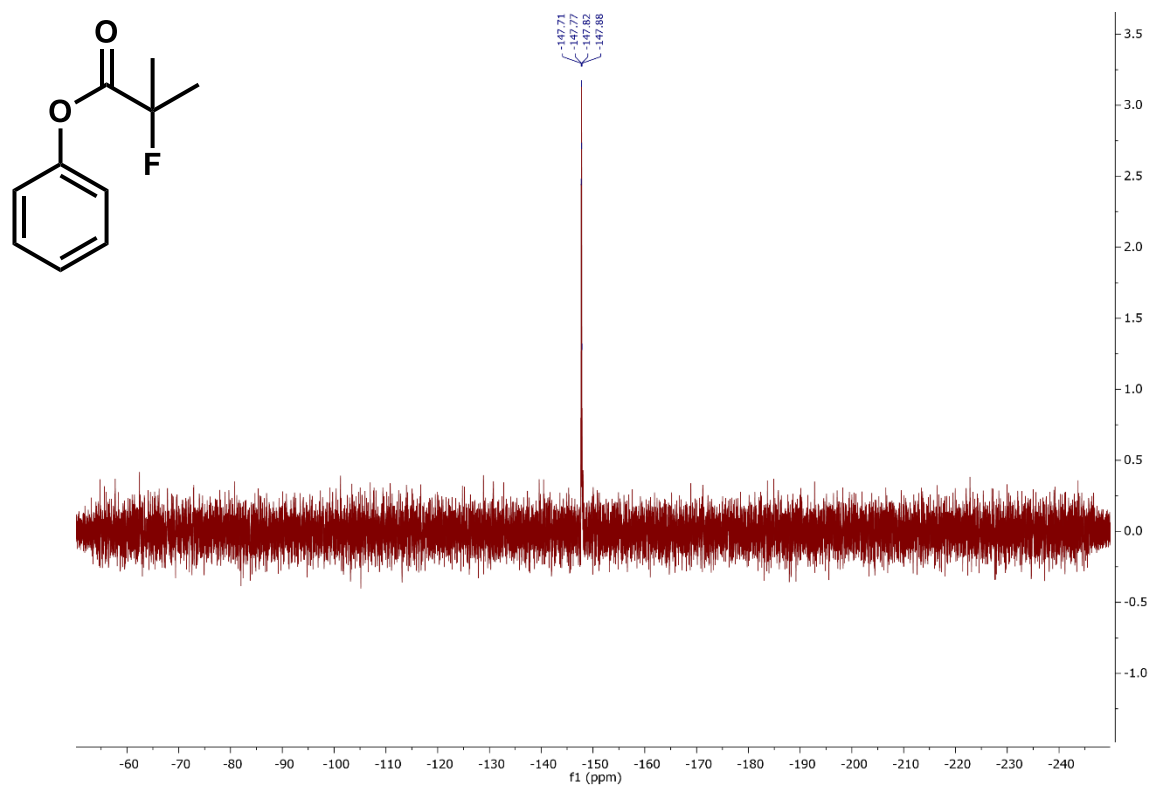**¹H NMR** (500 MHz, Chloroform-d)

148.36
146.39
144.02
124.07
121.25
119.20
119.07
109.46
109.33
107.48
107.37
89.71
89.58
88.11
87.98

¹³C NMR (126 MHz, Chloroform-d)

-137.16
-145.29
-145.33
-145.41
-145.45
-200.05
-200.09
-200.19
-200.23

1.00
1.25
1.10

¹⁹F NMR (376 MHz, Chloroform-d)

7.24
7.24
7.23
7.22
7.18
7.17
7.17
7.16
7.15
7.14
7.13
7.07
7.07
7.06
7.00
7.00
6.99
6.98
6.93
6.92
6.92
6.91
6.91
6.31
6.31
6.26
6.25
6.25
6.24
6.22
6.19
6.13
6.13
6.13
6.12
6.11
6.10
6.08
6.07
6.01
6.00
5.97
5.97
5.90
5.87
5.79
5.77

1.00
2.29
1.20
1.09
1.15
0.60

¹H NMR (500 MHz, Chloroform-d)

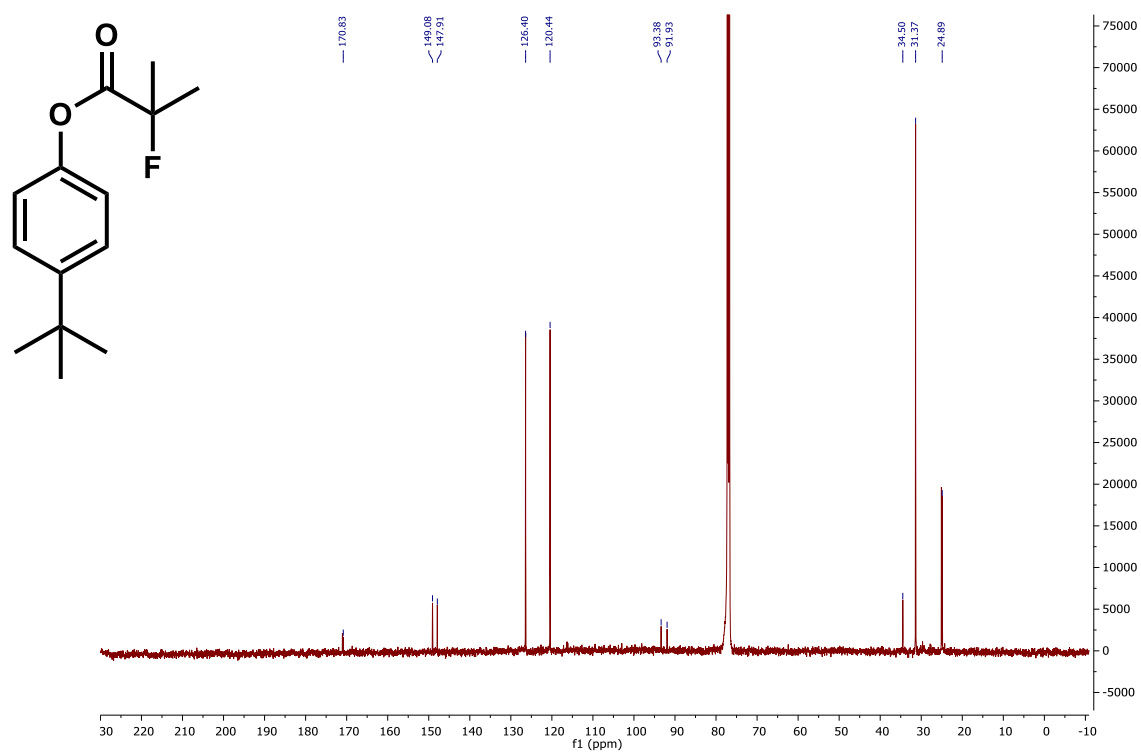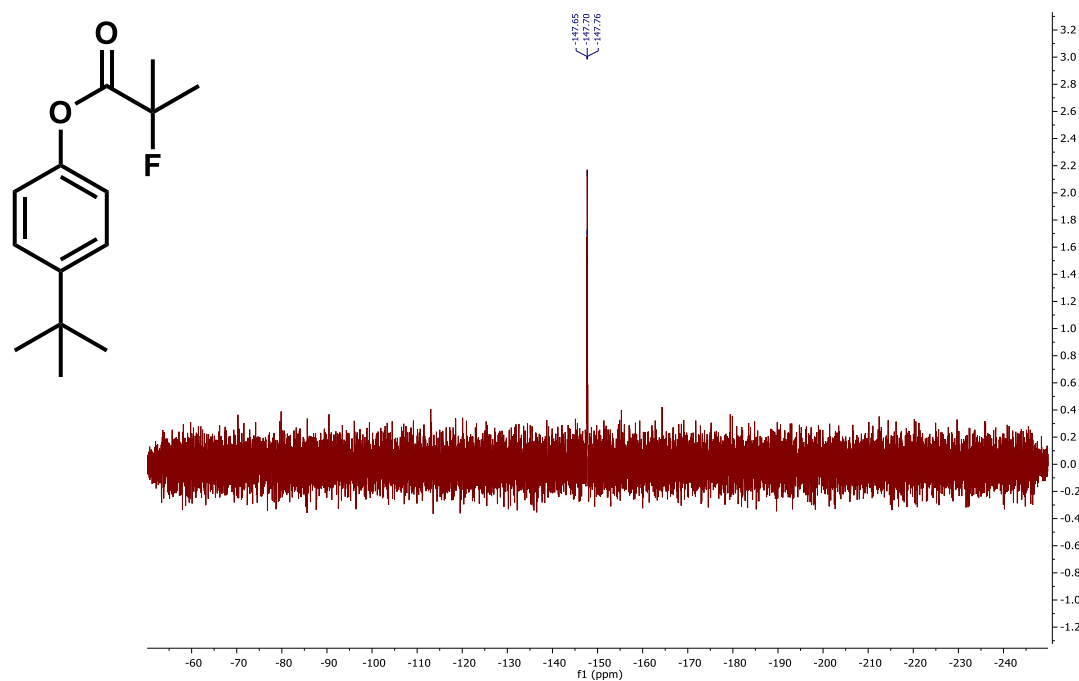**¹³C NMR** (126 MHz, Chloroform-d)

¹⁹F NMR (376 MHz, Chloroform-d)

diastereomer 1

¹H NMR (500 MHz, Chloroform-d)

¹³C NMR (126 MHz, Chloroform-d)

diastereomer 1

¹⁹F NMR (376 MHz, Chloroform-d)

diastereomer 2

¹H NMR (500 MHz, Chloroform-d)

¹³C NMR (126 MHz, Chloroform-d)

diastereomer 2

¹⁹F NMR (376 MHz, Chloroform-d)

¹H NMR (500 MHz, Chloroform-d)

¹³C NMR (126 MHz, Chloroform-d)

¹⁹F NMR (376 MHz, Chloroform-d)

diastereomer 1

¹H NMR (500 MHz, Chloroform-d)

¹³C NMR (126 MHz, Chloroform-d)

diastereomer 1

¹⁹F NMR (376 MHz, Chloroform-d)

diastereomer 2

¹H NMR (500 MHz, Chloroform-d)

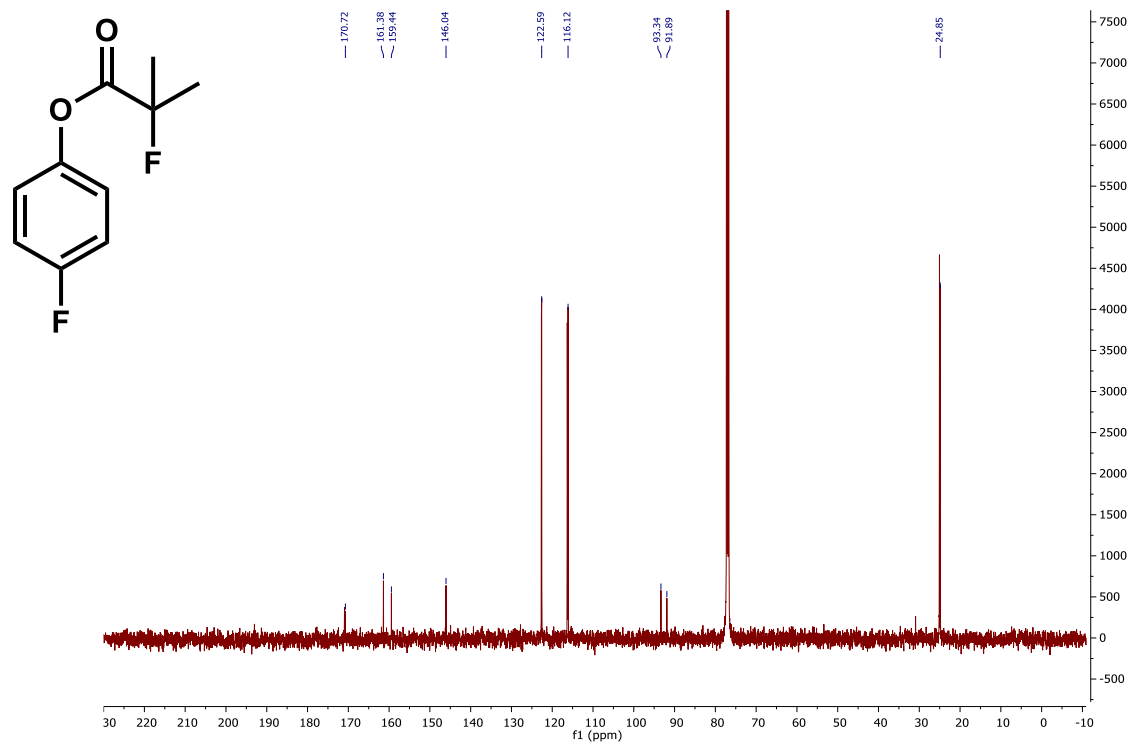**¹³C NMR** (126 MHz, Chloroform-d)

19F NMR (376 MHz, Chloroform-d)

¹H NMR (500 MHz, Chloroform-d)

¹³C NMR (126 MHz, Chloroform-d)

diastereomer 1

^{19}**F NMR** (376 MHz, Chloroform-d)
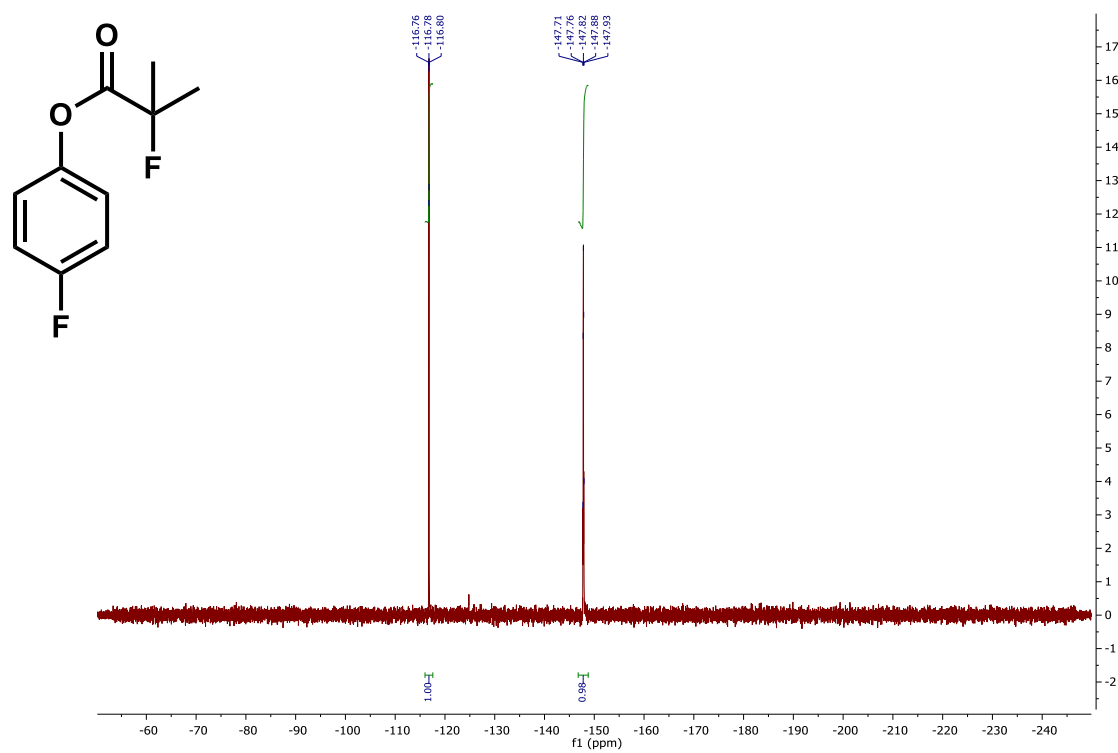

diastereomer 2

(mixed with

diastereomer 1)

¹H NMR (500 MHz, Chloroform-d)

¹³C NMR (126 MHz, Chloroform-d)

diastereomer 2

(mixed with

diastereomer 1)

diastereomer 2

(mixed with

diastereomer 1)

¹⁹F NMR (376 MHz, Chloroform-d)

2. NMR Spectra for 3-Fluoro-2-iodobenzofuran
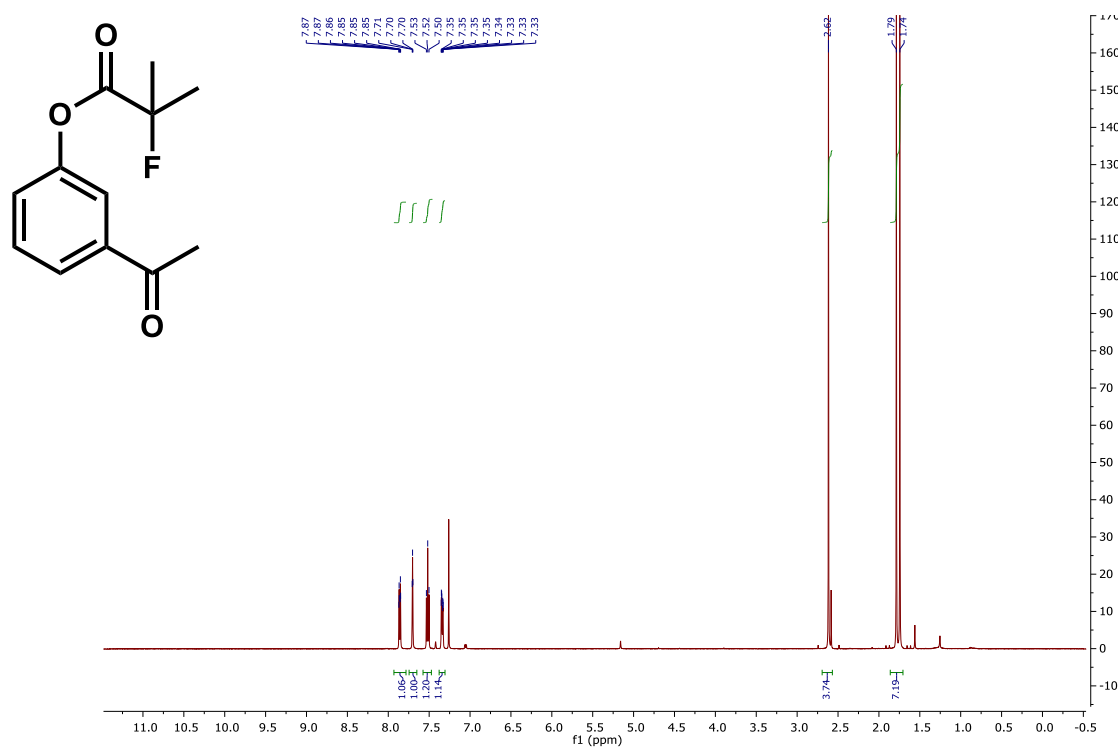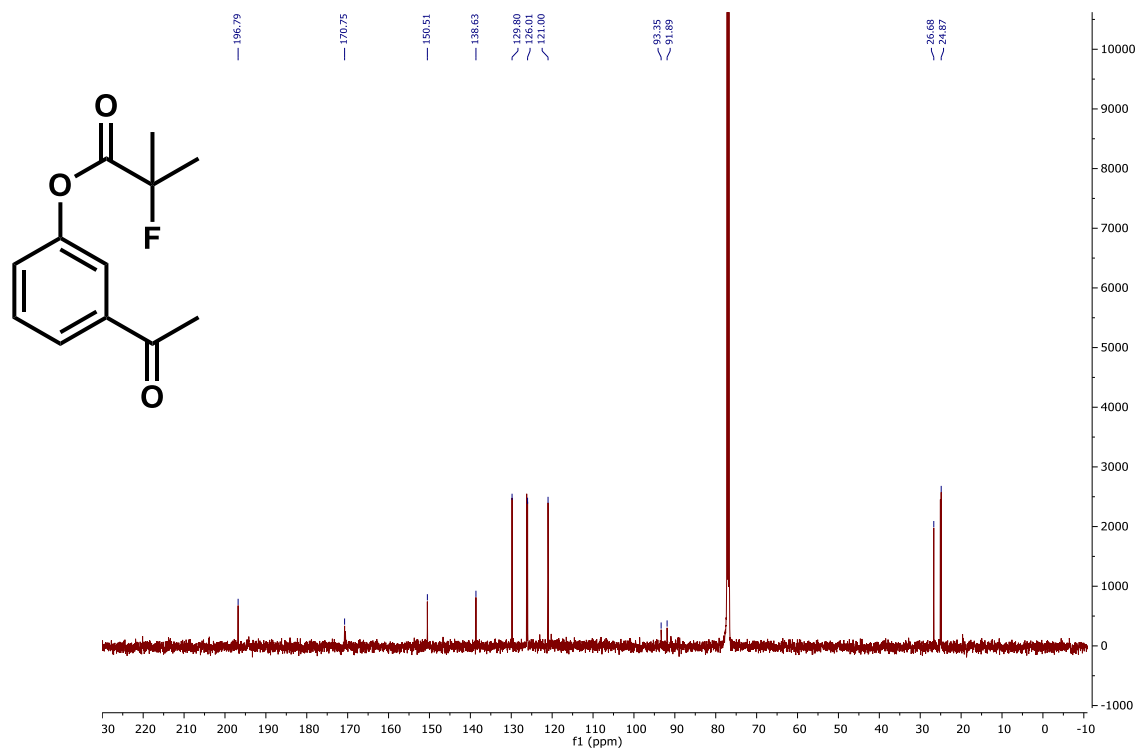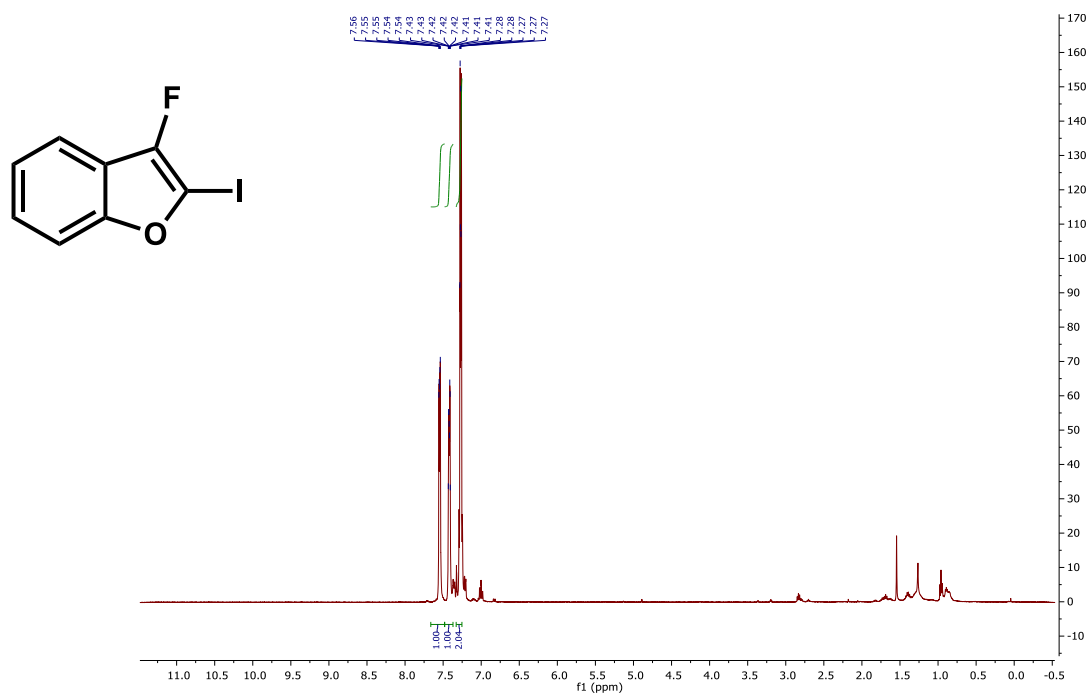

¹H NMR (500 MHz, Chloroform-d)
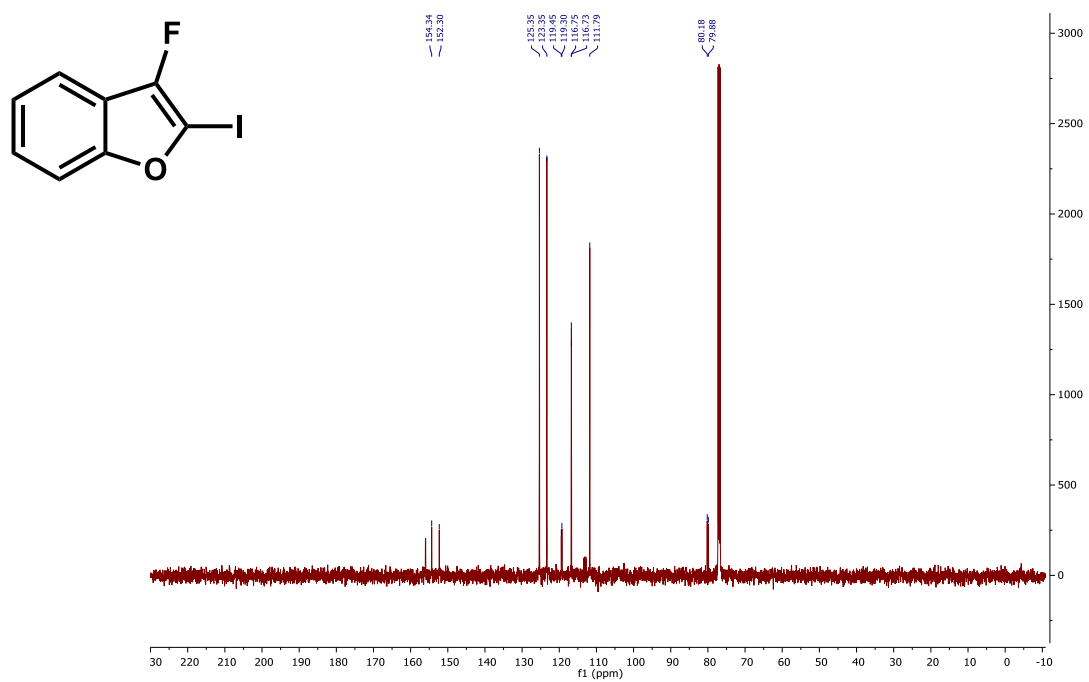
¹³C NMR (126 MHz, Chloroform-d)
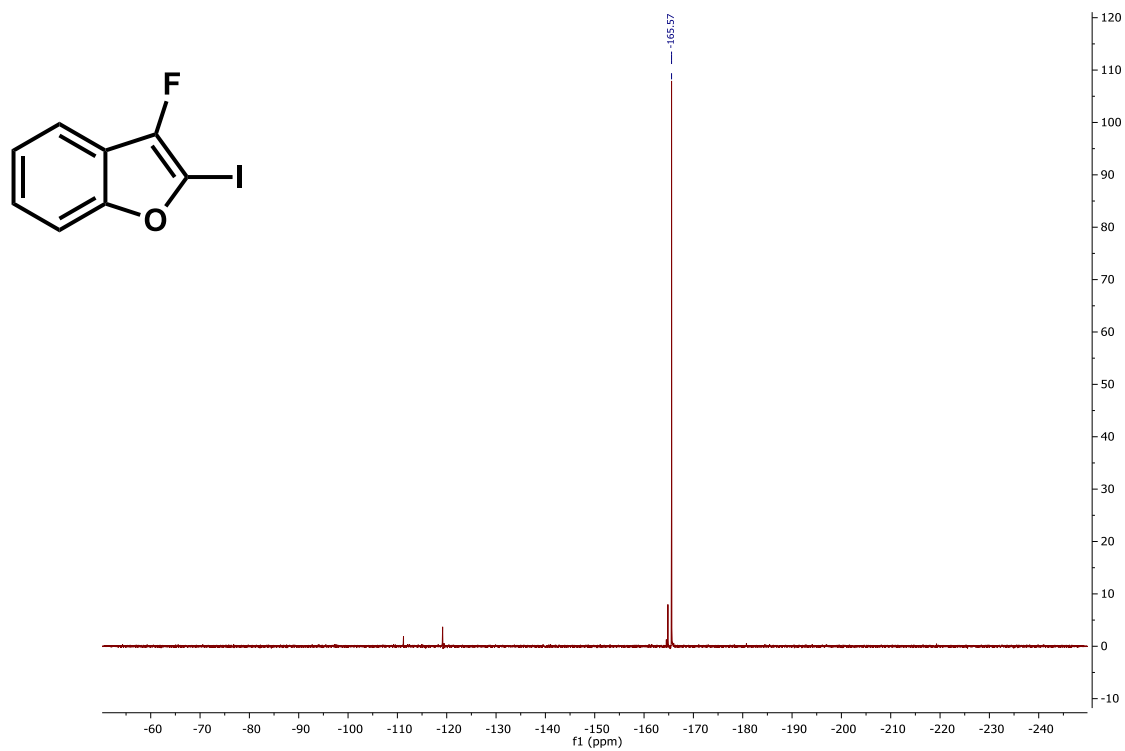
¹⁹F NMR (376 MHz, Chloroform-d)

3. NMR Spectra for (3-Fluorobenzofuran-2-yl)trimethylsilane
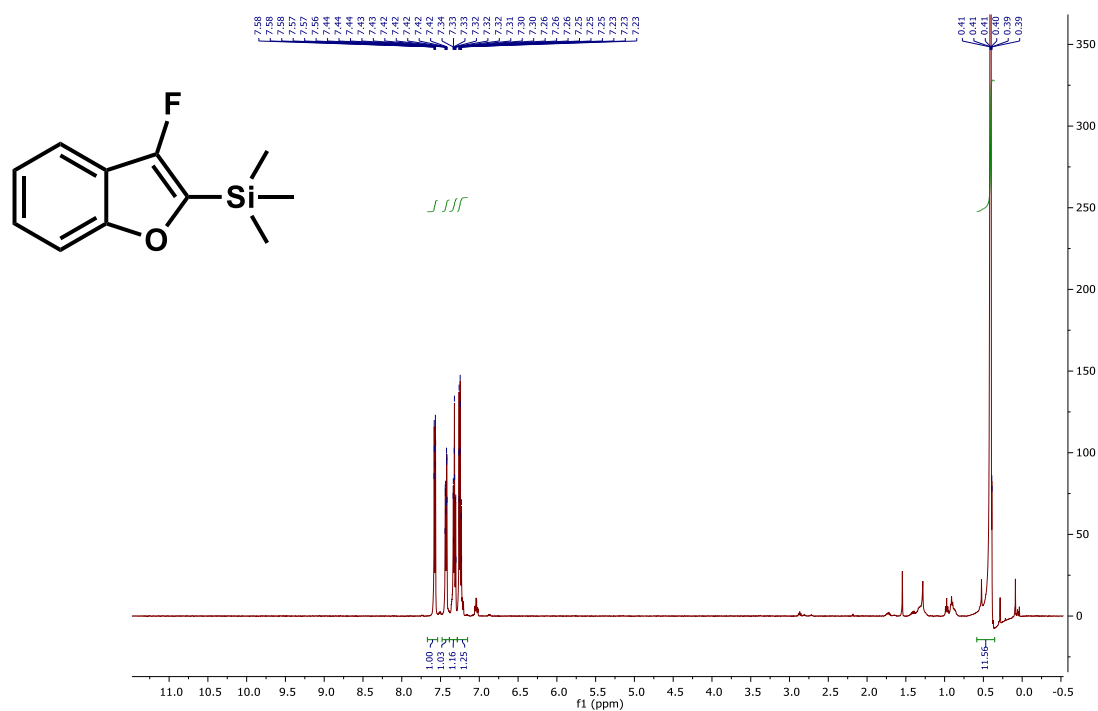
¹H NMR (500 MHz, Chloroform-d)

¹³C NMR (126 MHz, Chloroform-d)

19F NMR (376 MHz, Acetone-*d*₆) δ -169.72.
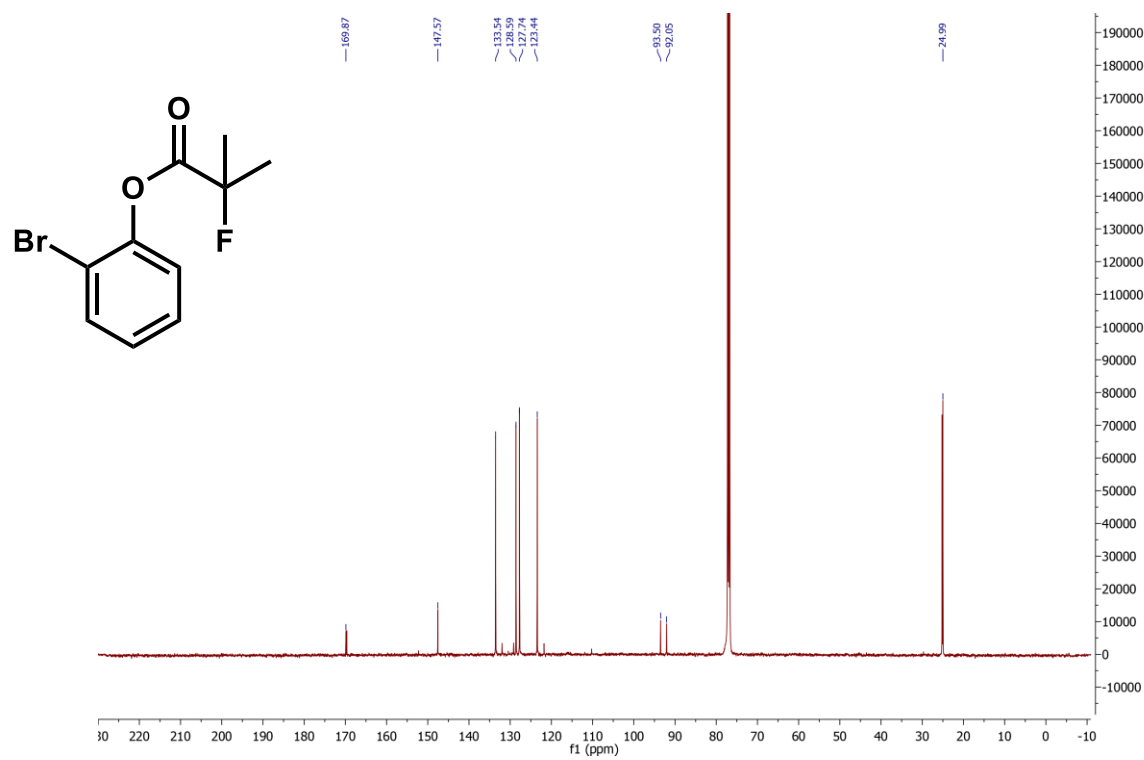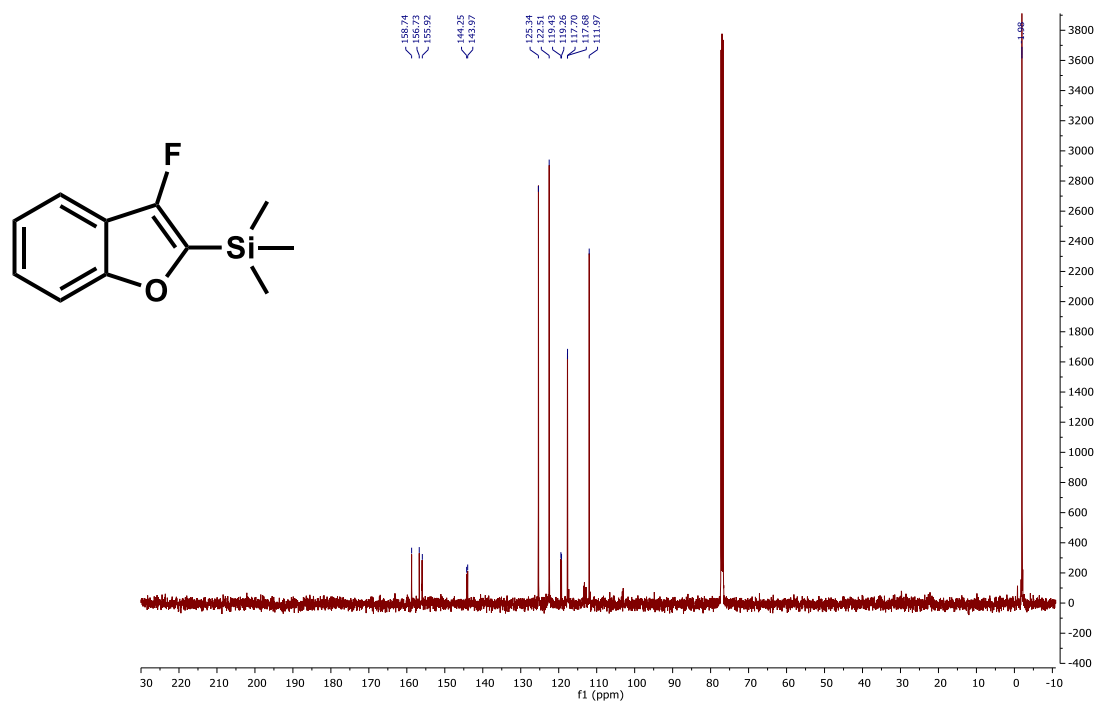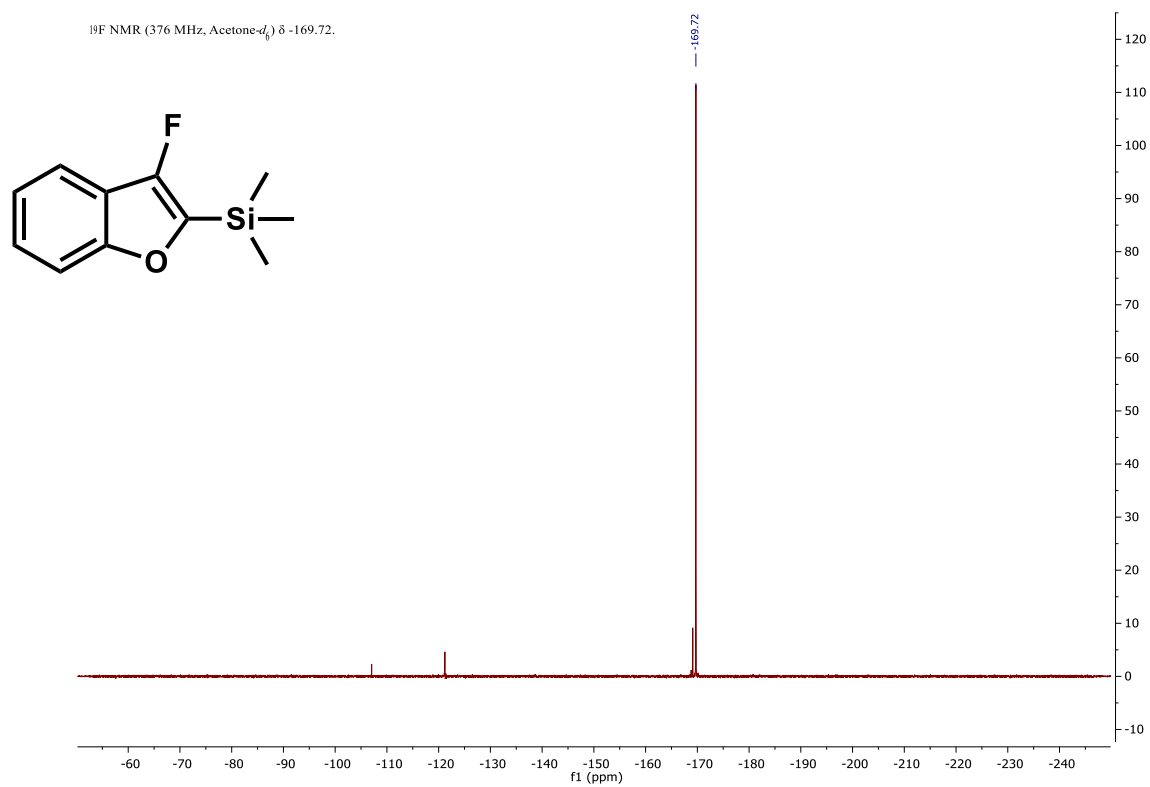

¹⁹F NMR (376 MHz, Chloroform-d)

4. NMR Spectra for (3-Fluorobenzofuran-2-yl)(phenyl)methanol

¹H NMR (400 MHz, Chloroform-d)

¹³C NMR (126 MHz, Chloroform-d)

−174.71
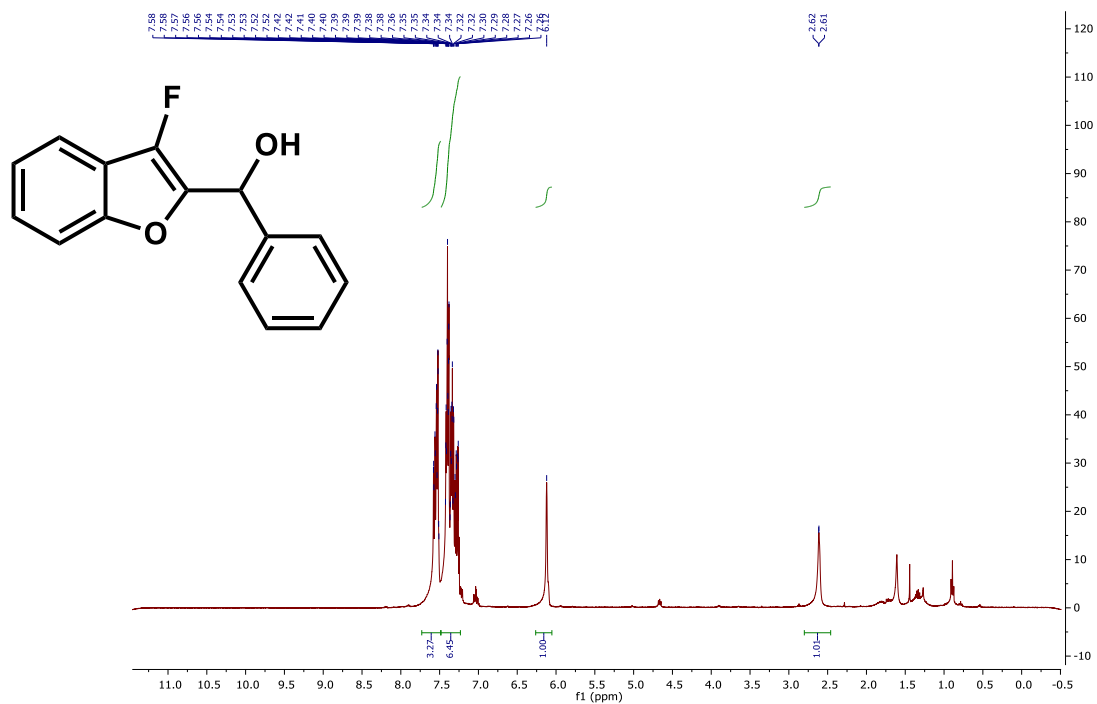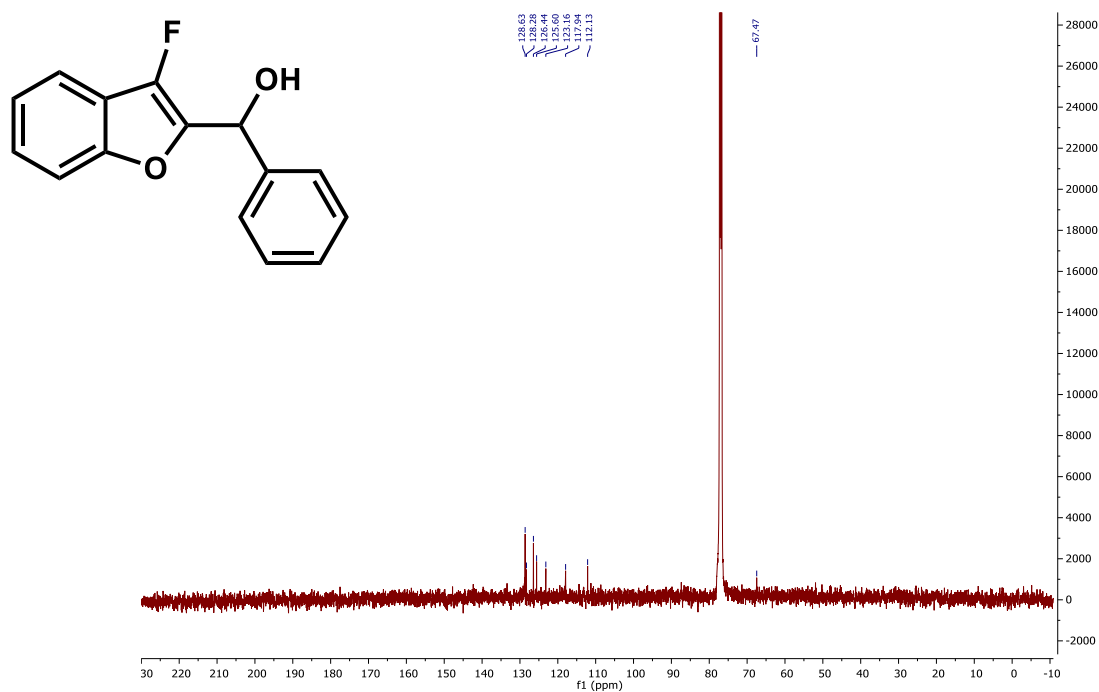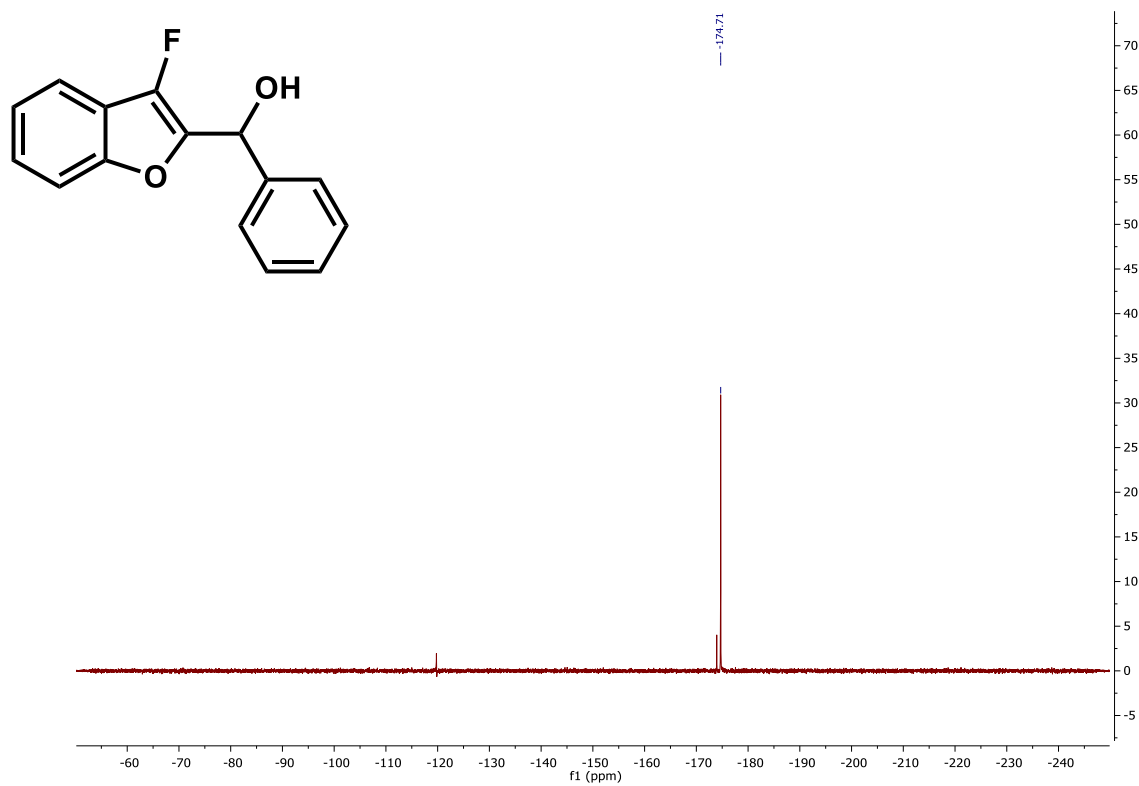
¹⁹F NMR (376 MHz, Chloroform-d)

Reference

1.   Bohm, H. J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Muller, K.; Obst-Sander, U.; Stahl, M., Fluorine in medicinal chemistry. *Chembiochem* **2004,** *5* (5), 637−43.

2.   Smart, B. E., Fluorine substituents effects (on bioactivity). *Journal of Fluorine Chemistry* **2001,** *109*, 3−11.

3.   HANSCH, C.; LEO, A.; TAFT, R. W., A Survey of Hammett Substituent Constants and Resonance and Field Parameters. *Chemical Reviews* **1991,** *91*, 165−195.

4.   Hansch, C.; Rockwell, S. D.; Jow, P. Y. C.; Leo, A.; Steller, E. E., Substituent Constants for Correlation Analysis *Journal of Medicinal Chemistry* **1977,** *20*, 304−306.

5.   Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Xikaitani, D.; Lien, E. J., Aromatic" Substituent Constants for Structure-Activity Correlations. *Journal of Medicinal Chemistry* **1973,** *16* (11), 1207−1217.

6.   Leo, A.; Hansch, C.; Elkins, D., Partition Coeffficients And Their Uses. *Chemical Reviews* **1971,** *71* (6), 525−616.

7.   Bondi, A., van der Waals Volumes and Radii. *The Journal OF Physical Chemistry* **1964,** *68* (3), 441−451.

8.   Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A., Applications of Fluorine in Medicinal Chemistry. *Journal of Medicinal Chemistry* **2015,** *58* (21), 8315−8359.

9.   Peters, D., Problem of the Lengths and Strengths of Carbon—Fluorine Bonds. *The Journal of Chemical Physics* **1963,** *38* (2), 561−563.

10.   O'Hagan, D., Understanding organofluorine chemistry. An introduction to the C−F bond. *Chem Soc Rev* **2008,** *37* (2), 308−19.

11.   Dunitz, J. D., Organic fluorine: odd man out. *Chembiochem* **2004,** *5* (5), 614−21.

12.   Schneider, H.-J., Hydrogen bonds with fluorine. Studies in solution, in gas phase and by computations, conflicting conclusions from crystallographic analyses. *Chemical Science* **2012,** *3* (5), 1381.

13.   Pham, M.; Gdaniec, M.; Połonski, T., Three-Center CF,,,HN Intramolecular Hydrogen Bonding in the 2,6-Bis(2,6-difluorophenyl)piperidine Systems. *Journal of Organic Chemistry* **1998,** *63*, 3731−3734.

14.   Evans, T. A.; Seddon, K. R., Hydrogen bonding in DNA—a return to the status quo. *Chemical Communication* **1997**, 2023−2024.

15.   Lahmani, F.; Zehnacker, A.; Denisov, G.; Furin, G. G., Laser-Induced Fluorescence Study of the S0-S1 Transition of 1- and 2-Perfluoronaphthol in a Supersonic Jet. *Journal of Physical Chemistry* **1996,** *100*, 8633−8639--.

16.   Abraham, R. J.; Smith, T. A. D.; Thomas, W. A., Conformational analysis. Part 28.' OH . F hydrogen bonding and the conformation of trans-2-fluorocyclohexanol. *J. Chem. Soc. Perkin Trans. 2* **1996**, 1949−1955.

17.   Berger, R.; Resnati, G.; Metrangolo, P.; Weber, E.; Hulliger, J., Organic fluorine compounds: a great opportunity for enhanced materials properties. *Chem Soc Rev* **2011,** *40* (7), 3496−508.

18.   Cametti, M.; Crousse, B.; Metrangolo, P.; Milani, R.; Resnati, G., The fluorous effect in biomolecular applications. *Chem Soc Rev* **2012,** *41* (1), 31−42.

19.   Anton, D., Surface-Fluorinated Coatings. *Advanced Materials* **1998,** *10*, 1197−1205.

20.   Berkessel, A.; Adrio, J. A.; Huettenhain, D.; Neudorfl, J. M., Unveiling the "Booster Effect" of Fluorinated Alcohol Solvents: Aggregation-Induced Conformational Changes and Cooperatively Enhanced H-Bonding. *J Am Chem Soc* **2006,** *128*, 8421−8426.

21.   Paulini, R.; Muller, K.; Diederich, F., Orthogonal multipolar interactions in structural chemistry and biology. *Angew Chem Int Ed Engl* **2005,** *44* (12), 1788−805.

22.   Olsen, J. A.; Banner, D. W.; Seiler, P.; Wagner, B.; Tschopp, T.; Obst-Sander, U.; Kansy, M.; Muller, K.; Diederich, F., Fluorine interactions at the thrombin active site: protein backbone fragments H−C(alpha)-C=O comprise a favorable C−F environment and interactions of C−F with electrophiles. *Chembiochem* **2004,** *5* (5), 666−75.

23.   Olsen, J.; Seiler, P.; Wagner, B.; Fischer, H.; Tschopp, T.; Obst-Sander, U.; Banner, D. W.; Kansy, M.; Müller, K.; Diederich, F., A fluorine scan of the phenylamidinium needle of tricyclic thrombin inhibitors: effects of fluorine substitution on pKa and binding affinity and evidence for intermolecular C–F --- CN interactions. *Org Biomol Chem* **2004,** *2*, 1339−1352.

24.   Hof, F.; Scofield, D. M.; Schweizer, W. B.; Diederich, F., A weak attractive interaction between organic fluorine and an amide group. *Angew Chem Int Ed Engl* **2004,** *43* (38), 5056−9.

25.   Olsen, J. A.; Banner, D. W.; Seiler, P.; Obst Sander, U.; D'Arcy, A.; Stihle, M.; Muller, K.; Diederich, F., A fluorine scan of thrombin inhibitors to map the fluorophilicity/fluorophobicity of an enzyme active site: evidence for C−F...C=O interactions. *Angew Chem Int Ed Engl* **2003,** *42* (22), 2507−11.

26.   Kim, C. Y.; Chandra, P. P.; Jain, A.; Christianson, D. W., Fluoroaromatic-Fluoroaromatic Interactions between Inhibitors Bound in the Crystal Lattice of Human Carbonic Anhydrase II. *J Am Chem Soc* **2001,** *123*, 9620−9627.

27.   Biffinger, J. C.; Kim, H. W.; DiMagno, S. G., The polar hydrophobicity of fluorinated compounds. *Chembiochem* **2004,** *5* (5), 622−627.

28.   Hoffmann-Roder, A.; Schweizer, E.; Egger, J.; Seiler, P.; Obst-Sander, U.; Wagner, B.; Kansy, M.; Banner, D. W.; Diederich, F., Mapping the fluorophilicity of a hydrophobic pocket: synthesis and biological evaluation of tricyclic thrombin inhibitors directing fluorinated alkyl groups into the p pocket. *ChemMedChem* **2006,** *1* (11), 1205−15.

29.   Schweizer, E.; Hoffmann-Roder, A.; Scharer, K.; Olsen, J. A.; Fah, C.; Seiler, P.; Obst-Sander, U.; Wagner, B.; Kansy, M.; Diederich, F., A fluorine scan at the catalytic center of thrombin: C−F, C−OH, and C−OMe bioisosterism and fluorine effects on pKa and log D values. *ChemMedChem* **2006,** *1* (6), 611−21.

30.   Meyer, E. A.; Castellano, R. K.; Diederich, F., Interactions with Aromatic Rings in Chemical and Biological Recognition. *Angew Chem Int Ed Engl* **2003,** *42*, 1210−1250.

31.   Roth, B. D.; Ortwine, D. F.; Hoefle, M. L.; Stratton, C. D.; Sliskovic, D. R.; Wilson, M. W.; Newton, R. S., Inhibitors of Cholesterol Biosynthesis. 1. trans -6-(2-Pyrrol- l-ylethyl)-4-hydroxypyran-2-ones, a Novel Series of HMG-CoA Reductase Inhibitors. 1. Effects of Structural Modifications at the 2- and 5-Positions of the Pyrrole Nucleus *J. Med. Chem.* **1990,** *33*, 21−31.

32.   Grunewald, G. L.; Seim, M. R.; Lu, J.; Makboul, M.; Criscione, K. R., Application of the Goldilocks Effect to the Design of Potent and Selective Inhibitors of Phenylethanolamine N-Methyltransferase: Balancing pKa and Steric Effects in the Optimization of 3-Methyl-1,2,3,4-tetrahydroisoquinoline Inhibitors by â-Fluorination. *J. Med. Chem.* **2006,** *49*, 2939−2952.

33.   Domagala, J. M.; Heifetz, C. L.; Mich, T. F.; Nichols, J. B., 1-Ethyl-7-[3-[(ethy1amino)methyll- l-pyrrolidinyll-6,8-difluoro- 1,4-dihydro-4-oxo-3-quinolinecarboxylic Acid. New Quinolone Antibacterial with Potent Gram-positive Activity *J. Med. Chem.* **1986,** *29*, 445−448.

34.   Domagala, J. M.; Hanna, L. D.; Heifetz, C. L.; Hutt, M. P.; Mich, T. F.; P.Sanchez, J.; Solomon, M., New Structure-Activity Relationships of the Quinolone Antibacterials Using the Target Enzyme. The Development and Application of a DNA Gyrase Assay *J. Med. Chem.* **1986,** *29*, 394−404.

35.   Kotoris, C. C.; Chen, M.-J.; Taylor, S. D., NOVEL PHOSPHATE MIMETICS FOR THE DESIGN OF NON-PEPTIDYL INHIBITORS OF PROTEIN TYROSINE PHOSPHATASES *Bioorg. Med. Chem. Lett.* **1998,** *8*, 3275−3280.

36.   Koga, H.; Itoh, A.; Murayama, S.; Suzue, S.; Irikura, T., Structure-Activity Relationships of Antibacterial 6,7- and 7,8-Disubstituted 1 -A1 kyl- 1,4-dihydro-4-oxoquinoline-3-carboxylic Acids. *J. Med. Chem.* **1980,** *23*, 1358−1363.

37.   Chou, Y. L.; Davey, D. D.; Eagen, K. A.; Griedel, B. D.; R.Karanjawala; Phillips, G. B.; Sacchi, K. L.; Shaw, K. J.; Wu, S. C.; Lentz, D.; Liang, A. M.; Trinh, L.; Morrissey, M. M.; Kochanny, M. J., *Bioorg. Med. Chem. Lett.* **2003,** *13*, 507−511.

38.   Abbate, F.; Casini, A.; Scozzafava, A.; T.Supuran, C., *J. Enzyme Inhib. Med. Chem* **2003,** *18*, 303 − 308.

39.   Kim, C.-Y.; Chang, J. S.; Doyon, J. B.; Teaster T. Baird, J.; Fierke, C. A.; Jain, A.; Christianson, D. W., Contribution of Fluorine to Protein-Ligand Affinity in the Binding of Fluoroaromatic Inhibitors to Carbonic Anhydrase II. *J Am Chem Soc* **2000,** *122*, 12125−12134.

40.   DerHovanessian, A.; Doyon, J. B.; Jain, A.; Rablen, P. R.; Sapse, A. M., Models of F,H Contacts Relevant to the Binding of Fluoroaromatic Inhibitors to Carbonic Anhydrase II. *Org.*

Lett. **1999,** *1*, 183−185.

41.   Piepenbrink, K. H.; Borbulevych, O. Y.; Sommese, R. F.; Clemens, J.; Armstrong, K. M.; Desmond, C.; Do, P.; Baker, B. M., Fluorine substitutions in an antigenic peptide selectively modulate T-cell receptor binding in a minimally perturbing manner. *Biochem J* **2009,** *423* (3), 353−361.

42.   Terrence R. Burke, J. B. Y.; Yan, X.; Wang, S.; Jia, Z.; Chen, L.; Zhang, Z.-Y.; Barford, D., Small Molecule Interactions with Protein-Tyrosine Phosphatase PTP1B and Their Use in Inhibitor Design. *Biochemistry* **1996,** *35*, 15989−15996.

43.   Clader, J. W., The Discovery of Ezetimibe: A View from Outside the Receptor. *J. Med. Chem.* **2004,** *47*, 1−9.

44.   Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C., Synthesis and Biological Evaluation of the 1,5-Diarylpyrazole Class of Cyclooxygenase-2 Inhibitors: Identification of 4-[5-(4-Methylphenyl)-3-   (trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide   (SC-58635, Celecoxib). *J. Med. Chem.* **1997,** *40*, 1347−1365.

45.   Shimizu, M.; Hiyama, T., Modern synthetic methods for fluorine-substituted target molecules. *Angew Chem Int Ed Engl* **2004,** *44* (2), 214−31.

46.   Middleton, W. J.; Bingham, E. M., a-Fluorination of Carbonyl Compounds with CF3OF *J Am Chem Soc* **1980,** *102*, 4845−4846.

47.   Gensler, W. J.; Ahmed, Q. A.; Leeding, M., Fluorination of Methyl Isobutyrate with Perchloryl Fluoride. *Journal of Organic Chemistry* **1968,** *33*, 4279−4281.

48.   Fujisawa, H.; Fujiwara, T.; Takeuchi, Y.; Omata, K., Synthesis and Optical Resolution of 2-Aryl-2-fluoropropionic Acids, Fluorinated Analogues of Non-steroidal Anti-inflammatory Drugs (NSAIDs). *Chem. Pharm. Bull.* **2005,** *53*, 524−528.

49.   Chernick, C. L.; Claassen, H. H.; Fields, P. R.; Hyman, H. H.; Malm, J. G.; Manning, W. M.; Matheson, M. S.; Quarterman, L. A.; Schreiner, F.; Selig, H. H.; Sheft, I.; Siegel, S.; Sloth, E. N.; Stein, L.; Studier, M. H.; Weeks, J. L.; Zirin, M. H., Fluorine Compounds of Xenon and Radon. *Science* **1962**, *138*, 136−138.

50.   Ramsden, C. A.; Smith, R. G., On the Modes of Reaction of Xenon Difluoride with Organic Substrates: The Influence of Solvent and Vessel. *J Am Chem Soc* **1998**, *120*, 6842−6843.

51.   Differding, E.; Ofner, H., N-Fluorobenzenesulfonimide: A Practical Reagent For Electrophilic Fluorinations. *Synlett* **1991**, 187−189.

52.   Barnette, W. E., N-Fluoro-N-alkylsulfonamides: Useful Reagents for the Fluorination of Carbanions. *J. Am. Chem. SOC.* **1984,** *106*, 452−454

53.   Davis, F. A.; Zhou, P.; Murphy, C. K., ASYMMETRIC FLUORINATION OF

ENOLATES WITH N-FLUORO 2,10-(3,3-DICHLOROCAMPHORSULTAM) *Tetrahedron Letters* **1993,** *34*, 3971−3974.

54.   Resnati, G.; Desmarteau, D. D., N-Fluorobis[(trifluoromethyl)sulfonyl]imide: An Efficient Reagent for the a-Fluorination of Functionalized Carbonyl Compounds *Journal of Organic Chemistry* **1991,** *56*, 4925−4929.

55.   Davis, F. A.; Han, W., N-FLUORO-0-BENZENEDISULFONIMIDE: A USEFUL NEW FLUORINATING REAGENT *Tetrahedron Letters* **1991,** *32*, 1631−1634.

56.   Differding, E.; Lang, R. W., Preparation and Synthetic Application of a Saccharin Derived N-Fluorosultam. *Helv. Chim. Acta* **1989,** *72*, 1248−1252.

57.   Differding, E.; Lang, R. W., NEW FLUORINATING REAGENTS -THE FIRST ENANTIOSELECTIVE FLUORINATION REACTION *Tetrahedron Letters* **1988,** *29*, 6087−6090.

58.   Umemoto, T.; Nagayoshi, M.; Adachi, K.; Tomizawa, G., Synthesis, Properties, and Reactivity of N,N′-Difluorobipyridinium and Related Salts and Their Applications as Reactive and Easy-To-Handle Electrophilic Fluorinating Agents with High Effective Fluorine Content. *Journal of Organic Chemistry* **1998,** *63*, 3379−3385.

59.   Umemoto, T.; Tomizawa, G., Highly Selective Fluorinating Agents: A Counteranion-Bound N-Fluoropyridinium Salt System. *Journal of Organic Chemistry* **1995,** *60*, 6563−6570.

60.   Umemoto, T.; Harasawa, K.; Tomizawa, G.; Kawada, K.; Tomita, K., Syntheses and Properties of N-Fluoropyridinium. *Bull. Chem. Soc. Jpn.* **1991,** *64*, 1081−1092.

61.   Umemoto, T.; Fukami, S.; Tomizawa, G.; Harasawa, K.; Kawada, K.; Tomita, K., Power and Structure-Variable Fluorinating Agents. The N-Fluoropyridinium Salt System. *J Am Chem Soc* **1990,** *112*, 8563−8575.

62.   Umemoto, T.; Tomizawa, G., BASE-INITIATED REACTIONS OF N-FLUOROPYRIDINIUM SALTS; A NOVEL CYCLIC CARBENE PROPOSED AS A REACTIVE SPECIES'. *Tetrahedron Letters* **1987,** *28*, 2705−2708.

63.   Tomita, K.; Kawada, K.; Umemoto, T., USE AND APPLICATION OF NEW FLUORINATING AGENTS, FLUOROPYRIDINIUM TRIFLATE AND ITS DERIVATIVES *J. Fluorine Chem.* **1987,** *35*, 14.

64.   Umemoto, T.; Tomita, K., N-FLUOROPYRIDINIUM TRIFLATE AND ITS ANALOGS, THE FIRST STABLE 1:l SALTS OF PYRIDINE NUCLEUS AND HALOGEN ATOM *Tetrahedron Letters* **1986,** *27*, 3271−3274.

65.   Umemoto, T.; Kawada, K.; K. Tomita, N-FLUOROPYRIDINIUM TRIFLATE AND ITS DERIVATIVES: USEFUL FLUORINATING AGENTS. *Tetrahedron Letters* **1986,** *27*.

66.   Banks, R. E.; Mohialdinkhaffaf, S. N.; Lal, G. S.; Sharif, I.; Syvret, R. G., l-Alkyl-4-fluoro-l,4-diazoniabicyclo[2.2.2]octane Salts: a Novel Family of Electrophilic Fluorinating Agents. *J. Chem. Soc. Chem. Commun.* **1992**, 595−596.

67.	Hull, K. L.; Anani, W. Q.; Sanford, M. S., Palladium-Catalyzed Fluorination of Carbon-Hydrogen Bonds. *Journal of American Chemistry Society* **2006,** *128*, 7134−7135.

68.	Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; García-Fortanet, J.; Kinzel, T.; Buchwald, S. L., Formation of ArF from LPdAr(F): Catalytic Conversion of Aryl Triflates to Aryl Fluorides. *Science* **2009,** *325*, 1661−1664.

69.	Chambers, R. D.; Hutchinson, J., Elemental fluorine Preparation of a-fluoroketones *J. Fluorine Chem.* **1998,** *89*, 229−232.

70.	Purrington, S. T.; Lazaridis, N. V.; Bumgardner, C. L., PREPARATION OF a-FLUOROALDEHYDES AND a-FLUOROKETONES USING DILUTE FLUORINE *Tetrahedron Letters* **1986,** *27*, 2715−2716.

71.	Gershon, H.; Schulman, S. G.; Spevack, A. D., Organic Fluorine Compounds Action of Perchloryl Fluoride on Substituted Ethyl Cyanoacetates and Animal Toxicities of the Fluorinated Products. *J. Med. Chem.* **1967,** *10*, 536−541.

72.	Inman, C. E.; Oesterling, R. E.; Tyczkowski, E. A., Reactions of Berchloryl Fluoride with Organic Compounds. II. Fluorination of Certain Active Methylene Compounds. *J Am Chem Soc* **1958,** *80*, 6533−6535.

73.	Shapiro, B. L.; Chrysam, M. M., cr-Fluoro-3,3,5,5-Tetrasubstituted Cyclohexanones. I. Synthesis and Conformational Analysis. *J. Org. Chem.* **1973,** *38*, 880−893.

74.	Sheppard, W. A., Mechanism of Fluorination by Perchloryl Fluoride *Tetrahedron Letters* **1969,** *10*, 83−84.

75.	Stavber, S.; Zupan, M., Room-temperature Fluorination of Alkenes with Caesium Fluoroxysulphate *J. Chem. Soc. Chem. Commun.* **1981**, 795−796.

76.	Zajc, B.; Zupan, M., Fluorination with Xenon Difluoride. 27. The Effect of Catalyst on Fluorination of 1,3-Diketones and Enol Acetates *Journal of Organic Chemistry* **1982,** *47*, 573−575.

77.	Lal, G. S.; Pez, G. P.; Syvret, R. G., Electrophilic NF Fluorinating Agents. *Chemical Reviews* **1996,** *96*, 1737−1755.

78.	Davis, F. A.; Han, W.; Murphy, C. K., Selective, Electrophilic Fluorinations Using N-Fluoro-o-benzenedisulfonimide. *Journal of Organic Chemistry* **1995,** *60*, 4730−4737.

79.	Lal, G. S., Site-Selective Fluorination of Organic Compounds Using l-Alkyl-4-fluoro-l,4-diazabicyclo[2.2.2]octane Salts (Selectfluor Reagents). *Journal of Organic Chemistry* **1993,** *58*, 2791−2796.

80.	Cahard, D.; Audouard, C.; Plaquevent, J. C.; Roques, N., Design, Synthesis, and Evaluation of a Novel Class of Enantioselective Electrophilic Fluorinating Agents: N-Fluoro Ammonium Salts of cinchona Alkaloids (F-CA-BF4). *Organic Letters* **2000,** *2*, 3699−3701.

81.	Frantz, R.; Hintermann, L.; Perseghini, M.; Broggini, D.; Togni, A., Titanium-Catalyzed Stereoselective Geminal Heterodihalogenation of b-Ketoesters. *Org. Lett.* **2003,** *5*, 1709−1712.

82.   Piana, S.; Devillers, I.; Togni, A.; Rothlisberger, U., The Mechanism of Catalytic Enantioselective Fluorination: Computational and Experimental Studies. *Angew. Chem. Int. Ed.* **2002,** *41*, 979−982.

83.   Hintermann, L.; Togni, A., Catalytic Enantioselective Fluorination of b-Ketoesters. *Angew. Chem. Int. Ed.* **2000,** *39*, 4359−4362.

84.   Hintermann, L.; Perseghini, M.; Togni, A., Development of the titanium-TADDOLate-catalyzed asymmetric fluorination of beta-ketoesters. *Beilstein J Org Chem* **2011,** *7*, 1421−1435.

85.   Bertogg, A.; Hintermann, L.; Huber, D. P.; Perseghini, M.; Sanna, M.; Togni, A., Substrate Range of the Titanium TADDOLate Catalyzed Asymmetric Fluorination of Activated Carbonyl Compounds. *Helv. Chim. Acta.* **2012,** *95*, 353−403.

86.   Ma, J.-A.; Cahard, D., Copper(II) triflate-bis(oxazoline)-catalysed enantioselective electrophilic fluorination of β-ketoesters. *Tetrahedron: Asymmetry* **2004,** *15* (6), 1007-1011.

87.   Shibata, N.; Kohno, J.; Takai, K.; Ishimaru, T.; Nakamura, S.; Toru, T.; Kanemasa, S., Highly enantioselective catalytic fluorination and chlorination reactions of carbonyl compounds capable of two-point binding. *Angew Chem Int Ed Engl* **2005,** *44* (27), 4204−4207.

88.   Althaus, M.; Togni, A.; Mezzetti, A., Asymmetric oxidative α-fluorination of 2-alkylphenylacetaldehydes with AgHF2 and ruthenium/PNNP catalysts. *Journal of Fluorine Chemistry* **2009,** *130* (8), 702−707.

89.   Althaus, M.; Becker, C.; Togni, A.; Mezzetti, A., Ruthenium-Catalyzed Asymmetric Electrophilic Fluorination of 1,3-Dicarbonyl Compounds. *Organometallics* **2007,** *26*, 5902−5911.

90.   Suzuki, S.; Furuno, H.; Yokoyama, Y.; Inanaga, J., Asymmetric fluorination of β-keto esters catalyzed by chiral rare earth perfluorinated organophosphates. *Tetrahedron: Asymmetry* **2006,** *17* (4), 504−507.

91.   Suzuki, S.; Kitamura, Y.; Lectard, S.; Hamashima, Y.; Sodeoka, M., Catalytic asymmetric mono-fluorination of alpha-keto esters: synthesis of optically active beta-fluoro-alpha-hydroxy and beta-fluoro-alpha-amino acid derivatives. *Angew Chem Int Ed Engl* **2012,** *51* (19), 4581−4585.

92.   Hamashima, Y.; Yagi, K.; Takano, H.; Tamas, L.; Sodeoka, M., An Efficient Enantioselective Fluorination of Various b-Ketoesters Catalyzed by Chiral Palladium Complexes. *J. Am. Chem. Soc.* **2002,** *124*, 14530−14531.

93.   Hamashima, Y.; H.Takano; Hotta, D.; Sodeoka, M., Immobilization and Reuse of Pd Complexes in Ionic Liquid: Efficient Catalytic Asymmetric Fluorination and Michael Reactions with b-Ketoesters. *Org. Lett.* **2003,** *5*, 3225−3228.

94.   Hamashima, Y.; Suzuki, T.; Shimura, Y.; Shimizu, T.; Umebayashi, N.; Tamura, T.; Sasamoto, N.; Sodeoka, M., An efficient catalytic enantioselective fluorination of β-ketophosphonates using chiral palladium complexes. *Tetrahedron Letters* **2005,** *46* (9), 1447−1450.

95.   Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Tsuchiya, Y.; Moriya, K.-i.; Goto, T.; Sodeoka, M., Highly enantioselective fluorination reactions of β-ketoesters and β-ketophosphonates catalyzed by chiral palladium complexes. *Tetrahedron* **2006,** *62* (30), 7168−7179.

96.   Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sodeoka, M., Catalytic Enantioselective Fluorination of Oxindoles. *J. Am. Chem. Soc.* **2005,** *127*, 10164−10165.

97.   Suzuki, T.; Goto, T.; Hamashima, Y.; Sodeoka, M., Enantioselective Fluorination of tert-Butoxycarbonyl Lactones and Lactams Catalyzed by Chiral Pd(II)-Bisphosphine Complexes. *J. Org. Chem.* **2007,** *72*, 246−250.

98.   Shibata, N.; Suzuki, E.; Takeuchi, Y., A Fundamentally New Approach to Enantioselective Fluorination Based on Cinchona Alkaloid Derivatives/Selectfluor Combination. *J. Am. Chem. Soc.* **2000,** *122*, 10728−10729.

99.   Shibata, N.; Suzuki, E.; Asahi, T.; Shiro, M., Enantioselective Fluorination Mediated by Cinchona Alkaloid Derivatives/Selectfluor Combinations: Reaction Scope and Structural Information for N-Fluorocinchona Alkaloids. *J. Am. Chem. Soc.* **2001,** *123*, 7001−7009.

100.   Shibata, N.; Ishimaru, T.; Suzuki, E.; Kirk, K. L., Enantioselective Fluorination Mediated by N-Fluoroammonium Salts of Cinchona Alkaloids: First Enantioselective Synthesis of BMS-204352 (MaxiPost). *J. Org. Chem.* **2003,** *68*, 2494−2497.

101.   Li, J.; Cai, Y.; Chen, W.; Liu, X.; Lin, L.; Feng, X., Highly enantioselective fluorination of unprotected 3-substituted oxindoles: one-step synthesis of BMS 204352 (MaxiPost). *J Org Chem* **2012,** *77* (20), 9148−55.

102.   Xu, J.; Hu, Y.; Huang, D.; Wang, K.-H.; Xu, C.; Niu, T., Thiourea-Catalyzed Enantioselective Fluorination of β-Keto Esters. *Advanced Synthesis & Catalysis* **2012,** *354* (2-3), 515−526.

103.   Shibata, N.; Suzuki, E.; Takeuchi, Y., A Fundamentally New Approach to Enantioselective Fluorination Based on Cinchona Alkaloid Derivatives/Selectfluor Combination. *J. Am. Chem. Soc.* **2000,** *122*, 10728−10729.

104.   Enders, D.; Hüttl, M., Direct Organocatalytic α-Fluorination of Aldehydes and Ketones. *Synlett* **2005,** *2005* (06), 0991−0993.

105.   Beeson, T. D.; MacMillan, D. W. C., Enantioselective Organocatalytic r-Fluorination of Aldehydes. *J. Am. Chem. Soc.* **2005,** *127*, 8826−8828.

106.   Marigo, M.; Fielenbach, D.; Braunton, A.; Kjaersgaard, A.; Jorgensen, K. A., Enantioselective formation of stereogenic carbon-fluorine centers by a simple catalytic method. *Angew Chem Int Ed Engl* **2005,** *44* (24), 3703−3706.

107.   Steiner, D. D.; Mase, N.; Barbas, C. F., 3rd, Direct asymmetric alpha-fluorination of aldehydes. *Angew. Chem. Int. Ed.* **2005,** *44* (24), 3706−3710.

108.   Kwiatkowski, P.; Beeson, T. D.; Conrad, J. C.; MacMillan, D. W., Enantioselective

organocatalytic alpha-fluorination of cyclic ketones. *J Am Chem Soc* **2011,** *133* (6), 1738−1741.

109.   Schulte, M. L.; Lindsley, C. W., *Org. Lett.* **2011,** *13*, 5684−5687.

110.   Erb, J.; Alden-Danforth, E.; Kopf, N.; Scerba, M. T.; Lectka, T., Combining asymmetric catalysis with natural product functionalization through enantioselective alpha-fluorination. *J Org Chem* **2010,** *75* (3), 969−71.

111.   Paull, D. H.; Scerba, M. T.; Alden-Danforth, E.; Widger, L. R.; Lectka, T., Catalytic, Asymmetric α-Fluorination of Acid Chlorides: Dual Metal-Ketene Enolate Activation. *J. Am. Chem. Soc.* **2008,** *130*, 17260−17261.

112.   McPake, C. B.; Sandford, G., Selective Continuous Flow Processes Using Fluorine Gas. *Organic Process Research & Development* **2012,** *16* (5), 844−851.

113.   Clark, J. H., Fluoride Ion as a Base in Organic Synthesis. *Chem. Rev.* **1980,** *80*, 429−452.

114.   Liotta, C. L.; Harris, H. P., The Chemistry of "Naked" Anions. I. Reactions of the 18-Crown-6 Complex of Potassium Fluoride with Organic Substrates in Aprotic Organic Solvents. *J. Am. Chem. Soc.* **1974,** *96*, 2250−2252.

115.   Kim, D. W.; Song, C. E.; Chi, D. Y., New Method of Fluorination Using Potassium Fluoride in Ionic Liquid: Significantly Enhanced Reactivity of Fluoride and Improved Selectivity. *J. Am. Chem. Soc.* **2002,** *124*, 10278−10279.

116.   Kim, D. W.; Jeong, H.-J.; Litn, S. T.; Sohn, M.-H.; Katzenellenbogen, J. A.; Chi, D. Y., Facile Nucleophilic Fluorination Reactions Using tert-Alcohols as a Reaction Medium: Significantly Enhanced Reactivity of Alkali Metal Fluorides and Improved Selectivity

J. Org. Chem. **2008,** *73*, 957−962.

117.   Kim, D. W.; Ahn, D.-S.; Oh, Y.-H.; Lee, S.; Kil, H. S.; Oh, S. J.; Lee, S. J.; Kim, J. S.; Ryu, J. S.; Moon, D. H.; Chi, D. Y., A New Class of SN2 Reactions Catalyzed by Protic Solvents: Facile Fluorination for Isotopic Labeling of Diagnostic Molecules. *J. Am. Chem. Soc.* **2006,** *128*, 16394−16397.

118.   Ung, G.; Bertrand, G., C-F bond activation with an apparently benign ethynyl dithiocarbamate, and subsequent fluoride transfer reactions. *Chemistry* **2012,** *18* (41), 12955−12957.

119.   Liu, Y.; Chen, C.; Li, H.; Huang, K.-W.; Tan, J.; Weng, Z., Efficient SN2 Fluorination of Primary and Secondary Alkyl Bromides by Copper(I) Fluoride Complexes. *Organometallics* **2013,** *32* (21), 6587−6592.

120.   Dang, H.; Mailig, M.; Lalic, G., Mild copper-catalyzed fluorination of alkyl triflates with potassium fluoride. *Angew Chem Int Ed Engl* **2014,** *53* (25), 6473−6476.

121.   Umemoto, T.; Singh, R. P.; Xu, Y.; Saito, N., Discovery of 4-tert-Butyl-2,6-dimethylphenylsulfur Trifluoride as a Deoxofluorinating Agent with High Thermal Stability as Well as Unusual Resistance to Aqueous Hydrolysis, and Its Diverse Fluorination Capabilities Including Deoxofluoro-Arylsulfinylation with High Stereoselectivity. *J. Am. Chem. Soc.* **2010,**

132, 18199−18205.

122. Bi, X., Deoxo-Fluor [Bis(2-methoxyethyl)aminosulfur Trifluoride]: An Advanced Nucleophilic Fluorinating Reagent in Organic Synthesis. *Synlett* **2006,** *2006* (15), 2515−2516.

123. Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M., Bis(2-methoxyethyl)aminosulfur trifluoride: a new broad-spectrum deoxofluorinating agent with enhanced thermal stability. *Chem. Commun.* **1999**, 215−216.

124. Messina, P. A.; Mange, K. C.; Middleton, W. J., AMINOSULFUR TRIFLUORIDES: RELATIVE THERMAL STABILITY *J. Fluorine Chem.* **1989,** *42*, 137−143.

125. Mange, K. C.; Middleton, W. J., FLUORINATION OF CYCLOHEXANOLS WITH 4-MORPHOLINOSULFUR TRIFLUORIDE. *J. Fluorine Chem.* **1989,** *43*, 405-413.

126. Markovskij, L. N.; Pashinnik, V. E.; Kirsanov, A. V., Application of Dialkylaminosulfur Trifluorides in the Synthesis of Fluoroorganic Compounds. *Synthesis* **1973**, 787−789.

127. Sheppard, W. A., Alkyl- and Arylsulfur Trifluorides. *J. Am. Chem. Soc.* **1962,** *84*, 3058−3063.

128. Sheppard, W. A., ARYLSULFUR TRIFLUORIDES AND PENTAFLUORIDES. *J. Am. Chem. Soc.* **1960,** *82*, 4751−4752.

129. Middleton, W. J., New Fluorinating Reagents. Dialkylaminosulfur Fluorides. *J. Org. Chem.* **1975,** *40*, 574−578.

130. Tang, P.; Wang, W.; Ritter, T., Deoxyfluorination of phenols. *J Am Chem Soc* **2011,** *133* (30), 11482−11484.

131. Hayashi, H.; Sonoda, H.; Fukumura, K.; Nagata, T., 2,2-Difluoro-1,3-dimethylimidazolidine (DFI). A new fluorinating agent. *Chemical Communications* **2002,** (15), 1618−1619.

132. Fuchigami, T.; Fujita, T., Electrolytic Partial Fluorination of Organic Compounds. The First Electrosynthesis of Hypervalent Iodobenzene Difluoride Derivatives and Its Application to Indirect Anodic gem-Difluorination. *J. Org. Chem.* **1994,** *59*, 7190−7192.

133. Yoshiyama, T.; Fuchigami, T., Anodic gem-Difluorination of Dithioacetals. *Chem. Lett.* **1992**, 1995−1998.

134. Haufe, G., Triethylamine Trishydrofluoride in Synthesis. *J. Prakt. Chem.* **1996,** *338*, 99−113.

135. Bucsi, I.; Torok, B.; Marco, A. I.; Rasul, G.; Prakash, G. K. S.; Olah, G. A., Stable Dialkyl Ether/Poly(Hydrogen Fluoride) Complexes: Dimethyl Ether/Poly(Hydrogen Fluoride), A New, Convenient, and Effective Fluorinating Agent. *J. Am. Chem. Soc.* **2002,** *124*, 7728−7736.

136. York, C.; Prakash, G. K. S.; Olah, G. A., Desulfurative Fluorination Using Nitrosonium Tetrafluoroborate and Pyridinium Poly(Hydrogen Fluoride). *Tetrahedron* **1996,** *52*, 9−14.

137. Olah, G. A.; Li, X. Y.; Wang, Q.; Prakash, G. K. S., Poly-4-vinylpyridinium

Poly(Hydrogen Fluoride): A Solid Hydrogen Fluoride Equivalent Reagent. *Synthesis* **1993**, 693−699.

138.   Olah, G. A.; T.Welch, J.; Vankar, Y. D.; Nojima, M.; Kerekes, I.; Olah, J. A., Synthetic Methods and Reactions. 63.' Pyridinium Poly(hydrogen fluoride) (30% Pyridine-70% Hydrogen Fluoride): A Convenient Reagent for Organic Fluorination Reactions. *J. Org. Chem.* **1979,** *44*.

139.   Pilcher, A. S.; Ammon, H. L.; Deshong, P., Utilization of Tetrabutylammonium (Triphenyl1silyl)difluorosilicate as a Fluoride Source for Nucleophilic Fluorination. *J. Am. Chem. Soc.* **1995,** *117*, 5166−5167.

140.   Shimizu, M.; Nakahara, Y.; Yoshioka, H., Chemoselective Fluorination For Primary Alcohol. *Tetrahedron Lett.* **1985,** *26*, 4207−4210.

141.   Cox, D. P.; Terpinski, J.; Lawrynowicz, W., "Anhydrous" Tetrabutylammonium Fluoride: A Mild but Highly Efficient Source of Nucleophilic Fluoride Ion *J. Org. Chem.* **1984,** *49*, 3216−3219.

142.   Ishikawa, N.; Kitazume, T.; Yamazaki, T.; Mochida, Y.; Tatsuno, T., ENHANCED EFFECT OF SPRAY-DRIED POTASSIUM FLUORIDE ON FLUORINATION *Chem. Lett.* **1981**, 761−764.

143.   Gerstenberger, M. R. C.; Haas, A., Methods of Fluorination in Organic Chemistry. *Angew. Chem. Int. Ed.* **1981,** *20*, 647−667.

144.   Hasek, W. R.; W. C. Smith, V. A.; Engelhardt, V. A., The Chemistry of Sulfur Tetrafluoride. II. The Fluorination of Organic Carbonyl Compounds. *J. Am. Chem. Soc.* **1960,** *82*, 543−551.

145.   Smith, W. C.; Tullock, C. W.; Muetterties, E. L.; Hasek, W. R.; Fawcett, F. S.; Engelhardt, V. A.; Coffman, D. D., FLUORINATION REACTIONS OF SULFUR TETRAFLUORIDE. *J. Am. Chem. Soc.* **1959,** *81*, 3165−3166.

146.   Kirihara, M.; Niimi, K.; Okumura, M.; Momose, T., Fluorinative Beckmann Frangmentation : Fluorinative α-Cleavage of Cyclic ketoximes by Diethylaminosulfur Trifluoride. *Chem. Pharm. Bull.* **2000,** *48*, 220−222.

147.   Kirihara, M.; Niimi, K.; Momose, T., Fluorinative a-cleavage of cyclic ketoximes with diethylaminosulfur trifluoride: an efficient synthesis of fluorinated carbonitriles. *Chem. Commun.* **1997**, 599−600.

148.   Middleton, W. J.; Bingham, E. M., a,a-Difluoroarylacetic Acids: Preparation from (Diethyl1amino)sulfur Trifluoride and a-Oxoarylacetates *J. Org. Chem.* **1980,** *45*, 2883−2887.

149.   Das, S.; Chandrasekhar, S.; Yadav, J. S.; Grée, R., Ionic liquids as recyclable solvents for diethylaminosulfur trifluoride (DAST) mediated fluorination of alcohols and carbonyl compounds. *Tetrahedron Letters* **2007,** *48* (30), 5305−5307.

150.   Ratcliffe, A. J.; Warner, I., Reaction of Secondary Amides with Diethylaminosulphur Trifluoride *Tetrahedron Lett.* **1995,** *36*, 3881−3884.

151. Hudlicky, M., REACTION OF EPOXIDES WITH DIETHYLAMINOSULFUR TRIFLUORIDE *J. Fluorine Chem.* **1987,** *36*, 373−384.

152. Ferreira, S., Diethylaminosulfur Trifluoride (DAST). *Synlett* **2006,** *2006* (07), 1130−1131.

153. Shellhamer, D. F.; Briggs, A. A.; Miller, B. M.; Prince, J. M.; Scott, D. H.; Heasley, V. L., Reaction of aminosulfur trifluorides with alcohols: inversion vs. retention. *J. Chem. Soc. Perkin Trans. 2* **1996**, 973−977.

154. Hagele, G.; Haas, A., Fluorination of 2-oxo-ethane derivatives with diethylaminosulfur trifluoride (DAST). *J. Fluorine Chem.* **1996,** *76*, 15−19.

155. Shellhamer, D. F.; Anstine, D. T.; Gallego, K. M.; Ganesh, B. R.; Hanson, A. A.; Hanson, K. A.; Henderson, R. D.; Prince, J. M.; Heasley, V. L., Reaction of diethylaminosulfur trifluoride with diols. *J. Chem. Soc. Perkin Trans. 2* **1995**, 861−866.

156. Pansare, S. V.; Vederas, J. C., Reaction of .beta.-hydroxy .alpha.-amino acid derivatives with (diethylamino)sulfur trifluoride (DAST). Synthesis of .beta.-fluoro .alpha.-amino acids. *J. Org. Chem.* **1987,** *52*, 4804−4810.

157. Posner, G. H.; Haines, S. R., A CONVENIENT, ONE-STEP, HIGH-YIELD REPLACEMENT OF AN ANOMERIC HYDROXYL GROUP BY A FLUORINE ATOM USING DAST. PREPARATION OF GLYCOSYL FLUORIDES. *Tetrahedron Lett.* **1985,** *1985*, 5−8.

158. Castillon, S.; Dessinges, A.; Faghih, R.; Lukacs, G.; Olesker, A.; Thang, T. T., Synthesis of 2'-C-Fluoro-@-daunomycin. An Example of Configurational Retention in Fluorodehydroxylation with Diethylaminosulfur Trifluoride. *J. Org. Chem.* **1985,** *50*, 4913−3917.

159. Boulton, K.; Cross, B. E., Synthesis of gem-Difluoro Derivatives of Natural Products by the Reaction of Ketones with Diethylaminosulphur Trifluoride. *J. Chem. Soc. Perkin Trans. 1* **1979**, 1354−1357.

160. Tewson, T. J.; Welch, M. J., New Approaches to the Synthesis of 3-Deoxy-3-fluoro-D-glucose. *J. Org. Chem.* **1978,** *43*, 1090−1092.

161. Sutherland, A.; Vederas, J. C., The first isolation of an alkoxy-N,N-dialkylaminodifluorosulfane from the reaction of an alcohol and DAST: an efficient synthesis of (2S,3R,6S)-3-fluoro-2,6-diaminopimelic acid. *Chem. Commun.* **1999**, 1739−1740.

162. Bennua-Skalmowski, B.; Vorbruggen, H., A Facile Conversion of Primary or Secondary Alcohols with n-Perfluorobutanesulfonyl Fluoride/1,8-Diazabicyclo[5,4.0]undec-7-ene into their Corresponding Fluorides. *Tetrahedron Lett.* **1995,** *36*, 2611−2614.

163. Yin, J. J.; Zarkowsky, D. S.; Thomas, D. W.; Zhao, M. M.; Huffman, M. A., Direct and Convenient Conversion of Alcohols to Fluorides. *Org. Lett.* **2004,** *6*, 1465-1468.

164. Yarovenko, N. N.; Raksha, M. A., *Zh. Obshch. Khim.* **1959,** *29* (2159-2163).

165.   Takaoka, A.; Iwakiri, H.; Ishikawa, N., F-Propene-Dialkylamine Reaction Products as Fluorinating Agents. *Bull. Chem. Soc. Jpn.* **1979,** *52*, 3377-3380.

166.   Petrov, V. A.; Swearingen, S.; Hong, W.; Petersen, W. C., 1,1,2,2-Tetrafluoroethyl-N,N-dimethylamine: a new selective fluorinating agent. *J. Fluorine Chem.* **2001,** *109*, 25−31.

167.   Surmont, R.; Verniest, G.; De Groot, A.; Thuring, J. W.; De Kimpe, N., Morpholinosulfur Trifluoride (Morph-DAST)-Mediated Rearrangement in the Fluorination of Cyclic α,α-Dialkoxy Ketones toward 1,2-Dialkoxy-1,2-difluorinated Compounds. *Advanced Synthesis & Catalysis* **2010,** *352* (16), 2751−2756.

168.   Lal, G. S.; Lobach, E.; Evans, A., Fluorination of Thiocarbonyl Compounds with Bis(2-methoxyethyl)aminosulfur Trifluoride (Deoxo-Fluor Reagent): A Facile Synthesis of gem-Difluorides. *J. Org. Chem.* **2000,** *65*, 4830−4832.

169.   Chang, Y.; Tewari, A.; Adi, A.-I.; Bae, C., Direct nucleophilic fluorination of carbonyl groups of benzophenones and benzils with Deoxofluor. *Tetrahedron* **2008,** *64* (42), 9837−9842.

170.   Krow, G. R.; Lin, G. L.; Moore, K. P.; Thomas, A. M.; DeBrosse, C.; Ross, C. W.; Ramjit, H. G., Novel Selectfluor and Deoxo-Fluor-Mediated Rearrangements. New 5(6)-Methyl and Phenyl Methanopyrrolidine Alcohols and Fluorides. *Org. Lett.* **2004,** *6*, 1669−1672.

171.   Singh, R. P.; Shreeve, J. M., One-Pot Route to New a,a-Difluoroamides and a-Ketoamides. *J. Org. Chem.* **2003,** *68*, 6063−6065.

172.   Singh, R. P.; Twamley, B.; Shreeve, J. M., Polyfluoroether Derivatives via Nucleophilic Fluorination of Glyoxal Hydrates with Deoxofluor. *J. Org. Chem.* **2002,** *67*, 1918−1924.

173.   Singh, R. P.; Shreeve, J. M., Nucleophilic fluorination of amino alcohols and diols using Deoxofluor. *J. Fluorine Chem.* **2002,** *116*, 23−26.

174.   Singh, R. P.; Shreeve, J. M., Recent Advances in Nucleophilic Fluorination Reactions of Organic Compounds Using Deoxofluor and DAST. *Synthesis* **2002**, 2561−2578.

175.   Singh, R. P.; Shreeve, J. M., Concentration-Dependent Reactions of Deoxofluor with Arylglyoxal Hydrates: A New Route to Polyfluoro Ethers. *Org. Lett.* **2001,** *3*, 2713−2715.

176.   Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. S., Bis(2-methoxyethyl)aminosulfur Trifluoride: A New Broad-Spectrum Deoxofluorinating Agent with Enhanced Thermal Stability. *J. Org. Chem.* **1999,** *64*, 7048−7054.

177.   Hagooly, Y.; Cohen, O.; Rozen, S., A general route for constructing difluoromethyl ethers. *Tetrahedron Letters* **2009,** *50* (4), 392−394.

178.   Farooq, U.; Shah, A. U.; Wirth, T., Hypervalent bromine compounds: smaller, more reactive analogues of hypervalent iodine compounds. *Angew Chem Int Ed Engl* **2009,** *48* (6), 1018−1020.

179.   Cohen, O.; Hagooly, Y.; Rozen, S., Replacing the carbonyl's oxygen with the difluoromethyl group. *Tetrahedron* **2009,** *65* (7), 1361−1365.

180.   Hagooly, Y.; Sasson, R.; Welch, M. J.; Rozen, S., Preparation of Alkyl and Aryl Chlorodifluoromethyl Ethers Using BrF3. *European Journal of Organic Chemistry* **2008,** *2008* (17), 2875−2880.

181.   Hagooly, Y.; Rozen, S., Constructing the OCF2O Moiety Using BrF3. *J. Org. Chem.* **2008,** *73*, 6780−6783.

182.   Rozen, S., Attaching the Fluorine Atom to Organic Molecules Using BrF3 and Other Reagents Directly Derived from F2. *Acc. Chem. Res.* **2005,** *38*, 803−812.

183.   Sasson, R.; Hagooly, A.; Rozen, S., Novel Method for Incorporating the CHF2 Group into Organic Molecules Using BrF3. *Org. Lett.* **2003,** *5*, 769−771.

184.   Singh, R. P.; Umemoto, T., 4-Fluoropyrrolidine-2-carbonyl fluorides: useful synthons and their facile preparation with 4-tert-butyl-2,6-dimethylphenylsulfur trifluoride. *J Org Chem* **2011,** *76* (9), 3113−3121.

185.   Beaulieu, F.; Beauregard, L.-P.; Courchesne, G.; Couturier, M.; LaFlamme, F.; LHeureux, A., Aminodifluorosulfinium Tetrafluoroborate Salts as Stable and Crystalline Deoxofluorinating Reagents. *Org. Lett.* **2009,** *11*, 5050−5053.

186.   L'Heureux, A.; Beaulieu, F.; Bennett, C.; Bill, D. R.; Clayton, S.; Laflamme, F.; Mirmehrabi, M.; Tadayon, S.; Tovell, D.; Couturier, M., Aminodifluorosulfinium salts: selective fluorination reagents with enhanced thermal stability and ease of handling. *J Org Chem* **2010,** *75* (10), 3401−3411.

187.   McMurtrey, K. B.; Racowski, J. M.; Sanford, M. S., Pd-Catalyzed CH Fluorination with Nucleophilic Fluoride. *Org. Lett.* **2012,** *14*, 4094−4097

188.   Liu, W.; Huang, X.; Cheng, M.-J.; Nielsen, R. J.; III, W. A. G.; Groves, J. T., Oxidative Aliphatic C-H Fluorination with Fluoride Ion Catalyzed by a Manganese Porphyrin. *Science* **2012,** *337*, 1322−1325.

189.   Andrieux, C. P.; Differding, E.; Robert, M.; Saveant, J. M., Controlling Factors of Stepwise Versus Concerted Reductive Cleavages. Illustrative Examples in the Electrochemical Reductive Breaking of Nitrogen-Halogen Bonds in Aromatic N- H alosult ams. *J. Am. Chem. Soc.* **1993,** *115*, 6592−6599.

190.   Rueda-Becerril, M.; Sazepin, C. C.; Leung, J. C.; Okbinoglu, T.; Kennepohl, P.; Paquin, J. F.; Sammis, G. M., Fluorine transfer to alkyl radicals. *J Am Chem Soc* **2012,** *134* (9), 4026−4029.

191.   Bloom, S.; Pitts, C. R.; Miller, D. C.; Haselton, N.; Holl, M. G.; Urheim, E.; Lectka, T., A polycomponent metal-catalyzed aliphatic, allylic, and benzylic fluorination. *Angew Chem Int Ed Engl* **2012,** *51* (42), 10580−10583.

192.   Pitts, C. R.; Bloom, S.; Woltornist, R.; Auvenshine, D. J.; Ryzhkov, L. R.; Siegler, M. A.; Lectka, T., Direct, catalytic monofluorination of sp(3) C-H bonds: a radical-based mechanism

with ionic selectivity. *J Am Chem Soc* **2014,** *136* (27), 9780−9791.

193.   Xia, J. B.; Ma, Y.; Chen, C., Vanadium-Catalyzed C(sp3)-H Fluorination Reactions. *Org Chem Front* **2014,** *1* (5), 468−472.

194.   Amaoka, Y.; Nagatomo, M.; Inoue, M., Metal-Free Fluorination of C(sp3)-H Bonds Using a Catalytic N-Oxyl Radical. *Org. Lett.* **2013,** *15*, 2160−2163.

195.   Pitts, C. R.; Ling, B.; Woltornist, R.; Liu, R.; Lectka, T., Triethylborane-initiated radical chain fluorination: a synthetic method derived from mechanistic insight. *J Org Chem* **2014,** *79* (18), 8895−9.

196.   Bloom, S.; Knippel, J. L.; Lectka, T., A photocatalyzed aliphatic fluorination. *Chem. Sci.* **2014,** *5* (3), 1175−1178.

197.   Halperin, S. D.; Fan, H.; Chang, S.; Martin, R. E.; Britton, R., A convenient photocatalytic fluorination of unactivated C-H bonds. *Angew Chem Int Ed Engl* **2014,** *53* (18), 4690−4693.

198.   Kee, C. W.; Chin, K. F.; Wong, M. W.; Tan, C. H., Selective fluorination of alkyl C-H bonds via photocatalysis. *Chem Commun (Camb)* **2014,** *50* (60), 8211−8214.

199.   Yin, F.; Wang, Z.; Li, Z.; Li, C., Silver-catalyzed decarboxylative fluorination of aliphatic carboxylic acids in aqueous solution. *J Am Chem Soc* **2012,** *134* (25), 10401−10404.

200.   Leung, J. C.; Chatalova-Sazepin, C.; West, J. G.; Rueda-Becerril, M.; Paquin, J. F.; Sammis, G. M., Photo-fluorodecarboxylation of 2-aryloxy and 2-aryl carboxylic acids. *Angew Chem Int Ed Engl* **2012,** *51* (43), 10804−10807.

201.   Wolan, J. T.; Hoflund, G. B., Surface characterization study of AgF and AgF, powders using XPS and ISS *Applied Surface Science* **1998,** *125*, 251−258.

202.   Priest, H. F.; Swinehert, C. F., Anhydrous Metal Fluorides. *Inorg. Synth. Inorganic Syntheses.* **1950,** *3*, 171−183.

203.   Polczynski, P.; Jurczakowski, R.; Grochala, W., Stabilization and strong oxidizing properties of Ag(II) in a fluorine-free solvent. *Chem Commun (Camb)* **2013,** *49* (68), 7480−7482.

204.   LEVEC, J.; SLIVNIK, J.; ZEMVA, B., ON THE REACTION BETWEEN XENON AND FLUORINE. *J. Inorg, Nucl. Chem* **1974,** *36*, 997−1001.

205.   Zweig, A.; Fischer, R. G.; Lancaster, J. E., New Method for Selective Monofluorination of Aromatics Using Silver Difluoride. *J. Org. Chem.* **1980,** *45*, 3597−3603.

206.   Durie, A. J.; Slawin, A. M.; Lebl, T.; O'Hagan, D., The synthesis of eta-1,2,3,4,5,6-hexafluorocyclohexane (benzene hexafluoride) from benzene. *Angew Chem Int Ed Engl* **2012,** *51* (40), 10086−10088.

207.   Fier, P. S.; Hartwig, J. F., Selective C-H Fluorination of Pyridines and Diazines Inspired by a Classic Amination Reaction.   .

208.   Zhang, Q. W.; Brusoe, A. T.; Mascitti, V.; Hesp, K. D.; Blakemore, D. C.; Kohrt, J. T.;

Hartwig, J. F., Fluorodecarboxylation for the Synthesis of Trifluoromethyl Aryl Ethers. *Angew Chem Int Ed Engl* **2016,** *55* (33), 9758−9762.

209.   Pang, X.; Xiang, L.; Ma, J.; Yang, X.; Yan, R., Halogenations of substituted 2-alkylquinoline with iodine and halide exchange with AgF2. *RSC Adv.* **2016,** *6* (113), 111713−111717.

210.   Sheppard, W., ARYLSULFUR TRIFLUORIDES AND PENTAFLUORIDES. *J. Am. Chem. Soc.* **1960** *82*, 4751−4752.

211.   Sheppard, W. A., Alkyl- and Arylsulfur Trifluorides. *J. Am. Chem. Soc.* **1962,** *84*, 3058−3063.

212.   Umemoto, T.; Singh, R. P.; Xu, Y.; Saito, N., Discovery of 4-tert-Butyl-2,6-dimethylphenylsulfur Trifluoride as a Deoxofluorinating Agent with High Thermal Stability as Well as Unusual Resistance to Aqueous Hydrolysis, and Its Diverse Fluorination Capabilities Including Deoxofluoro-Arylsulfinylation with High Stereoselectivity. *J. Am. Chem. Soc.* **2010,** *132*, 18199−18205.

213.   Davis, F. A.; Han, W.; Murphy, C. K., Selective, Electrophilic Fluorinations Using N-Fluoro-o-benzenedisulfonimide. *J. Org. Chem.* **1996,** *60*, 4730−4737.

214.   Differding, E.; Ofner, H., N-FLUOROBENZENEDISULFONIMIDE: A Practical Reagent for Electrophilic Fluorinations. *Synlett* **1991**, 187−189.

215.   Davis, F. A.; Han, W., N-FLUORO-0-BENZENEDISULFONIMIDE: A USEFUL NEW FLUORINATING REAGENT *Tetrahedron Lett.* **1991,** *32*, 1631−1634.

216.   Rozen, S.; Menahem, Y., A Novel Fluorinating Method for the Synthesis of a-fluoroketones. *Tetrahedron Lett.* **1979,** *8*, 725−728.

217.   Mohr, J. T.; Nishimata, T.; Behenna, D. C.; Stoltz., B. M., Catalytic Enantioselective Decarboxylative Protonation. *J. Am. Chem. Soc.* **2006,** *128*, 11348−11349.

218.   Shimizu, I.; Ishii, H., Synthesis of a-Fluoroketones Based on Palladium-Catalyzed Decarboxylation Reactions of Allyl b-Keto Carboxylates. *Tetrahedron* **1994,** *50*, 487-495.

219.   Satoh, T.; Shishikura, J.-i.; Yamakawa, K., Ring-Opening Fluorination of a,b-Epoxy Sulfoxides: A Novel Synthesis of a-Fluoroketones. *Chem. Pharm. Bull.* **1990,** *38*, 1798−1800.

220.   Wu, S. W.; Liu, F., Synthesis of alpha-Fluoroketones from Vinyl Azides and Mechanism Interrogation. *Org Lett* **2016,** *18* (15), 3642−3645.

221.   Ahlsten, N.; Martin-Matute, B., Ir-catalysed formation of C-F bonds. From allylic alcohols to alpha-fluoroketones. *Chem Commun (Camb)* **2011,** *47* (29), 8331−8333.

222.   He, Y.; Zhang, X.; Shen, N.; Fan, X., Synthesis of α-fluoroketones and α-fluoroenones in aqueous media. *Journal of Fluorine Chemistry* **2013,** *156*, 9−14.

223.   Zhao, H.; Fan, X.; Yu, J.; Zhu, C., Silver-catalyzed ring-opening strategy for the synthesis of beta- and gamma-fluorinated ketones. *J Am Chem Soc* **2015,** *137* (10), 3490−3493.

224. Ren, S.; Feng, C.; Loh, T. P., Iron- or silver-catalyzed oxidative fluorination of cyclopropanols for the synthesis of beta-fluoroketones. *Org Biomol Chem* **2015,** *13* (18), 5105−5109.

225. Bloom, S.; Bume, D. D.; Pitts, C. R.; Lectka, T., Site-Selective Approach to beta-Fluorination: Photocatalyzed Ring Opening of Cyclopropanols. *Chem. Eur. J.* **2015,** *21* (22), 8060−8063.

226. LIEBMAN, J. F.; GREENBERG, A., A Survey of Strained Organic Molecules. *Chem. Rev.* **1976,** *76*, 311−365.

227. Hamilton, J. G.; Pake, W. E., Bonding in Cyclopropane *J. Am. Chem. Soc.* **1993,** *115*, 4159−4164.

228. K. Peter C. Vollhardt, N. E. S., Organic Chemistry; Palgrave version: Structure and Function, Seventh Edition

229. Meijere, A. d., Bonding Properties of Cyclopropane and Their Chemical Consequences *Angew. Chem. Int. Ed.* **1979,** *18*, 809−886.

230. Allen, F. H.; Kennard, O.; Watson, D. G., Tables of Bond Lengths determined by X-Ray and Neutron Diffraction. Part I. Bond Lengths in Organic Compounds *J. Chem. Soc. Perkin Trans. 2* **1987**, S1−S19

231. Reissig, H.-U., Donor−Acceptor-Substituted Cyclopropane Derivatives and Their Application in Organic Synthesis. *Chem. Rev.* **2003,** *103*, 1151−1196.

232. Murai, S.; Ryu, I.; Sonoda, N., SILOXYCYCLOPROPANES. USEFUL SYNTHETIC INTERMEDIATES *Organomet. Chem.* **1983,** *250*, 121−133.

233. Mirano, S.; Izumi, Y.; Fujii, H.; Hashimoto, H., Preparation of Trimethylsilyloxycyclopropanes from Enol Ethers by Means of the Diethylzinc/Chloroiodomethane/Oxygen System. *Synthesis* **1977**, 700.

234. Wenkert, E., Oxycyclopropanes in Organochemical Synthesis. *Acc. Chem. Res.* **1980,** *13*, 27−31.

235. Brownbridge, H., Silyl Enol Ethers in Synthesis. *Synthesis* **1983**, 1.

236. Conia, J. M., THE CYCLOPROPANATION OF SILYL ENOL ETHERS. A POWERFUL SYNTHETIC TOOL. *Pure Appl. Chem.* **1975,** *43*, 317−326.

237. Murai, S.; Aya, T.; Sonoda, N., Synthesis of 1-Hydroxybicyclo[n.l.O]alkanes from'Silyl Alkenyl Ethers. A Novel Class of Cyclopropanolsl. *J. Org. Chem.* **1973,** *38*, 4354−4356.

238. DENIS, J. M.; GIRARD, C.; CONIA, J. M., Improved Simmons-Smith Reactions. *Synthesis* **1872**, 549−551.

239. Brogan, J. B.; Zercher, C. K., Zinc-Mediated Conversion of β-Keto Esters to γ-Keto Esters. *J. Org. Chem.* **1997,** *62*, 6444−6446.

240.   Csuk, R.; Horing, U.; Schaade, M., Chain extension of aldonolactones by samarium iodide mediated Dreiding-Schmidt reactions and samarium assisted imamoto reactions. *Tetrahedron* **1996,** *52*, 9759−9776.

241.   Imamoto, T.; Hatajima, T.; Takiyama, N.; Takeyama, T.; Kamiya, Y.; Yoshizawa, T., Reactions of carbonyl compounds with benzyl chloromethyl ether of diiodomethane in the presence of samarium(II) iodide or metallic samarium. New routes to 1,2-diols, iodohydrins and cyclopropanols. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3127−3135.

242.   Imamoto, T.; Kamiya, Y.; Hatajima, T.; Takahashi, H., Tandem one-carbon homologation of esters to cyclopropanols. *Tetrahedron Lett. 1989, 30, 5149.* **1989,** *30*, 5149−5152.

243.   Imamoto, T.; Takeyama, T.; Koto, H., The reaction of carbonyl compounds with diiodomethane in the presence of samarium: Novel syntheses of iodohydrins and cyclopropanols. *Tetrahedron Lett.* **1986,** *27*, 3243−3246.

244.   Imamoto, T.; Takiyama, N., Divalent samarium-induced cyclopropanation of lithium enolates. A one-pot synthesis of cyclopropanols from ketones. *Tetrahedron Lett.* **1987,** *28*, 1307−1308.

245.   Sasaki, M.; Collin, J.; Kagan, H. B., Double cyclization of allyloxybenzoic acid chlorides mediated by samarium diiodide giving cyclopropanols. *Tetrahedron Lett.* **1988,** *29*, 6105−6106.

246.   Simmons, H. E.; Smith, R. D., A New Synthesis of Cyclopropanes. *J. Am. Chem. Soc.* **1959,** *81*, 4256−4264.

247.   Simmons, H. E.; Smith, R. D., A NEW SYNTHESIS OF CYCLOPROPANES FROM OLEFINS. *J. Am. Chem. Soc.* **1958,** *80*, 5323−5324.

248.   Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Pritytskaya, T. S., *J. Org. Chem. USSR (Engl. Transl.)* **1989,** *25*, 2027.

249.   Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A., Titanium(IV) Isopropoxide-Catalyzed Formation of 1-Substituted Cyclopropanols in the Reaction of Ethylmagnesium Bromide with Methyl Alkanecarboxylates. *Synthesis* **1991**, 234.

250.   Kasatkin, A.; Sato, F., Diastereoselective Synthesis of trans-l,2-Disubstituted Cyclopropanols from Homoallyl or Bis-Homoallyl Esters via Tandem Intramolecular Nucleophilic Acyl Substitution and Intramolecular Carbonyl Addition Reactions Mediated by Ti(OPr-i) 4 / 2 i-PrMgBr Reagent *Tetrahedron Lett.* **1995,** *36*, 6079−6082.

251.   Lee, J.; Kang, C. H.; Kim, H.; Cha, J. K., Intramolecular Hydroxycyclopropanation of ω-Vinyl Carboxylic Esters. *J. Am. Chem. Soc.* **1996,** *118*, 291−292.

252.   Lee, J.; Kim, H.; Cha, J. K., A New Variant of the Kulinkovich Hydroxycyclopropanation. Reductive Coupling of Carboxylic Esters with Terminal Olefins. *J. Am. Chem. Soc.* **1996,** *118*, 4198−4199.

253.   Lee, J.; Kim, H.; Bae, J. G.; Cha, J. K., A New Preparation of Cyclopropanone Hemiketals by Reductive Coupling of Terminal Olefins with Ethylene Carbonate. *J. Org. Chem.*

1996, *61*, 4878−4879.

254.   Salaün, J., Cyclopropanone hemiacetals. *Chem. Rev.* **1983,** *83*, 619-632.

255.   Gibson, D. H.; De Puy, C. H., Cyclopropanol Chemistry. *Chem. Rev.* **1974,** *74*, 605−623.

256.   Fadel, A.; Tesson, N., Preparation of enantiomerically pure (1S,2S)-1-aminocyclopropanephosphonic acid from methylcyclopropanone acetal via spirophosphonate intermediates. *Tetrahedron: Asymmetry* **2000,** *11*, 2023−2031.

257.   Fadel, A., A new and convenient synthesis of 1-aminocyclopropanecarboxylic acid from cyclopropanone acetal. *Tetrahedron* **1991,** *47*, 6265−6274.

258.   Fadel, A.; Tesson, N., Synthesis of Enantiomerically Pure (1S,2S)-1-Aminocyclopropanephosphonic Acids from (2S)-Methylcyclopropanone Acetal. *Eur. J. Org. Chem. 2000, 2153* **2000**, 2153−2159.

259.   Fadel, A.; Khesrani, A., A straightforward synthesis of both enantiomers of allo-norcoronamic acids and allo-coronamic acids, by asymmetric Strecker reaction from alkylcyclopropanone acetals. *Tetrahedron: Asymmetry* **1998,** *9*, 305−320.

260.   Fadel, A., A New and First Enantiomeric Synthesis of Chiral 1-Amino-2,2-dimethylcyclopropanecarboxylic Acids from Dimethylcyclopropanone Acetal. *Synlett* **1993**, 503−505.

261.   Stolle, A.; Becker, H.; Salaün, J.; de Meijere, A., The virtue of methylenecyclopropane terminators in intramolecular Pauson-Khand reactions. *Tetrahedron Lett.* **1994,** *35*, 3517−3520.

262.   Stolle, A.; Becker, H.; Salaün, J.; de Meijere, A., Enantioselective construction of spiro{cyclopropane-14′-bicyclo[3.3.0]oct-1-en-3-ones}. *Tetrahedron Lett.* **1994,** *35*, 3521−3524.

263.   Chevtchouk, T.; Ollivier, J.; Salaün, J., Asymmetric alkylidenecyclopropanes from the regioselective reduction of π 1,1-dimethyleneallyl palladium complexes. *Tetrahedron: Asymmetry* **1997,** *8*, 1005−1009.

264.   Estieu, K.; Paugam, R.; Ollivier, J.; Salaün, J.; Cordero, F. M.; Goti, A.; Brandi, A., New Alkylidenecyclopropane Amino Acid Derivatives for an Efficient Construction of the 6H-Pyrrolo[3,4-b]pyridine Skeleton. *J. Org. Chem.* **1997,** *62*, 8276−8277.

265.   Ollivier, J.; Girard, N.; Salaün, J., Electrophilic Substitutions of 1-Alkenylcyclopropyl Esters: Diethylzinc-Mediated Umpolung of π-1,1-Dimethyleneallyl Palladium Complexes. *Synlett* **1999**, 1539−1542.

266.   Pisaneschi, F.; Cordero, F. M.; Goti, A.; Paugam, R.; Ollivier, J.; Brandi, A.; Salaün, J., Diastereoselective cycloaddition of alkylidenecyclopropane nitrones from palladium(0)-catalyzed nucleophilic substitution of asymmetric 1-alkenylcyclopropyl esters by amino acids. *Tetrahedron: Asymmetry* **2000,** *11*, 897−909.

267.   Cordero, F. M.; Pisaneschi, F.; Goti, A.; Ollivier, J.; Salaün, J.; Brandi, A., New Synthesis of β-Lactams by Ethylene Extrusion from Spirocyclopropane Isoxazolidines. *J. Am. Chem. Soc.* **2000,** *122*, 8075−8076.

268.   Ollivier, J.; Dorizon, P.; Piras, P. P.; de Meijere, A.; Salaün, J., Strain, silyl and steric effects on the regioselectivity of palladium(0) catalyzed allyl esters reduction as alternative to the Wittig reaction. *Inorg. Chim. Acta 1994, 222, 37* **1994,** *222*, 37−49.

269.   Atlan, V.; Racouchot, S.; Pubin, M.; Bremer, C.; Ollivier, J.; de Meijere, A.; Salaün, J., Diastereoselective palladium(0)-catalyzed azidation of 1-alkenylcyclopropyl esters: asymmetric synthesis of (−)-(1R,2S)-norcoronamic acid. *Tetrahedron: Asymmetry 1998, 9, 1131* **1998,** *19*, 1131−1135.

270.   Stolle, A.; Ollivier, J.; Piras, P. P.; Salaün, J.; de Meijere, A., Nucleophilic substitutions of 1-alkenylcyclopropyl esters and 1-alkynylcyclopropyl chlorides catalyzed by palladium(0). *J. Am. Chem. Soc.* **1992,** *114*, 4051−4067.

271.   Chevtchouk, T.; Ollivier, J.; Salaün, J., Optically active cyclobutanones and γ-butyrolactones from asymmetric alkylidenecyclopropanes. *Tetrahedron: Asymmetry* **1997,** *8*, 1011−1014.

272.   Racouchot, S.; Sylvestre, I.; Ollivier, J.; Kozyrkov, Y. Y.; Pukin, A.; Kulinkovich, O. G.; Salaün, J., Titanium-Mediated Diastereoselective Formation of (E)- or (Z)-2-Substituted 1-Vinylcyclopropanols: Scope and Limitation, Applications. *Eur. J. Org. Chem. 2002, 2160.* **2002**, 2160−2176.

273.   Sylvestre, I.; Ollivier, J.; Salaün, J., Titanium-mediated diastereoselective formation of (E)-2-alkyl-1-ethenylcyclopropanols from β-haloesters. *Tetrahedron Lett.* **2001,** *42*, 4991−4994.

274.   Aufranc, P.; Ollivier, J.; Stolle, A.; Bremer, C.; El-Sayed, M.; de Meijere, A.; Salaün, J., Regioselective palladium (O) catalyzed azidation and amination of 1-alkenylcyclpropyl esters: a new route to 2,3-methanoamino acids. *Tetrahedron Lett.* **1993,** *34*, 4193−4196.

275.   Racouchot, S.; Ollivier, J.; Salaün, J., Titanium-Mediated Diastereoselective Formation of (Z)-1-(1-Alkenyl)-2-substituted-cyclopropyl Esters Efficient Precursors of (Z)-2,3-Methanoamino Acids. *Synlett* **2000**, 1729−1732.

276.   Lechevallier, A.; Huet, F.; Conia, J. M., Etude des petits cycles—XLII: Synthese des α-cyclopropylidene-cetones et aldehydes. *Tetrahedron* **1983,** *39*, 3307.

277.   Kimura, M.; Horino, Y.; Mukai, R.; Tanaka, S.; Tamaru, Y., Strikingly Simple Direct α-Allylation of Aldehydes with Allyl Alcohols: Remarkable Advance in the Tsuji−Trost Reaction. *J. Am. Chem. Soc.* **2001,** *123*, 10401−10402.

278.   Kozyrkov, Y. Y.; Pykin, A.; Kulinkovich, O. G.; Ollivier, J.; Salaün, J., A convenient approach to substituted 1-(1-alkenyl)cyclopropanols: a new preparation of 2,3-methanoamino acids. *Tetrahedron Lett.* **2000,** *41*, 6399−6402.

279.   Jiao, J.; Nguyen, L. X.; Patterson, D. R.; II, R. A. F., An Efficient and General Approach to a-Functionalized Ketones. *Org. Lett.* **2007,** *9*, 1323−1326.

280.   Ye, Z.; Dai, M., An Umpolung Strategy for the Synthesis of beta-Aminoketones via Copper-Catalyzed Electrophilic Amination of Cyclopropanols. *Org Lett* **2015,** *17* (9), 2190−2193.

281.   Ye, Z.; Gettys, K. E.; Shen, X.; Dai, M., Copper-Catalyzed Cyclopropanol Ring Opening Csp(3)-Csp(3) Cross-Couplings with (Fluoro)Alkyl Halides. *Org Lett* **2015,** *17* (24), 6074−6077.

282.   Li, Y.; Ye, Z.; Bellman, T. M.; Chi, T.; Dai, M., Efficient Synthesis of beta-CF3/SCF3-Substituted Carbonyls via Copper-Catalyzed Electrophilic Ring-Opening Cross-Coupling of Cyclopropanols. *Org Lett* **2015,** *17* (9), 2186−2189.

283.   Ren, R.; Zhao, H.; Huan, L.; Zhu, C., Manganese-Catalyzed Oxidative Azidation of Cyclobutanols: Regiospecific Synthesis of Alkyl Azides by C-C Bond Cleavage. *Angew Chem Int Ed Engl* **2015,** *54* (43), 12692−12696.

284.   Ren, R.; Wu, Z.; Xu, Y.; Zhu, C., C-C Bond-Forming Strategy by Manganese-Catalyzed Oxidative Ring-Opening Cyanation and Ethynylation of Cyclobutanol Derivatives. *Angew Chem Int Ed Engl* **2016,** *55* (8), 2866−2869.

285.   Huan, L.; Zhu, C., Manganese-catalyzed ring-opening chlorination of cyclobutanols: regiospecific synthesis of γ-chloroketones. *Org. Chem. Front.* **2016,** *3* (11), 1467−1471.

286.   Xie, T.; Zhou, L.; Shen, M.; Li, J.; Lv, X.; Wang, X., Diastereoselective synthesis of cis-1,2-disubstituted cyclopropanols and cyclopent-3-enols via SmI2 mediated C–N(Bt) bond cleavage. *Tetrahedron Letters* **2015,** *56* (26), 3982−3987.

287.   Rubina, M.; Rubin, M., REARRANGEMENT OF CYCLOPROPYLBORANE INTO BORETANE *Chemistry of Heterocyclic Compounds* **2012,** *48*, 807−821.

288.   Ishida, N.; Okumura, S.; Nakanishi, Y.; Murakami, M., Ring-opening Fluorination of Cyclobutanols and Cyclopropanols Catalyzed by Silver. *Chemistry Letters* **2015,** *44* (6), 821−823.

289.   Shinde, S. S.; Lee, B. S.; Chi, D. Y., Synergistic Effect of Two Solvents, tert-Alcohol and Ionic Liquid, in One Molecule in Nucleophilic Fluorination. *Org. Lett.* **2008,** *10*, 733−735.

290.   Finkelstein, H., Darstellung organischer Jodide aus den entsprechenden Bromiden und Chloriden. *Ber. Dtsch. Chem. Ges.* **1910,** *43*, 1528−1532.

291.   Nishikata, T.; Ishida, S.; Fujimoto, R., Site-Selective Tertiary Alkyl-Fluorine Bond Formation from alpha-Bromoamides Using a Copper/CsF Catalyst System. *Angew. Chem. Int. Ed.* **2016,** *55* (34), 10008−10012.

292.   Bloom, S.; Pitts, C. R.; Woltornist, R.; Griswold, A.; Holl, M. G.; Lectka, T., Iron(II)-Catalyzed Benzylic Fluorination. *Org. Lett.* **2013,** *15*, 1722−1724.

293.   Bloom, S.; Sharber, S. A.; Holl, M. G.; Knippel, J. L.; Lectka, T., Metal-catalyzed benzylic fluorination as a synthetic equivalent to 1,4-conjugate addition of fluoride. *J. Org. Chem.* **2013,** *78* (21), 11082−11086.

294.   Rozen, S.; Faust, Y.; Ben-Yakov, H., A new method for fluorination of sterols. *Tetrahedron Lett.* **1979,** *20*, 1823-1826.

295.   Jr., R. C. F.; Schleyer, P. v. R., The Proton Magnetic Resonance Spectra of Adamantane and Its Derivatives. *J. Org. Chem.* **1965,** *30*, 789−96.

296.   Chung, W. S.; Turro, N. J.; Silver, J.; Noble, W. J. L., Modification of face selectivity by inclusion in cyclodextrins. *J. Am. Chem. Soc.* **1990,** *112*, 1202−1205.

297.   Schwertfeger, H.; Würtele, C.; Hausmann, H.; Dahl, J. E. P.; Carlson, R. M. K.; Fokin, A. A.; Schreiner, P. R., Selective Preparation of Diamondoid Fluorides[1]. *Advanced Synthesis & Catalysis* **2009,** *351* (7-8), 1041−1054.

298.   Knoll, W.; Mieusset, J.-L.; Arion, V. B.; Brecker, L.; Brinker, U. H., 2H-Azirines from a Concerted Addition of Alkylcarbenes to Nitrile Groups. *Org. Lett.* **2010,** *12*, 2366−2369.

299.   Silhar, P.; Silvaggi, N. R.; Pellett, S.; Capkova, K.; Johnson, E. A.; Allen, K. N.; Janda, K. D., Evaluation of adamantane hydroxamates as botulinum neurotoxin inhibitors: synthesis, crystallography, modeling, kinetic and cellular based studies. *Bioorg Med Chem* **2013,** *21* (5), 1344−1348.

300.   Olah, G. A.; Bollinger, J. M., Stable carbonium ions. XLVIII. Halonium ion formation via neighboring halogen participation. Tetramethylethylene halonium ions. *J. Am. Chem. Soc.* **1967,** *89*, 4744−4752.

301.   Xia, J. B.; Zhu, C.; Chen, C., Visible light-promoted metal-free C-H activation: diarylketone-catalyzed selective benzylic mono- and difluorination. *J. Am. Chem. Soc.* **2013,** *135* (46), 17494−17500.

302.   Ventre, S.; Petronijevic, F. R.; MacMillan, D. W., Decarboxylative Fluorination of Aliphatic Carboxylic Acids via Photoredox Catalysis. *J. Am. Chem. Soc.* **2015,** *137* (17), 5654−5657.

303.   Fujisawa, H.; Takeuchi, Y., Simple Procedure for Preparation of alpha-Fluoro Esters by Fluorination of Ester Enol Silyl Ethers with Perchloryl fluoride. *Journal of Fluorine Chemistry* **2002,** *117*, 173−176.

304.   Rozen, S., Elemental Fluorine as a "Legitimate" Reagent for Selective Fluorination of Organic Compounds. *Acc. Chem. Res.* **1988,** *21*, 307−312.

305.   Rozen, S.; Hagooly, A.; Harduf, R., Synthesis of alpha-Fluorocarboxylates from the Corresponding Acids Using Acetyl Hypofluorite. *J. Org. Chem.* **2001,** *66*, 7464−7468.

306.   Gao, Y.; Luo, J.; Yao, Z.-J.; Guo, R.; Zou, H.; Kelley, J.; Voigt, J. H.; Yang, D.; Burke, T. R., Inhibition of Grb2 SH2 Domain Binding by Non-Phosphate-Containing Ligands. 2. 4-(2-Malonyl)phenylalanine as a Potent Phosphotyrosyl Mimetic†. *Journal of Medicinal Chemistry* **2000,** *43* (5), 911−920.

307.   Brown, W. D.; Teuber, L.; Dyhring, T.; Strøbæk, D.; Jessen, C., Novel quinazoline derivatives and their medical use *US Patent WO 2007057447 A1*.

308.   Fry, A. J.; Migron, Y., A Convenient New Synthesis of alpha-Fluorocarbonyl Compounds. *Tetrahedron Lett.* **2015,** *36*, 3357−3360.

309.   Zhang, M.; Gong, Y.; Wang, W., A Two-Step Sequence to Ethyl α-Fluorocyclopropanecarboxylates Through MIRC Reaction of Ethyl Dichloroacetate and Highly

Regioselective Fluorination. *Eur. J. Org. Chem.* **2013,** *2013* (32), 7372−7381.

310.   Yang, H.; Xu, B.; Hammond, G. B., Highly Regioselective Fluorination and Iodination of Alkynyl Enolates. *Org. Lett.* **2008,** *10*, 5589−5591.

311.   Lee, S. Y.; Neufeind, S.; Fu, G. C., Enantioselective nucleophile-catalyzed synthesis of tertiary alkyl fluorides via the alpha-fluorination of ketenes: synthetic and mechanistic studies. *J Am Chem Soc* **2014,** *136* (25), 8899−8902.

312.   Sugiura, M.; Ashikari, Y.; Nakajima, M., One-Pot Synthesis of beta,beta-Disubstituted alpha,beta-Unsaturated Carbonyl Compounds. *J Org Chem* **2015,** *80* (17), 8830−8835.

313.   Cao, J. J.; Zhou, F.; Zhou, J., Improving the atom efficiency of the Wittig reaction by a "waste as catalyst/co-catalyst" strategy. *Angew. Chem. Int. Ed.* **2010,** *49* (29), 4976−4980.

314.   GARDNER, P. D.; HORTON, W. J., SEVEN-MEMBERED RING COMPOUNDS.* VI.1 BROMINATION OF 2,3,4-TRIMETHOXYBENZOSUBERONE. *J. Org. Chem.* **1954,** *19*, 213−217.

315.   Yang, X.; Birman, V. B., Acyl Transfer Catalysis with 1,2,4-Triazole Anion. *Org. Lett.* **2009,** *11*, 1499.

316.   Weng, S.-S.; Ke, C.-S.; Chen, F.-K.; Lyu, Y.-F.; Lin, G.-Y., Transesterification catalyzed by iron(III) β-diketonate species. *Tetrahedron* **2011,** *67* (9), 1640−1648.

317.   Racys, D. T.; Sharif, S. A.; Pimlott, S. L.; Sutherland, A., Silver(I)-Catalyzed Iodination of Arenes: Tuning the Lewis Acidity of N-Iodosuccinimide Activation. *J Org Chem* **2016,** *81* (3), 772−780.

318.   Schick, H.; Ludwig, R.; Kleiner, K.; Kunath, A., Synthesis of substituted β-lactones by a Reformatsky reaction of carbonyl compounds, phenyl α-bromoalkanoates, and indium. *Tetrahedron* **1995,** *51*, 2939−2946.

319.   Collins, K. D.; Glorius, F., *Nat. Chem.* **2013,** *5*, 597.

320.   Khanam, H.; Shamsuzzaman, Bioactive Benzofuran derivatives: A review. *Eur J Med Chem* **2015,** *97*, 483−504.

321.   Hiremathad, A.; Patil, M. R.; K. R, C.; Chand, K.; Santos, M. A.; Keri, R. S., Benzofuran: an emerging scaffold for antimicrobial agents. *RSC Adv.* **2015,** *5* (117), 96809−96828.

322.   Bach, T.; Bartels, M., Regioselective C–C Bond Formation Reactions on 2,3-Dibromo- and 2,3,5- Tribromobenzofuran as an Access to Multiply Substituted Benzofurans. Total Syntheses of Eupomatenoids 3, 4, 5, 6, and 15. *Synthesis* **2003,** *6*, 925−935.

323.   Hurd, C. D.; Oliver, G. L., The Cleavage of Phenyl Alkyl Ethers and O-Heterocyclic Compounds by Sodium in Liquid Ammonia. *J. Am. Chem. Soc.* **1959,** *81*, 2795−2798.

324.   Wacek, A. V.; Eppinger, H. O.; Bézard, A., Über den Abbau von Cumaronen und Thionaphthen durch Ozon. *Ber. dtsch. Chem. Ges. A/B* **1940,** *73*, 521−531.

325.   Fuerst, D. E.; Stoltz, B. M.; Wood, J. L., Synthesis of C(3) Benzofuran-Derived Bisaryl

Quaternary Centers: Approaches to Diazonamide A. *Org. Lett.* **2000,** *2*, 3521-3523.

326.   Gigant, N.; Claveau, E.; Bouyssou, P.; Gillaizeau, I., Diversity-Oriented Synthesis of Polycyclic Diazinic Scaffolds. *Org. Lett.* **2012,** *14*, 844−847.

327.   Wu, D.; Mei, H.; Tan, P.; Lu, W.; Zhu, J.; Wang, W.; Huang, J.; Li, J., Total synthesis of the 2-arylbenzo[b]furan-containing natural products from Artocarpus. *Tetrahedron Lett.* **2015,** *56* (29), 4383−4387.

328.   L'Helgoual'ch, J.-M.; Seggio, A.; Chevallier, F.; Yonehara, M.; Jeanneau, E.; Uchiyama, M.; Mongin, F., Deprotonative Metalation of Five-Membered Aromatic Heterocycles Using Mixed Lithium-Zinc Species. *J. Org. Chem.* **2008,** *73*, 177−183.

329.   Hung, N. T.; Hussain, M.; Malik, I.; Villinger, A.; Langer, P., Site-selective Suzuki cross-coupling reactions of 2,3-dibromobenzofuran. *Tetrahedron Lett.* **2010,** *51* (18), 2420−2422.

330.   Carlsson, B.; Singh, B. N.; Temciuc, M.; Nilsson, S.; Li, Y.-L.; Mellin, C.; Malm, J., Synthesis and Preliminary Characterization of a Novel Antiarrhythmic Compound (KB130015) with an Improved Toxicity Profile Compared with Amiodarone. *J. Med. Chem.* **2002,** *45*, 623−630.

331. Yamaguchi, T.; Irie, M., Photochromism of Bis(2-alkyl-1-benzofuran-3-yl)perfluorocyclopentene Derivatives. *J. Org. Chem.* **2005,** *70*, 10323−10328.

332.   Zhang, W.; Wang, P. G., Ytterbium(III) Trifluoromethanesulfonate Catalyzed Electrophilic Aromatic Substitution with Glyoxalate and Lipase-Mediated Product Resolution: A Convenient Route to Optically Active Aromatic r-Hydroxy Esters. *J. Org. Chem.* **2000,** *65*, 4732−4735.

333.   Stoermer, R.; Kahlert, B., Ueber das 1- und 2-Bromcumaron. *Ber. Dtsch. Chem. Ges.* **1902,** *35*, 1633.

334.   Bordwell, F. G., Equilibrium Acidities in Dimethyl Sulfoxide Solution. *Acc. Chem. Res.* **1988,** *21*, 456−463.

335.   Quasdorf, K. W.; Antoft-Finch, A.; Liu, P.; Silberstein, A. L.; Komaromi, A.; Blackburn, T.; Ramgren, S. D.; Houk, K. N.; Snieckus, V.; Garg, N. K., Suzuki-Miyaura cross-coupling of aryl carbamates and sulfamates: experimental and computational studies. *J. Am. Chem. Soc.* **2011,** *133* (16), 6352−6363.

336.   Taylor, R. H.; Felpin, F.-X., Suzuki−Miyaura Reactions of Arenediazonium Salts Catalyzed by Pd(0)/C. One-Pot Chemoselective Double Cross-Coupling Reactions. *Org. Lett.* **2007,** *9*, 2911−2914.

337.   Bach, T.; Bartels, M., Synthesis of eupomatenoids by three consecutive transition metal-catalyzed cross-coupling reactions. *Tetrahedron Lett.* **2002,** *43*, 9125−9127.

338.   Mustafa, A., Benzofurans. *The Chemistry of Heterocyclic Compounds* **2008,** *29*, 56.

339.   Balaban, A. T.; Oniciu, D. C.; Katritzky, A. R., Aromaticity as a Cornerstone of Heterocyclic Chemistry. *Chem. Rev.* **2004,** *104*, 2777−2812.

340.	Wang, J.; Sanchez-Rosello, M.; Acena, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H., Fluorine in pharmaceutical industry: fluorine-containing drugs introduced to the market in the last decade (2001-2011). *Chem. Rev.* **2014,** *114* (4), 2432−2506.

341.	Wang, M.; Liu, X.; Zhou, L.; Zhu, J.; Sun, X., Fluorination of 2-substituted benzo[b]furans with Selectfluor. *Org. Biomol. Chem.* **2015,** *13* (11), 3190−3193.

342.	Fang, H.; Guo, L.; Zhang, Y.; Yao, W.; Huang, Z., A Pincer Ruthenium Complex for Regioselective C-H Silylation of Heteroarenes. *Org. Lett.* **2016,** *18* (21), 5624−5627.

343.	Pu, S.; Wang, R.; Liu, G.; Liu, W.; Cui, S.; Yan, P., Photochromism of new unsymmetrical diarylethene derivatives bearing both benzofuran and thiophene moieties. *Dyes and Pigments* **2012,** *94* (2), 195−206.

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