Metall-vermittelte Allylsubstitution fluorierter Olefine und Synthese von Fluortrifluormethylgruppen

Dissertation

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Vom Fachbereich Chemie der Philipps-Universität Marburg
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als Dissertation angenommen am:

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Zweitgutachter: Prof. Dr. Paultheo von Zezschwitz

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Wegen euch, ist Deutschland meine zweite Heimat geworden.

The only way to conquer fear is to face it. - Schwimmschule Frankfurt

Abbreviation

Ac	Acetyl
APCI	Atmospheric pressure chemical ionization
Ar	Aryl
ATR	Attenuated total reflection
9-BBN	9-Borabicyclo[3.3.1]nonane
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
B.p.	Boiling point
Bpin	Bis(pinacolato)diboron
Bu	Butyl
calc.	Calculated
cat.	Catalyst
Cbz	Benzyloxycarbonyl
CDI	1,1'-carbonyldiimidazole
CI	Chemical ionization
COD	Cyclooctadien
CuTc	Copper(I) thiophene-2-carboxylate
Cy	Cyclohexyl
dba	Bibenzylideneacetone
dppe	1,2-Bis(diphenylphosphino) ethane
dppf	1,1'-Bis(diphenylphosphino) ferrocene
dppp	1,3-Bis(diphenylphosphino) propane
DABCO	1,4-Biazabicyclo-(2.2.2)octane
DAST	Diethylaminosulfur trifluoride
DBH	1,3-Dibromo-5,5-dimethylhydantoin
DCC	*N*,*N*'-Dicyclohexylcarbodiimide
DFMBA	*N*,*N*-Diethyl-*α*,*α*-difluoro(*m*-methylbenzyl)amine
DIBAH	Diisobutyl aluminium hydride
DIH	1,3-Diiodo-5,5-dimethylhydantoin
DIP-Cl	Diisopinocampheylborane chloride
DIPEA	*N*,*N*-Diisopropylethylamine
DMAP	4-(Dimethylamino)-pyridine
DMF	Dimethylformamide
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	Dimethyl sulfoxide
EDG	Electron donating group
ee	Enantiomeric excess
EI	Electron ionization
eq	Equivalent
ESI	Electrospray ionization
Et	Ethyl
et al.	Et alia
EWG	Electron withdrawing group
FTF	Fluorotrifluoromethyl
GC	Gas chromatography
HOMO	Highest occupied molecular orbital
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
*i*Pr	Isopropyl
IR	Infrared spectroscopy
LDA	Lithium diisopropylamide
LG	Leaving group

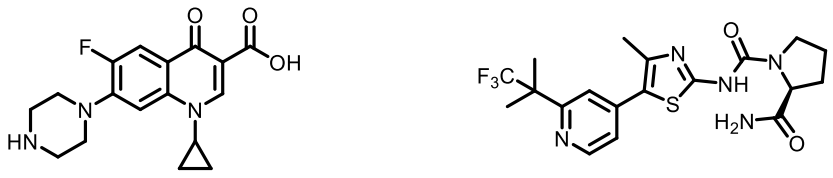
$LiAlH_4$	Lithium aluminum hydride
LUMO	Lowest occupied molecular orbital
m	*meta*
MeCN	Acetonitrile
Mp.	Melting point
m/z	Mass-to-charge ratio
MTPA	*α*-Methoxy-*α*-trifluoromethylphenylacetic acid
Me	Methyl
m.p.	Melting point
MS	Molecular sieve
Naph	Naphthyl
NBS	*N*-Bromosuccinimide
NFPy	*N*-Fluoropyridinium triflate
NSFI	*N*-Fluorobenzenesulfonimide
n-BuLi	*n*-Butyllithium
$NaBH_4$	Sodium borohydride
NMR	Nuclear magnetic resonance spectroscopy
Nu	Nucleophile
o	*ortho*
p	*para*
Ph	Phenyl
PTFE	Polytetrafluoroethylene
py	Pyridine
SET	Single electron transfer
S_N2	Bimolecular nucleophilic substitution
TBDMS	*tert*-Butyldimethylsilyl
TEMPO	2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
TMEDA	*N*,*N*,*N*′,*N*′-tetramethyl-1,2-ethylenediamine
TMS	Tetramethylsilane
Ts	*p*-Toluenesulfonyl, tosyl
UV	Ultraviolet

Contents

1 Introduction

Fluorine ranks as the 13th most abundant element in the Earth's crust and the most abundant halogen on the earth. Most of fluorine-containing compounds exist as fluorides in fluorite (CaF_2), nature produces only a limited array of structurally simple fluorine-containing organic molecules.[1] The unique properties of fluorine have led to broad applications of organofluorine compounds, including the early examples as refrigerants, propellants, fire extinguishers and polytetrafluoroethylene (PTFE or Teflon) and, more recently in liquid crystals displays.[2] Particularly relevant to this work is the noteworthy impact of fluorine in argochemistry and pharmaceutical chemistry.[3,4]

Until 2020, about 20% of the commercial pharmaceuticals are fluoro-pharmaceuticals, which contains at least one fluorine atom or a fluorinated functional group (e.g. trifluoromethyl group). Fluorine also plays a unique role in the development of agrochemical. Until 2019, about 16% launched agrochemicals contain at least one fluorine atom.[5] The first fluoro-pharmaceutical, fluodrocortisone, was brought to the market in 1954. In 1993, fluoroquinolone (e.g. ciprofloxacin (**1**)) was introduced as a second significant group of fluoro-pharmaceuticals. In terms of fluorinated functional group, CF_3-substitued drugs rank right after the fluorine-substituted drugs, according to the statistics in 2019. As an example, alpelisib (**2**), a CF_3-containing drug, is marketed by Novartis and used for treating breast cancer (Figure 1).[6]



Ciprofloxavin, **1**
Bayer, 1983

Alpelisib, **2**
Novartis, 2019

Figure 1: Two representative examples of fluoro-pharmaceuticals, Ciprofloxacin (**1**) and Alpelisib (**2**).

There are several reasons for the incorporation of fluorine into pharmaceuticals. First, as the most electronegative element, fluorine induces bond polarization and can therefore change the lipophilicity or hydrophilicity of organic molecules. Moreover, the high electronegativity of fluorine can be also used to influence the p*K*a value of the compound. Second, fluorine has a similar van der Waals radius of hydrogen, replacement of hydrogen through fluorine is therefore possible without changing dramatically the molecular structure.[4] Third, incorporation of fluorine enhances the metabolic stability of pharmaceuticals, as C-F bond is the strongest bond in organic chemistry.[7] At last, the strong polarized C-F bond makes it possible for fluorine to

acts as a weak H-bond acceptor, this interaction can be used to increase binding affinity or selectivity in drug design.[8]

1.1 Fluorination Methods

The introduction of fluorine or trifluoromethyl group into organic molecules include three main strategies: nucleophilic fluorination, electrophilic fluorination and radical fluorination. One type of nucleophile fluorination reagents are fluoride sources include alkali-metal fluorides (e.g. KF, CsF), HF-based reagents (e.g. py/HF **3**, DMPU/HF **4**, Et_3N/HF), tetraalkylammonium fluorides (e.g. TBAF **5**), and hypervalent halogen-based reagent (e.g. *p*-Tol-IF_2 **6**). These reagents can be used for fluorination of alkyl or aryl substrates containing a leaving group. The other type of reagent is the deoxofluorination reagents (e.g. DAST **7**, Deoxofluor **8**, PhenoFluor **9** [9]), they can be used for fluorination of alcohol substrates (Figure 2).[10]

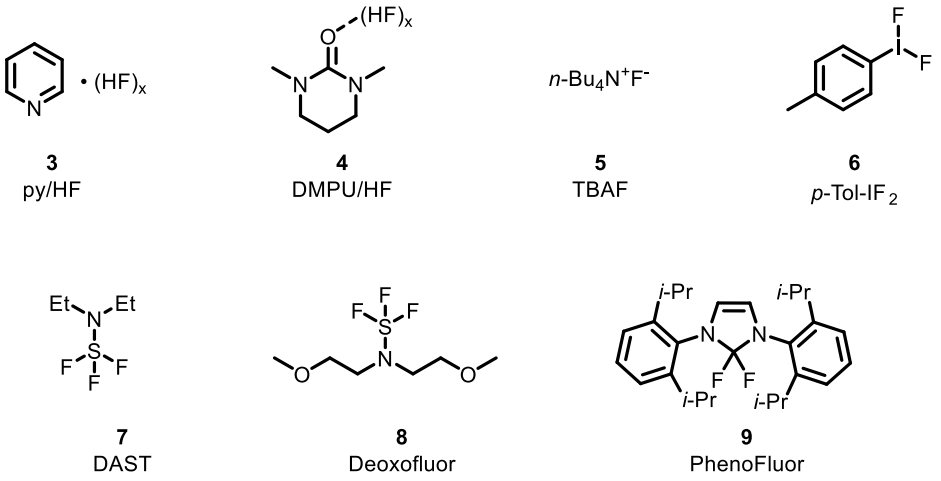
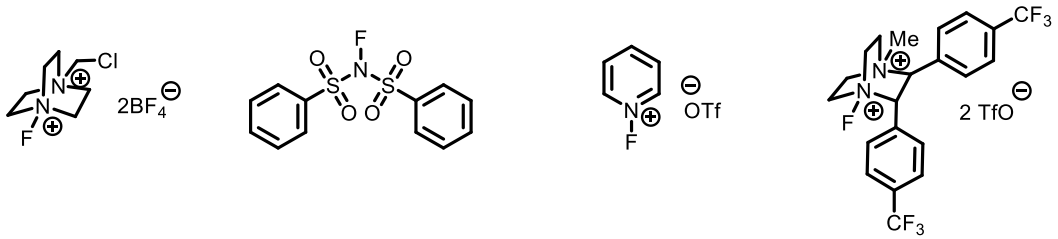


Figure 2: Examples of nucleophilic fluorination reagents.

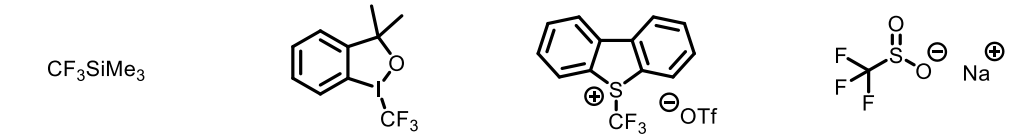
Electrophilic fluorination reagent can be seen as equivalent of "F^+" source, although the exact mechanism is still controversial. the common reagents used today are typically N-F bond based and bench stable, the representative examples are Selectfluor **10** (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo [2.2.2] octane bis(tetrafluoroborate)), NSFI **11** (*N*-fluorobenzenesulfonimide) and NFPy **12** (*N*-fluoropyridinium triflate). There are also modern chiral variants based on these reagents, one representative example is the chiral Selectfluor reagent **13** (Figure 3).[10]



10 Selectfluor | **11** NSFI | **12** NFPy | **13** chiral Selectfluor

Figure 3: Examples of electrophilic fluorination reagents.

Introduction of trifluoromethyl group to organic molecules follows similar strategies. The most common nucleophilic reagent for trifluoromethylation is CF_3SiMe_3, known as RUPPERT's reagent **14**.[11] The representative reagent for electrophilic trifluoromethylation is the TOGNI'S reagent **15**, a hypervalent iodine-based compound.[12] UMEMOTO's reagent **16** represents the sulfur-derived electrophilic trifluoromethylating reagent.[13] LANGLOIS's reagent **17** is useful as a radical trifluoromethylation reagent for alkenes and arenes and often applied for late stage functionalization (Figure 4).[14]

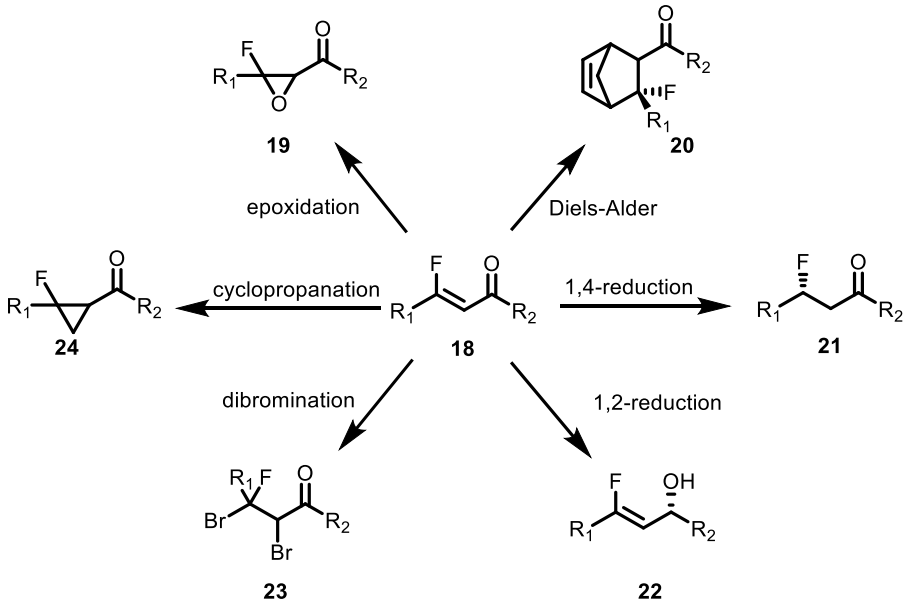


14 Ruppert's reagent | **15** Togni's reagent | **16** Umemoto's reagent | **17** Langlois's reagent

Figure 4: Examples of trifluoromethylation reagents.

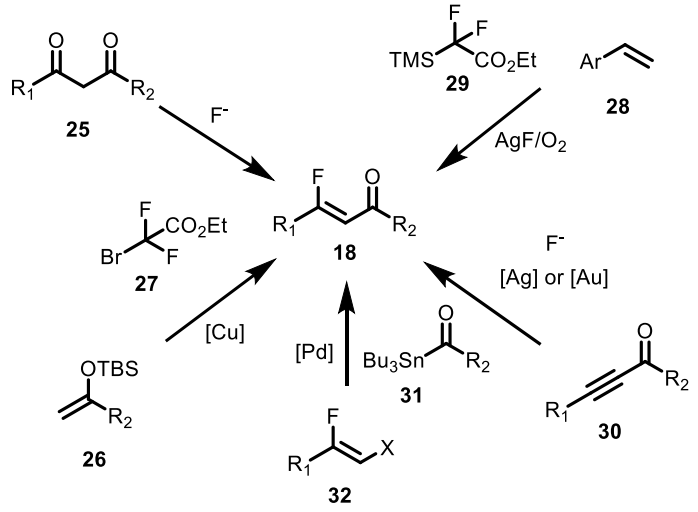
1.2 Synthesis of *β*-Fluoroenones

β-Fluoroenone **18** have gained attention for their capability to synthesize complex organofluorine molecules. They provide synthetic access for further fluorinated motifs, including tetra-substituted carbon centers through DIELS-ALDER reactions, epoxidation, cyclopropanation, bromination and 1,2-reduction reactions. First studies of such derivatizations have already been initiated by WANG *et al.*[15] Also, through asymmetric 1,2-reduction reaction, 3-fluoro-allylic alcohol **22** can be obtained, which can be applied as fluorinated substrates for asymmetric allylic substitution [16,17] (Scheme 1).



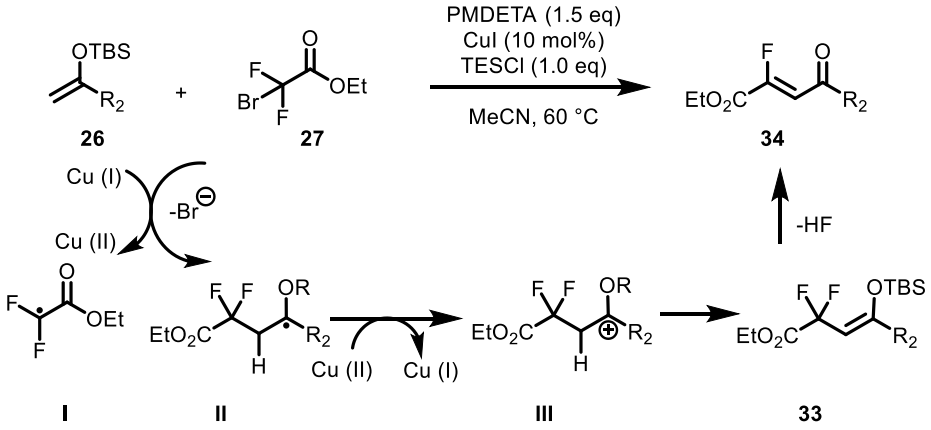
Scheme 1: Further derivatization of *β*-fluoroenones.

In contrast to readily available *α*-fluoroenones through JULIA-Olefination,[18] there are limited methods available for accessing *β*-fluoroenones **18**. The representative methods are described in Scheme 2.



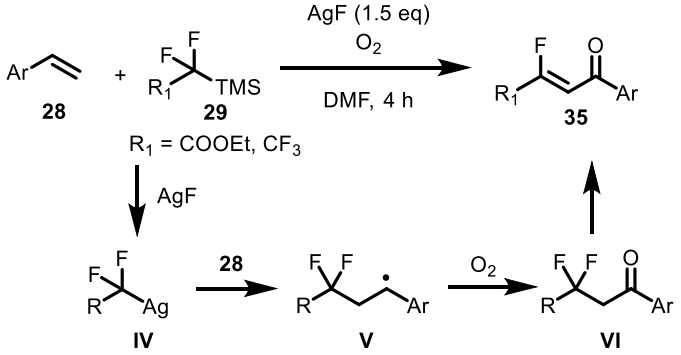
Scheme 2: Synthetic methods to access *β*-fluoroenones.

Preparation of *β*-fluoroenones through HF elimination from perfluoroalkyl carbonyl compound have been though reported in 1982, but only with limited examples.[19] WANG *et al.* reported in 2018 a Cu-amine catalyzed method synthesizing *β*-fluoroenones from silyl enol ether **26** or ketone.[15] The reaction starts from generation of the fluoroalkyl radical **I** through SET. Addition of the radical **I** to silyl enol ether **26** generates the radical **II**, which is oxidized to the carbocation **III** and subsequently eliminates to **33**. The radical mechanism is supported by the photochemical synthesis of *β*-fluoroenones from HE *et al.*, employing similar starting materials under visible light-promoted reaction conditions. As described in this study, the compound **33** is found to be unstable, leading to defluorination on silica gel and formation of the **34** (Scheme 3).[20]



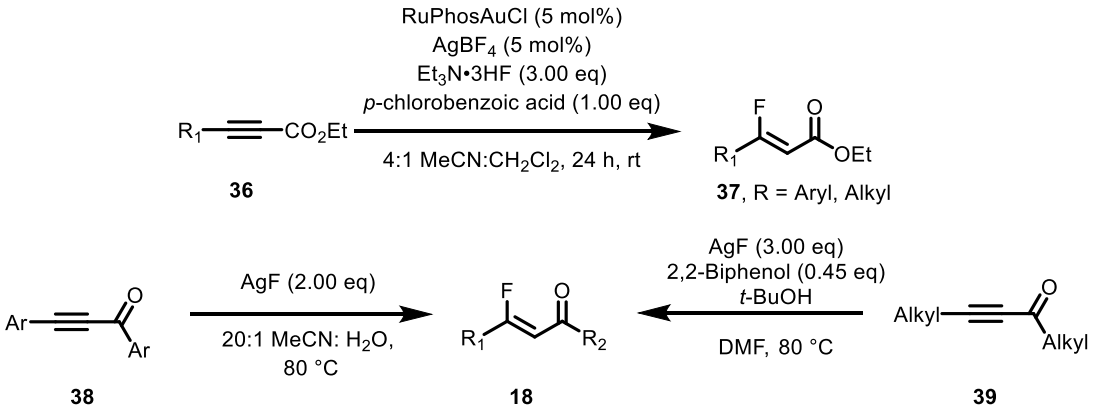
Scheme 3: Cu-amine catalyzed synthesis of *β*-fluoroenones **34** from silyl enol ethers **26**.

The synthesis of *β*-fluoroenones from arylalkenes was reported by CAI *et al.* in 2016.[21] Mechanistically, an $AgCF_2R$ **IV** (R = COOEt or CF_3) species is generated *in situ* using AgF and the TMS-substituted compound **29**, which can be synthesized from the corresponding bromides. Addition of alkene **28** produces the radical **V**, which can be captured in a radical trapping experiment with TEMPO. The oxidation of **V** and subsequent elimination of HF gives the desired product **35** with up to 85% yield (Scheme 4).



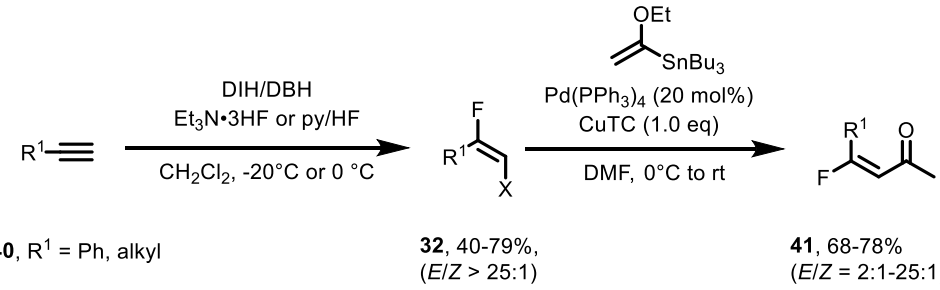
Scheme 4: AgF-promoted oxidative synthesis of *β*-fluoroenone **35** from arylalkene **28**.

Hydrofluorination of electron-deficient alkynes is one of most common method to access the *β*-fluoroenones. One representative example is the hydrofluorination of ester-substituted alkynes **36** with $Et_3N{\cdot}3HF$ catalyzed by a RuPhos-ligated gold(I) complex, as reported by TOSTE *et al.* in 2018. Another example is the AgF-assisted hydrofluorination of *β*-aryl ynones **38**, yielding the *β*-aryl-*β*-fluoroenones, as reported by JIANG *et al.* in 2021.[22] The method was extended by KOERT *et al.* to synthesize *β*-alkyl-*β*-fluoroenones from **39** by adding 2,2-biphenol to suppress the formation of the furan side products.[16] All reported examples exhibited high *Z*/*E* diastereomeric ratios (Scheme 5).



Scheme 5: Synthesis of *β*-fluoroenones **18**, **37** through hydrofluorination of alkynes **36**, **38** and **39**.

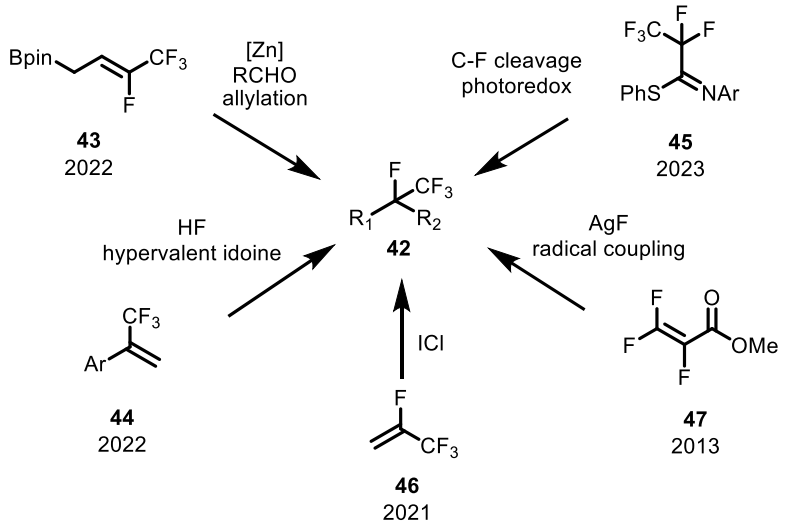
The exploration for a selective approach to obtain (*E*)-*β*-fluoroenones was initiated in my master's thesis. Synthesis of (*E*)-*β*-fluoroenones **41** starting from terminal alkynes **40** was achieved in two steps. Halofluorination of terminal alkynes according to GOUVERNEUR *et al.* [23] and ROLANDO *et al.*[24] gives the fluoroalkenes **32** in good *E*/*Z* selectivity. Pd(0)-catalyzed LIEBESKIND type of cross-coupling and enol ether hydrolysis was able to give **41** in good yield under mild conditions (Scheme 6).



Scheme 6: Synthesis of (*E*)-*β*-fluoroenones **41** through halofluorination of **40** and Pd-catalyzed cross-coupling reaction with **32**.

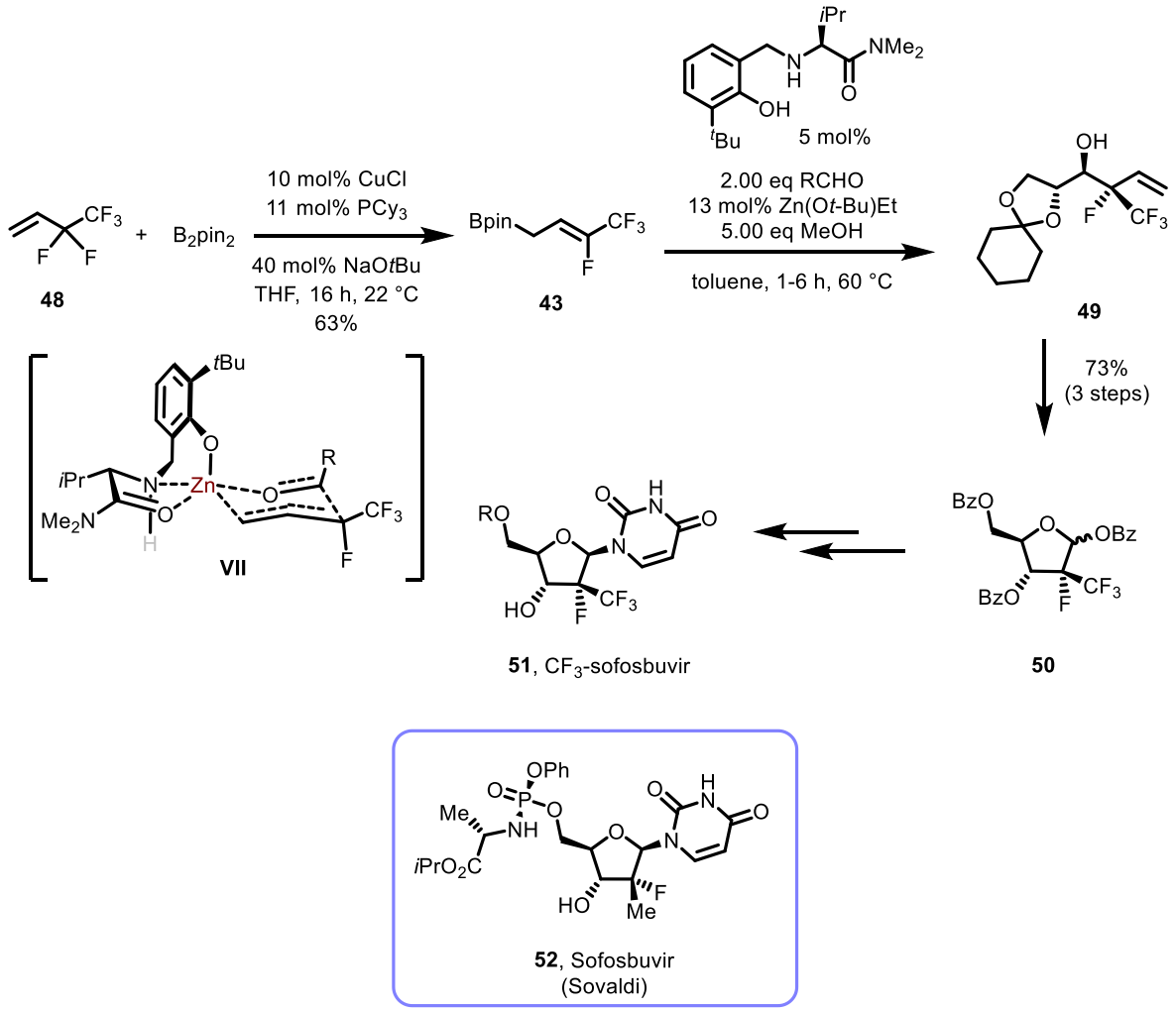
1.3 Synthesis of Tetra-substituted FTF-containing Tertiary Carbon Centers

Approaches for synthesizing tetra-substituted carbon centers containing FTF (**F**luoro**tri**fluoromethyl) groups **42** are underdeveloped. Recently, there has been a growing interest in this field, driven by the significance of incorporating new fluorinated motifs in pharmaceutical and agrochemistry applications. The following scheme provides an overview of existing representative methodologies, encompassing both racemic and enantioselective approaches. Details of each methodology will be introduced in the following paragraphs, outlining the key mechanistic steps and the potential applications of the structural motif in future research (Scheme 7).



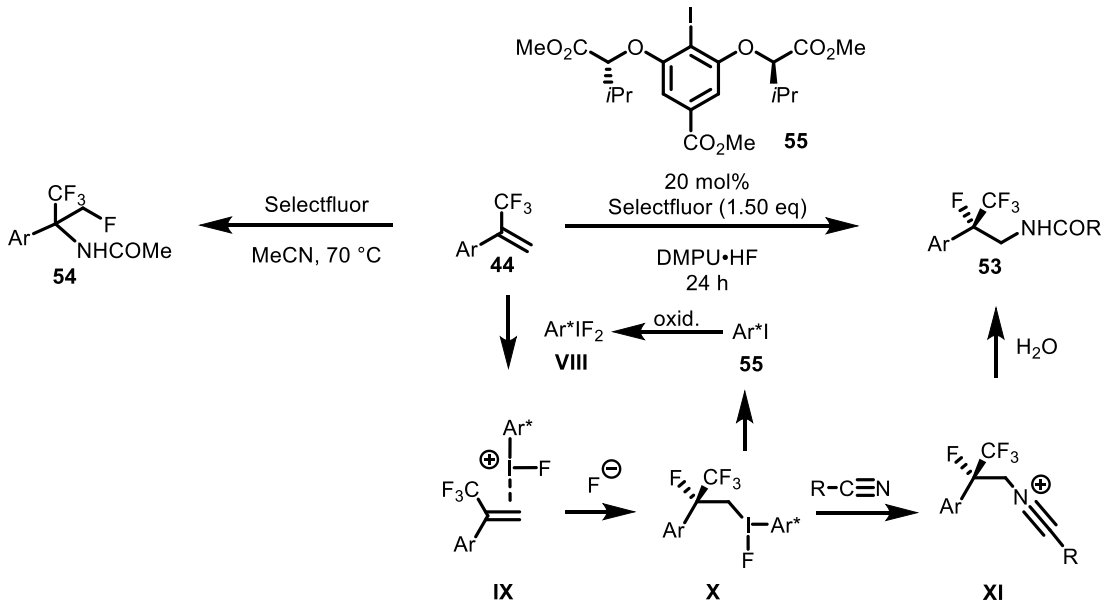
Scheme 7: Summary of the current methodologies concerning construction of the FTF group.

Given the evidence of advantageous influence of a trifluoromethyl group on the bioavailability and metabolic stability of a drug candidate, the pursuit of stereoselective routes for synthesizing unexplored furanosides with a FTF group at C2 is of particular importance. An example is the compound **51**, which is considered as analogue of the antiviral drug sofosbuvir (**52**, Sovaldi), which is used for the treatment of chronic hepatitis C virus infection. The method is based on the regioselective and enantioselective addition of CF_3- and F-substituted allylboronate **43** to aldehydes via the chiral aminophenol-zinc complex. The boronate **43** was prepared in multi-gram quantities from the commercially available pentafluorobutene **48**. When α,β-dialkoxy aldehyde was used as the electrophile, the γ-product **49** was formed in 95:5 γ:α ratio. In total, furanose **50** can be synthesized via **49** in 73% overall yield (Scheme 8).



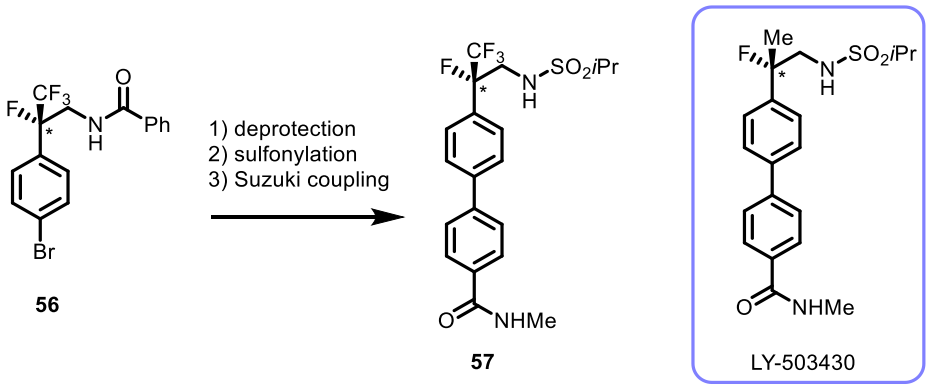
Scheme 8: Construction of FTF group in homoallylic alcohols toward synthesis of tetrafluoro-monosaccharides such as the antiviral drug sofosbuvir **52**, reported by HOVEYDA *et al.*[25]

GILMOUR *et al.* developed enantioselective hypervalent iodine (I)/(III) catalysis to construct FTF groups via fluor functionalization of alkene **44**.[26] This method provides facile access to tertiary, benzylic stereocenters bearing FTF groups. The reaction overrides the intrinsic substrate-based regioselectivity leading to compound **53** reported by LAL[27]. Under the optimized reaction condition, Selectfluor® is used as an oxidant to generate the chiral Ar*IF_2 **VIII** from aryl iodide **55** *in situ*, DMPU·HF or OLAH' reagent is used as a fluoride source, and MeCN employed as the solvent and nucleophile. The subsequent RITTER reaction with **XI** provides the amide **53** up to 89% yield and 86% *ee* (Scheme 9).



Scheme 9: Construction of chiral benzylic FTF group via iodine (I)/(III) catalysis.

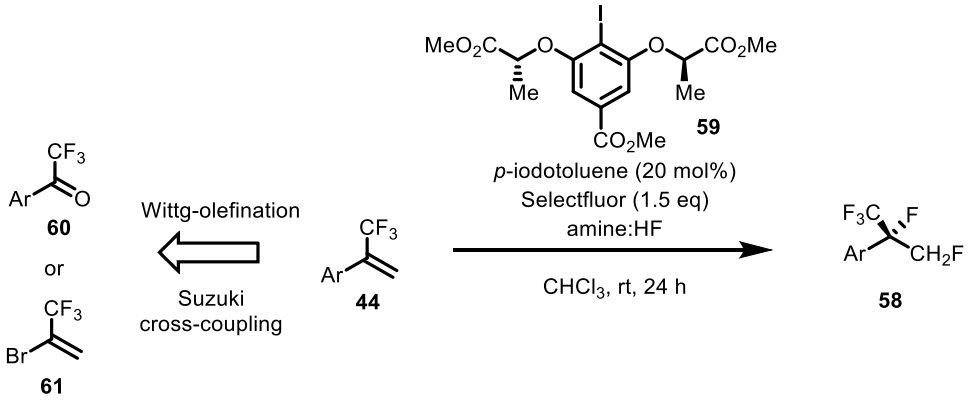
The synthetic utility of this method was demonstrated through a three-step synthesis of the compound **57** starting from **56,** which was synthesized under the standard condition. The absolute configuration was confirmed by X-ray crystallography. **57** is a CF_3 analog of an AMPA receptor positive allosteric modulator, LY-503430, which is developed by ELI LILLY and Company to treat Parkinson's Disease (Scheme 10).[28]



Scheme 10: Synthesis of the CF_3-analog **57** of LY-503430 from compound **56**.

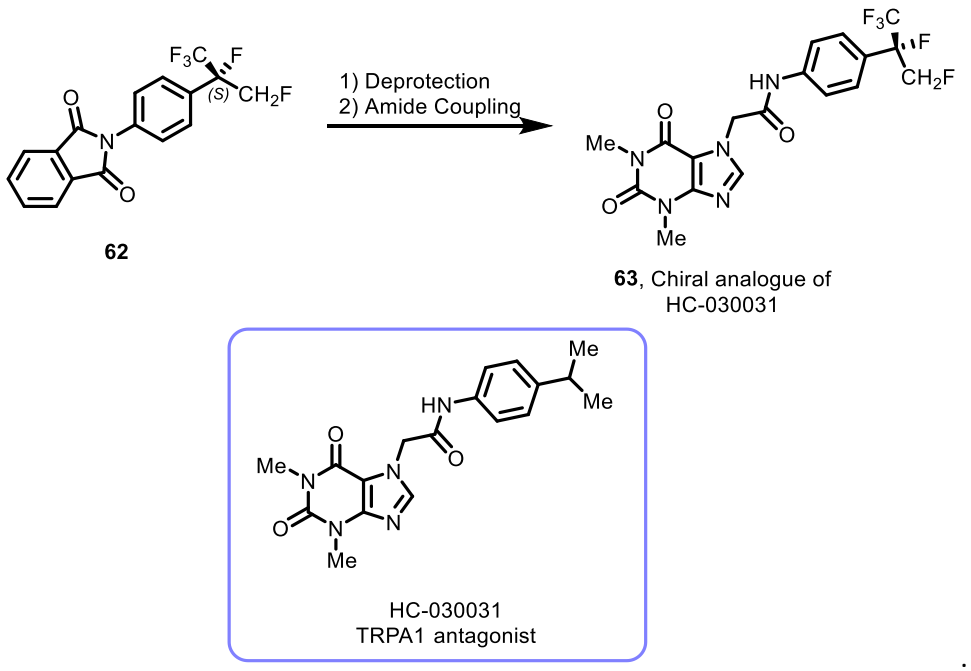
GILMOUR *et al.* also reported a I(I)/I(III) catalysis strategy to construct a chiral pentafluorinated isopropyl group with up to 90% yield (including inseparable side products) and 74% *ee*. This structural motif contains a stereocenter with the substituents F, CH_2F and CF_3, as represented in compound **58**.[29] The method is achieved by the difluorination of the α-CF_3-styrene **44** through the *in situ* generation of a chiral Ar*IF_2 species. Selectfluor® acts as an oxidant to oxidize the Ar*I, amine:HF acts as a fluoride source and a BRØNSTED acid, which activates the hypervalent iodide species.[30] The α-CF_3-styrenes can be easily synthesized by WITTIG

olefination or SUZUKI cross-coupling reactions. The catalysts ArI **59** are accessible from the corresponding resorcinol derivatives through MITSUNOBU reactions (Scheme 11).



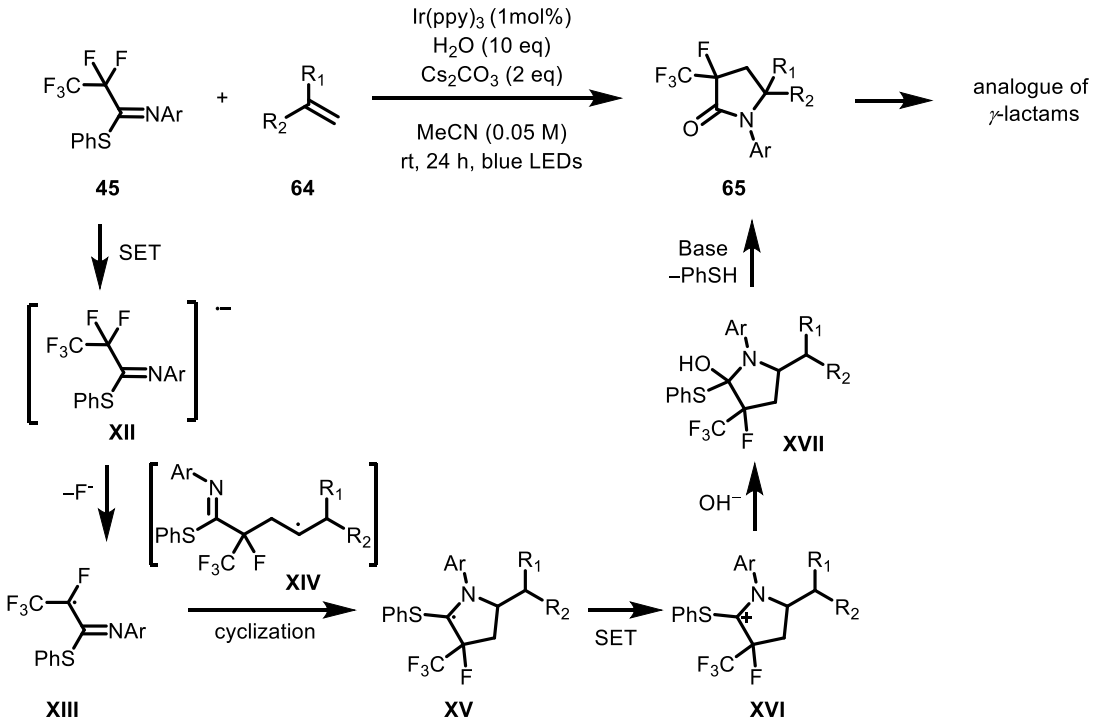
Scheme 11: Construction of chiral pentafluorinated isopropyl group via I(I)/I(III) catalysis.

To demonstrate the application of this motif in the context of drug discovery, a two-step synthesis of the chiral analogue **63** of the TRPA1 antagonist HC-030031 from the phthalimide derivative **62** was performed (Scheme 12).



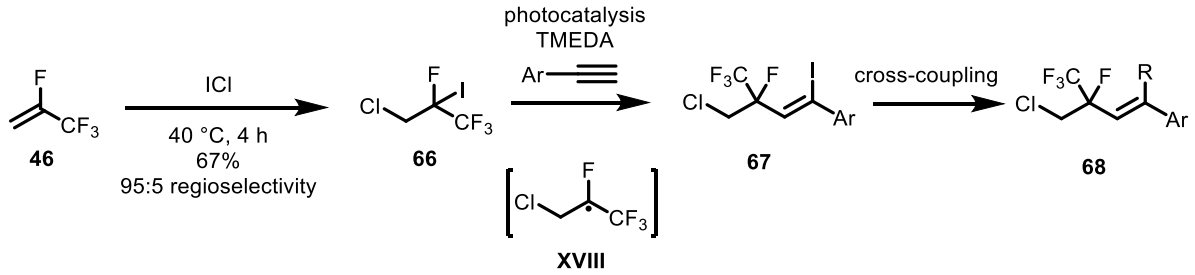
Scheme 12: Synthesis of the chiral analogue **63** of HC-030031 from compound **62**.

LIU *et al.* reported recently a defluorofunctionalization strategy to access the FTF-motif through visible-light promoted C-F bond activation of polyfluorinated iminosulfides **45**. This selective single $C_{(sp3)}$-F cleavage under redox-neutral conditions with alkene **64** and water affords a diverse array of FTF-containing *γ*-lactams. The mechanism involves firstly the generation of radical anion **XII** via SET. Afterwards, the C-F bond cleavage gives the radical **XIII**. Addition of the alkene **64** forms intermediate **XIV**, which allows the following cyclization to give the radical **XV**. The photoredox cycle is closed by forming the radical cation **XVI**, which is trapped by the hydroxide ion to afford **XVII**. At last, the elimination gives the desired product **65**. The method provides access to analog of *γ*-lactams containing small molecules such as KMN-19, a synthetic EP4 agonist (Scheme 13).[31]



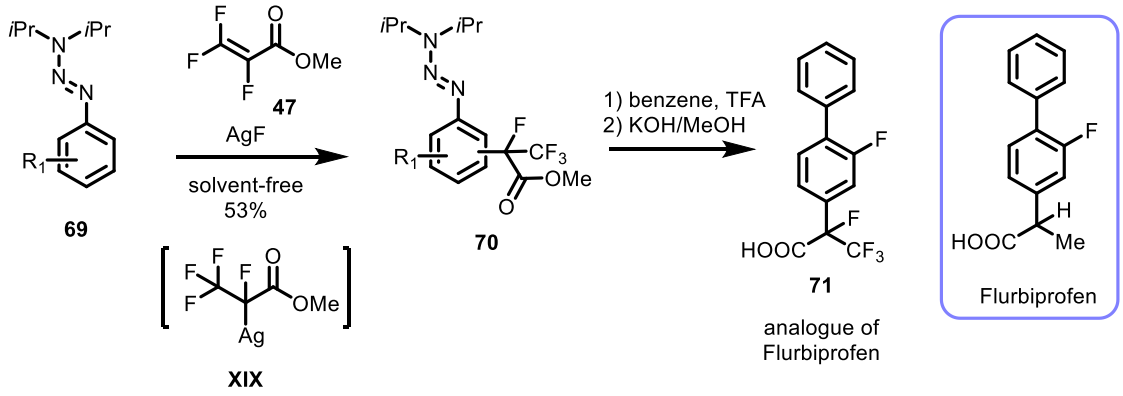
Scheme 13: Construction of FTF-*γ*-lactams via visible-light promoted C-F bond cleavage.

NOVÁK *et al.* reported a method of building γ-allylic-FTF group starting from the refrigerant gas HFO-1234yf **46**.[32] Reaction of ICl and **46** at 40 °C afforded the 3-chloro-1,1,1,2-tetrafluoro-2-iodopropane (**66**) as the main regioisomer in 67% yield. Photochemical addition through the fluoroalkyl radical **XVIII** to alkynes gave the products up to 92% yield and a wide scope. The role of TMEDA is to form electron donor-acceptor complex which promotes the formation of reactive radical species. The vinyl iodide **67** allows further cross-coupling reactions to form an array of FTF-containing allylic compounds **68** (Scheme 14).



Scheme 14: Synthesis of γ-allylic-FTF group from HFO-1234yf **46** and its photochemical application.

Construction of FTF group at benzylic position via radical mechanism was reported by BRÄSE *et al.*[33] In the presence of AgF, methyl 2,3,3-trifluoroacrylate (**47**) reacts with aryltriazene **69** giving FTF-substituted arene **70** up to 53% isolated yield. The arylpropanoic acid group is a general structural motif in most nonsteroidal anti-inflammatory drugs, such as flurbiprofen and ibuprofen. Synthesis of their fluorinated analogues has been developed since decades.[34] A two-step synthesis of the triazene **71**, an FTF-analogue of flurbiprofen, was demonstrated (Scheme 15).



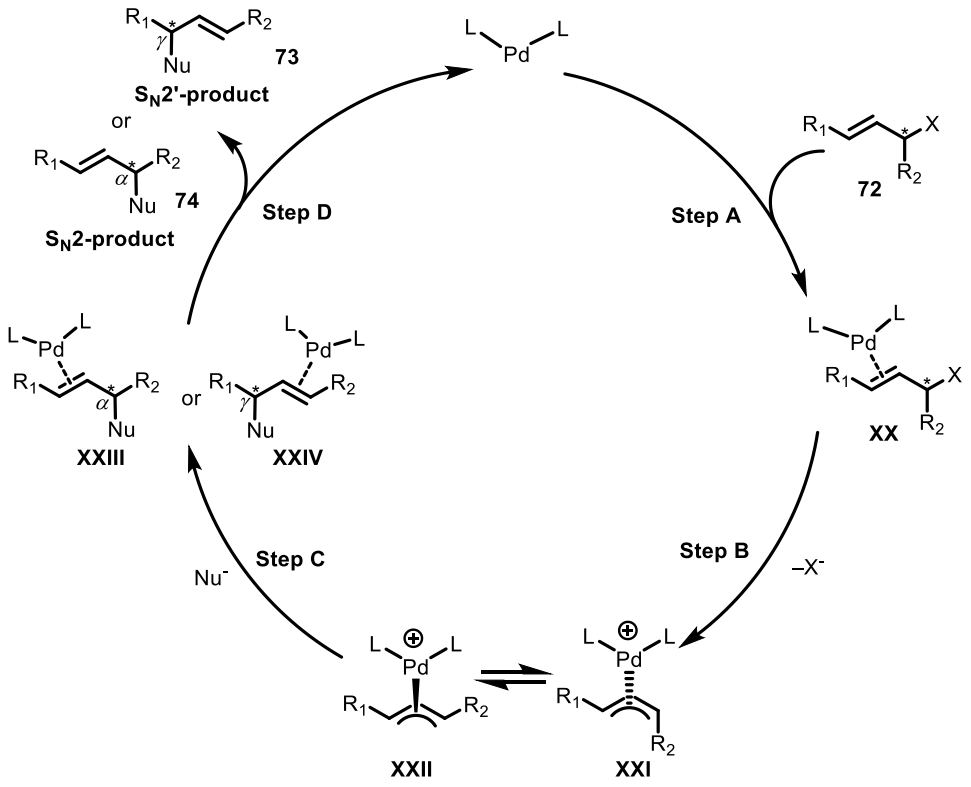
Scheme 15: Construction of benzylic FTF group via silver fluoride assisted fluorination and radical coupling with arenes.

1.4 Metal-mediated Allylic Substitution Reactions

Pd-catalyzed allylic substitution reactions

Allylic substitution without metal catalyst suffers from loss of regiochemistry, which is a challenge in organic synthesis. Transition metal catalyzed allylic substitutions is one of the most powerful methods to construct C-C bonds, it also finds applications in total synthesis of natural products.[35] The use of Pd catalyst allows control of both stereochemistry and regiochemistry. The Pd-mediated allylic substitution reaction, or the TSUJI-TROST reaction, was first pioneered by TSUJI and further expanded by TROST through application of phosphine ligands.[36,37]

There are generally two classes of nucleophiles applied in such reactions, the stabilized or soft nucleophiles (p*K*a of their conjugated acid <25), such as malonic esters, *β*-diketones, and the unstabilized or hard nucleophiles (p*K*a of their conjugated acid >25), typically organometallic compounds of main group metals (Mg, Zn, B, Sn etc.).[38] A general mechanism implying the possible regioselectivity of 1,3-disubstituted allylic substrates is described in Scheme 16.[39]

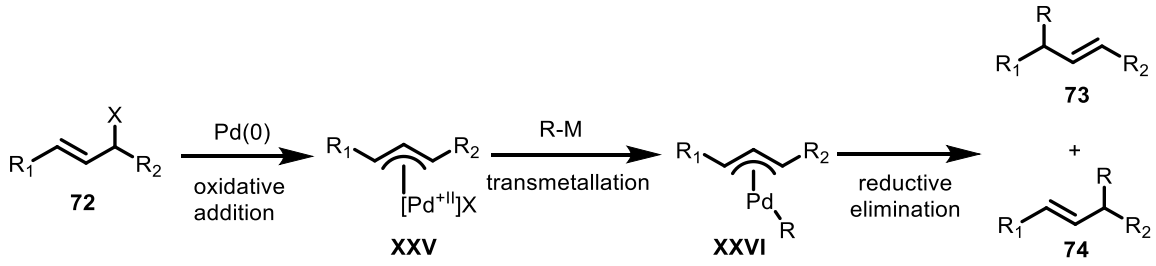


Scheme 16: General catalytic cycle of the asymmetric Pd-catalyzed allylic substitution reaction.

The catalytic cycle involves complexation/coordination (**XX**) (step A), ionization/oxidative addition (step B), nucleophilic addition, forming **XXIII** and **XXIV** (step C) and decomplexation/reductive elimination, giving the S_N2'-type product **73** or S_N2-type product **74** (step D). The regioselectivity can be affected by steric and electronic factors of the substrate,[40] or by the electronic character and symmetry of the ligands.[41,42] Except for step D, each step provides an opportunity for enantioselectivity. However, due to the η^3- η^1- η^3 racemization and (or) *syn*/*anti* exchange of the substituents (**XXI→XXII**), stereoerosion might take place during the reaction.[39,42,43]

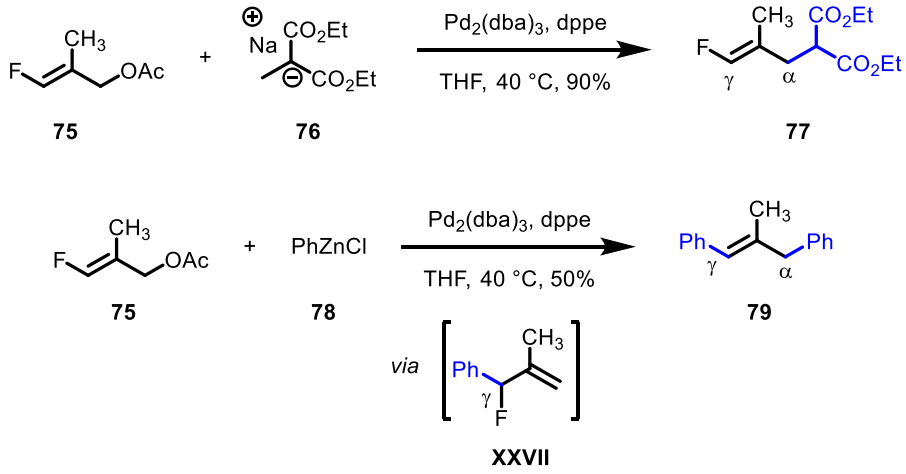
Regarding to stereochemistry, there is a significant difference between a soft and a hard nucleophile. In step A, the Pd(0) catalyst coordinates to the allylic electrophile from the opposite site to the leaving group, resulting in inversion of the configuration. While soft nucleophile adds directly to the η^3-π-allyl complex, resulting in a double inversion and hence net retention of the stereocenter. Hard nucleophile attacks at the palladium center and subsequently transfer to the allylic moiety, resulting in a net inversion of the stereocenter.[37]

TSUJI-TROST reaction with hard nucleophiles (e.g. R-B and R-Zn reagents) could be also viewed as cross-coupling reactions, as both type of reactions involve nucleophilic attack on coordinated π-allyl ligand **XXV**.[40] The nucleophilic addition could be viewed as a transmetallation step in Pd-catalyzed cross-coupling reactions. The reductive elimination can occur at either terminus to give regioisomeric products **73** and **74** (Scheme 17).[44]



Scheme 17: TSUJI-TROST reaction with organometallic reagent can be viewed as cross-coupling reactions.

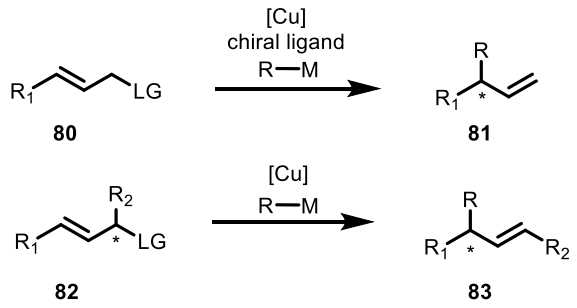
Generally, in Pd-catalyzed allylic substitution reactions, soft nucleophiles prefer to form S_N2-type product. There are several examples showing that hard nucleophiles lead to more formation of S_N2'-type of product. A reported example from SHI *et al.* showed different regioselectivities of hard and soft nucleophile.[45] The malonate **76** generates only the S_N2-type product **77** though nucleophilic attack at the α-position. In comparison, PhZnCl attacks initially at the γ-position and subsequently at the α-position, forming the product **79** (Scheme 18).



Scheme 18: Regioselectivity of palladium-cataylzed allylic substitution between soft nucleophile **76** or hard nucleophile **78** and fluorinated allylic acetate **75**.

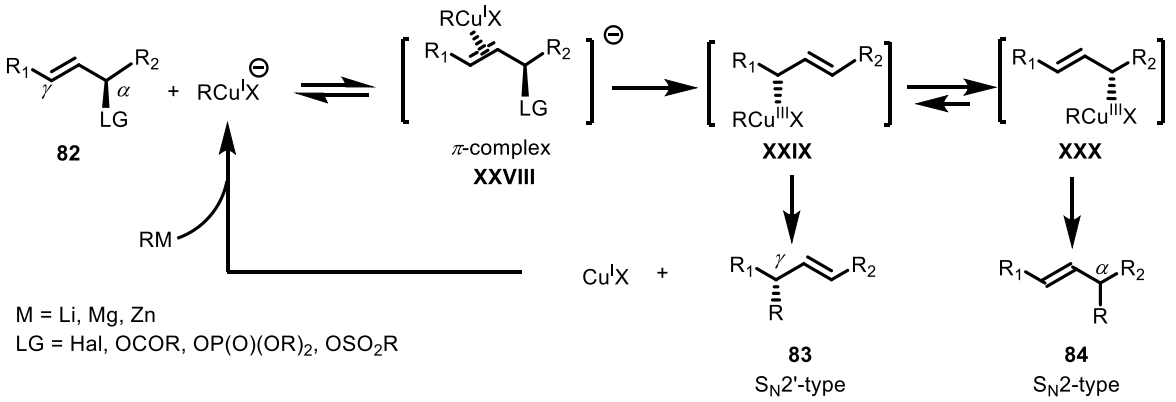
Cu-mediated allylic substitution reactions

The *γ*-regioselectivity of copper-mediated allylic substitutions distinguishes them significantly from allylic substitutions catalyzed by other transition metals. Therefore, they have been actively applied for constructing a quaternary carbon center. For asymmetric Cu-mediated allylic substitution, two common approaches can be used for this purpose, the first one uses primary allylic substrate **80** in combination of a chiral ligand including phosphite and phosphoramidite ligands. The second approach uses optical active secondary allylic substrate **72**, the chirality transfer relies on the *anti* or *syn* addition of the nucleophile to the leaving group. It is commonly anticipated that organocuprates will undergo *anti*-S_N2' reaction with allylic carboxylates, halides, phosphates and sulfonates. While this intrinsic stereocontrol can be overruled in favor of a *syn*-S_N2' addition through coordination to the organocopper reagent. Such reagent-directing groups include carbamate and (*O*/*S*)-benzothiazole group. This serves as a guide for predicting the stereochemistry of the product (Scheme 19).[46,47]



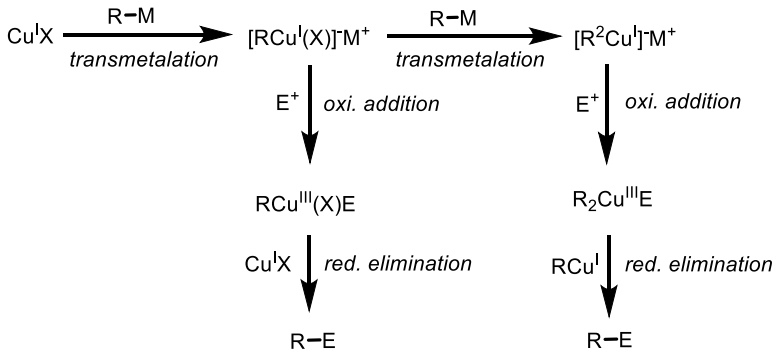
Scheme 19: Two common approaches to construct a chiral quaternary center through Cu-mediated allylic substitution.

Since this work utilizes the latter approach, the following mechanism focuses on this aspect. By applying different organocopper reagents and leaving groups, the stereochemistry and regiochemistry could be controlled to a certain degree. The reaction starts with the transmetalation of the CuX and organometallic reagent (R-M, M = Li, Mg, Zn). Afterwards, the coordination of the organocopper reagent on the double bond forms the *π*-complex **XXVIII**. Subsequently, the formation of the *γ*-*σ*-allylcopper(III) complex **XXIX** is favored, this complex can go through fast reductive elimination, generating the S_N2'-type product **83**. Alternatively, the *γ*-*σ*-allylcopper(III) complex **XXIX** can isomerize to the *α*-*σ*-allylcopper (III) complex **XXX** through the *σ*-*π*-*σ* isomerization, generating the S_N2-type product **84**. (Scheme 20).[48]



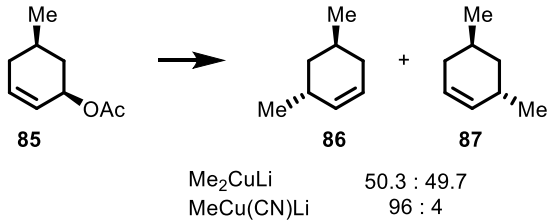
Scheme 20: General reaction mechanism between organocopper reagents and allylic electrophiles.

Both catalytic and stoichiometric copper-mediated allylic substitution reactions share a similar mechanistic pathway.[49] Comparing with the stoichiometric reaction, in the catalytic reaction, the last generated copper species will take part in the next catalytic cycle. What to be notice is, depending on the nucleophilicity and stoichiometry of the R-M reagent, monocuprate MeCu(CN)Li (also named as heterocuprate) or diorganocuprate Me_2CuLi (also named as homocuprate) can be formed, the different cuprate species leads to α- or γ- regioselectivity (Scheme 21).



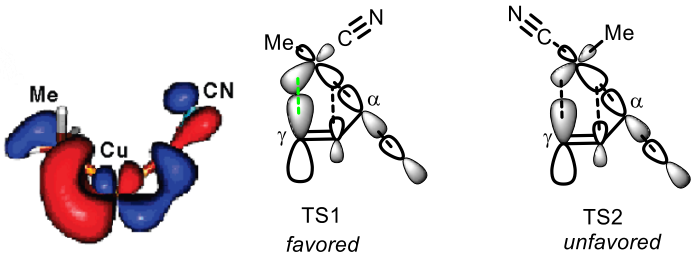
Scheme 21: Formation of heterocuprate and homocuprate through different stoichiometry of the organolithium reagent.

The reaction between the allylic acetate **85** and Me_2CuLi or MeCu(CN)Li is shown as an example. The result demonstrates the very different regioselectivity of monocuprate and hetereocuprate in allylic substitution reactions. While the homocuprate leads to a 1:1 ratio of the α-product **87** and γ-product **86**, the formation of the γ-product **86** is almost selective by applying the hetereocuprate (Scheme 22).



Scheme 22: Different results in regioselectivity of the allylic substitution reaction bewteen cyclohexenyl acetate and a homocupurate or hetereocuprate.

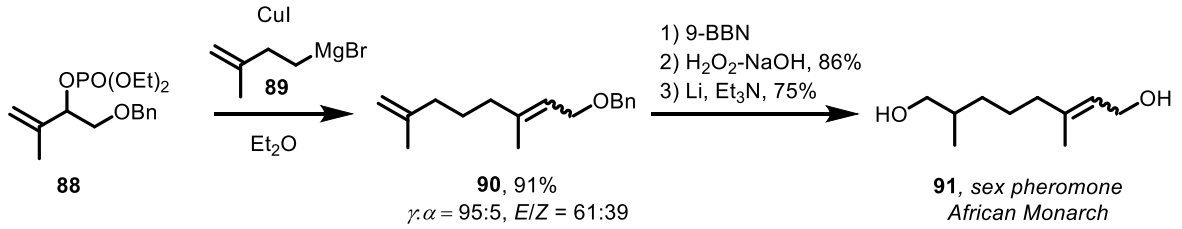
To understand the fundamental reactivity of organocopper reagents, NAKAMURA *et al.* studied the molecular orbital interactions between the different cuprate species and the allylic acetate. According to the orbital analysis, the regioselectivity took place in the oxidative addition step. In the case of RCu(CN)Li, the orbital interaction between the Cu-3d_{xz} orbital and the ligand orbital is out-of-phase. In the transition state, the stronger σ-donor ability of the Me group than the CN ligand leads to the desymmetrization of the 3d_{xz} orbital. As a result, the d-orbital on the side of Me is larger than the side of CN. At the same time, the C-O bond cleavage of the allylic electrophile leads to the mixing of the π^* and σ^*, which results a larger lobe of the LUMO of the γ side. Therefore, the orbital overlap of $MeCuCN^-$ with the allylic acetate is larger in TS1 than TS2, leading to the favored formation of the γ-product. One could say that the orbital dissymmetry of the R-Cu-CN is the major cause for the γ-regioselectivity.[50] In comparison, the intermediate formed from Me_2CuLi and the electrophile is symmetric and would lead to a non-regioselective reaction (Scheme 23).



Scheme 23: Molecular orbital interaction of the HOMO (Cu-3d_{xz} orbital of $MeCuCN^-$) and the LUMO (a mix of the π^* and σ^* orbital of the allylic acetate).

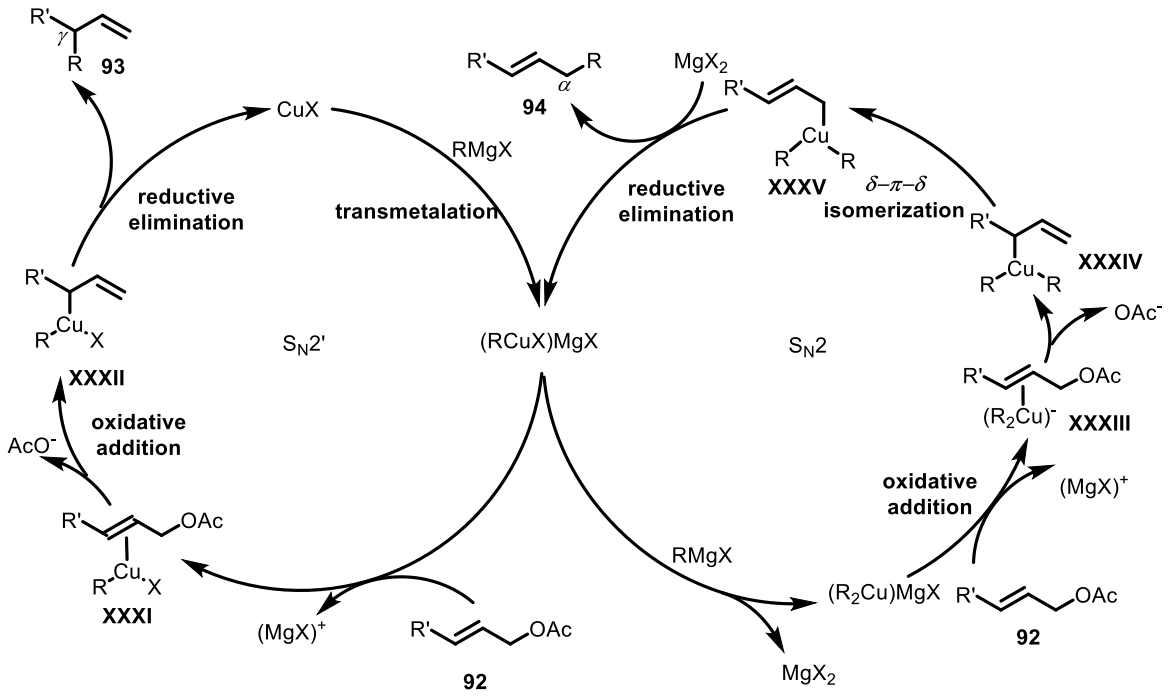
Cu-mediated allylic substitution reactions using GRIGNARD reagents

Copper-catalyzed allylic substitutions of GRIGNARD reagents can lead to both S_N2-and S_N2'-type of products. It has been concluded that the addition of Cu (I) salt can increase the yield and influence the regioselectivity.[51] A early application was demonstrated in the synthesis of the sex pheromone **91** of the male butterflies of the African Monarch.[52] The reaction between 3-methylbut-3-enyl magnesium bromide (**89**) and the allylic phosphate **88** was catalyzed by CuI, giving the desired product **90** in 91% in excellent regioselectivity. Further hydroboration and deprotection of the benzyl group yields the naturally occurring compound **91** (Scheme 24).



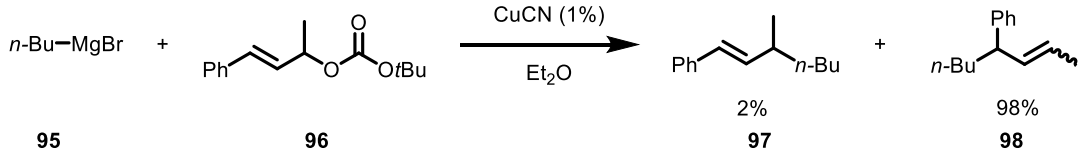
Scheme 24: An early application of copper-catalyzed allylic substitution using GRIGNARD reagent **89**.

There are intensive studies of the regiochemistry of copper-catalyzed GRIGNARD reactions with primary allylic electrophile, a general mechanism was proposed by BÄCKVALL *et al.*[53] Comparing with organolithium or organozinc reagent, the nucleophilicity of GRIGNARD reagents is medium, which allows control of the formation of either monocuprate (RCuX)MgX or diorganocuprate (R_2Cu)MgX by the stoichiometry and the speed of addition of the reagent.[54] In the catalytic cycle, the monocuprate (RCuX)MgX forms preferably the γ-π-complex **XXXII** and yields the S_N2' product **93**. When the monocuprate reacts with another equivalent of RMgX, the diorganocuprate (R_2Cu)MgX can be formed, in this case, the reductive elimination step is slower, allowing the isomerization to the α-π-complex **XXXIV**, which gives the S_N2 product **94** (Scheme 25).



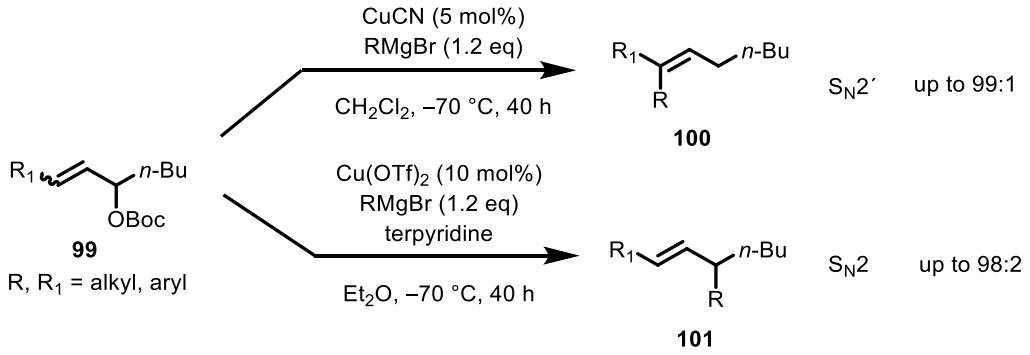
Scheme 25: Proposed mechanism for the copper-catalyzed GRIGNARD reactions with primary allylic acetate.

However, the control of the regioselectivity for internal allylic electrophiles remains challenging. Although electronically or sterically biased internal allylic system could be used to influence the regioselectivity, but the other factors can still dominate the selectivity. Such factors include the nature of the Cu (I) salt, the leaving group, the addition time of the GRIGNARD reagent with the Cu salt, the reaction temperature, solvent and so on. As the below example shows, although the S_N2 product **97** is thermodynamically favoured due to the conjugation with the phenyl ring. The reaction yields almost selectively the S_N2' product **98** as a mix of the *Z*- and *E*- Stereoisomers. It was also found out that aryl or vinyl GRIGNARD reagents generally shows poor regioselectivity in such reactions (Scheme 26).[55]



Scheme 26: CuCN-catalyzed allylic substition between alkyl GRIGANRD reagent **95** and carbonate **96** favors the formation the theromodynamically unfavored γ-product **98**.

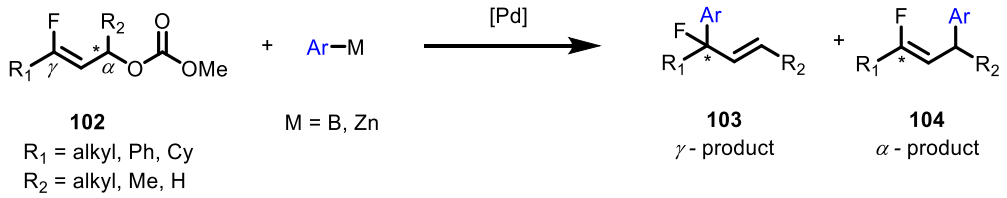
An example reported by TAMBAR *et al.* in 2023 demonstrated a catalyst-controlled method of unbiased internal allylic carbonates **99** to generate the S_N2 or S_N2' product in high regioselectivity and *E*-selectivity. By using CuCN or $Cu(OTf)_2$ as catalyst and different stoichiometry of RMgBr, the regioselectivity of the Cu-catalyzed reaction could be reversed.[56] To understand the origin of the regioselectivity, the author conducted mechanistic studies. The results suggest that the CuCN-catalyzed reaction forms a heterocuprate species EtCu(CN)MgBr, which prefers a π-complexation with the allylic substrate, followed by the oxidative addition from the π-complex generating the Cu (III) intermediate. Finally, the reductive elimination gives the S_N2' product **100**. In contrast, the $Cu(OTf)_2$-catalyzed reaction forms a homocuprate species $Et_2CuMgBr$, which forms a LEWIS acid-base complex with the allylic substrate, instead of the formation of the unstable π-complex due to the two electron donating ethyl groups. the nucleophilic attack of this anionic Cu(I) species on the substrate generates the Cu(III) intermediate. And finally, the reductive elimination gives the S_N2 product **101** (Scheme 27).



Scheme 27: A catalyst-controlled regioselective allylic substitution of unbiased internal allylic carbonate.

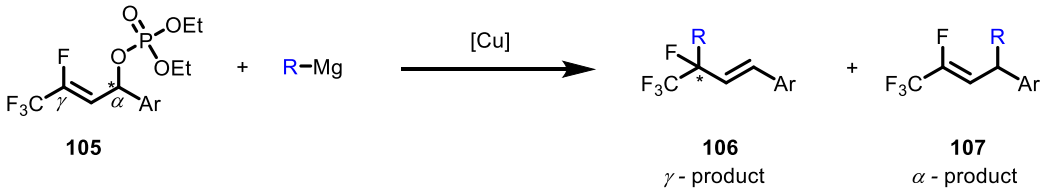
2 Goal Setting

The synthesis of tetra-substituted fluorine-containing carbon center, particularly the enantioselective approach, holds considerable importance in the field of pharmaceuticals. In this work, at first, the palladium-catalyzed allylic substitution reactions of fluorinated carbonate **102** should be investigated. Organoborane and organozinc reagents are selected as hard nucleophiles to study the regioselectivity, as there are few reported studies regarding these nucleophiles. The preparation of the allylic carbonate **102** can be guided by the previous work conducted by KOERT *et al*. (Scheme 28).[16]



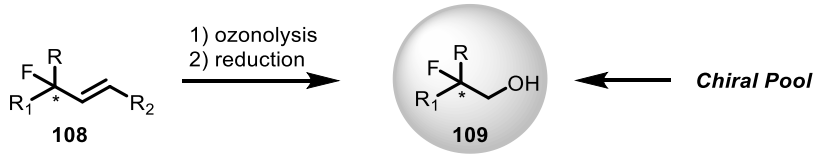
Scheme 28: Pd-catalyzed allylic substitution of fluorinated carbonate **102** using organoboron and organozinc reagent.

Secondly, copper-catalyzed allylic substitutions of tetra-fluorinated secondary phosphate **105** should be studied. This type of reaction employing GRIGNARD reagent typically exhibit a preference for γ-selectivity. This characteristic could be advantageous to obtain the desired tetra-substituted carbon center **106**. Additionally, a synthetic pathway to enantiopure phosphate should be developed to study the efficiency of chirality transfer using this method (Scheme 29).



Scheme 29: Cu-mediated allylic substation reaction of fluorinated phosphate **105** using GRIGNARD reagent.

Finally, it is crucial to confirm the absolute configuration of the stereocenter in the final product. This determination could be verified by X-ray analysis. Alternatively, a parallel synthesis from the chiral pool, involving ozonolysis and subsequent reduction reactions of compound **108**, could be employed to compare and confirm the absolute configuration (Scheme 30).



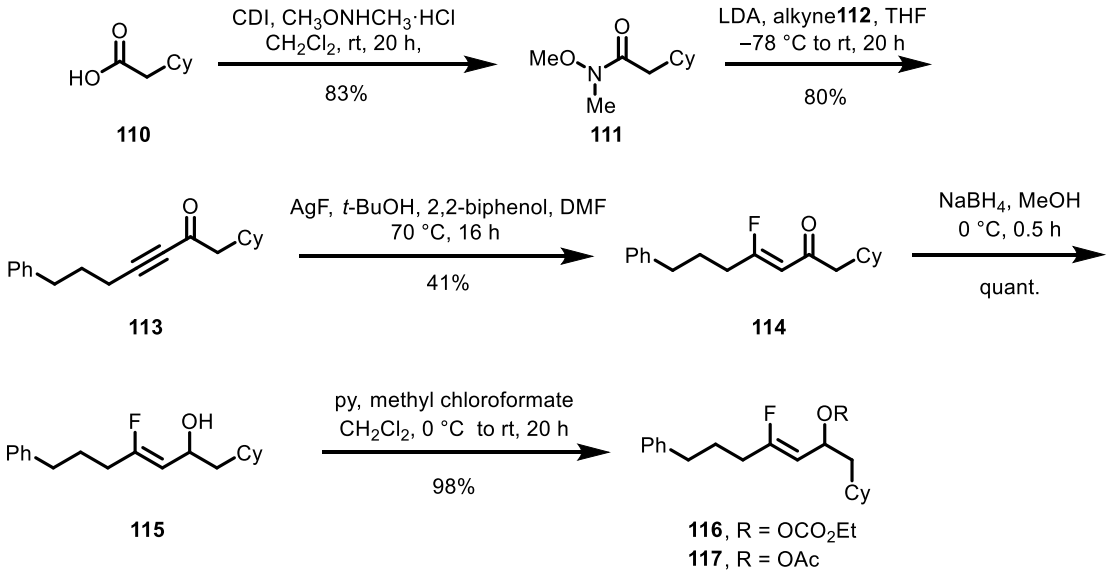
Scheme 30: Determination of the absolute configuration of the fluorinated stereo center.

3 Results and Discussion

3.1 Project A: Pd-catalyzed Cross-coupling Reaction of 3-Fluoroallylic Compounds

There are rare studies about Pd-catalyzed allyl-aryl cross-coupling reactions, particularly those involving fluorinated allylic compounds.[57] In the prior work conducted by KOERT *et al*. the enantioselective synthesis to 3-fluoroallylic alcohol derivatives has been established and studied for their reactivities with soft nucleophile (TMSCN) in allylic substitution reactions.[16,17] This has laid the groundwork for reactivity studies with organoboron and organozinc reagents, which will be referred as SUZUKI cross-coupling and NEGISHI cross-coupling in this work.

The synthesis of the fluorinated allylic carbonate **116** or acetate **117** consists of five steps, starting with the preparation of the WEINREB amide **111**. Deprotonation of the alkyne **112** with LDA enabled the nucleophilic attack on the electrophile. The resulted ynone **113** was fluorinated to **114** under the reported condition. According to the literature, this step is sluggish due to an identified side reaction forming furan as a side product, which explained the low yield of 41%. The reduction with $NaBH_4$ to **115** and carboxylation or acetylation resulted in excellent yield (Scheme 31).

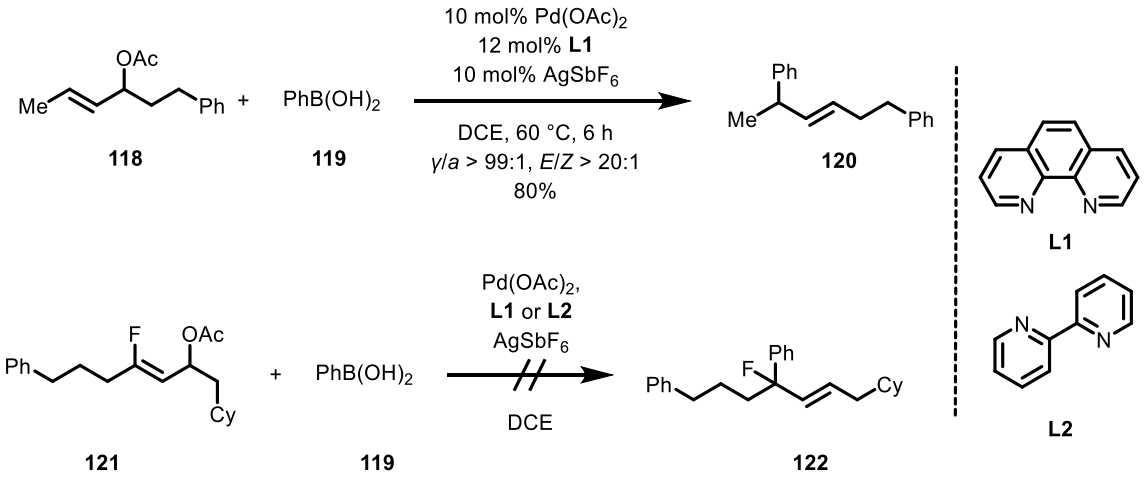


Scheme 31: Synthesis of the 3-fluoroallylic carbonate **116** and acetate **117** as allylic electrophiles for the coupling reactions

3.1.1 Pd-catalyzed Cross-coupling Reaction with Organoboron Reagents

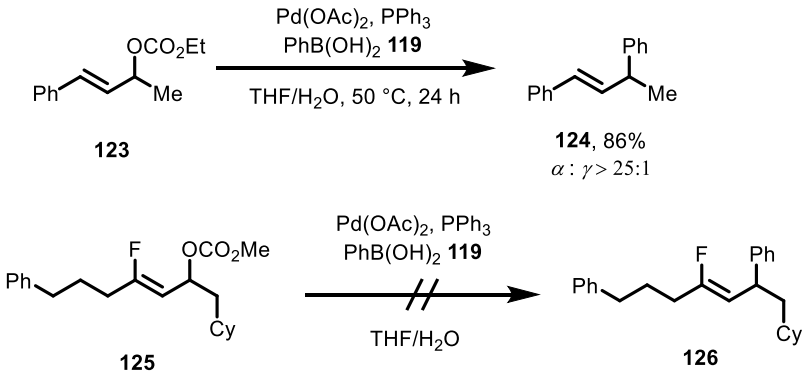
SUZUKI-MIYAURA cross-coupling offers the ready availability of the organoboron reagents and mild reaction condition. The typically catalyst include Pd(0) species such as $Pd(PPh_3)_4$, $Pd(dba)_2$ and $Pd(tBu_3P)_2$. Alternatively, Pd(II) species such as $Pd(OAc)_2$, $Pd(dppf)Cl_2$ and $PdCl_2(PPh_3)_2$ can be reduced to Pd(0) *in situ*. The typical solvents used are dioxane, DME, THF, DMF and alcohol solvents. Na_2CO_3, K_2CO_3, K_3PO_4, NaOH are commonly employed as base and 10-30% water is added as co-solvent.[58]

SUZUKI coupling reactions with allylic substrates have not been extensively explored. Moreover, the cross-coupling reaction between 3-fluoro allylic electrophiles and organoborane reagents is unknown in the literature.[59] SAWAMURA *et al.* reported a γ-selective Pd(II)-catalyzed allyl-aryl coupling with allylic acetate.[60] The intramolecular coordination of the acetoxy group could assist the β-acetoxy elimination. Under the same reaction condition, the cross-coupling reaction between **118** and phenylboronic acid **119** didn't yield the desired product. Varying the temperature or reaction time had not much influence on the outcome, only side product resulting from β-H elimination reaction could be observed (Scheme 32).



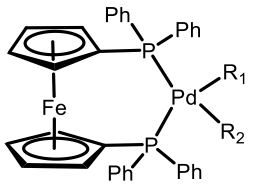
Scheme 32: Applying the reaction condition reported by SAWAMURA *et al.* led to no product.

ZHANG *et al.* disclosed the SUZUKI-MIYAURA cross-coupling reaction between secondary allylic carbonate **123** and arylboronic acid **119** with α-selectivity.[57] Under the same reaction condition, either α- nor γ- product could be obtained with the allylic carbonate. Also in this case, side product resulting from β-H elimination was observed (Scheme 33).



Scheme 33: Applying the reaction condition reported by ZHANG *et al.* led to no product.

It is known that *β*-H elimination is a competitive side reaction in SUZUKI reactions involving alkyl substrates.[61] But there is also literature supporting that Pd-η^3-allylic complex is less prone to *β*-H elimination than Pd-alkyl complex.[62] Through coordination of bidentate phosphine ligands such as dppf and dppb, the R_1 and R_2 group would be closer, increasing the orbital overlap between the two groups. In this way, the reductive elimination process can be accelerated. For example, the catalyst Pd(dppf)Cl_2 is believed to provide a more favorable ratio of rate constants for reductive elimination versus *β*-H elimination.[63,64] There are examples of using Pd(dppf)Cl_2 in $C_{(sp3)}$-$C_{(sp2)}$ SUZUKI coupling reactions.[65] Moreover, as a pre-formed complex, Pd(dppf)Cl_2 can be used without adding extra ligand. It is an air stable catalyst, comparing with the other pre-formed catalyst such as Pd(*t*$Bu_3P)_2$ and Pd(amphos)Cl_2. For these reasons, Pd(dppf)Cl_2 is a commonly applied Pd catalyst in the pharmaceutical industry (Scheme 34).[58]

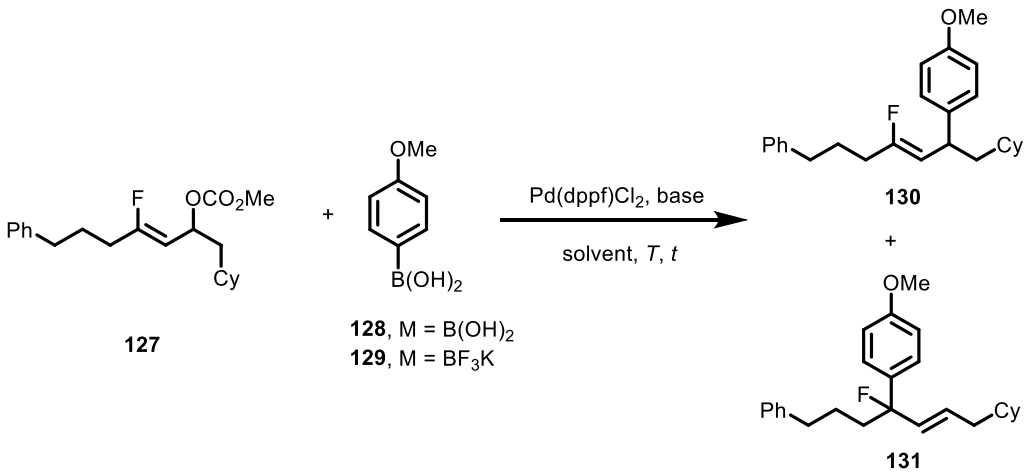


Scheme 34: The bite angle of the R_1 and R_2 group is reduced, as a result of the large bite angle (96°) of the P-Pd-P angle.

As the problem of the low polarity of the fluorinated products was noticed, the methoxy phenyl boronic acid **128** or BF_3K salt **129** was applied to increase the polarity of the products in the following reactions. Generally, allylic carbonates are more reactive than acetates in Pd(0)-catalyzed reactions of allylic compounds, there is example in the literature of SUZUKI cross-coupling reaction between benzylic carbonate and arylboronic acid.[63] Therefore, the carbonate was used as the standard substrate for the test conditions.

As presented in Table 1. The initial experiment was carried out at 80 °C in THF/H_2O, utilizing CsOAc as a base and Pd(dppf)Cl_2 as the catalyst. Under this condition, no conversion of the starting materials could be confirmed after 18 hours (entry 1). When a stronger base K_2CO_3 was used, the starting material was fully converted after 2 hours, but only trace of the fluorinated product **130** was observed, whereas the primary products remained defluorinated (entry 2). Changing the THF/H_2O ratio to 10:1 did not have notable influence on the outcome (entry 3). The water-free reaction in anhydrous DMF proceeded as well, but also only trace of product was observed (entry 4). BF_3K borate was subsequently employed for its higher reactivity and tolerance of functional groups.[66] Nevertheless, there was no notable improvement in our case (entry 5).

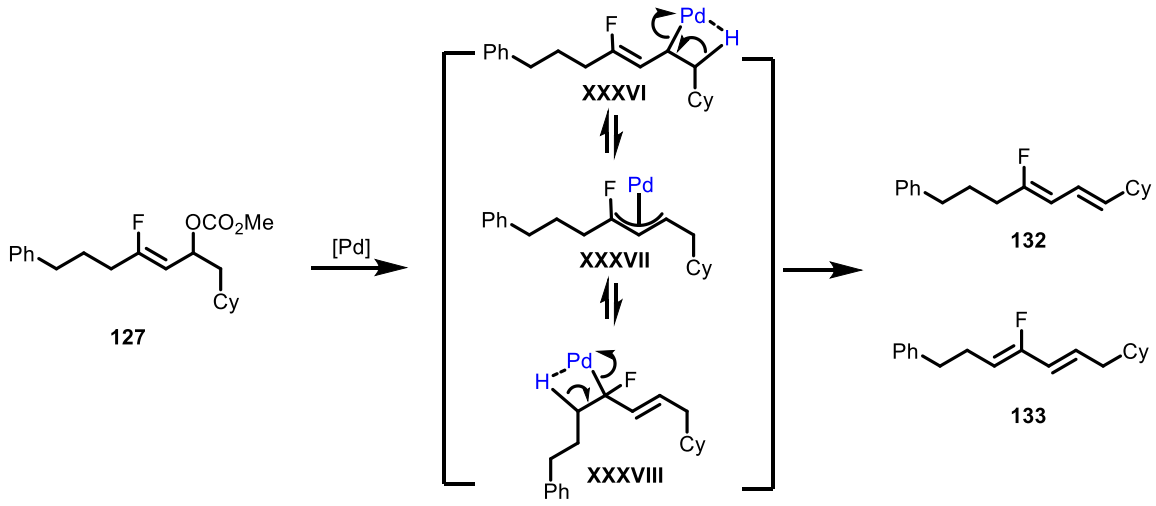
Table 1: Results of the SUZUKI-MIYAURA cross-coupling reaction between carbonate **127** and **128, 129**.



#	M[b]	Solvent	Base	T [°C]	t [h]	Conversion[c]	Product
1	$B(OH)_2$	THF/H_2O (5:1)	CsOAc	80	18	none	-
2	$B(OH)_2$	THF/H_2O (5:1)	K_2CO_3	70	2	full	trace
3	$B(OH)_2$	THF/H_2O (10:1)	K_2CO_3	70	2	full	trace
4	$B(OH)_2$	DMF	K_2CO_3	70	2	full	trace
5	BF_3K	THF/H_2O (5:1)	K_2CO_3	80	2	full	trace

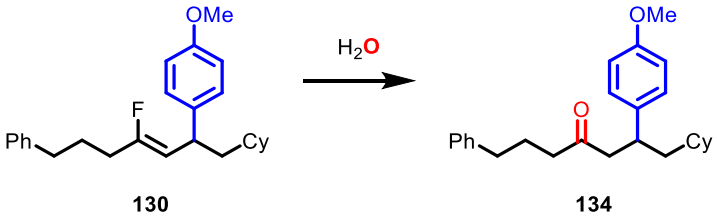
a) All reactions were performed at a 50 mg scale. b) 1.10 eq Boronic acid or BF_3K salt were used in all reactions. c) Analyzed by TLC and ^{19}F-NMR of the reaction mixture.

To gain insight into the reaction mechanism, sides products were isolated and characterized. Under all conditions (entry 2-5), the presence of conjugated diene **132** and **133** was detected, which were resulted from the β-H elimination of the Pd-allyl complex. Mechanistically, after oxidative addition of Pd(0) to the allylic substrate **127**, the η^3-allylic-complex **XXXVII** is generated. If the transmetalation step is too slow, the isomerization to the η^1-allylic-complex **XXXVI** or **XXXVIII** would allow the *syn*-elimination of the Pd-H, leading to the formation of dienes.[59] In the presence of base, the β-H elimination process is catalytic (Scheme 35).[67]



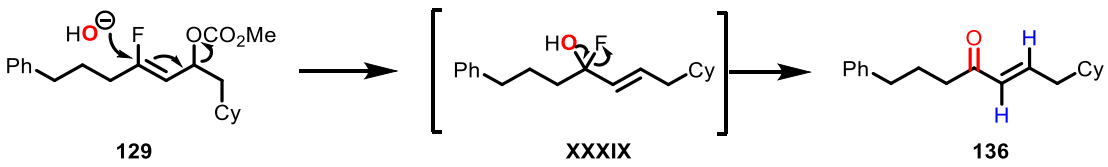
Scheme 35: Proposed mechanism for β-H elimination resulting in dienes as products.

Notably, when water is present in the reaction, the side product ketone **134** resulted from the addition of the aryl nucleophile could be confirmed through NMR analysis and mass spectroscopy. ^{19}F-NMR analysis revealed defluorination of the compound. This observation indicates that the transmetalation actually took place, however, after the reductive elimination, the fluorinated olefin **130** underwent hydrolysis, giving the ketone **134** as the final product (Scheme 36).



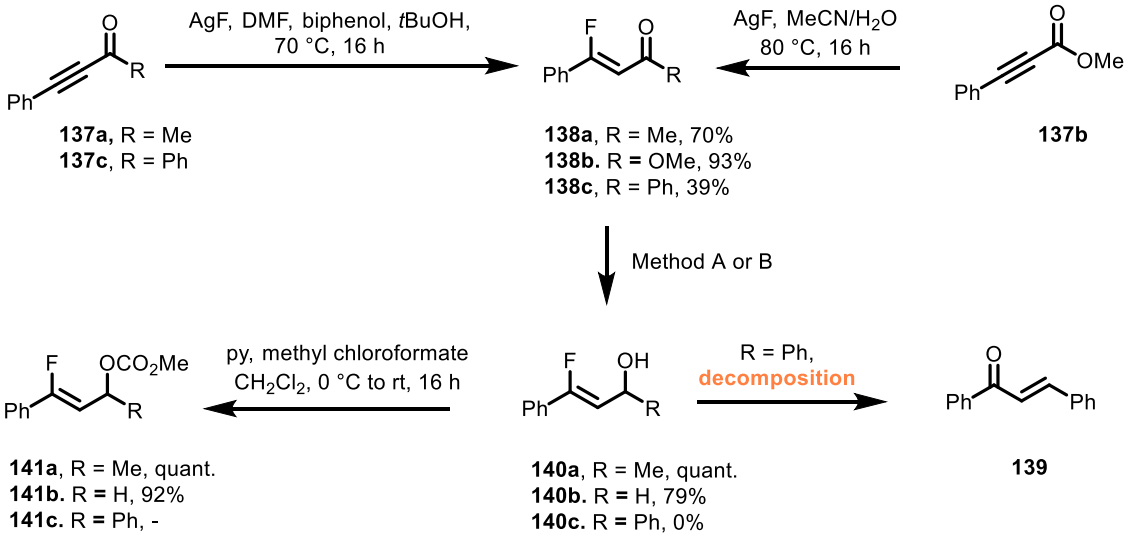
Scheme 36: Hydrolysis of the desired product **130** could form the ketone **134**.

Another defluorinated product that could be confirmed through NMR analysis is the 1,4-unsaturated ketone **136**. This is evident from the distinct signals of the two olefinic protons at 6.05 ppm and 6.77 ppm. Additionally, the carbonyl group was clearly identified at 201 ppm. This transformation is likely attributed to the γ-substitution of hydroxide on the allylic system. After fluoride cleavage through the intermediate, ketone **136** was formed as a product (Scheme 37).



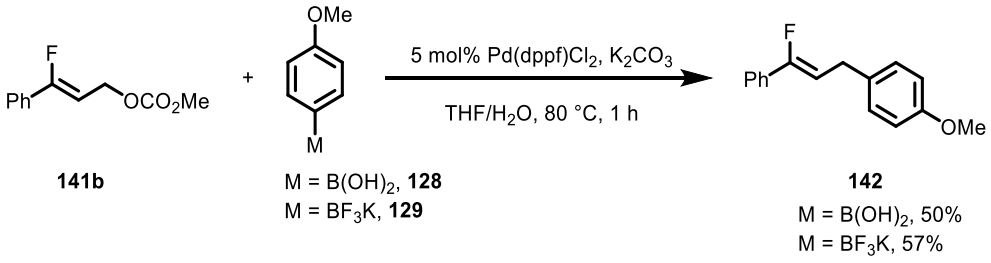
Scheme 37: Proposed mechanism for the formulation of ketone **136**.

To assess the impact of β-H elimination of different substrates, the SUZUKI reaction with other carbonates was investigated. Carbonate **141a**, which has β-hydrogen on one side, and biphenyl carbonate **141c**, which lacks β-H, as well as primary carbonate **141b** were planned as substrates. The synthesis of the substrates **138a** and **138c** was carried out using the same method as previously described. Notably, the alcohol **140c** rapidly decomposed to the compound **139** at room temperature, making it impossible to synthesize the corresponding biphenyl carbonate **141c**. The synthesis of the primary carbonate **141b** followed a slightly altered method, using AgF in $MeCN/H_2O$ and the propiolate **137b** (Scheme 38).



Scheme 38: Synthesis of allylic carbonates **141.** Method A: $NaBH_4$, MeOH, 0 °C, 1 h. Method B: DIBAH, CH_2Cl_2, 0 °C, 1 h.

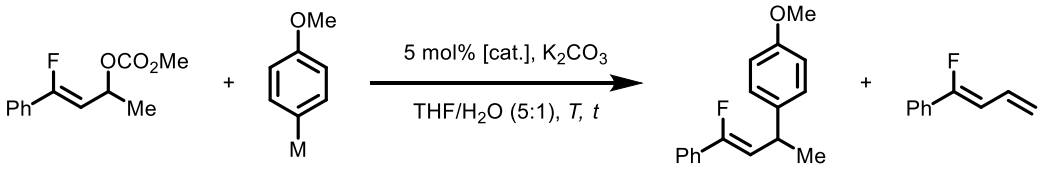
At first, the coupling reaction with primary carbonate **141b** using methoxy boronic acid **128** and BF_3K salt **129** was conducted. After 1 h reaction time, product **142** could be isolated in 50% and 57% yield, respectively. Furthermore, the reaction exhibited only α-regioselectivity. This reaction confirmed the feasibility of the SUZUKI coupling reaction involving an α-benzylic fluorinated primary carbonate (Scheme 39).



Scheme 39: SUZUKI cross-coupling reaction between primary carbonate **141b** and aryl compound **128**, **129**.

To compare the results, the α-benzylic fluorinated secondary carbonate **141a** bearing a methyl group is further examined. As presented in Table 2, when employing Pd(dppf)Cl_2 as the catalyst and K_2CO_3 as the base at 80 °C, complete conversion of the carbonate substrate was achieved within just one hour. From the array of mixed products obtained, only **143** and **144** were fluorinated, with 17% and 9% yield, respectively (entry 1). The reaction conducted at 60 °C yielded similar results (entry 2). Changing the boronic acid to the trifluoroborate appeared to have no impact on the outcome (entry 3). Comparing with the results from the carbonate **127** (see Table 1), it is clear that the number of β-H atoms of the allylic carbonate significantly influences the reaction's outcome.

Table 2: Results of the SUZUKI-MIYAURA cross-coupling reaction of carbonate **141a**.



141a M = $B(OH)_2$, **128** M = BF_3K, **129** **143** **144**

#	M	Catalyst	Ligand	T [°C]	t [h]	Conversion	Yield 143	Yield 144
1	$B(OH)_2$	Pd(dppf)Cl_2	-	80	1	full	**17%**	**9%**
2	$B(OH)_2$	Pd(dppf)Cl_2	-	60	1	full	**11%**	**6%**
3	BF_3K	Pd(dppf)Cl_2	-	60	1	full	**10%**	**5%**
4	$B(OH)_2$	$Pd(OAc)_2$	PPh_3	50	24	full	**0%**	**80%**

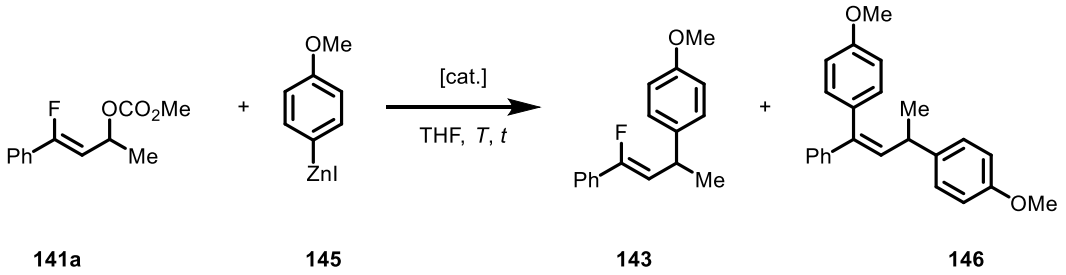
The reaction condition using $Pd(OAc)_2$ as a catalyst and PPh_3 as a ligand, which was reported by ZHANG *et al.* [57] was also tested. As a result, instead of the substitution product **143**, the fluorinated diene **144** was yielded as the main product (entry 4). Comparing the results with the coupling reaction with the non-fluorinated allylic carbonate **123** (described in Scheme 33), it becomes evident that fluorine at the allylic position has a substantial influence on the SUZUKI cross-coupling reactions.

To summarize the SUZUKI coupling reaction involving the fluorinated allylic substrates, it can be assumed that the high electronegativity of the fluorine atom facilitates the Pd-H elimination through the more electropositive η^3-allyl intermediate. While a stronger base can enhance the transmetallation and reductive elimination, it failed to prevent Pd-H elimination. Conversely. employing no base or a weaker base resulted in no reaction, creating a dilemma. The use of water promotes the formation of the ate complex and accelerates the transmetalation, however, it also induces hydrolysis of the desired product.

3.1.2 Pd-catalyzed Cross-coupling Reaction with Organozinc Reagents

Organo aryl zinc reagent reacts primarily with π-allyl palladium complex by attacking the Pd-center. After rearrangement to a σ-complex, the organic ligand can be transferred to the allyl system via rapid reductive elimination.[45] To tackle the problem associated with β-H elimination and defluorination in the reaction, NEGISHI cross-coupling reaction was considered. Furthermore, the absence of water and base in the reaction serves to minimize the possibility of defluorination. As reported by TAKAGI *et al.*,[68] the aryl-allyl cross coupling between allylic halides and aryl zinc iodide afforded allylbenzenes in high yields, $Pd(dba)_2$ proved to be the most efficient catalyst in this reaction, also $Pd(PPh_3)_4$ was an effective catalyst.

Table 3: NEGISHI cross-coupling reactions between aryl-substituted fluorinated carbonate **141a** and *p*-OMePhZnI **145**.



141a **145** **143** **146**

#	ArZnI 145 [eq]	Catalyst	[eq]	T [°C]	t [h]	Yield[a] 143	Yield[a] 146	Ratio *α:γ*
1	1.10	$Pd(dba)_2$	0.05	rt	16	trace	-	-
2	0.90	$Pd(PPh_3)_4$	0.10	rt	16	35%	10%	4:1
3	2.00	$Pd(PPh_3)_4$	0.10	rt	3	35%	30%	1:1
4	3.00	$Pd(PPh_3)_4$	0.10	rt	1.5	41%	35%	1:1
5	3.00	$Pd(PPh_3)_4$	0.05	rt	3	**44%**	**37%**	**1:1**
6	3.00	$Pd(PPh_3)_4$	0.05	0	3	n. r.	-	-
7	3.00	$Pd(PPh_3)_4$	0.05	rt	72	30%	45%	1:2
8	3.00	-	-	rt	72	n. r.	n. r.	-

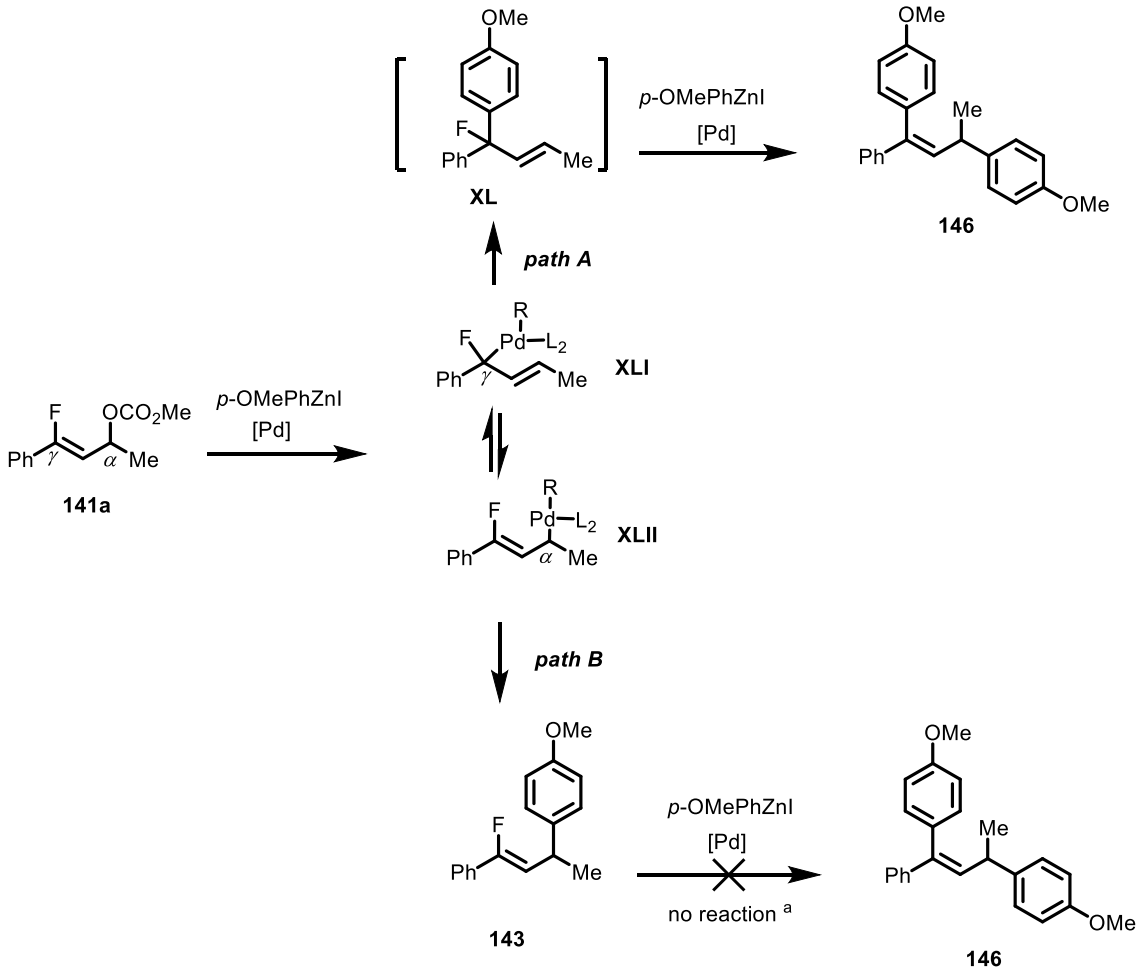
a) *Z/E* stereoisomers ratio > 25:1, isolated yield.

As presented in Table 3, $Pd(dba)_2$ led to no formation of product after 16 hours (entry 1). After switching the catalyst to $Pd(PPh_3)_4$, the desired product **143** was isolated in 35% yield. Moreover, 10% side product **146** could be isolated, likely arising from the double substitution of the nucleophile (entry 2). Increasing the amount of *p*-OMePhZnI **145** to two equivalents expedited the reaction, however, it led to the increased formation of the side product **146** (entry 3). By using three equivalents of ArZnI, the reaction was completed in 1.5 hours, leading to an overall improvement of the yield. However, it also further increased formation of the side

product **146** (entry 4). The highest achievable yield, at 44%, for the desired product was obtained when employing 5 mol% of $Pd(PPh_3)_4$ at room temperature with a reaction time of 3 hours (entry 5). Lowering the reaction temperature to 0 °C led to no reaction under the same condition (entry 6). Extending the reaction time to 72 hours had a detrimental impact on the overall outcome, resulting in an increased formation of **146** and reduced formation of **143**. This suggests that the compound **146** is the thermodynamically favored product (entry 7). An experiment was conducted to compare the reaction in the absence of the catalyst, and no reaction was observed (entry 8).

It is noteworthy that, in all NEGISHI cross-coupling reactions, the diene **144**, which was a predominant side product in SUZUKI cross-coupling reactions, was only detectable in traces via ^{19}F-NMR. This observation suggests the effective suppression of β-H elimination. One plausible explanation is that, during the transmetalation step, organozinc compounds undergo transmetalation to palladium faster than organoboron compounds.[69] Instead, the double substituted product **146** became a competing side product in all reactions. To explain the formation of **146**, two possible mechanistic paths are described in Scheme 40.

After oxidative addition of the Pd catalyst, the aryl nucleophile could attack the Pd center followed by rearrangement to a σ-complex, forming the intermediate **XLI** or **XLII**. Then, the organic group could transfer to the allyl system via rapid reductive elimination forming **XL** or **143**. In the case of path A, the intermediate **XL** is firstly formed as a result of the γ-regioselectivity. Subsequently, another equivalent of the nucleophile could add to the methyl-terminus of the allylic system, with fluoride as a leaving group. In contrast, path B exhibits α-regioselectivity in the initial reaction, yielding the desired product **143**. Upon the addition of another equivalent of the nucleophile to the fluorine-terminus, the side product **146** could be also generated.[45] To prove which path is more plausible, an experiment was carried out using compound **143** as a starting material for the further substitution reaction. The experiment failed to proceed further with just one equivalent of the *p*-OMePhZnI, providing clear evidence that path A is the feasible route (Scheme 40).



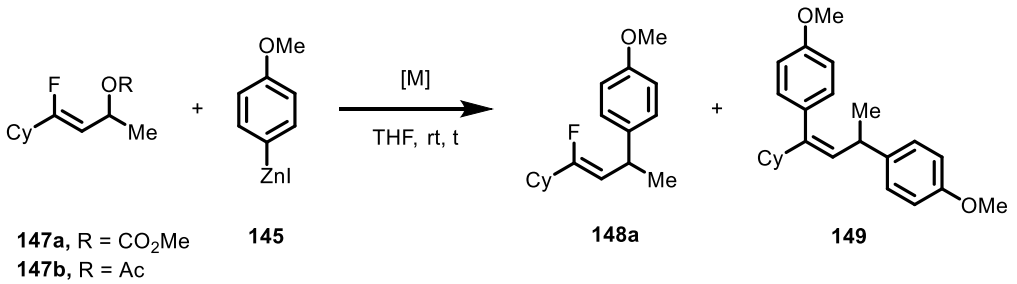
Scheme 40: Possible paths for the formation of the double addition product **146**. a) Reaction condition: 1.00 eq *p*-OMePhZnI **145**, 5 mol% $Pd(PPh_3)_4$, rt, 16 h

In sum, the fluorinated secondary allylic carbonate exhibited enhanced reactivity in NEGISHI cross-coupling reactions, giving in total 81% yield under the optimized reaction conditions. As expected, β-H elimination and defluorination reactions were significantly reduced, compared to the results from SUZUKI cross-coupling reactions. Nevertheless, regioselectivity has emerged as a challenge. The desired product and the side product are isolated in 44% and 37%, nearly in a 1:1 ratio.

The unsatisfactory regioselectivity may be attributed to various factors. On one hand, the benzylic position of the fluoride stabilizes the allylic cation through the phenyl ring's +M effect, thereby promoting the formation of intermediate **XL** (refer to Scheme 40) and resulting in γ - regioselectivity. On the other hand, the intermediate **XL** can be favored due to the reduced steric hindrance of the methyl group compared to the phenyl ring, leading to the γ-regioselectivity.[70]

To test this hypothesis, the following experiments using an alkyl-substituted carbonate were conducted for comparison. As shown in Table 4, the alkyl-substituted carbonate **147a** gave in total largely improved regioselectivity. It is noteworthy that the concentration of the reaction has an impact on the regioselectivity. At the concentration of 0.17 M, the products **148a** and **149** are isolated in 4:1 ratio, with 56% and 13% yield, respectively (entry 1). When the concentration was lowered to 0.10 M, the regioselectivity was improved to 5:1. Additionally, the total yield was increased to 82% (entry 2). Further decrease of the concentration to 0.06 M gave the optimal regioselectivity among all cases, but the total yield dropped to 70% (entry 3). To compare the influence of the leaving group, acetate **147b** was also tested under the same reaction condition. As a result, the reaction showed a slower rate, the regioselectivity was not improved, either (entry 4).

Table 4: NEGISHI cross-coupling reactions between Cy-substituted fluorinated substrate **147** and *p*-OMePhZnI **145**.



147a, R = CO_2Me
147b, R = Ac

145

148a

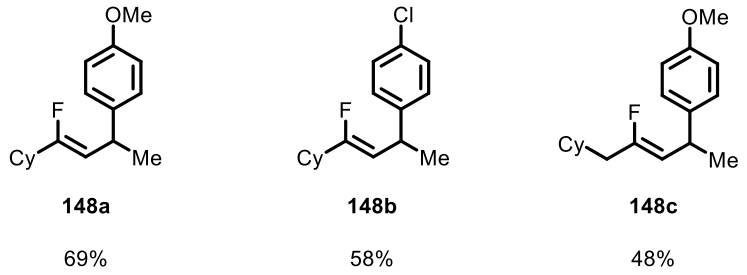
149

#	ArZnI 145 [eq]	R	Catalyst	[eq]	c [M]	t [h]	Yield 148a	Yield 149	Ratio *α:γ*
1	3.00	CO_2Me	$Pd(PPh_3)_4$	0.05	0.17	24	56%	13%	4:1
2	3.00	CO_2Me	$Pd(PPh_3)_4$	0.05	0.10	24	69%[b]	13%	5:1
3	3.00	CO_2Me	$Pd(PPh_3)_4$ [a]	0.05	0.06	24	**65%**	**5%**	**13:1**
4	3.00	Ac	$Pd(PPh_3)_4$	0.05	0.06	72	67%	6%	11:1

a) No reaction was observed when $Pd(dppf)Cl_2$ or $Pd_2(dba)_3$ were used as the catalyst. b) The reaction using chiral starting material under this reaction condition gave the same yield.

When comparing the results from the aryl-substituted carbonate **141a** with those of the alkyl-substituted carbonate **147a**, it becomes evident that the regioselectivity is significantly higher for the alkyl-substituted carbonate **147a**. This affirms our initial assumption that the regioselectivity is influenced by the benzylic position.

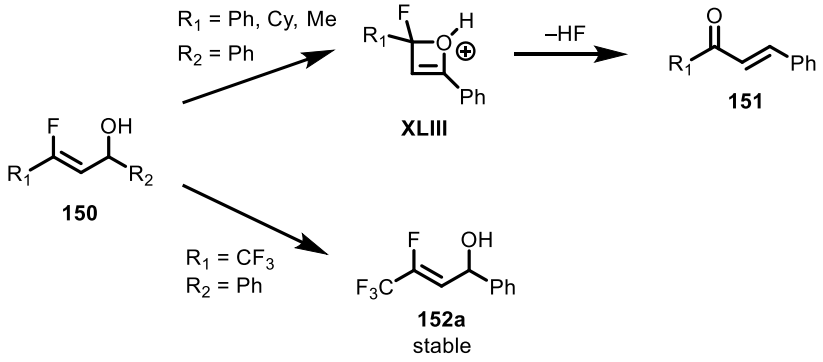
Two other substrates, **148b** and **148c**, were synthesized under the optimized reaction condition. As shown in Scheme 41, the two substrates using different organozinc compound and different alkyl carbonate were yielded in 58% and 48%, respectively. The result of the scope shown limited applicability of this method, since both steric and electronic factors exert influences. Moreover, due to the instability of the zinc reagent, the problem of the reproducibility was also a constant problem for these reactions. Another challenge in this project is also the inability to determine the enantioselectivity, as the scalemic product cannot be separated on common HPLC columns (Scheme 41).



Scheme 41: Scope of the substrates under optimized reaction condition: 3.00 eq ArZnX, 0.10 M, 5 mol% $Pd(PPh_3)_4$ at rt.

Rearrangement of 3-fluoro alcohols

In the previous synthesis of allylic alcohol (Scheme 38), it was noted when R_2 is a phenyl group, the alcohol was instable and decomposed spontaneously to the ketone **151**. In fact, the rearrangement of this compound has been reported.[71] Through isotope labelled experiments, it was revealed that the benzylic alcohol undergoes intramolecular nucleophilic addition to form the cyclic intermediate **XLIII**. Subsequently, HF elimination results in the formation of compound **151**. Surprisingly, this rearrangement was not observed when R_1 is a CF_3 group. The corresponding alcohol proves to be stable at room temperature under air for months. This observation lays the groundwork for the subsequent studies of compound **152** (Scheme 42).



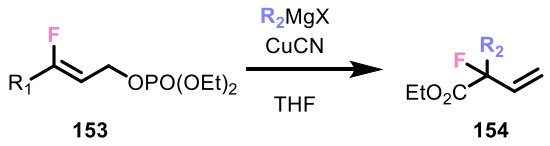
Scheme 42: Plausible explanation for the defluorination of alcohol **150**.

3.2 Project B: Cu-mediated Allylic Substitution of 3-Fluoroallylic Phosphates

Copper (I)-mediated allylic substitutions reactions using allylic phosphates show generally γ - regioselectivity.[72] In combination with chiral allylic phosphate, these reactions can yield highly enantioselective products by transferring chirality. Given the ready availability of chiral alcohols derivatives, this method is frequently applied in asymmetric allylic substitution reactions.[73]

Despite intensive research regarding copper-mediated allylic substitution reactions, the majority of them have focused on primary or cyclic allylic phosphates.[47] Studies on such reactions involving fluorinated allylic phosphates are rather scarce. KONNE *et al.* reported γ-selective allylic substitution reactions using primary fluoroallylic phosphate **153** with various cyanocuprates.[74] YAMAZAKI *et al.* demonstrated that the Cu(I)-cataylzed reaction using trifluoromethyl substituted allylic phosphate **155** also exhibited favorable γ-regioselectivity.[75] Both methodologies enable the installation of tetra-substituted carbon centers containing a C-F or a C-CF_3 bond as final products (Scheme 43).

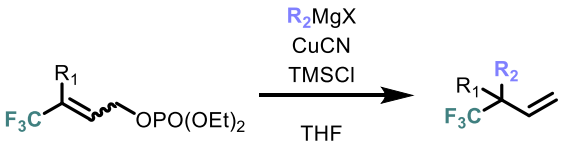
a) Konno *et al.*, 2012



153 **154**

R_1 = CO_2Et; R_2 = alkyl
R_1 = Cy, *n*-C_8H_{17}; R_2 = *n*-Bu

b) Yamazaki *et al.*, 2014



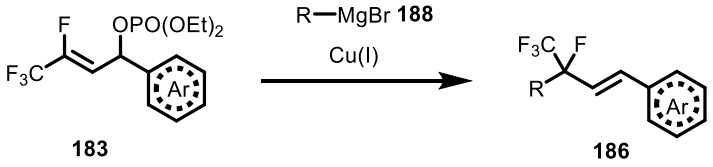
155 **156**

R_1 = CH_2CH_2Ph, *n*-C_6H_{17}, Ph; R_2 = alkyl

Scheme 43: Studies conducted by KONNO and YAMAZAKI *et al.* on allylic substation of primary phosphates **153**, **155** utilizing CuCN and GRIGNARD reagent.

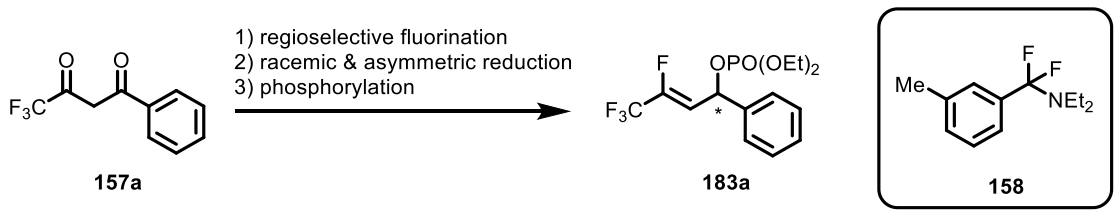
Inspired by these studies, this work aims to study the Cu(I)-mediated allylic substitutions of secondary phosphate **183** using various GRIGNARD reagents. The development of this type of reaction is encouraged by several advantages:

Firstly, the high *γ*-regioselectivity of the reaction enables the generation of a tertiary carbon center **186**, incorporating both a C-F and C-CF_3 substituent on the same carbon atom. So far, synthetic methods of such fluorinated motifs remain quite limited. Secondly, comparing with other organometallic reagents, a wide range of stable and commercially available GRIGNARD reagents are accessible. Additionally, the aryl substituents in phosphate **183** could be easily diversified, which allows the study of electronic influence on the selectivity (Scheme 44).



Scheme 44: Intended study of project B.

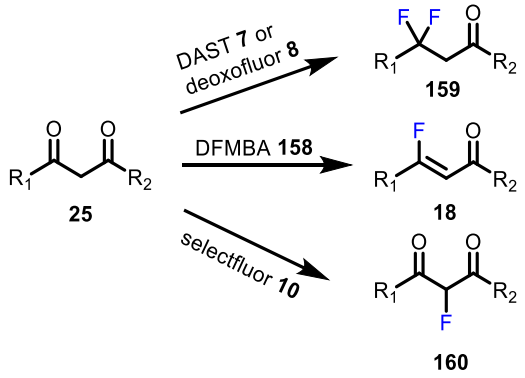
To begin the study, a test substrate should be synthesized through a three-step synthesis. Through reduction and phosphorylation reaction, the phosphate **183a** could be synthesized from the *β*-fluoroenone. The phenyl-substituted fluoroenone should be acquired via the regioselective fluorination using *N*, *N*-diethyl-*α*, *α*-difluoro-*m*-methylbenzylamine (DFMBA, **158**) of the 1,3-dione **157a**. This method was published by SANO *et al.*[76] The trifluoromethyl-*β*-diketones **157a** could be synthesized through CLAISEN condensation reactions, they are often commercially available due to their efficient application in the synthesis of heterocyclic structures in pharmaceutical chemistry (Scheme 45).[77]



Scheme 45: Synthetic plan for the preparation of the fluorinated allylic phosphate **183a**.

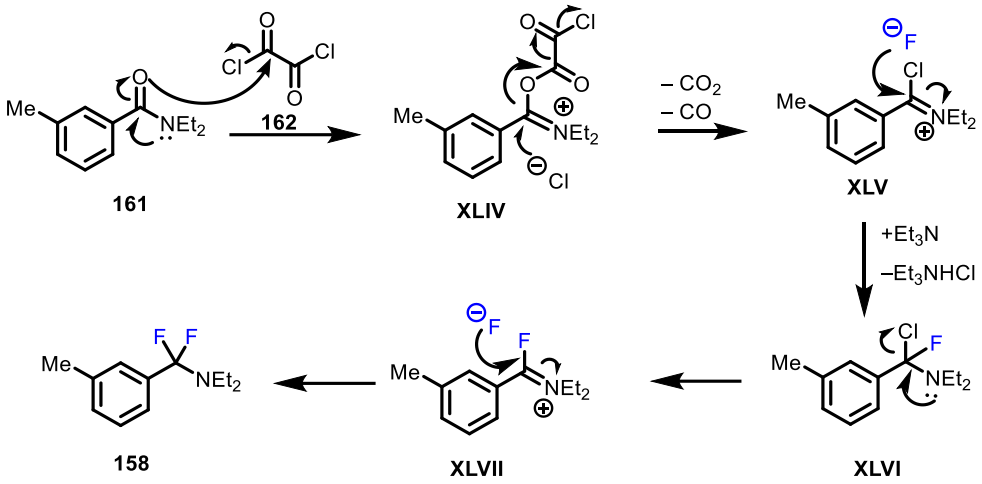
3.2.1 Fluorination of *β*-Diketones

β-Fluoro-*α*,*β*-unsaturated ketones, or *β*-fluoroenones **18**, can be synthesized via the deoxyfluorination of *β*-diketones **25** using DFMBA **158**. This reagent is commonly used for its high regioselectivity. Fluorination reagents like DAST **7** or deoxofluor **8** are although most widely used nucleophilic fluorination reagents, but when reacting with *β*-diketone, they generally lead to polyfluorinated products **159**.[78] While the fluorination of *β*-fluoroenones using electrophilic fluorination reagent like selectfluor® **10**, yields *α*-fluoro-*β*-diketones **160**.[79] Besides the use for *β*-diketones, synthesis of *gem*-difluorides from aldehydes could be also effectively achieved using DFMBA **158** (Scheme 46).[80]



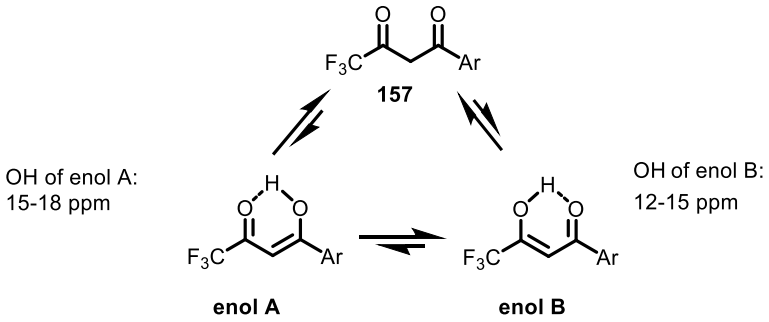
Scheme 46: Fluorination of *β*-diketones **25** using different fluorination reagents shows different selectivity.

The synthesis of DFMBA can be achieved in a one-pot reaction using amide **161**. Similar to the VILSMEIER–HAACK reaction mechanism, the reaction started with the addition of the amide on the oxalyl chloride, forming the intermediate **XLIV**. The removal of the CO and CO_2 is the driving force of the further reaction. Afterwards, with the addition of Et_3N and $Et_3N{\cdot}HF$, the first fluoride can attack the carbonyl, with chloride as the leaving group, forming intermediate **XLV**. In the reaction, Et_3N serves as a base to neutralize the generated HCl in the reaction, giving Et_3NHCl salt as a precipitate. Subsequently, the second addition of the fluoride on the intermediate **XLVII** yields the DFMBA. It can be isolated in 53% through vacuum distillation. Several details should be mentioned regarding this reaction. Firstly, the amide and DFMBA have similar boiling point, making it difficult to separate them through distillation. Secondly, the chemical shift of both compounds in ^1H are close as well, therefore, the calculation of the yield from a mixture containing both compounds is not possible. At last, the isolated DFMBA is a colorless liquid, it can be stored under argon for several months, without decomposing or damaging the glassware. This fact makes DFMBA **158** a very useful fluorination reagent. (Scheme 47).



Scheme 47: Mechanism of the formation of DFMBA **158** from amide **161**. Reaction condition: 1) 3.00 eq **162**, 40 °C, 2 h in CH_2Cl_2. 2) 0.75 eq $Et_3N{\cdot}HF$, 1.34 eq Et_3N, rt, 2 h in CH_2Cl_2.

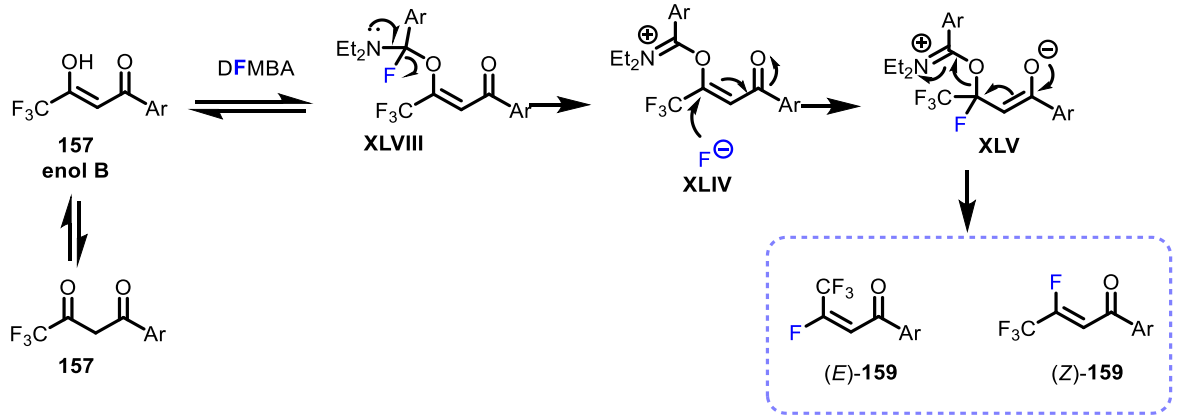
There are several studies explaining the keto-enol equilibrium of aryl trifluoromethyl-*β*-diketones **157**.[81] According to these studies, in polar aprotic solvents, there is a general preference for aryl trifluoromethyl-*β*-diketones in chelated cis-enol form, than in its diketone form. The equilibrium between enol A and enol B depends on the substituents on the aromatic system. The form B is dominant when the substituent is a phenyl ring possessing functional groups like -F, -NO_2, -Me, -OMe etc. Moreover, when the substituent is a pyridyl or a naphthyl group, enol B is preferred as well (Scheme 48).



Scheme 48: Keto-enol equilibrium of **157**, the chemical shift refers to the ^{1}H-NMR experiment in $CDCl_3$.

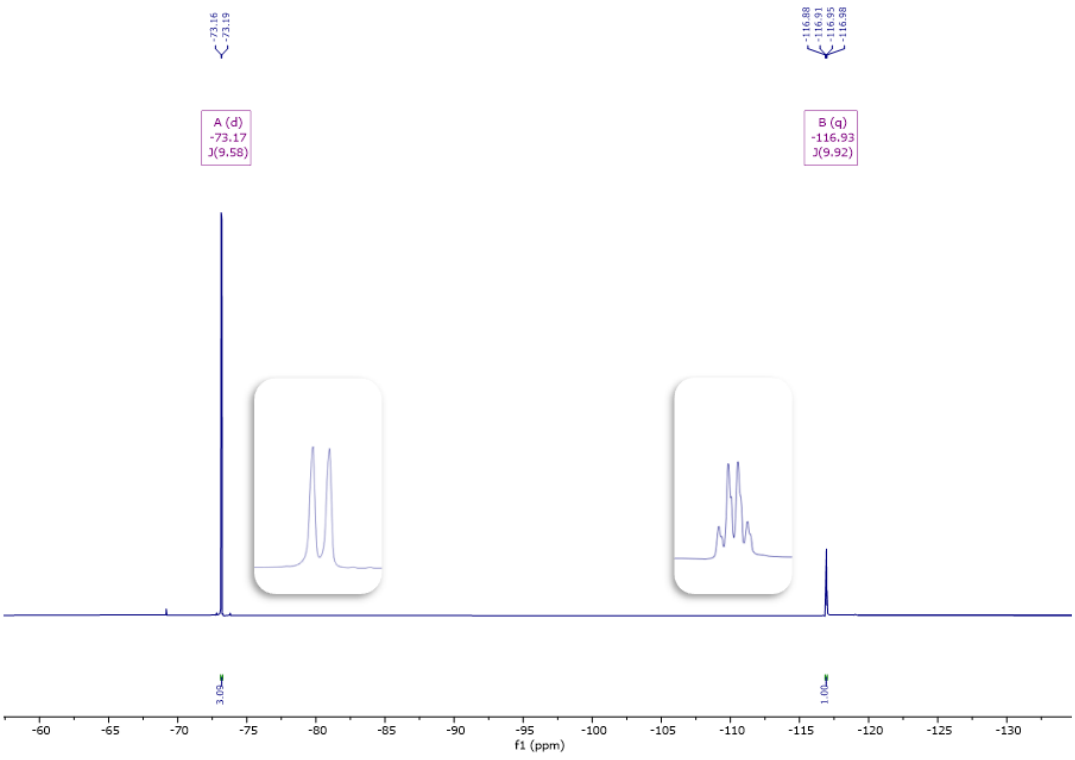
The deoxyfluorination reaction starts with the nucleophilic substitution of the enol **157** on the DFMBA, which serves as an activation step for the enol group. Afterwards, elimination of the fluoride forms the intermediate **XLIV**. Subsequent 1,4-addition of the fluoride and elimination of the amide gives the desired product **159**. Depending on the different reactivity of the enols, fluorination of the aryl trifluoromethyl *β*-diketone **157** could take place at different OH group, generating different fluorination product. The fact that most of the test substrates only yielded

the desired product **159**, shows high preference for this reaction of enol B than enol A. The reaction generally gives the (*Z*) and (*E*)-*β*-fluoroenones as products (Scheme 49).



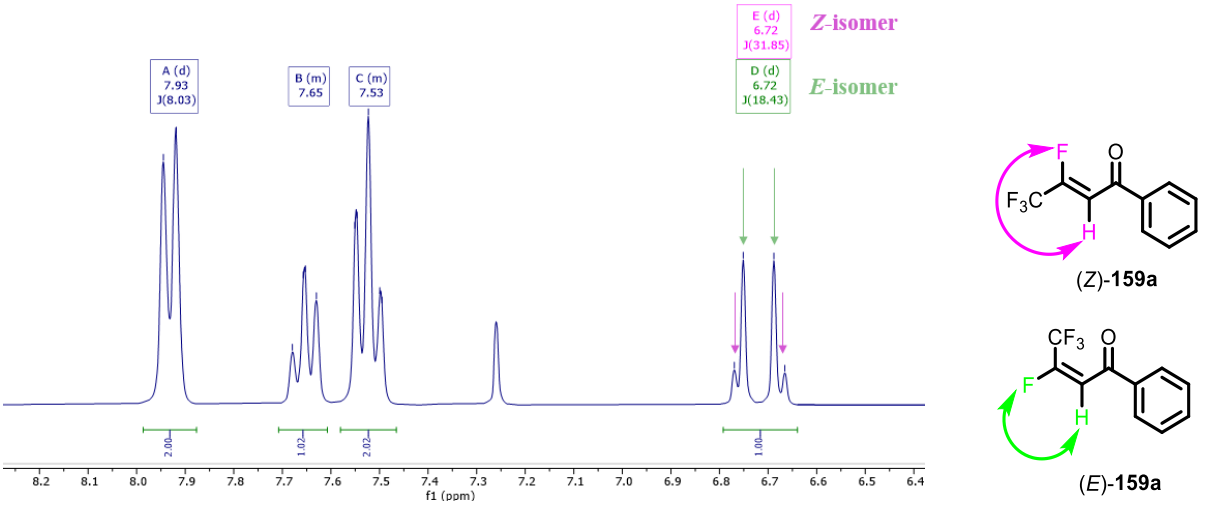
Scheme 49: Mechanism of the deoxyfluorination of *β*-diketone **157** using DFMBA.

The reaction process can be effectively monitored by ^{19}F-NMR, given the clear distinction in chemical shifts between the starting material and product. In ^{19}F spectrum, the CF_3-*β*-diketone **157** appears as a singlet in ^{19}F-NMR, the product *β*-fluoroenone **159** contains a set of signals: the F peak generally appears as quartet, at −113 to −120 ppm, the CF_3 peak as doublet, at −73 to −74 ppm (Scheme 50).



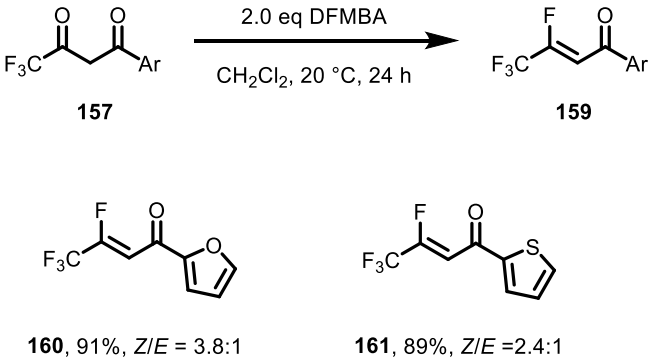
Scheme 50: ^{19}F-NMR at 282 MHz of (*Z*)-*β*-fluoroenone **159**, the F peak generally appears as quartet, at −113 to −120 ppm, the CF_3 peak as doublet, at −73 to −74 ppm.

The *Z*/*E* stereoselectivity is an intriguing aspect of this reaction. As expected, the two stereoisomers can be differentiated by its polarity and NMR spectra. The *Z*-isomer of *β*-fluoroenone is generally less polar than the *E*-isomer, which enables the separation of them through chromatography. Moreover, the chemical shift of the olefin-H in ^{1}H-NMR is slightly different. Also, the peaks of F and CF_3 of *E*/*Z* isomers in ^{19}F-NMR are distinct from each other, they show generally characteristic chemical shift and multiplicity. At last, the ^{3}J-coupling constant of the H-F is characteristic in both isomers. While the H and F are *trans* in the *Z*-isomer, the coupling constant is around 28-32 Hz. In the case of *E*-isomer, the H and F atoms are *cis* across the double bond, leading to a smaller coupling constant, which is around 15-20 Hz. As an example, the ^{1}H-NMR spectrum containing a mixture of *Z*/*E* isomers of compound **159** is presented in Scheme 51.



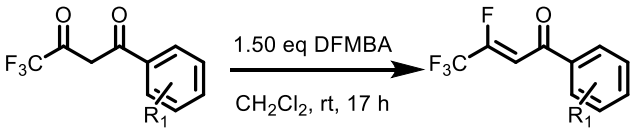
Scheme 51: ^{1}H-NMR at 300 MHz ($CDCl_3$) of a *β*-fluoroenone containing both (*Z*)- and (*E*)-isomers.

HARA *et al.* reported 4 substrates including phenyl-, furanyl-, thionyl- and naphthyl-CF_3-diketone for the fluorination of DFMBA. In all cases, (*Z*)-*β*-diketone was yielded as the main isomer. The two heteroaromatic substrates **160** and **161** are shown in Scheme 52.

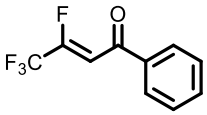


Scheme 52: Fluorination of two heteroaromatic CF_3-*β*-diketone **160**, **161** reported by HARA *et al.* Reaction condition: 2.0 eq DFMBA, 20 °C, 24 h in CH_2Cl_2.

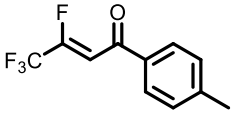
In this study, the scope of the fluorination was broadened. Most of these substrates achieved a yield over 80%. In the case of pyridinyl-diketone **157o**, only 31% of the desired product **159o** was isolated, formation of a poly-fluorinated side product was observed. As a result of the electron-deficient nature of the pyridine ring, C-H fluorination can occur.[82] The *p*-F substituted substrate **159n** exhibited a low yield of 21%, which could be a result of S_NAr reaction, with F^- as a leaving group. Notably, selective fluorination of *α*-substituted cyclic substrates including tetralone **159p**, indanone **159q, 159r** and acenaphthylenone **159s** were also successful. Additionally, based on the *Z*/*E* ratio of the isolated products. The electronic influence of the phenyl ring on the *Z*/*E* stereoselectivity could be compared. The substrates **159c**, **159d**, **159e**, **159i**, **159n**, **159o** which bears EWGs including -Cl, -CF_3, -NO_2, -F, -pyridyl shown slightly higher *Z*/*E* stereoselectivity. While substrates substituted by -CH_3 **159b**, -OMe **159m**, -phenyl **159l**, -furanyl **160**, -thiophenyl **161** (in Scheme 52) at *p*-position resulted in lower *Z*/*E* stereoselectivity. The *α*-substituted tetralone **159p** exhibited a *Z*/*E* ratio of 1.6:1, the lowest among all the substrates. It can be assumed this is a result of the electron rich double bond, which facilitates the isomerization of the *Z*/*E* products. This observed trend of *Z*/*E* stereoselectivity is similar to the study of *β*-fluoroenones reported by WANG *et al.*, in which the double bond is connected to a -CO_2Et group instead of a -CF_3 group (Scheme 53).[15]



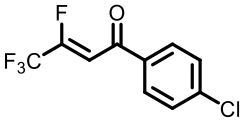
157 **159**



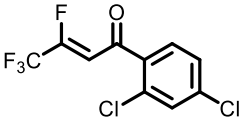
159a, 99%, *Z*/*E* = 5.2:1



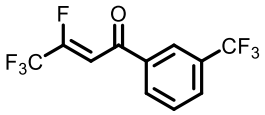
159b, 89%, *Z*/*E* = 4.6:1



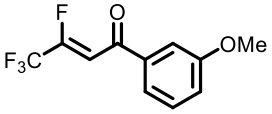
159c, 89%, *Z*/*E* = 5.0:1



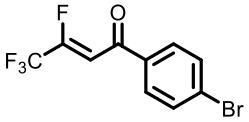
159d, 82%, *Z*/*E* = 5.5:1



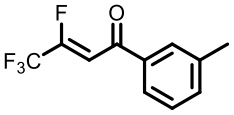
159e, 70%, *Z*/*E* = 6.8:1



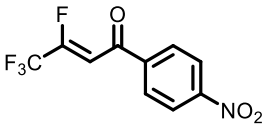
159f, 62%, *Z*/*E* = 5.0:1



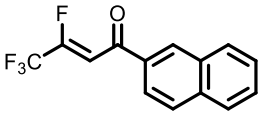
159g, 88%, *Z*/*E* = 4.3:1



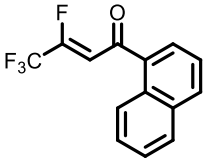
159h, 79%, *Z*/*E* = 5.8:1



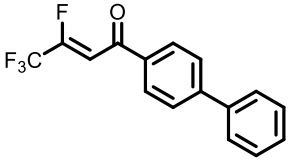
159i, 59%, *Z*/*E* > 25:1



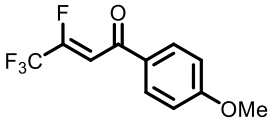
159j, 91%, *Z*/*E* = 5.1:1



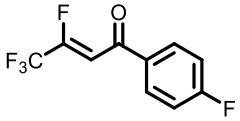
159k, quant, *Z*/*E* = 6.8:1



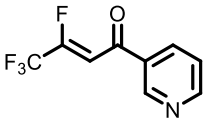
159l, 80%, *Z*/*E* = 4.6:1



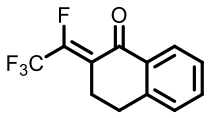
159m, 85%, *Z*/*E* =2.5:1



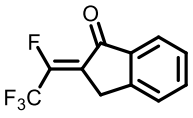
159n, 21%, *Z*/*E* = 5.6:1



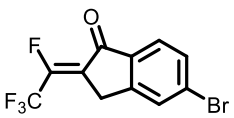
159o, 31%, *Z*/*E* > 25:1



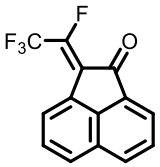
159p, 82%, *Z*/*E* = 1.6:1



159q, 48%, *Z*/*E* =2.6:1



159r, 58%, *Z*/*E* =3.9:1



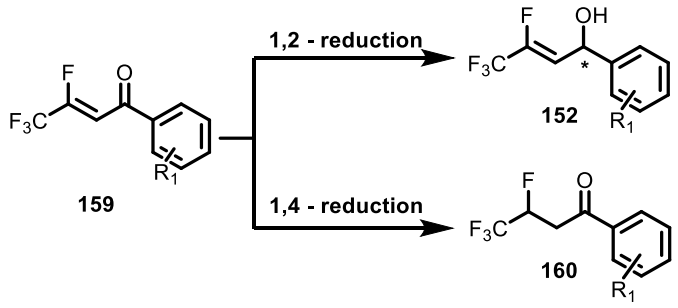
159s, 62%, *Z*/*E* =14.5:1

Scheme 53: Scope of the fluorination of *β*-diketones **157** using DFMBA.

Overall, the fluorination of *β*-diketones **157** using DFMBA demonstrated good functional group tolerance and excellent yield. The synthesized *β*-fluoroenones **159** displayed remarkable stability, as they could be stored over months at −19 °C without undergoing decomposition or isomerization of the double bond.

3.2.2 Racemic and Asymmetric Reduction of *β*-Fluoroenones

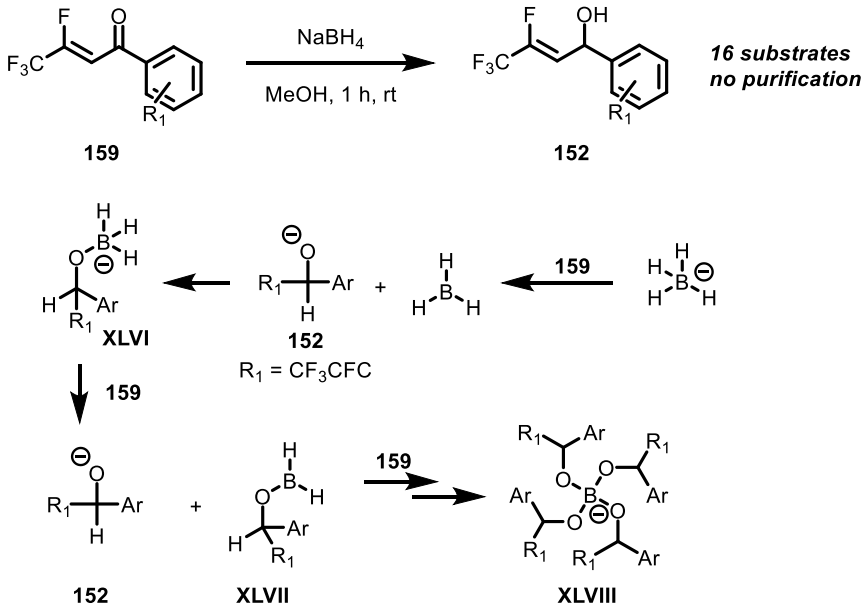
The next step was the selective 1,2-reduction of *β*-fluoroenones. Given the conjugated system of the *α, β*-unsaturated carbonyl, a significant challenge in this reaction lies in the competing 1,4-reduction of the conjugated double bond. Additionally, to facilitate the subsequent synthesis of the chiral phosphates, a highly enantioselective reduction method is essential for introducing the chirality to the molecule (Scheme 54).



Scheme 54: Possible 1,2-reduction and 1,4-reduction reaction of *β*-fluoroenone **159**.

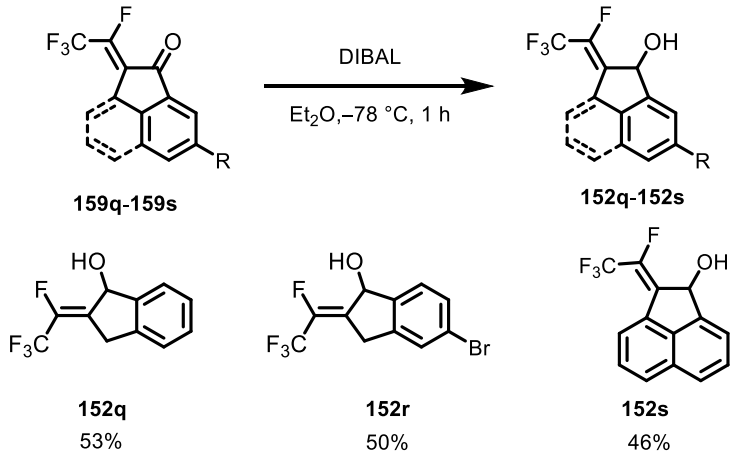
Racemic reduction of *β*-fluoroenones

In our case, using sodium boron hydride in MeOH proved to be efficient for the reduction of the standard substrate **159a**.[67] Therefore, this was set as the standard reaction condition for the other substrates. For most substrates, purification through column chromatography was not necessary. The allylic alcohols could be directly used in the subsequent phosphorylation, the total yield was counted over two steps (Scheme 55).



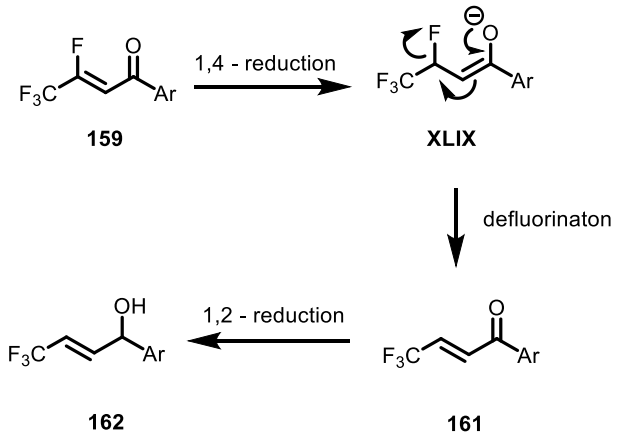
Scheme 55: Mechanism of the racemic reduction of ketone **159** by $NaBH_4$.

For the cyclic substrates, $NaBH_4$ led to no formation of the desired alcohol. Using DIBAL in Et_2O at −78 °C proved to be more effective, resulting in around 50% yield in average (Scheme 56).



Scheme 56: Racemic reduction of cyclic substrates **159q**-**159s** by DIBAL.

With both $NaBH_4$ or DIBAL as a reducing reagent, the alcohol **162** could be observed as a side product in different amounts. In a few cases, the structure can be confirmed by the reported NMR-data.[83] This is somewhat unexpected, since an usual 1,4-reduction would lead to the reduction of the double bond. It can be assumed that, after the 1,4-addition of the hydride, F^- acted as a leaving group, forming the compound **161**. Through a subsequent 1,2-reduction, the alcohol **162** can be formed. The ratio of the side product can be calculated by integration of the peaks in the ^{19}F-NMR. The reason is that the alcohol **162** shows a singlet from the CF_3 group, while the desired product shows two distinct peaks, a doublet and a quartet in 3:1 ratio, as a result of the F/CF_3 coupling (Scheme 57).

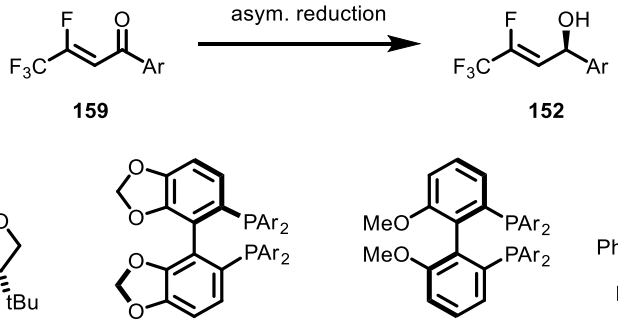


Scheme 57: Possible mechanism for the formation of side product **162**.

Asymmetric reduction of *β*-fluoroenones

To enable the chirality transfer in the allylic substitution, an effective asymmetric reduction from *β*-fluoroenone to chiral alcohol **152** was examined. As presented in Table 5, $Ni(COD)_2$ in the combination with pinacolborane (HBPin) and the oxazolidine ligand **L3** was tested. This method was developed by KOERT *et al.* and can reduce alkyl-substituted *β*-fluoroenones in excellent *ee*. However, this reaction only gave 37% *ee* for CF_3-subsituted-*β*-fluoroenones, with a yield of 12% (entry 1).[16] As next, a method using $Cu(OAc)_2$ and diethoxymethylsilane (DEMS) reported by LIPSHUTZ *et. al* was tested. This method is known for its high regioselectivity and *ee*, as the *in situ* generated Cu-H favors the asymmetric 1,2-reductions of *α*-substituted unsaturated ketones. Two test reactions with ligands **L4** and **L5** were conducted at −25 °C in Et_2O, and gave 27% and 64% *ee,* respectively (entry 2, 3).[55,84]

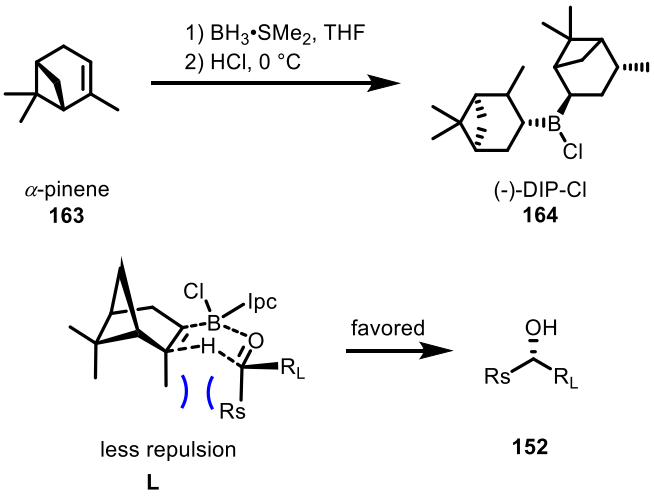
Table 5: Optimization of the asymmetric reduction.



#	Ar	Cat.	L	[eq]	Reagent	Solvent	T [°C]	t [h]	*ee* [%]	Yield [%]
1	Ph	$Ni(COD)_2$	**L3**	0.04	HBPin	toluene	−25	2	37	12
2	Ph	$Cu(OAc)_2 \cdot H_2O$	**L4**	0.03	DEMS	Et_2O	−25	3	27	54
3	Ph	$Cu(OAc)_2 \cdot H_2O$	**L5**	0.03	DEMS	Et_2O	−25	2	64	70
4	Ph	(-)DIPCl **164**	-	1.30	-	THF	rt	17	70	58
5	Ph	-	-	1.00	BINAL	THF	−78	0.5	-	trace
6	Ph	(*S*)-*o*-tolyl-CBS **166a**	-	0.20	$BH_3 \cdot Me_2S$		−30	17	80	54
7	Ph	(*R*)-Me-CBS **166b**	-	0.20	$BH_3 \cdot Me_2S$		−30	0.5	87	72
8	Ph	(*R*)-Me-CBS **166b**	-	0.20	catecholborane		−30	17	-	trace
9	Ph	(*S*)-spiroborate ester **163**	-	0.10	$BH_3 \cdot Me_2S$	THF	rt	1	99	85
10	Naph	(*S*)-spiroborate ester **163**	-	0.10	$BH_3 \cdot Me_2S$	THF	rt	1	97	78

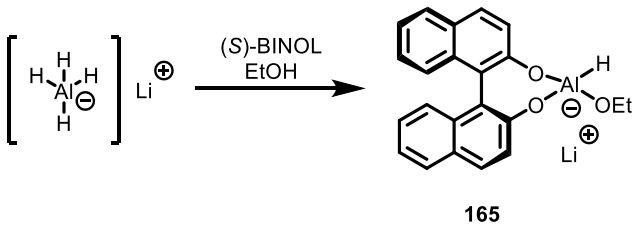
a) The *ee* of the alcohols are determined by their corresponding phosphate, as it allows optimal separation on HPLC column.

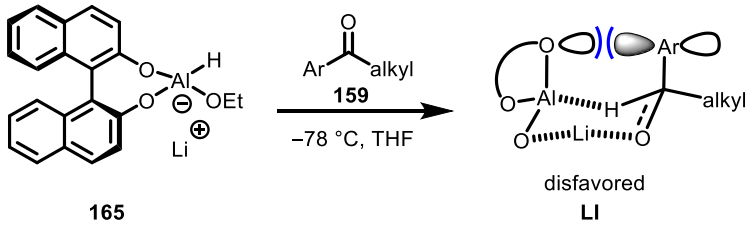
As the *ee* was unsatisfactory, a more targeted reduction method was investigated. BROWN *et al.* have extensively demonstrated the remarkable utility of DIP-Chloride **164** for the reduction of aryl alkyl ketones with predictable stereochemistry.[85] KITAZUME *et al.* reported the use of commercially available DIP-chloride for reducing *α*, *β*-unsaturated ketones containing a CF_3 group. This reaction was carried out at room temperature in THF for 17 hours, resulting in the alcohol **152** with 70% *ee* (entry 4) (Scheme 58).[84,86]



Scheme 58: a) Synthesis of DIP-Cl **164** from *α*-pinene **163**; b) Transition state of the transfer hydrogenation favors formation of the (*R*)-enantiomer.

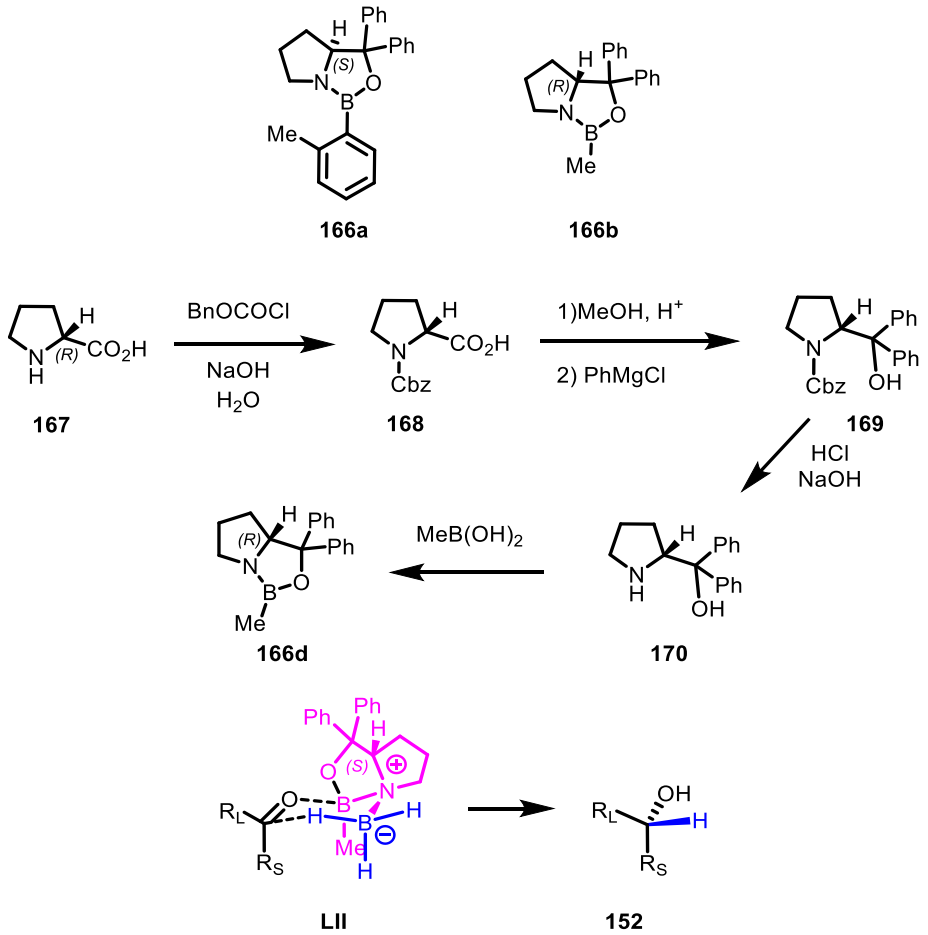
NOYORI's BINAL reagent **165** is a classic chiral hydride reagent for enantioselective reduction of aryl trifluoromethyl ketones. BINAL **165** can be prepared by using lithium aluminum hydride with equimolar amounts of BINOL and a simple alcohol. The *n*-*π** repulsion between the oxygen non-bonding orbital and the LUMO of the aryl group is disfavored, which results in the enantioselective reduction of the ketone **159**. The 1,3-diaxial repulsion could raise with the increasing the bulkiness of the alkyl group but the effect of the *n*-*π** repulsion is more dominant, as shown in the intermediate **LI** (Scheme 59).[87]





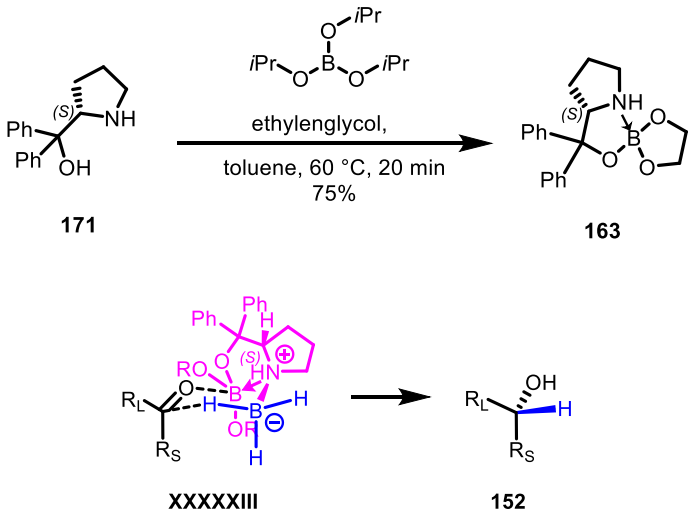
Scheme 59: *In situ* prepared BINAL through and transition state of the reduction mechanism.[88]

Given that the CBS reagent **166** is widely employed as one of the most common asymmetric reducing agents for ketones, various conditions of CBS-reduction using $BH_3 \cdot Me_2S$ or catecholborane were explored. The reaction employing (*S*)-*o*-tolyl-CBS **166a** as a catalyst resulted in 80% *ee* (entry 6). Using (*R*)-Me-CBS catalyst **166b** at −30 °C gave 87% *ee* with a 72% yield, and the reaction was completed within 30 minutes (entry 7). Changing to catecholborane led to no formation of the desired product (entry 8) (Scheme 60).



Scheme 60: The hydride is delivered via a six-membered cyclic transition state in CBS reduction.[69]

Finally, using a catalytic amount of (*S*)-spiroborate ester **163** and one equivalent $BH_3 \cdot Me_2S$ gave the desired alcohol **152** in 99% *ee* with 85% yield (entry 9). The naphthyl-substituted fluoroenone **159j** was reduced under the same reaction condition, which gave 97% *ee* and 78% yield (entry 10). This method was reported by ORTIZ *et al.* for asymmetric reduction of acetophenone and other aromatic ketone at room temperature.[89] The catalyst **163** can be synthesized from the commercially available amino alcohol **171** in one step. Unlike the air and moisture sensitive CBS catalysts, the synthesized spiroborate ester is a solid can be stored under air at room temperature, making it an extremely useful reagent.[90] It can be assumed that, the reduction reaction using the spiroborate ester **163** goes through a similar transition state as CBS-reduction, giving only one preferred enantiomer (Scheme 61).

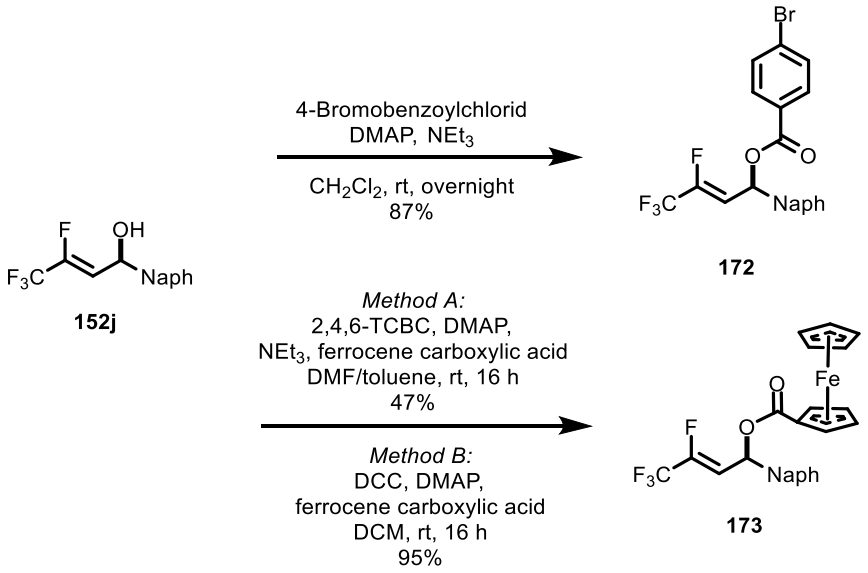


Scheme 61: Synthesis of (*S*)-spiroborate ester **163** and proposed mechanism of the transition state.

Determination of the absolute configuration of alcohol 152

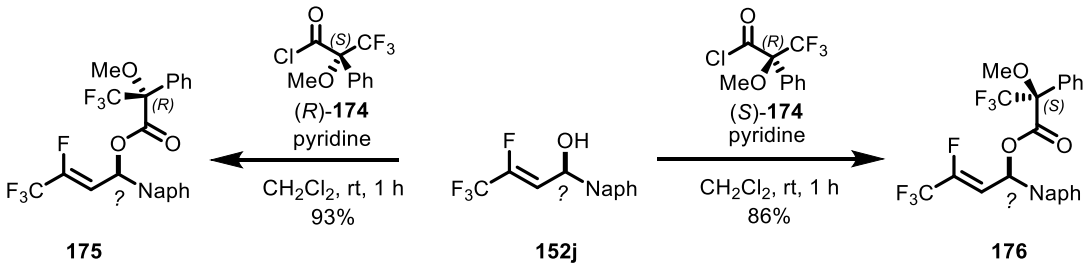
As next, the absolute configuration of the alcohol **152** after the reduction using (*S*)-spiroborate ester should be determined. Crystallization of the chiral biphenyl-substituted alcohol **152l,** *p*-NO_2Ph alcohol **152i** and naphthyl alcohol **152j** were attempted, since they were the only solids among all the alcohols. However, despite numerous attempts, suitable crystals for X-ray diffraction analysis could not be obtained.

To increase the possibility of crystallization, further reactions to functionalize the allylic alcohol **152j** were conducted. Unfortunately, the benzoyl bromide **172** was obtained as a viscous oil. YAMAGUCHI esterification of the alcohol with ferrocene carboxylic acid yielded only 47% product, whereas esterification using dicyclohexylcarbodiimid (DCC) achieved a higher 95% yield. The resulting compound **173** was put into crystallization process. However, the only crystals obtained was identified as dicyclohexylurea, which was possibly resulted from hydrolyzation of the DCC residue during the crystallization process (Scheme 62).[91]



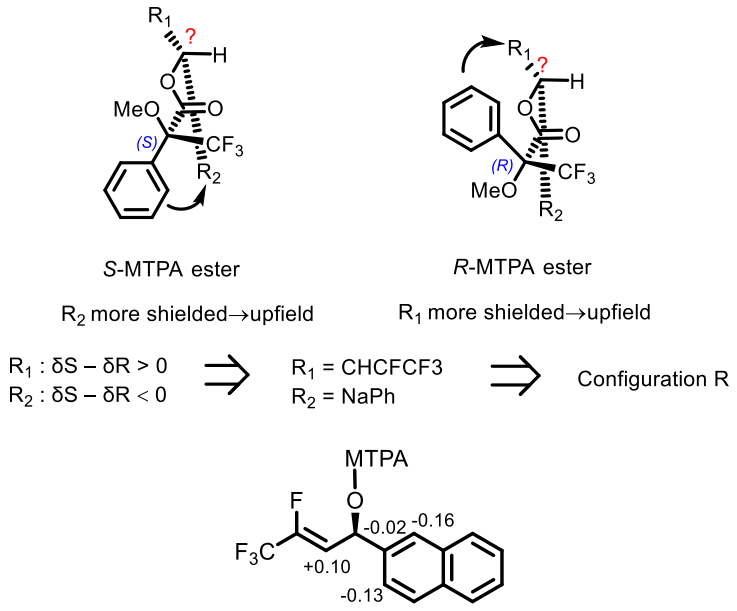
Scheme 62: Further functionalization of the allylic alcohol **152j** to facilize the crystallization.

As crystallization proved challenging, the classic MOSHER-ester analysis method was considered. The key principle of this method is that the aryl group of the MOSHER's ester impose an anisotropic, magnetic shielding effect on protons residing above (or below) the plane of the aryl ring. Two diastereomers **175**, **176** were successfully obtained using (*R*)- and (*S*)- 3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride (MTPA-Cl) **174**, yielding 86% and 93%, respectively (Scheme 63).



Scheme 63: Synthesis of the diastereomers **175**, **176** using (*R*)-MTPA-Cl and (*S*)-MTPA-Cl.

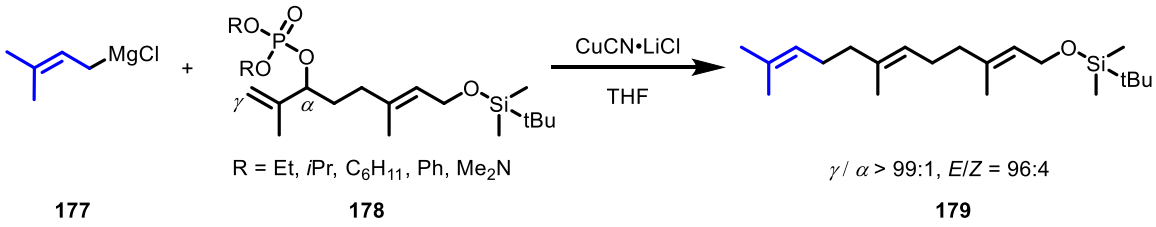
In the (*S*)-MTPA ester, the R_2 group which is closer to the phenyl group is more shielded and would shift to the upfield in the spectrum. While in the (*R*)-MTPA ester, the R_1 group would shift to the upfield. According to the NMR analysis, R_1 is the CHCFCF3 group, and R_2 the naphthyl group, the absolute configuration of the chiral carbon is (*R*). This result is in accordance with the prediction by ORTIZ.[92] Through the comparison of the proton and fluorine signals of esters **176 (*S*)** and **175 (*R*)** [$\Delta\delta^{SR}$ ($=\delta^{S}-\delta^{R}$)] the absolute configuration of the stereocenter was determined as ***R*** (Scheme 64).



Scheme 64: Principle of MOSHER-ester analysis and ^{1}H-NMR-shift of the MTPA-ester **175**, **176**.

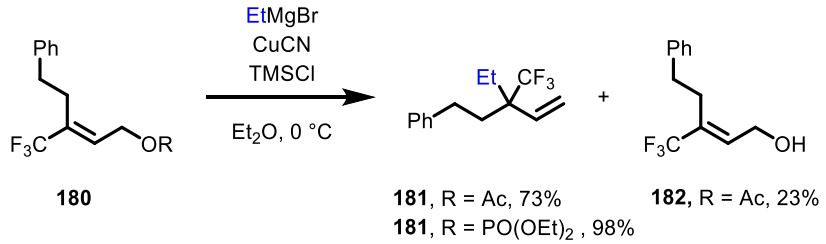
3.2.3 Phosphorylation of 3-Fluoroallylic Alcohols

The next step involves the phosphorylation of the obtained allylic alcohols. Typically, a phosphate ester serves as the leaving group in copper-mediated allylic substitution reactions, as it solves the problem of stereo- and regioselectivity. The C-O bond can be easily cleaved due to the acidity of the phosphoric acid.[52] For instance, YAMAMOTO *et al.* demonstrated the effectiveness of various phosphate ester derivatives **178** as leaving groups in these reactions, comparing the performance with acetate, chloride or mesylate (Scheme 65).[72]



Scheme 65: Employment of phosphate ester derivatives **178** as leaving groups in Cu(I) mediated allylic substitutions, reported by YAMAMOTO *et al.*

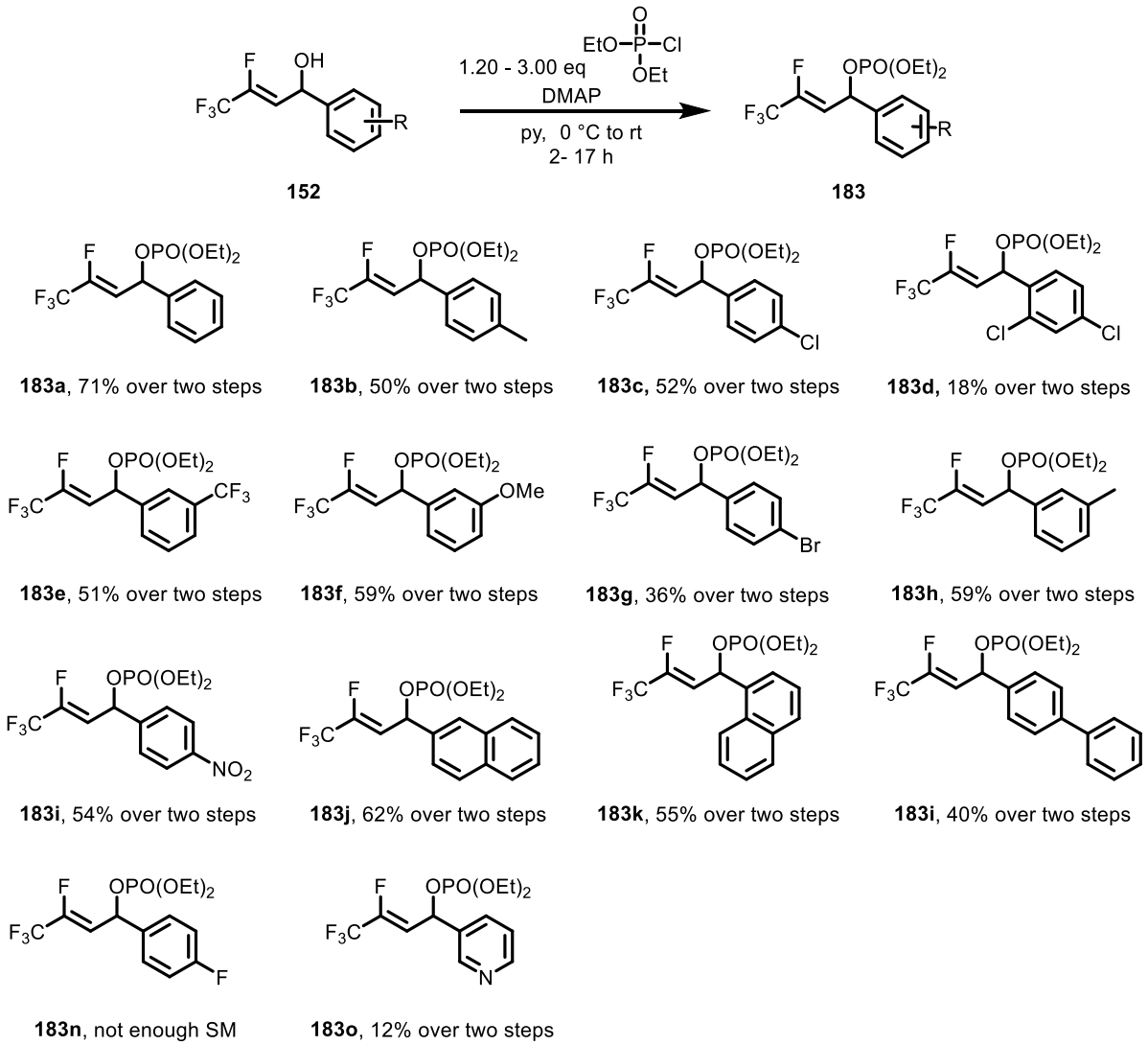
For copper-catalyzed allylic substitution of CF_3-substituted allylic alcohol derivatives, YAMAZAKI *et al.* could demonstrate that phosphate ester as a leaving group led to no formation of the deacetylated allylic alcohol as side product (Scheme 66).[75]



Scheme 66: Employment of phosphate ester as leaving group for CF_3-substitued allylic substrate, reported by YAMAZAKI *et al.*

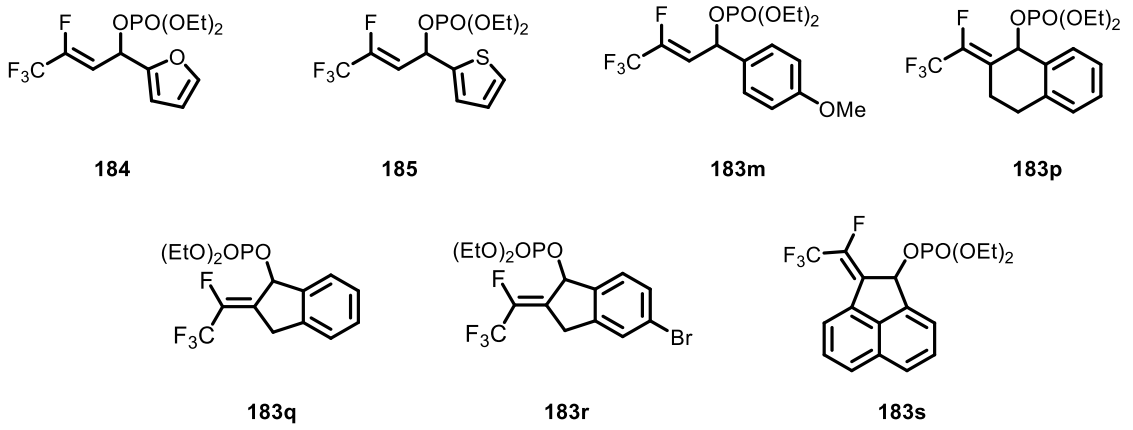
In this study, diethyl chlorophosphate was utilized to convert the alcohol to the corresponding diethylphosphate esters, as it is readily commercially available. This compound can be also prepared by the chlorination of diethylphosphite using CCl_4, known as the ATHERTON-TODD reaction. Diethyl chlorophosphate acts as a highly electrophilic phosphorylating reagent, with nucleophilic substitution occurring at the phosphorus atom.

In the phosphylation reaction, pyridine was employed as the base, along with a catalytic amount of DMAP. The amount of diethyl chlorophosphate employed varied between 1.20 to 3.00 equivalents, depending on the reaction process. The overall reaction yield reached around 50% over two steps, including the reduction reaction by $NaBH_4$. (*Z*)-allylic alcohols **152** served as the starting material, no isomerization of the double bond was observed after the phosphorylation. In most cases, 10-20 % starting materials could be recovered. Stronger bases such as Et_3N, *n*-BuLi, as well as less nucleophilic bases like DIPEA, were also tested, but none of them led to an improved yield. The challenge of the reaction also lies on the reproducibility, which is likely due to the instability of the phosphates on silica gel. With yields of 18% and 36%, the di-Cl-substituted substrate **183d** and Br-substituted **183g** exhibit lower yields than the average. S_NAr could be a side reaction for these substrates, given that -Cl and -Br can act as leaving groups. The low yield of substrate **183o** might be a result of the nucleophilic nitrogen in the pyridine ring. (Scheme 67).



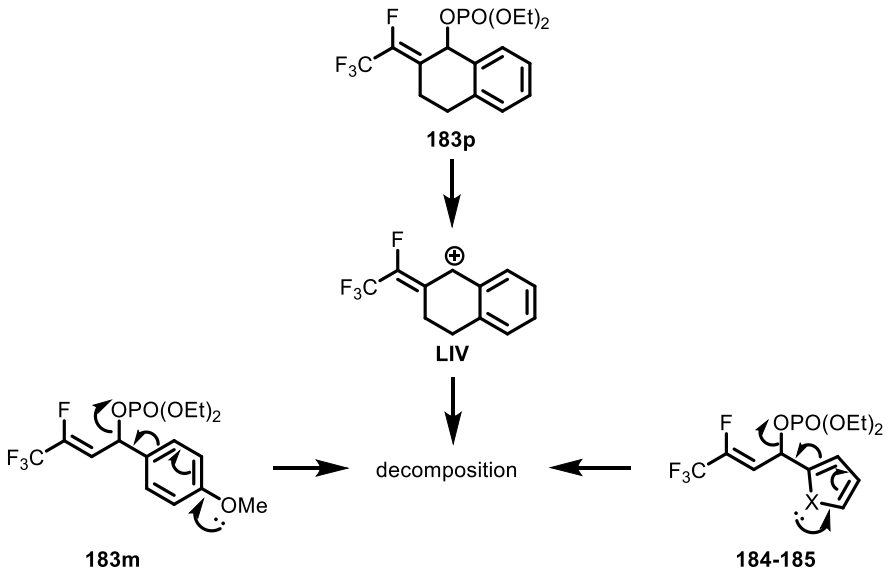
Scheme 67: Scope of the phosphorylation under the standard reaction condition.

Substrates **184**, **185** which are substituted with an electron-rich heteroaromatic ring, **183m** and *α*-substituted cyclic phosphates **183p**-**183s** were not successfully obtained. According to ^{31}P-NMR revealed absence of the phosphate esters, indicating decomposition of the desired product. Notably, the failure to obtain *p*-OMe-substituted phosphate **183m**, in contrast to the successful synthesis of *m*-OMe-substituted phosphate **183f**, suggests that the electron-rich system contributes to the instability of the phosphate (Scheme 68).



Scheme 68: Substrate that were not obtained due to failed phosphorylation.

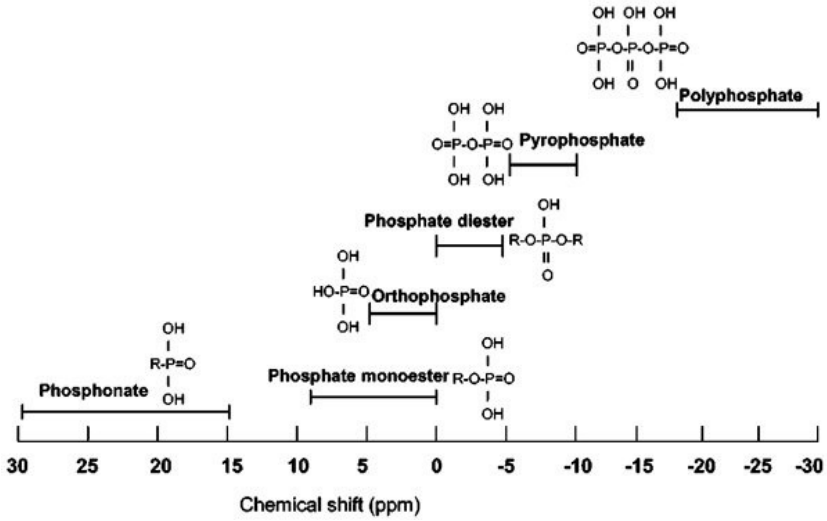
A proposed mechanism for the decomposition of several phosphates is described. For the phosphate **183m** and the heteroaromatic substituted substrates **184**, **185**, the phosphate is instable as a result of the electron rich system. For the cyclic phosphate, the cation intermediate **LIV** is well-stabilized due to the phenyl ring and the adjacent methylene group. This mechanism is also representative for the decomposition of the other cyclic phosphates **183q**-**183s** (Scheme 69).



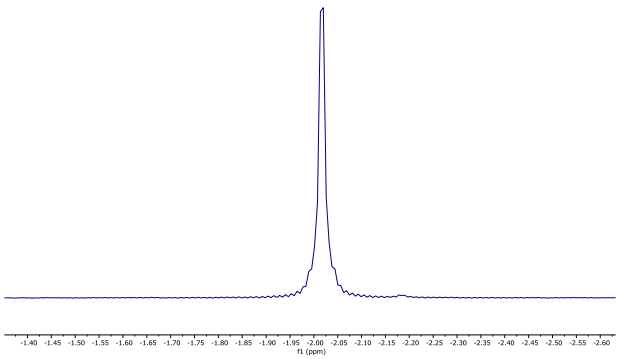
Scheme 69: Possible explanation for the decomposition of several phosphates.

As commonly known, ^{31}P-NMR is one of the frequently employed NMR techniques, since ^{31}P also processes a nuclear pin of 1/2. In addition to ^{1}H and ^{19}F-NMR measurements, ^{31}P-NMR was also measured for these substrates. As a result, the chemical shift of these phosphate esters falls within the range of −1.21 to −2.02 ppm, which corresponds to the known value of the phosphate diester in the literature (Scheme 70a). ^{31}P has only one naturally occurring stable isotope, it produces rather small but recognizable NMR signals. Notably, phosphorus also exhibits a relatively high gyromagnetic ratio 17.2 MHz/T, about 40% of ^{1}H (42.6 MHz/T), resulting in a resonance frequency about 60% lower than that of ^{1}H (Scheme 70b).[93]

a)



b)



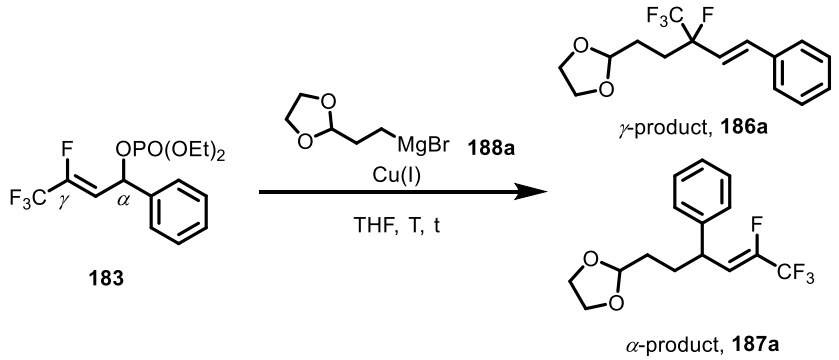
Scheme 70: a) ^{31}P chemical shift range of common P-containing functional groups based on literature. [94] b) The chemical shift of the obtained phosphate esters **183a-183o** falls within the range of −1.21 to −2.02 ppm, as a singlet.

3.2.4 Cu(I)-mediated Allylic Substitution of 3-Fluoroallylic Phosphates

The primary focus of this study is to establish a methodology for the copper-mediated allylic substitution of the obtained 3-fluoroallylic phosphates. To achieve optimal *γ*-selectivity in such reactions, low-order organocuprates are commonly employed.[95]

To optimize the reaction condition, the phosphate **183** was used as the model substrate. The acetal-protected GRIGNARD reagent **188a** was chosen as the model nucleophile for two main reasons: firstly, it allows further functionalization of the acetal moiety; secondly, it enhances the polarity of the products, facilitating easier preparative handing of the formed products. This increased polarity is advantageous for the optimal separation of the *α*- and *γ*-isomers on the column, particularly given the relatively nonpolar nature of the FTF group.

Table 6: Optimization of the copper(I)-mediated allylic substitution.



#	Cu(I)	[eq]	RMgBr [eq]	T [°C]	t [h]	Ratio *γ* : *α*	Yield [%]
1	CuCN	2.20	2.20	−40	2	3:1	76
2	CuCN·2LiCl	2.20	2.20	−40	1	**>25:1**	**87**
3	CuCN·2LiCl	2.20	2.20	−30	2	14:1	85
4	CuCN·2LiCl	2.20	2.20	−78	17	-	-
5	CuCN·2LiCl	1.10	1.10	−40	1	15:1	86
6	CuCN·2LiCl	0.20	2.20	−40	1	5:1	89
7	CuCN·2LiCl	1.10	2.20	−40	1	4:1	90
8	CuI·2LiCl	2.20	2.20	−40	1	8:1	96
9	-	-	2.20	−40	1	-	-

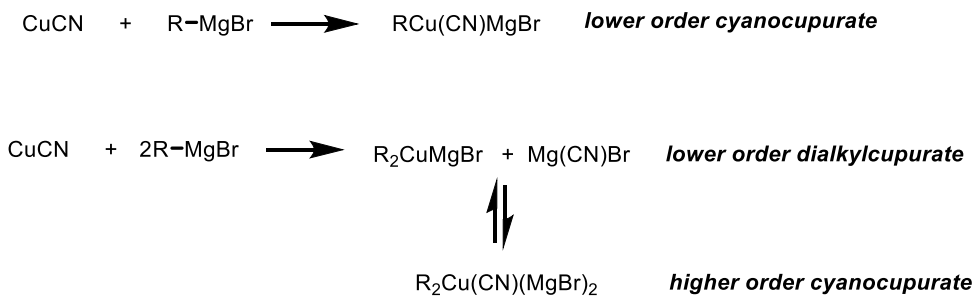
Initially, 2.20 equivalents of CuCN at −40 °C in THF was applied, which gave 76% yield, with a ratio of the *γ*- and *α*- product in 3:1. It turned out that the *α*- and *γ*- regioisomers are still inseparable. But the ratio of these two products can be confirmed by the integration of the corresponding signals in ^{19}F-NMR. The distinguishment is possible since the $C_{(sp3)}$-F of the FTF

group has a characteristic chemical shift between −170 and −180 ppm in the ^{19}F-NMR, while the olefin−F from the *α*-product lies between −130 to −140 ppm (entry 1).

Several studies from YANAGISAWA *et al.*[72] and KNOCHEL *et al.* [96] showed that utilization of CuCN·2LiCl led to enhanced regioselectivity. The CuCN·2LiCl solution can be generally prepared through drying CuCN and LiCl under vacuum at 120 °C, the 1 M solution in THF is also commercially available. Under the same reaction conditions, changing the copper source to CuCN·2LiCl improved the yield to 87% and the *γ*-regioselectivity to >25:1 (entry 2). When the reaction temperature was raised to −30 °C, the reaction showed decreased formation of *γ*-product (entry 3). Decreasing the reaction temperature to −78 °C inhibited the reaction (entry 4). Reducing the organocopper reagent to 1.10 eq showed a negative impact on the regioselectivity (entry 5). Furthermore, application of catalytic amounts of CuCN·2LiCl or altering the ratio of copper reagent to GRIGNARD reagent lowered the regioselectivity (entry 6 and 7), which indicates the stoichiometric use of a cuprate type RCu(CN)MgBr as optimal (entry 2). CuI·2LiCl could improve the total yield to 96% but proved to be less effective in terms of regioselectivity (entry 8). A control experiment using only GRIGNARD reagent was conducted and no formation of product could be observed (entry 9) (Table 6).

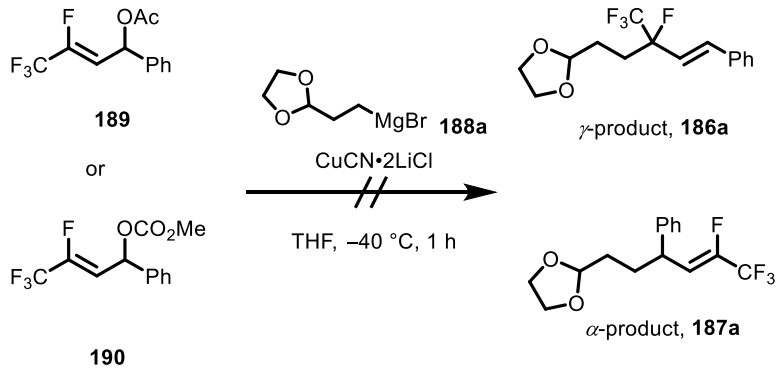
The results suggest that formation of the stochiometric amount of cyanocuprates are essential for the high *γ*-regioselectivity. Also, LiCl plays an important role in the regioselectivity. While the effect of LiCl on organocuprate reagent remains in debate, it is generally accepted that LiCl has a positive effect on the solubility of CuCN in organic solvents. Studies from LEI *et al.* provided evidence for the formation of a key intermediate $[CuX_2]^-$ Li^+ ate complex in solution.[97]

Utilization of 1:1 ratio of the CuCN and GRIGNARD reagent forms only the lower order cyanocuprate RCu(CN)MgBr at −40 °C, when the temperature is raised to −30 °C or above, the formation of the dialkylcupurate $R_2CuMgBr$, a GILMAN-type reagent would increase. Besides, when two equivalents of the GRIGNARD reagent are present, the dialkylcupurate is mainly formed, formation of higher order cyanocupurate or other cuprate species are also possible, but the nature of the exact reactive species remain unclear.[98] Several studies suggest an equilibrium between the dialkylcuprate $R_2CuMgBr$ and the higher order cyanocuprate $R_2CuCN(MgBr)_2$ in solution. Studies from BÄCKVALL *et al.* shows that lower order and higher order cyanocuprates preferably lead to the *γ*-regioselectivity, while dialkylcupurate gives the *α*-regioselectivity (Scheme 71). [51,99]



Scheme 71: Formation of possible reactive cuprate species from CuCN and GRIGNARD reagent.

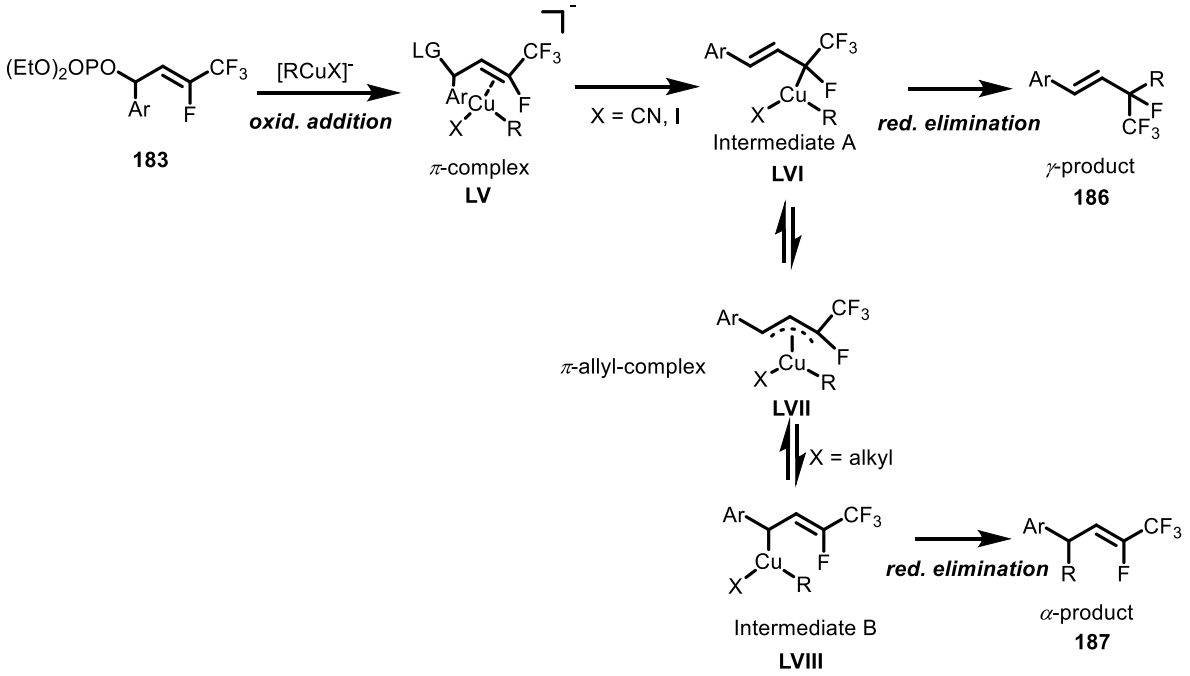
To compare the effectiveness of phosphate as leaving group, allylic acetate **189** and carbonate **190** were synthesized and tested under the same reaction condition. No formation of the α- or γ- product could be observed (Scheme 72).



Scheme 72: No formation of desired product when using acetate or carbonate as a leaving group.

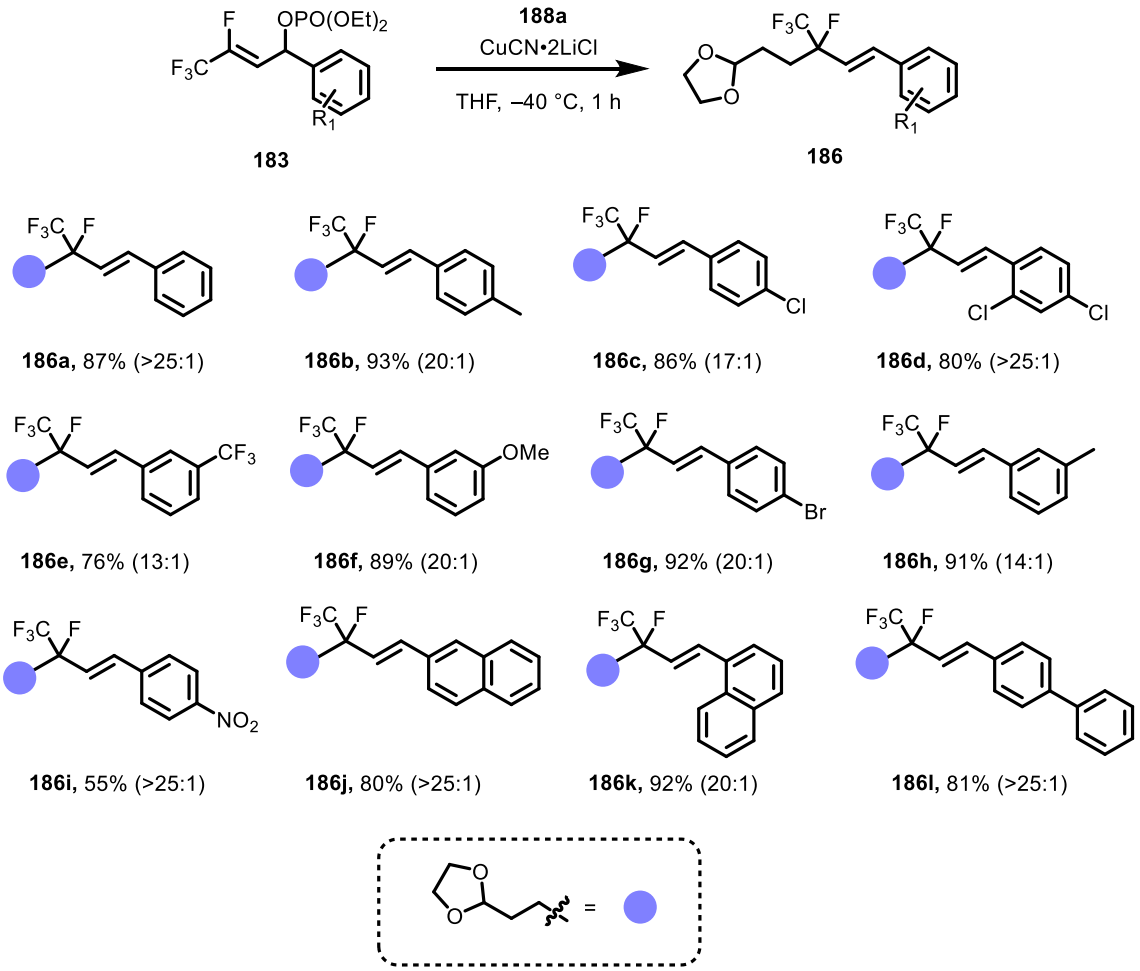
Based on the experimental results, the following mechanism can be postulated: followed by the S_N2'-selective oxidative addition of the organocuprate, Cu(I) adds to the double bond of the allylic substrate, forming initially the π-complex **LV**. Subsequently, the intermediate A **LVI** is formed. However, it can isomerize through the π-allyl-complex **LVII** to intermediate B **LVIII**. Reductive elimination of the intermediate A and B forms the corresponding regioisomer. When X is a non-transfer group like CN^- or I^-, the electron withdrawing group enhances the rate of reductive elimination against the rate of isomerization between the allyl intermediates. In this way, the γ-product **186** is preferably formed. When X is an alkyl group, in the case of dialkylcupurate, the rate of reductive elimination is much slower, so that the intermediate A can isomerize to the intermediate B through the π-allyl intermediate **LVII**, leading to formation of the α-product **187**.[100] Moreover, when X was changed to iodide, the regioselectivity was lowered, suggests that both intermediates were formed in this case. Notably, in our case, the stochiometric amount of the RCu(CN)MgBr gives the optimal regioselectivity, as it is essential to drive the equilibrium to the intermediate A.[53] The regioselectivity also depends on the other factors including reaction temperature and solvent. In general, due to the difficulty of isolation

and characterization of these intermediate complexes, the exact reaction mechanism remains controversial (Scheme 73).



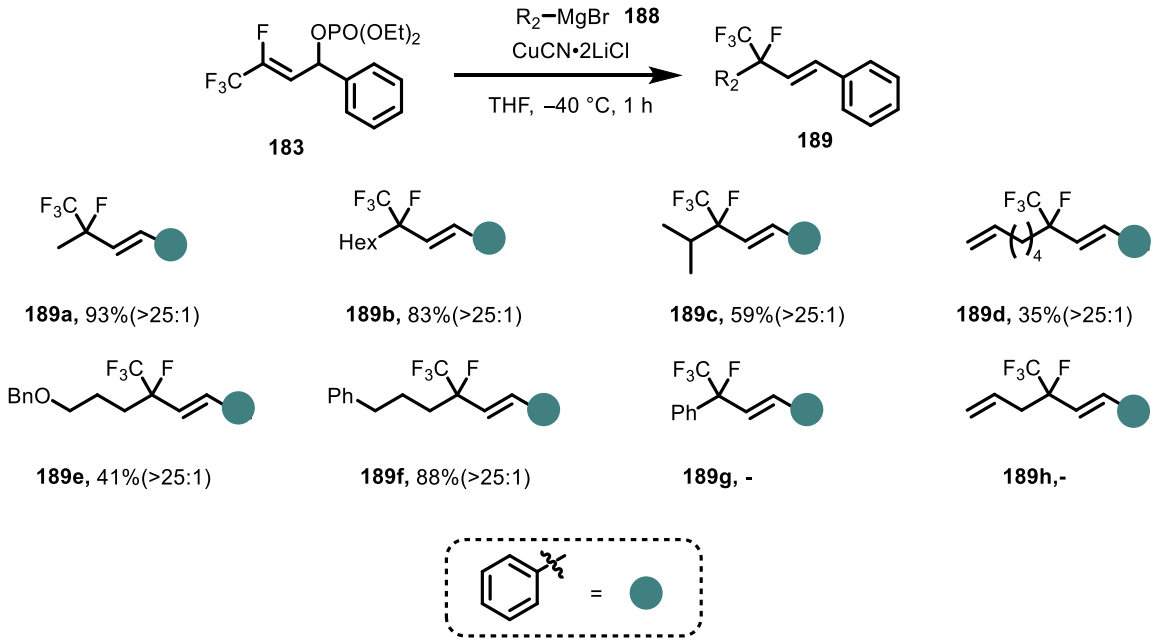
Scheme 73: Postulated reaction mechanism for the different α- and γ- regioselectivity.

Subsequently, phosphates bearing different substituents on the phenyl ring and two naphthyl-phosphates were examined. In total, very good yield, ranging from 80%-93% were achieved. An exception was found with the substrate bearing a NO_2-group **186i**, which only led to 55% yield. This is somehow not surprising, as it is a known fact that GRIGNARD reagent could add to an aromatic nitro group, an example is the BARTOLI indole synthesis.[101] Moreover, good regioselectivities ranging from 13:1 to greater than 25:1 were achieved for all cases, only substrates **186e** and **186h** showed lowered γ-regioselectivity. The ratio of the γ:α product was determined by ^{19}F-NMR. It is also noteworthy that only *E*-stereoisomers were obtained for all substrates, showing the high *E*-stereoselectivity of this reaction (Scheme 74).



Scheme 74: Scope of the allylic substitution using various phosphates **183**. Isolated yields, the ratio of the *γ*:*α* product was determined by ^{19}F-NMR and presented in parenthesis.

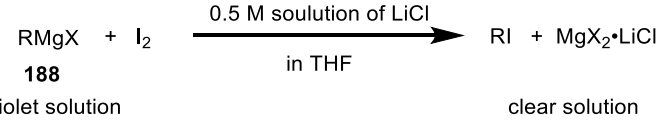
A range of GRIGNARD reagents **188** was also examined under the optimized conditions. The *γ*-regioselectivity proved to be excellent across all cases. HexylMgBr, MeMgBr and Ph(CH$_2$)$_3$MgBr exhibited very good yield, reaching 83%, 88% and 93%, respectively, which demonstrates the excellent tolerance of alkyl GRIGNARD reagents. *i*PrMgBr resulted in a 59% yield, likely attributed to the steric hinderance of the isopropyl group during oxidative addition of the *i*PrCu(CN)MgBr. HexenylMgBr and BnO(CH$_2$)$_3$MgBr resulted in 35% and 41% yield, respectively, which is rather low in comparison. Notably, no desired product was observed when allylMgCl was employed. Defluorination of the CF$_3$ group was observed when PhMgBr was applied, forming the *gem*-difluoro side product based on the ^{19}F-NMR analysis. This type of Cu-*β*-F elimination forming *gem*-difluoroalkenes has been reported (Scheme 75).[102]

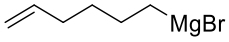


Scheme 75: Scope of the allylic substitution using various GRIGNARD reagents. Isolated yields, the ratio of the *γ*:*α* product was determined by ^{19}F-NMR and presented in parenthesis.

One of the challenges is that the GRIGNARD reagents must be prepared freshly and titrated before use. The titration is performed according to the standard procedure developed by KNOCHEL *et al.*[103] This method is based on the rapid reaction between organometallic compounds and iodine in THF saturated with LiCl. A sharp color change from purple to a colorless, clear solution at the end point of the titration could be easily observed, indicating the complete consumption of iodine. The concentration of the GRIGNARD reagent is determined from the amount of consumed iodine and the GRIGNARD reagent, the results are shown in Table 7. The titration should be conducted carefully, as the concentration must be determined precisely to ensure the 1:1 ratio of the GRIGNARD and the CuCN·2LiCl in the reaction.

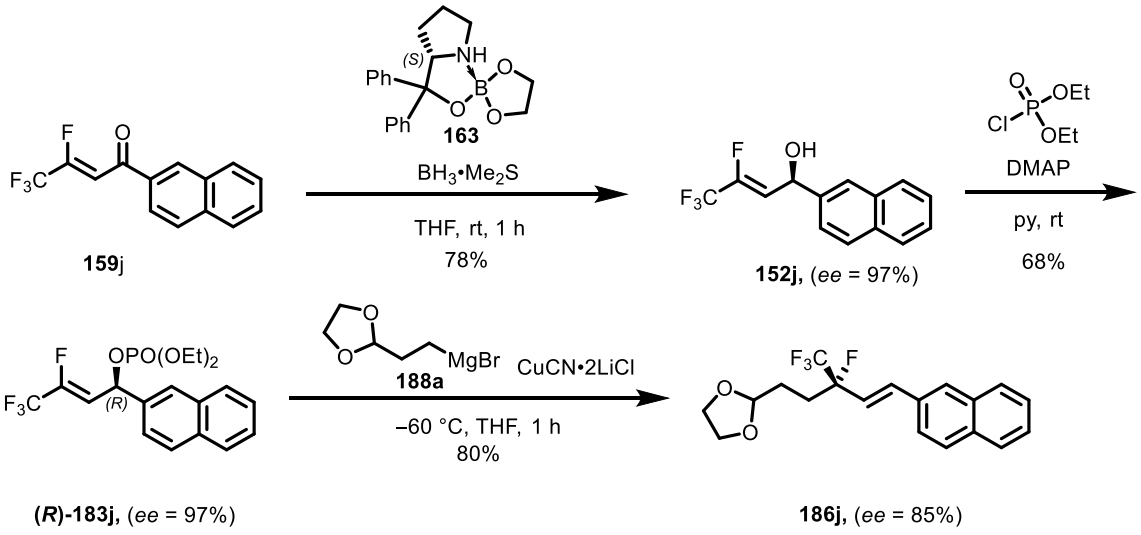
Table 7: Determination of the concentration of the GRIGNARD reagents.



#	RMgX	Determined Concentration [M]
1	MeMgBr	1.83
2	HexylMgBr	1.23
3	*i*-PrMgBr	1.18
4		0.26
5	$Ph(CH_2)_3MgBr$	1.02
6	$BnO(CH_2)_3MgBr$	0.58
7	PhMgBr	1.00
8		1.53

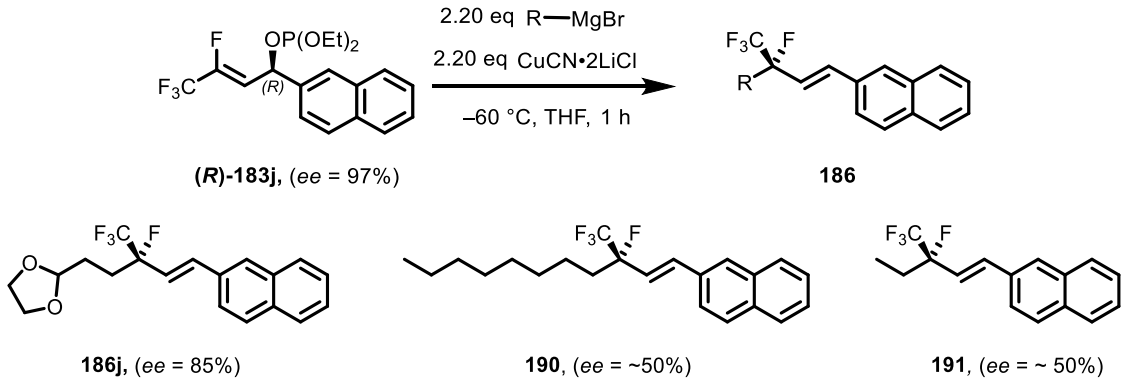
Chirality transfer of the chiral allylic phosphate to FTF group

Transferring chirality from enantiopure substrate to chiral product is one of the common methods to generate enantiomerically-enriched molecules. The synthesis of chiral FTF stereo center remains unexplored. Therefore, the chirality transfer from the allylic phosphate to the corresponding FTF-allylic compound was studied for (*R*)-**183j**, as it allows optimal enantiomer analysis of the phosphate and the product **186j** on chiral HPLC. The synthesis of the corresponding chiral phosphate (*R*)-**183j** followed the procedure which was previously described. As the enantiomers of the alcohol **152j** were not separable on HPLC, the *ee* of the chiral alcohol was not able to be measured. Alternatively, the *ee* of the phosphate was confirmed by HPLC, with 97% *ee* as the result. With the standard conditions at −40 °C, utilizing 2.20 eq GRIGNARD reagent und 2.20 eq CuCN·2LiCl, 78% *ee* was obtained. When the temperature was lowered to −60 °C, 85% *ee* could be achieved. Rasing the amount of the both reagents to 3.00 equivalents didn't have significant influence on the *ee*. A further decrease of temperature was not considered since the reaction does not proceed at −78 °C (Scheme 76).



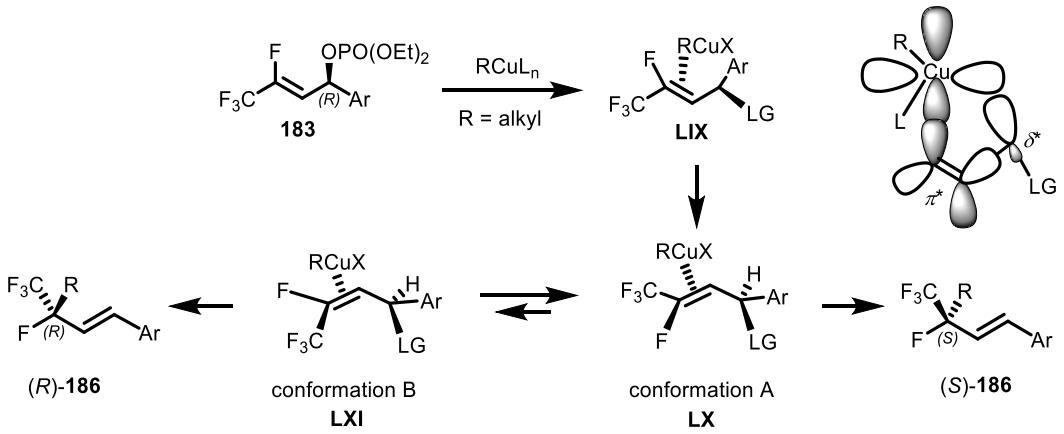
Scheme 76: Asymmetric synthesis of FTF compound **186j** through chirality transfer from phosphate **183j**.

Ethyl GRIGNARD and octyl GRIGNARD were also tested under the same reaction conditions. In both cases, the *ee* resulted in the range of 50%. The exact ratio of the compound **190** and **191** couldn't be determined, since the two peaks of the enantiomers in HPLC diagram partially overlapped. The separation on HPLC couldn't be improved due to the low polarity of the compounds (Scheme 77).



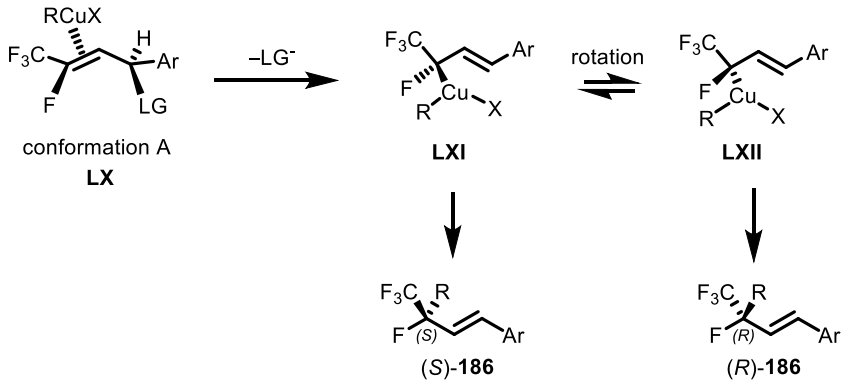
Scheme 77: Asymmetric synthesis of FTF compounds **186j**, **190** and **191.**

According to the study from COREY and BOAZ, the symmetry of the d orbital from Cu allows simultaneous binding between the d orbital and the π^* orbital of the C=C bond, as well as the overlapping between d orbital and the antibonding orbital σ^* of the C-O bond. This leads to the *anti*-S_N2' selectivity of the stereochemistry. In our case, the alkyl group of the RCu(CN)MgBr should attack the allylic system *anti* to the phosphate group, the oxidative addition of the cuprate follows on the backside of the plane, forming the intermediate **LIX**. In the transition state, both conformations A and B are possible, while conformation A **LX** is more favored due to less allylic 1,3-strain. This principle has been described to control the stereochemistry of open-chain substrates in S_N2' allylic substitution.[104] As a result, if R is an alkyl group, the acquired FTF center should be (*S*)-configurated (Scheme 78).



Scheme 78: Favored formation of (*S*)-**186** over (*R*)-**186** and the orbital interaction between *d*-Cu and π^* (C=C) and σ^* (C-X).

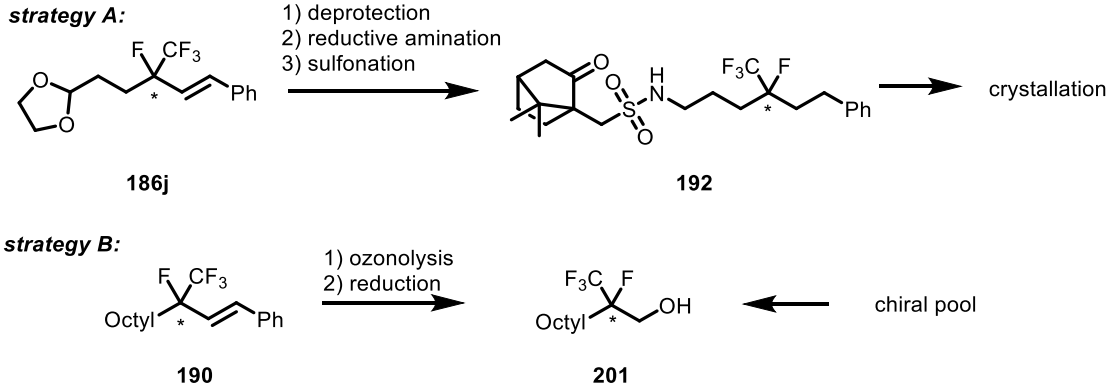
To explain the stereoerosion of this reaction, the following reaction mechanism can be proposed. After the oxidative addition, forming the Cu(III) species, the η^1-Cu-allylic complex A **LXI** is formed. The intermediate A **LXI** can isomerize through rotation to intermediate A' **LXII**, as the two intermediates are similar in energy. The equilibration between the two intermediates could account for the loss of chiral information. BÄCKVALL *et al.* conducted intensive on the origin of the loss of chiral information in Cu(I)-catalyzed allylic substitution reactions. They pointed out that electron-deficient substrates led to a higher loss of chiral information, which is in accordance with the electron-deficiency of the tetra-fluorinated allylic substrates. Also, an electron-deficient allyl ligand on copper(III) is more reluctant to participate in reductive elimination, which leads to a longer equilibration time for the allyl intermediates, resulting in greater loss of chiral information (Scheme 79).[98,105]



Scheme 79: Possible explanation for the observed stereoerosion.

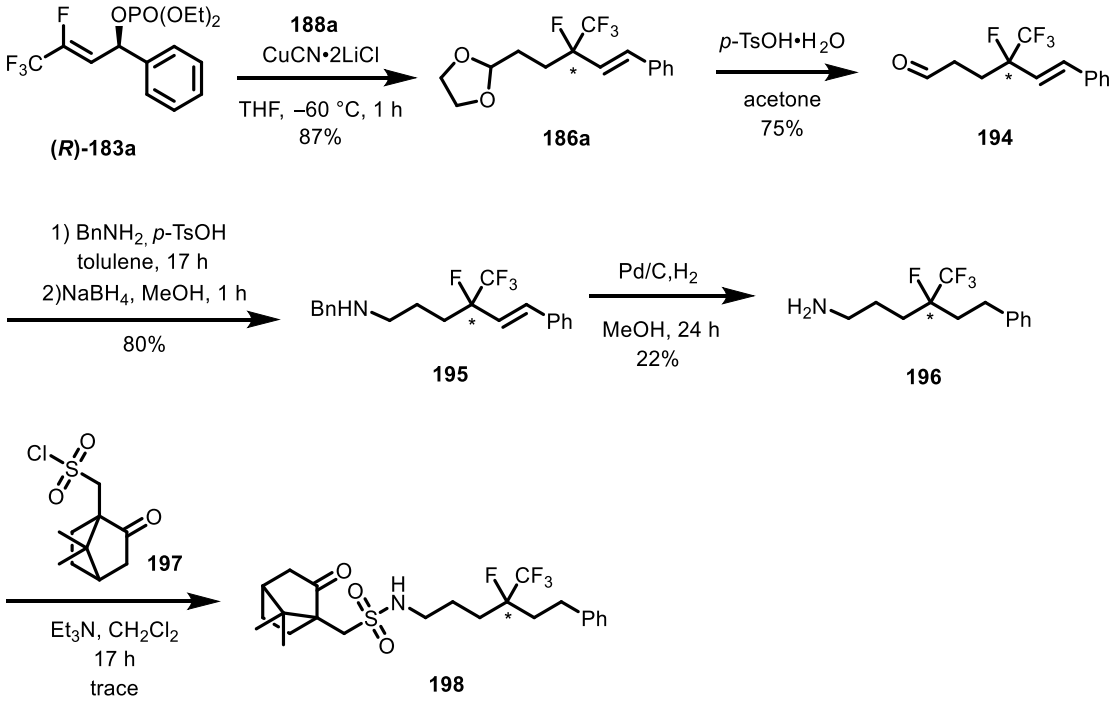
Determination of the FTF stereocenter

To determine whether the FTF stereocenter corresponds to the predicted configuration, two strategies were considered. Strategy A is based on the single-crystal X-ray diffraction analysis. It begins with the deprotection of the acetal group in compound **186j**, subsequent reductive amination using $BnNH_2$ should yield the Bn-protected amine. In the final step, the amine could be converted to sulfonyl amide **192**, suitable for crystallization. Strategy B involves converting the octyl-substituted compound to chiral alcohol **201** through ozonolysis and reduction, which can be synthesized from the chiral pool. By comparing optical rotation values or employing chiral chromatographic analysis, it would be also possible to determine the absolute configuration of the stereocenter (Scheme 80).



Scheme 80: Two strategies employed to determinate the FTF stereocenter.

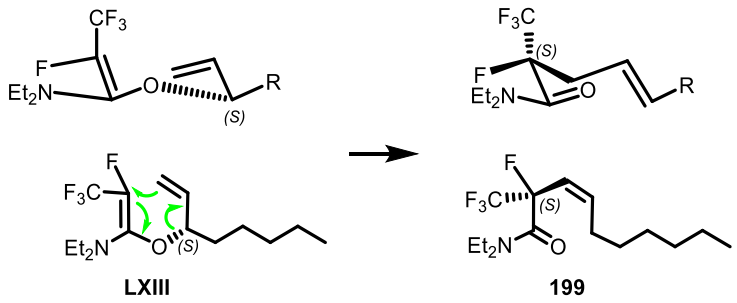
The results of strategy A are shown below. Deprotection of the acetal in acetone produced aldehyde **194** in 75% yield. Reductive amination conducted using a DEAN-STARK apparatus resulted in 80% yield. The hydrogenation of the Bn-protected amine **195** using Pd/C gave the primary amine **196** in only 22%, along with a side product in which only the double bond was hydrogenated. After sulfonation using (+)-campher-10-sulfonylchlorid **197**, only a trace of product **198** could be obtained, which was not possible to be crystallized. The synthesis sequence was not scaled up since strategy B resulted in better results (Scheme 81).



Scheme 81: Strategy A to determine the absolute configuration of FTF stereocenter.

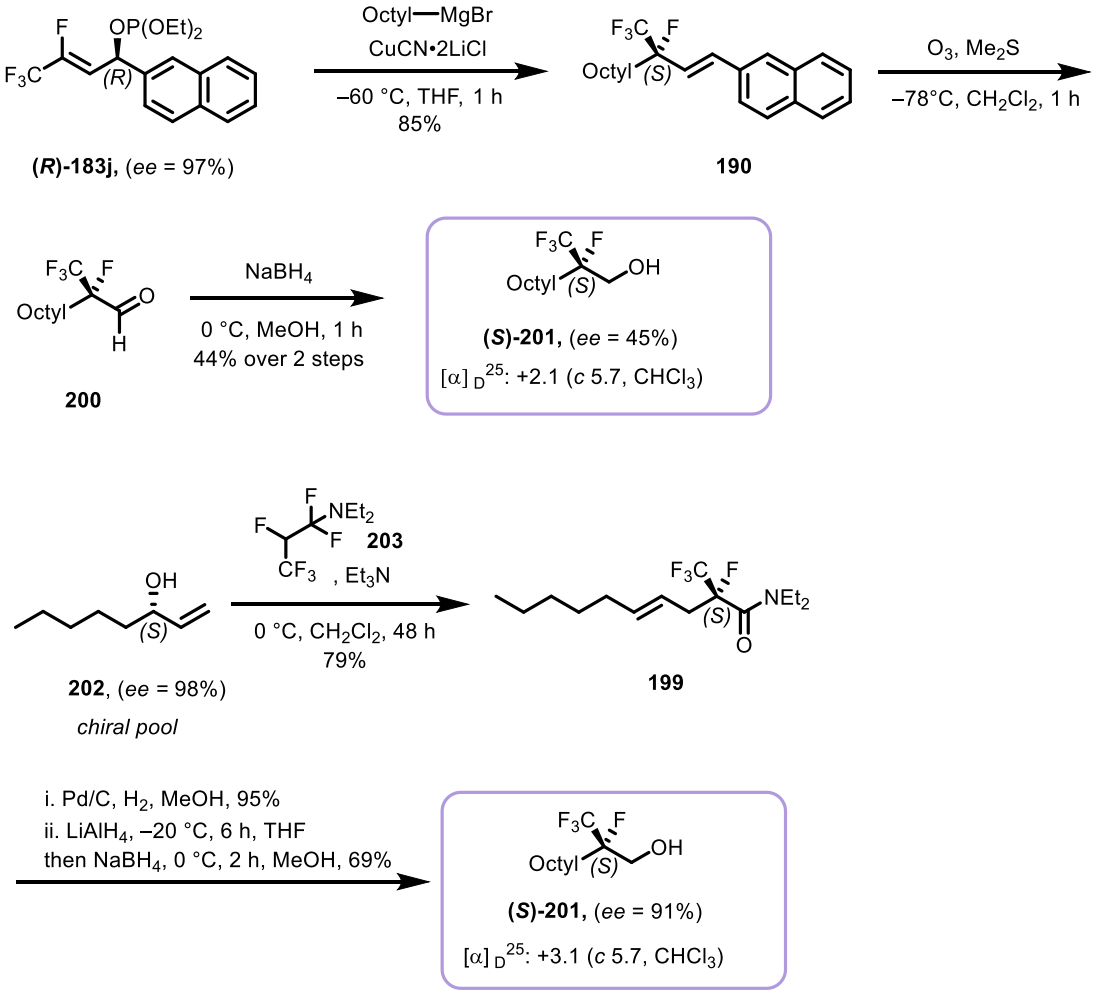
In strategy B, the octyl substituted compound **190** was converted into the primary alcohol **201** via ozonolysis and subsequent reduction. The alcohol can be also obtained in one step from **190**, if $NaBH_4$ is used instead of Me_2S at the quenching step of the ozonolysis. For comparison reasons, a reported chiral pool synthesis to the (*S*)-alcohol **201** was reproduced, this route was reported.[105,106] It started from the chiral (*S*)-allylic alcohol **202**, which is commercially available in 98% *ee* (Scheme 83).

Through an enantioselective ESCHENMOSER-CLAISEN rearrangement[107] with ISHIKAWA's reagent, amide (*S*)-**199** was obtained in 79% yield. The rearrangement is known for converting allylic alcohol **202** to form a *γ*, *σ*- unsaturated amide (*S*)-**199** *via* a highly ordered chair-like transition state **LXIII** (Scheme 82).[108]



Scheme 82: Transition state of Claisen rearrangement via chair transition state **LXIII**.

Hydrogenation of the **199** with Pd/C and subsequent reduction with $LiAlH_4$ and $NaBH_4$ gave the (*S*)-alcohol **201**. Comparison based on chiral GC proved that the (*S*)-alcohol **201** is the main enantiomer resulted from the asymmetric allylic substitution, with a 45% *ee*. The MOSHER ester analysis and measured optical rotation value supported the *ee* value as well. In summary, using (*R*)-allylic phosphate **183j** as starting material, the absolute configuration of the resulted FTF compound after chirality transfer corresponds to the predict configuration (*S*) (Scheme 83).

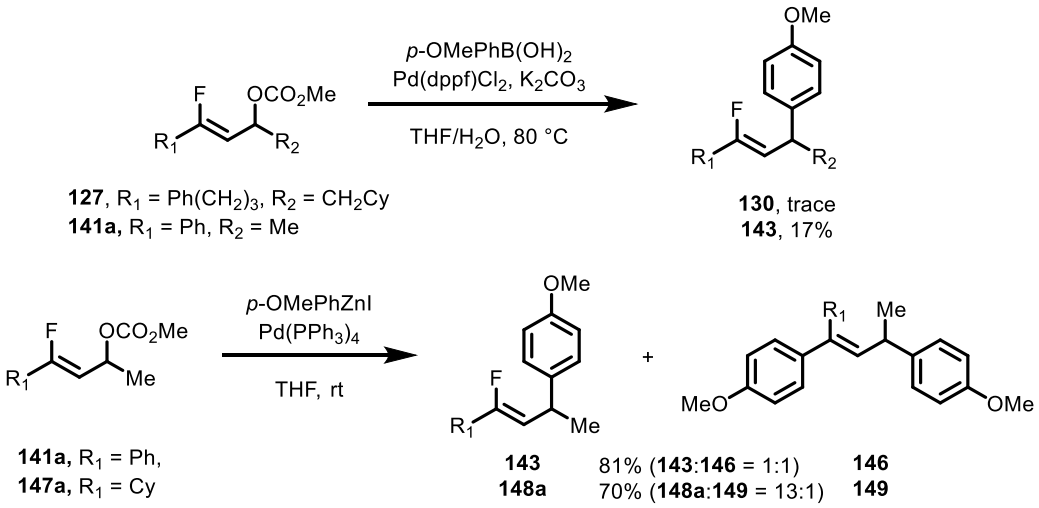


Scheme 83: Strategy B to determine the absolute configuration of FTF stereocenter.

4 Summary

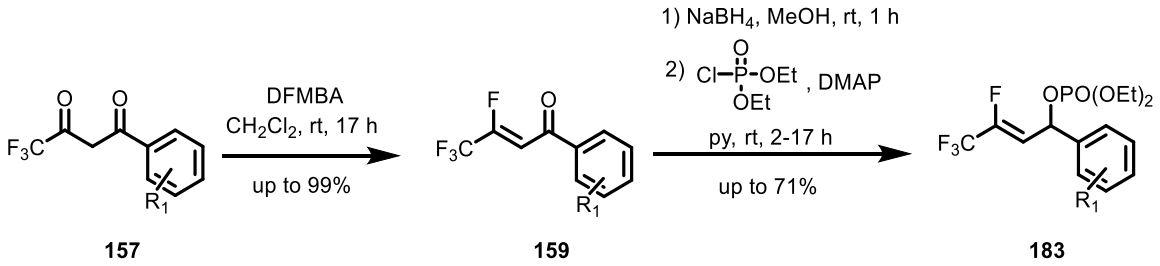
In project A, the Pd-catalyzed cross-coupling reactions utilizing organozinc or organoboron reagents with fluorinated allylic secondary carbonates were studied. The primary emphasis was on aryl-ally cross-coupling reactions employing aryl nucleophiles.

The NEGISHI coupling gave overall higher yield of the desired product **143** and **148a** when comparing with SUZUKI coupling, as *β*-H-elimination and defluorination reaction could be largely reduced. Due to the limited applicability of the substrate scope and the inability to determine the enantioselectivity of the products, using the NEGISHI coupling for the functionalization of fluorinated allylic compounds remains challenging. In both coupling reactions, no *γ*-products could be isolated, although they were confirmed as active intermediates leading to the double addition product **146** or **149** (Scheme 84).



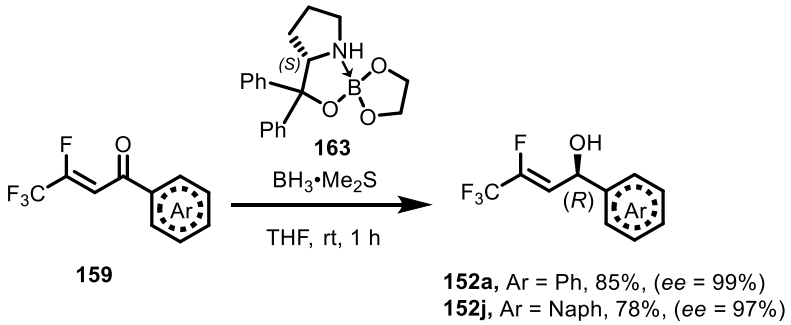
Scheme 84: Summary of the SUZUKI and NEGISHI coupling reactions using different substrates.

To address the challenge, the project B was initiated with the aim of enhancing the *γ*-regioselectivity and creating more stable F-containing tetra-substituted carbon centers. To this end, the Cu-mediated allylic substitution of secondary allylic phosphate **183** utilizing GRIGNARD reagent was studied. The phosphate **183** was synthesized in three steps. The regioselective fluorination using DFMBA of the 1,3-diketone **157** provides the fluoroenone **159**. Subsequent racemic reduction and phosphorylation resulted in various allylic phosphates **183** (Scheme 85).



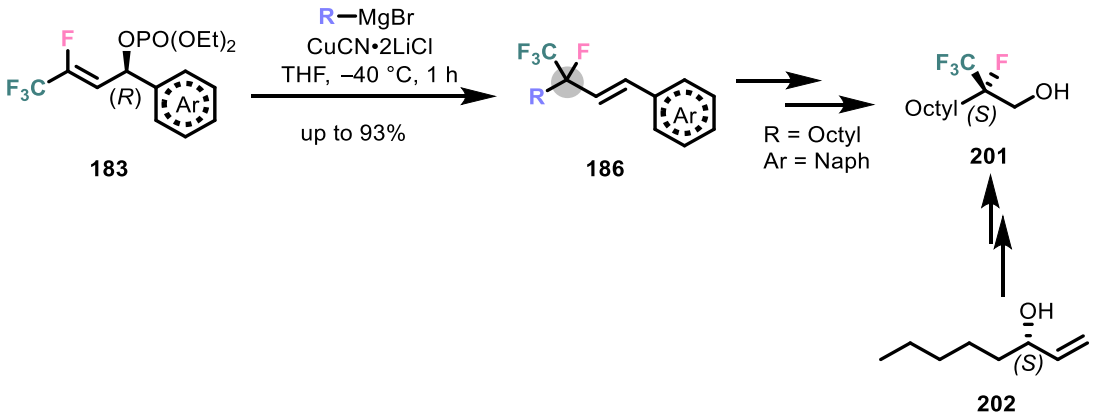
Scheme 85: Synthesis of phosphate **183** through fluorination, racemic reduction and phosphorylation.

To investigate the potential for chirality transfer in subsequent allylic substitution reactions, the enantioselective synthesis of chiral alcohol **152** from the fluoroenone **159** was explored. The asymmetric 1,2-reduction utilizing a chiral spiroborate ester **163** exhibited high enantioselectivity for substrate **152a** and **152j** (Scheme 86).



Scheme 86: Enantioselective reduction of fluoroenone **159**.

Compound **186** was synthesized utilizing CuCN·2LiCl and various GRIGNARD reagent. The reaction demonstrated a broad substrate scope, high γ-regioselectivity and excellent (*E*)-stereoselectivity. To date, this is the first method applying allylic substitution reactions to install FTF-group. Chirality transfer from enantiopure phosphates **183** to the corresponding scalemic products indicate the stereoselective potential of this method. The absolute configuration was determined by a chiral pool synthesis using the alcohol **202** (Scheme 87).[113]

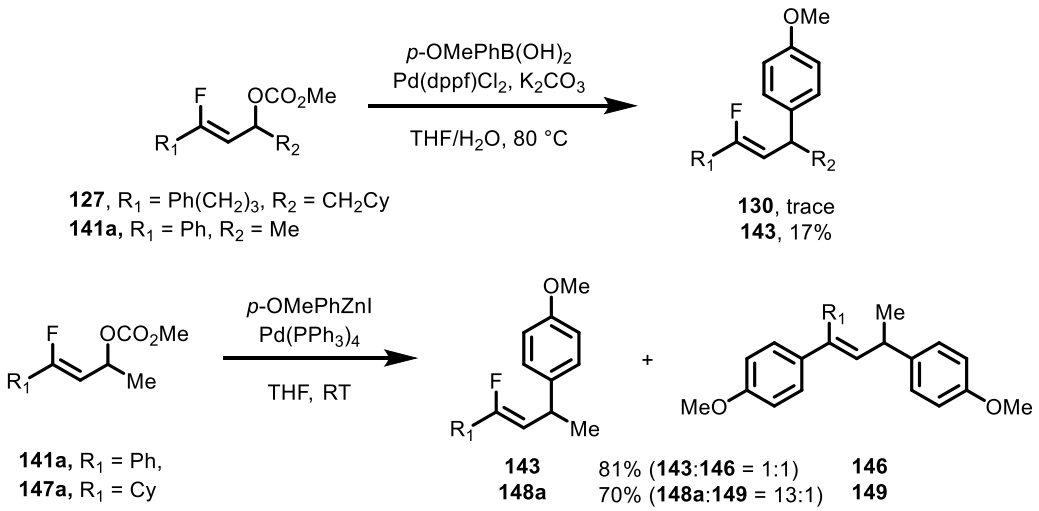


Scheme 87: Cu(I)-mediated allylic substitution of phosphate **183** and determination of the stereocenter subsequent to the chirality transfer.

Zusammenfassung

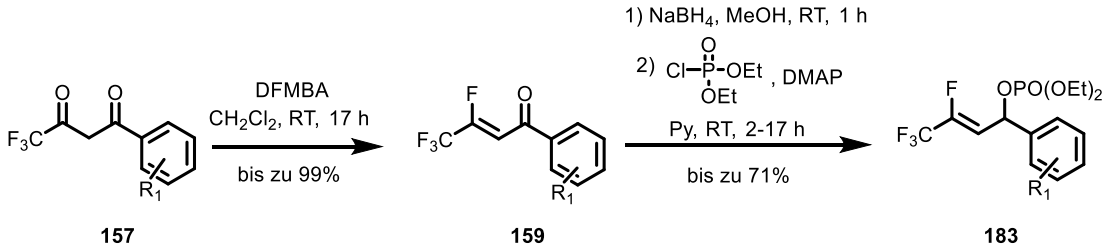
In Projekt A wurden die Pd-katalysierten Kreuzkupplungsreaktionen unter Verwendung von Organozink- oder Organobor-Reagenzien mit fluorierten sekundären Allylcarbonaten untersucht. Der Schwerpunkt lag dabei auf Aryl-Ally-Kreuzkupplungsreaktionen unter Verwendung von Aryl-Nukleophilen.

Die NEGISHI-Kupplung ergab im Vergleich zur SUZUKI-Kupplung insgesamt eine höhere Ausbeute der gewünschten Produkte **143** und **148a**, da die *β*-H-Eliminierung und die Defluorierungsreaktion weitgehend reduziert werden konnten. Aufgrund der begrenzten Anwendbarkeit des Substrats und der Schwierigkeit, die Enantioselektivität der Produkte zu bestimmen, bleibt die Verwendung der NEGISHI-Kupplung für die Funktionalisierung von fluorierten Allylverbindungen eine Herausforderung. In beiden Kupplungsreaktionen konnten keine *γ*-Produkte isoliert werden, obwohl sie als aktive Zwischenprodukte identifiziert wurden, die zu den Doppeladditionsprodukten **146** oder **149** führten (Scheme 88).



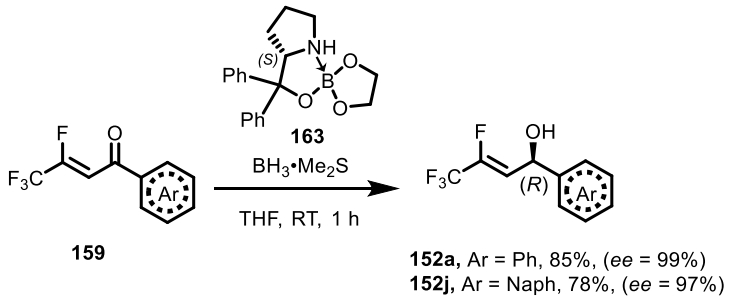
Scheme 88: Zusammenfassung der SUZUKI- und NEGISHI-Kupplungsreaktionen unter Verwendung verschiedener Substrate.

Um das Problem zu lösen, wurde das Projekt B mit dem Ziel initiiert, die *γ*-Regioselektivität zu verbessern und stabilere F-haltige tetrasubstituierte Kohlenstoffzentren zu schaffen. Zu diesem Zweck wurde die Cu-vermittelte allylische Substitution des sekundären Allylphosphats **183** unter Verwendung der GRIGNARD-Reagenzien untersucht. Das Phosphat **183** wurde in drei Schritten synthetisiert. Die regioselektive Fluorierung des 1,3-Diketons **157** mit DFMBA liefert das Fluoroenon **159**. Die anschließende racemische Reduktion und Phosphorylierung führte zu verschiedenen Allylphosphaten **183** (Scheme 89).



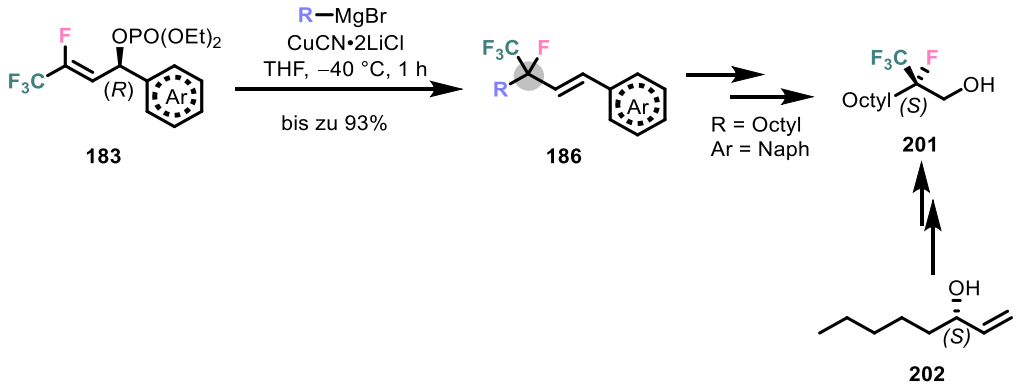
Scheme 89: Synthese von Phosphat **183** durch Fluorierung, racemische Reduktion und Phosphorylierung.

Um das Potenzial für den Chiralitätstransfer in nachfolgenden allylischen Substitutionsreaktionen zu untersuchen, wurde die enantioselektive Synthese des chiralen Alkohols **152** aus dem Fluoroenon **159** erforscht. Die asymmetrische 1,2-Reduktion unter Verwendung eines chiralen Spiroboratesters **163** zeigte eine hohe Enantioselektivität für die Substrate **152a** und **152j** (Scheme 90).



Scheme 90: Enantioselektive Reduktion von Fluoroenon **159**.

Die Verbindung **186** wurde unter Verwendung von CuCN·2LiCl und verschiedenen GRIGNARD-Reagenzien synthetisiert. Die Reaktion zeigte eine hohe Toleranz gegenüber funktionellen Gruppen in der Substratbreite, hohe γ-Regioselektivität und eine ausgezeichnete (*E*)-Stereoselektivität. Bislang ist dies die erste Methode, bei der allylische Substitutionsreaktionen zur Installation der FTF-Gruppe eingesetzt werden. Der Chiralitätstransfer von enantiomerenreinen Phosphaten **183** zu den entsprechenden skalemischen Produkten zeigt das stereoselektive Potenzial dieser Methode. Die absolute Konfiguration wurde durch eine *chiral-pool*-Synthese unter Verwendung des Alkohols **202** bestimmt (Scheme 91).



Scheme 91: Cu(I)-vermittelte allylische Substitution von Phosphat **183** und Bestimmung des Stereocenters nach dem Chiralitätstransfer.

5 Experimental

5.1 General Methods and Materials

All non-aqueous reactions were carried out under argon atmosphere using flame-dried glassware unless noted otherwise. All solvents were distilled by rotary evaporation prior to use. Solvents for non-aqueous reactions were dried prior to use: THF was dried and degassed with KOH and subsequently distilled from sodium/benzophenone or Solvona® under nitrogen atmosphere. CH_2Cl_2, MeCN were dried and distilled from CaH_2 under nitrogen atmosphere. MeOH was dried and degassed by distillation with Mg-turnings (5 g/L) under nitrogen atmosphere. Toluene was dried and degassed with Solvona® and distilled under nitrogen atmosphere. All commercially available reagents and reactants were used without purification unless otherwise noted.

Thin Layer Chromatography (TLC)

Thin layer chromatography (TLC) was performed to monitor reactions using MERCK silica gel 60 F_{245} plates. Visualization was performed by fluorescence quenching under UV-light (254, 365 nm) or by staining the TLC plates with potassium permanganate solution.

Flash Column Chromatography

Chromatographic purification of products was performed using Merck silica gel 60 (230 – 400 mesh) by application of positive pressure. Concentration under reduced pressure was performed by rotary evaporation at 40 °C and (or) by exposing to high vacuum at room temperature.

Nuclear Magnetic Resonance Spectroscopy (NMR)

NMR spectra were recorded on a Bruker AV II 300 MHz, AVIII HD 300 MHz, AV III 500 MHz, or AVII 600 MHz spectrometer by the NMR service department of the Philipps-Universität Marburg. Unless noted otherwise, measurements were conducted at an ambient temperature of 300 K. The chemical shift δ is listed in ppm referenced against tetramethylsilane (TMS, $\delta = 0$ ppm) with the residual solvent signal as internal standard. Measurements were performed with $CDCl_3$ (^{1}H: $\delta = 7.26$ ppm; ^{13}C: $\delta = 77.16$ ppm) as solvent. ^{19}F-NMR measurements were

calibrated to trichlorofluoromethane ($CFCl_3$, $\delta = 0$ ppm) as external standard. Multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

High-Resolution Mass Spectrometry (HRMS)

Mass spectra were recorded by the mass service department of the Philipps-Universität Marburg. HR-ESI and APCI mass spectra were acquired with an LTQ-FT Ultra mass spectrometer (*Thermo Fischer Scientific*). The resolution was set to 100.000. The ion masses *m*/*z* are given in units (u).

Infrared Spectroscopy (IR)

IR spectra were recorded on a Bruker IFS 200 spectrometer. The absorption bands are given in wave numbers (cm^{-1}). Intensities are reported as follows: s = strong, m = medium, w = weak, br = broad band.

Melting point

Melting points were determined on a Mettler Toledo MP70 using one end closed capillary tubes.

Optical Rotation

Optical rotations were determined at 20 °C for the Na-D wavelength (589 nm) with a Krüss P8000-T polarimeter.

X-Ray Crystallography

Single crystal X-ray diffraction measurements were measured by members of the department for crystal structure analysis of the Philipps-Universität Marburg with a STOE STADIVARI or a Bruker AXS D8 Quest diffractometer. Obtained diffraction data were evaluated and the corresponding crystal structure resolved by Dr. (RUS) Sergei I. Ivlev.

Room temperature was 24 – 26 °C.

High-Performance Liquid Chromatography (HPLC)

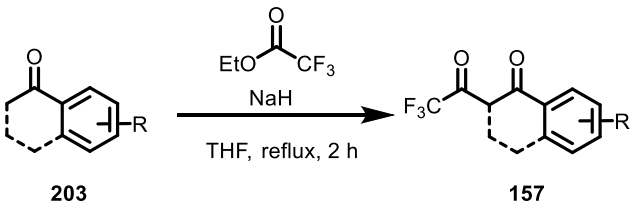
Chiral HPLC chromatography was performed with an Agilent 1200 or Agilent 1260 HPLC system using *n*-hexane/isopropanol as mobile phase. All the HPLC conditions were detailed in the individual procedures. The type of the columns, mobile phase and the flow rate were specified in the individual procedures.

Gas Chromatography (GC)

GC analysis was performed with an Agilent GC 7820A using chiral Hydrodex *β*-TBDAc column.

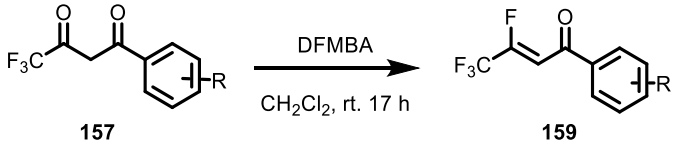
5.2 General Procedures

General Procedure I



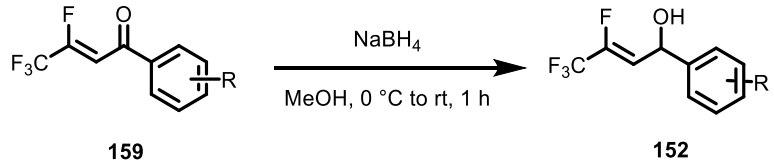
To a suspension of NaH (60% dispersion in mineral oil, 1.20 eq) in THF (1 mL/mmol) was added ethyl trifluoroacetate (2.40 eq). After stirring at rt for 10 min, the mixture was cooled to 0 °C and a solution of ketone (**203**, 1.00 eq) in THF (1 mL/mmol) was added dropwise. The reaction mixture was refluxed using an oil bath for 2 h, cooled to rt and poured onto ice-cold 1 M HCl (50 mL), and diluted with EtOAc (30 mL). The aqueous phase was extracted three times with EtOAc (20 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by recrystallisation in pentane or column chromatography (*n*-pentane/Et_2O) on silica gel.

General Procedure II



N,*N*-Diethyl-*α*,*α*-difluoro-(*m*-methylbenzyl)amine (DFMBA) (1.50 eq) was dissolved in CH_2Cl_2 (3 mL/mmol). 1,3-Dione **157** (1.00 eq) was added and the reaction was stirred for 17 h. The solution was poured onto saturated aqueous $NaHCO_3$ solution (30 mL) and diluted with Et_2O (20 mL). The aqueous phase was extracted three times with Et_2O (20 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by column chromatography (*n*-pentane/Et_2O) on silica gel to yield fluoroenone **159**.

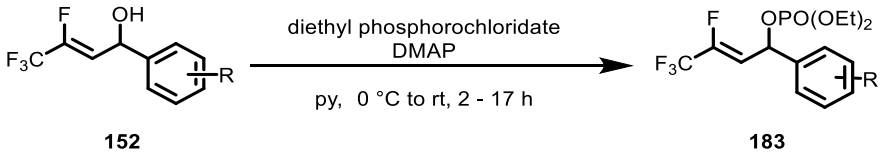
General Procedure III



159 **152**

Fluoroenone **159** (1.00 eq) was dissolved in anhydrous MeOH (5 mL/mmol) and the solution was cooled to 0 °C. $NaBH_4$ (1.20 eq) was added and the mixture was stirred for 1 h at 0 °C. The reaction was quenched with H_2O and diluted with Et_2O (10 mL). The aqueous phase was extracted three times with Et_2O (10 mL). The combined organic layers were washed with saturated aqueous NaCl solution (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting allylic alcohol **152** was used for the phosphorylation without further purification.

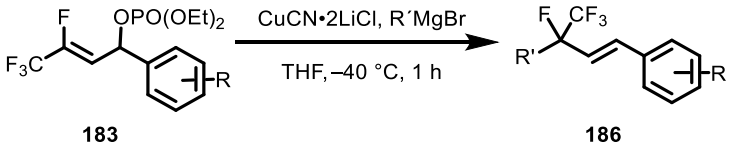
General Procedure IV



152 **183**

The allylic alcohol **152** (1.00 eq) was dissolved in pyridine (1 mL/mmol). DMAP (0.10 eq) and diethyl phosphorochloridate (1.20 -3.00 eq) were added at 0 °C. The solution was stirred for 2-17 h at rt. The reaction was quenched by saturated aqueous NH_4Cl solution and diluted with Et_2O (10 mL). The aqueous phase was extracted three times with Et_2O (10 mL), the combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by column chromatography (*n*-pentane/Et_2O) on silica gel to obtain the allylic phosphate **183**.

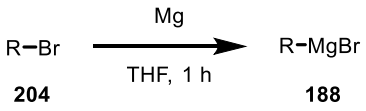
General Procedure V



183 **186**

CuCN·2LiCl solution (1 M in THF) was dissolved in THF (2 mL/mmol) and cooled to −40 °C. GRIGNARD solution in Et_2O was added and the mixture was stirred for 1 h. The allylic phosphate **183** dissolved in THF (5 mL/mmol) was added dropwise. The reaction was stirred for 1 h at −40 °C, then quenched with saturated aqueous NH_4Cl solution (1-2 mL). The aqueous phase was extracted three times with Et_2O (10 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by column chromatography (*n*-pentane/Et_2O) on silica gel to obtain the product.

General Procedure VI

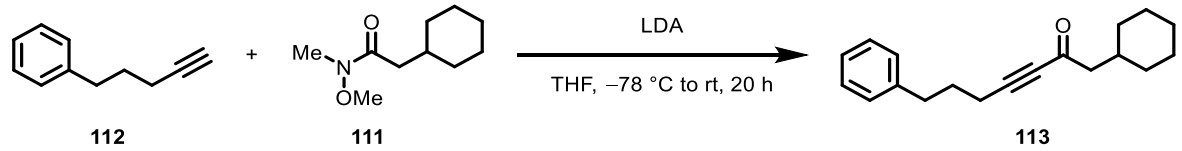


204 **188**

Magnesium turnings (2.00 eq) was charged in a round bottom flask. THF (1 mL/ mmol) was added, followed by the slow addition of the corresponding bromide **204** (1.00 eq) in THF (1 mL/mmol). Hot water bath (~70 °C) was used for initiation of the reaction. The mixture was stirred vigorously at room temperature for 1 h. The reaction solution was subsequently titrated with an iodine solution in THF (saturated with LiCl) to determine the concentration of the GRIGNARD reagent **188**.

5.3 Experimental & Characterization Data

1-Cyclohexyl-7-phenylhept-3-yn-2-one (113)



112 **111** **113**

Acetylene **112** [144.22, ρ = 0.95]	1.00 eq	13.9 mmol	2.00 g
WEINREB amide **111** [185.27]	1.00 eq	13.9 mmol	2.57 mL
n-BuLi (2.5 M in hexane)	1.15 eq	15.9 mmol	6.38 mL
Diisopropylamine [101.19, ρ = 0.72]	1.30 eq	18.0 mmol	2.53 mL
THF			40.0 mL

Diisopropylamine (2.53 mL, 18.0 mmol, 1.30 eq) was dissolved in anhydrous THF (40 mL) and cooled to –78 °C before *n*-BuLi (2.5 M in hexane, 15.9 mL, 1.15 eq) was added and the solution was stirred for 1 h at 0 °C. It was cooled to –78 °C and acetylene **112** (2.00 g, 13.9 mmol, 1.00 eq) was added. The solution was stirred for 1 h at –78 °C before WEINREB amide **111** (2.57 mL, 13.9 mmol, 1.00 eq) was added. The solution was stirred for 20 h while warming up to rt. Aqueous HCl-solution (2 M, 50 mL) was added and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL) and saturated aqueous NaCl-solution (50 mL), dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica using 20:1 (*n*-pentane/Et_2O) providing the desired ynone **113** as a colorless oil (2.97 g, 11.1 mmol, 80%).

TLC: R_f = 0.57 (*n*-pentane/EtOAc 20:1).

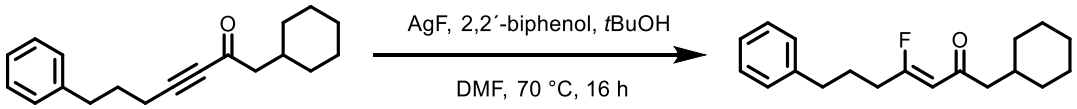
^{1}H-NMR: (300 MHz, $CDCl_3$) δ = 7.34 – 7.27 (m, 2H, CH_{arom}), 7.25 – 7.16 (m, 3H, CH_{arom}), 2.74 (t, J = 7.5 Hz, 2H, CH_2), 2.41 (d, J = 7.0 Hz, 2H, CH_2CO), 2.37 (t, J = 7.0 Hz, 2H, CH_2), 2.01 – 1.86 (m, 1H & 2H, CH_{Cy} & $CH_2CH_2CH_2$), 1.79 – 1.59 (m, 5H, CH_{Cy}), 1.33 – 1.14 (m, 3H, CH_{Cy}), 1.06 – 0.92 (m, 2H, CH_{Cy}) ppm.

^{13}C-NMR: (75 MHz, $CDCl_3$) δ = 188.2 (*C*=O), 141.0 (C_{arom}), 128.6 (4C, C_{arom}), 126.3 (C_{arom}), 93.4 (*C*≡CC=O), 81.8 (C≡*C*C=O), 53.3 (CH_2C=O), 34.8 (CH_2Ph), 34.6 (C_{Cy}), 33.2 (2C, C_{Cy}), 29.4 (CH_2), 26.3 (C_{Cy}), 26.2 (2C, C_{Cy}), 18.4 (CH_2) ppm.

HRMS: ESI (+); (*m/z*) calc. for $C_{19}H_{24}ONa^+$ $[M+Na]^+$: 291.1719; found 291.1718.

FT-IR: Film; $\tilde{\nu}$ (cm^{-1}) = 3026 (w), 2921 (s), 2850 (w), 2208 (m), 1667 (s), 1602 (w), 1495 (w), 1449 (m), 1425 (w), 1401 (w), 1349 (w), 1327 (w), 1283 (w), 1253 (w), 1233 (w), 1211 (w), 1175 (w), 1154 (w), 1110 (w), 1079 (w), 1050 (w), 1010 (w), 964 (w), 934 (w), 910 (w), 846 (w), 799 (w), 745 (m), 699 (s), 598 (w), 562 (w), 489 (w).

(*Z*)-1-Cyclohexyl-4-fluoro-7-phenylhept-3-en-2-one (114)



113 **114**

Ynone **113** [268.40]	1.00 eq	7.45 mmol	2.00 g
2,2´-Biphenol [186.20]	0.45 eq	3.35 mmol	0.62 g
AgF [126.87]	3.00 eq	22.4 mmol	2.84 g
*t*BuOH			1.50 mL
DMF			15.0 mL

Following the procedure from KOERT *et al.*[16], ynone **113** (2.00 g, 7.45 mmol, 1.00 eq) was dissolved in anhydrous DMF (15 mL), before AgF (2.84 g, 22.4 mmol, 3.00 eq), 2,2´-biphenol (0.62 g, 3.35 mmol, 0.45 eq) and *t*BuOH (1.50 mL) were added. The reaction mixture was heated at 70 °C for 16 h in absence of light. The mixture was filtered through a pad of silica and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica using 20:1 (*n*-pentane/Et_2O) providing the desired *β*-fluoroenone (0.87 g, 3.03 mmol, 41%) as a yellow oil **114**.

TLC: R_f = 0.50 (*n*-pentane/EtOAc 10:1).

^{1}H-NMR: (300 MHz, $CDCl_3$) δ = 7.30 (m, 2H, CH_{arom}), 7.30 – 7.10 (m, 3H, CH_{arom}), 5.32 (d, *J* = 38.4 Hz, 1H, CFC*H*), 2.72 (t, *J* = 7.62 Hz, 2H, CH_2), 2.53 (dd, *J* = 6.80, 2.01 Hz, 2H, CH_2), 2.32 (dt, *J* = 17.20, *J* = 7.52 Hz, 2H, CH_2), 2.01

(m, 3H, CH_2 and CH_{cy}), 1.80 – 1.63 (m, 5H, CH_{cy}), 1.42 – 1.10 (m, 3H, CH_{Cy}), 1.00 (s, 2H, CH_{cy}) ppm.

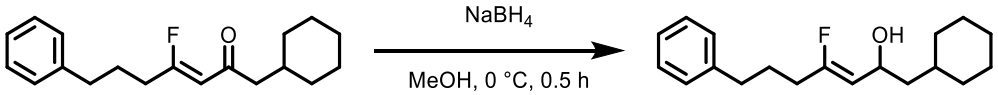
^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −80.1 (C*F*) ppm.

^{13}C-NMR: (75 MHz, $CDCl_3$) δ = 198.6 (d, J = 2.2 Hz, *C*O), 170.0 (d, J = 283.6 Hz, *C*F), 141.0 (C_{arom}), 128.6 (2C, C_{arom}), 128.5 (2C, C_{arom}), 126.3 (C_{arom}), 109.1 (d, J = 7.5 Hz, *C*H), 51.2 (d, J = 4.9 Hz, *C*H_2CO), 35.0 (*C*H_2), 34.2 (C_{cy}), 33.4 (2C, C_{cy}), 32.5 (d, J = 25.5 Hz, *C*H_2), 27.3 (d, J = 1.6 Hz, *C*H_2), 26.4 (C_{cy}), 26.3 (2C, C_{cy}) ppm.

HRMS: ESI(+); (*m/z*) calc. for $C_{19}H_{25}FOH^+$ $[M+H]^+$ 289.1962, found 289.1969.

FT-IR: Film; $\tilde{\nu}$ (cm^{-1}) = 2922 (s), 2850 (w), 1702 (w), 1665 (s), 1496 (w), 1449 (m), 1403 (w), 1377 (w), 1333 (w), 1287 (w), 1257 (w), 1217 (w), 1188 (w), 1144 (w), 1084 (w), 1029 (w), 972 (w), 910 (m), 816 (w), 733 (s), 700 (w), 648 (w), 541 (w), 491 (w).

(*Z*)-4-Fluoro-4-phenylbut-3-en-2-ol (115)



114 **115**

Fluoroenone **114** [288.41]	1.00 eq	1.61 mmol	464 mg
$NaBH_4$	1.20 eq	1.93 mmol	73.0 mg
MeOH			8.0 mL

Fluoroenone **114** (464 mg, 1.61 mmol, 1.00 eq) was dissolved in anhydrous MeOH (8 mL) and the solution was cooled to 0 °C. $NaBH_4$ (73.0 mg, 1.93 mmol, 1.20 eq) were added and the mixture was stirred for 1 h at 0 °C. It was quenched with H_2O and diluted with Et_2O. The layers were separated and the aqueous one was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL) solution, dried over

anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The product **115** (454 mg, 1.56 mmol, 97%) was isolated as a yellow oil.

TLC: R_f = 0.30 (*n*-pentane/EtOAc 10:1).

^{1}H-NMR: (300 MHz, C_6D_6) δ = 7.22 – 7.10 (m, 2H, C*H*$_{arom}$), 7.10 (m, 3H, C*H*$_{arom}$), 4.78 (q, *J* = 6.8 Hz, 1H, C*H*OH), 4.47 (dd, *J* = 37.5 Hz, *J* = 8.7 Hz, 1H, CFC*H*), 2.41 (t, *J* = 7.4 Hz, 2H, C*H*$_2$Ph), 2.00 – 1.83 (m, 2H, C*H*$_2$), 1.83 – 1.53 (m, 8H, C*H*$_{cy}$ and C*H*$_2$), 1.35 (s, 2H, C*H*$_2$CHOH), 1.25 – 1.05 (m, 3H, C*H*$_{cy}$), 1.00 – 0.78 (m, 2H, C*H*$_{cy}$) ppm.

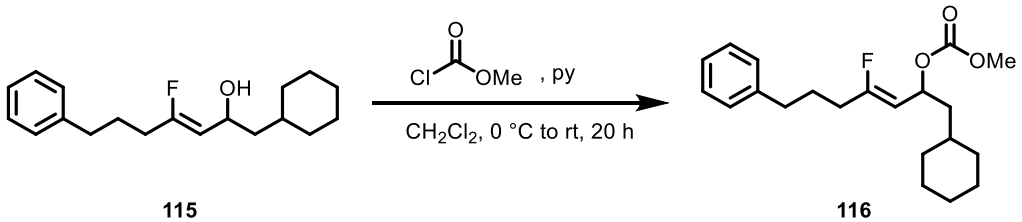
^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −105.8 (C*F*) ppm.

^{13}C-NMR: (75 MHz, $CDCl_3$) δ = 160.0 (d, *J* = 256.2 Hz, *C*F), 141.9 (*C*$_{arom}$), 128.7 (4C, *C*$_{arom.}$), 126.3 (*C*$_{arom}$), 110.9 (d, *J* = 13.1 Hz, *C*HCF), 63.2 (d, *J* = 5.7 Hz, *C*HOH), 45.8 (*C*H$_2$CHOH), 35.2 (*C*H$_2$Ph), 34.5 (*C*$_{cy}$), 34.1 (*C*$_{cy}$), 33.5 (*C*$_{cy}$), 31.5 (d, *J* = 27.3 Hz, *C*H$_2$), 28.0 (d, *J* = 1.4 Hz, *C*H$_2$), 27.0 (*C*$_{cy}$), 26.8 (*C*$_{cy}$), 26.7 (*C*$_{cy}$) ppm.

HRMS: APCI(+); *m/z* calc. for $C_{19}H_{27}O$ $[M-F]^+$: 271.2056, found: 271.2066.

FT-IR: Film; $\tilde{\nu}$ (cm^{-1}) = 3328 (w), 3027 (w), 2920 (s), 2849 (m), 1704 (m), 1603 (w), 1495 (w), 1449 (m), 1329 (w), 1261 (w), 1205 (w), 1181 (w), 1130 (w), 1081 (w), 1059 (w), 1017 (m), 983 (w), 966 (w), 910 (w), 877 (m), 854 (w), 816 (w), 744 (m), 699 (s), 590 (w), 561 (w), 498 (m).

(*Z*)-4-Fluoro-4-phenylbut-3-en-2-yl methyl carbonate (116)



115 116

Allylic alcohol **115** [290.42]	1.00 eq	1.61 mmol	467 mg
Methyl chloroformate [ρ = 1.22]	3.00 eq	4.82 mmol	0.37 mL
Pyridine [ρ = 0.98]	3.00 eq	4.82 mmol	0.38 mL
CH_2Cl_2			8.0 mL

Allylic alcohol **115** (467 mg, 1.61 mmol, 1.00 eq) was dissolved in CH_2Cl_2 (8.0 mL) and the solution was cooled on ice. Pyridine (0.38 mL, 4.82 mmol, 3.00 eq) and methyl chloroformate (0.37 mL, 4.82 mmol, 3.00 eq) were added and the solution was stirred for 17 h at rt. The reaction flask was cooled on ice and the reaction mixture was quenched with 1 M HCl (10 mL). The product was extracted into CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (10 mL), washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica using 20:1 (*n*-pentane/EtOAc) as a colorless oil **116** (392 mg, 1.12 mmol, 70%).

TLC: R_f = 0.48 (*n*-pentane/EtOAc 20:1).

^{1}H-NMR : (300 MHz, $CDCl_3$) δ = 7.33 – 7.27 (m, 2H, CH_{arom}), 7.23 – 7.14 (m, 3H, CH_{arom}), 5.60 (dt, J = 8.8, J = 7.0 Hz, 1H, C*H*O), 4.60 (dd, J = 35.9 Hz, J = 9.2 Hz, 1H, CFC*H*), 3.76 (s, 3H, CH_3), 2.64 (t, J = 7.6 Hz, 2H, CH_2Ph), 2.20 (dt, J = 16.9 Hz, J = 7.3 Hz, 2H, CFCH_2), 1.84 (tt, J = 7.8 Hz, J = 7.6 Hz, 2H, CH_2), 1.77 – 1.59 (m, 6H, CH_{cy}), 1.43 – 1.15 (m, 5H, CH_{cy} and CH_2), 1.02 – 0.87 (m, 2H, CH_{cy}) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −101.6 (C*F*) ppm.

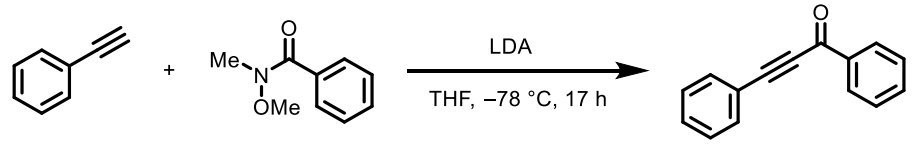
^{13}C-NMR: (75 MHz, $CDCl_3$) δ = 162.0 (d, J = 262.0 Hz, *C*F), 155.2 (O*C*O_2), 141.6 (*C*$_{arom}$), 128.6 (2C, *C*$_{arom}$), 128.5 (2C, *C*$_{arom}$), 126.1 (*C*$_{arom}$), 105.3 (d, J = 12.9 Hz, *C*H), 70.8 (d, J = 5.8 Hz, H*C*O), 54.7 (*C*H_3), 42.4 (*C*H_2), 35.0 (*C*H_2Ph), 34.0(*C*$_{cy}$), 33.3 (2C, *C*$_{cy}$), 31.3 (d, J = 26.6 Hz, *C*H_2), 27.6 (d, J = 1.7 Hz, *C*H_2), 26.6 (*C*$_{cy}$), 26.3 (2C, *C*$_{cy}$).

HRMS: ESI(+); *m/z* calc. for $C_{21}H_{29}FO_3Na$ $[M+Na]^+$: 371.1993, found: 371.1993.

FT-IR: Film; $\tilde{\nu}$ (cm^{-1}) = 3027 (w), 2922 (m), 2851 (w), 1782 (w), 1747 (s), 1705 (w), 1603 (w), 1496 (w), 1443 (m), 1353 (w), 1310 (w), 1259 (s), 1219 (w), 1159 (m), 1058 (w), 1029 (w), 965 (w), 937 (m), 877 (w), 817 (w), 791 (w), 746 (w), 699 (m), 561 (w), 489 (w).

Subsequent attempts at an allylic substitution reaction using this substrate were not successful.

1,3-Diphenylprop-2-yn-1-one (137c)



205 **206** **137c**

Phenylacetylene (**205**) [102.14, ρ = 0.93]	1.00 eq	29.4 mmol	3.23 mL
WEINREB amide **206** [165.19]	1.00 eq	29.4 mmol	4.85 mL
n-BuLi (2.5 M in hexane)	1.15 eq	33.8 mmol	13.5 mL
Diisopropylamine [101.19, ρ = 0.72]	1.30 eq	38.2 mmol	5.37 mL
THF			90.0 mL

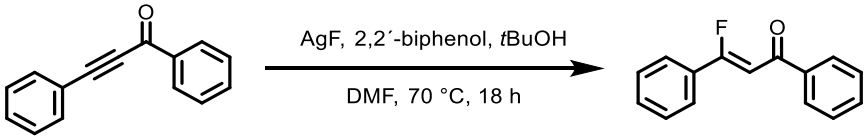
Diisopropylamine (4.85 mL, 29.4 mmol, 1.30 eq) was dissolved in THF (90 mL) and cooled to –78 °C before *n*-BuLi (2.5 M in hexane, 13.5 mL, 1.15 eq) was added and the solution was stirred for 1 h at 0 °C. It was cooled to –78 °C and phenylacetylene (**205**) (3.23 mL, 29.4 mmol, 1.00 eq) was added. The solution was stirred for 1 h at –78 °C before WEINREB amide **206** (4.85 mL, 29.4 mmol, 1.00 eq) was added. The solution was stirred for 17 h while warming up to rt. Aqueous HCl-solution (2 M, 100 mL) was added and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (100 mL) and saturated aqueous NaCl-solution (100 mL), dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica using 40:1 to 10:1 (*n*-pentane/Et_2O) providing the desired ynone **137c** as a yellow oil (4.85 g, 23.5 mmol, 80%).

TLC: R_f = 0.3 (*n*-pentane/EtOAc 40:1).

^{1}H-NMR: (300 MHz, $CDCl_3$) δ = 8.41 – 8.13 (m, 2H, CH_{arom}), 7.77 – 7.59 (m, 3H, CH_{arom}), 7.59 – 7.35 (m, 5H, CH_{arom}) ppm.

The analytical data corresponds to the literature.[109]

(*Z*)-3-Fluoro-1,3-diphenylprop-2-en-1-one (138c)



137c **138c**

Ynone **137b** [206.24]	1.00 eq	9.70 mmol	2.00 g
2,2´-Biphenol [186.20]	0.45 eq	4.36 mmol	0.81 g
AgF [126.9]	3.00 eq	29.1 mmol	3.69 g
*t*BuOH			2.00 mL
DMF			20.0 mL

Following the procedure from KOERT *et al.*[16], ynone **137c** (2.00 g, 9.70 mmol, 1.00 eq) was dissolved in anhydrous DMF (20 mL), before AgF (3.69 g, 29.1 mmol, 3.00 eq), 2,2´-biphenol (0.81 g, 4.36 mmol, 0.45 eq) and *t*BuOH (2.00 mL) were added. The reaction mixture was heated at 70 °C for 18 h in absence of light. The mixture was filtered through a pad of silica and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica using 20:1 (*n*-pentane/Et_2O) providing the desired *β*-fluoroenone **138c** (0.84 g, 3.69 mmol, 38%) as a yellow oil.

TLC: R_f = 0.2 (*n*-pentane/EtOAc 20:1)

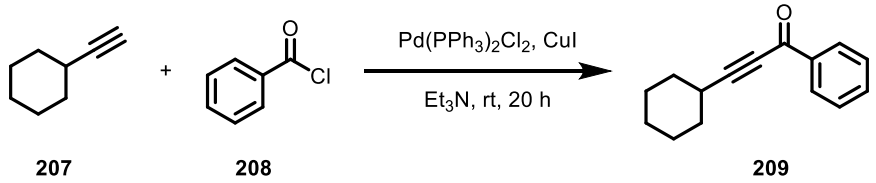
^{1}H-NMR: (300 MHz, $CDCl_3$) δ = 8.06 – 7.88 (m, 2H, CH_{arom}), 7.76 (dd, J = 7.9, 1.8 Hz, 2H, CH_{arom}), 7.68 – 7.37 (m, 6H, CH_{arom}), 6.80 (d, J = 34.0 Hz, 1H, C*H*CF) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −96.5 ppm.

The analytical data corresponds to the literature.[110]

Efforts to further reduce the substrate **138c** to allylic alcohol were unsuccessful due to the alcohol's inherent instability.

3-Cyclohexyl-1-phenylprop-2-yn-1-one (209)



207 208 209

Cyclohexylacetylen (**207**) [108.18, ρ = 0.83]	1.00 eq	18.5 mmol	2.42 mL
Benzoyl chloride (**208**) [140.57, ρ = 1.21]	1.00 eq	18.5 mmol	2.15 mL
$Pd(PPh_3)_2Cl_2$ [701.9]	0.01 eq	185 µmol	130 mg
CuI [190.45]	0.02 eq	370 µmol	70.4 mg
Et_3N [101.19, ρ = 0.73]	1.10 eq	20.3 mmol	2.84 mL
THF			9.0 mL

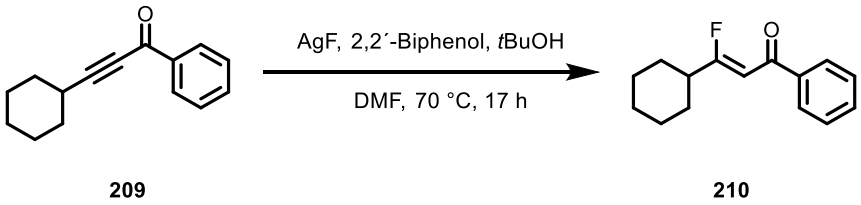
A solution of the cyclohexylacetylen **207** (2.42 mL, 18.5 mmol, 1.00 eq) was added in THF to a mixture of the benzoyl chloride **208** (2.15 mL, 18.5 mmol, 1.0 eq), $Pd(PPh_3)_2Cl_2$ (130 mg, 0.01 eq, 185 µmol), copper (I) iodide (70.4 mg, 0.02 eq, 370 µmol) and triethylamine (2.84 mL, 1.10 eq, 20.3 mmol) in THF (9.0 mL) in a round-bottom flask. The reaction mixture was stirred for 20 h at room temperature. The solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography on silica using 40:1 (*n*-pentane/ethyl acetate) providing the desired ynone **209** (3.32 g, 15.6 mmol, 85%) as a yellow oil.

TLC: R_f = 0.3 (*n*-pentane/EtOAc 40:1)

^{1}H-NMR: (300 MHz, $CDCl_3$) δ = 8.37 – 7.78 (m, 2H, CH_{arom}), 7.63 – 7.55 (m, 1H, CH_{arom}), 7.53 – 7.38 (m, 2H, CH_{arom}), 2.83 – 2.48 (m, 1H, C*H*), 2.13 – 1.84 (m, 2H, CH_{cy}), 1.77 (m, 2H, CH_{cy}), 1.70 – 1.50 (m, 3H, CH_{cy}), 1.49 – 1.31 (m, 3H, CH_{cy}) ppm.

The analytical data corresponds to the literature.[111]

(*Z*)-3-Cyclohexyl-3-fluoro-1-phenylprop-2-en-1-one (210)



209 **210**

Ynone **209** [212.29]	1.00 eq	7.06 mmol	1.50 g
2,2´-Biphenol [186.20]	0.45 eq	3.18 mmol	0.59 g
AgF [126.87]	3.00 eq	21.2 mmol	2.69 g
*t*BuOH			1.40 mL
DMF			14.0 mL

Following the procedure from KOERT *et al.*[16], ynone **209** (1.50 g, 7.06 mmol, 1.00 eq) was dissolved in anhydrous DMF (14 mL), before AgF (2.69 g, 21.2 mmol, 3.00 eq), 2,2´-biphenol (0.59 g, 3.18 mmol, 0.45 eq) and *t*BuOH (1.40 mL) were added. The reaction mixture was heated at 70 °C for 17 h in absence of light. The mixture was filtered through a pad of silica and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica using 20:1 (*n*-pentane/Et_2O) providing the desired *β*-fluoroenone **210** (0.56 g, 2.41 mmol, 34%) as a yellow solid.

TLC: R_f = 0.5 (*n*-pentane/EtOAc 20:1)

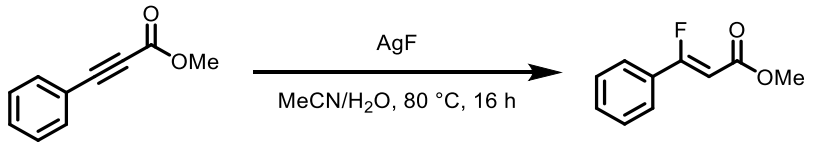
^{1}H-NMR: (300 MHz, $CDCl_3$) δ = 7.93 – 7.75 (m, 2H, CH_{arom}), 7.61 – 7.39 (m, 3H, CH_{arom}), 6.01 (d, J = 35.4 Hz, 1H, C*H*CF), 2.27 (m, 1H, C*H*), 2.05 – 1.60 (m, 5H, CH_{cy}), 1.46 – 1.11 (m, 5H, CH_{cy}) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = –84.5 (C*F*) ppm.

^{13}C-NMR: (75 MHz, $CDCl_3$) δ = 189.4 (CO), 174.7 (d, J = 288.6 Hz, CH*C*F), 138.6 (C_{arom}), 132.8 (C_{arom}), 128.6 (C_{arom}), 128.4 (C_{arom}), 101.7 (d, J = 5.8 Hz, *C*HCF), 41.9 (d, J = 22.3 Hz, *C*HC$_{cy}$), 29.7 (d, J = 2.4 Hz, C_{cy}), 25.8 (C_{cy}), 25.7 (C_{cy}) ppm.

Efforts to further reduce the substrate **210** to allylic alcohol were unsuccessful due to the alcohol's inherent instability.

Methyl (*Z*)-3-fluoro-3-phenylacrylate (138b)



137b **138b**

Ynone **137c** [160.17, ρ = 1.09]	1.00 eq	6.24 mmol	1.00 g
AgF [126.9]	2.00 eq	12.5 mmol	1.58 g
H_2O			0.62 mL
MeCN			12.0 mL

Following the procedure from JIANG *et al.*[22], Ynone **137b** (1.00 g, 6.24 mmol, 1.00 eq) was dissolved in MeCN (12 mL), before AgF (1.58 g, 12.5 mmol, 2.00 eq), and H_2O (0.62 mL) were added. The reaction mixture was heated at 80 °C for 16 h in absence of light. The mixture was filtered through a pad of silica and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica using 20:1 (*n*-pentane/EtOAc) providing the desired *β*-fluoroenone **138b** (1.05 g, 5.80 mmol, 93%) as a yellow oil.

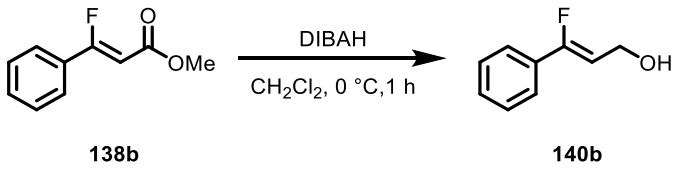
TLC: R_f = 0.3 (*n*-pentane/ EtOAc 20:1)

^{1}H-NMR: (300 MHz, $CDCl_3$) δ = 7.65 (dd, J = 8.1, 1.7 Hz, 2H, CH_{arom}), 7.58 – 7.37 (m, 2H, CH_{arom}), 5.91 (d, J = 33.5 Hz, 1H, C*H*CF), 3.79 (s, 3H, CH_3) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = –95.6 (C*F*)ppm.

The analytical data corresponds to the literature.[112]

(*Z*)-3-Fluoro-3-phenylprop-2-en-1-ol (140b)



138b **140b**

Acrylate **138b** [180.18]	1.00 eq	3.75 mmol	0.68 g
DIBAH [1.0 M in hexane]	2.50 eq	9.37 mmol	9.37 mL
CH_2Cl_2			8.0 mL

DIBAH (9.37 mL, 1.0 M in hexane, 3.75 mmol, 2.50 eq) was added to a solution of acrylate **138b** (0.68 g, 3.75 mmol, 1.00 eq) in anhydrous CH_2Cl_2 (8.0 mL) and the reaction mixture was stirred for 1 h at 0 °C. An aqueous HCl-solution (2 M, 5.0 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 10.0 mL). The combined organic layers were washed with saturated aqueous NaCl solution (10.00 mL), dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica using 4:1 (*n*-pentane/Et_2O) providing the desired allylic alcohol **140b** (0.29 g, 1.93 mmol, 52%) as a colorless oil.

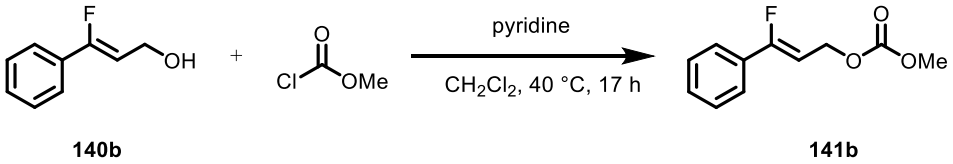
TLC: R_f = 0.3 (*n*-pentane/EtOAc 4:1).

^{1}H-NMR: (300 MHz, $CDCl_3$) δ = 7.61 – 7.48 (m, 2H, CH_{arom}), 7.37 (m, 3H, CH_{arom}), 5.66 (dd, J = 36.8, 7.8 Hz, 1H, C*H*CF), 4.45 (dd, J = 7.2, 2.1 Hz, 2H, CH_2), 1.93 (s, 1H, O*H*) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −117.2 (C*F*) ppm.

The analytical data corresponds to the literature.[113]

(*Z*)-3-Fluoro-3-phenylallyl methyl carbonate (141b)



140b **141b**

Allylic alcohol **140b** [152.17]	1.00 eq	3.27 mmol	500 mg
Methyl chloroformate [ρ = 1.22]	2.30 eq	7.52 mmol	0.58 mL
Pyridine [ρ = 0.98]	8.25 eq	27.0 mmol	2.17 mL
CH_2Cl_2			6.0 mL

Following the procedure from HARTWIG *et. al.*[114], allylic alcohol **140b** (500 mg, 3.27 mmol, 1.00 eq) was dissolved in CH_2Cl_2 (8 mL), and cooled on ice. Pyridine (2.17 mL, 27.0 mmol, 8.25 eq) was added, followed by methyl chloroformate added dropwise (0.58 mL, 7.52 mmol, 2.30 eq). The ice bath was removed, and the reaction mixture was heated at 40 °C for 17 h. The reaction flask was cooled on ice and the reaction mixture was quenched with 1 M HCl (10 mL). The product was extracted into CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (20 mL), washed with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash on silica using 10:1 (*n*-pentane/Et_2O) as a colorless oil (632 mg, 3.01 mmol, 92%).

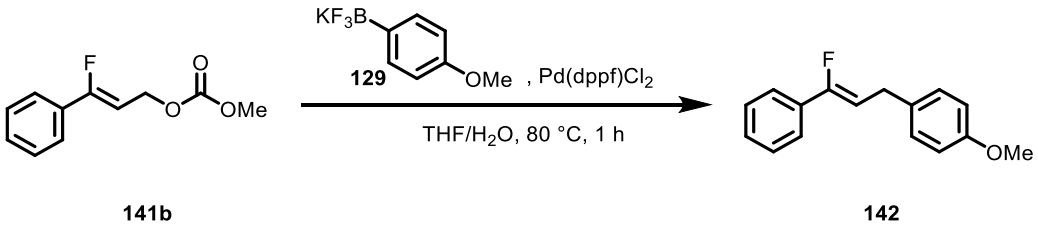
TLC: R_f = 0.5 (*n*-pentane/EtOAc 10:1).

^{1}H-NMR: (300 MHz, $CDCl_3$) δ = 7.60 – 7.49 (m, 2H, CH_{arom}), 7.43 – 7.33 (m, 3H, CH_{arom}), 5.65 (dt, *J* = 35.0, 7.5 Hz, 1H, C*H*CF), 4.93 (dd, *J* = 7.4, 1.9 Hz, 2H, CH_2), 3.81 (s, 3H, CH_3) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −113.9 (C*F*)ppm.

The analytical data corresponds to the literature.[114]

(*Z*)-1-(3-Fluoro-3-phenylallyl)-4-methoxybenzene (142)



141b **142**

Carbonate **141b** [210.20]	1.00 eq	238 µmol	50.0 mg
BF_3K salt **129** [214.04]	1.10 eq	262 µmol	56.0 mg
$Pd(dppf)Cl_2$ [731.71]	0.05 eq	12.0 µmol	8.70 mg
K_2CO_3 [138.21]	2.00 eq	476 µmol	65.8 mg
THF/H2O			0.70 mL
H_2O			0.14 mL

To a solution of carbonate **141b** (50.0 mg, 238 µmol, 1.00 eq) and BF_3K salt **129** (56.0 mg, 263 µmol, 1.10 eq) and K_2CO_3 (65.8 mg, 476 µmol, 2.00 eq) in THF/H_2O (5:1), $Pd(dppf)Cl_2$ (8.70 mg, 12.0 µmol, 0.05 eq) was added and stirred at 80 °C for 1 h. After brine was added, the mixture was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica using 40:1 (*n*-pentane/Et_2O) providing the product **142** (33.0 mg, 135 µmol, 57%) as a colorless oil.

TLC: R_f = 0.40 (*n*-pentane/EtOAc 40:1).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.55 – 7.50 (m, 2H, C*H*$_{arom}$), 7.41 – 7.29 (m, 3H, C*H*$_{arom}$), 7.24 – 7.18 (m, 2H, C*H*$_{arom}$), 6.88 – 6.84 (m, 2H, C*H*$_{arom}$), 5.58 (dt, *J* = 37.0, 7.5 Hz, 1H, C*H*CF), 3.80 (s, 3H, C*H*$_3$), 3.59 (dd, *J* = 7.7, 1.8 Hz, 2H, C*H*$_2$) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −121.4 (C*F*) ppm.

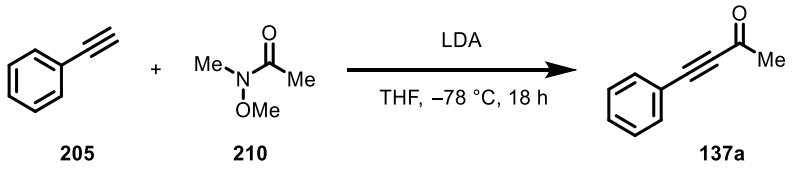
^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 158.3 (*C*OCH3), 156.9 (d, *J* = 247.1 Hz, *C*F), 132.7 (d, *J* = 28.8 Hz, *C*$_{arom}$CF), 132.4 (d, *J* = 1.8 Hz, *C*$_{arom}$CH$_2$), 129.5 (*C*$_{arom}$),

128.7 (C_{arom}), 128.6 (d, J = 2.2 Hz), 124.2 (d, J = 7.1 Hz, C_{arom}), 114.1 (C_{arom}), 105.5 (d, J = 17.2 Hz, *C*HCF), 55.4 (CH_3), 29.7 (d, J = 5.9 Hz, CH_2) ppm.

HRMS: (FD+); *m/z* calc. for $C_{16}H_{15}FO[M]^+$ 242.11069, found 242.11161.

IR: Film; $\tilde{\nu}$ (cm^{-1}): 3061 (w), 3032 (w), 3000 (w), 2933 (w), 2907 (w), 2835 (w), 1675 (w), 1610 (w), 1583 (w), 1510 (s), 1462 (w), 1444 (w), 1298 (w), 1282 (w), 1242 (s), 1176 (m), 1108 (w), 1071 (w), 1034 (m), 983 (m), 942 (w), 918 (w), 856 (w), 820 (m), 759 (s), 738 (w), 690 (m), 619 (w), 558 (w), 519 (w), 422 (w).

4-Phenylbut-3-yn-2-one (137a)



205 210 137a

Phenylacetylene (**205**) [102.14, ρ = 0.93]	1.00 eq	27.3 mmol	3.00 mL
WEINREB amide **210** [103.12, ρ = 0.97]	1.00 eq	27.3 mmol	2.90 mL
n-BuLi (2.5 M in hexane)	1.15 eq	31.4 mmol	12.5 mL
Diisopropylamine [101.19, ρ = 0.72]	1.30 eq	35.5 mmol	5.00 mL
THF			80.0 mL

Diisopropylamine (5.0 mL, 35.5 mmol, 1.30 eq) was dissolved in anhydrous THF (80 mL) and cooled to –78 °C before *n*-BuLi (2.5 M in hexane, 12.5 mL, 1.15 eq) was added and the solution was stirred for 1 h at 0 °C. It was cooled to –78 °C and phenylacetylene (3.00 mL, 27.3 mmol, 1.00 eq) was added. The solution was stirred for 1 h at –78 °C before WEINREB amide **210** (2.90 mL, 27.3 mmol, 1.00 eq) was added. The solution was stirred for 18 h while warming up to rt. Aqueous HCl-solution (2 M, 100 mL) was added and the aqueous layer was extracted with Et_2O (3 × 50.0 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (100 mL) and saturated aqueous NaCl-solution (100 mL), dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash

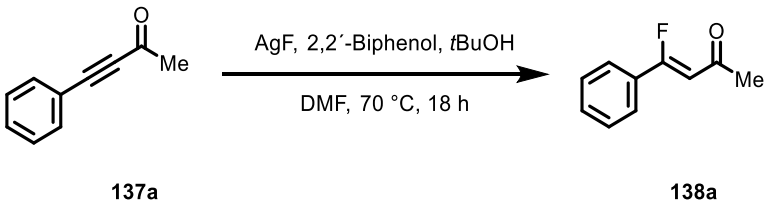
chromatography on silica using 10:1 (*n*-pentane/Et_2O) providing the desired ynone **137a** as a yellow oil (3.79 g, 23.8 mmol, 87%).

TLC: R_f = 0.6 (*n*-pentane/EtOAc 10:1).

^{1}H-NMR: (300 MHz, $CDCl_3$) δ = 7.63 – 7.45 (m, 2H, CH_{arom}), 7.50 – 7.31 (m, 3H, CH_{arom}), 2.45 (s, 3H, CH_3) ppm.

The analytical data corresponds to the literature.[115]

(*Z*)-4-Fluoro-4-phenylbut-3-en-2-one (138a)



137a **138a**

Ynone **137a** [144.17]	1.00 eq	9.10 mmol	1.31 g
2,2´-Biphenol [186.20]	0.45 eq	4.10 mmol	0.76 g
AgF [125.9]	3.00 eq	27.3 mmol	3.46 g
*t*BuOH			1.80 mL
DMF			18.0 mL

Following the procedure from KOERT *et al.*[16], ynone **137a** (1.31 g, 9.10 mmol, 1.00 eq) was dissolved in anhydrous DMF (18 mL), before AgF (3.46 g, 27.3 mmol, 3.00 eq), 2,2´-biphenol (0.76 g, 4.10 mmol, 0.45 eq) and *t*BuOH (1.80 mL) were added. The reaction mixture was heated at 70 °C for 18 h in absence of light. The mixture was filtered through a pad of silica and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica using 20:1 (*n*-pentane/Et_2O) providing the desired *β*-fluoroenone **138a** (1.05 g, 6.40 mmol, 70%) as a yellow solid.

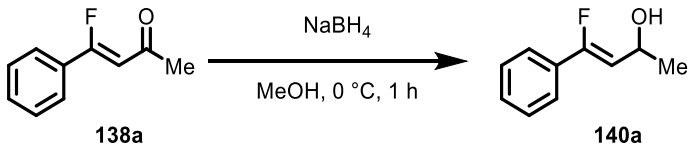
TLC: R_f = 0.3 (*n*-pentane/EtOAc 20:1).

^{1}H-NMR: (300 MHz, $CDCl_3$) δ = 7.70 – 7.61 (m, 2H, CH_{arom}), 7.54 – 7.37 (m, 3H, CH_{arom}), 6.07 (d, J = 37.2 Hz, 1H, CHCF), 2.51 (d, J = 4.1 Hz, 3H, CH_3) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −96.3 (CF) ppm.

The analytical data corresponds to the literature.[116]

(*Z*)-4-Fluoro-4-phenylbut-3-en-2-ol (140a)



138a 140a

Fluoroenone **138a** [164.18]	1.00 eq	5.69 mmol	0.93 g
$NaBH_4$	1.20 eq	6.83 mmol	0.26 g
MeOH			28.0 mL

Fluoroenone **138a** (0.93 g, 5.69 mmol, 1.00 eq) was dissolved in anhydrous MeOH (28 mL) and the solution was cooled to 0 °C. $NaBH_4$ (0.26 g, 6.83 mmol, 1.20 eq) were added and the mixture was stirred for 1 h at 0 °C. It was quenched with H_2O (10 mL) and diluted with Et_2O (20 mL). The layers were separated and the aqueous one was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with saturated aqueous NaCl solution, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The product **140a** (0.94 g, 5.67 mmol, 99%) was isolated as a white solid. Notice: The allylic alcohol **140a** undergoes rapid defluorination, to prevent decomposition, should be promptly utilized in the subsequent step.

TLC: R_f = 0.10 (*n*-pentane/EtOAc 10:1).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.52 (m, 2H, CH_{arom}), 7.42 – 7.32 (m, 3H, CH_{arom}), 5.51 (dd, J = 36.9, 8.3 Hz, 1H, CHCF), 5.08 – 4.90 (m, 1H, CHCH$_3$), 1.66 (s, 1H, OH), 1.39 (d, J = 6.4 Hz, 3H, CH_3) ppm.

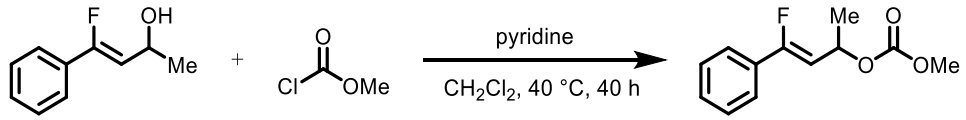
^{19}F-NMR: (235 MHz, $CDCl_3$) δ = −118.0 (CF) ppm.

^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 157.0 (d, J = 250.2 Hz, *C*F), 131.9 (C_{arom}), 129.4 (C_{arom}), 128.7 (d, J = 1.9 Hz, C_{arom}), 124.5 (d, J = 7.2 Hz, C_{arom}), 110.3 (d, J = 14.8 Hz, *C*HCF), 62.3 (d, J = 6.5 Hz, *C*HOH), 23.6 (CH_3) ppm.

FT-IR: Film; $\tilde{\nu}$ (cm^{-1}): 3437 (w), 3060 (w), 2969 (w), 2929 (w), 1671 (m), 1622 (w), 1597 (w), 1579 (w), 1493 (w), 1447 (m), 1372 (w), 1334 (w), 1294 (w), 1261 (w), 1216 (m), 1181 (w), 1121 (w), 1067 (w), 1023 (w), 1001 (m), 966 (w), 916 (w), 829 (w), 804 (w), 756 (m), 691 (s), 664 (w), 583 (w), 528 (w).

HRMS: (EI+); *m/z* Calc. for $C_{10}H_{11}FO$ $[M]^+$: 166.07939, found 166.07892.

(*Z*)-4-Fluoro-4-phenylbut-3-en-2-yl methyl carbonate (141a)



140a **141a**

Allylic alcohol **140a** [166.20]	1.00 eq	3.01 mmol	500 mg
Methyl chloroformate [ρ = 1.22]	3.00 eq	9.03 mmol	0.70 mL
Pyridine [ρ = 0.98]	3.00 eq	9.03 mmol	0.73 mL
CH_2Cl_2			15.0 mL

Allylic alcohol **140a** (500 mg, 3.01 mmol, 1.00 eq) was dissolved in CH_2Cl_2 (15.0 mL) and the solution and cooled on ice. Pyridine (0.73 mL, 9.03 mmol, 3.00 eq) and methyl chloroformate (0.70 mL, 9.03 mmol, 3.00 eq) were added and the solution was stirred for 40 h at 40 °C The reaction flask was cooled on ice and the reaction mixture was quenched with 1 M HCl (10 mL). The product was extracted into CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with water (20 mL), washed with brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash on silica using 20:1 (*n*-pentane/Et_2O) as a colorless oil **141a** (413 mg, 1.84 mmol, 61%).

TLC: R_f = 0.50 (*n*-pentane/EtOAc 20:1).

FT-IR: Film; $\tilde{\nu}$ (cm^{-1}): 2985 (w), 2957 (w), 1744 (s), 1681 (w), 1580 (w), 1495 (w), 1443 (m), 1377 (w), 1329 (w), 1261 (s), 1160 (w), 1105 (w), 1076 (w), 1041 (m), 1004 (w), 941 (m), 921 (w), 867 (w), 813 (w), 791 (w), 764 (m), 691 (m), 652 (w), 633 (w), 544 (w), 511 (w), 480 (w), 429 (w).

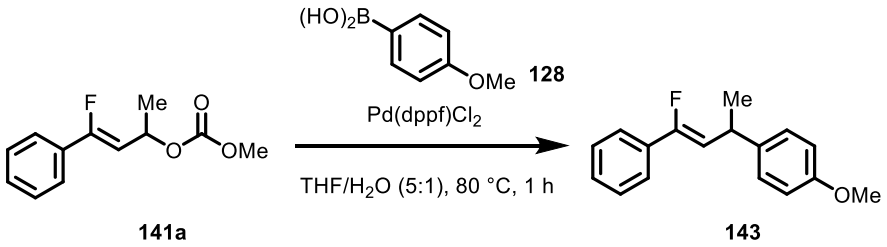
^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.59 – 7.47 (m, 2H, CH_{arom}), 7.43 – 7.27 (m, 3H, CH_{arom}), 5.83 (dq, J = 8.6, 6.5 Hz, 1H, CHCH$_3$), 5.50 (dd, J = 35.2, 8.6 Hz, 1H, CHCF), 3.78 (s, 1H, OCH_3), 1.49 (d, J = 6.5 Hz, 1H, CHCH_3) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −114.4 ppm.

^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 158.0 (d, J = 254.0 Hz, CF), 155.1 (CO), 131.4 (d, J = 28.3 Hz, C_{arom}CF), 129.7 (C_{arom}), 128.6 (d, J = 2.0 Hz, C_{arom}), 124.7 (d, J = 7.3 Hz, C_{arom}), 105.5 (d, J = 14.6 Hz, CHCF), 69.4 (d, J = 6.5 Hz, CHCH$_3$), 54.8 (OCH$_3$), 20.9 (d, J = 1.4 Hz, CH$_3$) ppm.

HRMS: (ESI+); *m/z* calc. for $C_{12}H_{13}FO_3Na$ $[M+Na]^+$ 247.0741, found 247.0741.

(*Z*)-1-(4-Fluoro-4-phenylbut-3-en-2-yl)-4-methoxybenzene (143)



Carbonate **141a** [224.23]	1.00 eq	223 µmol	50.0 mg
Boronic acid **128** [151.96]	1.10 eq	245 µmol	37.3 mg
$Pd(dppf)Cl_2$ [731.71]	0.05 eq	11.0 µmol	8.20 mg
K_2CO_3 [138.20]	2.20 eq	491 mmol	67.8 mg
H_2O			0.14 mL
THF			0.70 mL

To a solution of carbonate **141a** (50.0 mg, 223 µmol, 1.00 eq) and boronic acid **128** (37.3 mg, 245 µmol, 1.10 eq) and K_2CO_3 (67.8 mg, 491 µmol, 2.20 eq) in THF/H_2O (0.84 mL), Pd(dppf)Cl_2 (8.20 mg, 11.0 µmol, 0.05 eq) was added and stirred at 80 °C for 1 h. After brine was added, the mixture was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica using 40:1 (*n*-pentane/Et_2O) providing the product **143** (7.00 mg, 27.3 µmol, 17%) as a colorless oil.

TLC: R_f = 0.30 (*n*-pentane/EtOAc 20:1).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.43 (dd, *J* = 7.1, 1.7 Hz, 2H, CH_{arom}), 7.30 – 7.13 (m, 5H, CH_{arom}), 6.79 (d, *J* = 8.7 Hz, 2H, CH_{arom}), 5.44 (dd, *J* = 36.3, 10.3 Hz, 1H, C*H*CF), 4.16 – 3.91 (m, 1H, C*H*CH_3), 3.71 (s, 3H, OCH_3), 1.36 (d, *J* = 7.1 Hz, 3H, CH_3) ppm.

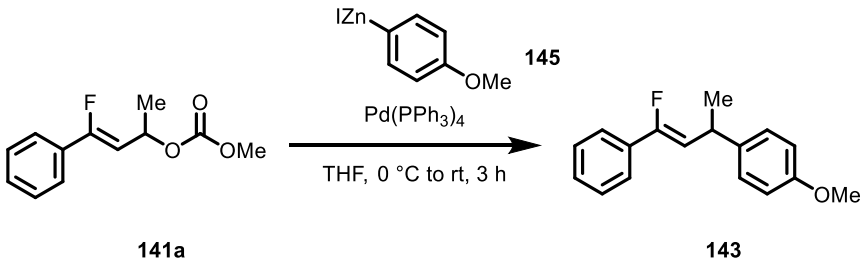
^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −121.4 (C*F*) ppm.

^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 158.2 ($C_{arom}OCH_3$), 155.6 (d, *J* = 246.7 Hz, *C*F), 138.0 (C_{arom}), 132.8 (d, *J* = 28.5 Hz, C_{arom}), 128.7 (C_{arom}), 128.5 (C_{arom}), 127.9 (C_{arom}), 124.2 (d, *J* = 7.2 Hz, C_{arom}), 114.1 (C_{arom}), 111.8 (d, *J* = 17.1 Hz, *C*HCF), 55.4 (O*C*H_3), 34.1 (d, *J* = 4.8 Hz, *C*HCH_3), 22.0 (*C*H_3) ppm.

HRMS: (FD+); *m/z* calc. for $C_{17}H_{17}FO$ $[M]^+$ 256.12634, found 256.12762.

FT-IR: Film; $\tilde{\nu}$ (cm^{-1}): 2962 (m), 2928 (w), 2835 (w), 1672 (w), 1610 (w), 1582 (w), 1511 (m), 1446 (w), 1413 (w), 1373 (w), 1257 (s), 1177 (w), 1079 (w), 1019 (s), 864 (w), 798 (s), 764 (w), 692 (w), 624 (w), 551 (w), 408 (w).

(*Z*)-1-(4-Fluoro-4-phenylbut-3-en-2-yl)-4-methoxybenzene (143)



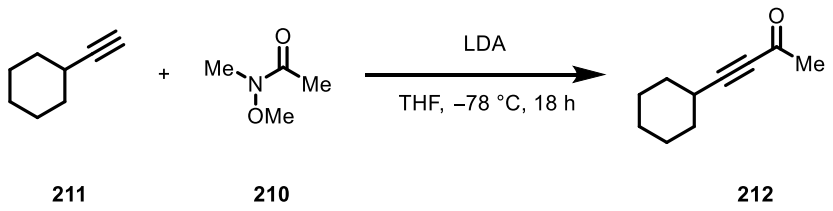
141a **143**

Carbonate **141a** [224.23]	1.00 eq	0.17 mmol	38.4 mg
(4-Methoxyphenyl)zinc(II) iodide **145** [0.5 M in THF]	3.00 eq	0.51 mmol	1.03 mL
$Pd(PPh_3)_4$ [1155.59]	0.05 eq	9.00 µmol	9.90 mg

To $Pd(PPh_3)_4$ (9.90 mg, 9.00 µmol, 0.05 eq) were added carbonate **141a** (38.4 mg, 0.17 mmol, 1.00 eq) and a 0.5 M THF solution of **145** (1.03 mL, 0.51 mmol, 3.0 eq) at 0 °C and stirred for 10 min. The reaction was warmed up to rt and stirred for 3 h. The resulting mixture was quenched by the addition of aqueous HCl (5 mL) and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with H_2O solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica using 20:1 (*n*-pentane/Et_2O) providing the product **143** (20.0 mg, 76.1 µmol, 44%, *Z*/*E* > 25:1) as a colorless oil.

The analytic data of compound **143** is identical with the compound resulted from the SUZUKI coupling.

4-Cyclohexylbut-3-yn-2-one (212)



211 **210** **212**

Cyclohexylacetylen (**211**) [108.18, ρ = 0.83]	1.00 eq	18.5 mmol	2.42 mL
WEINREB amide **210** [103.12, ρ = 0.97]	1.00 eq	18.5 mmol	1.97 mL
n-BuLi (2.5 M in hexane)	1.15 eq	21.3 mmol	8.50 mL
Diisopropylamine [101.19, ρ = 0.72]	1.30 eq	24.0 mmol	3.38 mL
THF			55.0 mL

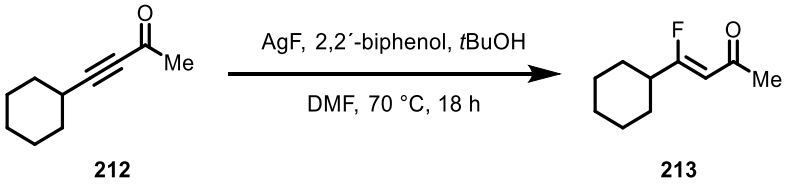
Diisopropylamine (3.38 mL, 35.5 mmol, 1.30 eq) was dissolved in anhydrous THF (55 mL) and cooled to –78 °C before *n*-BuLi (2.5 M in hexane, 8.50 mL, 21.3 mmol, 1.15 eq) was added and the solution was stirred for 1 h at 0 °C. It was cooled to –78 °C and cyclohexylacetylen (2.42 mL, 18.5 mmol, 1.00 eq) was added. The solution was stirred for 1 h at –78 °C before WEINREB amide **210** (1.97 mL, 18.5 mmol, 1.00 eq) was added. The solution was stirred for 18 h while warming up to rt. Aqueous HCl-solution (2 M, 50 mL) was added and the aqueous layer was extracted with Et_2O (3 × 50.0 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL) and saturated aqueous NaCl-solution (50 mL), dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica using 10:1 (*n*-pentane/Et_2O) providing the desired ynone **212** as a yellow oil (2.38 g, 15.8 mmol, 86%).

TLC: R_f = 0.4 (*n*-pentane/EtOAc 20:1)

^{1}H-NMR: (300 MHz, $CDCl_3$) δ = 2.68 – 2.45 (m, 1H, C*H*), 2.32 (s, 3H, CH_3), 1.92 – 1.65 (m, 4H, CH_{cy}), 1.61 – 1.21 (m, 6H, CH_{cy}) ppm.

The analytical data corresponds to the literature.[117]

(*Z*)-4-Cyclohexyl-4-fluorobut-3-en-2-one (213)



212 **213**

Ynone **212** [150.22]	1.00 eq	8.65 mmol	1.30 g
2,2´-Biphenol [186.20]	0.45 eq	3.89 mmol	0.73 g
AgF [126.87]	3.00 eq	26.0 mmol	3.29 g
*t*BuOH			1.70 mL
DMF			17.0 mL

Following the procedure from KOERT *et al.*[16], ynone **212** (1.30 g, 8.65 mmol, 1.00 eq) was dissolved in anhydrous DMF (17 mL), before AgF (3.29 g, 26.0 mmol, 3.00 eq), 2,2´-biphenol (0.73 g, 3.89 mmol, 0.45 eq) and *t*BuOH (1.70 mL) were added. The reaction mixture was heated at 70 °C for 18 h in absence of light. The mixture was filtered through a pad of silica and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica using 20:1 (*n*-pentane/Et_2O) providing the desired *β*-fluoroenone **213** (0.94 g, 5.54 mmol, 64%) as a yellow solid.

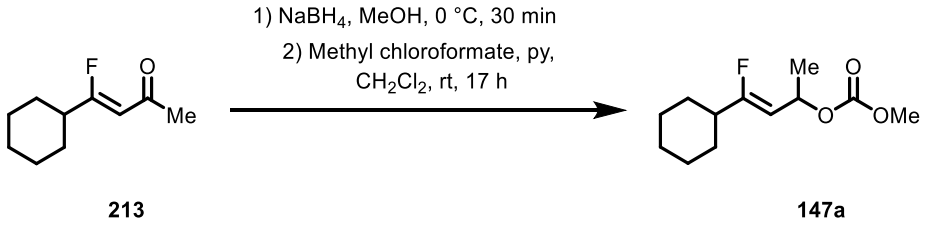
^{1}H-NMR: (300 MHz, $CDCl_3$) δ = 5.27 (d, J = 39.2 Hz, 1H, C*H*CF), 2.33 (d, J = 3.9 Hz, 3H, CH_3), 1.96 – 1.62 (m, 5H, CH_{cy}), 1.41 – 1.04 (m, 6H, CH_{cy}) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −84.23 (C*F*) ppm.

^{13}C-NMR: (75 MHz, $CDCl_3$) δ = 197.0 (*C*O), 175.2 (d, J = 284.7 Hz, CH*C*F), 107.4 (d, J = 8.4 Hz, *C*HCF), 41.5 (d, J = 23.4 Hz, *C*HC_{cy}), 31.3 (d, J = 6.5 Hz, C_{cy}), 29.5 (d, J = 2.5 Hz, C_{cy}), 25.8 (C_{cy}), 25.7 (C_{cy}) ppm.

HRMS: (ESI+); *m/z* calc. for $C_{10}H_{15}FONa$ $[M+Na]^+$: 193.0999, found 193.1000.

(*Z*)-4-Cyclohexyl-4-fluorobut-3-en-2-yl methyl carbonate (147a)



213 **147a**

Fluoroenone **213** [170.23]	1.00 eq	2.94 mmol	0.50 g
$NaBH_4$ [37.83]	1.20 eq	3.53 mmol	0.13 g
MeOH			15.0 mL
Methyl chloroformate [ρ = 1.22]	3.00 eq	8.81 mmol	0.68 mL
Pyridine [ρ = 0.98]	3.00 eq	8.81 mmol	0.71 mL
CH_2Cl_2			15.0 mL

β-Fluoroenone **213** (0.50 g, 2.94 mmol, 1.00 eq) was dissolved in anhydrous MeOH (15 mL) and the solution was cooled to 0 °C. $NaBH_4$ (0.13 g, 3.53 mmol, 1.20 eq) were added and the mixture was stirred for 2 h at 0 °C. The reaction was quenched with H_2O and diluted with Et_2O. The layers were separated and the aqueous one was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with saturated aqueous NaCl solution, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The resulting allylic alcohol (0.94 g, 5.67 mmol, 99%) was isolated as a white solid. Subsequently, the alcohol was dissolved in CH_2Cl_2 (15 mL) and the solution was cooled to 0 °C. Pyridine (0.71 mL. 8.81 mmol, 3.00 eq) and methyl chloroformate (0.68 mL, 8.81 mmol. 3.00 eq) were added and the solution was stirred for 17 h at rt. The reaction was quenched with saturated aqueous NaCl solution (15 mL) and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (15 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica using 10:1 (*n*-pentane/Et_2O) providing the carbonate **147a** (0.56 g, 2.44 mmol, 83% over two steps) as a colorless oil.

TLC: R_f = 0.30 (*n*-pentane/EtOAc 40:1).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 5.61 (dq, J = 8.7, 6.4 Hz, 1H, C*H*CH_3), 4.63 (ddd, J = 36.8, 8.7, 0.8 Hz, 1H, C*H*CF), 3.76 (s, 3H, CH_3), 2.14 – 1.99 (m, 1H, CH_{cy}), 1.85 (q, J = 6.5 Hz, 2H, CH_{cy}), 1.80 – 1.72 (m, 2H, CH_{cy}), 1.71 – 1.61 (m, 1H, CH_{cy}), 1.35 (d, J = 6.5 Hz, 3H, CH_3), 1.31 – 1.11 (m, 5H, CH_{cy}) ppm.

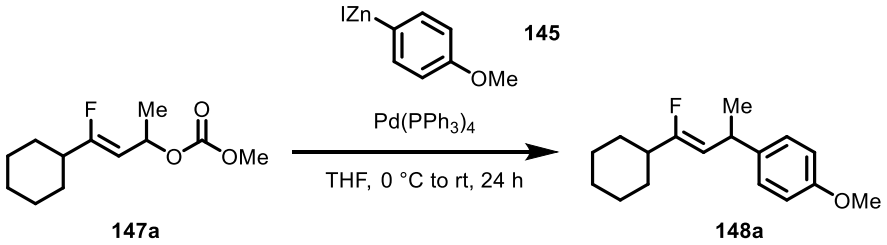
^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −106.0 (C*F*) ppm.

^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 165.7 (d, J = 263.1 Hz, *C*OCH_3), 155.0 (*C*OOMe), 103.4 (d, J = 12.9 Hz, *C*HCF), 69.2 (d, J = 7.2 Hz, *C*HCH_3), 54.5 (O*C*H_3), 40.2 (d, J = 24.5 Hz, C_{cy}), 29.6 (dd, J = 12.5, 2.5 Hz, C_{cy}), 25.9 (C_{cy}), 25.7 (d, J = 1.8 Hz, C_{cy}), 21.0 (*C*H_3) ppm.

HRMS: (ESI+); *m/z* calc. for $C_{12}H_{19}FO_3Na$ $[M+Na]^+$: 253.1210, found 253.1212.

FT-IR: Film; $\tilde{\nu}$ (cm^{-1}): 2984 (w), 2930 (m), 2855 (w), 1746 (s), 1702 (w), 1443 (m), 1377 (w), 1349 (w), 1331 (w), 1259 (s), 1192 (w), 1173 (w), 1151 (w), 1131 (w), 1038 (m), 1000 (w), 945 (m), 895 (w), 869 (w), 841 (w), 819 (w), 791 (m), 717 (w), 694 (w), 537 (w), 475 (w).

(*Z*)-1-(4-Cyclohexyl-4-fluorobut-3-en-2-yl)-4-methoxybenzene (148a)



Carbonate **147a** [230.28]	1.00 eq	0.45 mmol	104 mg
(4-Methoxyphenyl)zinc(II) iodide (**145)** [0.5 M in THF]	3.00 eq	1.35 mmol	2.70 mL
$Pd(PPh_3)_4$ [1155.59]	0.05 eq	22.0 µmol	26.0 mg
THF			2.00 mL

To $Pd(PPh_3)_4$ (26.0 mg, 22.0 µmol, 0.05 eq) were added carbonate **147a** (104 mg, 0.45 mmol, 1.00 eq) and a 0.5 M THF solution of **145** (2.70 mL, 1.35 mmol, 3.00 eq) at 0 °C and stirred for 10 min. The reaction was warmed up to rt and stirred for 24 h. The resulting mixture was

quenched by the addition of aqueous HCl (5 mL) and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with H_2O solution, dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica using 40:1 (*n*-pentane/Et_2O) providing the product **148a** (81.0 mg, 0.31 mmol, 69%, *Z*/*E* = 10:1) as a colorless oil.

TLC: R_f = 0.60 (*n*-pentane/EtOAc 40:1).

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 7.17 (d, *J* = 8.4 Hz, 2H, CH_{arom}), 6.84 (d, *J* = 8.7 Hz, 2H, CH_{arom}), 4.60 (ddd, *J* = 38.3, 9.4, 0.6 Hz, 1H, C*H*CF), 3.87 (dq, *J* = 9.6, 7.1 Hz, 1H, C*H*CH_3), 3.79 (s, 3H, OCH_3), 2.14 – 1.99 (m, 1H, CH_{cy}), 1.90 – 1.82 (m, 2H, CH_{cy}), 1.79 – 1.70 (m, 2H, CH_{cy}), 1.70 – 1.63 (m, 1H, CH_{cy}), 1.31 (d, *J* = 7.1 Hz, 3H, CH_3), 1.28 – 1.12 (m, 5H, CH_{cy}) ppm.

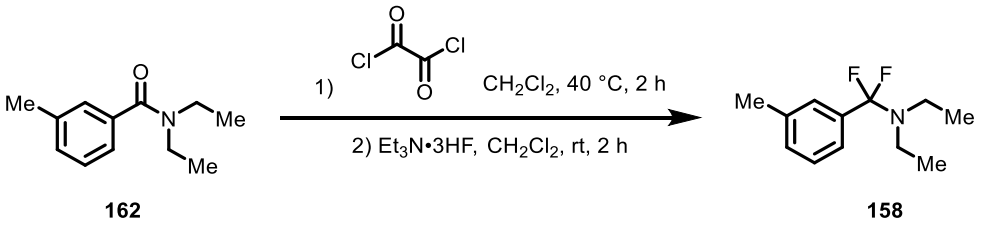
^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −113.9 (C*F*) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 162.8 (d, *J* = 255.3 Hz, *C*F), 157.9 (C_{quart}), 138.8 (C_{quart}), 127.8(C_{arom}), 113.9 (C_{arom}), 108.7 (d, *J* = 15.4 Hz, *C*HCF), 55.4 (*C*H_3), 40.6 (d, *J* = 25.6 Hz, C_{cy}), 33.3 (d, *J* = 5.4 Hz, C_{cy}), 30.1 (d, *J* = 3.0 Hz, C_{cy}), 26.2 (C_{cy}), 26.0 (C_{cy}), 22.5 (*C*H_3) ppm.

HRMS: (FD+); *m/z* calc. for $C_{17}H_{23}FO$ [M]+ 262.17329, found 262.17425.

IR: Film; $\tilde{\nu}$ (cm^{-1}): 2926 (s), 2854 (w), 1696 (m), 1611 (w), 1583 (w), 1510 (s), 1450 (m), 1372 (w), 1302 (w), 1245 (s), 1178 (m), 1159 (w), 1110 (w), 1039 (m), 997 (w), 931 (w), 894 (w), 869 (w), 827 (m), 741 (w), 553 (w).

_N_-(Difluoro(_m_-tolyl)methyl)-_N_-ethylethanamine (158)



162 **158**

Amide **162** [191.27, ρ = 1.00]	1.00 eq	36.1 mmol	6.90 mL
Oxalic chloride [126.93, ρ = 1.48]	3.00 eq	38.9 mmol	3.34 mL
$Et_3N{\cdot}3HF$ [161.21, ρ = 0.99]	0.75 eq	26.7 mmol	4.35 mL
Et_3N [101.19, ρ = 0.73]	1.34 eq	48.3 mmol	6.71 mL
CH_2Cl_2			35.0 mL

The product was prepared by a modification of a reported procedure.[76] To a CH_2Cl_2 (35 mL) solution of amide **162** (6.90 mL, 36.1 mmol), was added dropwise at 0 °C a CH_2Cl_2 (20 mL) solution of oxalyl chloride (3.34 mL, 38.9 mmol) and the mixture was stirred at 40 °C for 2 h. The mixture was cooled again to 0 °C, and $Et_3N{\cdot}3HF$ (4.35 mL, 26.7 mmol) and Et_3N (6.71 mL, 48.3 mmol) were added. The mixture was stirred at rt for 2 h and a generated precipitate was separated by filtration over celite. The precipitate was washed with CH_2Cl_2 (2 × 100 mL), the combined filtrate was concentrated under reduced pressure. Pentane (2 × 100 mL) was added to the residue and the generated precipitate was removed by filtration. The combined filtrate was concentrated under reduced pressure. Distillation of the residue gave DFMBA **158** (4.1 g, 19.2 mmol, 53%) as a colorless oil. DFMBA should be stored under argon atmosphere to avoid decomposition.

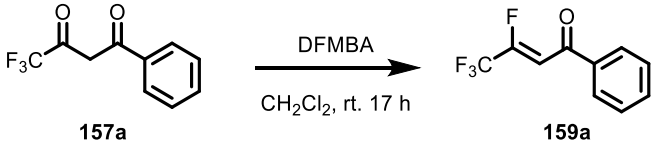
^{1}H-NMR: (300 MHz, $CDCl_3$), δ = 7.34-7.31 (m, 2H, CH_{arom}), 7.25-7.15 (m, 2H, CH_{arom}), 2.81 (q, J = 7.1 Hz, 4H, 2CH_2), 2.32 (s, 3H, CH_3), 0.98 (t, J = 7.1 Hz, 6H, 2CH_3) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$), δ = 18.3 (s, 2F) ppm.

B.p. 45–55 °C/0.001 mbar.

The analytical data corresponds to the literature.[118]

(*Z*)-3,4,4,4-Tetrafluoro-1-phenylbut-2-en-1-one (159a)



Diketone **157a** [216.16]	1.00 eq	4.63 mmol	1.00 g
DFMBA [ρ = 1.03]	2.00 eq	0.51 mmol	1.92 mL
CH_2Cl_2			9.0 mL

was obtained following general procedure II using the corresponding 1,3-dione **157a** (1.00 g, 4.63 mmol). Purification by column chromatography using 20:1 (*n*-pentane/Et_2O) afforded **159a** (0.99 g, 4.58 mmol, 99%, *Z*/*E* = 5.2:1) as a yellow solid.

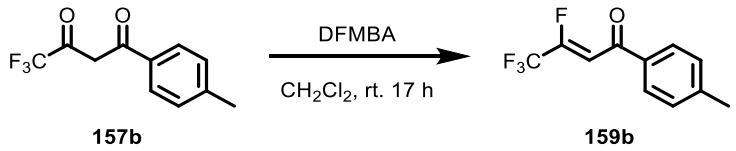
TLC: R_f = 0.45 (*n*-pentane/EtOAc 20:1).

^{1}H-NMR: (300 MHz, $CDCl_3$) δ = 7.98 – 7.87 (m, 2H, CH_{arom}), 7.73 – 7.42 (m, 1H, CH_{arom}),7.61 – 7.42 (m, 2H, CH_{arom}), 6.71 (d, *J* = 30.5 Hz, 1H, CH_{arom}) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −73.2 (d, *J* = 9.8 Hz, CF_3), −116.9 (q, *J* = 9.8 Hz, C*F*) ppm.

The analytical data corresponds to the literature.[119]

(*Z*)-3,4,4,4-Tetrafluoro-1-(*p*-tolyl)but-2-en-1-one (159b)



157b 159b

Diketone **157a** [230.19]	1.00 eq	2.17 mmol	0.50 g
DFMBA [ρ = 1.03]	1.50 eq	3.26 mmol	0.68 mL
CH_2Cl_2			2.0 mL

was obtained following general procedure II using the corresponding 1,3-dione **157b** (0.50 g, 2.17 mmol). Purification by column chromatography using 20:1 (*n*-pentane/Et_2O) afforded **159b** (0.45 g, 1.94 mmol, 89%, *Z*/*E* = 4.6:1) as a yellow oil.

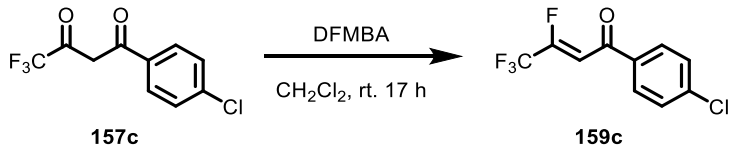
TLC: R_f = 0.50 (*n*-pentane/Et_2O 20:1).

^{1}H-NMR: (300 MHz, $CDCl_3$) δ = 7.82 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 6.76 – 6.61 (m, 1H), 2.44 (s, 3H) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −73.2 (d, *J* = 9.7 Hz, C*F*$_3$), −117.7 (q, *J* = 9.9 Hz, C*F*) ppm.

The analytical data corresponds to the literature.[76]

(*Z*)-1-(4-Chlorophenyl)-3,4,4,4-tetrafluorobut-2-en-1-one (159c)



Diketone **157c** [250.60]	1.00 eq	2.00 mmol	0.50 g
DFMBA [ρ = 1.03]	1.50 eq	3.00 mmol	0.62 mL
CH_2Cl_2			2.0 mL

was obtained following general procedure II using the corresponding 1,3-dione **157c** (0.50 g, 2.00 mmol). Purification by column chromatography using 20:1 (*n*-pentane/Et_2O) afforded **159c** (0.45 g, 1.77 mmol, 89%, *Z*/*E* = 5.0:1) as a yellow solid.

TLC: R_f = 0.50 (*n*-pentane/EtOAc 20:1).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.86 (m, 2H, CH_{arom}), 7.50 (d, *J* = 8.7 Hz, 1H, CH_{arom}), 6.67 (d, *J* = 32.3 Hz, 1H, C*H*) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −73.2 (d, *J* = 9.7 Hz, CF_3), −115.9 (q, *J* = 9.7 Hz, C*F*) ppm.

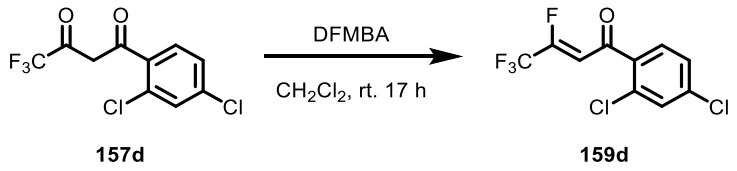
^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 185.5 (*C*O), 151.6 (dq, *J* = 284.6, 40.1 Hz, *C*F), 141.2 (C_{quart}), 134.7 (C_{quart}), 130.3 (C_{arom}), 129.5 (C_{arom}), 117.9 (qd, *J* = 273.8, 40.6 Hz, *C*F_3), 109.8 – 103.2 (m, *C*H) ppm.

HRMS: (EI+); *m/z* calc. for $C_{10}H_5ClF_4O$ $[M]^+$: 215.9965, found 251.9971.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 3071 (w), 2037 (w), 1809 (w), 1706 (m), 1670 (w), 1590 (m), 1489 (w), 1402 (w), 1376 (w), 1292 (m), 1264 (w), 1201 (w), 1152 (s), 1092 (m), 1076 (w), 1026 (w), 1009 (m), 889 (w), 861 (w), 826 (m), 802 (w), 742 (w), 707 (w), 648 (m), 575 (w), 533 (m), 477 (w), 444 (w), 408 (w).

Mp.: 41.6−44.0 °C.

(*Z*)-1-(2,4-Dichlorophenyl)-3,4,4,4-tetrafluorobut-2-en-1-one (159d)



157d **159d**

Diketone **157d** [285.04]	1.00 eq	1.75 mmol	0.50 g
DFMBA [ρ = 1.03]	1.50 eq	2.63 mmol	0.55 mL
CH_2Cl_2			1.8 mL

was obtained following general procedure II using the corresponding 1,3-dione **157d** (0.50 g, 1.75 mmol). Purification by column chromatography using 20:1 (*n*-pentane/Et_2O) afforded **159d** (0.41 g, 1.44 mmol, 82%, *Z*/*E* = 5.5:1) as a white solid.

TLC: R_f = 0.37 (*n*-pentane/EtOAc 50:1).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.53 (d, *J* = 8.3 Hz, 1H, CH_{arom}), 7.48 (d, *J* = 1.9 Hz, 1H, CH_{arom}), 7.38 (dd, *J* = 8.3, 2.0 Hz, 1H, CH_{arom}), 6.58 (d, *J* = 30.1 Hz, 1H, C*H*) ppm.

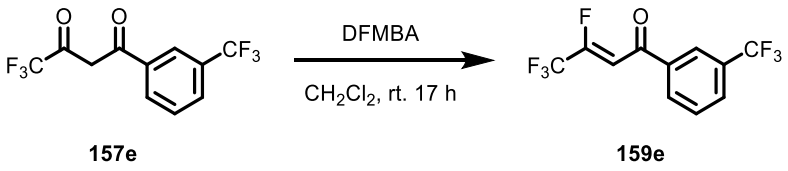
^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −73.5 (d, *J* = 9.3 Hz, CF_3), −114.9 (q, *J* = 9.4 Hz, C*F*) ppm.

^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 186.9 (*C*O), 152.3 (dq, *J* = 288.0, 40.1 Hz, *C*F), 139.5 (C_{quart}), 136.2 (C_{quart}), 133.2 (C_{quart}), 131.6 (C_{arom}), 131.0 (C_{arom}), 128.2 (C_{arom}), 118.1 (qd, *J* = 274.1, 40.5 Hz, *C*F_3), 112.9 – 107.1 (m, *C*H) ppm.

HRMS: (EI+); *m/z* calc. for $C_{10}H_{15}Cl_2F_4O$ $[M]^+$: 285.9575, found 285.9594.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 3090 (w), 1705 (m), 1671 (w), 1584 (m), 1554 (w), 1467 (w), 1370 (m), 1298 (m), 1266 (w), 1206 (m), 1158 (s), 1105 (m), 1081 (w), 1012 (w), 871 (w), 825 (m), 776 (w), 708 (w), 682 (w), 648 (w), 583 (w), 529 (w), 465 (w).

(*Z*)-3,4,4,4-Tetrafluoro-1-(3-(trifluoromethyl)phenyl)but-2-en-1-one (159e)



157e **159e**

Diketone **157e** [284.16]	1.00 eq	3.52 mmol	1.00 g
DFMBA [ρ = 1.03]	1.50 eq	5.28 mmol	1.09 mL
CH_2Cl_2			7.0 mL

was obtained following general procedure II using the corresponding 1,3-dione **157e** (1.00 g, 3.52 mmol). Purification by column chromatography using 20:1 (*n*-pentane/Et_2O) afforded **159e** (0.71 g, 2.47 mmol, 70%, *Z*/*E* = 6.8:1) as a colorless oil.

TLC: R_f = 0.45 (*n*-pentane/EtOAc 20:1).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 8.17 (s, 1H, CH_{arom}), 8.10 (d, J = 7.9 Hz, 1H, CH_{arom}), 7.91 (d, J = 7.6 Hz, 1H, CH_{arom}), 7.69 (t, J = 8.0 Hz, 1H, CH_{arom}), 6.72 (d, J = 30.6 Hz, 1H, C*H*) ppm.

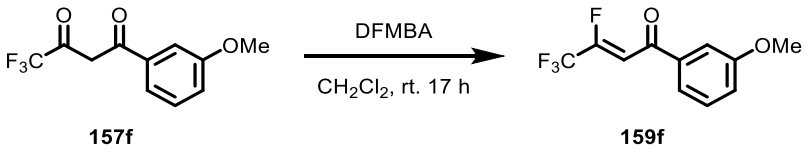
^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −62.9 (d, J = 2.9 Hz, CF_3), −73.2 (dd, J = 9.4, 3.1 Hz, CFCF_3), −114.6 (m, C*F*) ppm.

^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 185.6 (*C*O), 152.4 (dq, J = 286.6, 40.1 Hz, *C*F), 137.1 (C_{quart}), 132.2 (C_{arom}), 132.2 (q, J = 33.3 Hz, C_{quart}), 131.1 (q, J = 3.6 Hz, C_{arom}), 130.2 (C_{arom}), 125.9 (q, J = 3.8 Hz, C_{arom}), 122.7 (d, J = 268.3 Hz, *C*F_3), 117.0 (qd, J = 274.0, 41.0 Hz, CF*C*F_3), 107.4 (m, *C*H).

HRMS: (EI+); *m/z* calc. for $C_{11}H_5F_7O$ $[M]^+$: 286.0229, found 286.0203.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 3080 (w), 1708 (m), 1678 (w), 1612 (w), 1594 (w), 1439 (w), 1371 (w), 1334 (m), 1292 (m), 1248 (w), 1208 (w), 1159 (w), 1131 (s), 1100 (w), 1073 (w), 1039 (w), 1001 (w), 924 (w), 889 (w), 855 (w), 809 (m), 772 (w), 728 (w), 693 (m), 655 (w), 630 (m), 578 (w), 501 (w), 417 (w).

(*Z*)-3,4,4,4-Tetrafluoro-1-(3-methoxyphenyl)but-2-en-1-one (159f)



157f **159f**

Diketone **157f** [246.19]	1.00 eq	4.06 mmol	1.00 g
DFMBA [ρ = 1.03]	1.50 eq	6.09 mmol	1.26 mL
CH_2Cl_2			8.0 mL

was obtained following general procedure II using the corresponding 1,3-dione **157f** (1.00 g, 4.06 mmol). Purification by column chromatography using 20:1 (*n*-pentane/Et_2O) afforded **159f** (0.62 g, 2.51 mmol, 62%, *Z*/*E* = 5.0:1) as a light-yellow oil.

TLC: R_f = 0.39 (20:1 *n*-pentane/Et_2O).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.51 – 7.34 (m, 4H, CH_{arom}), 7.19 (ddd, *J* = 8.1, 2.7, 1.1 Hz, 1H, CH_{arom}), 6.71 (d, *J* = 31.1 Hz, 1H, C*H*), 3.87 (s, 3H, CH_3) ppm.

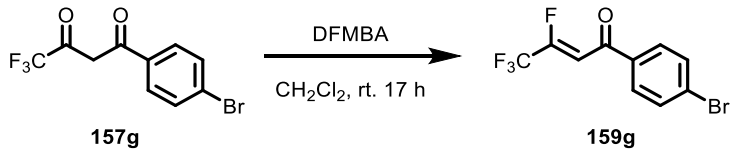
^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −73.2 (d, *J* = 10.2 Hz, CF_3), −117.0 (q, *J* = 9.8 Hz, C*F*) ppm.

^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 186.4 (*C*O), 160.3 (C_{quart}), 151.3 (dq, *J* = 284.0, 39.9 Hz, *C*F), 137.7 (C_{quart}), 130.1 (C_{arom}), 121.7 (C_{arom}), 121.2 (C_{arom}), 117.9 (qd, *J* = 273.7, 40.6 Hz, *C*F_3), 112.7 (C_{arom}), 108.4 – 107.2 (*C*H), 55.7 (*C*H_3) ppm.

HRMS: (EI+); *m/z* calc. for: $C_{11}H_8F_4O_2$ $[M]^+$: 248.0460, found: 248.0487.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 3493 (w), 2987 (w), 2841 (w), 1718 (w), 1603 (w), 1490 (w), 1459 (w), 1440 (w), 1394 (w), 1350 (m), 1265 (m), 1200 (m), 1146 (m), 1028 (w), 986 (s), 906 (w), 856 (w), 829 (w), 788 (w), 764 (w), 698 (m), 631 (w), 544 (w), 480 (w).

(*Z*)-1-(4-Bromophenyl)-3,4,4,4-tetrafluorobut-2-en-1-one (159g)



Diketone **157g** [295.06]	1.00 eq	1.70 mmol	0.50 g
DFMBA [ρ = 1.03]	1.50 eq	2.54 mmol	0.53 mL
CH_2Cl_2			1.70 mL

was obtained following general procedure II using the corresponding 1,3-dione **157g** (0.50 g, 1.70 mmol). Purification by column chromatography using 20:1 (*n*-pentane/Et_2O) afforded **159g** (0.44 g, 1.49 mmol, 88%, *Z*/*E* = 4.3:1) as a white solid.

TLC: R_f = 0.54 (*n*-pentane/Et_2O 40:1).

^{1}H-NMR: (300 MHz, $CDCl_3$) δ = 7.82 – 7.74 (m, 2H, CH_{arom}), 7.67 (d, *J* = 8.6 Hz, 2H, CH_{arom}), 6.85 – 6.37 (d, 1H, C*H*) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −73.2 (d, *J* = 9.7 Hz, CF_3), −115.8 (q, *J* = 9.7 Hz, C*F*) ppm.

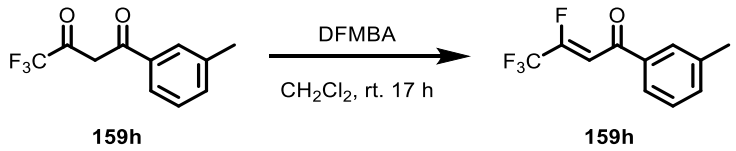
^{13}C-NMR: (76 MHz, $CDCl_3$) δ = 185.7 (*C*O), 151.8 (dq, *J* = 288.4, 43.0 Hz, *C*F), 135.1 (C_{quart}), 132.6 (C_{arom}), 130.3 (C_{arom}), 130.0 (C_{quart}), 117.9 (qd, *J* = 273.8, 40.5 Hz, *C*F_3), 107.7 – 107.4 (m, *C*F) ppm.

HRMS: (EI+); *m/z* calc. for $C_{10}H_5BrF_4O$ $[M]^+$: 295.9460, found 295.9460.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 1704 (s), 1654 (s), 1587 (s), 1379 (s), 1314 (s), 1209 (s), 1144 (s), 1080 (s), 1006 (m), 890 (m), 839 (m), 819 (s), 800 (s), 736 (m), 645 (w), 462 (s).

Mp.: 63.2−64.9 °C.

(*Z*)-3,4,4,4-Tetrafluoro-1-(*m*-tolyl)but-2-en-1-one (159h)



159h 159h

Diketone **159h** [230.19, ρ = 1.25]	1.00 eq	4.34 mmol	0.80 mL
DFMBA [ρ = 1.03]	1.50 eq	6.51 mmol	1.35 mL
CH_2Cl_2			9.0 mL

was obtained following general procedure II the corresponding 1,3-dione **159h** (1.00 g, 4.34 mmol). Purification by column chromatography using 10:1 (*n*-pentane/Et_2O) afforded **159h** (0.80 g, 3.43 mmol, 79%, *Z*/*E* = 5.8:1) as a light-yellow oil.

TLC: R_f = 0.72 (*n*-pentane/Et_2O 10:1).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.89 – 7.72 (m, 2H, CH_{arom}), 7.58 – 7.54 (m, 1H, CH_{arom}), 7.50 (t, *J* = 7.6 Hz, 1H, CH_{arom}), 6.82 (d, *J* = 31.1 Hz, 1H, C*H*), 2.54 (s, 3H, CH_3) ppm.

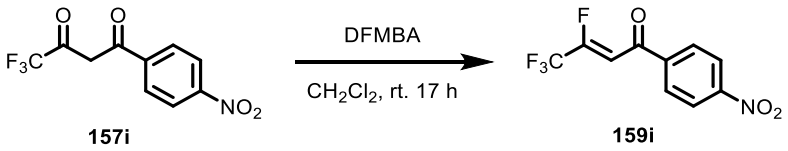
^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −73.2 (d, *J* = 9.8 Hz, CF_3), −117.2 – -117.5 (m, C*F*) ppm.

^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 186.8 (*C*O), 151.1 (dq, *J* = 283.3, 39.8 Hz, *C*F), 139.1 (C_{quart}), 136.4 (C_{quart}), 135.4 (C_{arom}), 129.3 (C_{arom}), 129.0 (C_{arom}), 126.2 (C_{arom}), 118.0 (qd, *J* = 273.7, 40.8 Hz, *C*F_3), 108.0 (p, *J* = 3.1 Hz, *C*H), 21.5 (*C*H_3) ppm.

HRMS: (EI+); *m/z* calc. for $C_{11}H_8F_4O$ $[M]^+$: 232.0511, found 232.0510.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 3066 (w), 2926 (w), 1811 (w), 1705 (m), 1664 (w), 1604 (w), 1585 (w), 1485 (w), 1431 (w), 1368 (m), 1295 (m), 1203 (m), 1153 (s), 1075 (m), 1000 (w), 928 (w), 891 (w), 864 (w), 794 (m), 720 (w), 689 (m), 629 (m), 578 (w), 519 (w), 470 (w), 420 (w).

(*Z*)-3,4,4,4-Tetrafluoro-1-(4-nitrophenyl)but-2-en-1-one (159i)



Diketone **157i** [261.16]	1.00 eq	1.07 mmol	0.28 g
DFMBA [ρ = 1.03]	1.50 eq	1.60 mmol	0.33 mL
CH_2Cl_2			2.0 mL

was obtained following general procedure II using the corresponding 1,3-dione **157i** (0.28 g, 1.07 mmol). Purification by column chromatography using 20:1 (*n*-pentane/Et_2O) afforded **159i** (0.16 g, 0.63 mmol, 59%, *Z*/*E* > 25:1) as a yellow oil.

TLC: R_f = 0.30 (*n*-pentane/Et_2O 20:1).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 8.38 (d, *J* = 8.9 Hz, 2H, CH_{arom}), 8.08 (d, *J* = 8.6 Hz, 2H, CH_{arom}), 6.73 (d, *J* = 28.7 Hz, 1H, C*H*) ppm.

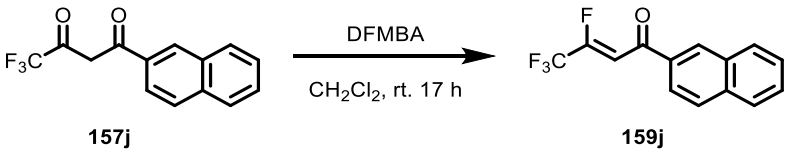
^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −73.2 (d, *J* = 9.3 Hz, CF_3), −113.2 (q, *J* = 9.3 Hz, C*F*) ppm.

^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 185.2 (*C*O), 152.6 (dq, *J* = 286.9, 40.8 Hz, *C*F), 151.1 (C_{quart}), 140.7 (C_{quart}), 129.9 (C_{arom}), 124.4 (C_{arom}), 117.7 (qd, *J* = 274.2, 40.2 Hz, *C*F_3), 107.2 – 106.8 (m, *C*H) ppm.

HRMS: (EI+); *m/z* calc. for $C_{10}H_5F_4NO_3$ $[M]^+$: 263.0206, found 263.0216.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 3110 (w), 2962 (w), 2922 (w), 2854 (w), 1705 (m), 1681 (w), 1604 (w), 1527 (s), 1410 (w), 1377 (w), 1348 (m), 1293 (m), 1261 (m), 1200 (w), 1154 (s), 1130 (w), 1079 (w), 1024 (w), 1012 (w), 874 (w), 851 (w), 797 (s), 752 (w), 711 (w), 642 (w), 574 (w), 508 (w), 456 (w).

(*Z*)-3,4,4,4-Tetrafluoro-1-(naphthalen-2-yl)but-2-en-1-one (159j)



157j 159j

Diketone **157j** [266.22]	1.00 eq	1.88 mmol	0.50 g
DFMBA [ρ = 1.03]	2.00 eq	3.76 mmol	0.78 mL
CH_2Cl_2			4.0 mL

was obtained following general procedure II using the corresponding 1,3-dione **157j** (0.50 g, 1.88 mmol). Purification by column chromatography using 20:1 (*n*-pentane/Et_2O) afforded **159j** (0.46 g, 1.70 mmol, 91%, *Z*/*E* = 5.1:1) as a white solid.

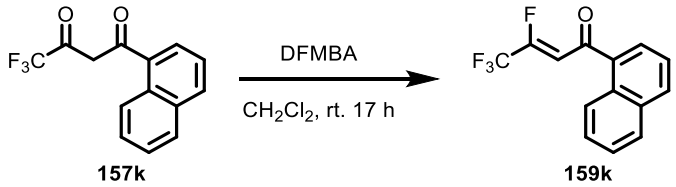
TLC: R_f = 0.50 (*n*-pentane/EtOAc 20:1).

^{1}H-NMR: (300 MHz, $CDCl_3$) δ = 8.40 (s, 1H, CH_{arom}), 8.11 – 7.81 (m, 4H, CH_{arom}), 7.74 – 7.50 (m, 2H, CH_{arom}), 6.86 (d, *J* = 30.7 Hz, 1H, C*H*) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −73.1 (d, *J* = 9.9 Hz, CF_3), −117.1 (q, *J* = 9.8 Hz, C*F*) ppm.

The analytical data corresponds to the literature.[78]

(*Z*)-3,4,4,4-Tetrafluoro-1-(naphthalen-2-yl)but-2-en-1-one (159k)



Diketone **157k** [266.22]	1.00 eq	2.56 mmol	0.68 g
DFMBA [ρ = 1.03]	1.50 eq	3.84 mmol	0.79 mL
CH_2Cl_2			6.0 mL

was obtained following general procedure II using the corresponding 1,3-dione **157k** (0.68 g, 2.56 mmol). Purification by column chromatography using 20:1 (*n*-pentane/Et_2O) afforded **159k** (0.69 g, 2.56 mmol, quant., *Z*/*E* = 6.8:1) as a colorless oil.

TLC: R_f = 0.48 (*n*-pentane/Et_2O 20:1).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 8.76 (dd, *J* = 8.6, 1.0 Hz, 1H, C*H*$_{arom}$), 8.08 (dt, *J* = 8.6, 1.1 Hz, 1H, C*H*$_{arom}$), 7.91 (tt, *J* = 8.5, 1.1 Hz, 2H, C*H*$_{arom}$), 7.67 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H, C*H*$_{arom}$), 7.59 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H, C*H*$_{arom}$), 7.55 (dd, *J* = 8.2, 7.2 Hz, 1H, C*H*$_{arom}$), 6.71 (d, *J* = 31.2 Hz, 1H, C*H*) ppm.

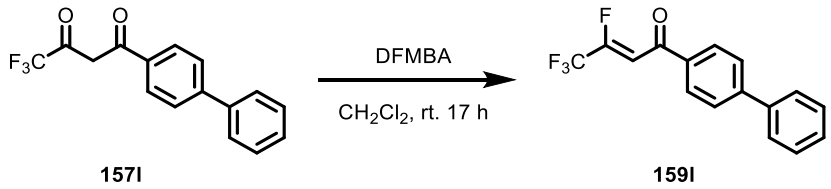
^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −73.1 (d, *J* = 9.8 Hz, C*F*$_3$), −117.1 (q, *J* = 7.9 Hz, C*F*) ppm.

^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 189.1 (*C*O), 150.9 (dq, *J* = 283.4, 39.9 Hz, *C*F), 134.8 (*C*$_{arom}$), 134.1 (*C*$_{quart}$), 133.9 (*C*$_{quart}$), 130.5 (d, *J* = 1.4 Hz, *C*$_{arom}$), 130.4 (*C*$_{quart}$), 128.9 (*C*$_{arom}$), 128.8 (*C*$_{arom}$), 127.1 (*C*$_{arom}$), 125.5 (*C*$_{arom}$), 124.5 (*C*$_{arom}$), 118.0 (qd, *J* = 273.8, 40.8 Hz, *C*F_3), 110.7 (t, *J* = 2.9 Hz, *C*H) ppm.

HRMS: (EI+); *m/z* calc. for: $C_{14}H_8F_4O_1$ $[M]^+$: 268.0511, found: 268.0520.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 3056 (w), 1945 (w), 1809 (w), 1702 (m), 1655 (m), 1593 (w), 1573 (w), 1509 (m), 1461 (w), 1437 (w), 1368 (m), 1290 (m), 1268 (w), 1233 (w), 1202 (w), 1151 (s), 1102 (w), 1068 (w), 1025 (w), 962 (w), 859 (w), 844 (w), 804 (m), 776 (s), 736 (w), 699 (w), 677 (w), 630 (w), 613 (w), 578 (w), 499 (w), 455 (w), 417 (w).

(*Z*)-1-([1,1'-Biphenyl]-4-yl)-3,4,4,4-tetrafluorobut-2-en-1-one (159l)



157l 159l

Diketone **157l** [292.26]	1.00 eq	3.42 mmol	1.00 g
DFMBA [ρ = 1.03]	1.50 eq	5.13 mmol	1.06 mL
CH_2Cl_2			12.0 mL

was obtained following general procedure II using the corresponding 1,3-dione **157l** (1.00 g, 3.42 mmol). Purification by column chromatography using 20:1 (*n*-pentane/Et_2O) afforded **159l** (0.80 g, 2.72 mmol, 80%, *Z*/*E* = 4.6:1) as a yellow oil.

TLC: R_f = 0.80 (*n*-pentane/Et_2O 10:1).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 8.00 (d, *J* = 9.4 Hz,2H, C*H*$_{arom}$), 7.74 (d, *J* = 12.5 Hz, 2H, C*H*$_{arom}$), 7.64 (d, *J* = 12.6 Hz, 2H, C*H*$_{arom}$), 7.53 – 7.46 (m, 2H, C*H*$_{arom}$), 7.43 (d, *J* = 17.3 Hz, 1H, C*H*$_{arom}$), 6.75 (d, *J* = 31.0 Hz, 1H, C*H*) ppm.

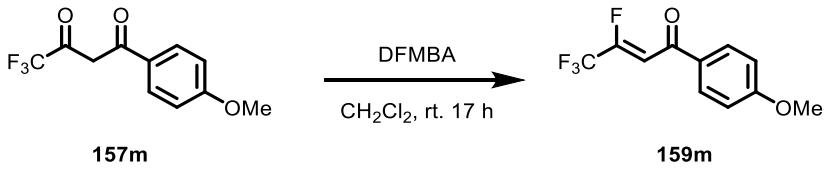
^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −73.1 (d, *J* = 9.8 Hz, C*F*$_3$), −117.0 (q, *J* = 9.8 Hz, C*F*) ppm.

^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 186.2 (*C*O), 151.2 (dq, *J* = 283.3, 39.8 Hz, *C*FCF$_3$), 147.3 (*C*$_{quart}$), 139.6 (*C*$_{quart}$), 135.1 (*C*$_{quart}$), 129.5 (*C*$_{arom}$), 129.2 (*C*$_{arom}$), 128.8 (*C*$_{arom}$), 127.8 (*C*$_{arom}$), 127.5 (*C*$_{arom}$), 117.9 (qd, *J* = 273.7, 40.7 Hz, CF*C*F$_3$), 108.0 (p, *J* = 3.0 Hz, *C*H) ppm.

HRMS: (EI+); *m/z* calc. for: $C_{16}H_{10}F_4O_1$ $[M]^+$: 294.0668, found: 294.0648.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 1700 (m), 1643 (m), 1601 (m), 1384 (m), 1320 (w), 1301 (s), 1210 (s), 1142 (m), 1081 (m), 1031 (w), 1003 (w), 891 (w), 859 (w), 834 (m), 771 (m), 734 (m), 678 (m), 622 (w), 579 (w), 505 (w), 448 (w).

(*Z*)-3,4,4,4-Tetrafluoro-1-(4-methoxyphenyl)but-2-en-1-one (159m)



157m **159m**

Diketone **157m** [246.19]	1.00 eq	1.22 mmol	0.30 g
DFMBA [ρ = 1.03]	1.50 eq	1.83 mmol	0.38 mL
CH_2Cl_2			1.20 mL

was obtained following general procedure II using the corresponding 1,3-dione **157m** (0.30 g, 1.22 mmol). Purification by column chromatography using 20:1 (*n*-pentane/Et_2O) afforded **159m** (0.26 g, 1.04 mmol, 85%, *Z*/*E* = 2.5:1) as a yellow oil.

TLC: R_f = 0.25 (*n*-pentane/EtOAc 20:1).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.93 – 7.75 (m, 2H, CH_{arom}), 6.99 (d, *J* = 8.9 Hz, 2H, CH_{arom}), 6.65 (d, *J* = 32.1 Hz, 1H, C*H*), 3.90 (s, 3H, CH_3) ppm.

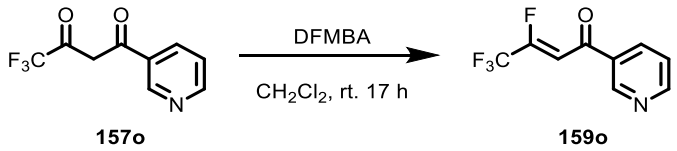
^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −73.1 (d, *J* = 10.1 Hz, CF_3), −118.4 (d, *J* = 10.1 Hz, C*F*) ppm.

^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 184.9 (*C*O), 164.7 (C_{quart}), 150.4 (qd, *J* = 281.2, 39.4 Hz, CF*C*F_3), 131.3 (C_{arom}), 129.3 (C_{quart}), 117.9 (dq, *J* = 273.4, 41.1 Hz), 114.3 (C_{arom}), 108.8 – 104.2 (m, *C*H), 55.6 (*C*H_3) ppm.

HRMS: (ESI+); *m/z* calc. for: $C_{11}H_8F_4O_2Na$ $[M+Na]^+$: 271.0353, found: 271.0354.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 3017 (w), 2941 (w), 2846 (w), 1701 (w), 1663 (w), 1599 (s), 1575 (w), 1512 (w), 1464 (w), 1424 (w), 1377 (m), 1313 (w), 1297 (w), 1264 (m), 1238 (w), 1201 (w), 1166 (s), 1127 (w), 1076 (w), 1023 (w), 865 (w), 835 (m), 782 (w), 693 (w), 636 (w), 608 (w), 572 (w), 516 (w).

(*Z*)-3,4,4,4-Tetrafluoro-1-(pyridin-2-yl)but-2-en-1-one (159o)



157o 159o

Diketone **157o** [217.15]	1.00 eq	4.61 mmol	1.00 g
DFMBA [ρ = 1.03]	1.50 eq	6.91 mmol	1.43 mL
CH_2Cl_2			15.0 mL

was obtained following general procedure II using the corresponding 1,3-dione **157o** (1.00 g, 4.61 mmol). Purification by column chromatography using 2:1 (*n*-pentane/Et_2O) afforded **159o** (0.31 g, 1.43 mmol, 31%, *Z*/*E* > 25:1) with the *N*, *N*-diethyl-3-methylbenzamide as a yellow oil.

TLC: R_f = 0.30 (*n*-pentane/EtOAc 2:1).

^{1}H-NMR: (300 MHz, $CDCl_3$), δ = 9.11 (s, 1H), 8.85 (d, *J* = 4.8 Hz, 1H), 8.21 (dd, *J* = 8.0 Hz, 1.8 Hz, 1H), 7.48 (dd, *J* = 8.3 Hz, 4.5 Hz, 1H), 6.71 (d, *J* = 30.8 Hz, 1H) ppm.

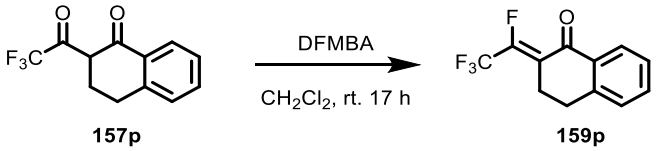
^{19}F-NMR: (282 MHz, CDCl3), δ = − 73.2 (d, *J* = 9.5 Hz, C*F3*), − 114.2 (q, *J* = 9.5 Hz, 1F, C*F*) ppm.

^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 185.5 (*C*O), 154.6 (C_{arom}), 152.2 (dq, *J* = 286.7, 40.2 Hz, *C*CF_3), 150.1 (C_{arom}), 136.0 (C_{arom}), 131.9 (C_{quart}), 124.0 (C_{arom}), 117.7 (qd, *J* = 273.9, 40.4 Hz, CF*C*F_3), 107.1 (m, *C*HCF) ppm.

HRMS: (EI+): *m/z* calc. for: $C_9H_5F_4NO$ $[M]^+$, 219.0307, found: 219.0311.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 1705 (w), 1626 (w), 1586 (m), 1421 (w), 1367 (w), 1332 (w), 1299 (w), 1194 (s), 1153 (w), 1105 (w), 1081 (w), 1025 (w), 804 (w), 730 (w), 702 (w), 636 (w).

(*Z*)-2-(Perfluoroethylidene)-3,4-dihydronaphthalen-1(2H)-one (159p)



157p 159p

Diketone **157p** [217.15]	1.00 eq	2.06 mmol	0.50 g
DFMBA [ρ = 1.03]	1.20 eq	2.47 mmol	0.51 mL
CH_2Cl_2			6.0 mL

was obtained following general procedure II using the corresponding 1,3-dione **157p** (0.50 g, 2.06 mmol). Purification by column chromatography using 20:1 (*n*-pentane/Et_2O) afforded **159p** (0.41 g, 1.69 mmol, 82%, *Z*/*E* = 1.6:1) as a yellow solid.

TLC: R_f = 0.50 (*n*-pentane/EtOAc 20:1).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 8.09 (dd, *J* = 7.8, 1.4 Hz, 1H, CH_{arom}), 7.54 (td, *J* = 7.5, 1.5 Hz, 1H, CH_{arom}), 7.43 – 7.35 (m, 1H, CH_{arom}), 7.31 – 7.27 (m, 1H, CH_{arom}), 3.12 (t, *J* = 6.3 Hz, 2H, CH_2), 3.03 – 2.95 (m, 2H, CH_2CCF) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −66.3 (d, *J* = 6.7 Hz, CF_3), −119.8 (q, *J* = 6.3 Hz, F, C*F*) ppm.

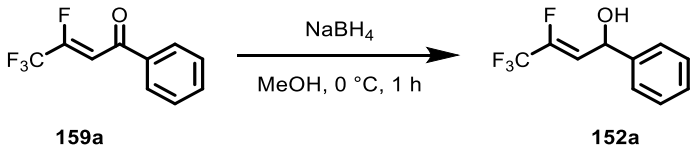
^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 184.9 (d, *J* = 9.5 Hz,*C*O), 148.1 (dq, *J* = 270.5, 42.3 Hz, *C*F), 143.1 (C_{quart}), 134.4 (C_{arom}), 132.8 (d, *J* = 4.5 Hz, C_{quart}), 128.9 (C_{arom}), 128.1 (C_{arom}), 127.5 (C_{arom}), 124.6 – 124.2 (m, C_{quart}CF), 118.4 (qd, *J* = 274.0, 41.7 Hz, *C*F_3), 29.0 (d, *J* = 2.5 Hz, *C*H_2), 25.5 (d, *J* = 7.1 Hz, *C*H_2CCF) ppm.

HRMS: (EI+); *m/z* calc. for $C_{12}H_8F_4O$ $[M]^+$: 244.0511, found 244.0560.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 2943 (w), 2261 (w), 1699 (w), 1653 (m), 1599 (w), 1483 (w), 1455 (w), 1436 (w), 1327 (s), 1296 (w), 1247 (w), 1189 (w), 1149 (s), 1092 (w), 1023 (w), 1009 (w), 964 (w), 942 (m), 910 (w), 895 (m), 841 (m), 799 (w), 773 (w), 736 (s), 671 (w), 655 (m), 582 (w), 474 (w), 436 (w).

Mp.: 56.5−59.2 °C.

(*Z*)-3,4,4,4-tetrafluoro-1-phenylbut-2-en-1-ol (152a)



159a 152a

Fluorenone **159a** [218.15]	1.00 eq	1.76 mmol	383 mg
$NaBH_4$ [37.83]	1.20 eq	2.11 mmol	79.7 mg
MeOH			8.0 mL

Following general procedure III using the *β*-fluoroenone **159a** (383 mg, 1.76 mmol,) the crude product was purified by column chromatography using 4:1 (*n*-pentane/Et_2O) giving the product **152a** as a yellow oil (384 mg, 1.74 mmol, 99%).

TLC: R_f = 0.30 (*n*-pentane/Et_2O 4:1).

^{1}H-NMR: (300 MHz, $CDCl_3$) δ = 7.35 – 7.18 (m, 5H, CH_{arom}), 5.84 – 5.67 (m, 1H, C*H*CF), 5.63 (d, *J* = 8.6 Hz, 1H, C*H*OH), 2.06 (s, 1H, O*H*) ppm.

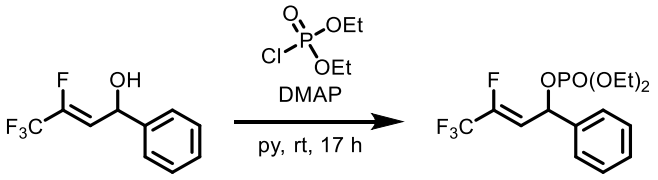
^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −72.8 (d, *J* = 11.2 Hz, CF_3), −133.6 (q, *J* = 11.1 Hz, F, C*F*) ppm.

^{13}C-NMR: (76 MHz, $CDCl_3$) δ = 145.8 (qd, *J* = 261.5, 39.7 Hz, CFCF_3), 141.0 (d, *J* = 1.7 Hz, C_{quart}), 129.1 (C_{arom}), 128.7 (C_{arom}), 125.9 (C_{arom}), 118.3 (dq, *J* = 271.8, 41.5 Hz, C*F*CF_3), 115.4 (dq, *J* = 6.3, 3.1 Hz, *C*HCF), 67.0 (d, *J* = 4.0 Hz, *C*HOH) ppm.

HRMS: (EI+); *m/z* calc. for $C_{12}H_8F_4O$ $[M]^+$: 220.05113, found 220.05217.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 3352 (w), 1715 (w), 1454 (w), 1354 (m), 1237 (w), 1198 (m), 1146 (s), 1103 (w), 1075 (w), 1047 (w), 1003 (w), 875 (w), 853 (w), 761 (w), 701 (m).

(*Z*)-Diethyl (3,4,4,4-tetrafluoro-1-phenylbut-2-en-1-yl) phosphate (183a)



152a **183a**

Alcohol **152a** [220.17]	1.00 eq	1.74 mmol	384 mg
DMAP [122.17]	0.10 eq	176 µmol	21.4 mg
Diethyl phosphorochloridate [172.55, ρ = 1.19]	3.00 eq	5.27 mmol	0.76 mL
Pyridine			1.8 mL

was obtained following general procedure IV using the corresponding alcohol **152a** (386 mg, 1.76 mmol). Purification by column chromatography using 1:1 (*n*-pentane/Et_2O) afforded **183a** (445 mg, 1.25 mmol, 72%) as a yellow oil.

TLC: R_f = 0.20 (*n*-pentane/Et_2O 1:1).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.45 – 7.32 (m, 5H, CH_{arom}), 6.21 (t, J = 8.7 Hz, 1H, C*H*O), 5.92 (dd, J = 31.3, 9.4 Hz, 1H, C*H*CF), 4.38 – 3.60 (m, 4H, 2CH_2), 1.26 (dqd, J = 20.4, 7.0, 1.0 Hz, 6H, 2CH_3) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −72.9 (d, J = 11.1 Hz, CF_3), −130.8 (q, J = 10.9 Hz, C*F*) ppm.

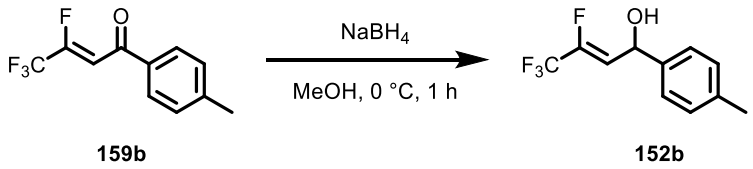
^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 146.2 (dq, J = 265.0, 40.0 Hz, *C*F), 137.6 (d, J = 5.4 Hz, C_{quart}), 129.3 (C_{arom}), 129.1 (C_{arom}), 126.4 (C_{arom}), 118.1 (qd, J = 272.1, 40.9 Hz, *C*F_3), 112.8 (dq, J = 6.2, 3.2 Hz, *C*HCF), 71.5 (t, J = 4.3 Hz, *C*HO), 64.2 (d, J = 5.7 Hz, 2*C*H_2), 16.0 (t, J = 6.6 Hz, 2*C*H_3) ppm.

^{31}P-NMR: (122 MHz, $CDCl_3$) δ = −2.02 ppm.

HRMS: (ESI+); *m/z* calc. for $C_{14}H_{17}F_4O_4PNa$ $[M+Na]^+$: 379.0695, found 379.0695.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 2987 (w), 2912 (w), 1719 (w), 1456 (w), 1394 (w), 1353 (w), 1272 (m), 1201 (m), 1148 (m), 1071 (w), 1030 (s), 985 (w), 903 (w), 836 (w), 818 (w), 734 (w), 700 (m), 619 (w), 599 (w), 557 (w), 535 (w).

(*Z*)-3,4,4,4-Tetrafluoro-1-(*p*-tolyl)but-2-en-1-ol (152b)



159b **152b**

Fluorenone **159b** [232.19]	1.00 eq	1.29 mmol	300 mg
$NaBH_4$ [37.83]	1.20 eq	1.55 mmol	58.7 mg
MeOH			6.0 mL

Following general procedure III using the *β*-fluoroenone **159b** (300 mg, 1.29 mmol), the crude product was obtained as a yellow oil and directly used in the phosphorylation without further purification.

TLC: R_f = 0.10 (*n*-pentane/Et_2O 20:1).

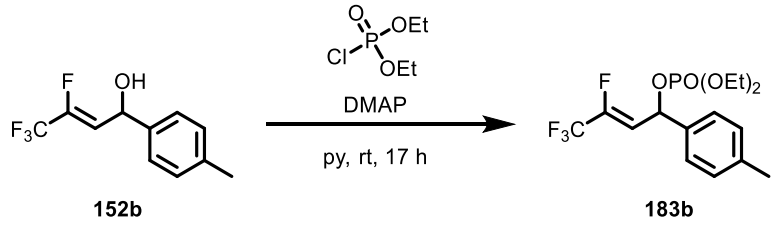
^{1}H-NMR: (300 MHz, $CDCl_3$) δ = 7.40 – 7.08 (m, 5H, CH_{arom}), 5.88 (dd, *J* = 31.9, 9.4 Hz, 1H, C*H*CF), 5.77 – 5.62 (m, 1H, C*H*OH), 2.39 (s, 3H, CH_3), 2.10 (d, *J* = 3.3 Hz, 1H, O*H*) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −72.8 (d, *J* = 11.2 Hz, CF_3), −133.8 (q, *J* = 11.1 Hz, C*F*) ppm.

^{13}C NMR: (126 MHz, $CDCl_3$) δ = 145.6 (dq, *J* = 261.3, 39.6 Hz, *C*FCF_3), 138.7 (C_{arom}), 138.6 (C_{arom}), 129.8 (C_{arom}), 125.9 (C_{arom}), 125.8 (C_{arom}), 118.3 (qd, *J* = 271.8, 41.5 Hz, CF*C*F_3), 115.5 (dq, *J* = 6.5, 3.2 Hz, *C*HCF), 66.8 (d, *J* = 3.8 Hz, *C*HOH), 21.3 (*C*H_3).

HRMS: (EI+); *m/z* calc. for $C_{11}H_{10}F_4O_1$ $[M]^+$: 234.06678, found 234.06757.

(*Z*)-Diethyl (3,4,4,4-tetrafluoro-1-(*p*-tolyl)but-2-en-1-yl) phosphate (183b)



152b 183b

Alcohol **152b** [234.19]	1.00 eq	1.29 mmol	303 mg
DMAP [122.17]	0.10 eq	129 µmol	15.8 mg
Diethyl phosphorochloridate [172.55, ρ = 1.19]	2.00 eq	2.58 mmol	0.37 mL
Pyridine			1.3 mL

was obtained following general procedure IV using the corresponding alcohol **152b** (303 mg, 1.29 mmol). Purification by column chromatography using 1:2 (*n*-pentane/Et_2O) afforded **183b** (240 mg, 0.648 mmol, 50% over two steps) as a yellow oil.

TLC: R_f = 0.40 (*n*-pentane/Et_2O 1:2).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.30 – 7.28 (m, 2H, CH_{arom}), 7.22 – 7.15 (m, 2H, CH_{arom}), 6.17 (t, J = 8.6 Hz, 1H, C*H*O), 5.92 (dd, J = 30.7, 8.0 Hz, 1H, C*H*CF), 4.20 – 3.79 (m, 4H, 2CH_2), 2.35 (s, 3H, CH_3), 1.44 – 0.85 (m, 6H, 2CH_3) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −72.9 (d, J = 11.0 Hz, CF_3), −131.1 (q, J = 10.9 Hz, C*F*) ppm.

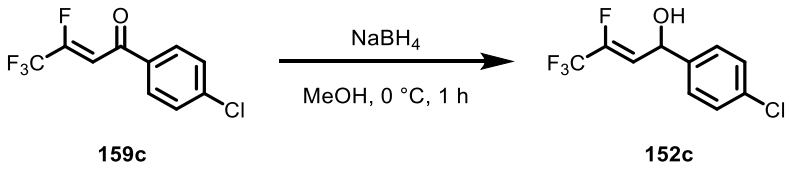
^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 146.0 (dq, J = 264.6, 39.9 Hz, *C*F), 139.3 (C_{quart}), 134.7 (d, J = 5.4 Hz, C_{quart}), 129.8 (C_{arom}), 126.3 (C_{arom}), 118.1 (qd, J = 272.0, 41.0 Hz, *C*F_3), 112.9 (dq, J = 6.2, 3.1 Hz, *C*HCF), 71.5 – 64.1 (m, *C*HO), 64.1 (d, J = 5.7 Hz, 2*C*H_2), 21.3 (*C*H_3), 16.1 (t, J = 6.9 Hz, 2*C*H_3) ppm.

^{31}P-NMR: (202 MHz, $CDCl_3$) δ = −2.01 ppm.

HRMS: (ESI+); *m/z* calc. for $C_{15}H_{19}F_4O_4PNa$ $[M+Na]^+$: 393.0849, found 393.0849.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 2987 (w), 1719 (w), 1515 (w), 1446 (w), 1351 (w), 1271 (m), 1199 (m), 1147 (m), 1105 (w), 1027 (w), 981 (s), 904 (w), 838 (w), 810 (m), 771 (w), 751 (w), 717 (w), 694 (w), 554 (m).

(*Z*)-1-(4-Chlorophenyl)-3,4,4,4-tetrafluorobut-2-en-1-ol (152c)



159c **152c**

Fluorenone **159c** [252.59]	1.00 eq	1.19 mmol	300 mg
$NaBH_4$ [37.83]	1.20 eq	1.43 mmol	53.9 mg
MeOH			5.0 mL

Following general procedure III using the *β*-fluoroenone **159c** (300 mg, 1.19 mmol), the crude product was obtained as a yellow oil and directly used in the phosphorylation without further purification.

TLC: R_f = 0.10 (20:1 *n*-pentane/Et_2O).

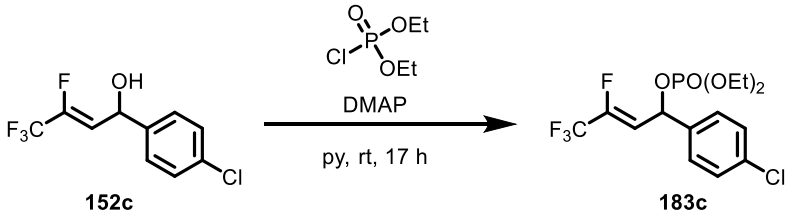
^{1}H-NMR: (300 MHz, $CDCl_3$) δ = 7.54 – 6.99 (m, 4H, CH_{arom}), 5.92 – 5.36 (m, 2H, C*H*OH and C*H*CF), 2.19 (s, 1H, O*H*) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −72.8 (d, *J* = 11.1 Hz, CF_3), −132.9 (q, *J* = 10.9 Hz, C*F*) ppm.

^{13}C-NMR: (75 MHz, $CDCl_3$) δ = 145.9 (qd, *J* = 261.9, 39.7 Hz, CF*C*F_3), 139.3 (C_{quart}), 134.4 (C_{arom}), 129.1 (C_{arom}), 127.1 (C_{arom}), 118.1 (dq, *J* = 272.0, 41.5 Hz, *C*FCF3), 115.7 – 114.7 (*C*HCF), 66.2 (d, *J* = 4.0 Hz, *C*HOH) ppm.

HRMS: (EI+); *m/z* calc. for $C_{10}H_7ClF_4O_1$ $[M]^+$: 254.01216, found 254.01032.

(*Z*)-1-(4-Chlorophenyl)-3,4,4,4-tetrafluorobut-2-en-1-yl diethyl phosphate (183c)



Alcohol **152c** [254.61]	1.00 eq	1.19 mmol	303 mg
DMAP [122.17]	0.10 eq	119 µmol	14.5 mg
Diethyl phosphorochloridate [172.55, ρ = 1.19]	1.20 eq	1.43 mmol	0.21 mL
Pyridine			1.2 mL

was obtained following general procedure IV using the corresponding alcohol **152c** (303 mg, 1.19 mmol). Purification by column chromatography using 1:2 (*n*-pentane/Et_2O) afforded **183c** (240 mg, 0.61 mmol, 52% over two steps) as a yellow oil.

TLC: R_f = 0.40 (*n*-pentane/Et_2O 1:2).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.40 – 7.35 (m, 2H, CH_{arom}), 7.37 – 7.31 (m, 2H, CH_{arom}), 6.18 (t, J = 8.6 Hz, 1H, C*H*O), 5.88 (dd, J = 31.1, 8.7 Hz, 1H, C*H*CF), 4.19 – 3.89 (m, 4H, 2CH_2), 1.27 (dtd, J = 17.9, 7.1, 1.1 Hz, 6H, 2CH_3) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −72.9 (d, J = 10.8 Hz, CF_3), −130.1 (q, J = 10.9 Hz, C*F*) ppm.

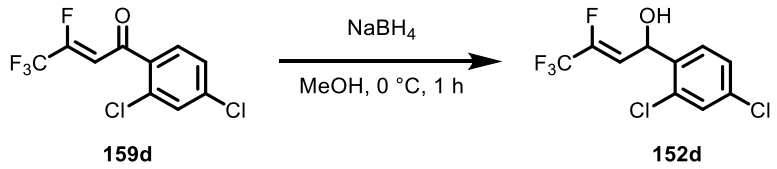
^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 146.3 (dq, J = 265.6, 40.0 Hz, *C*F), 136.0 (d, J = 5.7 Hz, C_{quart}), 135.1 (C_{quart}), 129.2 (C_{arom}), 127.6 (C_{arom}), 117.9 (qd, J = 272.2, 40.8 Hz, *C*F_3), 112.3 (dq, J = 6.1, 3.2 Hz, H*C*F), 70.8 – 70.6 (m, *C*HO), 64.2 (d, J = 5.7 Hz, 2*C*H_2), 16.1 – 15.9 (m, 2*C*H_3) ppm.

^{31}P-NMR: (122 MHz, $CDCl_3$) δ = −2.02 ppm.

HRMS: (ESI+); *m/z* calc. for $C_{14}H_{16}ClF_4O_4PNa$ $[M+Na]^+$: 413.0304, found 413.0304.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 2988 (w), 2912 (w), 1720 (w), 1492 (w), 1445 (w), 1394 (w), 1368 (w), 1350 (w), 1273 (m), 1201 (m), 1150 (m), 1095 (w), 1030 (s), 986 (w), 904 (w), 838 (w), 818 (m), 757 (w), 706 (w), 679 (w), 557 (m), 534 (w).

(*Z*)-1-(2,4-Dichlorophenyl)-3,4,4,4-tetrafluorobut-2-en-1-ol (152d)



159d 152d

Fluorenone **159d** [287.03]	1.00 eq	696 µmol	200 mg
$NaBH_4$ [37.83]	1.20 eq	835 µmol	31.6 mg
MeOH			3.5 mL

Following general procedure III using the *β*-fluoroenone **159d** (200 mg, 696 µmol), the crude product **152d** was purified by column chromatography using 4:1 (*n*-pentane/Et_2O) giving the product as a white solid (179 mg, 618 µmol, 89%).

TLC: R_f = 0.53 (*n*-pentane/Et_2O 4:1).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.55 (d, *J* = 8.4 Hz, 1H, C*H*$_{arom}$), 7.40 (d, *J* = 2.1 Hz, 1H, C*H*$_{arom}$), 7.33 (dd, *J* = 8.3 Hz, 2.1 Hz, 1H, C*H*$_{arom}$), 6.01 (dd, *J* = 8.8 Hz, 3.9 Hz, 1H, C*H*$_{arom}$), 5.72 (dd, *J* = 32.1 Hz, 8.8 Hz, 1H, C*H*CF), 2.37 (d, *J* = 4.1 Hz, 1H, O*H*) ppm.

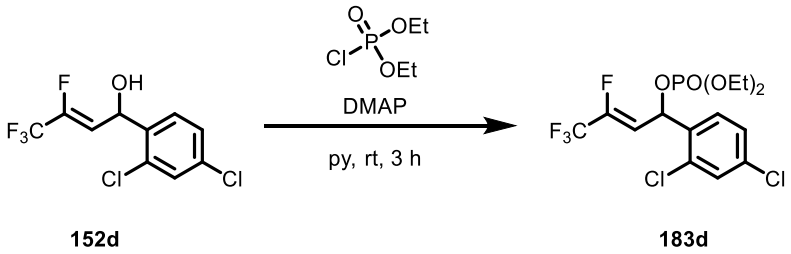
^{19}F-NMR: (282 MHz, $CDCl_3$) δ = − 72.8 (d, *J* = 11.0 Hz, C*F*$_3$), − 130.5 (q, *J* = 10.9 Hz, 1F, C*F*) ppm.

^{13}C-NMR: (125 MHz, $CDCl_3$) δ = 146.6 (dq, *J* = 264.8, 39.6 Hz, *C*FCF$_3$), 136.9 (*C*$_{quart}$), 135.0 (*C*$_{quart}$), 133.0 (*C*$_{quart}$), 129.8 (*C*$_{arom}$), 128.4 (*C*$_{arom}$), 128.0 (*C*$_{arom}$), 120.4 (qd, *J* = 272.8, 41.0 Hz, CF*C*F$_3$), 113.2 – 113.1 (m, *C*HCF), 63.8 (d, *J* = 3.8 Hz, *C*HOH) ppm.

HRMS: (EI+); *m/z* calc. for $C_{10}H_6Cl_1F_4O$ $[M\text{-}Cl]^+$: 253.00433, found 253.00648.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 3363 (w), 1717 (w), 1590 (w), 1563 (w), 1472 (w), 1359 (m),1267 (w), 1200 (m), 1151 (s), 1103 (w), 1048 (w), 1004 (w), 874 (w), 824 (m), 758 (w), 693 (w), 575 (w), 482 (w).

(*Z*)-1-(2,4-Dichlorophenyl)-3,4,4,4-tetrafluorobut-2-en-1-yl diethyl phosphate (183d)



152d **183d**

Alcohol **152d** [254.61]	1.00 eq	552 µmol	160 mg
DMAP [122.17]	0.10 eq	119 µmol	14.5 mg
Diethyl phosphorochloridate [172.55, ρ = 1.19]	3.00 eq	1.66 mmol	0.24 mL
Pyridine			0.5 mL

was obtained following general procedure IV using the corresponding alcohol **152d** (160 mg, 0.55 mmol). Purification by column chromatography using 1:1 (*n*-pentane/Et_2O) afforded **183d** (46.1 mg, 108 µmol, 20%) as a yellow oil.

TLC: R_f = 0.21 (*n*-pentane/Et_2O 1:1).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.53 (d, J = 8.4 Hz, 1H, CH_{arom}), 7.42 (d, J = 2.1 Hz, 1H, CH_{arom}), 7.33 (dd, J = 8.4, 2.1 Hz, 1H, CH_{arom}), 6.46 (t, J = 8.7 Hz, 1H, C*H*O), 5.75 (dd, J = 31.4, 9.0 Hz, 1H, C*H*CF), 4.46 – 3.45 (m, 4H, 2CH_2), 1.29 (tdd, J = 7.0, 5.8, 1.0 Hz, 6H, 2CH_3) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −72.9 (d, J = 10.7 Hz, CF_3), −127.6 (q, J = 10.8 Hz, C*F*) ppm.

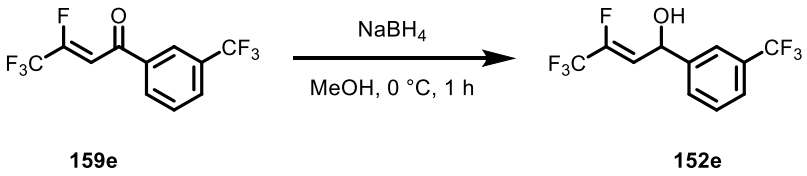
^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 147.0 (dq, J = 268.7, 39.8 Hz, *C*FCF_3), 135.7 (C_{quart}), 134.1 (dd, J = 6.1, 1.9 Hz, (C_{quart}), 132.9 (C_{quart}), 129.9 (C_{arom}), 128.8 (C_{arom}), 128.0 (C_{arom}), 118.0 (qd, J = 272.5, 40.8 Hz, CF*C*F_3), 112.2 – 109.9 (m, *C*HCF), 68.2 (t, J = 4.3 Hz, *C*HO), 64.5 – 64.4 (m, 2*C*H_2), 16.1 (d, J = 6.7 Hz, 2*C*H_3) ppm.

^{31}P-NMR: (202 MHz, $CDCl_3$) δ = −1.65 ppm.

HRMS: (ESI+); *m/z* calc. for $C_{14}H_{15}Cl_2F_4O_4PNa$ $[M+Na]^+$: 446.9913, found 446.9908.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 1475 (w), 1370 (w), 1350 (w), 1275 (m), 1203 (m), 1153 (m), 1122 (w), 1103 (w), 1034 (s), 1009 (w), 825 (w).

(*Z*)-3,4,4,4-Tetrafluoro-1-(3-(trifluoromethyl)phenyl)but-2-en-1-ol (152e)



159e **152e**

Fluorenone **159e** [286.15]	1.00 eq	738 µmol	211 mg
$NaBH_4$ [37.83]	1.20 eq	886 µmol	33.5 mg
MeOH			4.0 mL

Following general procedure III using the *β*-fluoroenone **159e** (211 mg, 738 µmol), the crude product was obtained as a colorless oil and directly used in the phosphorylation without further purification.

TLC: R_f = 0.33 (*n*-pentane/Et_2O 10:1).

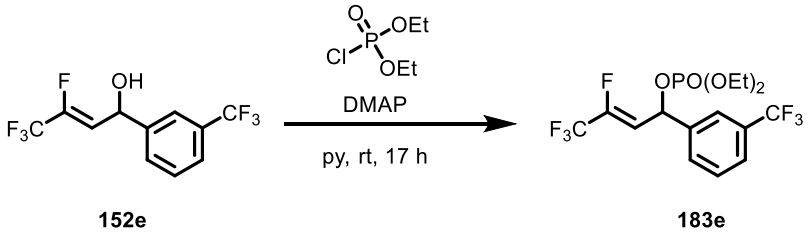
^{1}H-NMR: (300 MHz, $CDCl_3$) δ = 7.74 – 7.66 (m, 1H, CH_{arom}), 7.66 – 7.40 (m, 3H, CH_{arom}), 6.06 – 5.62 (m, 2H, C*H*CF and C*H*OH), 2.37 (bs, 1H, O*H*) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −62.7 (CF_3), −72.8 (d, *J* = 10.9 Hz, CFCF_3), −132.4 (q, *J* = 11.0 Hz, C*F*CF_3).

^{13}C-NMR: (75 MHz, $CDCl_3$) δ = 146.2 (dq, J = 262.8, 39.9 Hz, *C*FCF_3), 141.7 (C_{quart}), 131.4 (q, *J* = 32.4 Hz, C_{arom}), 129.4 (C_{arom}), 129.1 (C_{arom}), 125.3 (q, *J* = 3.8 Hz, C_{arom}), 123.89 (*C*F_3), 122.56 (q, *J* = 4.0 Hz, C_{arom}), 118.02 (qd, *J* = 272.0, 41.3 Hz, CF*C*F_3), 114.74 (d, *J* = 4.4 Hz, *C*HCF), 66.16 (d, *J* = 4.1 Hz, *C*HOH) ppm.

HRMS: (EI+); *m/z* calc. for $C_{11}H_7F_7O$ $[M]^+$: 288.03851, found 288.03764.

(*Z*)-Diethyl (3,4,4,4-tetrafluoro-1-(3-(trifluoromethyl)phenyl)but-2-en-1-yl) phosphate (183e)



152e 183e

Alcohol **152e** [288.16]	1.00 eq	738 µmol	213 mg
DMAP [122.17]	0.10 eq	74.0 µmol	9.00 mg
Diethyl phosphorochloridate [172.55, ρ = 1.19]	3.00 eq	2.21 mmol	0.32 mL
Pyridine			0.7 mL

was obtained following general procedure IV using the corresponding alcohol **152e** (213 mg, 738 µmol). Purification by column chromatography using 1:1 (*n*-pentane/Et_2O) afforded **183e** (161 mg, 378 µmol, 51% over two steps) as a colorless oil.

TLC: R_f = 0.20 (*n*-pentane/Et_2O 1:1).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.70 – 7.64 (m, 1H, CH_{arom}), 7.65 – 7.61 (m, 1H, CH_{arom}), 7.59 – 7.51 (m, 2H, CH_{arom}), 6.27 (t, *J* = 8.6 Hz, 1H, C*H*O), 5.90 (dd, *J* = 31.1, 8.8 Hz, 1H, C*H*CF), 4.19 – 3.96 (m, 4H, 2CH_2), 1.36 – 1.16 (m, 6H, 2CH_3) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −62.8 (CF_3), −72.9 (d, *J* = 10.7 Hz, CFCF_3), −129.5 (q, *J* = 10.8 Hz, C*F*) ppm.

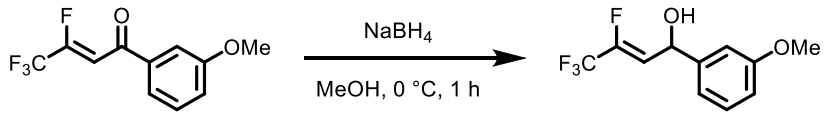
^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 146.8 (dq, *J* = 266.2, 40.1 Hz, *C*F), 138.7 (dd, *J* = 5.7, 1.7 Hz, C_{quart}), 131.6 (q, *J* = 32.6 Hz, $C_{quart}CF_3$), 129.8 (C_{arom}), 129.7 (C_{arom}), 126.1 (q, *J* = 3.7 Hz, C_{arom}), 123.8 (q, *J* = 272.3 Hz, *C*F_3), 123.1 (q, *J* = 3.8 Hz, C_{arom}), 116.9 (qd, *J* = 272.4, 41.0 Hz, *C*F_3CF), 112.2 (dq, *J* = 6.1, 3.2 Hz, *C*HCF), 70.8 (t, *J* = 4.4 Hz, *C*HO), 64.4 (d, *J* = 5.7 Hz, 2CH_2), 16.1 (t, *J* = 7.1 Hz, 2CH_3) ppm.

^{31}P-NMR: (202 MHz, $CDCl_3$) δ = −1.33 ppm.

HRMS: (EI+); *m/z* calc. for $C_{15}H_{16}F_7O_4P$ $[M]^+$: 424.0674, found 424.0669.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 2989 (w), 2914 (w), 1719 (w), 1450 (w), 1327 (m), 1273 (m), 1200 (w), 1154 (w), 1126 (m), 1073 (w), 1012 (s), 913 (w), 848 (w), 829 (w), 804 (m), 766 (w), 703 (m), 662 (w), 621 (w), 596 (w), 551 (m), 475 (w).

(*Z*)-3,4,4,4-Tetrafluoro-1-(3-methoxyphenyl)but-2-en-1-ol (152f)



159f **152f**

Fluorenone **159f** [248.18]	1.00 eq	1.35 mmol	340 mg
$NaBH_4$ [37.83]	1.20 eq	1.63 mmol	60.0 mg
MeOH			6.5 mL

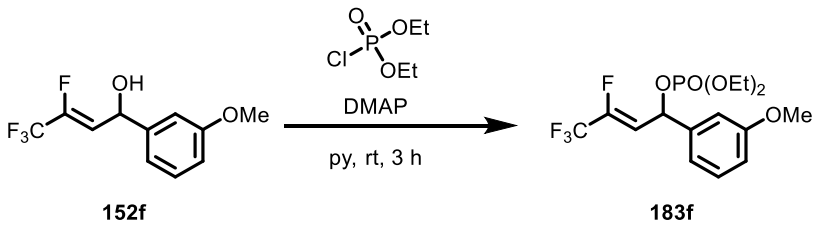
Following general procedure III using the *β*-fluoroenone **159f** (340 mg, 1.35 mmol), the crude product was obtained as a light-yellow oil and directly used in the phosphorylation without further purification.

TLC: R_f = 0.06 (*n*-pentane/Et_2O 20:1).

^{1}H-NMR: (300 MHz, $CDCl_3$) δ = 7.31 (t, *J* = 7.6 Hz, 1H, CH_{arom}), 7.03 – 6.83 (m, 3H, CH_{arom}), 5.84 (dd, *J* = 32.1, 8.9 Hz, 1H, C*H*CF), 5.75 – 5.67 (m, 1H, C*H*OH), 3.83 (s, 3H, CH_3) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$); δ = −72.8 (d, *J* = 11.2 Hz, CF_3), −133.5 (q, *J* = 11.0 Hz, C*F*) ppm.

(*Z*)-Diethyl (3,4,4,4-tetrafluoro-1-(3-methoxyphenyl)but-2-en-1-yl) phosphate (183f)



152f 183f

Alcohol **152f** [250.19]	1.00 eq	1.32 mmol	330 mg
DMAP [122.17]	0.10 eq	0.13 mmol	20.0 mg
Diethyl phosphorochloridate [172.55, ρ = 1.19]	3.00 eq	3.96 mmol	0.57 mL
Pyridine			1.3 mL

was obtained following general procedure IV using the corresponding alcohol **152f** (330 mg, 1.32 mmol). Purification by column chromatography using 1:1 (*n*-pentane/Et2O) afforded **183f** (300 mg, 0.78 mmol, 59% over two steps) as a colorless oil.

TLC: R_f = 0.19 (*n*-pentane/Et_2O 1:1).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.31 (t, *J* = 7.9 Hz, 1H, CH_{arom}), 6.97 (ddd, *J* = 7.9, 1.5, 0.7 Hz, 1H, CH_{arom}), 6.94 (t, *J* = 2.1 Hz, 1H, CH_{arom}), 6.90 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H, CH_{arom}), 6.17 (t, *J* = 8.6 Hz, 1H, C*H*O), 5.90 (dd, *J* = 30.7, 9.6 Hz, 1H, C*H*CF), 4.17 – 3.95 (m, 4H, 2CH_2), 3.82 (s, 3H, CH_3), 1.27 (dtd, *J* = 14.6, 7.1, 1.0 Hz, 6H, 2CH_3) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −72.9 (d, *J* = 10.9 Hz, CF_3), −130.9 (q, *J* = 10.9 Hz, C*F*) ppm.

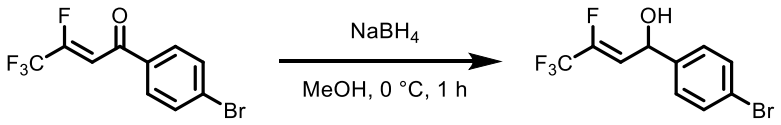
^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 160.4 (C_{quart}), 146.4 (dq, *J* = 264.8, 40.0 Hz, *C*F), 139.3 (d, *J* = 5.1 Hz, C_{quart}), 130.5 (C_{arom}), 118.7 (C_{arom}), 118.3 (qd, *J* = 273.4, 42.0 Hz, CF_3), 114.9 (C_{arom}), 112.9 (dq, *J* = 6.1, 3.1 Hz, *C*HCF), 112.1 (C_{arom}), 71.6 (t, *J* = 4.3 Hz, *C*HO), 64.5 (d, *J* = 5.8 Hz, 2*C*H_2), 55.7, 16.4 (dd, *J* = 7.0, 5.3 Hz, 2*C*H_3) ppm.

^{31}P-NMR: (202 MHz, $CDCl_3$) δ = −1.32 ppm.

HRMS: (EI+); *m/z* calc. for $C_{15}H_{19}F_4O_5P_1$ $[M]^+$: 386.0906, found 386.0946.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 3493 (w), 2987 (w), 2841 (w), 1718 (w), 1603 (w), 1490 (w), 1459 (w), 1440 (w), 1394 (w), 1350 (m), 1265 (m), 1200 (m), 1146 (m), 1028 (w), 986 (s), 906 (w), 856 (w), 829 (w), 788 (w), 764 (w), 698 (m), 631 (w), 544 (w), 480 (w).

(*Z*)-1-(4-Bromophenyl)-3,4,4,4-tetrafluorobut-2-en-1-ol (152g)



159g **152g**

Fluorenone **159g** [297.05]	1.00 eq	897 µmol	267 mg
$NaBH_4$ [37.83]	1.20 eq	1.08 mmol	40.7 mg
MeOH			4.5 mL

Following general procedure III using the *β*-fluoroenone **159g** (267 mg, 897 µmol), the crude product was purified by column chromatography using 4:1 (*n*-pentane/Et_2O) giving the product as a colorless oil (212 mg, 709 µmol, 79%).

TLC: R_f = 0.38 (*n*-pentane/Et_2O 4:1).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.54-7.51 (m, 2H, CH_{arom}), 7.29-7.27 (m, 2H, CH_{arom}), 5.80 (dd, *J* = 32.1 Hz, 8.9 Hz, 1H, C*H*CF), 5.71 (dd, *J* = 8.6 Hz, 2.7 Hz, 1H, C*H*OH), 2.22 (d, *J* = 3.6 Hz, 1H, O*H*) ppm.

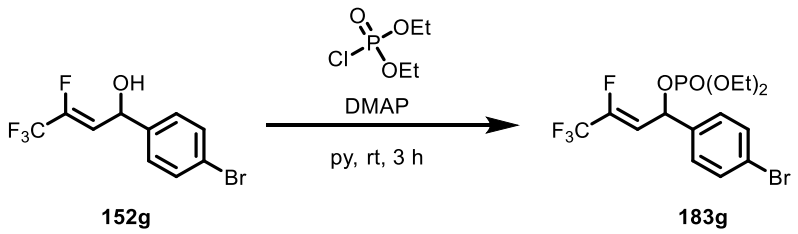
^{19}F-NMR: (282 MHz, $CDCl_3$) δ = − 72.8 (d, *J* = 11.0 Hz, CF_3), − 132.9 (q, *J* = 11.0 Hz, C*F*) ppm.

^{13}C-NMR: (125 MHz, $CDCl_3$) δ = 146.0 (dq, *J* = 262.2, 39.8 Hz, *C*F), 139.9 (C_{arom}), 132.2 (C_{arom}), 127.6 (C_{arom}), 122.6 (C_{arom}), 118.2 (qd, *J* = 271.9, 41.2 Hz, *C*F_3), 115.1-115.0 (m, *C*HCF), 66.3 (d, *J* = 3.8 Hz, *C*HOH) ppm.

HRMS: (EI+); *m/z* calc. for $C_{10}H_7BrF_4O$ [M]+, 297.96164, found 297.96198.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 3352 (w), 1716 (w), 1487 (w), 1403 (w), 1355 (m), 1196 (s),1146 (s), 1094 (w), 1071 (w), 1047 (w), 1005 (m), 877 (w), 854 (w), 821 (m), 709 (m), 548 (w), 522 (w).

(*Z*)-1-(4-Bromophenyl)-3,4,4,4-tetrafluorobut-2-en-1-yl diethyl phosphate (183g)



Alcohol **152g** [299.06]	1.00 eq	645 µmol	193 mg
DMAP [122.17]	0.10 eq	65.0 µmol	7.90 mg
Diethyl phosphorochloridate [172.55, ρ = 1.19]	3.00 eq	1.94 mmol	0.28 mL
Pyridine			0.7 mL

was obtained following general procedure IV using the corresponding alcohol **152g** (193 mg, 645 µmol). Purification by column chromatography using 1:1 (*n*-pentane/Et_2O) afforded **183g** (127 mg, 293 µmol, 45%) as a yellow oil.

TLC: R_f = 0.19 (*n*-pentane/Et_2O 1:1).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.54 (d, *J* = 8.5 Hz, 2H, CH_{arom}), 7.28 (d, *J* = 8.4 Hz, 2H, CH_{arom}), 6.17 (t, *J* = 8.6 Hz, 1H, C*H*O), 5.87 (dd, *J* = 30.8, 9.5 Hz, 1H, C*H*CF), 4.16 – 3.90 (m, 4H, 2CH_2), 1.28 (dtd, *J* = 17.2, 7.1, 1.0 Hz, 6H, 2CH_3).

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −72.9 (d, *J* = 10.7 Hz, CF_3), −130.0 (q, *J* = 10.8 Hz, C*F*) ppm.

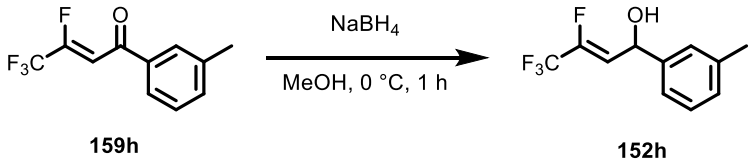
^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 146.5 (dq, *J* = 265.6, 40.0 Hz, *C*F), 136.7 (d, *J* = 5.7 Hz, C_{quart}), 132.3 (C_{arom}), 128.0 (C_{arom}), 123.4 ((C_{quart}), 118.0 (qd, *J* = 272.2, 40.9 Hz, *C*F_3), 112.5 – 112.2 (m, *C*HCF), 70.9 (t, *J* = 4.4 Hz, *C*HO), 64.4 (d, *J* = 5.8 Hz, 2CH_2), 24.2 – 13.0 (m, 2CH_3).

^{31}P-NMR: (202 MHz, $CDCl_3$) δ = −1.30 ppm.

HRMS: (EI+); *m/z* calc. for $C_{14}H_{16}BrF_4O_4P$ $[M]^+$: 433.9906, found 433.9913.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 2955 (w), 2886 (w), 1489 (m), 1451 (w), 1402 (w), 1306 (w), 1290 (w), 1259 (w), 1178 (s), 1144 (w), 1120 (w), 1072 (w), 1029 (w), 1011 (m), 969 (s), 945 (w), 894 (w), 855 (w), 805 (m), 717 (w), 499 (w).

(*Z*)-3,4,4,4-Tetrafluoro-1-(*m*-tolyl)but-2-en-1-ol (152h)



159h 152h

Fluorenone **159h** [232.18]	1.00 eq	1.73 mmol	410 mg
$NaBH_4$ [37.83]	1.20 eq	2.08 mmol	78.5 mg
MeOH			9.0 mL

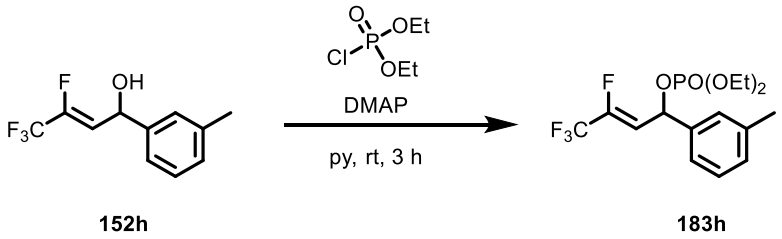
Following general procedure III using the *β*-fluoroenone **159h** (410 mg, 1.73 mmol), the crude product **152g** was obtained as a light-yellow oil and directly used in the phosphorylation without further purification.

TLC: R_f = 0.20 (*n*-pentane/Et_2O 20:1).

^{1}H-NMR: (300 MHz, $CDCl_3$); δ = 7.38 – 7.06 (m, 4H, CH_{arom}), 5.86 (dd, J = 32.3 Hz, 8.9 Hz, 1H, C*H*CF), 5.70 (d, J = 8.9 Hz, 1H, C*H*OH), 2.38 (s, 3H, CH_3) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$); δ = −72.8 (d, J = 11.2 Hz, CF_3), −133.7 (q, J = 11.1 Hz, C*F*) ppm.

(*Z*)-Diethyl (3,4,4,4-tetrafluoro-1-(*m*-tolyl)but-2-en-1-yl) phosphate (183h)



152h **183h**

Alcohol **152h** [234.19]	1.00 eq	1.30 mmol	386 mg
DMAP [122.17]	0.10 eq	130 µmol	15.8 mg
Diethyl phosphorochloridate [172.55, ρ = 1.19]	3.00 eq	3.90 mmol	0.56 mL
Pyridine			1.3 mL

was obtained following general procedure IV using corresponding alcohol **152h** (386 mg, 1.30 mmol). Purification by column chromatography using 1:1 (*n*-pentane/Et_2O) afforded **183h** (380 mg, 1.02 mmol, 59% over two steps) as a yellow oil.

TLC: R_f = 0.29 (*n*-pentane/Et_2O 1:1).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.32 – 7.25 (m, 1H, CH_{arom}), 7.21 – 7.10 (m, 3H, CH_{arom}), 6.16 (t, J = 8.6 Hz, 1H, C*H*O), 5.91 (dd, J = 32.9, 9.2 Hz, 1H, C*H*CF), 4.17 – 3.85 (m, 4H, 2CH_2), 2.37 (s, 3H, CH_3), 1.26 (dtd, J = 17.0, 7.1, 1.1 Hz, 6H, 2CH_3) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −72.8 (d, J = 11.0 Hz, CF_3), −131.1 (q, J = 10.9 Hz, C*F*) ppm.

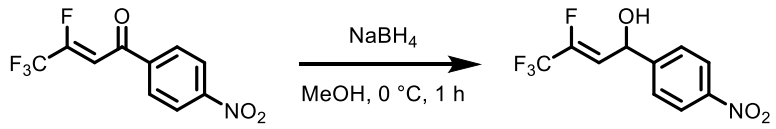
^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 145.9 (dq, J = 264.6, 39.9 Hz), 138.8 (C_{quart}), 137.4 (d, J = 5.7 Hz, C_{quart}), 129.9 (C_{arom}), 128.9 (C_{arom}), 126.9 (C_{arom}), 123.3 (C_{arom}), 118.0 (qd, J = 272.1, 41.0 Hz, *C*F_3), 112.7 (dq, J = 6.2, 3.1 Hz, *C*HCF), 72.7 – 70.1 (m, *C*HO), 64.1 (d, J = 5.8 Hz, 2*C*H_2), 21.4 (*C*H_3), 15.9 (t, J = 6.8 Hz, 2*C*H_3) ppm.

^{31}P-NMR: (202 MHz, $CDCl_3$) δ = −1.32 ppm.

HRMS: (EI+); *m/z* calc. for $C_{15}H_{19}F_4O_4P$ $[M]^+$: 370.0957, found 370.0950.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 3500 (w), 2986 (w), 2914 (w), 1718 (w), 1610 (w), 1485 (w), 1446 (w), 1349 (m), 1268 (m), 1200 (m), 1147 (m), 1021 (s), 984 (w), 898 (w), 858 (w), 831 (w), 790 (w), 765 (w), 701 (m), 629 (w), 604 (w), 576 (w), 543 (w), 462 (w).

(*Z*)-3,4,4,4-Tetrafluoro-1-(4-nitrophenyl)but-2-en-1-ol (152i)



159i 152i

Fluorenone **159i** [263.15]	1.00 eq	630 µmol	165 mg
$NaBH_4$ [37.83]	1.20 eq	756 µmol	28.6 mg
MeOH			3.2 mL

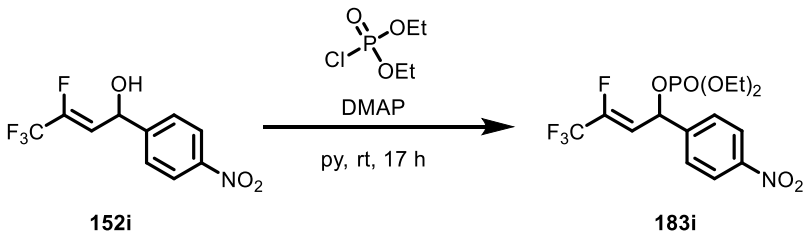
Following general procedure III using the *β*-fluoroenone **159i** (165 mg, 630 µmol), the crude product was obtained as a yellow solid and directly used in the phosphorylation without further purification.

TLC: R_f = 0.05 (20:1 *n*-pentane/Et_2O).

^{1}H-NMR: (300 MHz, $CDCl_3$) δ = 8.26 (d, J = 8.3 Hz, 2H, CH_{arom}), 7.59 (d, J = 8.3 Hz, 2H, CH_{arom}), 5.93 – 5.71 (m, 2H, C*H*OH and C*H*CF), 2.32 (d, J = 3.4 Hz, 1H, O*H*) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −72.8 (d, J = 10.9 Hz, CF_3), −131.5 (q, J = 10.8 Hz, C*F*) ppm.

(*Z*)-Diethyl (3,4,4,4-tetrafluoro-1-(4-nitrophenyl)but-2-en-1-yl) phosphate (183i)



Alcohol **152i** [265.16]	1.00 eq	627 µmol	166 mg
DMAP [122.17]	0.10 eq	63.0 µmol	7.70 mg
Diethyl phosphorochloridate [172.55, ρ = 1.19]	3.00 eq	1.88 mmol	0.27 mL
Pyridine			0.60 mL

was obtained following general procedure IV using the corresponding alcohol **152i** (166 mg, 627 µmol). Purification by column chromatography using 1:2 (*n*-pentane/Et_2O) afforded **183i** (137 mg, 341 µmol, 54% over two steps) as a yellow oil.

TLC: R_f = 0.10 (*n*-pentane/Et_2O 1:1).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 8.28 (d, *J* = 8.8 Hz, 2H, CH_{arom}), 7.59 (d, *J* = 8.7 Hz, 2H, CH_{arom}), 6.31 (t, *J* = 8.6 Hz, 1H, C*H*O), 6.02 – 5.80 (dd, *J* = 30.3, 8.8 Hz, 1H, C*H*CF), 4.37 – 3.86 (m, 4H, 2CH_2), 1.30 (dtd, *J* = 15.1, 7.1, 1.0 Hz, 6H, 2CH_3) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −72.9 (d, *J* = 10.7 Hz, CF_3), −128.6 (q, *J* = 10.7 Hz, C*F*) ppm.

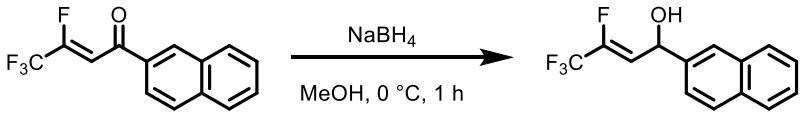
^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 148.3 (C_{quart}), 146.9 (dq, *J* = 268.9, 39.4 Hz, *C*F), 144.4 (d, *J* = 5.5 Hz, C_{quart}), 127.1 (C_{arom}), 124.4 (C_{arom}), 117.8 (qd, *J* = 272.4, 40.7 Hz, *C*F_3), 112.5 – 110.1 (m, *C*HCF), 70.3 (t, *J* = 4.3 Hz, *C*HO), 64.6 (d, *J* = 5.7 Hz, 2*C*H_2), 16.1 (dd, *J* = 6.8, 2.6 Hz, 2*C*H_3).

^{31}P-NMR: (122 MHz, CDCl3) δ = −1.97 ppm.

HRMS: (ESI+); *m/z* calc. for $C_{14}H_{16}F_4NO_6PNa$ $[M+Na]^+$: 424.0544, found 424.0549.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 2988 (w), 1720 (w), 1608 (w), 1526 (m), 1446 (w), 1347 (m), 1271 (m), 1201 (m), 1148 (m), 1106 (w), 1021 (w), 1003 (s), 906 (w), 854 (m), 807 (w), 748 (w), 704 (m), 660 (w), 599 (w), 555 (w), 528 (m).

(*Z*)-3,4,4,4-Tetrafluoro-1-(naphthalen-2-yl)but-2-en-1-ol (152j)



159j **152j**

Fluorenone **159j** [268.21]	1.00 eq	694 µmol	186 mg
$NaBH_4$ [37.83]	1.20 eq	832 µmol	31.5 mg
MeOH			3.5 mL

Following general procedure III using the *β*-fluoroenone **159i** (186 mg, 694 µmol), the crude product was obtained as a white solid and directly used in the phosphorylation without further purification.

TLC: R_f = 0.30 (*n*-pentane/Et_2O 10:1).

^{1}H-NMR: (500 MHz, $CDCl_3$), δ = 7.89-7.85 (m, 4H, CH_{arom}), 7.55-7.51 (m, 2H, CH_{arom}), 7.48 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H, CH_{arom}), 5.98-5.88 (m, 2H, C*H*OH), 2.42 (m, 1H, O*H*) ppm.

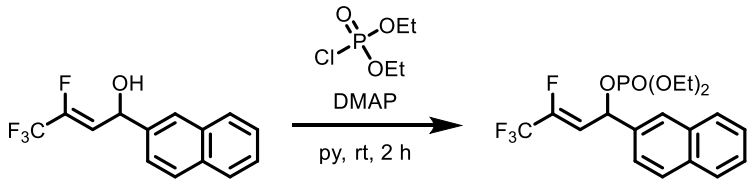
^{19}F-NMR: (282 MHz, $CDCl_3$), δ = −72.7 (d, *J* = 11.2 Hz, CF_3), −133.2 (q, *J* = 11.1 Hz, C*F*) ppm.

^{13}C-NMR: (125 MHz, $CDCl_3$), δ = 145.8 (dq, *J* = 261.7, 39.7 Hz, *C*FCF_3), 138.2 (C_{quart}), 133.4 (C_{quart}), 133.3 (C_{quart}), 129.1 (C_{arom}), 128.2 (C_{arom}), 127.9(C_{arom}), 126.7 (C_{arom}), 126.6 (C_{arom}), 124.9 (C_{arom}), 123.6 (C_{arom}), 118.3 (qd, *J* = 271.9, 41.5 Hz, CF*C*F_3), 115.4-115.2 (m, *C*HCF), 67.1 (d, *J* = 3.8 Hz, *C*HOH) ppm;

HRMS: (EI+); *m/z* calc. for $C_{14}H_{10}F_4O$ $[M]^+$: 270.0668, found 270.0675.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 3263 (w), 1355 (m), 1274 (w), 1238 (w), 1201 (w), 1162 (s), 1124 (w), 1100 (m), 1041 (m), 1001 (m), 966 (w), 952 (w), 900 (w), 882 (w), 858 (m), 846 (w), 822 (m), 775 (w), 748 (s), 689 (m), 661 (w), 622 (w), 599 (w), 573 (w), 548 (w), 528 (w), 482 (s), 430 (w), 409 (w).

(*Z*)-Diethyl (3,4,4,4-tetrafluoro-1-(naphthalen-2-yl)but-2-en-1-yl) phosphate 183j



152j **183j**

Alcohol **152j** [270.23]	1.00 eq	694 µmol	188 mg
DMAP [122.17]	0.10 eq	69.4 µmol	8.48 mg
Diethyl phosphorochloridate [172.55, ρ = 1.19]	2.00 eq	1.39 mmol	0.20 mL
Pyridine			1.40 mL

was obtained following general procedure IV using the corresponding alcohol **152j** (188 mg, 694 µmol). Diethyl phosphorochloridate (2.00 eq) was added additionally after 1 h. The reaction was stirred in total for 2 h at room temperature. Purification by column chromatography using 1:1 (*n*-pentane/Et_2O) afforded phosphate **183j** (184 mg, 430 µmol, 62% over two steps) as a colorless oil.

TLC: R_f = 0.20 (*n*-pentane/Et_2O 1:1).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.93 – 7.81 (m, 4H, CH_{arom}), 7.58 – 7.51 (m, 2H, CH_{arom}), 7.49 (dd, *J* = 8.5, 1.9 Hz, 1H, CH_{arom}), 6.38 (t, *J* = 8.6 Hz, 1H, C*H*O), 6.01 (dd, *J* = 31.1, 8.8 Hz, 1H, C*H*CF), 4.34 – 3.79 (m, 4H, 2CH_2), 1.34 – 1.15 (m, 6H, 2CH_3) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −72.8 (d, *J* = 10.8 Hz, CF_3), −130.5 (q, *J* = 11.0 Hz, C*F*) ppm.

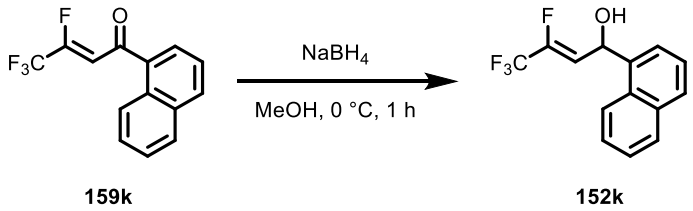
^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 146.3 (dq, J = 265.2, 39.9 Hz, *C*F), 134.8 (d, J = 4.9 Hz, C_{quart}), 133.6 (C_{quart}), 133.2 (C_{quart}), 129.2 (C_{arom}), 128.3 (C_{arom}), 127.9 (C_{arom}), 127.0 (C_{arom}), 126.9 (C_{arom}), 125.8 (C_{arom}), 123.5 (C_{arom}), 118.1 (qd, J = 272.3, 41.0 Hz), 112.9 – 112.3 (m), 72.5 – 67.7 (m), 64.3 (dd, J = 5.9, 1.6 Hz), 16.1 (dd, J = 9.2, 6.9 Hz) ppm.

^{31}P-NMR: (202 MHz, $CDCl_3$) δ = −1.21 ppm.

HRMS: (ESI+); *m/z* calc. for $C_{18}H_{19}F_4O_4PNa$ $[M+Na]^+$: 429.0849, found 429.0858.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 3058 (w), 2986 (w), 2911 (w), 1718 (w), 1510 (w), 1478 (w), 1445 (w), 1347 (w), 1270 (m), 1200 (m), 1146 (m), 1114 (w), 982 (s), 953 (w), 856 (w), 816 (m), 747 (m), 692 (m), 657 (w), 625 (w), 537 (w), 478 (s).

(*Z*)-3,4,4,4-Tetrafluoro-1-(naphthalen-2-yl)but-2-en-1-ol (152k)



159k **152k**

Fluorenone **159k** [268.21]	1.00 eq	1.60 mmol	430 mg
$NaBH_4$ [37.83]	1.20 eq	1.92 mmol	70.0 mg
MeOH			8.0 mL

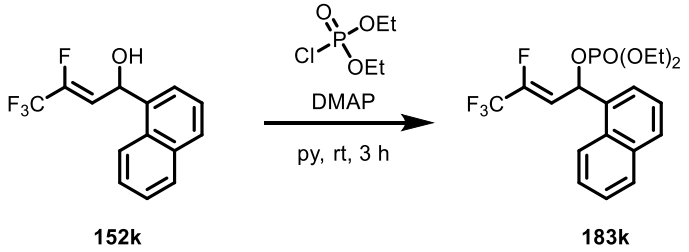
Following general procedure III using the *β*-fluoroenone **159k** (430 mg, 1.60 mmol), the crude product was obtained as a white solid and directly used in the phosphorylation without further purification.

TLC: R_f = 0.10 (*n*-pentane/Et_2O 20:1).

^{1}H-NMR: (300 MHz, $CDCl_3$); δ = 8.12 (d, J = 8.4 Hz, 1H, CH_{arom}), 7.89 (dd, J = 13.8, 7.9 Hz, 2H, CH_{arom}), 7.69 (d, J = 7.1 Hz, 1H, CH_{arom}), 7.64 – 7.43 (m, 3H, CH_{arom}), 6.46 – 6.38 (m, 1H, C*H*OH), 6.02 (dd, J = 32.9, 8.7 Hz, 1H, C*H*CF) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$); δ = −72.7 (d, J = 10.9 Hz, CF_3), −132.5 (q, J = 11.0 Hz, C*F*) ppm.

(*Z*)-Diethyl (3,4,4,4-tetrafluoro-1-(naphthalen-1-yl)but-2-en-1-yl) phosphate (183k)



152k **183k**

Alcohol **152k** [270.23]	1.00 eq	1.58 mmol	430 mg
DMAP [122.17]	0.10 eq	160 µmol	20.0 mg
Diethyl phosphorochloridate [172.55, ρ = 1.19]	3.00 eq	4.74 mmol	0.69 mL
Pyridine			1.30 mL

was obtained following general procedure IV using the alcohol **152k** (430 mg, 1.58 mmol). Purification by column chromatography using 1:1 (*n*-pentane/Et_2O) afforded **183k** (350 mg, 0.86 mmol, 55% over two steps) as a colorless oil.

TLC: R_f = 0.19 (*n*-pentane/Et_2O 1:1).

^{1}H-NMR: (300 MHz, $CDCl_3$) δ = 8.11 (d, *J* = 8.1 Hz, 1H, C*H*$_{arom}$), 7.90 (t, *J* = 7.0 Hz, 2H, C*H*$_{arom}$), 7.72 – 7.45 (m, 4H, C*H*$_{arom}$), 6.86 (t, *J* = 8.7 Hz, 1H, C*H*O), 6.10 (dd, *J* = 31.4, 9.0 Hz, 1H, C*H*CF), 4.01 (tt, *J* = 14.6, 7.3 Hz, 4H, 2C*H*$_2$), 1.20 (dt, *J* = 20.7, 7.0 Hz, 6H, 2C*H*$_3$) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −72.9 (d, *J* = 10.9 Hz, C*F*$_3$), −130.9 (q, *J* = 10.9 Hz, C*F*) ppm.

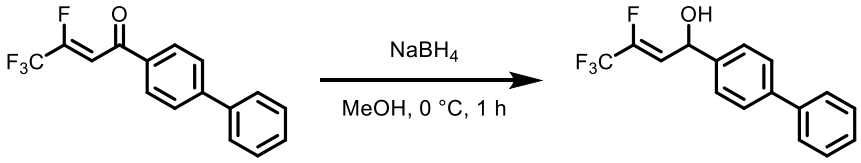
^{13}C-NMR (126 MHz, $CDCl_3$) δ = 146.4 (dq, *J* = 266.1, 39.5 Hz, *C*F), 134.0 (*C*$_{quart}$), 133.1 (d, *J* = 5.4 Hz, *C*$_{quart}$), 130.0 (*C*$_{arom}$), 129.9 (*C*$_{quart}$), 129.1 (*C*$_{arom}$), 127.0 (*C*$_{arom}$), 126.2 (*C*$_{arom}$), 125.3 (*C*$_{arom}$), 125.1 (*C*$_{arom}$), 122.9 (d, *J* = 1.8 Hz, *C*$_{arom}$), 118.5 (qd, *J* = 270.6, 42.1 Hz, *C*F$_3$), 112.4 (dq, *J* = 5.9, 3.1 Hz, *C*HCF), 69.9 (t, *J* = 4.5 Hz, *C*HO), 64.1 (dd, *J* = 5.7, 2.2 Hz, 2*C*H$_2$), 15.9 (dd, *J* = 10.4, 6.8 Hz, 2*C*H$_3$) ppm.

^{31}P-NMR: (122 MHz, $CDCl_3$) δ = −1.99 ppm.

HRMS: (ESI+); *m/z* calc. for $C_{18}H_{19}F_4O_4PNa$ $[M+Na]^+$: 429.0849, found 429.0841.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 2987 (w), 1719 (w), 1604 (w), 1491 (w), 1459 (w), 1440 (w), 1351 (w), 1267 (m), 1202 (m), 1149 (m), 1033 (s), 906 (w), 857 (w), 830 (w), 789 (w), 699 (m), 545 (w).

(*Z*)-1-([1,1'-Biphenyl]-4-yl)-3,4,4,4-tetrafluorobut-2-en-1-ol (152l)



159l **152l**

Fluorenone **159l** [294.25]	1.00 eq	873 µmol	257 mg
$NaBH_4$ [37.83]	1.20 eq	1.05 mmol	39.6 mg
MeOH			4.0 mL

Following general procedure III using the *β*-fluoroenone **159l** (257 mg, 873 µmol), the crude product was obtained as a yellow solid and directly in the phosphorylation used without further purification.

TLC: R_f = 0.30 (*n*-pentane/Et_2O 10:1).

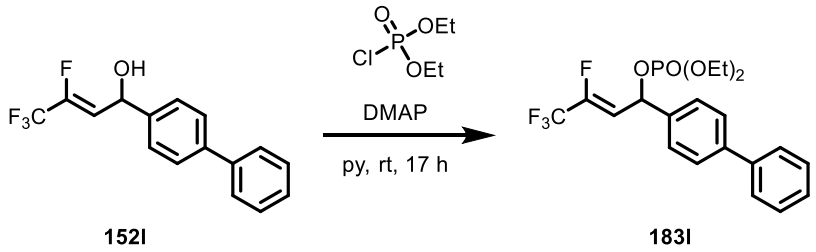
^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.73 – 7.54 (m, 4H, CH_{arom}), 7.53 – 7.43 (m, 4H, CH_{arom}), 7.42 – 7.32 (m, 1H, CH_{arom}), 5.90 (dd, *J* = 32.1, 9.3 Hz, 1H, C*H*CF), 5.80 (d, *J* = 8.8 Hz, 1H, C*H*OH), 2.19 (s, 1H, O*H*) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −72.7 (d, *J* = 11.2 Hz, CF_3), −133.4 (q, *J* = 11.0 Hz, C*F*) ppm.

^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 145.7 (dq, *J* = 261.4, 39.7 Hz, *C*FCF_3), 141.6 (C_{quart}), 140.5 (C_{quart}), 139.8 (C_{quart}), 128.9 (C_{arom}), 127.7 (C_{arom}), 127.6 (C_{arom}), 127.2 (C_{arom}), 126.3 (C_{arom}), 118.2 (qd, *J* = 271.9, 41.5 Hz, CF*C*F_3), 115.2 (dq, *J* = 6.5, 3.2 Hz, *C*HCF), 66.6 (d, *J* = 3.9 Hz, *C*HOH).

HRMS: (EI+); *m/z* calc. for $C_{16}H_{12}F_4O$ $[M]^+$: 296.08243, found 296.08346.

(*Z*)-1-([1,1'-Biphenyl]-4-yl)-3,4,4,4-tetrafluorobut-2-en-1-yl diethyl phosphate (183l)



152l **183l**

Alcohol **152l** [296.26]	1.00 eq	873 µmol	259 mg
DMAP [122.17]	0.10 eq	87.3 µmol	10.7 mg
Diethyl phosphorochloridate [172.55, ρ = 1.19]	1.20 eq	1.05 mmol	0.15 mL
Pyridine			1.0 mL

was obtained following general procedure IV using the alcohol **152l** (259 mg, 873 µmol). Purification by column chromatography using 1:1 (*n*-pentane/Et_2O) afforded phosphate **183l** (149 mg, 345 µmol, 40% over two steps) as a colorless oil.

TLC: R_f = 0.30 (*n*-pentane/Et_2O 1:1).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.68 – 7.56 (m, 4H, CH_{arom}), 7.51 – 7.42 (m, 4H, CH_{arom}), 7.37 (m, 1H, CH_{arom}), 6.27 (t, *J* = 8.6 Hz, 1H, C*H*O), 5.97 (dd, *J* = 31.2, 9.1 Hz, 1H, C*H*CF), 4.29 – 3.87 (m, 4H, 2CH_2), 1.33 – 1.20 (m, 6H, 2CH_3) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −72.8 (d, *J* = 11.2 Hz, CF_3), −130.7 (q, *J* = 10.9 Hz, C*F*) ppm.

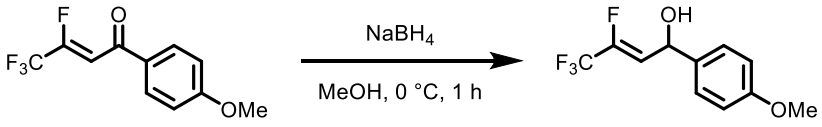
^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 146.2 (dq, *J* = 265.0, 39.8 Hz, *C*F), 142.3 (C_{quart}), 140.4 (C_{quart}), 136.5 (d, *J* = 5.4 Hz, C_{quart}), 129.0 (C_{arom}), 127.9 (C_{arom}), 127.8 (C_{arom}), 127.3 (C_{arom}), 126.8 (C_{arom}), 118.1 (qd, *J* = 272.2, 41.0 Hz, *C*F_3), 112.7 (dq, *J* = 6.1, 3.1 Hz, *C*HCF), 71.3 (t, *J* = 4.4 Hz, *C*HO), 64.3 (d, *J* = 5.7 Hz, 2*C*H_2), 16.1 (t, *J* = 6.6 Hz, 2*C*H_3) ppm.

^{31}P-NMR: (202 MHz, $CDCl_3$) δ = −1.25 ppm.

HRMS: (ESI+); *m/z* calc. for $C_{20}H_{21}F_4O_4PNa$ $[M+Na]^+$: 455.1006, found 455.1000.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 2987 (w), 1487 (w), 1352 (w), 1272 (m), 1202 (m), 1150 (m), 1106 (w), 1029 (s), 987 (w), 905 (w), 842 (w), 820 (w), 765 (w), 733 (w), 696 (w), 572 (w), 523 (w).

(*Z*)-3,4,4,4-Tetrafluoro-1-(4-methoxyphenyl)but-2-en-1-ol (152m)



159m **152m**

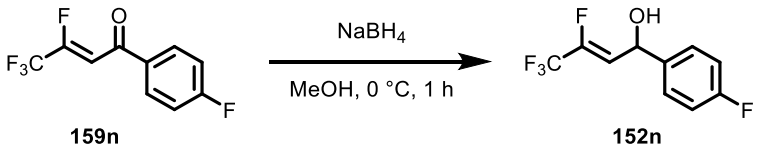
Fluorenone **159m** [248.18]	1.00 eq	698 µmol	173 mg
$NaBH_4$ [37.83]	1.20 eq	837 µmol	31.7 mg
MeOH			3.5 mL

Following general procedure III using the *β*-fluoroenone **159m** (173mg, 698 µmol), the crude product **152m** was obtained as a yellow oil and used directly in the phosphorylation used without further purification.

^{1}H-NMR: (300 MHz, $CDCl_3$) δ = 7.57 – 7.17 (m, 2H, CH_{arom}), 7.10 – 6.78 (m, 2H, CH_{arom}), 5.86 (dd, J = 32.3, 8.4 Hz, 1H, C*H*CF), 5.77 – 5.59 (m, 1H, C*H*OH), 3.82 (s, 3H, CH_3) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −72.8 (d, J = 11.0 Hz, CF_3), −133.9 (q, J = 11.1 Hz, CF) ppm.

(*Z*)-3,4,4,4-Tetrafluoro-1-(4-fluorophenyl)but-2-en-1-ol (152n)



Fluorenone **159n** [294.25]	1.00 eq	495 µmol	117 mg
$NaBH_4$ [37.83]	1.20 eq	594 mmol	22.5 mg
MeOH			2.5 mL

Following general procedure III using the *β*-fluoroenone **159n** (117 mg, 495 µmol), the crude product was purified by column chromatography using 4:1 (*n*-pentane/Et_2O) giving the product **152n** as a colorless oil (25.3 mg, 106 µmol, 21%).

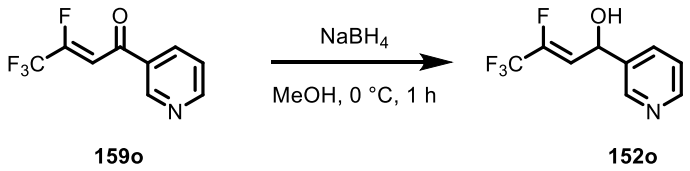
TLC: R_f = 0.43 (*n*-pentane/Et_2O 4:1).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.39-7.37 (m, 2H, CH_{arom}), 7.11-7.06 (m, 2H, CH_{arom}), 5.83 (dd, *J* = 32.2 Hz, 8.83 Hz, 1H, C*H*CF), 5.74 (d, *J* = 9.4 Hz, 1H, C*H*OH), 2.12 (d, *J* = 3.5 Hz, 1H, O*H*) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = − 72.8 (d, J = 11.0 Hz, CF_3), − 113.3 (s, CF_{arom}), − 133.3 (q, *J* = 11.0 Hz, C*F*) ppm.

HRMS: (EI+); *m/z* calc. for $C_{10}H_7F_5O$ $[M]^+$: 238.04171, found 238.04207.

(*Z*)-3,4,4,4-Tetrafluoro-1-(pyridin-3-yl)but-2-en-1-ol (152o)



159o **152o**

Fluorenone **159o** [294.25]	1.00 eq	838 µmol	184 mg
$NaBH_4$ [37.83]	1.20 eq	880 mmol	33.3 mg
MeOH			4.2 mL

Following general procedure III using the *β*-fluoroenone **159o** (184 mg, 838 µmol), the crude product was purified by column chromatography using 1:2 (*n*-pentane/Et_2O) giving the product **152o** as a yellow oil (93.8 mg, 424 µmol, 51%).

TLC: R_f = 0.38 (*n*-pentane/Et_2O 1:2).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 8.50-8.47 (m, 1H, CH_{arom}), 8.43 (dd, *J* = 4.9 Hz, 1.7 Hz, 1H, CH_{arom}), 7.81-7.75 (m, 1H, CH_{arom}), 7.33 (dd, *J* = 7.9 Hz, 4.9 Hz, 1H, CH_{arom}), 5.83 (dd, *J* = 33.1 Hz, 8.8 Hz, 1H, C*H*CF), 5.21 (dd, *J* = 8.5 Hz, 3.9 Hz, 1H, C*H*OH), 5.13 (brs, 1H, O*H*) ppm;

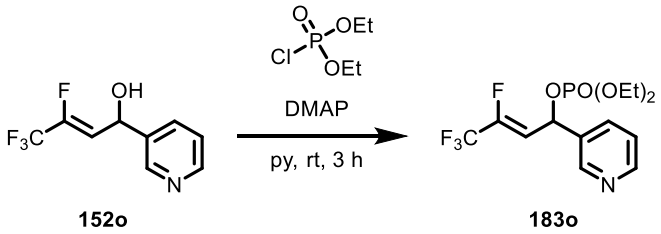
^{19}F-NMR: (282 MHz, $CDCl_3$) δ = − 72.8 (d, *J* = 11.0 Hz, CF_3), − 132.7 (q, *J* = 11.0 Hz, C*F*) ppm.

^{13}C-NMR: (125 MHz, $CDCl_3$) δ = 148.9 (*C*$_{arom}$), 147.1 (*C*$_{arom}$), 146.0 (dq, *J* = 262.0, 39.8 Hz, *C*F), 137.6 (*C*$_{arom}$), 134.3 (*C*$_{arom}$), 124.1 (*C*$_{arom}$), 118.2 (qd, *J* = 271.9, 41.4 Hz, *C*F_3), 115.4-115.1 (m, *C*HCF), 64.2 (d, *J* = 4.0 Hz, *C*HOH) ppm.

HRMS: (EI+); *m/z* calc. for $C_9H_7F_4NO$ $[M]^+$: 221.04638, found 221.04790.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 3163 (w), 2918 (w), 2852 (w), 1714 (w), 1596 (w), 1480 (w), 1428 (w), 1356 (m), 1248 (w), 1197 (m), 1147 (s), 1099 (w), 1067 (w), 1047 (w), 1030 (w), 1008 (w), 881 (w), 855 (w), 808 (w), 711 (m), 642 (w).

(*Z*)-Diethyl (3,4,4,4-tetrafluoro-1-(pyridin-3-yl)but-2-en-1-yl) phosphite (183o)



152o 183o

Alcohol **152o** [296.26]	1.00 eq	418 µmol	92.5 mg
DMAP [122.17]	0.10 eq	42.0 µmol	5.10 mg
Diethyl phosphorochloridate [172.55, ρ = 1.19]	3.00 eq	1.26 mmol	182 µL
Pyridine			4.2 mL

was obtained following general procedure IV using the alcohol **152o** (92.5 mg, 418 µmol). Purification by column chromatography using 1:5 (*n*-pentane/Et_2O) afforded phosphate **183o** (34.6 mg, 96.8 µmol, 23%) as a yellow oil.

TLC: R_f = 0.22 (*n*-pentane/Et_2O 1:5).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 8.65-8.61 (m, 2H, CH_{arom}), 7.73 (d, J = 7.6 Hz, 1H, CH_{arom}), 7.34 (dd, J = 7.9, 4.8 Hz, 1H, CH_{arom}), 6.24 (t, J = 8.4 Hz, 1H, CHO), 5.92 (dd, J = 30.9 Hz, 8.9 Hz, 1H, CHCF), 4.13-4.02 (m, 4H, 2CH_2), 1.31-1.23 (m, 6H, 2CH_3) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −72.9 (d, J = 10.7 Hz, CF_3), −129.0 (q, J = 10.7 Hz, CF) ppm.

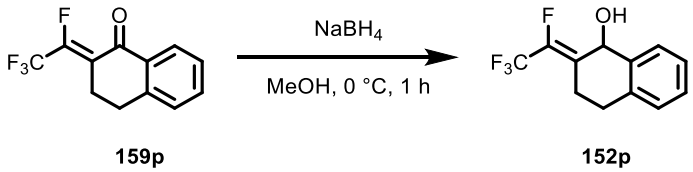
^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 150.5 (C_{arom}), 147.8 (C_{arom}), 146.7 (dq, J = 267.0, 40.1 Hz, CFCF$_3$), 134.0 (C_{arom}), 133.3 (d, J = 5.7 Hz, C_{quart}), 123.8 (C_{arom}), 117.8 (qd, J = 272.3, 40.7 Hz, CFCF$_3$), 111.8 (td, J = 5.9, 3.0 Hz, CHCF), 69.4 (t, J = 4.4 Hz, CHO), 64.4 (d, J = 5.7 Hz, 2CH$_2$), 16.0 (dd, J = 6.9, 5.0 Hz, 2CH_3) ppm.

^{31}P NMR: (202 MHz, $CDCl_3$) δ = −1.31 ppm.

HRMS: (EI+); *m/z* calc. for $C_{13}H_{16}F_4NO_4P$ $[M]^+$: 357.07531, found 357.07432.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 2988 (w), 1431 (w), 1352 (w), 1267 (w), 1203 (m), 1151 (m), 1117 (w), 1032 (s), 1000 (w), 806 (w), 712 (w).

(*Z*)-2-(Perfluoroethylidene)-1,2,3,4-tetrahydronaphthalen-1-ol (152p)



159p **152p**

Fluorenone **159p** [244.19]	1.00 eq	328 µmol	80.1 mg
$NaBH_4$ [37.83]	1.20 eq	394 µmol	14.9 mg
MeOH			1.5 mL

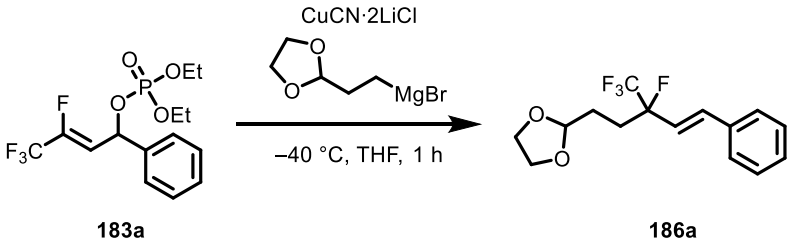
Following general procedure III using the *β*-fluoroenone **159p** (80.1 mg, 328 µmol), the crude product **152p** was obtained as a yellow oil and used directly in the phosphorylation without further purification, the corresponding phosphate was decomposed due to its inherent instability.

^{1}H-NMR: (300 MHz, $CDCl_3$) δ = 7.57 – 6.94 (m, 4H, CH_{arom}), 5.57 (s, 1H, C*H*), 5.20 (s, 1H, O*H*), 3.22 – 2.49 (m, 4H, 2CH_2) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −64.8 (d, *J* = 8.5 Hz), −130.1 (q, *J* = 8.6 Hz) ppm.

Racemic installation of FTF groups

(*E*)-2-(3-Fluoro-5-phenyl-3-(trifluoromethyl)pent-4-en-1-yl)-1,3-dioxolane (186a)



183a **186a**

Phosphate **183a** [356.25]	1.00 eq	132 µmol	47.0 mg
CuCN·2LiCl [1 M in THF]	2.20 eq	290 µmol	290 µL
GRIGNARD reagent **188a** [0.65 M in THF]	2.20 eq	290 µmol	447 µL
THF			1.2 mL

was obtained following general procedure V using the corresponding fluorophosphate **183a** (47.0 mg, 132 µmol). Purification by column chromatography using 10:1 (*n*-pentane/Et_2O) afforded the product **186a** (35.0 mg, 115 µmol, γ: α > 25:1, 87%) as a colorless oil.

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.44 – 7.40 (m, 2H, CH_{arom}), 7.39 – 7.34 (m, 2H, CH_{arom}), 7.34 – 7.28 (m, 1H, CH_{arom}), 6.88 (d, J = 16.2 Hz, 1H, CHC$_{arom}$), 6.07 (dd, J = 20.4, 16.9 Hz, 1H, CHCF), 4.94 (t, J = 4.3 Hz, 1H. CHCH_2), 4.32 – 3.54 (m, 4H, 2CH_2O), 2.30 – 1.94 (m, 2H, CH_2CF), 1.92 – 1.74 (m, 2H, CHCH_2) ppm.

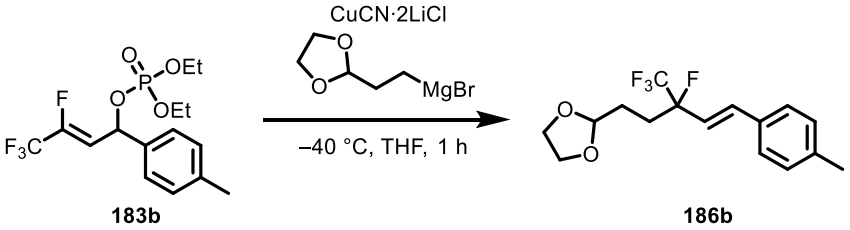
^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −80.9 (d, J = 7.1 Hz, CF_3), −176.6 (q, J = 7.3 Hz, CF) ppm.

^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 135.3 (C_{quart}), 134.7 (d, J = 11.0 Hz, CHC$_{arom}$), 128.9 (C_{arom}), 128.9 (C_{arom}), 127.1 (C_{arom}), 123.5 (qd, J = 284.7, 29.6 Hz, CF$_3$), 120.5 (d, J = 19.2 Hz, CHCF), 103.5 (CHCH_2), 94.8 (dq, J = 189.3, 31.1 Hz, CF), 65.2 (d, J = 4.3 Hz, 2CH$_2$O), 26.7 (d, J = 2.9 Hz, CHCH$_2$), 26.6 (d, J = 21.4 Hz, CH$_2$CF) ppm.

HRMS (EI+); *m/z* calc. for $C_{15}H_{16}F_4O_2$ $[M]^+$: 304.1086, found 304.1134.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 2955 (w), 2886 (w), 1657 (w), 1496 (w), 1450 (w), 1401 (w), 1306 (w), 1262 (w), 1177 (s), 1143 (w), 1117 (w), 1071 (w), 1028 (m), 966 (s), 893 (w), 794 (w), 748 (s), 692 (m), 572 (w), 493 (m).

(*E*)-2-(3-Fluoro-5-(*p*-tolyl)-3-(trifluoromethyl)pent-4-en-1-yl)-1,3-dioxolane (186b)



Phosphate **183b** [370.28]	1.00 eq	138 µmol	51.2 mg
CuCN·2LiCl [1 M in THF]	2.20 eq	304 µmol	304 µL
GRIGNARD reagent **188a** [0.43 M in THF]	2.20 eq	304 µmol	708 µL
THF			1.2 mL

was obtained following general procedure V using the corresponding fluorophosphate **183b** (51.2 mg, 138 µmol). Purification by column chromatography using 10:1 (*n*-pentane/Et_2O) afforded **186b** (41.0 mg, 0.129 µmol, *γ*: *α* = 20:1, 93%) as a colorless oil.

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.32 (d, J = 8.1 Hz, 2H, CH_{arom}), 7.16 (d, J = 7.9 Hz, 2H, CH_{arom}), 6.83 (d, J = 16.2 Hz, 1H, CHC$_{arom}$), 6.01 (dd, J = 20.3, 16.2 Hz, 1H, CHCF), 4.93 (t, J = 4.3 Hz, 1H, CHCH$_2$), 4.06 – 3.68 (m, 4H, 2CH_2O), 2.36 (s, 3H, CH_3), 2.27 – 1.92 (m, 2H, CH_2CF), 1.91 – 1.73 (m, 2H, CHCH_2) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −80.9 (d, J = 7.0 Hz, CF_3), −176.3 (q, J = 7.1 Hz, CF) ppm.

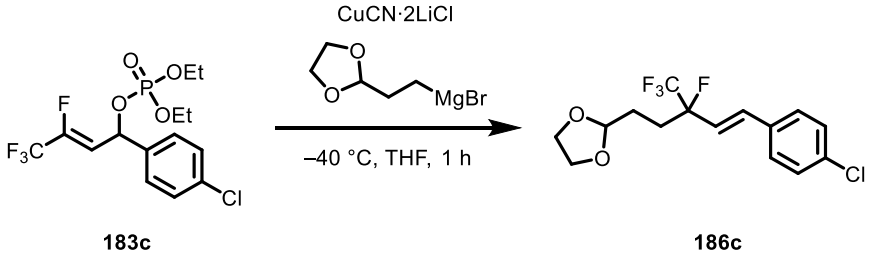
^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 138.9 (C_{quart}), 134.5 (d, J = 11.1 Hz, CHC$_{arom}$), 132.5 (C_{quart}), 129.6 (C_{arom}), 127.0 (C_{arom}), 123.4 (qd, J = 284.2, 30.3 Hz, CF$_3$), 119.3 (CHCF), 103.5 (CHCH$_2$), 94.8 (dq, J = 189.0, 31.1 Hz, CF), 65.2 (d, J =

4.4 Hz, 2*C*H$_2$O), 26.7 (d, *J* = 2.8 Hz, CH*C*H$_2$), 26.5 (d, *J* = 21.5 Hz, *C*H$_2$CF), 21.41 (*C*H$_3$) ppm.

HRMS: (EI+); *m/z* calc. for $C_{16}H_{18}F_4O_2$ $[M]^+$: 318.1243, found 318.1229.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 2955 (w), 2886 (w), 1515 (w), 1451 (w), 1414 (w), 1312 (w), 1262 (w), 1180 (s), 1145 (w), 1029 (w), 969 (m), 894 (w), 798 (w), 694 (w), 498 (w).

(*E*)-2-(5-(4-chlorophenyl)-3-fluoro-3-(trifluoromethyl)pent-4-en-1-yl)-1,3-dioxolane (186c)



183c **186c**

Phosphate **183c** [390.70]	1.00 eq	127 µmol	49.6 mg
CuCN·2LiCl [1 M in THF]	2.20 eq	279 µmol	279 µL
GRIGNARD reagent **188a** [0.43 M in THF]	2.20 eq	279 µmol	650 µL
THF			1.2 mL

was obtained following general procedure V using the corresponding fluorophosphate **183c** (49.6 mg, 127 µmol). Purification by column chromatography using 10:1 (*n*-pentane/Et$_2$O) afforded **186c** (37.0 mg, 109 µmol, *γ*: *α* = 17:1, 86%) as a colorless oil.

^{1}H-NMR: (500 MHz, $CDCl_3$) *δ* = 7.41 – 7.28 (m, 4H, C*H*$_{arom}$), 6.83 (d, *J* = 16.2 Hz, 1H, C*H*C$_{arom}$), 6.04 (dd, *J* = 19.9, 16.6 Hz, 1H, C*H*CF), 4.93 (t, *J* = 4.3 Hz, 1H, C*H*CH$_2$), 4.01 – 3.78 (m, 4H, 2C*H*$_2$O), 2.32 – 1.91 (m, 2H, C*H*CF), 1.92 – 1.68 (m, 2H, CHC*H*$_2$) ppm.

^{13}C-NMR: (126 MHz, $CDCl_3$) *δ* = 134.7 (*C*$_{quart}$), 133.8 (*C*$_{quart}$), 133.5 (d, *J* = 11.3 Hz, *C*HC$_{arom}$), 129.1 (*C*$_{arom}$), 128.3 (*C*$_{arom}$), 123.4 (qd, *J* = 284.5, 29.3 Hz, *C*F$_3$), 121.2 (d, *J* = 19.1 Hz, *C*HCF), 103.4 (*C*HCH$_2$), 94.7 (dq, *J* = 189.8, 31.2 Hz,

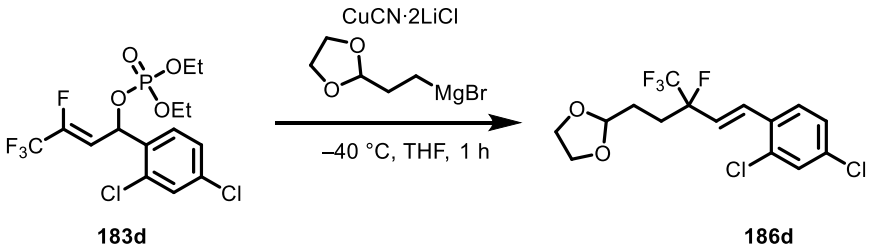
*C*F), 65.2 (d, *J* = 4.3 Hz, 2*C*H$_2$O), 26.7 (d, *J* = 2.9 Hz, CH*C*H$_2$), 26.5 (d, *J* = 21.5 Hz, *C*H$_2$CF) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −80.8 (d, *J* = 7.1 Hz, C*F*$_3$), −176.8 (q, *J* = 6.7 Hz, C*F*) ppm.

HRMS: (EI+); *m/z* calc. for $C_{15}H_{15}ClF_4O_2$ $[M]^+$:338.0697, found 338.0695.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 2956 (w), 2886 (w), 1492 (m), 1451 (w), 1407 (w), 1307 (w), 1259 (w), 1177 (s), 1143 (w), 1119 (w), 1093 (w), 1013 (m), 967 (s), 944 (w), 894 (w), 855 (w), 807 (m), 718 (m), 502 (m), 421 (w).

(*E*)-2-(5-(2,4-Dichlorophenyl)-3-fluoro-3-(trifluoromethyl)pent-4-en-1-yl)-1,3-dioxolane (186d)



183d 186d

Phosphate **183d** [425.14]	1.00 eq	89.0 µmol	37.8 mg
CuCN·2LiCl [1 M in THF]	2.20 eq	196 µmol	196 µL
GRIGNARD reagent **188a** [0.54 M in THF]	2.20 eq	196 µmol	362 µL
THF			1.2 mL

was obtained following general procedure V using the corresponding fluorophosphate **183d** (37.8 mg, 89.0 µmol). Purification by column chromatography using 10:1 (*n*-pentane/Et$_2$O) afforded **186d** (26.6 mg, 0.071 mmol, *γ*: *α* > 25:1, 80%) as a colorless oil.

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.44 (d, *J* = 8.4 Hz, 1H, C*H*$_{arom}$), 7.41 (d, *J* = 2.1 Hz, 1H, C*H*$_{arom}$), 7.24 (dd, *J* = 8.4, 2.3 Hz, 1H, C*H*$_{arom}$), 7.19 (d, *J* = 16.2 Hz, 1H, C*H*C$_{arom}$), 6.04 (dd, *J* = 19.5, 16.9 Hz, 1H, C*H*CF), 4.94 (t, *J* = 4.2 Hz, 1H,

C*H*), 4.00 – 3.82 (m, 4H, 2CH_2O), 2.37 – 1.95 (m, 2H,CH_2CF), 1.94 – 1.71 (m, 2H, CHCH_2) ppm.

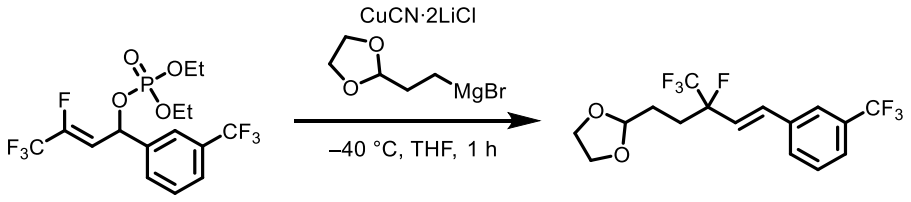
^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −80.7 (d, J = 7.2 Hz, CF_3), −176.5 (q, J = 7.2 Hz, C*F*) ppm.

^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 135.1 (C_{quart}), 134.5 (C_{quart}), 132.3 (C_{quart}), 130.3 (d, J = 11.8 Hz, CHC$_{arom}$), 129.9 (C_{arom}), 128.1 (C_{arom}), 127.5 (C_{arom}), 124.0 (d, J = 19.3 Hz, *C*HCF), 123.7 (qd, J = 284.7, 30.6 Hz, *C*F_3), 103.4 (*C*HCH_2), 94.7 (dq, J = 190.6, 31.2 Hz, *C*F), 65.3 (d, J = 4.3 Hz, 2*C*H_2O), 26.7 (d, J = 2.9 Hz, CH*C*H_2), 26.4 (d, J = 21.4 Hz, *C*H_2CF) ppm.

HRMS: (FD+); *m/z* calc. for $C_{15}H_{14}Cl_2F_4O_2$ $[M]^+$: 372.0307, found 372.0289.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 2884 (w), 1585 (w), 1471 (m), 1451 (w), 1385 (w), 1297 (w), 1260 (w), 1179 (s), 1141 (w), 1120 (w), 1102 (w), 1028 (w), 969 (m), 945 (w), 894 (w), 866 (w), 806 (m), 750 (w), 720 (w), 689 (w), 559 (w), 453 (w), 422 (w).

(*E*)-2-(3-Fluoro-3-(trifluoromethyl)-5-(3-(trifluoromethyl)phenyl)pent-4-en-1-yl)-1,3-dioxolane (186e)



183e 186e

Phosphate **183e** [424.25]	1.00 eq	94.3 µmol	40.0 mg
CuCN·2LiCl [1 M in THF]	2.20 eq	207 µmol	207 µL
GRIGNARD reagent **188a** [0.34 M in THF]	2.20 eq	207 µmol	610 µL
THF			1.2 mL

was obtained following general procedure V using the corresponding fluorophosphate **183e** (40.0 mg, 94.3 µmol). Purification by column chromatography using 10:1 (*n*-pentane/Et_2O) afforded **186e** (26.6 mg, 71.5 µmol, *γ*: *α* = 17:1, 76%) as a colorless oil.

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.70 – 7.65 (m, 1H, C*H*$_{arom}$), 7.61 – 7.56 (m, 2H, C*H*$_{arom}$), 7.52 – 7.43 (m, 1H, C*H*$_{arom}$), 6.91 (d, *J* = 16.2 Hz, 1H, C*H*C$_{arom}$), 6.14 (dd, *J* = 20.8, 16.8 Hz, 1H, C*H*CF), 4.93 (t, *J* = 4.2 Hz, 1H, C*H*O), 4.06 – 3.76 (m, 4H, 2C*H*$_2$O), 2.31 – 1.95 (m, 2H, C*H*$_2$CF), 1.93 – 1.71 (m, 2H, CHC*H*$_2$) ppm.

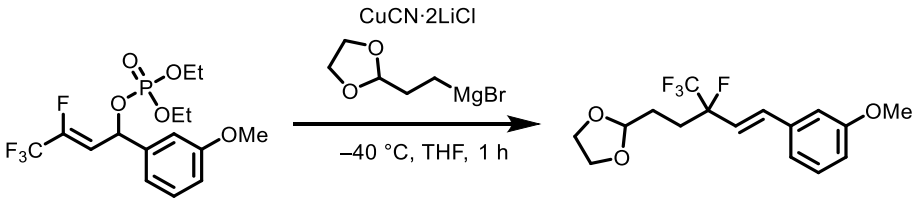
^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −62.8 (C*F*$_3$C$_{arom}$), −80.8 (d, *J* = 7.1 Hz, C*F*$_3$), −177.1 (q, *J* = 6.8 Hz, C*F*) ppm.

^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 135.8 (*C*$_{quart}$), 133.2 (d, *J* = 11.4 Hz, *C*HC$_{arom}$), 131.3 (q, *J* = 32.4 Hz, *C*$_{quart}$), 130.2 (*C*$_{arom}$), 129.3 (*C*$_{arom}$), 125.3 (q, *J* = 3.8 Hz, *C*$_{arom}$), 125.0 (*J* = 272.81 Hz, *C*F$_3$C$_{arom}$),123.6 (q, *J* = 3.8 Hz, *C*$_{arom}$), 123.6 (q, *J* = 272.7 Hz, *C*$_{arom}$), 122.3 (d, *J* = 19.0 Hz, *C*HCF), 123.1 (qd, *J* = 284.5, 29.5 Hz, CF*C*F$_3$), 103.2 (*C*HCH$_2$), 94.5 (dq, *J* = 190.3, 31.1 Hz, *C*FCF$_3$), 65.1 (d, *J* = 3.8 Hz, 2*C*H$_2$O), 26.5 (d, *J* = 2.8 Hz, CH*C*H$_2$), 26.3 (d, *J* = 21.3 Hz, *C*H$_2$CF) ppm.

HRMS: (EI+); *m/z* calc. for $C_{16}H_{15}F_7O_2$ $[M]^+$: 372.0960, found 372.0923.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 2957 (w), 2887 (w), 2254 (w), 1706 (w), 1660 (w), 1488 (w), 1442 (w), 1413 (w), 1331 (m), 1260 (w), 1166 (w), 1125 (s), 1073 (w), 1028 (w), 969 (m), 944 (w), 907 (s), 795 (w), 732 (s), 697 (w), 654 (w), 576 (w), 506 (w), 452 (w).

(*E*)-2-(3-Fluoro-5-(3-methoxyphenyl)-3-(trifluoromethyl)pent-4-en-1-yl)-1,3-dioxolane (186f)



183f **186f**

Phosphate **183f** [386.28]	1.00 eq	129 µmol	50.0 mg
CuCN·2LiCl [1 M in THF]	2.20 eq	285 µmol	285 µL
GRIGNARD reagent **188a** [0.52 M in THF]	2.20 eq	285 µmol	547 µL
THF			1.2 mL

was obtained following general procedure V using the corresponding fluorophosphate **183f** (50.0 mg, 129 µmol). Purification by column chromatography using 10:1 (*n*-pentane/Et_2O) afforded **186f** (38.5 mg, 115 µmol, γ: α = 20:1, 89%) as a colorless oil.

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.31 – 7.20 (m, 1H, CH_{arom}), 7.04 – 6.97 (m, 1H, CH_{arom}), 6.93 (dd, J = 2.6, 1.6 Hz, 1H, CH_{arom}), 6.88 – 6.80 (m, 2H, CH_{arom}), 6.05 (dd, J = 20.2, 15.6 Hz, 1H, C*H*CF), 4.92 (t, J = 4.3 Hz, 1H, C*H*O), 3.99 – 3.83 (m, 4H, 2CH_2O), 3.82 (s, 3H, OCH_3), 2.34 – 1.93 (m, 2H, CH_2CF), 1.90 – 1.72 (m, 2H, CHCH_2) ppm.

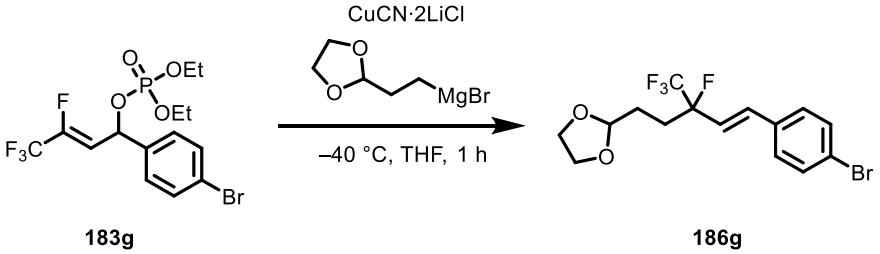
^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −80.9 (d, J = 7.1 Hz, CF_3), −176.7 (q, J = 7.3 Hz, C*F*) ppm.

^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 160.1 (C_{quart}), 136.7 (C_{quart}), 134.6 (d, J = 11.1 Hz, *C*HC$_{arom}$), 129.9 (C_{arom}), 123.4 (qd, J = 285.6, 29.7 Hz, *C*F_3), 120.8 (d, J = 19.2 Hz, *C*HCF), 119.7 (C_{arom}), 114.6 (C_{arom}), 112.4 (C_{arom}), 103.5 (*C*HCH_2), 94.9 (dq, J = 189.3, 30.8 Hz, *C*F), 65.2 (d, J = 4.3 Hz, 2CH_2O), 55.4 (CH_3), 26.7 (d, J = 2.9 Hz, CH*C*H_2), 26.6 (d, J = 21.5 Hz, *C*H_2CF) ppm.

HRMS: (EI+); *m/z* calc. for $C_{16}H_{18}F_4O_3$ $[M]^+$: 334.1192, found 334.1179.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 2956 (w), 2887 (w), 1602 (w), 1583 (w), 1491 (w), 1454 (w), 1435 (w), 1293 (w), 1259 (m), 1179 (s), 1159 (w), 1118 (w), 1043 (m), 971 (m), 945 (w), 875 (w), 778 (w), 687 (w).

(*E*)-2-(5-(4-Bromophenyl)-3-fluoro-3-(trifluoromethyl)pent-4-en-1-yl)-1,3-dioxolane (186g)



183g 186g

Phosphate **183g** [435.15]	1.00 eq	91.0 µmol	39.6 mg
CuCN·2LiCl [1 M in THF]	2.20 eq	200 µmol	413 µL
GRIGNARD reagent **188a** [0.48 M in THF]	2.20 eq	200 µmol	200 µL
THF			1.0 mL

was obtained following general procedure V using the corresponding fluorophosphate **183g** (39.6 mg, 91.0 µmol). Purification by column chromatography using 10:1 (*n*-pentane/Et_2O) afforded **186g** (32.0 mg, 83.5 mmol, γ: α = 20:1, 92%) as a colorless oil.

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.48 (d, J = 8.5 Hz, 2H, CH_{arom}), 7.28 (d, J = 8.4 Hz, 2H, CH_{arom}), 6.81 (d, J = 16.1 Hz, 1H, CHC$_{arom}$), 6.05 (dd, J = 20.3, 16.3 Hz, 1H, CHCF), 5.73 – 5.55 (m, 1H), 4.92 (t, J = 4.2 Hz, 1H, CHCH_2), 4.04 – 3.78 (m, 4H, 2CH_2O), 2.29 – 1.92 (m, 2H, CH_2CF), 1.91 – 1.70 (m, 2H, CHCH_2) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −80.8 (d, J = 7.0 Hz, CF_3), −176.7 (q, J = 7.2 Hz, CF) ppm.

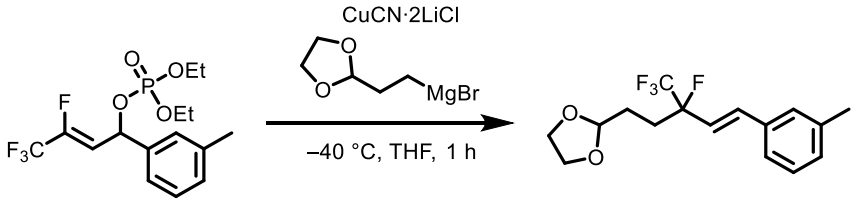
^{13}C-NMR (126 MHz, $CDCl_3$) δ = 134.1 (C_{quart}), 133.6 (d, J = 11.3 Hz, CHC$_{arom}$), 132.0 (C$_{arom}$), 128.6 (C$_{arom}$), 123.3 (qd, J = 284.6, 29.5 Hz, CF$_3$), 122.9 (C_{quart}), 121.2 (d, J = 19.1 Hz, CHCF), 103.4 (CHCH$_2$), 94.7 (dq, J = 190.0, 31.2 Hz, CF),

65.2 (d, J = 4.2 Hz, 2CH_2O), 26.6 (d, J = 2.9 Hz, CHCH_2), 26.4 (d, J = 21.4 Hz, CH_2CF) ppm.

HRMS: (EI+); *m/z* calc. for $C_{15}H_{15}BrF_4O_2$ $[M]^+$: 382.0192, found 382.0200.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 2955 (w), 2886 (w), 1489 (m), 1451 (w), 1402 (w), 1306 (w), 1290 (w), 1259 (w), 1178 (s), 1144 (w), 1120 (w), 1072 (w), 1029 (w), 1011 (m), 969 (s), 945 (w), 894 (w), 855 (w), 805 (m), 717 (w), 499 (w).

(*E*)-2-(3-Fluoro-5-(*m*-tolyl)-3-(trifluoromethyl)pent-4-en-1-yl)-1,3-dioxolane (186h)



183h **186h**

Phosphate **183h** [370.28]	1.00 eq	135 µmol	50.0 mg
CuCN·2LiCl [1 M in THF]	2.20 eq	297 µmol	297 µL
GRIGNARD reagent **188a** [0.52 M in THF]	2.20 eq	297 µmol	571 µL
THF			1.0 mL

was obtained following general procedure V using the corresponding fluorophosphate **183h** (50.0 mg, 135 µmol). Purification by column chromatography using 10:1 (*n*-pentane/Et_2O) afforded **186h** (39.0 mg, 123 µmol, γ: α = 14:1, 91%) as a colorless oil.

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.31 – 7.21 (m, 4H, CH_{arom}), 7.16 (dtd, J = 7.3, 1.7, 0.8 Hz, 1H, CH_{arom}), 6.87 (d, J = 16.2 Hz, 1H, CHC$_{arom}$), 6.08 (dd, J = 20.4, 16.2 Hz, 1H, CHCF), 4.96 (t, J = 4.3 Hz, 1H, C$H$$CH_2$), 4.19 – 3.81 (m, 4H, 2CH_2O), 2.39 (s, 3H, CH_3), 2.31 – 1.97 (m, 2H, CH_2CF), 1.95 – 1.76 (m, 2H, CHCH_2) ppm.

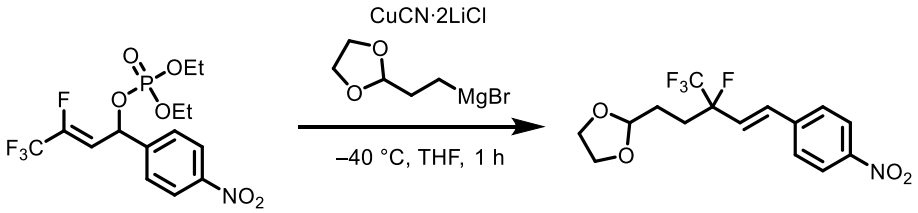
^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −80.9 (d, J = 7.0 Hz, CF_3), −176.6 (q, J = 7.4 Hz, CF) ppm.

^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 138.5 (C_{quart}), 135.2 (C_{quart}), 134.8 (d, J = 11.0 Hz, CHC$_{arom}$), 129.7 (C_{arom}), 128.8 (C_{arom}), 127.7 (C_{arom}), 124.3 (C_{arom}), 123.4 (qd, J = 284.5, 29.6 Hz, CFCF$_3$), 120.2 (d, J = 19.1 Hz, CHCF), 103.5 (CHCH$_2$), 94.8 (dq, J = 189.1, 31.0 Hz, CFCF$_3$), 65.2 (d, J = 4.2 Hz, 2CH$_2$O), 26.7 (d, J = 2.8 Hz, CHCH$_2$), 26.5 (d, J = 21.4 Hz, CH$_2$CF), 21.5 (CH$_3$) ppm.

HRMS: (EI+); *m/z* calc. for $C_{16}H_{18}F_4O_2$ $[M]^+$: 318.1243, found 318.1235.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 2956 (w), 2886 (w), 1451 (w), 1413 (w), 1301 (w), 1260 (w), 1181 (s), 1144 (w), 1118 (w), 1071 (w), 1030 (w), 970 (m), 945 (w), 882 (w), 777 (w), 690 (w).

(*E*)-2-(3-fluoro-5-(4-nitrophenyl)-3-(trifluoromethyl)pent-4-en-1-yl)-1,3-dioxolane (186i)



183i 186i

Phosphate **183i** [401.25]	1.00 eq	125 mol	50.0 mg
CuCN·2LiCl [1 M in THF]	1.10 eq	137 µmol	137 µL
GRIGNARD reagent [0.63 M in THF]	1.10 eq	137 µmol	218 µL
THF			1.0 mL

was obtained following general procedure V using the corresponding fluorophosphate **183i** (50.0 mg, 125 µmol). Purification by column chromatography using 5:1 (*n*-pentane/Et$_2$O) afforded **186i** (23.9 mg, 93.3 µmol, γ: α > 25:1, 55%) as a white solid.

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 8.25 (d, J = 8.8 Hz, 2H, CH_{arom}), 7.59 (d, J = 8.7 Hz, 2H, CH_{arom}), 6.97 (d, J = 16.2 Hz, 1H, CHC$_{arom}$), 6.26 (dd, J = 20.1, 16.3 Hz, 1H, CHCF), 4.95 (t, J = 4.2 Hz, 1H, CHCH$_2$), 4.05 – 3.85 (m, 4H, 2CH_2O), 2.36 – 1.97 (m, 2H, CH_2CF), 1.96 – 1.71 (m, 2H, CHCH_2) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −80.6 (d, J = 7.0 Hz, CF_3), −177.3 (q, J = 7.0 Hz, CF) ppm.

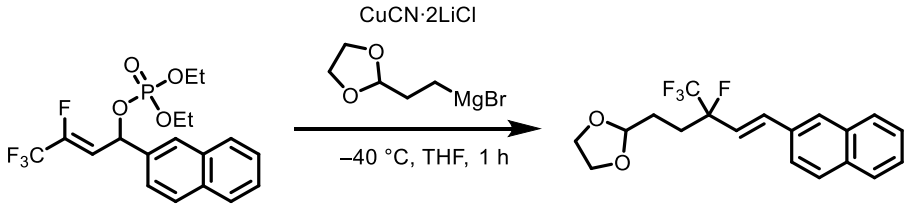
^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 147.7 (C_{quart}), 141.2 (C_{quart}), 132.5 (d, J = 11.4 Hz, CHC$_{arom}$), 127.7 (C_{arom}), 125.0 (d, J = 19.0 Hz, CHCF), 124.1 (C_{arom}), 123.0 (qd, J = 284.9, 29.6 Hz, CFCF$_3$), 103.1, 94.5 (dq, J = 191.1, 31.4 Hz, CFCF$_3$), 65.1 (d, J = 4.2 Hz, 2CH$_2$O), 26.5 (d, J = 2.9 Hz, CHCH$_2$), 26.2 (d, J = 21.4 Hz, CH$_2$CF) ppm.

HRMS: (EI+); *m/z* calc. for $C_{15}H_{15}F_4NO_4$ $[M]^+$: 349.0937, found 349.0926.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 2955 (w), 2886 (w), 1599 (w), 1518 (s), 1451 (w), 1413 (w), 1344 (s), 1305 (w), 1260 (w), 1179 (s), 1143 (w), 1111 (w), 1027 (w), 969 (m), 859 (m), 826 (w), 792 (w), 747 (w), 710 (w), 688 (w), 629 (w), 580 (w), 494 (w).

Mp.: 66.5−67.8 °C.

(*E*)-2-(3-Fluoro-5-(naphthalen-2-yl)-3-(trifluoromethyl)pent-4-en-1-yl)-1,3-dioxolane (186j)



183j 186j

Phosphate **183j** [406.31]	1.00 eq	123 µmol	50.0 mg
CuCN·2LiCl [1 M in THF]	2.20 eq	271 µmol	271 µL
GRIGNARD reagent **188a** [0.60 M in THF]	2.20 eq	271 µmol	451 µL
THF			1.2 mL

was obtained following general procedure V using the corresponding fluorophosphate **183j** (50.0 mg, 123 µmol). Purification by column chromatography using 10:1 (*n*-pentane/Et_2O) afforded **(*rac*)-186j** (35.0 mg, 98.9 µmol, *γ*: *α* > 25:1, 80%) as a white solid.

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.93 – 7.69 (m, 4H, CH_{arom}), 7.59 (dd, *J* = 8.5, 1.8 Hz, 1H, CH_{arom}), 7.54 – 7.42 (m, 2H, CH_{arom}), 7.04 (d, *J* = 16.1 Hz, 1H, CHC$_{arom}$), 6.19 (dd, *J* = 20.2, 16.1 Hz, 1H, CHCF), 4.95 (t, *J* = 4.3 Hz, 1H), 4.03 – 3.79 (m, 4H, 2CH_2O), 2.39 – 1.97 (m, 2H, CH_2CF), 1.96 – 1.76 (m, 2H, CHCH_2) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −80.8 (d, *J* = 7.1 Hz, CF_3), −176.5 (q, *J* = 7.5 Hz, CF) ppm.

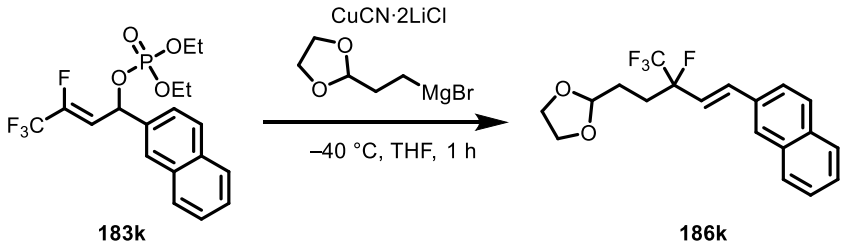
^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 134.7 (d, *J* = 11.1 Hz, CHC$_{arom}$), 133.5 (C_{quart}), 133.4 (C_{quart}), 132.5 (C_{quart}), 128.5 (C_{arom}), 128.2 (C_{arom}), 127.7 (C_{arom}), 127.7 (C_{arom}), 126.5 (C_{arom}), 126.5 (C_{arom}), 123.4 (C_{arom}), 123.3 (qd, *J* = 284.7, 29.6 Hz, CF$_3$), 120.6 (d, *J* = 19.3 Hz, CHCF), 103.4 (CHCH$_2$), 94.7 (dq, *J* = 189.4, 31.2 Hz, CF), 65.1 (d, *J* = 4.3 Hz, 2CH$_2$O), 26.6 (d, *J* = 2.9 Hz, CHCH$_2$), 26.5 (d, *J* = 21.4 Hz, CH$_2$CF) ppm.

HRMS: (EI+); *m/z* calc. for $C_{19}H_{18}F_4O_2$ $[M]^+$: 354.1243, found 354.1250.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 3058 (w), 2955 (w), 2886 (w), 1657 (w), 1598 (w), 1509 (w), 1451 (w), 1399 (w), 1360 (w), 1312 (w), 1260 (w), 1180 (s), 1114 (w), 1071 (w), 1028 (w), 969 (m), 895 (w), 863 (w), 810 (m), 747 (w), 718 (w), 694 (w), 476 (w).

Mp.: 80.3−82.3 °C.

(*E*)-2-(3-Fluoro-5-(naphthalen-1-yl)-3-(trifluoromethyl)pent-4-en-1-yl)-1,3-dioxolane (186k)



Phosphate **183k** [406.31]	1.00 eq	123 µmol	50.0 mg
CuCN·2LiCl [1 M in THF]	2.20 eq	271 µmol	271 µL
GRIGNARD reagent **188a** [0.43 M in THF]	2.20 eq	271 µmol	629 µL
THF			1.2 mL

was obtained following general procedure V using the corresponding fluorophosphate **183k** (50.0 mg, 123 µmol). Purification by column chromatography using 10:1 (*n*-pentane/Et_2O) afforded **186k** (40.1 mg, 113 µmol, γ: α = 20:1, 92%) as a colorless oil.

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 8.08 (d, J = 9.5 Hz, 1H, CH_{arom}), 7.92 – 7.81 (m, 2H, CH_{arom}), 7.67 (d, J = 15.9 Hz, 1H, CH_{arom}), 7.60 (d, J = 9.1 Hz, 1H, CH_{arom}), 7.59 – 7.49 (m, 2H, CH_{arom}), 7.47 (d, J = 15.4 Hz, 1H, CHC$_{arom}$), 6.11 (dd, J = 20.2, 15.8 Hz, 1H, CHCF), 4.98 (t, J = 4.2 Hz, 1H, CHCH_2), 4.04 – 3.82 (m, 4H, 2CH_2O), 2.37 – 2.01 (m, 2H, CH_2CF), 2.02 – 1.83 (m, 2H, CHCH_2) ppm.

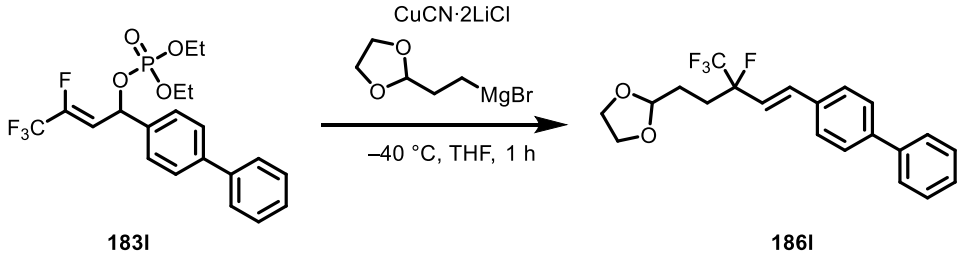
^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −80.8 (d, J = 7.1 Hz, CF_3), −176.2 (q, J = 5.4 Hz, CF) ppm.

^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 133.7 (C_{quart}), 133.2 (C_{quart}), 132.5 (d, J = 11.3 Hz, CHC$_{arom}$), 131.3 (C_{quart}), 129.2 (C_{arom}), 128.7 (C_{arom}), 126.7 (C_{arom}), 126.2 (C_{arom}), 125.6 (C_{arom}), 124.4 (C_{arom}), 123.7 (C_{arom}), 123.7 (d, J = 18.6 Hz, CHCF), 123.4 (qd, J = 284.3, 28.4 Hz, CF$_3$), 103.4 (CHCH_2), 94.9 (dq, J = 189.4, 31.1 Hz, CF), 65.2 (d, J = 4.3 Hz, 2CH$_2$O), 26.8 (d, J = 2.8 Hz, CHCH$_2$), 26.5 (d, J = 21.3 Hz, CH$_2$CF) ppm.

HRMS: (EI+); *m/z* calc. for $C_{19}H_{18}F_4O_2$ $[M]^+$: 354.1243, found 354.1257.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 3030 (w), 2944 (w), 2886 (w), 1655 (w), 1487 (w), 1451 (w), 1408 (w), 1379 (w), 1350 (w), 1317 (w), 1294 (w), 1258 (w), 1180 (s), 1151 (w), 1111 (w), 1072 (w), 1025 (w), 967 (m), 944 (w), 907 (w), 877 (w), 857 (w), 820 (w), 793 (w), 762 (s), 731 (m), 692 (m), 649 (w), 581 (w), 550 (w), 513 (w), 481 (m), 432 (w).

(*E*)-2-(5-([1,1'-Biphenyl]-4-yl)-3-fluoro-3-(trifluoromethyl)pent-4-en-1-yl)-1,3-dioxolane (186l)



183l 186l

Phosphate **183l** [432.35]	1.00 eq	116 µmol	50.0 mg
CuCN·2LiCl [1 M in THF]	2.20 eq	254 µmol	254 µL
GRIGNARD reagent **188a** [0.43 M in THF]	2.20 eq	254 µmol	591 µL
THF			1.2 mL

was obtained following general procedure V using the corresponding fluorophosphate **183l** (50.0 mg, 116 µmol). Purification by column chromatography using 10:1 (*n*-pentane/Et_2O) afforded **186l** (35.5 mg, 93.3 µmol, γ: α > 25:1, 81%) as a white solid.

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.62 (d, J = 12.8 Hz, 4H, CH_{arom}), 7.51 (d, J = 8.3 Hz, 2H, CH_{arom}), 7.47 (d, J = 13.6 Hz, 2H, CH_{arom}), 7.38 (d, J = 17.3 Hz, 1H, CH_{arom}), 6.93 (d, J = 16.2 Hz, 1H, CHC$_{arom}$), 6.12 (dd, J = 20.1, 15.8 Hz, 1H, CHCF), 4.96 (t, J = 4.3 Hz, 1H, CHCH_2), 4.02 – 3.84 (m, 4H, 2CH_2O), 2.37 – 1.97 (m, 2H, CH_2CF), 1.96 – 1.76 (m, 2H, CHCH_2) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −80.8 (d, J = 7.1 Hfz, CF_3), −176.6 (q, CF) ppm.

^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 141.7 (C_{quart}), 140.5 (C_{quart}), 134.3 (C_{quart}), 134.2 (C_{arom}), 129.0 (C_{arom}), 127.7 (C_{arom}), 127.5 (C_{arom}), 127.1 (C_{arom}), 123.4 (qd, J

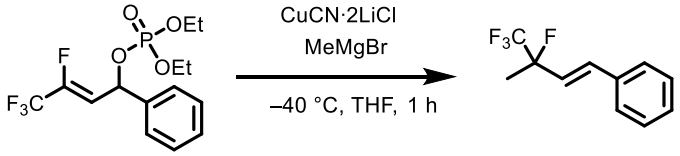
= 284.4, 29.5 Hz, *C*F_3), 120.4 (d, *J* = 19.1 Hz, *C*HCF), 103.4 (*C*HCH_2), 94.8 (dq, *J* = 189.4, 31.2 Hz, *C*F), 65.2 (d, *J* = 4.3 Hz, $2CH_2O$), 26.7 (d, *J* = 2.8 Hz, $CHCH_2$), 26.5 (d, *J* = 21.5 Hz, CH_2CF) ppm.

HRMS: (EI+); *m/z* calc. for $C_{21}H_{20}F_4O_2$ $[M]^+$: 380.1399, found 380.1390.

IR Film; $\tilde{\nu}$ (cm^{-1}) = 3059 (w), 2952 (w), 2882 (w), 1653 (w), 1592 (w), 1510 (w), 1476 (w), 1450 (w), 1396 (w), 1350 (w), 1307 (w), 1257 (w), 1178 (s), 1119 (w), 1083 (w), 1026 (w), 968 (m), 893 (w), 818 (w), 792 (w), 773 (m), 719 (w), 694 (w), 586 (w), 548 (w), 523 (w), 491 (w), 468 (w), 424 (w).

Mp.: 97.6−100.3 °C.

(*E*)-(3,4,4,4-Tetrafluoro-3-methylbut-1-en-1-yl)benzene (189a)



183a **189a**

Phosphate **183a** [356.25]	1.00 eq	140 µmol	50.0 mg
CuCN·2LiCl [1 M in THF]	1.10 eq	154 µmol	154 µL
GRIGNARD reagent [1.83 M in Et_2O]	1.10 eq	154 µmol	84.0 µL
THF			1.2 mL

was obtained following general procedure V using the corresponding fluorophosphate **183a** (50.0 mg, 140 µmol). Purification by column chromatography using *n*-pentane afforded **189a** (28.5 mg, 131 µmol, γ: α > 25:1, 93%) as a colorless oil.

TLC: R_f = 0.6 (*n*-pentane).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.46 – 7.41 (m, 2H, CH_{arom}), 7.39 – 7.34 (m, 2H, CH_{arom}), 7.34 – 7.30 (m, 1H, CH_{arom}), 6.88 (dd, *J* = 16.2, 1.6 Hz, 1H, C*H*), 6.32 – 6.13 (m, 1H, C*H*CF), 1.77 – 1.66 (m, 3H, CH_3) ppm.

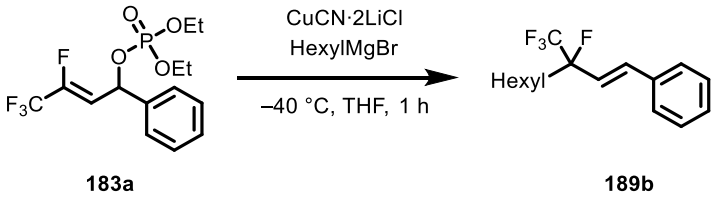
^{19}F-NMR (282 MHz, $CDCl_3$) δ = −82.0 (d, *J* = 7.5 Hz, *C*F_3), −163.2 (q, *J* = 7.4 Hz, *C*F).

^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 135.3 (C_{quart}), 134.2 (d, *J* = 10.7 Hz, *C*H), 129.0 (C_{arom}), 128.9 (C_{arom}), 127.1 (C_{arom}), 123.2 (qd, *J* = 282.6, 29.3 Hz, CF*C*F_3), 122.3 (d, *J* = 20.4 Hz, *C*HCF), 92.8 (dq, *J* = 183.1, 31.9 Hz, *C*FCF_3), 19.9 (d, *J* = 23.0 Hz, *C*H_3) ppm.

HRMS: (EI+); *m/z* calc. for $C_{11}H_{10}F_4$ $[M]^+$: 218.0719, found 218.0697.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 3031 (w), 3006 (w), 2927 (w), 1658 (w), 1581 (w), 1497 (w), 1452 (w), 1384 (w), 1315 (w), 1271 (w), 1234 (w), 1166 (s), 1098 (m), 1028 (w), 969 (m), 897 (w), 849 (w), 805 (w), 774 (w), 746 (s), 690 (m), 601 (w), 569 (w), 487 (w).

(*E*)-(3-Fluoro-3-(trifluoromethyl)non-1-en-1-yl)benzene (189b)



183a **189b**

Phosphate **183a** [356.25]	1.00 eq	140 µmol	50.0 mg
CuCN·2LiCl [1 M in THF]	1.10 eq	154 µmol	154 µL
GRIGNARD reagent [1.23 M in Et_2O]	1.10 eq	154 µmol	125 µL
THF			1.2 mL

was obtained following general procedure V using the corresponding fluorophosphate **183a** (50.0 mg, 154 µmol). Purification by column chromatography using *n*-pentane afforded **189b** (33.2 mg, 115 µmol, *γ*: *α* > 25:1, 83%) as a colorless oil.

TLC: R_f = 0.5 (*n*-pentane).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.47 – 7.41 (m, 5H, CH_{arom}), 6.86 (d, J = 16.2 Hz, 1H, C*H*), 6.07 (dd, J = 20.0, 16.1 Hz, 1H, C*H*CF), 2.16 – 1.74 (m, 2H, CFCH_2), 1.52 – 1.19 (m, 8H, 4CH_2), 0.96 – 0.73 (m, 3H, CH_3) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −80.9 (d, J = 7.1 Hz, CF_3), −176.2 (q, J = 6.6 Hz, C*F*) ppm.

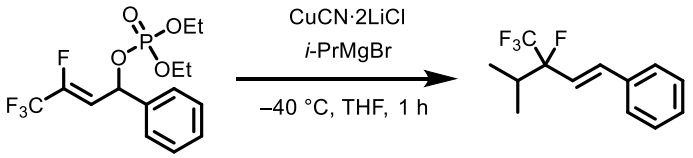
^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 135.4 (C_{quart}), 134.1 (d, J = 11.2 Hz, *C*H), 128.9 (C_{arom}), 128.8 (C_{arom}), 127.0 (C_{arom}), 123.5 (qd, J = 284.7, 29.6 Hz, CF*C*F_3), 120.9 (d, J = 19.1 Hz, C*H*CF), 95.1 (dq, J = 188.5, 30.7 Hz, *C*FCF_3), 32.6 (d, J = 21.5 Hz, *C*H_2CF), 31.7 (*C*H_2), 29.3 (*C*H_2), 22.7 (*C*H_2), 22.1 (d, J = 3.0 Hz, *C*H_2), 14.2 (*C*H_3) ppm.

HRMS: (EI+); *m/z* calc. for $C_{16}H_{20}F_4$ $[M]^+$: 288.1501, found 288.1506.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 3030 (w), 2958 (w), 2932 (w), 2859 (w), 1658 (w), 1581 (w), 1498 (w), 1452 (w), 1379 (w), 1298 (w), 1268 (w), 1176 (s), 1160 (w), 1120

(w), 1069 (w), 1046 (w), 967 (m), 914 (w), 894 (w), 851 (w), 791 (w), 746 (s), 690 (s), 647 (w), 587 (w), 570 (w), 524 (w), 499 (w), 430 (w).

(*E*)-(3-Fluoro-4-methyl-3-(trifluoromethyl)pent-1-en-1-yl)benzene (189c)



183a **189c**

Phosphate **183a** [356.25]	1.00 eq	69.0 µmol	24.7 mg
CuCN·2LiCl [1 M in THF]	1.10 eq	76.0 µmol	76.0 µL
GRIGNARD reagent [1.18 M in Et_2O]	1.10 eq	76.0 µmol	65.0 µL
THF			0.6 mL

was obtained following general procedure V using the corresponding fluorophosphate **183a** (24.7 mg, 69.0 µmol). Purification by column chromatography using *n*-pentane afforded **189c** (10.0 mg, 41.0 µmol, γ: α > 25:1, 59%) as a colorless oil.

TLC: R_f = 0.5 (*n*-pentane).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.47 – 7.40 (m, 2H, CH_{arom}), 7.38 – 7.34 (m, 2H, CH_{arom}), 7.33 – 7.28 (m, 1H, CH_{arom}), 6.88 (d, J = 16.1 Hz, 1H, C*H*), 6.12 (dd, J = 21.5, 15.4 Hz, 1H, C*H*CF), 2.43 – 2.31 (m, 1H, C*H*CH_3), 1.11 – 0.93 (m, 6H, CH_3).

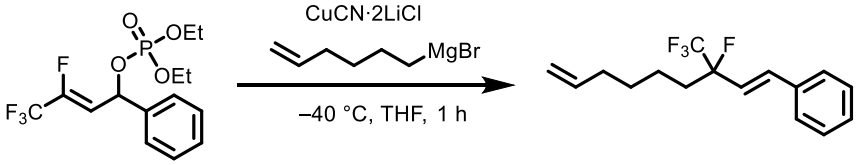
^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −76.8 (d, J = 6.3 Hz, CF_3), −175.8 (q, J = 6.6 Hz, C*F*).

^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 135.5 (C_{quart}), 134.3 (d, J = 11.4 Hz, C*H*), 128.7 (C_{arom}), 128.6 (C_{arom}), 126.9 (C_{arom}), 118.7 (d, J = 16.8 Hz C*H*CF), 32.1 (d, J = 21.9 Hz, C*H*CH_3), 17.1 (CH_3) ppm.

HRMS: (EI+); *m/z* calc. for $C_{13}H_{14}F_4$ $[M]^+$: 246.1032, found 246.1032.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 3030 (w), 2973 (w), 2926 (w), 2856 (w), 1656 (w), 1581 (w), 1497 (w), 1470 (w), 1451 (w), 1395 (w), 1375 (w), 1292 (w), 1265 (w), 1219 (w), 1181 (w), 1160 (s), 1117 (w), 1086 (w), 1070 (w), 1018 (w), 972 (m), 884 (), 851 (), 802 (w), 767 (w), 745 (m), 708 (w), 690 (m), 594 (w), 571 (w), 528 (w), 500 (w), 483 (w), 408 (w).

(*E*)-(3-Fluoro-3-(trifluoromethyl)nona-1,8-dien-1-yl)benzene (189d)



183a **189d**

Phosphate **183a** [356.25]	1.00 eq	140 µmol	50.0 mg
CuCN·2LiCl [1 M in THF]	1.10 eq	154 µmol	154 µL
GRIGNARD reagent [0.26 M in Et_2O]	1.10 eq	154 µmol	60.0 µL
THF			0.3 mL

was obtained following general procedure V using the corresponding fluorophosphate **183a** (50.0 mg, 140 µmol). Purification by column chromatography using *n*-pentane afforded **189d** (14.0 mg, 48.8 µmol, γ: α > 25:1, 35%) as a colorless oil.

TLC: R_f = 0.5 (*n*-pentane).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.49 – 7.42 (m, 2H, CH_{arom}), 7.42 – 7.36 (m, 2H, CH_{arom}), 7.37 – 7.31 (m, 1H, CH_{arom}), 6.89 (d, J = 16.2 Hz, 1H, CHCH_{arom}), 6.09 (dd, J = 20.7, 16.4 Hz, 1H, CHCF), 5.81 (ddt, J = 16.9, 10.2, 6.7 Hz, 1H, CHCH_2), 5.08 – 4.90 (m, 2H, CH_2), 2.15 – 1.78 (m, 4H, 2CH_2), 1.63 – 1.39 (m, 4H, 2CH_2) ppm.

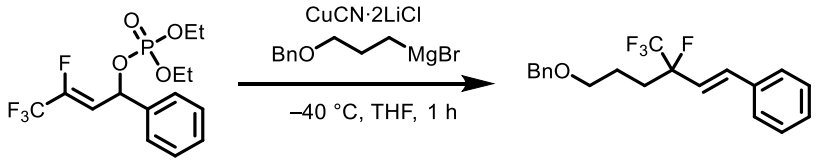
^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −80.9 (d, J = 7.0 Hz, CF_3), −176.2 (q, J = 6.6 Hz, CF) ppm.

^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 138.3 (*C*HCH$_2$), 135.3 (C_{quart}), 134.1 (d, *J* = 11.0 Hz, *C*HC$_{arom}$), 128.8 (*C*$_{arom}$), 128.7 (*C*$_{arom}$), 126.9 (*C*$_{arom}$), 123.4 (qd, *J* = 284.5, 29.7 Hz, CF*C*F$_3$), 120.7 (d, *J* = 19.4 Hz, *C*HCF), 114.8 (CH*C*H$_2$), 95.0 (qd, *J* = 187.6, 34.0 Hz, *C*FCF$_3$), 33.4 (*C*H$_2$), 32.3 (d, *J* = 21.5 Hz, *C*H$_2$), 28.8 (*C*H$_2$), 21.5 (d, *J* = 3.2 Hz, *C*H$_2$) ppm.

HRMS: (EI+); *m/z* calc. for $C_{16}H_{18}F_4$ $[M]^+$: 286.1345, found 286.1346.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 3065 (w), 3030 (w), 2933 (w), 2859 (w), 1657 (w), 1642 (w), 1581 (w), 1497 (w), 1450 (w), 1296 (w), 1268 (w), 1173 (s), 1117 (w), 1072 (w), 967 (m), 912 (m), 851 (w), 790 (w), 747 (s), 690 (s), 628 (w), 570 (w), 521 (w), 498 (w).

(*E*)-(6-(Benzyloxy)-3-fluoro-3-(trifluoromethyl)hex-1-en-1-yl)benzene (189e)



183a 189e

Phosphate **183a** [356.25]	1.00 eq	140 µmol	50.0 mg
CuCN·2LiCl [1 M in THF]	1.10 eq	154 µmol	154 µL
GRIGNARD reagent [0.58 M in Et_2O]	1.10 eq	154 µmol	266 µL
THF			0.3 mL

was obtained following general procedure V using the corresponding fluorophosphate **183a** (50.0 mg, 140 µmol). Purification by column chromatography using *n*-pentane afforded **189e** (20.0 mg, 57.0 µmol, *γ*: *α* > 25:1, 41%) as a colorless oil.

TLC: R_f = 0.2 (*n*-pentane/Et_2O 50:1).

^{1}H-NMR: (300 MHz, $CDCl_3$) δ = 7.47 – 7.27 (m, 10H, C*H*$_{arom}$), 6.86 (d, *J* = 16.2 Hz, 1H, C*H*C$_{arom}$), 6.06 (dd, *J* = 19.8, 16.5 Hz, 1H, C*H*CF), 4.50 (s, 2H, OC*H*$_2$C$_{arom}$), 3.99 – 3.00 (m, 2H, OC*H*$_2$), 2.32 – 1.64 (m, 4H, 2C*H*$_2$) ppm.

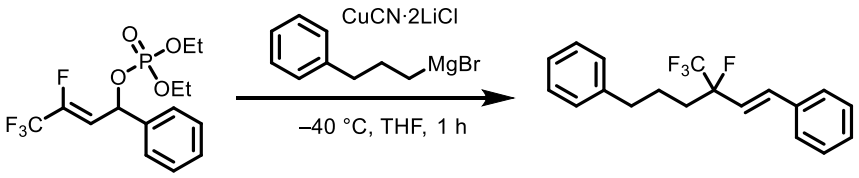
^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −80.9 (d, J = 7.1 Hz, CF_3), −176.5 (q, J = 7.6 Hz, CF) ppm.

^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 138.3 (C_{quart}), 135.1 (C_{quart}), 134.3 (d, J = 11.0 Hz, CHC$_{arom}$), 128.8 (C_{arom}),128.4 (C_{arom}),127.7 (C_{arom}), 126.9 (C_{arom}), 123.3 (qd, J = 284.6, 29.6 Hz, CF_3CF), 120.4 (d, J = 19.2 Hz, CHCF), 94.9 (dq, J = 189.0, 30.9 Hz, CFCF$_3$), 73.0 (OCH$_2$C$_{arom}$), 69.5 (OCH$_2$), 29.4 (d, J = 21.4 Hz, CH$_2$), 22.7 (d, J = 3.0 Hz, CH$_2$) ppm.

HRMS: (EI+); *m/z* calc. for $C_{20}H_{20}F_4O$ $[M]^+$: 352.1450, found 352.1440.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 3063 (w), 3031 (w), 2938 (w), 2860 (w), 2107 (w), 1954 (w), 1807 (w), 1657 (w), 1581 (w), 1496 (w), 1451 (w), 1361 (w), 1294 (w), 1265 (w), 1178 (s), 1153 (w), 1098 (m), 1029 (w), 968 (m), 902 (w), 850 (w), 793 (), 744 (), 692 (m), 611 (w), 570 (w), 495 (w), 459 (w), 408 (w).

(*E*)-(3-Fluoro-3-(trifluoromethyl)hex-1-ene-1,6-diyl)dibenzene (189f)



183a **189f**

Phosphate **183a** [356.25]	1.00 eq	281 µmol	100 mg
CuCN·2LiCl [1 M in THF]	1.10 eq	309 µmol	309 µL
GRIGNARD reagent [1.02 M in Et_2O]	1.10 eq	309 µmol	304 µL
THF			0.6 mL

was obtained following general procedure V using the corresponding fluorophosphate **183a** (100 mg, 281 µmol). Purification by column chromatography using *n*-pentane afforded **189f** (80.0 mg, 248 µmol, γ: α > 25:1, 88%) as a colorless oil.

TLC: R_f = 0.3 (*n*-pentane).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.43 – 7.25 (m, 8H, CH_{arom}), 7.23 – 7.13 (m, 3H, CH_{arom}), 6.82 (d, J = 16.2 Hz, 1H, CH), 6.03 (dd, J = 20.0, 13.6 Hz, 1H, CHCF), 2.74 – 2.58 (m, 2H, CH_2), 2.15 – 1.71 (m, 4H, 2CH_2) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −80.9 (d, J = 7.1 Hz, CF_3), −172.6 – -181.3 (m, CF) ppm.

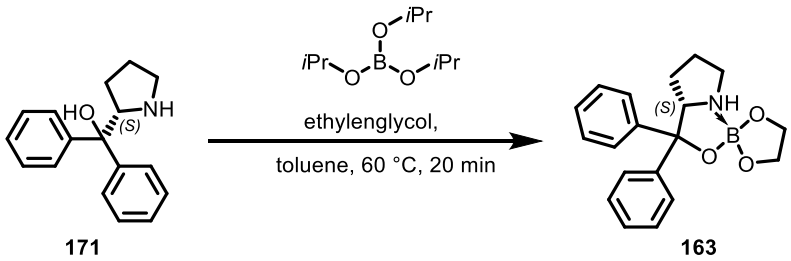
^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 141.3 (C_{quart}), 135.1 (C_{quart}), 134.2 (d, J = 11.1 Hz, CH), 128.8 (C_{arom}), 128.5 (C_{arom}), 128.4 (C_{arom}), 126.9 (C_{arom}), 126.1 (C_{arom}), 123.3 (qd, J = 284.51, 29.67 Hz, CFCF$_3$) 120.5 (d, J = 19.2 Hz, CHCF), 94.9 (dq, J = 189.0, 30.9 Hz, CFCF$_3$), 35.6 (CH$_2$), 31.9 (d, J = 21.4 Hz, CH$_2$), 23.9 (d, J = 3.0 Hz, CH$_2$) ppm.

HRMS: (EI+); *m/z* calc. for $C_{19}H_{18}F_4$ $[M]^+$: 322.1345, found 322.1369.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 3239 (w), 3063 (w), 3028 (w), 2960 (w), 2931 (w), 2858 (w), 1948 (w), 1657 (w), 1603 (w), 1496 (w), 1452 (w), 1296 (w), 1264 (w), 1170 (s), 1114 (m), 1074 (w), 1027 (w), 968 (m), 910 (w), 802 (m), 746 (s), 692 (s), 567 (w), 521 (w), 488 (m).

Asymmetric installation of FTF groups

(*S*)-3,3-Diphenyltetrahydro-3H-1l4-spiro[pyrrolo[1,2-c][1,3,2]oxazaborole-1,2'-[1,3,2]dioxaborolane] (163)



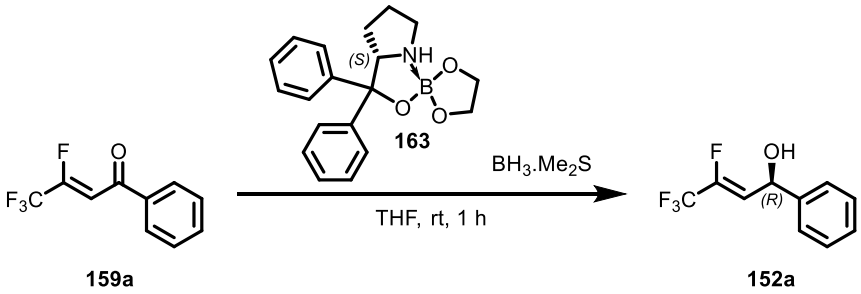
(*S*)-*α*,*α*-diphenyl(pyrrolidin-2-yl)methanol (**171**) [253.35]	1.00 eq	7.89 mmol	2.00 g
Ethylenglycol [62.07, ρ = 1.11]	1.00 eq	7.89 mmol	0.44 mL
Triisopropylborate [188.07, ρ = 0.82]	1.00 eq	7.89 mmol	1.80 mL
Toluene			30 mL

Triisopropyl borate (1.80 mL, 7.89 mmol, 1.00 eq) and dry ethylene glycol (0.44 mL, 0.49 mmol, 1.00 eq) were dissolved in toluene (20 mL). The reaction was heated to 80 °C and stirred for 20 min. The reaction mixture was cooled to 60 °C. A solution of (*S*)-*α*,*α*-diphenyl(pyrrolidin-2-yl)methanol (**171**, 2.00 g, 7.89 mmol, 1.00 eq) in toluene (10 mL) was added dropwise to the reaction mixture. After a white solid was precipitated, the suspension was stirred further for 20 min. The reaction mixture was allowed to reach room temperature. The reaction mixture was filtrated and washed with cold Et_2O (3 × 20 mL). After drying under vacuum the product **163** was obtained as a white solid (1.90 g, 5.90 mmol, 75%).

^{1}H-NMR: (300 MHz, $CDCl_3$) δ = 7.70 (d, J = 7.7 Hz, 2H, CH_{arom}), 7.55 (d, J = 7.6 Hz, 2H, CH_{arom}), 7.43 – 6.90 (m, 6H, CH_{arom}), 4.44 (m, CH), 4.22 (s, 1H, CH_2), 3.89 (s, 4H, 2CH_2), 3.40 (m, 1H, CH_2), 3.19 – 2.94 (m, 1H, CH_2), 2.12 (s, 1H, CH_2), 1.95 – 1.53 (m, 3H, CH_2) ppm.

The analytical data corresponds to the literature. [93]

(*R*,*Z*)-3,4,4,4-tetrafluoro-1-phenylbut-2-en-1-ol (152a)



Fluoroenone **159a** [218.15]	1.00 eq	1.38 mmol	300 mg
$BH_3 \cdot Me_2S$ [2 M in THF]	1.00 eq	1.38 mmol	0.69 mL
Borate ester **163** [322.19]	0.10 eq	138 µmol	44.3 mg
THF			10 mL

Borate ester **163** (44.3 mg, 138 µmol, 0.10 eq) was dissolved in 10 mL THF. $BH_3 \cdot Me_2S$ (0.69 mL, 2.0 M, 1.38 mmol, 1.00 eq) was added and stirred for 15 min. A solution of *β*-fluoroenone (**159a**, 300 mg, 1.38 mmol, 1.00 eq) in 3 mL THF was added over a time period of 1 hour. The reaction was quenched with MeOH (12 mL) and saturated NH_4Cl solution (10 mL) was added. The aqueous phase was extracted three times with CH_2Cl_2 (20 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography using 10:1 (*n*-pentane/Et_2O) on silica gel afforded the product **152a** as a colorless oil (257 mg, 1.17 mmol, 85%, 99% *ee*).

TLC: R_f = 0.30 (*n*-pentane/Et_2O 4:1).

^{1}H-NMR: (300 MHz, $CDCl_3$) δ = 7.35 – 7.18 (m, 5H, CH_{arom}), 5.84 – 5.67 (m, 1H, C*H*OH), 5.63 (d, *J* = 8.6 Hz, 1H, C*H*CF), 2.06 (s, 1H, O*H*) ppm.

^{19}F-NMR (282 MHz, $CDCl_3$) δ = −72.8 (d, *J* = 11.2 Hz, CF_3), −133.6 (q, *J* = 11.1 Hz, C*F*) ppm.

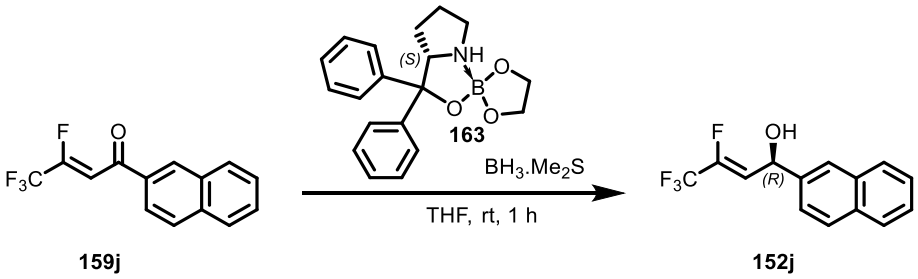
^{13}C-NMR (76 MHz, $CDCl_3$) δ = 145.8 (dq, *J* = 261.5, 39.7 Hz, *C*FCF_3), 141.0 (d, *J* = 1.7 Hz, $C_{quart.}$), 129.1 (C_{arom}), 128.7 (C_{arom}), 125.9 (C_{arom}), 118.3 (dq, *J* = 271.8, 41.5 Hz, CF*C*F_3), 115.4 (dq, *J* = 6.3, 3.1 Hz, *C*HCF), 67.0 (d, *J* = 4.0 Hz, *C*HOH) ppm.

HRMS: (EI+); *m/z* calc. for $C_{12}H_8F_4O_1$ $[M]^+$: 220.0511, found 220.0522.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 3352 (w), 1715 (w), 1454 (w), 1354 (m), 1237 (w), 1198 (m), 1146 (s), 1103 (w), 1075 (w), 1047 (w), 1003 (w), 1075 (w), 875 (w), 853 (w), 761 (w), 701 (m).

[α] D25: 6.2 (*c* 0.4, $CHCl_3$).

(*R*,*Z*)-3,4,4,4-Tetrafluoro-1-(naphthalen-2-yl)but-2-en-1-ol (152j)



Fluoroenone **159j** [268.21]	1.00 eq	1.01 mmol	300 mg
$BH_3 \cdot Me_2S$ [2 M in THF]	1.00 eq	1.01 mmol	0.51 mL
Borate ester **163** [322.19]	0.10 eq	101 µmol	32.6 mg
THF			10 mL

Borate ester **163** (32.6 mg, 0.101 mmol, 0.10 eq) was dissolved in 10 mL THF. $BH_3 \cdot Me_2S$ (0.51 mL, 2.0 M, 1.01 mmol, 1.00 eq) was added and stirred for 15 min. A solution of *β*-fluoroenone **159j** (300 mg, 1.01 mmol, 1.00 eq) in 3 mL THF was added over a time period of 1 h. The reaction was quenched with MeOH (12 mL) and saturated NH_4Cl solution (10 mL) was added. The aqueous phase was extracted three times with CH_2Cl_2 (20 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography using 5:1 (*n*-pentane/Et_2O) on silica gel afforded the product **152j** as a colorless oil (213 mg, 0.79 mmol, 78%, 97% *ee*).

TLC: R_f = 0.30 (*n*-pentane/Et_2O 10:1).

^{1}H-NMR: (500 MHz, $CDCl_3$), δ = 7.89-7.85 (m, 4H, CH_{arom}), 7.55-7.51 (m, 2H, CH_{arom}), 7.48 (dd, J = 8.4 Hz, 1.6 Hz, 1H, CH_{arom}), 5.98-5.88 (m, 2H, C*H*OH), 2.42 (m, 1H, O*H*) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$), δ = − 72.7 (d, J = 11.2 Hz, C*F3*), − 133.2 (q, J = 11.1 Hz, 1F, C*F*) ppm.

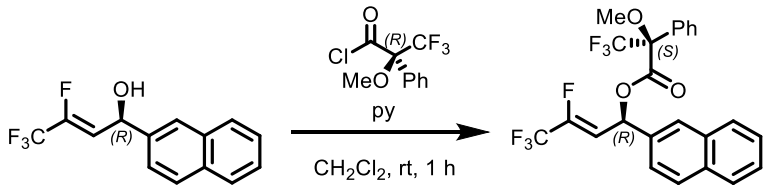
^{13}C-NMR: (125 MHz, $CDCl_3$), δ = 145.8 (dq, J = 261.7, 39.7 Hz, *C*FCF_3), 138.2 (C_{quart}), 133.4 (C_{quart}), 133.3 (C_{quart}), 129.1 (C_{arom}), 128.2 (C_{arom}), 127.9(C_{arom}), 126.7 (C_{arom}), 126.6 (C_{arom}), 124.9 (C_{arom}), 123.6 (C_{arom}), 118.3 (qd, J = 271.9, 41.5 Hz, CF*C*F_3), 115.4-115.2 (m, *C*HCF), 67.1 (d, J = 3.8 Hz, *C*HOH) ppm.

HRMS: (EI+); *m/z* calc. for $C_{14}H_{10}F_4O$ $[M]^+$: 270.0668, found 270.0675.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 3263 (w), 1355 (m), 1274 (w), 1238 (w), 1201 (w), 1162 (s), 1124 (w), 1100 (m), 1041 (m), 1001 (m), 966 (w), 952 (w), 900 (w), 882 (w), 858 (m), 846 (w), 822 (m), 775 (w), 748 (s), 689 (m), 661 (w), 622 (w), 599 (w), 573 (w), 548 (w), 528 (w), 482 (s), 430 (w), 409 (w).

$[\alpha]_D^{25}$: −96.5 (*c* 1.0, $CHCl_3$).

(*R*,*Z*)-3,4,4,4-tetrafluoro-1-(naphthalen-2-yl)but-2-en-1-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (176) (*S*)



152j **176**

Alcohol **152j** [270.23]	1.00 eq	74.0 µmol	20.0 mg
(*R*)-MOSHER acid chloride **174** [122.17, ρ = 1.35]	1.90 eq	141 µmol	13.0 µL
Pyridine [322.19, ρ = 0.98]	3.10 eq	230 µmol	18.0 µL
CH_2Cl_2			1.0 mL

According to the protocol from SHAO *et al*[92], (*R*)-MOSHER acid chloride (**174**, 13.0 µL, 141 µmol, 1.90 eq) was added to a solution of allylic alcohol **152j** (20.0 mg, 74.0 µmol, 1.00 eq) and anhydrous pyridine (18.0 µL, 230 µmol, 3.10 eq) in anhydrous dichloromethane (1.0 mL). Ethyl acetate (1.00 mL) and water (1.00 mL) were added after 1 h and the aqueous phase was extracted with ethyl acetate (3 × 2.00 mL). The combined organic phases were dried over anhydrous Na2SO4 and the solvent was removed in vacuo, before the crude product was purified by column chromatography 20:1 (*n*-pentane/EtOAc). MOSHER ester **176 (*S*)** (31.0 mg, 0.064 mmol, 86%) was obtained as colorless oil.

TLC: R_f = 0.50 (*n*-pentane/Et_2O 20:1).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.88 – 7.81 (m, 2H, CH_{arom}), 7.80 – 7.73 (m, 1H, CH_{arom}), 7.72 – 7.67 (m, 1H, CH_{arom}), 7.57 – 7.49 (m, 2H, CH_{arom}), 7.40 (d, *J* = 8.7 Hz, 3H, CH_{arom}), 7.31 (d, *J* = 17.8 Hz, 3H, CH_{arom}), 7.02 (d, *J* = 9.0 Hz, 1H,C*H*), 6.00 (dd, *J* = 31.0, 9.1 Hz, 1H, C*H*CF), 3.58 (d, *J* = 1.3 Hz, 3H, CH_3) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −71.6 (CF_3), −72.8 (d, *J* = 10.7 Hz, CFCF_3), −127.9 (q, *J* = 10.7 Hz, C*F*CF_3) ppm.

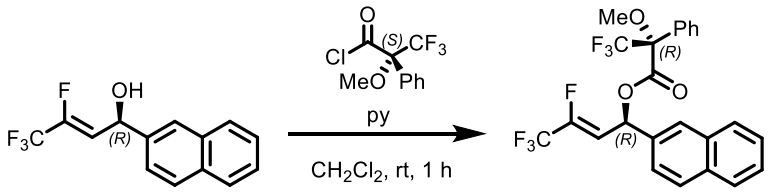
^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 165.2 (*C*O), 147.2 (dq, *J* = 267.4, 39.9 Hz, *C*FCF_3), 133.5 (C_{quart}), 133.3 (C_{quart}), 133.0 (C_{quart}), 131.8 (C_{quart}), 129.7 (C_{arom}), 129.1

(C_{arom}), 128.4 (C_{arom})f, 128.2 (C_{arom}), 127.8 (C_{arom}), 127.2 (C_{arom}), 127.0 (C_{arom}), 126.8 (C_{arom}), 126.2 (C_{arom}), 123.5 (C_{arom}), 123.2 (q, J = 288.96 Hz, C*C*F3), 117.9 (qd, J = 272.4, 40.7 Hz, *C*FCF$_3$), 110.7 (dd, J = 6.4, 3.4 Hz, *C*HCF), 84.7 (q, J = 28.1 Hz, *C*CF$_3$), 70.0 (d, J = 3.8 Hz, *C*H), 55.7 (*C*H$_3$) ppm.

HRMS: (ESI+); *m/z* calc. for $C_{24}H_{17}F_7O_3Na$ $[M+Na]^+$: 509.0958, found 509.0956.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 3064 (w), 2952 (w), 2851 (w), 1754 (m), 1718 (w), 1603 (w), 1498 (w), 1452 (w), 1364 (w), 1338 (w), 1271 (w), 1238 (w), 1154 (s), 1118 (w), 1081 (w), 1045 (w), 1014 (m), 995 (w), 964 (w), 919 (w), 896 (w), 858 (w), 842 (w), 816 (m), 748 (w), 722 (m), 696 (w), 659 (w), 541 (w), 478 (m).

(*R*,*Z*)-3,4,4,4-Tetrafluoro-1-(naphthalen-2-yl)but-2-en-1-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate 175 (*R*)



152j 175

Alcohol **152j** [270.23]	1.00 eq	74.0 µmol	20.0 mg
(*S*)-MOSHER acid chloride **174** [122.17, ρ = 1.35]	1.90 eq	141 µmol	13.0 µL
Pyridine [322.19, ρ = 0.98]	3.10 eq	230 µmol	18.0 µL
CH_2Cl_2			1.0 mL

According to the protocol from SHAO *et al*[92], (*S*)-MOSHER acid chloride (**174**, 13.0 µL, 0.14 mmol, 1.90 eq) was added to a solution of allylic alcohol (**152j**, 20.0 mg, 0.074 mmol, 1.00 eq) and anhydrous pyridine (18.0 µL, 0.23 mmol, 3.10 eq) in anhydrous dichloromethane (1.00 mL). Ethyl acetate (1.00 mL) and water (1.00 mL) were added after 1 h and the aqueous phase was extracted with ethyl acetate (3 × 2.00 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed in vacuo, before the crude product was purified by column chromatography 20:1 (*n*-pentane/EtOAc). MOSHER ester **175 (*R*)** (33.4 mg, 0.069 mmol, 93%) was obtained as colorless oil.

TLC: R_f = 0.50 (*n*-pentane/Et_2O 20:1).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.89 (d, *J* = 8.6 Hz, 1H, C*H*$_{arom}$), 7.87 – 7.84 (m, 3H, C*H*$_{arom}$), 7.60 – 7.50 (m, 2H, C*H*$_{arom}$), 7.47 – 7.41 (m, 3H, C*H*$_{arom}$), 7.43 – 7.37 (m, 1H, C*H*$_{arom}$), 7.38 – 7.32 (m, 2H, C*H*$_{arom}$), 7.04 (d, *J* = 8.8 Hz, 1H, C*H*), 5.90 (dd, *J* = 31.0, 8.9 Hz, 1H, C*H*CF), 3.48 (s, 3H, C*H*$_3$) ppm.

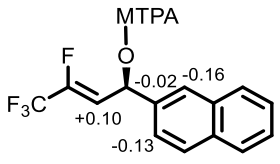
^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −71.4 (C*F*$_3$), −72.8 (d, *J* = 10.8 Hz, CFC*F*$_3$), −127.8 (q, *J* = 10.7 Hz, C*F*CF_3) ppm.

^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 165.4 (*C*O), 147.2 (dq, *J* = 267.5, 40.0 Hz, *C*FCF_3), 133.5 (*C*$_{quart}$), 133.1 (*C*$_{quart}$), 133.1 (*C*$_{quart}$), 131.8 (*C*$_{quart}$), 129.8 (*C*$_{arom}$), 129.3 (*C*$_{arom}$), 128.5 (*C*$_{arom}$), 128.3 (*C*$_{arom}$), 127.8 (*C*$_{arom}$), 127.3 (*C*$_{arom}$), 127.1(*C*$_{arom}$), 126.9 (*C*$_{arom}$), 126.5 (*C*$_{arom}$), 123.7 (*C*$_{arom}$), 123.2 (q, J = 288.57 Hz, C*C*F_3), 117.8 (qd, *J* = 272.4, 40.7 Hz, CF*C*F_3), 110.5 (m, *C*HCF), 84.6 (q, *C*CF_3), 70.1 (d, *J* = 3.5 Hz, *C*H), 55.6 (*C*H_3) ppm.

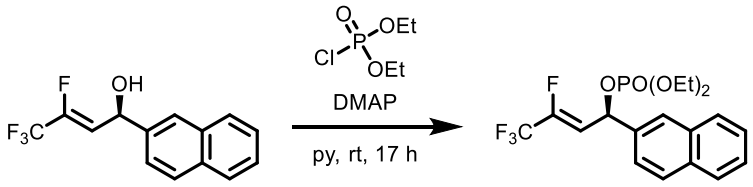
HRMS: (ESI+); *m/z* calc. for $C_{24}H_{17}F_7O_3Na$ $[M+Na]^+$: 509.0958, found 509.0942.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 3064 (w), 2952 (w), 2850 (w), 1753 (m), 1718 (w), 1603 (w), 1509 (w), 1497 (w), 1452 (w), 1363 (w), 1340 (w), 1270 (w), 1233 (w), 1153 (s), 1118 (w), 1082 (w), 1039 (w), 1013 (m), 993 (w), 965 (w), 919 (w), 895 (w), 858 (w), 842 (w), 816 (m), 764 (w), 749 (w), 721 (m), 697 (w), 659 (w), 603 (w), 553 (w), 478 (m), 440 (w).

Through the comparison of the proton and fluorine signals of esters **176 (*S*)** and **175 (*R*)** [$\Delta\delta^{SR}$ (=δ^S–δ^R)] the absolute configuration of the stereocenter was determined as ***R***.



(*R*,*Z*)-Diethyl (3,4,4,4-tetrafluoro-1-(naphthalen-2-yl)but-2-en-1-yl) phosphate (*R*)-183j



152j 183j

Alcohol **(*R*)-152j** [270.23]	1.00 eq	2.67 mmol	722 mg
DMAP [122.17]	0.10 eq	267 µmol	32.6 mg
Diethyl phosphorochloridate [172.45, ρ = 1.19]	2.00 eq	534 µmol	0.78 mL
Pyridine			2.7 mL

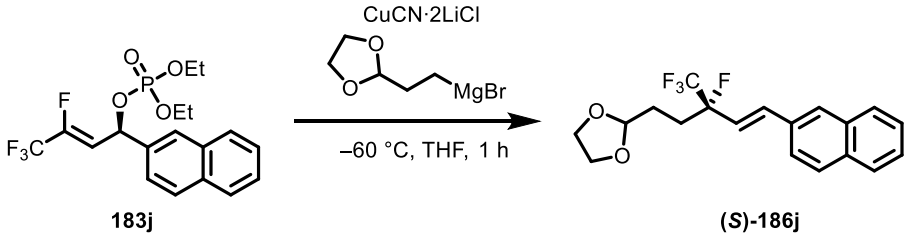
was obtained following general procedure IV using the corresponding fluoroenone **(*R*)-152j** (722 mg, 2.67 mmol). Purification by column chromatography using 1:1 (*n*-pentane/Et_2O) afforded phosphate **(*R*)-183j** (738 mg, 1.82 mmol, 68%, 97% *ee*) as a colorless oil.

The NMR-data was identical to the analytical data of the **(*rac*)-183j**.

s.r.: $[\alpha]_D^{25}$: -27.3 (*c* 1.0, $CHCl_3$).

HPLC: (*n*-hexane: isopropanol 95:5): enantiomers A & B: t_R(A) = 10.63 min, t_R(B) = 18.56 min.

(*S*,*E*)-2-(3-Fluoro-5-(naphthalen-2-yl)-3-(trifluoromethyl)pent-4-en-1-yl)-1,3-dioxolane (*S*)-186j



183j (*S*)-186j

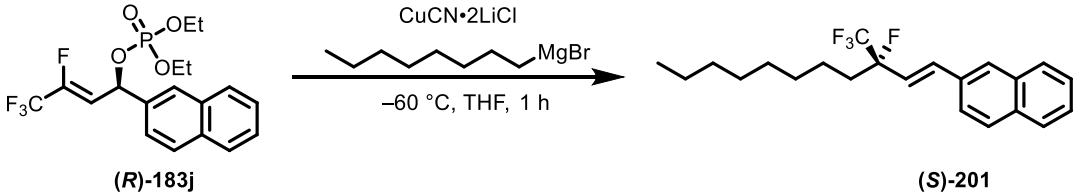
Phosphate **183j** [406.31]	1.00 eq	123 µmol	50.0 mg
CuCN·2LiCl [1 M in THF]	2.20 eq	271 µmol	271 µL
GRIGNARD reagent **188a** [0.65 M in THF]	2.20 eq	271 µmol	417 µL
THF			0.5 mL

was obtained following general procedure IV at –60 °C using the corresponding fluorophosphate **(*R*)-183j** (50.0 mg, 0.123 mmol). Purification by column chromatography using 10:1 (*n*-pentane/Et_2O) afforded **(*S*)-186j** (35.0 mg, 99.0 µmol, 80%, 85% *ee*) as a white solid. The NMR-data was identical to the analytical data of the **(*rac*)-186j**.

s.r.: $[\alpha]_D^{25}$: -8.0 (*c* 0.4, $CHCl_3$).

HPLC: (*n*-hexane: isopropanol 95:5): enantiomers A & B: t_R(A) = 14.60 min, t_R(B) = 21.26 min.

(*S*,*E*)-3-fluoro-1-(naphthalen-2-yl)-3-(trifluoromethyl)undec-1-en-4-one (*S*)-201



(*R*)-183j (*S*)-201

Phosphate **183j** [406.31]	1.00 eq	85.0 µmol	345 mg
CuCN·2LiCl [1 M in THF]	3.00 eq	255 µmol	255 µL
GRIGNARD reagent [0.65 M in THF]	3.00 eq	255 µmol	128 µL
THF			5 mL

was obtained following general procedure IV at –60 °C using the corresponding fluorophosphate **(*R*)-183j** (345 mg, 85.0 µmol). Purification by column chromatography using *n*-pentane afforded **(*S*)-201** (264 mg, 71.9 µmol, 85%) as a white solid. The compound could not be separated on chiral HPLC, resulting in the inability to measure its enantiomeric excess.

TLC: R_f = 0.50 (*n*-pentane).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 7.85 (m, 4H, CH_{arom}), 7.61 (dd, J = 8.5, 1.8 Hz, 1H, CH_{arom}), 7.55 – 7.35 (m, 2H, CH_{arom}), 7.03 (d, J = 16.2 Hz, 1H, C*H*), 6.20 (dd, J = 20.2, 16.0 Hz, 1H, C*H*CF), 2.28 – 1.80 (m, 2H, CH_2), 1.62 – 1.17 (m, 12H, 6CH_2), 0.90 – 0.85 (m, 3H, CH_3) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −80.8 (d, J = 7.1 Hz, CF_3), −176.0 (q, J = 6.9 Hz, C*F*).

^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 134.1 (d, J = 11.2 Hz, *C*H), 133.5 (d, J = 2.4 Hz, C_{quart}), 132.7 (C_{quart}), 128.5 (C_{arom}), 128.2 (C_{arom}), 127.7 (C_{arom}), 127.6 (C_{arom}), 126.5 (d, J = 9.5 Hz, C_{arom}), 123.5 (qd, J = 284.7, 29.6 Hz, CF*C*F_3), 123.4 (C_{arom}), 121.1 (d, J = 19.2 Hz, *C*HCF), 95.0 (dq, J = 188.6, 30.8 Hz, *C*FCF_3), 32.6 (d, J = 21.5 Hz), 31.8 (*C*H_2), 29.6 (*C*H_2), 29.2 (d, J = 19.9 Hz, *C*H_2), 22.6 (*C*H_2), 22.1 (d, J = 3.3 Hz, *C*H_2), 14.1 (*C*H_3) ppm.

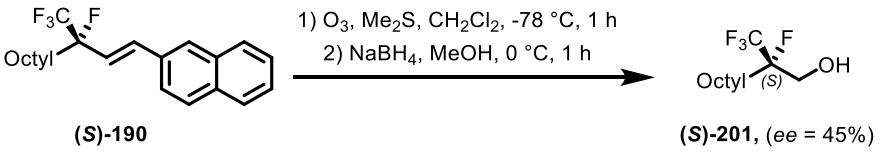
HRMS: (EI+); *m/z* calc. for $C_{22}H_{26}F_4$ $[M]^+$: 366.1971, found 366.1978.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 2956 (w), 2926 (m), 2855 (w), 1657 (w), 1497 (w), 1465 (w), 1452 (w), 1377 (w), 1296 (w), 1267 (w), 1175 (s), 1120 (w), 1070 (w), 969 (m), 851 (w), 805 (w), 747 (m), 691 (m), 570 (w), 524 (w), 497 (w).

s.r.: $[\alpha]_D^{25}$: −27.2 (*c* 1.0, $CHCl_3$).

Determination of the stereocenter

Synthesis of (*S*)-2-fluoro-2-(trifluoromethyl)undecan-1-ol (*S*)-201 via (*S*)-190



(*S*)-190 **(*S*)-201,** (*ee* = 45%)

Alkene **(*S*)-190** [366.44]	1.00 eq	819 µmol	300 mg
Me_2S [62.14, ρ = 0.85]	30.0 eq	24.6 mmol	1.80 mL
CH_2Cl_2			5 mL
$NaBH_4$ [37.83]	1.20 eq	983 µmol	37.2 mg
MeOH			4 mL

The allylic compound **(*S*)-190** (300 mg, 819 µmol, 1.00 eq) was dissolved in CH_2Cl_2 and cooled to –78 °C. Ozone gas was bubbled into the solution until the color turned blue. Dimethyl sulfide (1.80 mL, 30.0 eq, 24.6 mmol) was added and the mixture was allowed to warm to room temperature for 1 h. Water was added and the aqueous phase was extracted three times with CH_2Cl_2 (10 mL). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was dissolved in anhydrous MeOH (4 mL) and the solution was cooled to 0 °C. $NaBH_4$ (37.2 mg, 983 µmol, 1.20 eq) was added and the mixture was stirred for 1 h at 0 °C. It was quenched with H_2O and diluted with ethyl acetate. The layers were separated and the aqueous one was extracted with Et_2O. The combined organic layers were washed with saturated aqueous NaCl solution, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Purification by column chromatography using (*n*-pentane/Et_2O, 10:1) afforded **(*S*)-201** (90.0 mg, 368 µmol, 45%, 45% *ee*) as a colorless oil.

TLC: R_f = 0.40 (*n*-pentane/Et_2O 10:1).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 4.25 – 3.72 (m, 2H, C*H*$_2$OH), 2.02 – 1.84 (m, 2H, C*H*$_2$CF), 1.75 (t, *J* = 6.9 Hz, 1H, O*H*), 1.55 – 1.40 (m, 2H, C*H*$_2$), 1.37 – 1.23 (m, 10H, 5C*H*$_2$), 0.88 (t, *J* = 6.9 Hz, 3H, C*H*$_3$) ppm.

^{19}F-NMR (282 MHz, $CDCl_3$) δ = −78.5 (d, *J* = 6.7 Hz, C*F*$_3$), −178.6 (q, *J* = 6.7 Hz, C*F*) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 123.8 (qd, *J* = 285.2, 28.6 Hz, CFC*F*$_3$), 94.9 (dq, *J* = 184.5, 28.7 Hz, C*F*CF$_3$), 61.5 (dd, *J* = 25.7, 1.9 Hz, *C*H$_2$OH), 31.8 (*C*H$_2$), 29.9 (*C*H$_2$), 29.6 (d, *J* = 21.0 Hz, *C*H$_2$CF), 29.3 (*C*H$_2$), 29.2 (*C*H$_2$), 22.7 (*C*H$_2$), 22.2 (d, *J* = 5.7 Hz, *C*H$_2$), 14.1 (*C*H$_3$) ppm.

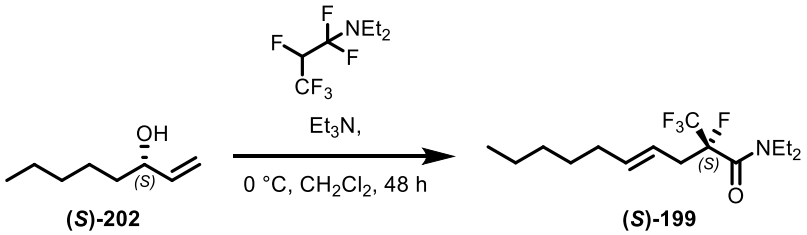
IR: Film; $\tilde{\nu}$ (cm^{-1}) = 3362 (w), 2958 (w), 2925 (m), 2856 (w), 1464 (w), 1378 (w), 1344 (w), 1175 (s), 1063 (w), 976 (w), 940 (w), 908 (w), 736 (w), 682 (w), 621 (w), 530 (w).

HRMS: (APCI-); *m/z* calc. for $C_{11}H_{19}F_4O$ [M-H]: 243.1378, found 243.1370.

s.r.: $[\alpha]_D^{25}$: +2.1 (*c* 5.7, $CHCl_3$).

GC: Method: 120 °C, 30 min hold. Enantiomers A & B: t_R(A) = 9.71 min, t_R(B) = 10.64 min.

(*S*, *E*)-*N*,*N*-Diethyl-2-fluoro-2-(trifluoromethyl)dec-3-enamide (*S*)-199



(*S*)-oct-1-en-3-ol **(*S*)-202** [128.22]	1.00 eq	1.75 mmol	225 mg
ISHIKAWA's reagent **203** [223.16, ρ = 1.23]	1.00 eq	1.75 µmol	318 µL
Triethylamine [101.19, ρ = 0.73]	2.00 eq	3.50 mmol	488 µL
CH_2Cl_2			5 mL

(*S*)-1-octen-3-ol (**(*S*)-202**) (225 mg, 1.75 mmol, 1.00 eq, 98% *ee*) was dissolved in CH_2Cl_2 (5 mL) and cooled to 0 °C, triethylamine (0.49 mL, 3.50 mmol, 2.00 eq) and ISHIKAWA's reagent (0.32 mL, 1.75 mmol, 1.00 eq) was added dropwise into the mixture. After the addition, the reaction mixture was stirred for 2 h at 0 °C and 48 h at room temperature. Saturated $NaHCO_3$ solution was added and the mixture was extracted with CH_2Cl_2. The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure, before the crude product was purified by column chromatography (*n*-pentane/Et_2O, 10:1). Amide **(*S*)-199** (433 mg, 1.39 mmol, 79%) was obtained as colorless oil.

TLC: R_f = 0.55 (*n*-pentane/Et_2O 10:1).

^{1}H-NMR: (500 MHz, $CDCl_3$) δ = 5.80 – 5.58 (m, 1H, C*H*), 5.52 – 5.25 (m, 1H, C*H*), 3.61 – 3.28 (m, 4H, 2NCH_2), 3.25 – 2.83 (m, 1H, CH_2), 2.58 – 3.10 (m, 2H, CH_2CHCHCF), 2.04 – 1.84 (m, 2H, CH_2), 1.39 – 1.20 (m, 6H, 2NCH$_2$CH_3), 1.19 – 1.12 (m, 6H, 3CH_2), 0.87 (t, *J* = 7.0 Hz, 3H, CH_3) ppm.

^{19}F-NMR: (282 MHz, $CDCl_3$) δ = −77.3 (d, *J* = 6.4 Hz), −172.8 (t, *J* = 6.0 Hz) ppm.

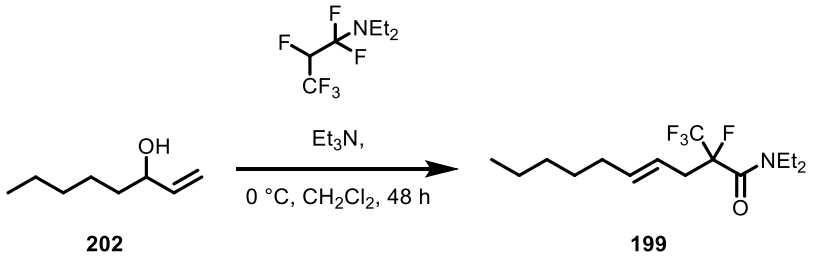
^{13}C-NMR: (126 MHz, $CDCl_3$) δ = 162.9 (d, *J* = 19.4 Hz, *C*O), 138.1 (*C*H), 122.3 (qd, *J* = 285.7, 29.0 Hz, CF*C*F$_3$), 119.4 (d, *J* = 2.3 Hz, *C*H), 96.9 (dq, *J* = 208.3, 28.7 Hz, *C*FCF$_3$), 43.3 (NCH_2), 42.6 (d, *J* = 17.7 Hz, NCH_2), 35.9 (d, *J* = 21.2 Hz, *C*H$_2$CHCHCF), 32.6 (*C*H$_2$), 31.3 (*C*H$_2$), 28.7 (*C*H$_2$), 22.5 (*C*H$_2$), 15.1 (d, *J* = 2.6 Hz, *C*H$_2$), 14.0 (*C*H$_3$), 12.4 (NCH$_2$*C*H$_3$) ppm.

HRMS: (ESI+); *m/z* calc. for $C_{15}H_{25}F_4NONa$ $[M+Na]^+$: 334.1764, found 334.1754.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 2960 (w), 2929 (m), 2857 (w), 1648 (s), 1487 (w), 1435 (m), 1382 (w), 1364 (w), 1275 (m), 1195 (s), 1166 (w), 1118 (w), 1082 (w), 974 (w), 708 (w), 656 (w).

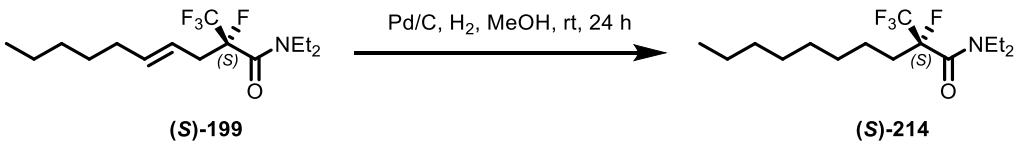
s.r.: $[\alpha]_D^{25}$: −16.8 (*c* 1.0, $CHCl_3$).

(*E*)-*N*,*N*-diethyl-2-fluoro-2-(trifluoromethyl)dec-3-enamide (*rac*)-199



Amide **(*rac*)-199** was synthesized from the racemic 1-octen-3-ol **(*rac*)-202** over the same procedure. The NMR-data was identical to the analytical data of the **(*S*)-199.**

(*S*)-*N*,*N*-diethyl-2-fluoro-2-(trifluoromethyl)decanamide (*S*)-214



Alkene **(*S*)-199** [311.36]	1.00 eq	1.39 mmol	430 mg
Pd/C	0.10 eq	139 µmol	14.8 mg
MeOH			3 mL

Alkene **(*S*)-199** (430 mg, 1.39 mmol, 1.00 eq) was dissolved in methanol (3 mL), palladium-carbon (14.8 mg, 139 µmol, 0.10 eq) was added under nitrogen. After the atmosphere was replaced with hydrogen, the mixture was stirred for 24 hours. The resulting mixture was filtered with celite and the filtrate was concentrated. The product **(*S*)-214** (410 mg, 1.33 mmol, 95%) was isolated as a colorless oil and used without further purification.

^{1}H-NMR (500 MHz, $CDCl_3$) δ = 3.73 – 3.30 (m, 4H, NCH_2), 2.45 – 1.89 (m, 2H, CH_2CF), 1.28 (m, 12H, 6CH_2), 1.25 – 1.15 (m, 6H, 2NCH$_2$CH_3), 0.89 (t, J = 6.8 Hz, 3H, CH_3) ppm.

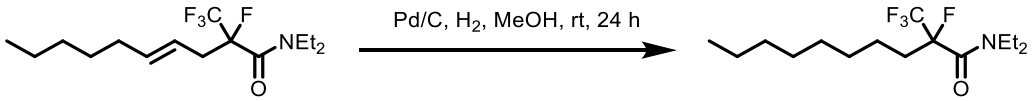
^{19}F-NMR (282 MHz, $CDCl_3$) δ = −77.6 (d, J = 6.7 Hz, CF_3), −173.6 (q, J = 6.5 Hz, CF) ppm.

^{13}C-NMR (126 MHz, $CDCl_3$) δ = 163.1 (d, J = 19.5 Hz, *C*O), 122.5 (qd, J = 285.6, 29.0 Hz, CF*C*F$_3$), 97.7 (dq, J = 206.7, 29.3 Hz, *C*FCF$_3$), 43.4 (N*C*H$_2$), 42.7 (d, J = 7.9 Hz, N*C*H$_2$), 32.5 (d, J = 21.4 Hz, *C*H$_2$CF), 31.8 (*C*H$_2$), 29.3 (*C*H$_2$), 29.2 (*C*H$_2$), 29.1 (*C*H$_2$), 22.6 (*C*H$_2$), 22.3 (d, J = 2.4 Hz,*C*H$_2$), 15.1 (d, J = 2.5 Hz, NCH$_2$C*H*$_3$), 14.1 (*C*H$_3$), 12.4 (NCH$_2$C*H*$_3$) ppm.

HRMS (ESI+); *m/z* calc. for $C_{15}H_{27}F_4NONa$ $[M+Na]^+$: 336.1921, found 336.1912.

IR: Film; $\tilde{\nu}$ (cm^{-1}) = 2929 (m), 2857 (w), 1648 (s), 1486 (w), 1435 (m), 1382 (w), 1364 (w), 1281 (w), 1260 (m), 1196 (s), 1121 (m), 1097 (w), 1020 (w), 912 (w), 802 (m), 734 (w), 706 (w), 654 (w), 619 (w).

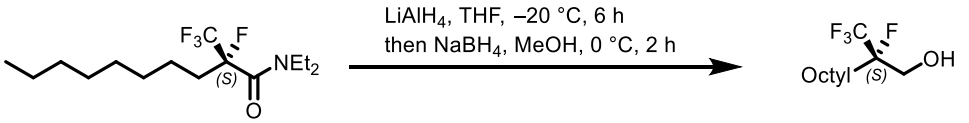
N,*N*-Diethyl-2-fluoro-2-(trifluoromethyl)decanamide (*rac*)-214



199 **214**

Alkane (***rac*)-214** was synthesized from the racemic amide **(*rac*)-199** over the same procedure. The NMR-data was identical to the analytical data of the **(*S*)-214.**

(*S*)-2-fluoro-2-(trifluoromethyl)decan-1-ol (*S*)-201



(*S*)-214 **(*S*)-201,** (*ee* = 91%)

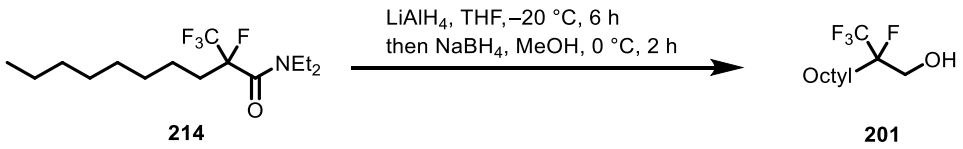
Alkene **(*S*)-214** [313.38]	1.00 eq	1.14 mmol	356 mg
$LiAlH_4$ [37.95]	0.50 eq	571 µmol	21.7 mg
$NaBH_4$ [37.83]	1.00 eq	1.14 mmol	43.2 mg
THF			4 mL
MeOH			1 mL

Into a suspension of $LiAlH_4$ (21.7 mg, 571 µmol, 0.50 eq) in THF (2 mL) was slowly added a solution of amide **(*S*)-214** (356 mg, 1.14 mmol, 1.00 eq) in THF (1 mL) at -20 °C and the reaction mixture was stirred for 6 hours at 0 °C. After cooling again to −20 °C, MeOH (1 mL) and $NaBH_4$ (43.2 mg, 1.14 mmol, 1.00 eq) were added to the reaction mixture. The reaction mixture was stirred for 2 hours at 0 °C and quenched with HCl. The layers were separated and the aqueous one was extracted with Et_2O. The combined organic layers were washed with saturated aqueous NaCl solution, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Purification by column chromatography using (*n*-pentane/Et_2O, 10:1) afforded **(*S*)-201** (0.19 g, 0.79 mmol, 69%, 91% *ee*) as a colorless oil. The NMR-data was identical to the analytical data of the **(*S*)-201** derived from compound **(*S*)-190**.

s.r.: $[\alpha]_D^{25}$: +3.1 (*c* 5.7, $CHCl_3$).

GC: Method: 120 °C, 30 min hold. Enantiomers A & B: t_R(A) = 9.70 min, t_R(B) = 10.55 min.

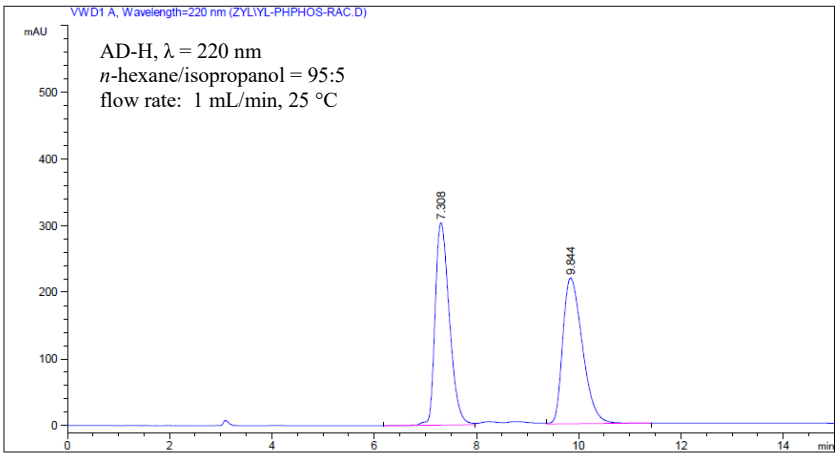
2-Fluoro-2-(trifluoromethyl)decan-1-ol (*rac*)-201

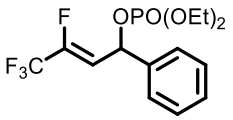


214 **201**

Alcohol (***rac*)-201** was synthesized from the racemic amide **(*rac*)-214** over the same procedure. The NMR-data was identical to the analytical data of the **(*S*)-201.**

HPLC & GC Data





(*rac*)-183a

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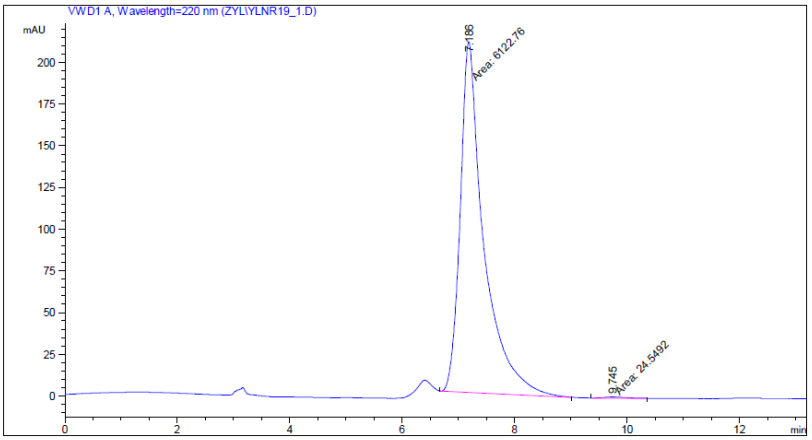
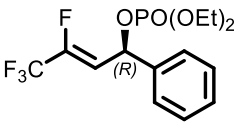
==================================================================
                    Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1   7.308 BV    0.3035 5886.42676  303.45697  50.1255
   2   9.844 VB    0.4203 5856.94531  218.59866  49.8745
```





(*R*)-183a

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==================================================================
                    Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Sample Amount:        :      1.00000  [ng/ul]   (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1   7.186 MM    0.4833 6122.75635  211.14806  99.6007
   2   9.745 MM    0.4883   24.54922 8.37861e-1   0.3993
```

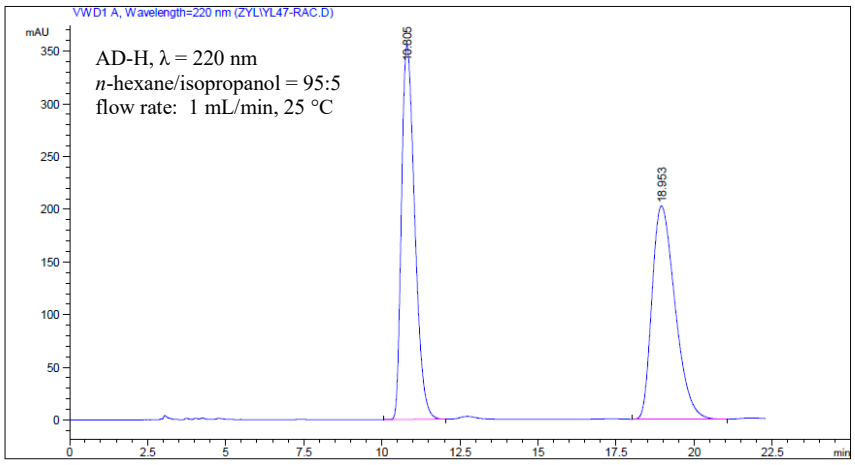

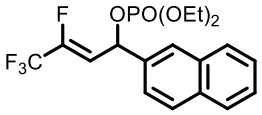

(*rac*)-183j

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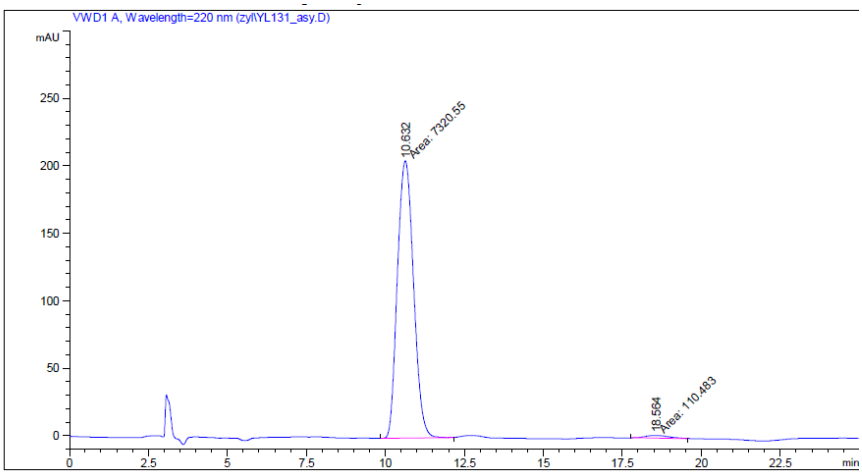
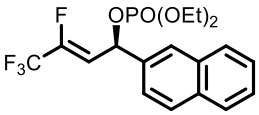
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s    [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  10.805 BB    0.4601 1.04661e4   355.35089  50.1605
   2  18.953 BB    0.8035 1.03991e4   202.31155  49.8395
```





(*R*)-183j

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======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      2.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.632 MM    0.5934 7320.55078  205.60765  98.5132
   2  18.564 MM    0.8504  110.48350    2.16523   1.4868
```

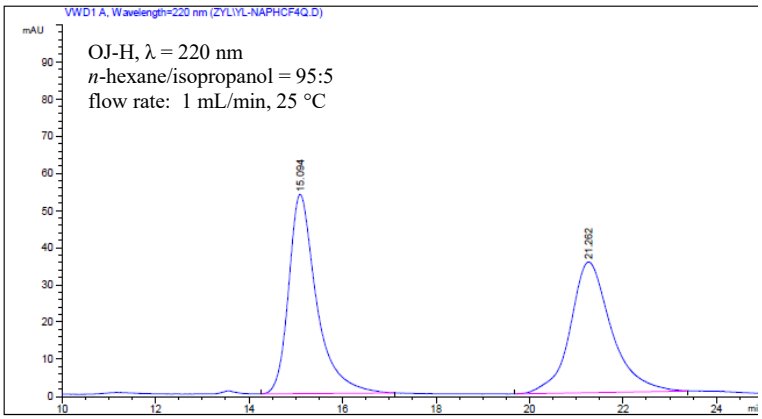

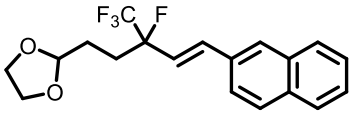

(*rac*)-186j

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================================================================
                    Area Percent Report
================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Sample Amount:        :      1.00000  [ng/ul]   (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
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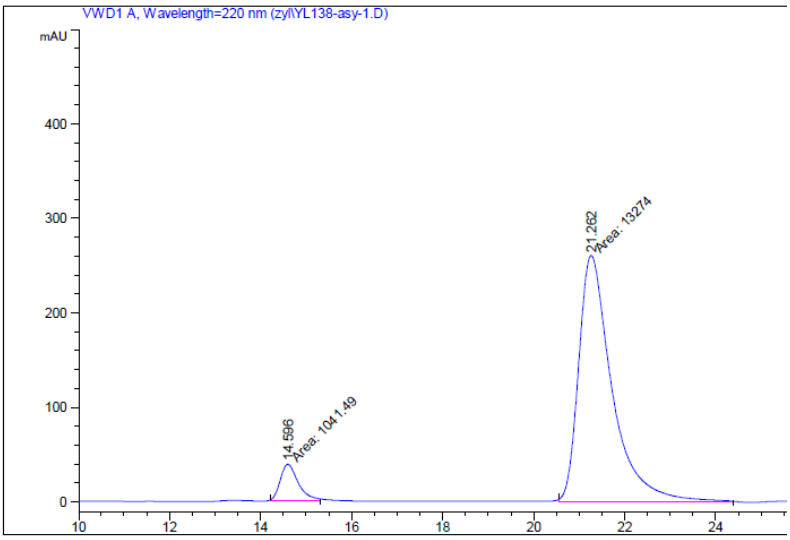
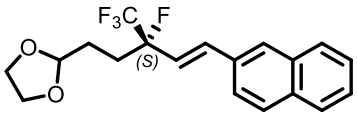
   2  21.262 BB    0.8678 2140.45776   35.14291  49.0573
```





(*S*)-186j

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================================================================
                    Area Percent Report
================================================================

Sorted By             :      Signal
Multiplier            :      2.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=220 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]  [mAU*s]      [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  14.596 MM    0.4540 1041.48828   38.23372   7.2753
   2  21.262 MM    0.8486 1.32740e4   260.71127  92.7247
```

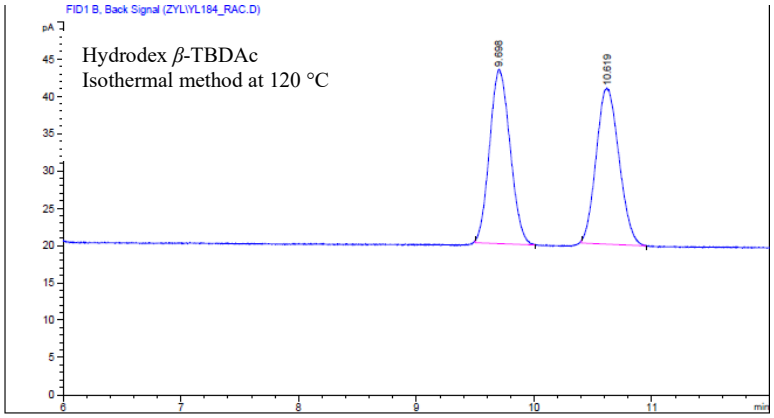

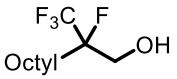

(*rac*)-201

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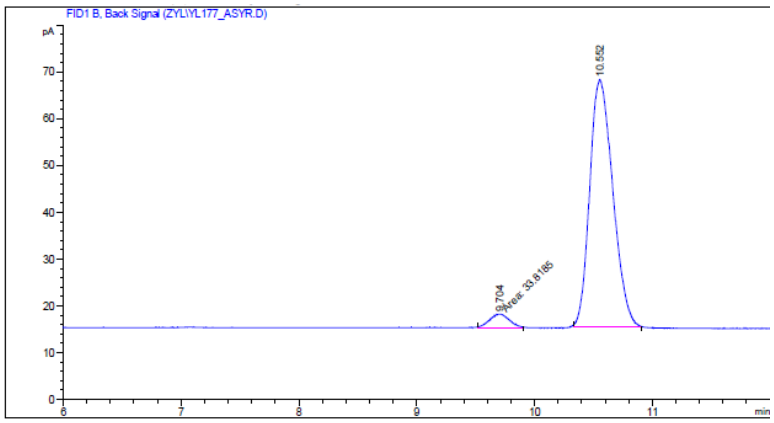
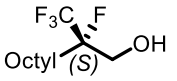
================================================================================
                            Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Sample Amount:                :      1.00000  [ng/ul]   (not used in calc.)
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 B, Back Signal

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]         %
----|-------|----|-------|----------|----------|--------|
   1   9.698 BB    0.1438  282.36349   23.36481 50.07567
   2  10.619 BB    0.1587  281.51013   20.90858 49.92433
```





(*S*)-201, (*ee* = 91%)

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================================================================================
                            Area Percent Report
================================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Sample Amount:                :      1.00000  [ng/ul]   (not used in calc.)
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 B, Back Signal

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]         %
----|-------|----|-------|----------|----------|--------|
   1   9.704 MM    0.1933   33.81853    2.91532  4.49125
   2  10.552 BB    0.1623  719.16833   52.88216 95.50875
```

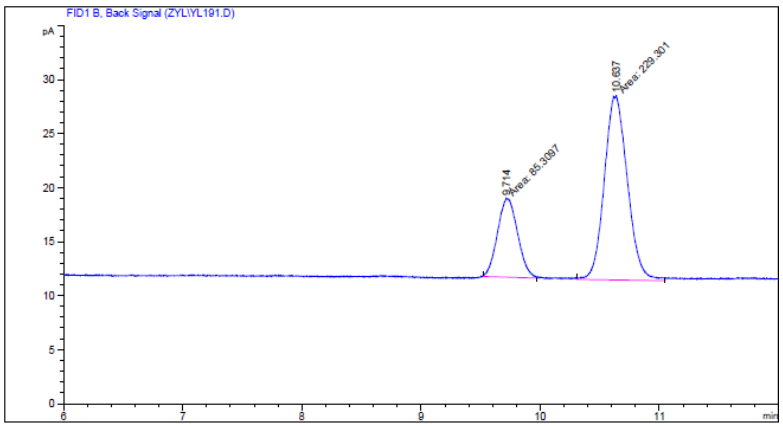

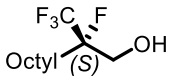

(*S*)-201, (*ee* = 45%)

```
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Sample Amount:        :      1.00000  [ng/ul]   (not used in calc.)
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 B, Back Signal

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1   9.714 MM    0.1947   85.30975    7.30251 27.11596
   2  10.637 MM    0.2237  229.30107   17.08743 72.88404
```

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Ich erkläre, dass eine Promotion noch an keiner anderen Hochschule als der Philipps-Universität Marburg, Fachbereich Chemie, versucht wurde.

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