RADICAL METHODS FOR THE SYNTHESIS OF FLUOROALKANES AND FLUOROMETHYL ARYL ETHERS AND COPPER-CATALYZED THREE-COMPONENT CARBOETHERIFICATION OF ALKENES

by

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École Supérieure de Chimie Physique Electronique de Lyon, 2012

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY in

THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES (Chemistry)

THE UNIVERSITY OF BRITISH COLUMBIA
(Vancouver)

December 2015

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Abstract

Fluorinated molecules have become popular compounds among pharmaceuticals. The introduction of fluorine atoms on bioactive compounds has indeed the potential to improve their biophysical properties. Given the utility of fluorinated substituents on pharmaceuticals, fluorine chemistry has become an area of intensive research. Despite the progress made in selective fluorination, however, radical fluorination has been limited notably due to the paucity of atomic fluorine sources. In this thesis, the uncovering of new atomic fluorine sources and the development of new radical fluorination methods will be described.

Chapter 1 presents the importance of fluorinated molecules and the currently available fluorinating agents. A discussion on radical fluorination is presented that includes the most recent advances in the field.

In Chapter 2, the exploratory work on the ability of electrophilic N—F fluorinating agents to transfer fluorine to alkyl radicals is detailed. Peresters were chosen as radical precursors and reacted with traditionally electrophilic fluorine sources, NFSI and Selectfluor®. Under those conditions, various fluoroalkanes could be synthesized in good yields.

A radical fluorination method subsequently developed using Selectfluor® is described in Chapter 3. The ability of phenoxyacetic acid derivatives to undergo fluorodecarboxylation under UV-light excitation using Selectfluor® was demonstrated. The methodology was successfully applied to the synthesis of mono- and difluoromethyl aryl ethers in 40 to 86% yields.

Chapter 4 details the application of the photofluorodecarboxylation to the synthesis of trifluoromethyl aryl ethers. It was found that the wavelength required for the substrate's excitation led to the decomposition of the desired products. A method using benzophenone as a photosentizer was developed allowing the use of another wavelength to promote the reaction, which proved to be substrate-dependent. The use of a faster fluorine transfer agent, XeF₂, allowed the synthesis of trifluoromethoxy arenes in good yields.

A copper-catalyzed difunctionalization of alkenes, developed in collaboration with Prof. Jieping Zhu, is presented in Chapter 5. This reaction allows the direct introduction of alkyl nitriles via C—H activation. A C—O bond and a C—C bond were created in a single step. A wide range of α-substituted styrenes were difunctionalized in yields up to 82%.
Preface

Part of Chapter 1 is based on a review written in collaboration with Dr. Rémy Hemelaere from the group of Prof. Jean-François Paquin at Université Laval, under the joined supervision of Prof. Paquin and my supervisor, Prof. Glenn Sammis. The initial literature review on the fluorination of alkenes and boronic acids, and the C—H fluorination methods was done by Dr. Hemelaere. The manuscript was written by myself, and edited by Dr. Hemelaere, Prof. Paquin and Prof. Sammis.

Chapter 2 is based on research performed in the group of Prof. Sammis with my colleagues Dr. Montserrat Rueda-Becerril and Dr. Joe C.T. Leung, in collaboration with Dr. Tulin Okbinoğlu and Prof. Pierre Kennepohl at the University of British Columbia and Prof. Paquin at Université Laval. This work was published in 2012: Rueda-Becerril, M.; Chatalova-Sazepin, C.; Leung, J. C. T.; Okbinoğlu, T.; Kennepohl, P.; Paquin, J.-F.; Sammis, G. M. J. Am. Chem. Soc. 2012, 134, 4026. The DFT calculations were performed by Prof. Kennepohl and Dr. Okbinoğlu. The fluorination studies described in Scheme 2.6 and the synthesis of compounds 2.22, 2.23, 2.24, and 2.27 were performed by Dr. Rueda-Becerril, and mentioned as such in the text. The synthesis of compounds 2.25 and 2.26 were performed by Dr. Leung, and mentioned as such in the text. I performed the other syntheses, characterizations and experimental work described in this chapter.

Chapter 3 is based on research performed in the group of Prof. Sammis with my colleagues Dr. Leung, Julian G. West and Dr. Rueda-Becerril, in collaboration with Prof. Paquin at Université Laval. This work was published in 2012: Leung, J. C. T.; Chatalova-Sazepin, C.; West, J. G.; Rueda-Becerril, M.; Paquin, J.-F.; Sammis, G. M. Angew. Chem. Int. Ed. 2012, 51, 10804. The decarboxylation reaction described in Scheme 3.8 and the synthesis of compounds 3.15a, 3.15b, 3.15e and 3.45 were performed by Dr. Leung, and mentioned as such in the text. The synthesis of compounds 3.15c and 3.15d was optimized by Dr. Leung and mentioned as such in the text. Compounds 3.15h, 3.15g and 3.33h were synthesized by Julian G. West, and mentioned as such in the text. I performed the other syntheses, characterizations and experimental work described in this chapter.

Chapter 4 is based on research performed in the group of Prof. Sammis. A patent has been filed for XeF₂ mediated fluorodecarboxylation: Sammis, G. M.; Chatalova-Sazepin, C. “Synthesis of Trifluoromethoxy Arenes” US Provisional Patent Application No. 62/193,269, 2015. A manuscript is currently under preparation based on the results described in Section 4.3.2. Substrate 4.44d was
synthesized by Lorenzo Frassoni, an undergraduate student under my supervision. I performed all other syntheses, characterizations and experimental work described in this chapter.

Chapter 5 is based on research performed as a doctoral exchange student in the group of Prof. Jieping Zhu at the École Polytechnique Fédérale de Lausanne, under the joined supervision of Dr. Qian Wang, Prof. Zhu and Prof. Sammis. The work described in this chapter has been published in 2015: Chatalova Sazepin, C.; Wang, Q.; Sammis, G. M.; Zhu, J. Angew. Chem. Int. Ed. Engl. 2015, 54, 5443. I wrote this manuscript in collaboration with Prof. Sammis and Prof. Zhu. All the syntheses, characterizations and experimental work described in this chapter were performed by me.
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<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>Ar</td>
<td>Aryl</td>
</tr>
<tr>
<td>BDE</td>
<td>Bond dissociation energy</td>
</tr>
<tr>
<td>BHT</td>
<td>Butylated hydroxytoluene, 2,6-di-t-butyl-4-methylphenol</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>BO&lt;sub&gt;XY&lt;/sub&gt;</td>
<td>Bond order between atoms X and Y</td>
</tr>
<tr>
<td>BOC</td>
<td>t-Butyloxy carbonyl</td>
</tr>
<tr>
<td>bpy</td>
<td>2,2'-Bipyridine</td>
</tr>
<tr>
<td>bpz</td>
<td>2,2'-Bipyrazine</td>
</tr>
<tr>
<td>brs</td>
<td>Broad singlet (NMR)</td>
</tr>
<tr>
<td>Bu</td>
<td>Butyl</td>
</tr>
<tr>
<td>Bz</td>
<td>Benzoate</td>
</tr>
<tr>
<td>°C</td>
<td>Degree Celsius</td>
</tr>
<tr>
<td>CAN</td>
<td>Ceric ammonium nitrate</td>
</tr>
<tr>
<td>CBz</td>
<td>Carboxybenzyl</td>
</tr>
<tr>
<td>CDI</td>
<td>1,1'-Carbonyldiimidazole</td>
</tr>
<tr>
<td>CT</td>
<td>Charge transfer</td>
</tr>
<tr>
<td>d</td>
<td>Doublet (NMR)</td>
</tr>
<tr>
<td>δ</td>
<td>Chemical shift</td>
</tr>
<tr>
<td>d&lt;sub&gt;1&lt;/sub&gt;</td>
<td>Relaxation delay</td>
</tr>
<tr>
<td>D&lt;sub&gt;XY&lt;/sub&gt;</td>
<td>X—Y bond strength</td>
</tr>
<tr>
<td>Δ</td>
<td>Heat</td>
</tr>
<tr>
<td>DAST</td>
<td>Diethylamino sulfur trifluoride</td>
</tr>
<tr>
<td>DABCO</td>
<td>1,4-diazabicyclo[2.2.2]octane</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo[5.4.0]undec-7-ene</td>
</tr>
<tr>
<td>DCC</td>
<td>N,N'-Dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>DCE</td>
<td>1,2-Dichloroethane</td>
</tr>
<tr>
<td>dd</td>
<td>Doublet of doublet (NMR)</td>
</tr>
<tr>
<td>ddd</td>
<td>Doublet of doublet of doublet (NMR)</td>
</tr>
<tr>
<td>Δε</td>
<td>Dielectric anisotropy</td>
</tr>
<tr>
<td>DHB</td>
<td>1,3-dibromo-5,5-dimethylhydantoin</td>
</tr>
<tr>
<td>ΔH&lt;sub&gt;25&lt;/sub&gt;</td>
<td>Enthalpy change at 25 °C</td>
</tr>
</tbody>
</table>
DIPEA  \( N,N\)-Diisopropylethylamine

dFCF\textsubscript{3}ppy  2-(2,4-Difluorophenyl)-5-(trifluoromethyl)pyridine

DFT  Density functional theory

DMAP  4-(Dimethylamino)pyridine

DMF  \( N,N\)-Dimethylformamide

DMPU  1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone

DNA  Deoxyribonucleic acid

dq  Doublet of quartet (NMR)

dtbpbpy  4,4'-Bis(t-butyl)-2,2'-bipyrdine

DTBP  Di-t-butylperoxide

\( E_{1/2} \)  Reduction potential

\( E^\circ \)  Standard reduction potential

\( E_s \)  Singlet energy

\( E_T \)  Triplet energy

\( E_{C50} \)  Half maximal effective concentration

EDG  Electron-donating group

EI  Electron impact

EPR  Electron paramagnetic resonance

ESI  Electrospray ionization

Et  Ethyl

E.T.  Electron transfer

EWG  Electron-withdrawing group

FCC  Flash column chromatography

FID  Flame ionization detector

GC  Gas chromatography

h  hour

HIV  Human immunodeficiency virus

HRMS  High resolution mass spectrometry

hv  light

i-  \textit{iso-}

IR  Infrared

k  Rate constant

\( J \)  Coupling constant

KHMDS  Potassium bis(trimethylsilyl)amide

\( \lambda_{\text{max}} \)  Maximum absorbance
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCD</td>
<td>Liquid crystal display</td>
</tr>
<tr>
<td>LDA</td>
<td>Lithium diisopropylamide</td>
</tr>
<tr>
<td>LED</td>
<td>Light-emitting diode</td>
</tr>
<tr>
<td>m</td>
<td>Multiplet (NMR)</td>
</tr>
<tr>
<td>M</td>
<td>Molar (mol/L)</td>
</tr>
<tr>
<td>m-</td>
<td>meta-</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>m-Chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>min</td>
<td>minute</td>
</tr>
<tr>
<td>m.p.</td>
<td>Melting point</td>
</tr>
<tr>
<td>Ms</td>
<td>Mesyl, methane sulfonyle</td>
</tr>
<tr>
<td>MS</td>
<td>Mass spectrometry</td>
</tr>
<tr>
<td>NFPy</td>
<td>N–Fluoropyridinium salt</td>
</tr>
<tr>
<td>NFSI</td>
<td>N–Fluorobenzenesulfonimide</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>o-</td>
<td>ortho-</td>
</tr>
<tr>
<td>ODS</td>
<td>Ozone depleting substance</td>
</tr>
<tr>
<td>p-</td>
<td>para-</td>
</tr>
<tr>
<td>Pc</td>
<td>Phthalocyanine</td>
</tr>
<tr>
<td>PE</td>
<td>Petroleum Ether</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>PIFA</td>
<td>(Bis(trifluorooctoxy)iodo)benzene</td>
</tr>
<tr>
<td>PPHF</td>
<td>Hydrogen fluoride pyridine, Olah's reagent</td>
</tr>
<tr>
<td>ppm</td>
<td>Part per million</td>
</tr>
<tr>
<td>ppy</td>
<td>2-phenylpyridine</td>
</tr>
<tr>
<td>Pr</td>
<td>Propyl</td>
</tr>
<tr>
<td>q</td>
<td>Quartet (NMR)</td>
</tr>
<tr>
<td>qX</td>
<td>Loewdin charge on atom X</td>
</tr>
<tr>
<td>rXY</td>
<td>XY bond distance</td>
</tr>
<tr>
<td>RCY</td>
<td>Radiochemical yield</td>
</tr>
<tr>
<td>r.t.</td>
<td>Room temperature</td>
</tr>
<tr>
<td>s</td>
<td>Singlet (NMR)</td>
</tr>
<tr>
<td>SAM</td>
<td>S-Adenosylmethionine</td>
</tr>
<tr>
<td>SCE</td>
<td>Saturated calomel electrode</td>
</tr>
<tr>
<td><strong>Selectfluor</strong></td>
<td>1-Chloromethyl-4-fluoro-1,4-diazeniabicyclo[2.2.2]octane bis(tetrafluoroborate)</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>σ</strong>*</td>
<td>Antibonding molecular orbital</td>
</tr>
<tr>
<td><strong>σ₁</strong></td>
<td>Inductive substituent constant</td>
</tr>
<tr>
<td><strong>σ₉</strong></td>
<td>Resonance substituent constant</td>
</tr>
<tr>
<td><strong>SET</strong></td>
<td>Single electron transfer</td>
</tr>
<tr>
<td><strong>Sn2</strong></td>
<td>Bimolecular nucleophilic substitution</td>
</tr>
<tr>
<td><strong>t</strong></td>
<td>tert-</td>
</tr>
<tr>
<td><strong>t</strong></td>
<td>Triplet (NMR)</td>
</tr>
<tr>
<td><strong>T₁</strong></td>
<td>Longitudinal relaxation time</td>
</tr>
<tr>
<td><strong>τ₁/₂</strong></td>
<td>Half-time to relaxation equilibrium</td>
</tr>
<tr>
<td><strong>TBAF</strong></td>
<td>Tetrabutylammonium fluoride</td>
</tr>
<tr>
<td><strong>TBAI</strong></td>
<td>Tetrabutylammonium iodide</td>
</tr>
<tr>
<td><strong>TEMPO</strong></td>
<td>(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl</td>
</tr>
<tr>
<td><strong>Tf</strong></td>
<td>Triflate, trifluoromethanesulfonate</td>
</tr>
<tr>
<td><strong>THF</strong></td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td><strong>TLC</strong></td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td><strong>TMS</strong></td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td><strong>TREAT-HF</strong></td>
<td>Triethylamine hydrogen fluoride</td>
</tr>
<tr>
<td><strong>TS</strong></td>
<td>Thymidylate synthase</td>
</tr>
<tr>
<td><strong>TTMSS</strong></td>
<td>Tris(trimethylsilyl)silane</td>
</tr>
<tr>
<td><strong>UV</strong></td>
<td>Ultraviolet</td>
</tr>
<tr>
<td><strong>χₚ</strong></td>
<td>Pauling's electronegativity</td>
</tr>
</tbody>
</table>
Acknowledgments

I would like to express my sincere gratitude to my supervisor, Prof. Glenn Sammis, for seeing in me a potential I didn’t know I had, and supporting me throughout my PhD to reach and exceed it. I deeply appreciate his dedication to education and to providing a stimulating environment for research. Glenn has taught me to stay positive and persevere despite the obstacles and to not settle for less. His seemingly endless enthusiasm and support both professionally and personally will never be forgotten. It has been a privilege to have him as a mentor.

I would also like to thank my committee, Prof. Gregory Dake, Prof. Laurel Schafer and Prof. Chris Orvig. I am particularly grateful to Prof. Dake for the time spent editing this thesis and his useful comments. A special thanks goes to Prof. Schafer for co-supervising me during my first year at UBC. Without her financial support, I would not have been able to pursue this PhD.

During my PhD, I had the chance to work in collaboration with Prof. Jieping Zhu in his laboratory at the EPFL. This has been a precious experience and I am grateful to Jieping for giving this chance. I would like to thank him for his support and excellent training. I have learned a lot from him and it has been an honor to work with such a knowledgeable chemist and admirable individual.

My graduate research would not have been possible without the work of the amazing people in the chemistry department. I would like to give thanks in particular to Dr. Maria Ezhova at the NMR facilities, for her help with instrumentation, notably the $^{19}$F NMR, for her understanding and for our supportive conversations. A special thanks to Marshall Lapawa who is a mass-spectrometry superhero, David Tonkin for his tireless efforts to fix the SFC, and Pat Olsthoorn for making the trip the ChemStores always a pleasure. I would also like to acknowledge the amazing work done by our secretary, Sheri Harbour. Her efficiency, her ability to solve any problem, and her constant sunny dispositions are admirable.

Financial support from the University of British Columbia through the Four Year Fellowship, the Gladys Estella Laird Research Fellowship and travel awards is gratefully acknowledged.

This work would not have been possible without the support of my friends and family, in and outside the lab, in Vancouver and all around the world. I would like to thank the people I
have shared my days, and sometimes nights, with in the Sammis Group: Montse, Maria, Jay, Nat, Joe, Hai, Robby, Julian, Jason, Wei, Meru, Max, Ben and Carolyn. I especially would like to thank Montse for being the spice in my lab life. She has been a mentor, a friend and a partner in crime. I am forever grateful for her constant support despite my mood swings, our deep conversations, her valuable advices, our singing out loud and dancing in the lab. She has been an inspiration for my PhD. I would also like to acknowledge her valuable research contributions, along with those of Dr. Joe Leung, Julian West, and Meruyert Binayeva who collaborated with me on several manuscripts.

A big thanks goes to my adoptive laboratory at the EPFL. I would like to thank in particular Dr. Qian Wang for her help with preparing our manuscript. I have a warm thought for the LSPN boys: JB, Thomas, Antonin, Dylan, Olivier and Cyril. They were always present for support (often in the form of chocolate), for a good laugh, and for valuable scientific discussions.

I would like to thank Leanne, for sharing my anxieties and always having a comforting word to say. She brought a lot of fun into my last few months in the lab; I wish I had met her sooner. Also thanks to the Dake group, in particular Emmanuel and Ben, for bringing their good mood across the hall.

I am particularly grateful to my roommate Soren for being such a great friend. He has been my home in Vancouver, always here to cheer me up after a hard day in the lab and to celebrate good news. A million thanks for all the good times we had together, from watching the Walking Dead or Wonders of the Universe to our bike adventures, and for teaching me the Canadian ways. I would also like to thank the people who made my stay in Vancouver so special, in particular Lucile.

I wish to thank my parents and my brother, for their unconditional love and support throughout my studies, even when I left so far away from home. I am forever grateful for the education my parents gave me and the values they taught me.

Finally, I would like to thank Pierre for his endless support during my PhD. He has always been there to encourage and reassure me. I have learned a lot from him. I would like to thank him for his insightful advices, which he gave me whether I’d like it or not; they were always for the best.
Chapter 1
Introduction

“Fluorine leaves nobody indifferent; it inflames emotions be that affections or aversions. As a substituent, it is rarely boring, always good for a surprise, but often completely unpredictable.”

Prof. M Schlosser

Fluorine, the most electronegative element of the periodic table, was the last halogen to be discovered. It had long been considered to be a laboratory curiosity until the production of fluorine gas in large scale became necessary for the Manhattan Project. The wartime progress in fluorine chemistry led to the quick development of fluorinated polymers (such as Teflon®), and to the emergence of organic fluorine chemistry. After the 1950’s, fluorine chemistry quickly developed, and fluorinated compounds found a widespread application in industry. The importance of fluorinated molecules in pharmaceuticals will be described in this chapter. The available methods for the selective introduction of fluorine will then be presented.

1.1 Importance of fluorinated molecules

1.1.1 A brief history of fluorine

Fluorine is commonly found in the earth’s crust as the mineral fluor spar (CaF₂). Fluorspar, also known as flu ores or fluorite, has been known since the 16th century and was used by miners to help reduce the amount of heat necessary to smelt ores. This property earned the mineral its name, derived from the latin word fluere - to flow.

In 1670, a glasscutter named Heinrich Schwanhard discovered that treating fluorspar with strong acids would etch glass, leading to the development of a new method for decorative glass etching. This experiment was later repeated by Carl Wilhelm Scheele, who concluded that a specific acid was liberated and named it fluoric acid.
In the early 19th century, the composition of the acid was debated among scientists. André-Marie Ampère noted that fluoric acid shared analogous properties with hydrochloric, hydrobromic and hydroiodic acids. Based on his observations, Ampère postulated the existence of a new halogen, and suggested it should be named *le fluor* – fluorine, based on the previously isolated chlorine, bromine and iodine. Many scientists attempted to isolate this new element, but all their efforts were unsuccessful. Many of them suffered severe poisoning and injuries that ultimately earned fluorine its reputation of a being dangerous reagent, or a “savage beast among the elements”. In 1886, Henri Moissan was able to produce fluorine gas by electrolysis of anhydrous fluoric acid in presence of KF. This great achievement earned him the Chemistry Nobel Prize in 1906.

### 1.1.2 Naturally occurring fluorinated compounds

Fluorine is the 13th most abundant element on the earth’s crust. Only a handful of naturally occurring organic molecules incorporates a fluorine atom. Most of those fluorinated compounds are abiogenic, and originate from thermal processes in the heart of volcanoes or during mining operations. Volcanoes produce, among other gases, enormous amounts of hydrofluoric acid (HF, up to hundreds of tons a day), and its reaction with hydrocarbons at high pressure and high temperature leads to the formation of a few fluorinated compounds, including some fluoroalkanes, fluoroalkenes and aromatic fluorides (Figure 1.1).

![Figure 1.1 Naturally occurring abiogenic fluorides](image_url)
Fluorinated molecules arising from biosynthetic processes (Figure 1.2) are, on the other hand, relatively rare in nature.\textsuperscript{9,10} Only 13 different fluorine-containing metabolites have been isolated from tropical and subtropical plants, and 8 of them are \(\omega\)-fluorinated homologues of long-chain fatty acids.\textsuperscript{10c} Fluoroacetate (1.11, Figure 1.2) was the first fluorinated natural product to be isolated. It can be found in a wide variety of plants in minute to large amounts. The presence of fluoroacetate renders those plants toxic, and has been responsible for major feedstock losses.\textsuperscript{10b,c} This toxicity is due to the conversion in vivo of fluoroacetate by enzymes to (2R,3S)-fluorocitrate (1.12, Figure 1.2), a potent aconitase inhibitor. Fluorocitrate can be found in forage plants such as soya bean or alfalfa, and concentration up to 30 \(\mu\)g/g and 60 \(\mu\)g/g have been detected in commercial tea and oatmeal respectively (well below toxicological significance).\textsuperscript{10b,c} A number of other organofluorine compounds have been found in the toxic seeds of an African shrub, \textit{Dichapetalum toxicarium}. Concentration up to 1800 \(\mu\)g/g of fluorinated fatty acids (1.13 to 1.20, Figure 1.2), such as \(\omega\)-fluorooleic and \(\omega\)-fluorocapric acids (1.13 and 1.16, Figure 1.2) have been measured.\textsuperscript{10b,c} Other biogenic fluorinated molecules are synthesized by microorganisms. Nucleocidine (1.21, Figure 1.2) was isolated in 1957 from a bacteria, \textit{Streptomyces calvus}. Its biosynthesis remains unclear. This compound showed potent antibiotic activity but was too toxic for clinical use.\textsuperscript{10b} Another bacteria, \textit{Streptomyces cattleya}, has been reported to produce an unusual amino-acid, 4-fluorothreonine (1.22, Figure 1.2). O'Hagan \textit{et al.} later showed that \textit{Streptomyces cattleya} was also capable of catalyzing the formation of fluoroacetate from fluoride ions and \(S\)-adenosylmethionine (SAM).\textsuperscript{10d} Finally, strong evidence presents fluoroacetaldehyde (1.23, Figure 1.2) as the natural precursor of both fluoroacetate and 4-fluorothreonine but the molecule hasn't been formally isolated from a plant.\textsuperscript{10c}
1.1.3 Impact of fluorine introduction on bioactive compounds

The relative paucity of naturally occurring fluorinated compounds contrasts with the abundance of fluorine-containing molecules in pharmaceuticals, agrochemicals and materials.\textsuperscript{11} Fluorine introduction has the potential to affect the physicochemical characteristics of a molecule and has, therefore, become a popular strategy for the synthesis of compounds with improved properties.\textsuperscript{11}

Fried \textit{et al.} first demonstrated in 1954 the potential importance of fluorinated molecules in pharmaceuticals.\textsuperscript{12} In their pioneering work, the authors synthesized the fluorinated derivatives of hydrocortisone (\textbf{1.24}, Figure 1.3), cortisone (\textbf{1.25}, Figure 1.3) and Thromboxane A2 (\textbf{1.26}, Figure 1.3). The anti-inflammatory activity of the fluorinated compounds was reported to be 4.5 to 10 times higher than that of their non-fluorinated counterparts.
A few years later, Heidelberg et al. reported the synthesis of 5-fluorouracil (1.27, Figure 1.4), a fluorinated pyrimidine, and demonstrated its potency as an anticancer drug. Metabolization of 5-fluorouracil generates in vivo a thymidylate synthase (TS) inhibitor, preventing the formation of the nucleoside thymidine and blocking DNA replication. 5-Fluorouracil has been widely used as an anticancer drug and TS inhibition is still one of the main strategies for suppressing cell division in cancerous tissues.

In the late 1970’s fluorinated compounds became an important part of the commercialized drugs. Currently, 15% of commercial drugs and 20% of drug candidates incorporate one or more fluorine atoms. Fluorination of bioactive molecules has been shown to affect their potency by modifying various physicochemical properties. Due to its electronegativity, fluorine affects the pKₐ of the neighboring functional groups. The modification of its acidity can influence the ability of a drug to bind to active sites. Moreover, the perturbation of the pKₐ can affect the absorption profile of a drug, and impact its bioavailability when orally administered. The introduction of fluorine atoms has also been shown to modify the lipophilicity of a drug, which influences its absorption and distribution. Fluorine can also have an impact on the conformation of a drug, as well as its ability to bind to receptors through non-bonding interactions. Finally, fluorine introduction can be used to increase the metabolic stability of a drug. Metabolization of bioactive compounds occurs notably via radical.
C–H bond oxidation by cytochrome P450 enzymes. Replacing the weak C–H bonds by stronger C–F bonds at those metabolically labile sites can prevent the fast degradation of the drug, allowing smaller doses to be used. Similarly, labile hydrogen atoms can be substituted by fluorine atoms to prevent in vivo racemization.\textsuperscript{16a,b,17} The electron-withdrawing effect of fluorine has also been shown to help reduce the rate of hydrolysis of certain drugs.\textsuperscript{16b} As a consequence, fluorine introduction has become a common strategy in drug design and has led to commercial drugs with improved activity compared to their non-fluorinated counterparts (Figure 1.5).\textsuperscript{16a,b,c} The steric bulk of the trifluoromethyl group of Prozac® (1.28, Figure 1.5), a top-selling antidepressant, is believed to modify the conformation of the phenoxy ring to better fit serotonin transporters.\textsuperscript{16b} In the case of cholesterol-absorption inhibitor Ezetimib (1.29, Figure 1.5), blocking of the metabolically labile position with fluorine allowed the lowering of the effective dose (EC\textsubscript{50}) by more than 50 fold.\textsuperscript{16b} The antibiotic Flurithromycin (1.30, Figure 1.5) is more stable than its non-fluorinated counterpart under acidic conditions.\textsuperscript{16a} Fluorine introduction was shown to improve the action of anti-HIV Efavirenz (1.31, Figure 1.5) by lowering the pKa of the neighboring carbamate involved in key hydrogen bondings.\textsuperscript{16a}

![Chemical structures](image)

**Figure 1.5 Examples of fluorinated commercialized drugs**

### 1.2 Ionic sources of fluorine in organic synthesis

#### 1.2.1 Fluoride (F⁻) as a nucleophile

The first example of nucleophilic substitution using fluoride (F⁻) was reported by Borodine in 1863.\textsuperscript{18} Fluoride is a poor nucleophile in solution: it is strongly solvated in protic solvents (hydration energy of 123 kcal/mol)\textsuperscript{19} and forms tight ion pairs in aprotic ones. Since Borodine’s
first report, many approaches have been devised to enhance the nucleophilicity of fluoride, allowing the development of nucleophilic fluorination.\textsuperscript{19,20}

Typical sources of “naked” (unpaired) fluorine are NaF, KF, CsF and AgF. The solubility and reactivity of alkali metal fluorides (NaF, KF, CsF) can typically be improved by increasing the reaction temperature,\textsuperscript{19} adding chelating agents such as crown ethers,\textsuperscript{21} or performing the reaction in chelating solvents such as glymes and glycols.\textsuperscript{19} Ionic pairing can be reduced using bulky, non-chelating counterions such as tetraalkylammonium ions.\textsuperscript{19,20a} Tetrabutylammonium fluoride, TBAF (1.32, Figure 1.6),\textsuperscript{22} has become a widely used source of nucleophilic fluorine. Hydrofluoric acid can also be used as a source of fluoride, but its corrosive nature had to be tamed by the use of nitrogen bases, such as triethylamine (1.33, TREAT—HF, Figure 1.6) or pyridine (1.34, PPHF, Olah’s reagent, Figure 1.6).\textsuperscript{19,20} The nucleophilicity of F\textsuperscript{−} can also be increased by associating it with soft Lewis acids such as late transition metals (Pd, Sn, Hg), sulfur (SF\textsubscript{4}, DAST, Deoxo-Fluor\textsuperscript{®} and related reagents, 1.35 to 1.38, Figure 1.7), or bromine (BrF\textsubscript{3}).\textsuperscript{20a} Sulfur-based reagents have notably found a widespread application in deoxofluorination and desulfofluorination reactions.\textsuperscript{23}

![Figure 1.6 Sources of "naked" fluoride](image-url)
1.2.2 Sources of electrophilic fluorine, “F⁺”

“F⁺” does not exist as an independent species.\textsuperscript{20a} Nucleophilic attack on fluorine can be rendered possible by attaching it to an electronegative leaving group with a withdrawing inductive effect.\textsuperscript{20} This is the case for F\textsubscript{2} (1.39, Figure 1.8) and reagents subsequently developed after the isolation of fluorine gas by Moissan (Figure 1.8).

\begin{align*}
\text{fluorine} & \quad \text{trifluoromethyl hypofluorite} \quad \text{acetyl hypofluorite} \quad \text{xenon difluoride} \\
F\textsubscript{2} & \quad F\textsubscript{3}CO\textsuperscript{\text{-}}F \quad \text{O=O} \quad \text{XeF}\textsubscript{2} \\
1.39 & \quad 1.40 \quad 1.41 \quad 1.42
\end{align*}

Figure 1.8 Early electrophilic fluorine sources

While early reactions using F\textsubscript{2} are most likely radical in nature and will be discussed in a later section (1.3.1), currently F\textsubscript{2} is mainly used as a source of electrophilic fluorine.\textsuperscript{24} Barton \textit{et al.} were the first to report the use of F\textsubscript{2} for electrophilic fluorination.\textsuperscript{25} Rozen later greatly expanded the scope of electrophilic fluorination using F\textsubscript{2}. The use of highly polar aprotic solvents or acids is key to enhance the ionic reactivity of fluorine.\textsuperscript{24bc} Diluting fluorine with inert gases helped controlling its reactivity and allowed the development of new electrophilic fluorinating agents. Trifluoromethyl hypofluorite (1.40, Figure 1.8) was first synthesized by Cady and Kellogg in 1948,\textsuperscript{26} but was popularized as electrophilic fluorine source by Barton \textit{et al.}\textsuperscript{27} Since this seminal work, trifluoromethyl hypofluorite, related fluoroxy reagents and acyl hypofluorites (such as acetyl hypofluorite, 1.41, Figure 1.8) have extensively been used for electrophilic fluorination.\textsuperscript{28} Despite the numerous methods for electrophilic fluorination
developed using these O—F reagents, their handling requires particular safety precautions as they should be considered as toxic reagents and latent explosives, which limits their application in modern fluorine chemistry. Xenon difluoride (1.42, Figure 1.8) is an easier to handle source of electrophilic fluorine. While it is also known to exhibit a radical behavior, its ionic reactivity can be enhanced through the use of protic solvents, acid catalysts or simply using a glass apparatus. The bonding of fluorine to the Lewis acids (hydrogen donor or borosilicate) increases the polarization of the Xe—F bond and favors the formation of F⁻ and FX⁺ from XeF₂.

The development of easier to handle, more stable N—F based reagents (Figure 1.9) led to great advances in electrophilic fluorination methods. Due to the stronger N—F bond, those reagents are more stable than the previously developed electrophilic fluorinating agents. Banks et al. synthesized the first of those compounds, N-fluoroperfluoropiperidine (1.43, Figure 1.9), and showed that it was capable of electrophilic fluorine transfer. Many N—F based reagents have been developed since, the most commonly used being N-fluoropyridinium salts (1.44, NFPy, Figure 1.9), 1-chloromethyl-4-fluoro-1,4-diaziabicyclo[2.2.2]octane bis(tetrafluoroborate) (F-TEDA-BF₄, or Selectfluor®, 1.45, Figure 1.9) and N-fluorobenzenesulfonimide (1.46, NFSI, Figure 1.9).

![Figure 1.9 Examples of N—F based reagents](image)

### 1.3 Sources of atomic fluorine, F⁻

The majority of fluorination methods relies on the use of electrophilic or nucleophilic species. A third approach to the fluorination of organic compounds that had been less explored utilizes radicals as reactive intermediates (Figure 1.10). This next section will present the available reagents for radical fluorination, and detail key examples of their radical reactivity.
1.3.1 F₂ as a source of atomic fluorine

The radical reactivity of fluorine has been recognized for almost a century. The following section will present the historical work on the action of fluorine on organic compounds by outlining examples where radical processes can be identified.

While only 1% of fluorine is dissociated at room temperature, the weak F—F bond (36 kcal/mol) can allow for homolytic cleavage. Due to the strength of C—F bonds (108 to 127 kcal/mol), the radical fluorination process is highly exothermic (Scheme 1.1) and often leads to incontrollable reactions, non-selective fluorinations and C—C bond disruptions.

![Diagram of radical fluorination process]

**Figure 1.10 Methods for fluorination**

F₂ → 2 F⁺ ΔH₂⁰: 37 kcal/mol
CH₄ + F₂ → CH₃⁺ + HF + F⁻ ΔH₂⁰: 4 kcal/mol
CH₄ + F⁻ → CH₃⁻ + HF ΔH₂⁰: -34 kcal/mol
CH₃⁺ + F₂ → CH₃F + F⁻ ΔH₂⁰: -69 kcal/mol
CH₃⁻ + CH₃ → H₂C—CH₃ ΔH₂⁰: -84 kcal/mol
CH₃⁻ + F⁻ → CH₃F ΔH₂⁰: -107 kcal/mol

**Scheme 1.1 Thermodynamic data for the fluorination of methane**

After his landmark work on the isolation of fluorine, Moissan tried reacting F₂ with organic compounds, but his efforts only resulted in explosions. The necessity of dissipating the heat of reaction was rapidly recognized, and led to a better control of the reaction conditions.
Bockemüller showed that the fluorination of butyric acid (1.48, Scheme 1.2) using F₂ yields a mixture of β- and γ-fluorinated acids (1.49 and 1.50, Scheme 1.2). The α-substituted product, regarded as the product of an ionic process, was not detected, hinting at a radical mechanism. Later work by Kharasch and Brown on the atomic chlorination of butyric acid also led to the formation of the β- and γ-halogenated acids, supporting the presence of radical intermediates in Bockemüller’s reaction.

\[
\begin{align*}
\text{O} & \quad \xrightarrow{F_2} \quad \text{F} \\
\text{OH} & \quad \text{CCl}_4, 0 \, ^\circ \text{C} & \quad \text{F} \\
\text{1.48} & \quad \text{1.49} \quad \text{1.50} \\
\end{align*}
\]

\[30\%\]

Scheme 1.2 Fluorination of butyric acid using F₂

While studying the fluorination of fluoroform (1.51, Scheme 1.3), Ruff reported the formation of not only carbon tetrafluoride but also of hexafluoroethane, showing radical carbon chain building during gas phase fluorination (1.52 and 1.53, Scheme 1.3). Similarly, products from radical recombination were detected by Bigelow et al. while studying the vapor phase fluorination of methane.

\[
\begin{align*}
\text{HCF}_3 & \quad F_2 & \quad \text{CF}_4 \quad \text{F}_2\text{C}\text{-CF}_3 \\
\text{1.51} & \quad \text{1.52} \quad \text{1.53} \\
\end{align*}
\]

Mechanism:

\[
\begin{align*}
\text{HCF}_3 + F_2 & \rightarrow \text{CF}_3 + HF + F' \\
\text{CF}_3 + F_2 & \rightarrow \text{CF}_4 \\
\text{CF}_3 + F' & \rightarrow \text{CF}_4 \\
\text{CF}_3 + \text{CF}_3 & \rightarrow \text{F}_2\text{C}\text{-CF}_3 \\
\end{align*}
\]

Scheme 1.3 Fluorination of fluoroform

When ethane was reacted with pure fluorine in the gas phase, fluoroform and carbon tetrafluoride were detected in addition to hexafluoroethane (1.53, Scheme 1.4). Bigelow et al.
hypothesized that fluoroform (1.51, Scheme 1.4) and carbon tetrafluoride (1.52, Scheme 1.4) emerged from the C—C bond disruption of hexafluoroethane, due to the heat of reaction, but the possibility of C—C bond breaking earlier in the perfluorination process cannot be excluded. Bigelow et al. later found that diluting of F₂ with N₂ would lead to milder reaction conditions and affords only partially fluorinated compounds.45

\[
\begin{align*}
\text{H}_3\text{C—CH}_3 & \xrightarrow{\text{F}_2} \text{HCF}_3 + \text{CF}_4 + \text{F}_3\text{C—CF}_3 \\
\end{align*}
\]

\[
\begin{align*}
\text{F}_3\text{C—CF}_3 & \rightarrow 2 \text{’CF}_3 \\
\text{’CF}_3 + \text{F}_2 & \rightarrow \text{CF}_4 + \text{F’} \\
\text{’CF}_3 + \text{C}_2\text{F}_x\text{H}_{6-x} & \rightarrow \text{HCF}_3 + \text{’C}_2\text{F}_x\text{H}_{5-x} \\
\text{x} & = 0 - 5
\end{align*}
\]

\textbf{Scheme 1.4 Fluorination of ethane using F₂}44

To provide evidence for the radical nature of the C—H fluorination with fluorine, Muller et al. studied the fluorine-initiated oxidation and chlorination of pentachloroethane.46 When reacting pentachloroethane (1.55, Scheme 1.5) with F₂ and excess Cl₂, hexachloroethane (1.56) was obtained as the major product. The postulated radical mechanism accounts for the formation of the major product and the small amounts of pentachlorofluoroethane (1.57) detected, formed during the initiation step (Scheme 1.5). When Cl₂ was replaced with O₂, trichloroacetyl chloride and carbonyl chloride were formed (1.58 and 1.59, Scheme 1.6). The product distribution is similar to the one observed in the radical chlorination of pentachloroethane in presence of O₂.46
Scheme 1.5 Fluorine-sensitized chlorination

Mechanism:

Scheme 1.6 Fluorine sensitized oxidation
Early reports of polymerization when reacting F$_2$ with unsaturated compounds provide further evidence of the radical reactivity of fluorine.$^{39}$ Bockemüller and Bigelow et al. observed the formation of polymerized, unsaturated fluorinated material when benzene and other aromatic compounds were subjected to fluorination conditions.$^{40,47}$ Bockemüller proposed a radical mechanism for the formation of the polymerized products (Scheme 1.7) and hypothesized that the reactive intermediates could be trapped by saturating the solution with bromine. Two brominated unsaturated compounds were isolated (1.65 and 1.66, Scheme 1.7). This experiment represents the first attempt to demonstrate experimentally the presence of radical intermediates in the aromatic fluorination using F$_2$.$^{39,40}$

Scheme 1.7 Postulate radical mechanism of the aromatic compounds fluorination using F$_2$ in presence of Br$_2$.40
Bockemüller and Miller et al. reported that the fluorination of tetrachloroethene (1.67, Scheme 1.8) yielded, in addition to the expected difluorotetrachloroethane (1.68), the dimeric octachlorodifluorobutane (1.69). Dimer formation can be explained by a radical recombination mechanism (Scheme 1.8). Miller et al. later performed mechanistic experiments by submitting the olefin to a fluorine mixture with excess oxygen. The oxygenated compounds obtained (Scheme 1.9) confirmed the presence of radical intermediates. The authors concluded that the first step of the mechanism is the radical addition of atomic fluorine to the alkene (Scheme 1.9). Using chlorine instead of oxygen, Miller et al. showed that fluorine can be used as a radical initiator for chlorination of tetrachloroethylene.

![Chemical structure and mechanism](image.png)

**Scheme 1.8 Fluorination of tetrachloroethylene using F₂**
Additionally, Miller et al. were able to generate atomic fluorine by reacting F$_2$ with alkenes and to demonstrate its high reactivity (Scheme 1.10). The reaction of a mixture of sym-difluorodichloroethylene (1.71) and chloroform (1.72) with F$_2$ at -75 °C led to the formation of a dimerized compound that can only be explained by the presence in solution of trichloromethyl radicals (1.73, Scheme 1.10). At -75 °C, chloroform is unreactive towards F$_2$, while alkenes react with F$_2$ producing atomic fluorine. The presence of trichloromethyl radicals can therefore only be explained by the H-abstraction from atomic fluorine, which illustrates its high reactivity even at low temperature.
The “indiscriminate reactivity” of atomic fluorine described by Miller et al. often leads to perfluorination\textsuperscript{51} and only one example of selective radical formation of C—F bonds using F\textsubscript{2} was described by Grakauskas in 1969. Alkyl fluorides could be accessed by treating various dicarboxylic acid salts with F\textsubscript{2} in water (Scheme 1.11).\textsuperscript{52} When the reaction was applied to monocarboxylic acid derivatives, polyfluorinated products were obtained. Acyl hypofluorites have been proposed as reactive intermediates. The author suggested that the acyl hypofluorites then undergo an ionic Hunsdiecker-type\textsuperscript{53} fluorodecarboxylation. Previous work by Cady et al. on the fluorodecarboxylation of acyl hypofluorites favors, however, a radical mechanism.\textsuperscript{54} Later work by Rozen et al. supports the presence of radical intermediates during the fragmentation (Scheme 1.11).\textsuperscript{55} This fluorodecarboxylation reaction was later employed by Machionni et al. for the synthesis perfluoropolyethers under UV-irradiation.\textsuperscript{56}
While the high reactivity of F$_2$ limits its application to selective radical fluorination, its potential for the synthesis of perfluorinated compounds was quickly recognized.$^{51}$ In the following years, great progress was made to design more practical reactors and more efficient perfluorination methods.$^{57}$ The formation of side products arising from radical side reactions indicates that those reactions are undoubtedly radical processes.$^{58}$ Perfluorinated compounds have found a widespread application, notably in materials.$^{11a}$

1.3.2 Fluoroxy reagents as atomic fluorine sources

The dilution of fluorine with inert gas allowed a better control of the fluorination reactions and led to the development of novel fluorinating agents such as the fluoroxy reagents (RO—F)$^{24}$ While fluoroxy reagents are mainly used as electrophilic fluorine sources (see Section 1.2.2)$^{28}$ the weak O—F bond (43 kcal/mol)$^{59}$ can allow for homolytic cleavage. The most studied hypofluorite is trifluoromethyl hypofluorite, a toxic gas with a boiling point of -95 °C.$^{60}$ In their early work on the reactivity of trifluoromethyl hypofluorite (1.40, Figure 1.8) with alkenes, Cady and Porter reported the formation of polymerized products, indicative of the presence of radical intermediates.$^{61}$ Under milder conditions (dilution with N$_2$), Cady and Allison reacted trifluoromethyl hypofluorite with saturated and unsaturated compounds.$^{62}$ UV-irradiation was necessary for the reaction to proceed. Reaction with methane yielded the C–H fluorination product (Scheme 1.12). Trifluoromethyl hypofluorite added across ethylene and cyclopropane (1.78 and 1.80, Scheme 1.12). Finally, the reaction of benzene and trifluoromethyl hypofluorite yielded two aromatic compounds, fluorobenzene and trifluoromethoxybenzene (1.82 and 1.83, Scheme 1.12).
Kollonitsch et al. further demonstrated the potential of UV-light mediated fluorination using CF$_3$OF.\textsuperscript{63} A slight modification of Cady and Allison’s procedure allowed the formation of fluorobenzene from benzene in 65\% yield. The reaction with toluene yielded a mixture of o-fluorotoluene and benzyl fluoride, while anisole was converted to a mixture of fluoroanisoles. Interestingly, this fluorination method could be used for the remote monofluorination of C(sp$^3$)—H bonds. The UV-irradiation of cyclohexane in presence of trifluoromethyl hypofluorite gave the monofluorinated product in 44\% yield (1.85, Scheme 1.13).\textsuperscript{63} Kollonitsch et al. also reported that the UV-light mediated fluorination could be applied to the monofluorination of nitrogen-containing compounds, including some amino-acid derivatives (1.90, Scheme 1.13).\textsuperscript{63,64}
The observed selectivity can be explained by a radical mechanism (Scheme 1.14).\textsuperscript{63,64} The O—F bond of trifluoromethyl hypofluorite photolyses under 370 nm irradiation, producing atomic fluorine and a trifluoromethoxy radical.\textsuperscript{65} Both fluorine and the trifluoromethoxy radical can perform the hydrogen abstraction, but the latter was invoked to be the radical chain carrier as fluorination involving free atomic fluorine usually lacks selectivity.\textsuperscript{64b} In all substrates, the most electron-rich C—H bond, located further away from the nitrogen, was selectively fluorinated, which is in agreement with the electrophilic character of the trifluoromethoxy radical.\textsuperscript{66}

Experimental evidence for the radical reactivity of trifluoromethyl hypofluorites with alkenes has also been presented. Johri and DesMarteau, and Navarrini et al. proposed a free-radical
mechanism based on the low regio- and stereoselectivity of the CF₃OF addition to alkenes.⁶⁷ Czarnowski et al. studied the gas phase reactivity of alkenes with trifluoromethyl hypofluorite and observed the formation of polymerized compounds.⁶⁸ Additionally, oxidized products were detected when the reaction was performed in presence of oxygen,⁶⁹ which is similar to what Miller observed with F₂ (Scheme 1.9). Finally, the presence of radical intermediates was evidenced by EPR experiments a decade later by Navarrini et al.⁷⁰

Wang and Rowland demonstrated the ability of CF₃OF to behave as a radical scavenger (Scheme 1.15).⁷¹ Ethyl radicals generated by the addition of tritium atoms were efficiently fluorinated in presence of the hypofluorite. Competition experiments using SH₂ as hydride source revealed that the fluorine transfer was only 0.25 slower than hydrogen abstraction.⁷¹

![Scheme 1.15 CF₃OF as radical scavenger](image)

Other higher hypofluorites have been synthesized and exhibit a similar reactivity to trifluoromethyl hypofluorite.⁷² The main use of fluoroxy reagents in synthesis as radical reagents is for the synthesis of fluoromonomers.⁷² The hypofluorites are highly reactive species and should be handle as such. The safety measures associated with their use certainly limits their broader laboratory use.⁷²

### 1.3.3 Xenon difluoride

The synthesis of the first noble gas compound, [Xe’PtF₆⁻], was reported by Bartlett at the University of British Columbia.⁷³ Inspired by this landmark discovery, Claassen et al. investigated the reaction of xenon with fluorine.⁷⁴ The authors reported the formation of XeF₄ along with a lower fluoride of xenon, which probably was xenon difluoride (XeF₂).⁷⁵ Two syntheses of XeF₂ were independently reported shortly after this report.⁷⁵ Xenon difluoride is a
commercially available white solid, easy to handle, which use doesn’t necessitate specialized glassware. Thus, it has been a popular reagent for electrophilic fluorination.\textsuperscript{30,76} XeF\textsubscript{2} can also behave as a radical fluorinating agent. The Xe–F bond has a low dissociation energy (60.4 kcal/mol),\textsuperscript{77} and its photolysis has been used to generate atomic fluorine in solution.\textsuperscript{78} Several factors can affect its reactivity. Ramsden \textit{et al.} found that the polarization of the Xe–F bond by some solvents (CH\textsubscript{2}Cl\textsubscript{2} or CHCl\textsubscript{3}), traces of acid or the walls of the glass vessel favors an ionic pathway, while plastic or alkali-washed flasks and acetonitrile favors radical pathways.\textsuperscript{79} For some fluorination reactions of alkenes, aromatic compounds and enolates, it is unclear whether the mechanism goes through an ionic or an electron transfer (E.T.) mechanism (Scheme 1.16).\textsuperscript{80}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{scheme16.png}
\caption{S\textsubscript{N}2 vs E.T. for fluorination using XeF\textsubscript{2}}
\end{figure}

Some other reactions using XeF\textsubscript{2} exhibit a clear radical behavior. XeF\textsubscript{2} can be used for the fluoro-desilylation of aryl silanes (1.93, Scheme 1.17).\textsuperscript{81} Evidence for the presence of radical intermediates was observed when the reaction was run in CHCl\textsubscript{3} instead of hexafluorobenzene. Chloro, proto and trichloromethyl derivatives (1.96, 1.97 and 1.98, Scheme 1.17) were detected, most likely arising from H- or Cl-abstraction by the solvent from the aryl radical, and recombination with CCl\textsubscript{3} radical. In CFCl\textsubscript{3}, only the chlorinated derivative was detected in addition to the main fluorinated product.\textsuperscript{81}
The use of XeF₂ in the Hunsdiecker-type fluorodecarboxylation reaction was first described by Patrick et al. (Scheme 1.18). The radical nature of the reaction was demonstrated through EPR and radical clock experiments. When hept-6-enoic acid (1.99, Scheme 1.18) was subjected to the decarboxylative fluorination conditions, the cyclized product, (fluoromethyl)cyclopentane, was obtained in 25% yield (1.101, Scheme 1.18). From this experiment, the rate constant of fluorine abstraction was calculated to be 1.1x10⁶ M⁻¹s⁻¹.
The mechanism described in Scheme 1.19 was proposed by Patrick et al. for the fluorodecarboxylation.\textsuperscript{83b} Initial reaction of the carboxylic acid with XeF\textsubscript{2} affords a xenon ester (a), Scheme 1.19. While Patrick et al. haven’t been able to isolate the ester, the formation of xenon esters from carboxylic acids and XeF\textsubscript{2} had previously been reported.\textsuperscript{84} Radical decarboxylation of the xenon ester (b), Scheme 1.19 furnishes an alkyl radical, as indicated by previous work by Eisenberg and DesMarteau,\textsuperscript{84b} as well as experimental evidence mentioned above (Scheme 1.18). The alkyl radical can subsequently be fluorinated by a xenon species (d), Scheme 1.19), or oxidized to a carbocation (c), Scheme 1.19). Attack of a fluoride ion on the carbocation affords the fluorinated product (e), Scheme 1.19). Alternatively, the fluorinated product can be obtained by nucleophilic displacement of CO\textsubscript{2}, Xe and F\textsuperscript{−} on the xenon ester by the fluoride ion (f), Scheme 1.19). For primary and secondary carboxylic acids, the incorporation of \textsuperscript{18}F when the reaction was run in presence of nucleophilic \textsuperscript{18}F indicates that an ionic mechanism (e) or f)) could be at play.\textsuperscript{83c} For tertiary and benzylic substrates no incorporation was observed, supporting a radical pathway.\textsuperscript{83c}
While the price of XeF$_2$ (58 $/g)^{32}$ limits its application in industrial scale syntheses, it remains a valuable laboratory reagent for the fluorinative decarboxylation.$^{86,87}$

### 1.3.4 Modern radical fluorination

The high reactivity of the aforementioned atomic fluorine sources has limited the possibilities of using radical fluorination as a viable alternative for the synthesis of fluorinated molecules. In 2012, Sammis, Paquin, Kennepohl et al. demonstrated that the N–F based reagents Selectfluor® and NFSI (1.45 and 1.46, Figure 1.9) can act as fluorine transfer agents to alkyl radicals.$^{88}$ This paper sparked a renaissance in the field of radical fluorination.$^{89,90}$ In the last three years, many novel methodologies have emerged for the fluorination of radical intermediates, at a rate of about a paper per month. This recent progress in radical fluorination has been reviewed this year by Paquin, Sammis et al.$^{90}$ Those methods rely on five main types of radical generation (Scheme 1.20):

![Scheme 1.19 Mechanism of the fluorodecarboxylation using XeF$_2$]

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Many methods have been developed in the past three years that utilize Selectfluor® and NFSI as fluorine transfer agent to radical generated by decarboxylation of carboxylic acids (Scheme 1.20, a)). Silver, direct light-excitation and photocatalysis have been used to induce the decarboxylation. C—F bonds can also be formed by fluorodeborylation of boronic acid derivatives (Scheme 1.20, b)). Another commonly used method for the formation of C(sp³)—F bonds is the fluorination of alkyl radicals generated by radical addition on alkenes (Scheme 1.20, c)). A wide variety of difunctionalized compounds can be accessed; hydrides and nitrogen, carbon, and phosphorous-centered radicals have been added to the alkenes. Many methodologies have been developed for the selective C(sp³)—H fluorination (Scheme 1.20, d)) either metal-catalyzed, metal-free or photocatalyzed. Finally, the latest approach developed for the radical formation of C(sp³)—F bonds is the C—C bond activation of cyclopropanols and cyclobutanols for the formation of β- and γ-fluorinated ketones (Scheme 1.20, e)).

In addition to Selectfluor® and NFSI, the N—F bond of NFPy salts (Figure 1.9) was shown to be relatively weak, and should be amenable for homolytic breaking. A method has been developed by Shigehisa, Hiroya et al. for the hydrofluorination of alkenes that utilizes a NFPy salt as fluorine transfer agent to alkyl radicals.
The previously described regain of interest for radical fluorination has led to the uncovering of new atomic fluorine transfer agents, the vast majority being metal-fluorides. In the silver-mediated or silver-catalyzed processes, Ag(III)—F has been proposed as fluorine transfer agent to radicals. Radial methods for the formation of C(sp³)—F bond have also been developed using manganese catalysis and strong evidence has been presented for a manganese-fluoride species acting as atomic fluorine source. Finally, two examples of fluorine transfer to radicals from BrF₃ and fluorinated solvents have also been reported.

1.3.5 Personal contribution

The following chapters will describe the work conducted in the Sammis group for the development of new methods for radical fluorination, and detail my contribution to those projects. Chapter 2 will focus on the uncovering of the radical reactivity of N—F based reagents and their use as fluorine transfer agents to alkyl radicals. The application of photoinduced radical fluorination to the synthesis of mono- and difluoromethyl aryl ethers, and trifluoromethylaryl ethers will be presented in Chapters 3 and 4 respectively. An alternative approach to trifluoromethoxylation that utilizes XeF₂ will be discussed in Chapter 4.

The last chapter of this thesis will focus on a different methodology involving radical intermediates, conducted in collaboration with Prof. Jieping Zhu at the École Polytechnique Fédérale de Lausanne (EPFL). The development of a copper-catalyzed intermolecular difunctionalization of alkenes will be presented.
Chapter 2
Fluorine transfer to alkyl radicals

Fluorinated molecules have found a widespread application in pharmaceuticals, agrochemicals and materials.\textsuperscript{11} Traditional methods for the incorporation of fluorine in organic compounds have focused on the use of ionic sources of fluorine ("F\textsuperscript{+}" and "F\textsuperscript{-}"). Radical fluorination is a complementary approach to those ionic methods that had historically been less explored. Only a few atomic fluorine sources were known (\(F_2\), hypofluorites, and XeF\(_2\), see Figure 1.8) and their reactivity, poor selectivity or cost has limited their application.

In this chapter, the studies demonstrating the ability of electrophilic N—F based reagents to act as selective atomic fluorine sources will be described. A method for the fluorination of alkyl radicals using these N—F based reagents will be presented.

2.1 N—F reagents as atomic fluorine sources

Advances in organofluorine chemistry led to the development of easy to handle and selective electrophilic sources of fluorine, in which the fluorine atom is bonded to a nitrogen atom (Figure 1.9). Because of their stability and their selectivity, these N—F based reagents quickly became the most widely used electrophilic fluorinating agents.\textsuperscript{19,20a,32}

2.1.1 Mechanism of fluorination with Selectfluor\textsuperscript{®}: \(S_N2\) vs. SET

The mechanism of fluorination using N—F based reagents (Selectfluor\textsuperscript{®}, NFSI and NFPy) has been debated since they were first developed.\textsuperscript{80f,g,107} Two pathways are possible for the fluorine transfer to a nucleophile (Scheme 2.1).\textsuperscript{80f} The first one is a classical bimolecular nucleophilic displacement (\(S_N2\)), in which the N—F bond is broken and the Nu—F bond is formed in a concerted mechanism. Another possibility involves a single electron transfer (SET) from the nucleophile to the electrophilic fluorinating agent. Subsequent fluorine transfer from the radical anion to the radical furnishes the fluorinated product.
Umemoto et al. observed that Grignard reagents, known to be involved in SET mechanisms, react with N-fluoropyridinium (NFPy) salts to yield fluorinated compounds, while organolithium do not. A SET mechanism was, therefore, proposed for the fluorination using NFPy salts. Umemoto et al. also reported a color change during the fluorination of 2-naphtol (2.1, Scheme 2.2) with N-fluoro-2,4-dichloropyridium (2.2, Scheme 2.2). This observation was later attributed by Kochi et al. to the charge transfer (CT) complex (2.6) arising from SET from the substrate to the fluorinating agent (Scheme 2.2).

Differding et al. were convinced that the fluorination reaction occurred through a S_N2 mechanism, and that the SET mechanism only accounted for non-fluorinated side products. The reaction of radical clock 2.7 (Scheme 2.3) with various N—F reagents did not provide any radical rearrangement products (2.10 and 2.11, Scheme 2.3). Reaction of 2.7 with XeF_2, known react via radical pathways, furnished traces of 2.11 in addition to the direct...
fluorination products.\textsuperscript{111} This was considered as strong evidence for the $S_{N}2$ pathway with N–F reagents. It is possible, however, that radical fluorination occurred faster than radical cyclization.\textsuperscript{107} While the rate constant for the cyclization of 2.7 was estimated to be in the order of $10^5$ s\textsuperscript{-1},\textsuperscript{107} Scaiano \textit{et al.} later reported that fluorine atoms react with organic substrates rapidly, with a rate constant between $10^9$ and $10^{11}$ s\textsuperscript{-1}.\textsuperscript{78}

![Scheme 2.3 Differding \textit{et al.}'s radical clock experiment\textsuperscript{111}]

Wong \textit{et al.} submitted a faster radical clock to fluorination conditions in the presence of various N—F based reagents (Scheme 2.4).\textsuperscript{112} The experiment was inconclusive for $N$-fluoropyridinium salts as no fluorinated products were detected. When NFSI was employed, the rearranged product 2.13 was detected, confirming the presence of radical intermediates. Fluorination using Selectfluor® only furnished the direct fluorination product 2.12 (Scheme 2.4), providing
no evidence for the intermediacy of radicals. The addition of radical inhibitors such as BHT or TEMPO, however, inhibited partially or totally the reaction with Selectfluor®\textsuperscript{112} Furthermore, the rapid reaction of TEMPO with Selectfluor® alone\textsuperscript{112} suggests the ability of the fluorinating agent to take part in SET reactions, preventing the authors from completely ruling out an SET mechanism\textsuperscript{107}.

\[ X^- + \text{Alkyl radical} \rightarrow \text{Fluorinated product} \]

\[ \text{Sn2} \]

\[ [X-F]^- + \text{Fluorinating agent} \rightarrow \text{Fluorinated radical} \]

\[ \text{MeOH} \rightarrow \text{Product} \]

\[ \text{MeOH} \rightarrow \text{Product} \]

\[ \text{MeOH} \rightarrow \text{Product} \]

Scheme 2.4 Radical clock experiment by Wong et al.\textsuperscript{112}

It was hypothesized in our group that those N—F reagents could be used as fluorinating agents for independently generated radicals (Scheme 2.5). This possibility was therefore investigated in collaboration with the group of Prof. Jean-François Paquin at Université Laval and Prof. Pierre Kennepohl at the University of British Columbia.
DFT calculations

A good indication of the ability of N—F reagents to act as atomic fluoride sources is their N—F bond strength. We collaborated with the Kennepohl group at the University of British Columbia to calculate some properties of the N—F bond of NFSI, Selectfluor\textsuperscript{®} and NFPy salts. The density functional theory (DFT) calculations were performed by Dr. Tulin Okbino{ş}lu and Prof. Pierre Kennepohl and the results obtained are summarized in Table 2.1.

**Table 2.1 Comparison of DFT-calculated properties of the N—F bond in NFSI, Selectfluor\textsuperscript{®}, and NFPY species\textsuperscript{ab}**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>$r_{NF}$ (pm)</th>
<th>BO\textsubscript{NF}</th>
<th>$D_{NF}$ (kcal/mol)</th>
<th>$q_F$</th>
<th>$r_{NF}$ (pm)</th>
<th>BO\textsubscript{NF}</th>
<th>$D_{NF}$ (kcal/mol)</th>
<th>$q_F$</th>
<th>$r_{NF}$ (pm)</th>
<th>BO\textsubscript{NF}</th>
<th>$D_{NF}$ (kcal/mol)</th>
<th>$q_F$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexane</td>
<td>143.8</td>
<td>0.839</td>
<td>63.4</td>
<td>-0.14</td>
<td>141.4</td>
<td>0.986</td>
<td>61.0</td>
<td>0.00</td>
<td>137.5</td>
<td>0.933</td>
<td>76.1</td>
<td>-0.02</td>
</tr>
<tr>
<td>THF</td>
<td>143.8</td>
<td>0.839</td>
<td>63.1</td>
<td>-0.14</td>
<td>141.9</td>
<td>0.966</td>
<td>61.7</td>
<td>-0.02</td>
<td>137.8</td>
<td>0.922</td>
<td>75.4</td>
<td>-0.05</td>
</tr>
<tr>
<td>CH\textsubscript{3}CN</td>
<td>143.7</td>
<td>0.837</td>
<td>63.3</td>
<td>-0.14</td>
<td>141.1</td>
<td>0.956</td>
<td>60.9</td>
<td>-0.03</td>
<td>137.8</td>
<td>0.915</td>
<td>75.1</td>
<td>-0.06</td>
</tr>
<tr>
<td>H\textsubscript{2}O</td>
<td>143.7</td>
<td>0.831</td>
<td>63.3</td>
<td>-0.14</td>
<td>141.2</td>
<td>0.956</td>
<td>62.2</td>
<td>-0.03</td>
<td>137.9</td>
<td>0.914</td>
<td>75.3</td>
<td>-0.06</td>
</tr>
</tbody>
</table>

\[a\] Calculations performed by Dr. Tulin Okbino{ş}lu and Prof. Pierre Kennepohl. [b] DFT calculations were performed using ORCA with the VWN/BP86 functional and the available TZV/P basis set for all atoms. Molecular geometries were optimized using the COSMO solvation model as implemented in ORCA. For each species, the N—F bond distance ($r_{NF}$ in pm), Mayer bond order (BO\textsubscript{NF}), and bond dissociation energy ($D_{NF}$ in kcal/mol) and the Loewdin charge on the fluorine atom ($q_F$) are given. \[c\] Computational results for the cationic reagents without counterions are shown in this table. Results from calculations with appropriate counterions differ slightly due to ion pairing effects; these differences do not affect the overall conclusions herein.
From Table 2.1 it can be noted that NFSI and Selectfluor® have similar N—F bond strength (or bond dissociation energy (BDE), $D_{NF}$). The stronger N—F bond of NPFy can be explained by a poor delocalization of the unpaired electron in the resulting sp²-hybridized nitrogen-centered radical. It is interesting to compare the average values of the $D_{NF}$ ofSelectfluor®, NFSI and NPFy (61 kcal/mol, 63 kcal/mol and 75 kcal/mol respectively) to those of reagents known to react via radical pathways (Figure 2.1). Tributylstannane (2.14) and tris(trimethylsilyl)silane (2.15) are two widely used hydrogen sources. Chlorine (2.16) and the $N$-halosuccinimides (2.17) are known to act as halogen transfer agents to radicals. The last two offer a particularly interesting point of comparison as they also possess an N—X bond. The N—F BDE of Selectfluor®, NFSI and NPFy falls between the BDE of those reagents, suggesting that Selectfluor®, NFSI and NPFy have the potential to be used as fluorine transfer agents.

![Figure 2.1 BDE of hydride or atomic halogen sources](Image)

**2.1.3 Experimental verification**

In order to verify experimentally that N—F reagents could act as atomic fluorine sources, Dr. Montserrat Rueda-Becerril studied their reactivity in presence of a known source of alkyl radicals, lauroyl peroxide (2.18, Scheme 2.6). This initial study focused on the reactivity of NFSI, as it is soluble in most organic solvents. Lauroyl peroxide was submitted to thermal and photochemical homolysis in presence of NFSI (Scheme 2.6). Under those conditions, the weak O—O bond ($D_{OO}$ 29.9 kcal/mol) of lauroyl peroxide fragments homolytically, yielding two acyl radicals. Those radicals then rapidly undergo extrusion of CO₂ to afford alkyl radicals (Scheme 2.6). The fluorinated product resulting from fluorine transfer to the alkyl radical, 1-fluoroundecane, was detected in both cases, in 20% and 34% yield respectively (2.19, Scheme 2.6). Those proof of concept experiments are particularly important as they represent the first examples of fluorine transfer to independently generated radicals.
2.2 Results and discussion

The scope of fluorides accessible via radical fluorination was next investigated to explore the potential of this methodology. More versatile radical precursors were necessary for the generation of the more stable tertiary and benzylic radicals and radicals α to heteroatoms. Indeed, diacyl peroxides leading to stable radicals are known to be particularly unstable and undergo rapid thermal decomposition.\(^\text{114}\)

2.2.1 Fluorination of \textit{t}-butyl peresters

Dr. Montserrat Rueda-Becerril identified \textit{t}-butyl peresters (Scheme 2.7) as practical sources of alkyl radicals for the radical fluorination reaction. Those peresters can be obtained directly from the corresponding carboxylic acids by coupling using \textit{N},\textit{N'}-dicyclohexylcarboimiide (DCC). Similarly to diacyl peroxides, \textit{t}-butyl peresters are known to undergo thermal homolysis to yield alkyl radicals (Scheme 2.7).\(^\text{115}\)
At this stage of the investigation, I formally joined the project to help with the challenging synthesis of some \( \text{t-buty1 peresters} \) (2.20 and 2.21, Figure 2.2). Because of the stability of the resulting tertiary and benzylic radicals, peresters 2.20 and 2.21 are thermally unstable, and prone to a quick homolysis of the O—O bond. Control of the temperature at every stage of the synthesis, including the purification (low temperature preparative TLC), was key to obtain enough material for the fluorination reaction.

The fluorination of the \( \text{t-buty1 peresters} \) was optimized by Dr. Montserrat Rueda-Becerril. She found that treating the radical precursors at 110 °C in presence of NFSI afforded the corresponding fluorides in moderate to excellent yields (Scheme 2.8). The higher yields observed for the secondary and tertiary substrates are in agreement with a slower rate of dimerization of the bulkier radicals in solution. In addition, this method was successfully employed for the synthesis of the fluorinated derivative of cholic acid (2.27). At that point, we were joined by Dr. Joe C.T. Leung, who optimized the fluorination of substrates 2.25 and 2.26. Fluoride 2.26 could also be obtained in good yield in acetonitrile (Scheme 2.8), solvent in which Selectfluor® is also soluble. Dr. Joe C.T. Leung was, therefore, able to demonstrated the ability of Selectfluor® to act as an atomic fluorine source for the synthesis of substrate 2.26, with an efficiency similar to NSFI (Scheme 2.8).
2.2.2 Personal contribution

2.2.2.1 Fluorination α to nitrogen

My initial work on the fluorination of alkyl radicals focused on radicals α to nitrogen, which are known to be more stable than their carbon-analogues.\textsuperscript{118} Perester 2.28 (Scheme 2.9), derived from glycine, was first investigated. Thermolysis of the perester led to complete consumption of the starting material in less than a minute, but no evidence of fluorination was observed. It is possible that the fluorinated product decomposed at the elevated temperature needed for the thermolysis, \textit{via} thermal BOC deprotection\textsuperscript{119} and/or elimination of HF.\textsuperscript{120} A more robust phthalimide protecting group (Scheme 2.9) was, therefore, employed. In addition to be more thermally stable, the phthalimide protecting group efficiently delocalizes the lone pair on the nitrogen, reducing the risk of HF elimination. With this protecting group, the glycine derivative could be successfully fluorinated in 47% yield.\textsuperscript{88}
Simple substrates have been successfully fluorinated using our radical fluorination methodology. Because of the potential application of this methodology to late-stage fluorination, more complex substrates were investigated: the perester derivatives of abietic acid 2.32 and (1S)-(−)-camphanic acid 2.33 (Figure 2.3).

Perester 2.32 proved to be extremely unstable. The formation of a new product that most certainly corresponded to the perester\textsuperscript{121} was observed by thin layer chromatography (TLC) but its thermal decomposition was too fast to allow any purification. Attempts to form the perester from the acid chloride resulted in decomposition of the starting material.

Perester 2.33 was subjected to the general fluorination conditions and the reaction was monitored over time by \textsuperscript{1}H NMR (30 min to 13 h). After 5 h, the signal corresponding to the \textit{t}-butyl protons was no longer observed, but no fluorinated product was detected. Bridgehead radicals are known to be difficult to form, especially for strained structures such as bicyclo[2.2.1]heptane derivatives,\textsuperscript{122} and the perester may have thermally decomposed \textit{via} other pathways, such as the Criegee rearrangement.\textsuperscript{123} (1S)-(−)-Camphanic acid was notably...
detected in the crude reaction mixture. Formation of the corresponding acid had previously been observed during the thermal decomposition of another bridgehead perester, 1-norbornyl t-butyl perester.\textsuperscript{124} Alternatively, the high reactivity of the bridgehead radical\textsuperscript{122} may have led to radical recombination in the solvent cage, similarly to what can be observed for reactive primary radicals\textsuperscript{116} but no evidence to support this pathway was observed.

### 2.3 One-pot procedure

The possibility of transferring atomic fluorine to alkyl radicals using N—F reagents has been successfully demonstrated. A limitation of the previously described method (see 2.2.1) is the difficulty to access some of the radical precursors. Tertiary peresters are particularly difficult to purify, as they tend to quickly decompose at room temperature via radical decarboxylation.\textsuperscript{115} It was hypothesized that synthesizing the peresters in presence of NFSI might allow to trap \textit{in-situ} the homolysis product. The possibility of a one-pot perester synthesis/ fluorination (Scheme 2.10) was, therefore, investigated.

![Scheme 2.10 Strategy for the one-pot fluorination procedure](image)

Carboxylic acids were activated by reaction with 1,1'-carbonyldiimidazole (CDI).\textsuperscript{125} Following removal of the solvent, the crude carboxylic acid derivatives were reacted with peroxides in presence of NFSI. The results obtained are presented in Table 2.2 and compared with the previously developed fluorination of peresters. Isolated yields for the perester synthesis are taken in account to compare the efficiency of the two methods. The one-pot procedure allowed access to primary fluorides in yields similar to those of the previously developed sequential method (entry 1, Table 2.2), but proved to be less efficient for the synthesis of secondary fluorides (entry 2, Table 2.2). Both the synthesis of the secondary perester and its fluorination were high yielding, leading to a high overall yield of fluorinated product. In the one-pot procedure, the presence of side products and impurities from each step probably leads to side reactions, diminishing the efficiency of the reaction. Overall higher yields of the tertiary fluoride were obtained using the one-pot procedure (entry 3, Table 2.2). The one-pot procedure could,
therefore, be used as an alternative method for substrates whose corresponding peresters are too unstable to be isolated. The abietic acid derivative (2.32, Figure 2.3), however, could not be fluorinated using the one-pot procedure.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Perester synthesis yield</th>
<th>Fluorination yield</th>
<th>Overall yield</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="2.33" alt="Image" /></td>
<td>96%</td>
<td>24%</td>
<td>23%</td>
<td>17%</td>
</tr>
<tr>
<td>2</td>
<td><img src="2.34" alt="Image" /></td>
<td>84%</td>
<td>98%</td>
<td>82%</td>
<td>40%</td>
</tr>
<tr>
<td>3</td>
<td><img src="2.35" alt="Image" /></td>
<td>19%</td>
<td>98%</td>
<td>19%</td>
<td>35%</td>
</tr>
</tbody>
</table>

Conditions: CDI (1.1 equiv.) in 0.1 M CH₂Cl₂, stirred at r.t. for 1 h. Solvent was evaporated. Diluted in CD₃CN 0.1 M under N₂. Hydrogen peroxide (1.5 equiv.), n-tetradecane (0.5 equiv.) and NFSI (5 equiv.) were added. Stirred 30 min at 0 °C and 15 min at 110 °C. Diluted 10x in benzene and analyzed by GC.

2.4 Conclusion

NFSI and Selectfluor®, two traditionally electrophilic sources of fluorine, were demonstrated to be efficient fluorine transfer agents to alkyl radicals. Primary, secondary, tertiary and benzylic radicals are amenable to the fluorination reaction. A wide range of organofluorides could be accessed by thermolysis of t-butyl peresters in presence of NFSI in moderate to excellent yields. I demonstrated that fluorination α to nitrogen atoms was possible but that the lone pairs of the heteroatom need to be delocalized to prevent elimination.

Since the thermal instability of some peresters can limit the applicability of this methodology, I investigated a one-pot procedure to avoid the purification of the unstable peresters. This methodology affords the corresponding fluorides in overall higher yields.
This seminal report has since opened the way to a renaissance in radical fluorination.\textsuperscript{89,90} The uncovering of the radical reactivity of those safe and selective atomic fluorine sources allowed the development of numerous methods for the formation of C(sp\textsuperscript{3})—F bonds as discussed in the introductory chapter. The mechanism of the fluorine transfer from NFSI to alkyl radicals is currently under investigation by Wei Zhang in our research group.

2.5 Experimental section

All reactions were performed under nitrogen atmosphere in flame-dried glassware unless otherwise noted. THF and dichloromethane were obtained from a MBRAUN MB-SPS solvent purification system. All other solvents were used without further purification. Methyl 4-phenylbutanoate, 2-phenylpropanoic acid, N-(t-butoxycarbonyl)glycine, N-phthaloylglycine and camphanic acid were purchased from commercial sources and used as received.

Flash column chromatography (FCC) was performed using Silicycle P60 silica: 230-400 mesh (40-63 μm) silica. Reactions were monitored using Merck Kieselgel 60F\textsubscript{254} aluminium or glass backed plates. Thin layer chromatography (TLC) plates were visualized by UV fluorescence (254 nm) and one of the following stains: KMnO\textsubscript{4}, ninhydrin, p-anisaldehyde, vanillin.

Infrared (IR) spectra were obtained using a Thermo Nicolet 4700 FT-IR spectrometer. Proton and carbon nuclear magnetic resonance (\textsuperscript{1}H NMR and \textsuperscript{13}C NMR) spectra were recorded using a Bruker AV-300 or AV-400 spectrometer. Fluorine nuclear magnetic resonance (\textsuperscript{19}F NMR) spectra were recorded using a Bruker AV-300. Chemical shifts (\(\delta\)) are reported in parts per million (ppm) relative to residual solvent peaks rounded to the nearest 0.01 for proton and 0.1 for carbon (ref: CHCl\textsubscript{3} [\textsuperscript{1}H: 7.26, \textsuperscript{13}C: 77.2], C\textsubscript{6}H\textsubscript{6} [\textsuperscript{1}H: 7.16, \textsuperscript{13}C: 128.0]). Coupling constants (\(J\)) are reported in Hz to the nearest 0.1 Hz. Peaks multiplicity is indicated as follows s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). High resolution mass spectra (HRMS) were recorded on either a Waters or Micromass LCT spectrometer. GC analyses were performed using a Varian CP-3800 Gas Chromatograph, equipped with an autosampler (10 μL syringe, 5.0 μL injection). GC-FID analysis: temperature-gradient oven (start at 80 °C for 1 min, then gradient from 80 °C to 300 °C at 30 °C/min), 250 °C injector temperature, 1.0 mL/min flow, He carrier gas, FactorFourTM Capillary Column VF-5ms (30 m x 0.25 mm, 0.25 μm), 300 °C front detector temperature.
2.5.1 Synthesis of perester precursor S3

![Synthesis of methyl 2-methyl-4-phenylbutanoate (S1)]

**Synthesis of methyl 2-methyl-4-phenylbutanoate (S1):**

To a solution of diisopropylamine (1.8 mL, 1.3 g, 13 mmol) in 14.0 mL of dry THF at -78 °C was added a 1.38 M solution of n-butyllithium in hexanes (8.5 mL, 12 mmol). The resulting solution was stirred at -78 °C for 30 min. To this mixture was added a solution of methyl 4-phenylbutanoate (1.82 g, 10.2 mmol) in 17 mL of dry THF, and the reaction was stirred for 30 min at -78 °C. Methyl iodide (1.9 mL, 4.3 g, 31 mmol) was then added in one portion and the resulting solution was stirred at r.t. for 18 h. The reaction was quenched with 20 mL of a saturated solution of NH₄Cl(aq.), diluted with 30 mL of H₂O, and extracted with 3x 20 mL of Et₂O. The combined organic layers were washed with 1x 20 mL of brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Flash column chromatography purification (9:1 hexanes/EtOAc) yielded methyl 2-methyl-4-phenylbutanoate S1 as a yellow oil (1.68 g, 8.75 mmol) in 86% yield. ¹H NMR (300 MHz; CDCl₃): δ 7.27 (dt, J = 8.1, 6.5 Hz, 5H), 3.71 (s, 3H), 2.65 (t, J = 7.9 Hz, 2H), 2.51 (t, J = 6.9 Hz, 1H), 2.05 (dd, J = 13.6, 7.7 Hz, 1H), 1.79-1.72 (m, 1H), 1.23 (d, J = 7.0 Hz, 3H). ¹³C NMR (75 MHz; CDCl₃): δ 177.1, 141.7, 128.5, 128.5, 126.0, 51.7, 39.1, 35.5, 33.6, 17.2. IR (neat): 3027, 2979, 1736, 1600, 1496, 1455, 1378, 1203, cm⁻¹. HRMS-ESI (m/z) [M+Na]+ calcd for C₁₂H₁₆O₂Na: 215.1048. Found: 215.1054.

**Synthesis of methyl 2,2-dimethyl-4-phenylbutanoate (S2):**

To a solution of diisopropylamine (0.28 mL, 0.20 g, 2.0 mmol) in 5.0 mL of dry THF at -78 °C, was added a 1.38 M solution of n-butyllithium in hexanes (1.4 mL, 2.0 mmol). The resulting solution was warmed to -10 °C and stirred for 20 min. The reaction mixture was cooled back to -78 °C, and a solution of S1 (190 mg, 0.988 mmol) in 1.5 mL of dry THF was added in one portion. The resulting solution was warmed to -10 °C, stirred for 20 min, and then cooled back
to -78 °C. A mixture of methyl iodide (90 μL, 1.5 mmol) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU, 20 μL, 0.17 mmol) in 5.0 mL of dry THF was cooled to -78 °C and then added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for an additional 45 min. The reaction was quenched with 30 mL of a saturated solution of NH₄Cl(aq.) and extracted with 3x 15 mL of Et₂O. The combined organic layers were washed with 1x 15 mL of brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. Flash column chromatography purification (10:1 hexanes/EtOAc) yielded methyl 2,2-dimethyl-4-phenylbutanoate (S2) as a clear colorless oil (24 mg, 0.12 mmol) in 12% yield. ¹H NMR (300 MHz; CDCl₃): δ 7.33-7.18 (m, 5H), 3.70 (s, 3H), 2.56 (dt, J = 8.0, 4.3 Hz, 2H), 1.87 (dt, J = 8.1, 4.3 Hz, 2H), 1.27 (s, 6H). ¹³C NMR (75 MHz; CDCl₃): δ 170.8, 142.4, 128.5, 125.9, 51.9, 42.9, 42.5, 31.7, 25.4. IR (neat): 3027, 2970, 1732, 1497, 1474, 1257, 1193 cm⁻¹. HRMS-ESI (m/z) [M+Na]⁺ calcd for C₁₃H₁₈O₂Na: 229.1204. Found: 229.1203.

Synthesis of 2,2-dimethyl-4-phenylbutanoic acid (S3):

To a 0.8 M solution of S2 (24 mg, 0.12 mmol) in methanol was added a 2.0 M NaOH(aq.) solution (0.16 mL, 0.58 mmol). The resulting reaction was stirred at reflux for 18 h. The reaction was allowed to cool to room temperature and concentrated under reduced pressure. The resulting solution was washed with 10 mL of Et₂O, acidified to pH = 2 with a 10% HCl(aq.) solution and then extracted with 3x 10 mL of Et₂O. The combined organic layers were washed with 1x 10 mL of brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure to yield 2,2-dimethyl-4-phenylbutanoic acid (S3) (14 mg, 0.073 mmol) as a white solid in 61% yield. m.p.: 93-95 °C. ¹H NMR (300 MHz; CDCl₃): δ 7.33-7.18 (m, 5H), 2.64 (dt, J = 8.2, 4.3 Hz, 2H), 1.90 (dt, J = 8.2, 4.3 Hz, 2H), 1.32 (s, 6H). ¹³C NMR (75 MHz; CDCl₃): δ 170.1, 142.2, 128.5, 128.50, 126.0, 42.6, 42.4, 31.6, 25.2. IR (neat): 3063, 2970, 1690, 1496, 1451, 1342, 1270, 1205 cm⁻¹. HRMS-ESI (m/z) [M+Na]⁺ calcd for C₁₂H₁₆O₂Na: 215.1048. Found: 215.1046.
2.5.2 Synthesis of t-butyl peresters

General procedure for the synthesis of t-butyl peresters:128

![chemical structure](attachment:image.png)

To a 0.1 M solution of the corresponding carboxylic acid (1.0 equiv.) in CH$_2$Cl$_2$, was added a catalytic amount (0.05 to 0.1 equiv.) of 4-(dimethylamino)pyridine (DMAP), followed by a 70% w/w solution of t-butylhydroperoxide in H$_2$O (1.05 equiv.). The reaction mixture was cooled to 0 °C and stirred for 5 min. To the reaction mixture was added a 0.2 M solution of N,N-dicyclohexylcarbodiimide (DCC) (1.1 equiv.) in CH$_2$Cl$_2$, and the resulting mixture was stirred at 0 °C for 30 min., then at room temperature for 18 h. The crude reaction was run through a silica plug with CH$_2$Cl$_2$ to remove solids and polar impurities.

Synthesis t-butyl 2,2-dimethyl-4-phenylbutaneperoxoate (2.20):

2,2-Dimethyl-4-phenylbutanoic acid (S3) (74 mg, 0.38 mmol) was subjected to the general t-butyl perester synthesis procedure. The resulting perester was found to be thermally unstable; it rapidly decomposed at 40 °C. The crude reaction mixture was purified by preparative TLC (10:1 pentane/Et$_2$O) at 5 °C followed by extraction from the silica with Et$_2$O. Filtration of the solids and removal of the solvent by rotary evaporation using a water bath to maintain the temperature of the containing flask at 0 °C afforded perester 2.20 (19 mg, 0.072 mmol) as a clear colorless oil in 19% yield. $^1$H (400 MHz; CDCl$_3$): δ 7.23 (m, 5H), 2.63-2.58 (m, 2H), 1.89-1.84 (m, 2H), 1.35 (s, 9H), 1.31 (s, 6H). $^{13}$C (101 MHz; CDCl$_3$): δ 174.4, 142.1, 128.6, 128.4, 126.1, 83.5, 43.1, 42.9, 31.6, 26.4, 25.4. IR (neat): 2980, 2927, 1765, 1455, 1366 cm$^{-1}$. HRMS-ESI (m/z) [M+Na]$^+$ calcd for C$_{16}$H$_{24}$O$_3$Na: 287.1623. Found: 287.1628.

Synthesis of t-butyl 2-phenylpropaneperoxoate 2.21:

2-Phenylpropanoic acid (0.76 g, 5.1 mmol) was subjected to the general t-butyl perester synthesis procedure to afford perester 2.21 as a colorless oil (0.96 g, 3.3 mmol) in 66% yield.
Chapter 2 Fluorine transfer to alkyl radicals

$^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.32 (m, 5H), 3.76 (q, $J = 7.2$ Hz, 1H), 1.57 (d, $J = 7.2$ Hz, 3H), 1.21 (s, 9H). $^{13}$C NMR (101 MHz; CDCl$_3$): $\delta$ 171.9, 139.6, 128.8, 127.6, 83.8, 43.2, 26.1, 18.5. IR (neat): 2981, 2935, 1773, 1717, 1686, 1453, 1366, 1191 cm$^{-1}$. HRMS-ESI (m/z) [M+Na]$^+$ calcd for C$_{13}$H$_{18}$O$_3$Na: 245.1154. Found: 245.1148.

Synthesis of t-butyl 2-((t-butoxycarbonyl)amino)ethaneperoxoate 2.28:

$\text{NH}_2\text{O}_2\text{O}_2\text{O}_2\text{O}_2$

N-(t-Butoxycarbonyl)glycine (502 mg, 2.87 mmol) was subjected to the general t-butyl perester synthesis procedure. Purification by flash column chromatography (5:1 PE/Et$_2$O) afforded perester 2.28 as a white solid (130 mg, 0.526 mmol) in 18% yield. $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 3.57 (s, 2H), 1.49 (s, 9H), 1.20 (s, 9H).

Synthesis of t-butyl 2-(1,3-dioxoisooindolin-2-yl)ethaneperoxoate 2.30:

$\text{O}_2\text{O}_2\text{O}_2\text{O}_2$

N-phthaloylglycine (514 mg, 2.51 mmol) was subjected to the general t-butyl perester synthesis procedure to afford perester 2.30 as a white solid (580 mg, 2.09 mmol) in 86% yield. Evaporation of the solvent was performed at 0 °C to prevent thermal decomposition of the resulting perester. $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.90 (dd, $J = 5.4$, 3.1 Hz, 2H), 7.76 (dd, $J = 5.5$, 3.1 Hz, 2H), 4.51 (s, 2H), 1.33 (s, 9H). $^{13}$C NMR (101 MHz; CDCl$_3$): $\delta$ 184.6, 167.3, 134.5, 132.0, 123.9, 84.8, 37.1, 26.2. IR (neat): 2983, 2939, 2117, 1774, 1724, 1416, 1393 cm$^{-1}$. HRMS-ESI (m/z) [M+Na]$^+$ calcd for C$_{14}$H$_{15}$NO$_5$Na: 300.0848. Found: 300.0846.

Synthesis of (1R, 4R)-t-butyl 7,7-dimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboperoxoate 2.33:

Camphanic acid (352 mg, 1.77 mmol) was subjected to the general t-butyl perester synthesis procedure. Purification by flash column chromatography (3:1 PE/Et$_2$O) afforded perester 2.33
as a white solid (376 mg, 1.39 mmol) in 78% yield. Evaporation of the solvent was performed at 0 °C to prevent thermal decomposition of the resulting perester. ¹H NMR (300 MHz; CDCl₃): δ 2.46 (ddd, J = 13.6, 10.8, 4.3 Hz, 1H), 2.08 (ddd, J = 13.6, 9.2, 4.4 Hz, 1H), 1.94 (ddd, J = 13.2, 10.8, 4.6 Hz, 1H), 1.71 (m, 1H), 1.36 (s, 9H), 1.13 (s, 3H), 1.09 (s, 3H), 1.02 (s, 3H). ¹³C NMR (101 MHz; CDCl₃): δ 177.86, 164.89, 90.62, 84.47, 54.39, 30.93, 28.77, 26.09, 16.97, 16.57, 9.71. IR (neat): 2979, 2933, 1793, 1367, 1250, 1089, 1027 cm⁻¹.

2.5.3 General radical fluorination procedure

To a microwave vial charged with NFSI (5 equiv.) under N₂ was added a 0.21 M stock solution of the radical precursor (1 equiv.) and internal standard (ethyl trifluoroacetate, 1 equiv.) in C₆D₆ or CD₃CN. The vial was sealed and the reaction was heated to reflux. The reaction mixture was then placed in an ice bath for 10 min. The crude reaction mixture was analyzed by ¹H and ¹⁹F NMR spectroscopy.

The NMR yield was calculated by comparison of the t₀ spectrum with the spectrum of the crude product mixture using CF₃CO₂Et as internal standard. A representative example of the spectra used for NMR yield determination is provided below.

2-(fluoromethyl)isoindoline-1,3-dione 2.31:

Perester 2.30 (18 mg, 0.063 mmol) was subjected to the general radical fluorination procedure in C₆D₆. The reaction vial was placed in an oil bath, heated to 130 °C and the reaction was stirred for 10 min. The reaction mixture was then placed in an ice bath for 10 min. ¹H and ¹⁹F NMR spectroscopy analysis of the crude reaction mixture confirmed the presence of
2-(fluoromethyl)isoindoline-1,3-dione 2.31. The reaction was repeated 3 times, to give 59%, 57% and 55% yield, or an average of 57% NMR yield.

Sample 1H NMR analysis: The top spectrum is the t0 spectrum showing the quartet of the internal standard CF3CO2Et (2H, 4.41 ppm) and the methylene singlet of perester 2.30 (2H, 4.17 ppm). From the integration, we can calculate the molar ratio of starting material to internal standard, which is 1.90. The second spectrum is of the crude reaction mixture with the doublet of the fluoroalkane 2.31 (2H, 5.27 ppm). From the integration, we can calculate the molar ratio of product to internal standard, which is 0.56:2. From those ratio, the NMR yield was calculated and is equal to:

\[
\frac{0.56}{1.90} = 57\%
\]

The third spectrum is the 1H{19F} spectrum of the crude reaction mixture, with the decoupled signal of the methylene singlet at 5.35 ppm to confirm fluorination.

Separately, the reaction was run on a 138 mg (0.500 mmol) scale under the same conditions used for the NMR scale reaction described above. Flash column chromatography purification on a triethylamine basified column (3:1 to 2:1 PE/Et2O) afforded 40.8 mg (0.227 mmol) of fluoride 2.31 as a white solid, in 45% yield. 1H NMR (300 MHz; C6D6): δ 7.33 (dd, J = 5.4, 3.1 Hz, 2H), 6.83 (dd, J = 5.3, 3.1 Hz, 2H), 5.30 (d, J = 52.4 Hz, 2H). 13C NMR (75 MHz; C6D6): δ 166.0, 134.1,
131.9, 123.7, 74.9 (d, J = 197.7 Hz). \( ^{19} \text{F} \{ ^{1} \text{H} \} \) NMR (282 MHz): \( \delta -174.23 \). IR (CDCl\(_3\)): 3495, 3043, 2356, 1784, 1732, 1421, 1368, 1329, 1195 cm\(^{-1}\). HRMS-ESI (m/z) [M+Na]\(^+\) calcd for \( \text{C}_9\text{H}_6\text{NO}_2\text{FNa} \): 202.0280. Found: 202.0278.

### 2.5.4 One-pot procedure

To a 0.1 M solution of the acid in CH\(_2\)Cl\(_2\) was added CDI (1.1 equiv.). The reaction was stirred at r.t. for 1 h. Solvent was evaporated and the resulting crude product was diluted in CD\(_3\)CN under \( \text{N}_2 \). A solution of hydrogen peroxide (1.5 equiv.), internal standard (\( n \)-tetradecane, 0.5 equiv.) and NFSI (5 equiv.) in CD\(_3\)CN (0.33 M in substrate) was added. The reaction was stirred 30 min at 0 °C and 15 min at 110 °C. The crude mixture was diluted 10x in benzene and analyzed by GC.
Chapter 3
Mono- and difluoromethyl aryl ethers
synthesis by fluorodecarboxylation

In Chapter 2, the ability of electrophilic fluorinating agents to transfer fluorine to alkyl radicals was demonstrated. A limitation of this radical fluorination method is the instability of the t-butyl peresters used as radical precursors. Their rapid thermal decomposition renders their synthesis challenging and might hinder the applicability of the reaction. While the one-pot perester formation/fluorination can be used as an alternative in some cases, a method that would directly utilize the carboxylic acid as radical precursor is highly desirable.

This chapter details the use of phenoxy acetic acid derivatives as radical precursors in a light-mediated fluorodecarboxylation reaction. Selectfluor® and UV-light irradiation are used to trigger the radical decarboxylation. This methodology was applied to the synthesis of mono- and difluorinated aryl ethers. To place this work in context, a presentation of the previous work on fluorodecarboxylation reactions will first be given. The relevance of mono- and difluoromethyl aryl ethers will then be presented, followed by an overview of the previously developed methods for their synthesis. The results of our work on the fluorodecarboxylation of phenoxyacetic acids will next be described and finally discussed in perspective with the newest advances in fluorodecarboxylation.

3.1 The fluorodecarboxylation reaction

A commonly used method that involves the generation of radical intermediates from carboxylic acids is the Hunsdiecker decarboxylative halogenation.82 This reaction allows the conversion of carboxylic acids to chlorine, bromine and iodine. The postulated mechanism for the Hunsdiecker reaction is described in Scheme 3.1. The formation of acyl hypohalites from the reaction between carboxylate salts (Ag, Tl, or Hg) and halogens is generally accepted.82 Acyl hypohalites then undergo a radical decarboxylation to afford the corresponding alkyl radicals. Strong evidence of the presence of radical intermediates has been observed, such as products from homocoupling or halogen abstraction from the solvent.82 Halogen transfer finally affords
the alkyl halides. The Hunsdiecker reaction can be used for the synthesis of organochlorides, bromines and iodides, but fewer methods exist for the conversion of carboxylic acids to fluorine.

![Scheme 3.1 Hunsdiecker reaction](image)

### 3.1.1 Fluorodecarboxylation of acyl hypofluorites

Acyl hypofluorites can be isolated and used as fluorinating agents (see Chapter 1, Section 1.2.2). A few examples of fluorodecarboxylations involving acyl hypofluorites have been described. Cady et al. reported that under thermal conditions, trifluoroacetyl (3.1) and pentafluoropropionyl hypofluorites (3.2) undergo fluorodecarboxylation to yield CF₄ and hexafluoroethane respectively (1.52 and 1.53, Scheme 3.2). The presence of radical intermediates was later demonstrated by Rozen et al.

![Scheme 3.2 Fluorodecarboxylation of trifluoroacetyl and pentafluoropropionyl hypofluorites](image)

As discussed in Chapter 1, the fluorodecarboxylation of dicarboxylate salts using F₂ reported by Grakauskas (see Scheme 1.11) most likely involve the decarboxylation of an *in-situ* formed acyl hypofluorite. A similar mechanism can be postulated for the fluorodecarboxylation of perfluorinated carboxylic acids reported by Marchionni et al. (Scheme 3.3). The scope of organofluorides accessible by fluorodecarboxylation using F₂, however, remains limited to
dicarboxylate salts and perfluorinated carboxylic acids as other substrates undergo competitive perfluorination.

\[
\begin{align*}
\text{HO} & \quad \text{O} \\
\text{F}_2 & \quad \text{C} \quad \text{O} \quad \left( F_2 \quad \text{C} \quad \text{O} \right) \quad \text{F}_2 \\
\text{F}_2 & \quad \text{OH} \\
\text{F}_2 & \quad \text{OH}
\end{align*}
\]

\[ F_2 \quad \text{C} \quad \text{O} \quad \left( F_2 \quad \text{C} \quad \text{O} \right) \quad \text{F}_2 \\
\text{F}_2 & \quad \text{OH}
\]

n/m = 1.2

Scheme 3.3 Synthesis of perfluoropolyethers by fluorodecarboxylation

3.1.2 XeF₂-mediated fluorodecarboxylation

Aliphatic carboxylic acids react with XeF₂ to afford the corresponding alkyl fluorides (see section 1.3.3). Xenon esters were postulated to be intermediates in the reaction (see Scheme 1.18). The mechanism of the decarboxylation reaction depends on the structure of the carboxylic acid. EPR studies and mechanistic experiments support the intermediacy of radicals. Incorporation of radiolabelled fluoride (\(^{18}\text{F}\)) was observed for the reaction of primary and secondary carboxylic acids, indicating that both ionic and radical mechanisms could be at play.

3.1.3 Silver-mediated decarboxylation

Following our report on the use of N—F reagents as atomic fluorine sources, Li et al., recognizing the potential of using N—F based reagents for the Hunsdiecker-type fluorination, developed a silver-catalyzed fluorodecarboxylation reaction using Selectfluor® as the fluoride source (Scheme 3.5). The formation of a highly oxidizing Ag(III) species from the reaction between Selectfluor® and Ag(I) was proposed as a first step. Oxidation of the carboxylate by Ag(III) triggers a radical decarboxylation, resulting in an alkyl radical. The authors suggested that fluorine transfer occurred from the \textit{in-situ} generated Ag(II)-fluoride species rather than from Selectfluor® itself. A wide range of alkyl fluorides could be accessed in good to excellent yields. Gouverneur et al. expanded the scope of this reaction to \(\alpha\)-fluorinated benzylic acids and demonstrated its applicability to the synthesis of \(^{18}\text{F}\)-labelled compounds (Scheme 3.4). The silver-catalyzed fluorodecarboxylation reaction was later applied to the synthesis of
β-fluorinated γ-butyrolactones (3.12, Scheme 3.6)\textsuperscript{91d} and of the anti-inflammatory agent fluticasone propionate.\textsuperscript{91e}

Scheme 3.4 Synthesis of di- and trifluoroarenes by fluorodecarboxylation (Li et al.)\textsuperscript{91b}

Scheme 3.5 Silver-catalyzed fluorodecarboxylation (Gouverneur et al.)\textsuperscript{91c}
3.1.4 Light-mediated decarboxylation of phenoxyacetic acids

Generation of radicals from carboxylic acids by in-situ formation of (diacyloxy)iodoarenes using hypervalent iodine reagents followed by photolysis had previously been reported. In the group of Prof. Sammis, Dr. Joe C.T. Leung investigated the possibility of using phenyliodine bis(trifluoroacetate) (PIFA, 3.13) in presence of NFSI to induce the fluorodecarboxylation of carboxylic acids (Scheme 3.7).

Mechanism:

Scheme 3.6 Synthesis of β-fluorinated γ-butyrolactones

Scheme 3.7 Fluorodecarboxylation using hypervalent iodine
Of the carboxylic acids subjected to the reaction conditions, only the substrates containing a \( \alpha \)-aryloxy ether moiety underwent decarboxylation. Control studies demonstrated that PIFA was not necessary for the reaction to occur, and that it only acted as a source of mild base. This realization led Dr. Joe C.T. Leung to develop a direct UV-light mediated fluorodecarboxylation of phenoxyacetic acids (Scheme 3.8).\(^{92a,130}\)

\[ \begin{aligned} &\text{NaOH} \quad \text{Selectfluor}^\circ \quad 300 \text{ nm} \\
&\text{H}_2\text{O/CH}_3\text{CN} \quad \rightarrow \quad 96\% \text{ NMR} \end{aligned} \]

**Scheme 3.8 UV-light mediated fluorodecarboxylation of phenoxyacetic acid derivatives**

Recognizing the potential of this reaction for the synthesis of fluoromethyl aryl ethers, the scope and the mechanism of this reaction were investigated. The results of our findings will be discussed in the following sections of this chapter (see: 3.3 and 3.4). To put this work in perspective, the relevance of mono- and difluoromethyl aryl ethers will first be presented, as well as an overview of the currently available methods for their synthesis.

### 3.2 Mono- and difluoromethyl aryl ethers

#### 3.2.1 Relevance of fluoromethyl aryl ethers

The monofluoromethyl aryl ether moiety is mainly found in positron emission tomography (PET) tracers (Figure 3.1).\(^{131}\) As the OCH\(_2\)F and OCH\(_3\) groups are bioisosteres,\(^{131a}\) the \(^{12}\text{C}\)-methoxy and \(^{18}\text{F}\)-fluoromethoxy groups can be interchanged on a tracer without influencing its structure or electronic properties,\(^{131a,132}\) while increasing its lifetime (\(^{18}\text{F}\) lifetime is 110 min vs. 20 min for \(^{12}\text{C}\)). Furthermore, the impact of fluorine atom on lipophilicity\(^{16b}\) may improve the blood-brain barrier passage of the tracer. For example, the \(^{18}\text{F}\)-fluoromethoxy group has been used to substitute \(^{123}\text{I}\) on cannabinoid receptors ligand tracers to help reduce their lipophilicity.\(^{131e}\)
Difluoromethyl aryl ethers are more broadly utilized in pharmaceutical and agrochemical compounds and materials. The introduction of the difluoromethoxy group in pharmaceuticals has notably the potential to affect the physicochemical properties of a molecule due to the presence of fluorine atoms (See section 1.1.3). Furthermore, the difluoromethyl group (CF₂H) is a lipophilic hydrogen donor, similarly to OH or NH, and can increase the binding of a drug to the receptor via hydrogen bonding. The fluorine atoms can also participate in the formation of weak binding interactions, as was observed for Roflumilast (3.23, Figure 3.2). Fluorine introduction can also be used to modulate the lipophilicity of a drug. Replacing methoxy groups by more hydrophobic difluoromethoxy groups has been notably shown to improve the activity of some anti-HIV drug candidates. The difluoromethoxy group has also been introduced to block the metabolization of cyclic nucleotide phosphodiesterase (PDE4) inhibitors derived from Roflumilast.
3.1.1 Synthesis of mono- and difluoromethyl aryl ethers: Previous work

Fluoromethyl aryl ethers can be obtained in low yields in two steps from phenol derivatives by nucleophilic displacement of chloromethyl aryl ethers (3.25, Scheme 3.9, a)\textsuperscript{134a,c}. Direct formation of fluoromethyl aryl ethers from phenols can be achieved through the use of electrophilic fluoromethylating agents (b, c, and d, Scheme 3.9).\textsuperscript{134c,140} Examples employing fluoromethylhalides are mainly encountered in the context of PET tracers’ synthesis. A more extensive study on the reactivity of one of those reagents, CH$_2$FCl, was reported, showing good to excellent yields for the synthesis of various fluoromethyl aryl ethers.\textsuperscript{141} Two sulfur-based reagents have been developed that allow the fluoromethylation of phenols. The synthesis of reagent 3.27, however, involves the generation of explosive azides.\textsuperscript{140b}
Benzylic alcohols (3.28) can undergo structural rearrangement when treated with XeF$_2$\textsuperscript{142} or difluoro-$\lambda^3$-bromane (Scheme 3.10) yielding fluoromethyl aryl ethers.\textsuperscript{143} Electron-poor substrates are compatible with both reaction conditions. Some electron-rich substrates could be accessed using difluoro-$\lambda^3$-bromane (3.29), albeit in low yields.\textsuperscript{143}
Benneche et al. reported the conversion of O,S-acetals (3.30) to fluoromethyl aryl ethers (Scheme 3.11). Using XeF₂, the acetals could be directly converted to the fluoromethoxybenzene derivatives. Conversion of the O,S-acetals (3.30) to sulfoxides (3.31) or chloromethyl aryl ethers (3.25) followed by treatment with DAST or TBAF respectively afforded the corresponding fluorinated ethers in moderate to good yields.
Finally, fluoromethyl aryl ethers have been synthesized using the aforementioned fluorodecarboxylation methods (see 3.1), either using XeF$_2$ or the silver-catalyzed fluorodecarboxylation developed by Li et al.

Difluoromethyl aryl ethers (3.33) are commonly synthesized from phenols by reaction with a difluorocarbene precursor. Miller and Thanassi described the first synthesis of difluoromethyl aryl ethers using a previously known difluorocarbene precursor, chlorodifluoromethane (3.32, Scheme 3.12). Decomposition of chlorodifluoromethane leads to a difluorocarbene that reacts with phenolates to furnish the fluorinated products. Sodium chlorodifluoroacetate (3.34, Scheme 3.12) and CF$_2$Br$_2$ were subsequently employed for the generation of difluorocarbene and the synthesis of difluoromethyl aryl ethers (Scheme 3.12). Those reagents are either ozone depleting substances (ODS) or derived from ODS and further efforts were directed toward the development of non-ODS based reagents (Scheme 3.12): fluorousulfonyldifluoroacetate (3.35), chlorodifluoromethyl phenyl sulfone (3.36), 2-chloro-2,2-difluoroacetophenone (3.37), diethyl bromodifluoromethylphosphonate (3.38), difluoromethyltriflate (3.39). One example of the formation of difluoromethyl aryl ether from phenols that doesn’t involve carbenes has also been reported using trifluoromethyl zinc bromide.
Difluoromethyl aryl ethers (3.33) can alternatively be obtained by treating benzaldehyde derivatives (3.40) with XeF₂ or difluoro-λ³-bromane (3.29) (Scheme 3.13). With XeF₂, electron-rich substrates suffer competitive ring fluorination. One example of arylformate conversion to difluoroether by DAST has also been reported.

Scheme 3.12 Difluoromethoxylation using difluorocarbene sources

Scheme 3.13 Difluoromethyl aryl ethers synthesis from aldehydes
3.3 Results and discussion

The photoinduced fluorodecarboxylation uncovered by Dr. Joe C.T. Leung (Scheme 3.8) was further studied by Dr. Leung, Julian G. West and myself for the synthesis of fluoromethyl aryl ethers. Section 3.3.3 will focus more specifically on my studies of the fluoromethyl ether synthesis. I then investigated the application of this reaction to the synthesis of difluoromethyl aryl ethers. The results obtained are described in section 3.3.5.

3.3.1 Procedure for the $^1$H and $^{19}$F NMR analysis of the crude reaction mixture

The crude reaction mixtures were analyzed using $^1$H and $^{19}$F NMR spectroscopy. The fluoroether protons ($\text{CH}_2\text{F}$ and $\text{CHF}_2$) of mono- and difluoromethyl aryl ethers produce distinctive signals that were used as handles for the determination of NMR yields using trimethoxybenzene (3.41, Figure 3.3) as an internal standard.

The methylene group of fluoromethylaryl ethers ($\text{CH}_2\text{F}$) appears as a doublet around 5.72 ppm with a coupling constant of $J = 54$ Hz (Figure 3.3) characteristic of the coupling with a geminal fluorine atom. Disappearance of the coupling when recording the proton spectra with fluorine decoupling ($^1\text{H}^{(19}\text{F})$ spectrum, Figure 3.3) helped identifying the methylene signal. The ether protons of difluoromethyl aryl ethers ($\text{CHF}_2$) appear as a triplet around 6.50 ppm, with a coupling constant of $J = 54$ Hz (Figure 3.4).
Figure 3.3 Representative examples of $^1$H and $^1$H-$^{19}$F spectra for the fluorodecarboxylation of phenoxyacetic acid derivatives
3.3.2 Contribution of Dr. Joe C.T. Leung and Julian G. West

Dr. Joe C.T. Leung found that the fluorodecarboxylation of phenoxyacetic acid yielded fluoride 3.15b in 84% NMR yield (Scheme 3.14). The isolation of 3.15b, however, proved to be challenging due to its high volatility. Substrates bearing electron-withdrawing substituents (3.15a, 3.15c and 3.15d, Scheme 3.14) were obtained respectively in 60%, 86% and 78% yield. The added molecular weight allowed achieving higher isolated yields. Secondary fluoride 3.15e could be formed via fluorodecarboxylation in 38% NMR yield (Scheme 3.14). The lower yield obtained for 3.15e can be explained by the possible degradation of the product via HF elimination under the reaction condition as attempts to isolate it only yielded the resulting vinyl enol ether (Scheme 3.15).
Julian G. West investigated the fluorination of alkyl-substituted substrates. Because of the presence of more hydrophobic substituents, acetonitrile was added as a co-solvent to improve the solubility of the carboxylic acids. The t-butyl substituted fluoroether (3.15f) was obtained in 83% isolated yields (Scheme 3.14). The reaction was also applicable to the synthesis of the t-butyl substituted difluoromethyl aryl ether 3.33a which was isolated in 78% yield. Substrate 3.15g, bearing benzylic protons, was only detected in 34% yield by NMR (Scheme 3.14).
3.3.3 Synthesis of monofluoromethyl aryl ethers

My studies on the synthesis of fluoromethyl aryl ethers initially focused on the influence of the electron-density on the fluorodecarboxylation reaction. NMR yields were measured as previously described (3.3.1). The clean crude reaction mixture and the non-polarity of the monofluoromethyl aryl ethers 3.15 allowed the use of a simple silica plug for the purification step. The volatility of some of the fluoromethyl aryl ethers, however, can be problematic for their isolation. The solvent was, therefore, evaporated under reduced pressure using a cold (0-5 °C) water bath.

Substrate 3.14h bearing an electron-withdrawing group at the para- position underwent smooth fluorodecarboxylation affording product 3.15h in 60% yield (Scheme 3.16). The position (para- or meta-) of the electron-poor substituent had not effect on the yield of the reaction as compound 3.15i was obtained in 57% isolated yield (3.15h and 3.15i, Scheme 3.16). The presence of two electron-withdrawing groups on the aryl ring, including one in the ortho- position did not impact the reaction yield and compound 3.15c was obtained in 68% yield (Scheme 3.16). Synthesis of product 3.15c was further optimized by Dr. Joe C.T. Leung (Scheme 3.14).

No fluoromethyl aryl ethers were detected when more electron-rich substrates were subjected to the fluorination conditions (3.15j and 3.15k, Scheme 3.16), regardless of the position of the electron-donating group. Selectfluor® is known to fluorinate electron-rich rings34b and the substrates most likely reacted via other pathways as unidentified fluorinated side products were detected in the crude reaction mixture. Adding an electron-withdrawing substituent to the ring to counterbalance the electron-donating effect of the methoxy group allowed the formation of product 3.15l in 58% yield NMR yield (Scheme 3.16). Switching the methoxy group for an electron-withdrawing ester group allowed some fluorination product to be formed in 18% yield (3.15m, Scheme 3.16). Replacing the electron-donating methyl ether by an electron-withdrawing mesyloxy group allowed the smooth fluorodecarboxylation of the phenoxyacetic acid derivative and afforded fluoride 3.15d in 91% NMR yield. Isolation of product 3.15d was later optimized by Dr. Joe C.T. Leung (Scheme 3.14).

Other substrates were then investigated to assess the full scope of the reaction. As previously observed by Julian. G. West, substrates containing weak C—H bonds where not compatible with the reaction conditions (3.15n, 3.15o and 3.15p, Scheme 3.16). Those compounds in their
excited state most likely undergo oxidation of weak C—H bonds by Selectfluor®. A derivative of the naturally occurring capsaicin, the active component of peppers, was also submitted to the fluorination conditions. No desired product (3.15q) was, however, detected. The electron-rich character of the ring as well as the presence of another reactive function (alkene) likely led to consumption of the starting material via side reactions.

Scheme 3.16 Synthesis of fluoromethyl aryl ethers

### 3.3.4 Fluorodecarboxylation of 2-aryl carboxylic acids

In addition to the 2-aryloxy carboxylic acids, 2-aryl carboxylic acids could be efficiently fluorinated under the reaction conditions (Scheme 3.17). Dr. Joe C.T. Leung submitted phenyl
acetic acid 3.44 to the general fluorodecarboxylation conditions and isolated benzyl fluoride 3.45 in 72% yield (Scheme 3.17).

I personally focused on the 2-acetoxyphenylacetic acid 3.46. Potassium carbonate was used as base instead of NaOH to prevent the hydrolysis of the acetyl group. Using those conditions, the fluoride 3.47 was obtained in 68% isolated yield (Scheme 3.17). Product 3.47 tends to decompose rapidly at room temperature. A fast purification was necessary to obtain high yields of the product, which was later kept at low temperature under inert atmosphere to prevent hydrolysis.

![Scheme 3.17 Fluorodecarboxylation of 2-aryl carboxylic acids](image)

### 3.3.5 Synthesis of difluoromethyl aryl ethers

We hypothesized that this process might be used for the synthesis of difluoromethyl aryl ethers. I therefore decided to explore the scope of fluorophenoxyacetic acid derivatives amenable to the reaction conditions (Scheme 3.18). Analysis of the crude reaction mixture was performed using $^1$H and $^{19}$F NMR as previously described (3.3.1). Similarly to the fluoromethyl aryl ethers 3.15, difluoromethyl aryl ethers can be purified by flushing through a silica plug. Careful evaporation of the solvent using a cold (0-5 °C) water bath was necessary to prevent evaporation of the desired products.
The unsubstituted difluoromethoxybenzene \(3.33b\) was detected by \(^1\)H NMR in 59\% yield. Isolation of \(3.33b\), however, proved to be challenging due to its volatility and the compound was only obtained in 25\% yield. Substrates bearing electron-withdrawing substituents underwent fluorodecarboxylation in higher yields (\(3.33c\), \(3.33d\) and \(3.33e\), Scheme 3.18), consistent with what had been observed for fluoromethyl aryl ethers (Scheme 3.16). The volatility of compound \(3.33c\), bearing a fluorine substituent, led to a discrepancy between the isolated and the NMR yield (44\% vs. 79\%, Scheme 3.18). The added molecular weight of product \(3.33d\) allowed its isolation in 64\% yield, a yield comparable to the 66\% yield observed by NMR. Substitution at the meta- position led to a decrease in yield and product \(3.33e\) was isolated in 46\% yield. Electron-rich difluoromethyl aryl ether \(3.33f\) could not be accessed using our fluorodecarboxylation method. The reaction of Selectfluor\textsuperscript{®} with the electron-rich aryl rings\textsuperscript{34b} might have led to side reaction of the starting material and/or the product. Unidentified fluorinated side products were detected by \(^{19}\)F NMR in the crude reaction mixture. Substrate \(3.33g\), bearing an electron-withdrawing mesyloxy group, could be detected in 22\% yield.

![Scheme 3.18 Synthesis of difluoromethyl aryl ethers](image-url)
3.4 Mechanism

We propose the mechanism presented in Scheme 3.19 for the light-mediated fluorodecarboxylation of 2-aryloxyacetic acids. Initial absorption of the UV radiation by the carboxylate leads to an excited state 3.49. Joschek and Grossweiner had reported that UV radiation of phenoxyacetic acid induces an excitation of the ring corresponding to $\pi \rightarrow \pi^*$ transition.¹⁵⁶ This direct excitation is further supported by mechanistic experiments performed by Dr. Joe C.T. Leung.¹³⁰ In the absence of light, no fluorodecarboxylation was observed. Furthermore, switching the irradiation wavelength away from the maximum absorption of the substrates (300 nm) led to a decrease in yield.¹³⁰ Selectfluor®, water and acetonitrile do not to absorb at 300 nm.¹³⁰ Finally, with the exception of 2-arylacetic acids, substrates lacking the $\alpha$-aryloxy moiety did not undergo decarboxylation.¹³⁰

![Scheme 3.19 Mechanism of the fluorodecarboxylation of phenoxyacetic acids](image)

Oxidation of the carboxylate in its excited state by Selectfluor® to the radical 3.50 (Scheme 3.19) followed by rapid decarboxylation furnishes intermediate 3.51 (Scheme 3.19). The ability of phenoxyacetic acid to eject an electron under UV-light excitation, leading to decarboxylation had previously been reported.¹⁵⁶ Finally, fluorine transfer from Selectfluor® to the resulting intermediate (3.51a, 3.51b, 3.51c, Scheme 3.19) furnishes the fluoromethyl aryl ether.
A similar mechanism can be proposed for the 2-arylacetic acids (Scheme 3.20). Joschek and Grossweiner reported that exposure of phenylacetic acid to UV-light leads to the excitation of the π-system of the aromatic ring. An electron is then emitted by the excited state.\textsuperscript{156} Gilbert et al. proposed that an internal electron transfer from the carboxylate moiety to the phenyl ring then occurs, affording the oxygen-centered radical 3.54.\textsuperscript{157} Radical decarboxylation followed by fluorine transfer finally affords products 3.45 or 3.47.

![Scheme 3.20 Mechanism of the fluorodecarboxylation of 2-arylacetic acids](image)

**Scheme 3.20 Mechanism of the fluorodecarboxylation of 2-arylacetic acids**

### 3.5 Discussion and recent developments.

The photofluorodecarboxylation of phenoxyacetic acid derivatives offers an interesting alternative to the existing methods for the synthesis of fluoromethyl aryl ethers. The desired compounds can be obtained in generally high yield using mild reaction conditions. The fluorodecarboxylation reaction is, however, less atom economical that methods allowing the direct conversion of phenols (Scheme 3.9). Indeed, the reaction requires the installation of the carboxylic acid moiety prior to the fluorodecarboxylation. The photofluorodecarboxylation reaction offers, nevertheless, several advantages compared to the direct fluoromethylation of phenols. The applicability of the reaction was demonstrated on a broader substrate scope. Bromine and chlorine substituents, for instance, were not tolerated using reagents 3.26 and 3.27 (Scheme 3.9). The fluorinating agent used in the photofluorodecarboxylation reaction, Selectfluor\textsuperscript{®}, is commercially available and easy to handle, contrarily to reagents 3.26 and 3.27 synthesized in 3 and 5 steps respectively, and CH\textsubscript{2}FCl which is a gas. The photofluorodecarboxylation of phenoxyacetic acid derivatives is also a less direct method than
the direct conversion of benzylic alcohols (Scheme 3.10), but allows the use of a less oxidizing and cheaper fluorine source. Finally, while the applicability of the photofluorodecarboxylation reaction for the synthesis of difluoromethyl aryl ethers was demonstrated, some methods for the difluoromethylation of phenols still allows access to a wider scope of products directly from the corresponding phenols.

The fluorodecarboxylation of phenoxyacetic acid derivatives proved to be sensitive to the electron density of the aryl ring: electron-rich substrates were not compatible with the reaction conditions as they undergo side reactions in presence of Selectfluor®. A similar scope limitation can be observed for most of the fluoromethyl aryl ether synthesis. Interestingly, however, the fluorodesulfurization reaction of O,S-acetals using XeF₂ (Scheme 3.11) allowed the synthesis of an electron-rich fluoromethyl aryl ether in excellent yield.¹⁴⁴a Electrophilic reagents most likely react with the electron-rich aryl ring leading to side products. This substrate scope limitation was later addressed by Dr. Joe C.T. Leung, who developed a photofluorodecarboxylation method using the milder³² NFSI (Scheme 3.21).⁹²b Under those newly developed conditions, more electron-rich substrates that previously underwent side reactions with Selectfluor® were amenable to the fluorodecarboxylation reaction.

![Scheme 3.14](image1)

**Scheme 3.14** Photodecarboxylation of phenoxyacetic acid derivatives

![Scheme 3.15](image2)

**Scheme 3.15** Photodecarboxylation of phenoxyacetic acid derivatives

![Scheme 3.16](image3)

**Scheme 3.16** Photodecarboxylation of phenoxyacetic acid derivatives

The photofluorodecarboxylation method described in this chapter and the photosensitized method later developed by Dr. Joe C.T. Leung both require the use of a UV-light source. The
specialized equipment needed for the UV-light irradiation can be a limitation to the use of those mono- and difluoromethyl aryl ether synthesis. A methodology was developed by Wolf, Sammis, Paquin et al. that allows the use of visible light irradiation (Scheme 3.22).\textsuperscript{93a} Using a ruthenium photocatalyst and Selectfluor®, various phenoxyacetic acid derivatives underwent efficient fluorodecarboxylation. While electron-rich substrates were also not compatible with the reaction conditions due to the presence of Selectfluor®, a broader range of fluoromethyl aryl ethers could be synthesized using this methodology than under direct UV-light irradiation. Most importantly, this report constitutes the first example of C(sp\textsuperscript{3})—F bond formation using photocatalysis. The authors used transient absorption spectroscopy to determine the mechanism of the reaction (Scheme 3.22). Those experiments revealed that Selectfluor® reacts with the excited state of the photocatalyst to produce a highly oxidizing ruthenium species. Oxidation of the carboxylate by ruthenium is followed by decarboxylation and fluorination of the resulting alkyl radical. The scope of carboxylic acids amenable to the photocatalyzed fluorodecarboxylation was later expanded by MacMillan et al.\textsuperscript{93b} By using a photocatalyst with a higher oxidation potential, the authors were able to fluorinated a wide range of aliphatic carboxylic acids in good to excellent yields. The reaction was applied to the synthesis of a fluoromethyl aryl ether, which was obtained in good yield.
More recently, a fluorodecarboxylation method that utilizes HF as the fluorine source was reported by Groves et al. (Scheme 3.23).\textsuperscript{104d} The use of a nucleophilic source of fluorine allowed notably to expand the scope of fluoromethyl aryl ethers to electron-rich substrates.
3.2 Conclusion

2-Aryloxy and 2-aryl carboxylic acids were shown to undergo fluorodecarboxylation when irradiated with UV-light in the presence of Selectfluor®. This methodology was used to access fluoromethyl aryl ethers. The electron-density of the ring influences the outcome of the reaction: electron-poor substrates undergo fluorodecarboxylation in good yields while electron-rich substrates decompose under the reaction conditions. Modifying the electron-density of the ring by the use of electron-withdrawing groups could help enabling the fluorodecarboxylation. Substrates bearing weak C—H bonds were not compatible with the reaction conditions. I was next able to apply this methodology to the synthesis of difluoromethyl aryl ethers, with similar scope limitations. The reaction most likely proceeds via direct excitation of the aryl ring by UV-light irradiation. Selectfluor® is proposed to act as oxidant and fluorine source.

3.3 Experimental section

Phenol, 4-fluorophenol, 4-bromophenol, 3-bromophenol, 1-{4-hydroxy-3-methoxyphenyl}ethane, 4-hydroxyphenyl methanesulfonate, 2-trimethylsilylethanol, 3-acetoxyphenol and products 3.14b, 3.14c and 3.46 were purchased from chemical suppliers and used as received.
All reactions were performed under nitrogen atmosphere in flame-dried glassware unless otherwise noted. N,N-Dimethylformamide (DMF) was dried over 4 Å molecular sieves, distilled under reduced pressure and stored over 4 Å molecular sieves under N₂. All other solvents were used without further purification. Photochemical reactions were performed in a Rayonet RPR-100 immersion photoreactor with 15 lamps (RPR-3000). A KD-Scientific KDS100 syringe pump was used for all slow additions.

Flash column chromatography was performed using Silicycle P60 silica: 230-400 mesh (40-63 μm) silica. Reactions were monitored using Merck Kieselgel 60F₂⁵⁴ aluminium or glass backed plates. TLC plates were visualized by UV fluorescence (254 nm) then one of the following stains: KMnO₄, p-anisaldehyde, vanillin.

Infrared (IR) spectra were obtained using a Thermo Nicolet 4700 FT-IR spectrometer. Proton and carbon nuclear magnetic resonance (¹H NMR and ¹³C NMR) spectra were recorded using a Bruker AV-300 or AV-400 spectrometer. Fluorine nuclear magnetic resonance (¹⁹F NMR) spectra were recorded using a Bruker AV-300. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual solvent peaks rounded to the nearest 0.01 for proton and 0.1 for carbon (ref: CHCl₃ [¹H: 7.26, ¹³C: 77.2], C₆H₆ [¹H: 7.16, ¹³C: 128.0], CH₃CN [¹H: 1.94, ¹³C: 118.7, 1.4]). Coupling constants (J) are reported in Hz to the nearest 0.1 Hz. Peaks multiplicity is indicated as follows s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). High resolution mass spectra (HRMS) were recorded on either a Waters or Micromass LCT spectrometer.

### 3.3.1 Synthesis of phenoxyacetic acid derivatives

![Chemical structure](image)

To a suspension of potassium carbonate (2.5 equiv.) in a 0.5 M solution of phenol derivative (1 equiv.) in DMF was added ethyl bromoacetate (1.2 equiv.) at room temperature using a syringe pump (0.6 mL/h). The reaction was then stirred for 2 h at r.t.. The reaction mixture was quenched with H₂O (the amount of DMF used) and extracted with Et₂O (3x half the amount of H₂O used). The organic layers were combined and washed with 15% w/w NaOH₃₅ (2x half the
amount of \( \text{H}_2\text{O} \) used) and with brine (1x half the amount of \( \text{H}_2\text{O} \) used). The organic extracts were dried over \( \text{Na}_2\text{SO}_4 \), filtered, and concentrated under reduced pressure. The crude ester was used without further purification.

To a 0.2 M solution of the crude ester in methanol was added 15% w/w \( \text{NaOH}(\text{aq.}) \) (1.5 equiv.) at r.t. The reaction mixture was stirred for 1 h, then poured into \( \text{Et}_2\text{O} \) (the amount of \( \text{NaOH}(\text{aq.}) \) used) and extracted with water (1x half the amount of \( \text{Et}_2\text{O} \) used) and with \( \text{NaOH}(\text{aq.}) \) (2x half the amount of \( \text{Et}_2\text{O} \) used). The combined aqueous layers were acidified to pH=2 with 10% w/w \( \text{HCl}(\text{aq.}) \) and extracted with \( \text{Et}_2\text{O} \) (3x with the amount of \( \text{HCl}(\text{aq.}) \) used). The combined organic layers were washed with brine, dried over \( \text{Na}_2\text{SO}_4 \), filtered, concentrated under reduced pressure, and then recrystallized to afford the aryloxyacetic acids.

**2-(4-acetyl-2-methoxyphenoxy)acetic acid (3.14l):**

![Chemical Structure of 2-(4-acetyl-2-methoxyphenoxy)acetic acid (3.14l)]

1-(4-hydroxy-3-methoxyphenyl)ethanone (800 mg, 4.80 mmol) was subjected to the general aryloxyacetic acids synthesis procedure. The crude ester was saponified, and product 3.14l was purified by recrystallization in hexanes/EtOAc to afford product 3.14l as a white solid (289 mg, 1.29 mmol, 27%). M.p.: 165-167 °C. \(^1\text{H NMR} (\text{CDCl}_3; 300 \text{ MHz}): \delta 7.58-7.54 (\text{m}, 2\text{H}), 6.89 (\text{d}, J = 8.2 \text{ Hz}, 1\text{H}), 4.78 (\text{s}, 2\text{H}), 3.96 (\text{s}, 3\text{H}), 2.58 (\text{s}, 3\text{H}).

**2-(4-((methylsulfonyl)oxy)phenoxy)acetic acid (3.14d):**

![Chemical Structure of 2-(4-((methylsulfonyl)oxy)phenoxy)acetic acid (3.14d)]

4-hydroxyphenyl methanesulfonate (1.34 g, 7.12 mmol) was subjected to the general aryloxyacetic acids synthesis procedure. The crude ester was purified by flash column chromatography (2:1 hexanes/EtOAc) prior to saponification. Recrystallization from hexanes/EtOAc yielded 2-(4-((methylsulfonyl)oxy)phenoxy)acetic acid (3.14d) as white crystals (432 mg, 1.75 mmol, 25% yield over 2 steps). M.p.: 148-151 °C. IR (neat): 3026, 1747, 1500, 1362, 1362, 1231, 1169 cm\(^{-1}\). \(^1\text{H NMR} (\text{CD}_3\text{CN}; 300 \text{ MHz}): \delta 7.23 (\text{d}, J = 9.0 \text{ Hz}, 2\text{H}), 6.97 (\text{d}, J = 9.0 \text{ Hz}, 2\text{H}), 4.68 (\text{s}, 2\text{H}), 3.16 (\text{s}, 3\text{H}). \(^{13}\text{C NMR} (\text{CD}_3\text{CN}; 100 \text{ MHz}): \delta 170.4, 157.8, 144.6,
124.4, 117.7, 65.9, 37.8. HRMS-ESI (m/z) [M+H]^+ calcd for C_{9}H_{18}O_{6}SNa: 269.0096. Found: 269.0097.

**(E)-2-(2-methoxy-5-((9-methyldec-6-enamido)methyl)phenoxy)acetic acid (3.14q):**

The ester was furnished by Dr. Montserrat Rueda-Becerril. 327 mg (0.835 mmol) of the ester were submitted to the saponification conditions and recrystallized from hexanes/EtOAc to afford the pure acid 3.14q as a white solid (190 mg, 0.522 mmol, 63% yield). ¹H NMR (CDCl₃; 300 MHz): δ 6.88-6.81 (m, 3H), 5.71 (s, 1H), 5.36-5.33 (m, 3H), 4.66 (s, 2H), 4.38 (d, J = 5.7 Hz, 2H), 3.88 (s, 3H), 2.22-2.20 (m, 2H), 2.00-1.97 (m, 1H), 1.68-1.63 (m, 2H), 1.41-1.15 (m, 4H), 0.95 (d, J = 6.7 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H).

### 3.3.2 Synthesis of 2-(3-acetoxyphenoxy)acetic acid (3.14m):

**Synthesis of 2-(trimethylsilyl)ethyl 2-bromoacetate (S4):**

2-Trimethylsilylethanol (2.85 mL, 19.9 mmol) and pyridine (1.72 mL, 21.4 mmol) were dissolved in 47 mL of CH₂Cl₂. The reaction was cooled to 0 °C. Bromoacetyl chloride (1.60 mL, 19.1 mmol) was added dropwise and the reaction was warmed to room temperature and stirred for 1 h. The crude reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography (20:1 hexanes/EtOAc) afforded product S4 as a colorless oil (3.27 mg, 13.8 mmol, 68% yield). The data obtained for compound
S4 matched literature characterization data.\textsuperscript{158} \textsuperscript{1}H NMR (CDCl\textsubscript{3}; 300 MHz): δ 4.29-4.26 (m, 2H), 3.81 (s, 2H), 1.06-1.01 (m, 2H), 0.05 (s, 9H).

**Synthesis of 2-(trimethylsilyl)ethyl 2-(3-acetoxyphenoxy)acetate (S5):**

![Chemical structure of S5]

Potassium carbonate (1.40 g, 10.1 mmol) was added to a solution of 3-acetoxyphenol (608 mg, 4.00 mmol) dissolved in 5 mL of DMF. S4 (1.91 g, 8.00 mmol) was dissolved in 3 mL of DMF and added dropwise to the reaction mixture. The reaction was stirred at r.t. for 16 h, quenched with 10 mL of H\textsubscript{2}O and extracted 3x with 10 mL of Et\textsubscript{2}O. The combined organic layers were washed 2x with 10 mL of 15% NaOH\textsubscript{(aq.)}, 2x with 10 mL of 10% HCl\textsubscript{(aq.)}, and 1x with 10 mL of brine, dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure. Purification by flash column chromatography (5:1 hexanes/Et\textsubscript{2}O) afforded product S5 as a colorless oil (657 mg, 2.11 mmol, 53% yield). \textsuperscript{1}H NMR (CDCl\textsubscript{3}; 300 MHz): δ 7.31-7.25 (m, 1H), 6.80-6.73 (m, 2H), 6.66 (t, J = 2.3 Hz, 1H), 4.58 (s, 2H), 4.33-4.27 (m, 2H), 2.29 (s, 2H), 1.05-1.00 (m, 2H), 0.05 (s, 9H).

**Synthesis of 2-(3-acetoxyphenoxy)acetic acid (3.14m):**

![Chemical structure of 3.14m]

To a solution of S5 (304 mg, 0.980 mmol) in THF (10 mL) was added TBAF (0.1 M in THF, 1.5 mL, 1.5 mmol). The reaction was stirred at r.t. for 3 h, then quenched with 20 mL of H\textsubscript{2}O, acidified to pH = 6 and washed 3x with 15 mL of Et\textsubscript{2}O. The combined organic washes were discarded. The aqueous layer was acidified to pH = 2 and extracted 3x with 15 mL of Et\textsubscript{2}O. The combined organic layers were washed with brine, dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (95:5 CH\textsubscript{2}Cl\textsubscript{2}/MeOH) to afford product 3.14m as a colorless oil (61 mg, 0.29 mmol, 29% yield). \textsuperscript{1}H NMR (CDCl\textsubscript{3}; 300 MHz): δ 7.31 (t, J = 8.2 Hz, 1H), 6.82-6.76 (m, 2H), 6.70-6.69 (m, 1H), 4.67 (s, 2H), 2.30 (s, 3H).
3.3.3 Synthesis of monofluoromethyl aryl ethers

To a 0.1 M solution of aryloxyacetic acid (1.0 equiv.) in water (argon sparged) or a 2:1 water/acetonitrile mixture (argon sparged) was added a 5.0 M NaOH(aq) solution (1.5 equiv.). The reaction mixture was stirred until all of the acid was dissolved. Selectfluor® (3.5 equiv.) was added and the reaction mixture was stirred until all solids were dissolved. The reaction vessel was placed in the photoreactor and exposed to 300 nm light for 1 h. The reaction mixture was diluted with water (half the amount of H₂O/CH₃CN used) and extracted with Et₂O (3x half the amount of H₂O/CH₃CN used). The combined organic layers were washed with a 10% NaOH(aq) solution (2x half the amount of H₂O/CH₃CN used), dried over Na₂SO₄, filtered and partially concentrated under reduced pressure in a cold (0-5 °C) water bath. The solution of fluorinated product was washed through a short plug of silica with chloroform and the solvent was removed under reduced pressure in a cold (10 °C) water bath to afford the fluorinated product.

1-bromo-4-(fluoromethoxy)benzene (3.15h):

Chemical Formula: C₇H₆BrFO
Molecular Weight: 205.02

IR (neat): 2926, 2359, 1701, 1605, 1502, 1452, 1380, 1212, 1143, 1039, 964, 770, 693 cm⁻¹.

1H NMR (CDCl₃; 300 MHz): δ 7.46-7.41 (m, 2H), 6.99-6.95 (m, 2H), 5.68 (d, J = 54.4 Hz, 2H). 13C NMR (CDCl₃; 100 MHz): δ 155.8, 132.8, 118.6, 116.3, 100.8 (d, J = 219.7 Hz). As the literature characterization data did not include 19F NMR, the information is provided: 19F{¹H} NMR (CDCl₃; 282 MHz): δ -149.6.

1-bromo-3-(fluoromethoxy)benzene (3.15i):

Chemical Formula: C₇H₆BrFO
Molecular Weight: 205.02

IR (neat): 2926, 2359, 1701, 1605, 1502, 1452, 1380, 1212, 1143, 1039, 964, 770, 693 cm⁻¹.

1H NMR (CDCl₃; 300 MHz): δ 7.47-7.44 (m, 2H), 6.99-6.96 (m, 2H), 5.68 (d, J = 54.4 Hz, 2H). 13C NMR (CDCl₃; 100 MHz): δ 155.8, 132.8, 118.4, 116.3, 100.8 (d, J = 219.7 Hz). As the literature characterization data did not include 19F NMR, the information is provided: 19F{¹H} NMR (CDCl₃; 282 MHz): δ -149.6.
must be handled with care under anhydrous conditions to prevent decomposition.

\[ 1594, 1474, 1220 \text{ cm}^{-1}. \]

\[ ^1H \text{ NMR (CDCl}_3; 300 \text{ MHz}): \delta 7.28-7.18 \text{ (m, 3H), 7.04-7.02 \text{ (m, 1H), 5.70 (d, } J = 54.2 \text{ Hz, 1H).} \]

\[ ^13C \text{ NMR (CDCl}_3; 100 \text{ MHz): } \delta 157.5, 130.8, 126.7, 122.8, 120.1, 115.4, 100.6 \text{ (d, } J = 220.0 \text{ Hz).} \]

\[ ^19F\{^1H \text{ NMR (CDCl}_3; 282 \text{ MHz): } \delta -149.7. \]

HRMS-El (m/z) \([M]^+\) calcd for C\(_7\)H\(_5\)BrFO: 205.95656. Found: 205.95658.

\[ \text{2,4-dichloro-1-(fluoromethoxy)benzene (3.15c)}: \]

\[ \begin{align*}
\text{Chemical Formula: C}_7\text{H}_5\text{Cl}_2\text{FO} \\
\text{Molecular Weight: 195.02}
\end{align*} \]

2-(2,4-dichlorophenoxy)acetic acid \[ 3.14c \] (110 mg, 0.498 mmol) was subjected to the general photofluorodecarboxylation conditions in water/acetonitrile. 2,4-dichloro-1-(fluoromethoxy)benzene \[ 3.15c \] was obtained as a pale orange solid (66 mg, 0.34 mmol, 68% yield). M.p.: 46.5-47.5 °C. IR (neat): 3105, 3083, 2952, 1476, 1390, 1296, 1234 cm\(^{-1}. \)

\[ ^1H \text{ NMR (CDCl}_3; 300 \text{ MHz): } \delta 7.43 \text{ (d, } J = 2.4 \text{ Hz, 1H), 7.24 \text{ (dd, } J = 8.8, 2.4 \text{ Hz, 1H), 7.15 \text{ (dd, } J = 8.8, 0.7 \text{ Hz, 1H), 5.72 \text{ (d, } J = 53.9 \text{ Hz, 2H).} \]

\[ ^13C \text{ NMR (CDCl}_3; 75 \text{ MHz): } \delta 151.2 \text{ (d, } J = 3.0 \text{ Hz), 130.3, 129.2, 128.0, 125.1 \text{ (d, } J = 2.2 \text{ Hz), 118.4 \text{ (d, } J = 1.7 \text{ Hz), 101.1 \text{ (d, } J = 222.0 \text{ Hz).} \]

\[ ^19F \text{ NMR (CDCl}_3; 282 \text{ MHz): } \delta -149.9 \text{ (d, } J = 54.2 \text{ Hz).} \]

HRMS-El (m/z) \([M]^+\) calcd for C\(_7\)H\(_5\)OCl\(_2\)F\(_1\): 193.97015. Found: 193.97045.

\[ \text{3.3.4 Synthesis of fluoro(phenyl)methyl acetate (3.47)} \]

Acetyl mandelic acid \[ 3.46 \] (108 mg, 0.559 mmol) was subjected to the general photofluorodecarboxylation conditions in water/acetonitrile for 2.5 h. Fluoro(phenyl)methyl acetate \[ 3.47 \] was obtained as a colorless oil (64.3 mg, 0.382 mmol, 68% yield). IR (neat): 3034, 1775, 1367, 1211 cm\(^{-1}. \)

\[ ^1H \text{ NMR (CDCl}_3; 300 \text{ MHz): } \delta 7.31 \text{ (m, 2H), 7.28 \text{ (d, } J = 55.1 \text{ Hz, 1H), 7.06-7.04 \text{ (m, 3H), 1.54 \text{ (s, 3H).} \]

\[ ^13C \text{ NMR (CDCl}_3; 101 \text{ MHz): } \delta 169.1, 134.5, 130.3, 128.7, 126.2 \text{ (d, } J = 5.7 \text{ Hz), 101.6 \text{ (d, } J = 220.7 \text{ Hz), 20.9.} \]

\[ ^19F \text{ NMR (CDCl}_3; 282 \text{ MHz): } \delta -122.7 \text{ (d, } J = 55.1 \text{ Hz).} \]

HRMS-El (m/z) \([M]^+\) calcd for C\(_8\)H\(_9\)FO\(_2\): 168.05866. Found: 168.05875. Product \[ 3.47 \] must be handled with care under anhydrous conditions to prevent decomposition.
3.3.5 Synthesis of 2-fluoro aryloxyacetic acids

Potassium carbonate was suspended in a 0.5 M solution of phenol derivative (1 equiv.) in DMF. Ethyl bromofluoroacetate (2.5 equiv.) was added at a rate of 0.6 mL/h at r.t. and the reaction was allowed to stir for an additional 3 h. The reaction mixture was quenched with H₂O (the amount of DMF used) and extracted with Et₂O (3x half the amount of H₂O used). The combined organic layers were washed with 15% w/w NaOH (aq.) (2x half the amount of H₂O used) and with brine (half the amount of H₂O used), dried over Na₂SO₄ and concentrated under reduced pressure. The crude ester was purified by flash column chromatography prior to saponification.

To a 0.2 M solution of the ester in methanol was added 15% w/w NaOH (aq.) (1.5 equiv.). The reaction was stirred at r.t. for 2 h, diluted with H₂O (half the amount of NaOH (aq.) used), and washed with Et₂O (3x with the amount of H₂O used). The aqueous layer was acidified to pH = 7 with 10% w/w HCl (aq.), washed with Et₂O (3x with the amount of H₂O used), acidified to pH = 6, washed with Et₂O (3x with the amount of H₂O used), acidified to pH < 2 and extracted with Et₂O (3x with the amount of H₂O used). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. Recrystallization afforded the pure fluoroaryloxyacetic acids.

2-fluoro-2-phenoxyacetic acid (3.42b):

Phenol (388 mg, 4.13mmol) was subjected to the general 2-fluoroaryloxyacetic acid synthesis procedure. The crude ester was purified by flash column chromatography (20:1 hexanes/EtOAc) prior to saponification. Recrystallization from hexanes yielded 2-fluoro-2-phenoxyacetic acid (3.42b) as white crystals (156 mg, 0.917 mmol, 22% yield over 2 steps). M.p.: 61-63 °C. IR (neat): 3400, 1643, 1492, 1214 cm⁻¹. ¹H NMR (CDCl₃; 300 MHz): δ 7.40-7.34 (m, 2H), 7.20-7.13 (m, 3H), 6.03 (d, J = 59.5 Hz, 1H). ¹³C NMR (CDCl₃; 100 MHz): δ 167.7, 155.8, 130.1, 124.9, 117.6, 102.4 (d, J = 231.7 Hz). ¹⁹F{¹H} NMR (CDCl₃; 282 MHz): δ -129.9. HRMS-ESI (m/z) [M-H]⁻ calcd for C₈H₆FO₃: 169.0301. Found: 169.0297.
2-fluoro-2-(4-fluorophenoxy)acetic acid (3.42c):

4-Fluorophenol (413 mg, 3.68 mmol) was subjected to the general 2-fluoroaryloxyacetic acid synthesis procedure. The crude ester was purified by flash column chromatography (10:1 hexanes/EtOAc) prior to saponification. Recrystallization from hexanes/EtOAc yielded 2-fluoro-2-(4-fluorophenoxy)acetic acid (3.42c) as white flakes (135 mg, 0.717 mmol, 20% yield over 2 steps) m.p.: 47-49 °C. IR (neat) 3434, 1705, 1513, 1273 cm⁻¹. ¹H NMR (CDCl₃; 300 MHz): δ 7.13-7.04 (m, 4H), 5.93 (d, J = 59.5 Hz, 1H). ¹³C NMR (CDCl₃; 100 MHz): δ 167.0, 159.8 (d, J = 244.4 Hz), 151.8, 119.5 (d, J = 8.5 Hz), 116.6 (d, J = 23.5 Hz), 102.9 (d, J = 233.3 Hz). ¹⁹F{¹H} NMR (CDCl₃; 282 MHz): δ -118.6, -130.0. HRMS ESI (m/z) [M-H]⁻ calcd for C₈H₅F₂O₃: 187.0207. Found: 187.0203.

2-(4-bromophenoxy)-2-fluoroacetic acid (3.42d):

4-Bromophenol (865 mg, 5.00 mmol) was subjected to the general 2-fluoroaryloxyacetic acid synthesis procedure. The crude ester was used without further purification. Recrystallization from hexanes/EtOAc yielded 2-(4-bromophenoxy)-2-fluoroacetic acid (3.42d) as a white solid (603 mg, 2.42 mmol, 48% yield over 2 steps). m.p.: 64-67 °C. IR (neat) 3534, 1983, 1704, 1587, 1470, 1437, 1271 cm⁻¹. ¹H NMR (CDCl₃; 300 MHz): δ 7.49-7.46 (m, 2H), 7.04-7.02 (m, 2H), 5.97 (d, J = 59.2 Hz, 1H). ¹³C NMR (CDCl₃; 75 MHz): δ 166.9 (d, J = 31.3 Hz), 154.8, 133.0, 119.5, 117.7, 102.2 (d, J = 233.0 Hz). ¹⁹F{¹H} NMR (CDCl₃; 282 MHz): δ -130.6. HRMS ESI (m/z) [M-H]⁻ calcd for C₈H₅BrFO₃: 249.94639. Found: 249.94639.

2-(3-bromophenoxy)-2-fluoroacetic acid (3.42e):

3-Bromophenol (519 mg, 3.00 mmol) was subjected to the general 2-fluoroaryloxyacetic acid synthesis procedure. The crude ester was used without further purification. Recrystallization
from hexanes yielded 2-(3-bromophenoxy)-2-fluoroacetic acid (3.42e) as a white solid (520 mg, 2.10 mmol, 70% yield over 2 steps). m.p.: 62-66 °C. IR (neat): 3447, 2360, 1710, 1583, 1271 cm⁻¹. ¹H NMR (CDCl₃; 300 MHz): δ 7.34-7.21 (m, 3H), 7.11-7.08 (m, 1H), 6.00 (d, J = 59.0 Hz, 1H). ¹³C NMR (CDCl₃; 100 MHz): δ 168.2, 156.2, 131.2, 128.1, 123.1, 121.2, 116.3, 102.0 (d, J = 233.3 Hz). ¹⁹F NMR (CDCl₃; 282 MHz): δ -130.50 (d, J = 59.2 Hz). HRMS-ESI (m/z) [M-H]· calcd for C₆H₅BrFO₃: 246.9406. Found: 246.9406.

3.3.6 Synthesis of monofluoromethyl aryl ethers

To a 0.1 M solution of 2-fluoro-2-aryloxyacetic acid (1.0 equiv.) in water (argon sparged) or a 2:1 water/acetonitrile mixture (argon sparged) was added a 5.0 M NaOHₙaq solution (1.5 equiv.). The reaction mixture was stirred until all of the acid was dissolved. Selectfluor® (3.5 equiv.) was added under N₂ and the reaction mixture was stirred until all solids were dissolved. The reaction vessel was placed in the photoreactor and exposed to 300 nm light for 2.5 h. The reaction mixture was diluted with water (half the amount of H₂O/CH₃CN used) and extracted with Et₂O (3x half the amount of H₂O/CH₃CN used). The combined organic layers were washed with a 10% NaOHₙaq solution (2x half the amount of H₂O/CH₃CN used) and with brine (1x half the amount of H₂O/CH₃CN used), dried over Na₂SO₄, filtered and partially concentrated under reduced pressure in a cold (0-5 °C) water bath. The solution of fluorinated product was purified using a short plug of silica with chloroform and the solvent was removed under reduced pressure in a cold (0-5 °C) to afford the fluorinated product.

(Difluoromethoxy)benzene (3.33b):

![Difluoromethoxy)benzene (3.33b)]

2-fluoro-2-phenoxyacetic acid (3.42b) (93 mg, 0.54 mmol) was subjected to the general photofluorodecarboxylation conditions in water. Difluoromethoxybenzene (3.33b) was obtained as a slightly yellow oil (20 mg, 0.14 mmol, 25% yield). The data obtained for compound 3.33b matched the literature characterization data.¹⁴³b ¹H NMR (CDCl₃; 300 MHz): δ 7.42-7.10 (m, 5H), 6.50 (t, J = 72.0 Hz, 1H). ¹⁹F{¹H} NMR (CDCl₃; 282 MHz): δ -81.1.
1-(difluoromethoxy)-4-fluorobenzene (3.33c):

2-fluoro-2-(4-fluorophenoxy)acetic acid (3.42c) (95 mg, 0.51 mmol) was subjected to the general photofluorodecarboxylation conditions in water. 1-(difluoromethoxy)-4-fluorobenzene (3.33c) was obtained as a slightly yellow oil (36 mg, 0.22 mmol, 44% yield). The data obtained for compound 3.33c matched the literature characterization data.\(^{143b}\) ¹H NMR (CDCl\(_3\); 300 MHz): δ 7.13-7.02 (m, 4H), 6.46 (t, \(J = 73.7\) Hz, 1H). \(^{19}\)F{¹H} NMR (CDCl\(_3\); 282 MHz): δ -81.4, -117.5.

1-bromo-4-(difluoromethoxy)benzene (3.33d):

2-(4-bromophenoxy)-2-fluoroacetic acid (3.42d) (130 mg, 0.520 mmol) was subjected to the general photofluorodecarboxylation conditions in water. 1-bromo-4-(difluoromethoxy)benzene (3.33d) was obtained as a slightly yellow oil (75 mg, 0.34 mmol, 64% yield). The data obtained for compound 3.33d matched the literature characterization data.\(^{143b}\) ¹H NMR (CDCl\(_3\); 300 MHz): δ 7.48 (d, \(J = 8.8\) Hz, 2H), 7.02 (d, \(J = 8.8\) Hz, 2H), 6.48 (t, \(J = 73.4\) Hz, 1H). \(^{13}\)C NMR (CDCl\(_3\); 100 MHz): δ 150.2, 133.0, 121.7, 118.6, 115.7 (t, \(J = 259.0\) Hz). \(^{19}\)F{¹H} NMR (CDCl\(_3\); 282 MHz): δ -81.6.

1-bromo-3-(difluoromethoxy)benzene (3.33e):

2-(3-bromophenoxy)-2-fluoroacetic acid (3.42e) (126 mg, 0.507 mmol) was subjected to the general photofluorodecarboxylation conditions in water. 1-bromo-3-(difluoromethoxy)benzene (3.33e) was obtained as a slightly yellow oil (53 mg, 0.24 mmol, 46% yield). IR (neat): 2923, 2360, 1590, 1473, 1125 cm\(^{-1}\). ¹H NMR (CDCl\(_3\); 300 MHz): δ 7.35-7.21 (m, 3H), 7.09-7.06 (m, 1H), 6.50 (t, \(J = 73.3\) Hz, 1H). \(^{13}\)C NMR (CDCl\(_3\); 100 MHz): δ 151.7, 131.0, 128.8, 123.2, 123.0, 118.5,
115.7 (t, J = 260 Hz). $^{19}$F{¹H} NMR (CDCl₃; 282 MHz): δ -81.6. HRMS-EI (m/z) [M]+ calcd for C$_7$H$_5$F$_2$BrO: 223.94714. Found: 223.94696.
Chapter 4

Synthesis of trifluoromethyl aryl ethers by fluorodecarboxylation

Trifluoromethyl aryl ethers are an increasingly popular motif among pharmaceuticals, agrochemicals and materials. Despite the recent advances in the synthesis of fluorinated compounds, trifluoromethyl aryl ethers remain challenging to synthesize and only a few methods are available to access them. As part of our work on radical fluorination methods, we sought to develop a new approach to trifluoromethoxy arenes using radical intermediates. In Chapter 3 of this thesis, a method for the synthesis of mono- and difluoromethyl aryl ethers by light-mediated photofluorodecarboxylation of phenoxyacetic acid derivatives was described. The development of a similar procedure for the synthesis of trifluoromethyl aryl ethers by fluorodecarboxylation of difluorophenoxyacetic acid derivatives is detailed in this chapter.

The relevance of trifluoromethyl aryl ethers in pharmaceutical, agrochemical and material chemistry, as well as the currently available methods for their synthesis will first be presented. The synthesis of trifluoromethyl aryl ethers by light-mediated fluorodecarboxylation of difluorophenoxyacetic acid derivatives will then be described. The scope and challenges associated with this reaction will be discussed. An alternative fluorodecarboxylation method using XeF₂ that doesn’t require light promotion will then be presented.

4.1 Relevance of trifluoromethyl aryl ethers

The trifluoromethoxy (OCF₃) group has been described as a “pseudo-halogen” or a “super-halogen” Similarly to halogens, the trifluoromethoxy group is electron-withdrawing by induction and electron-donating by resonance. It is, however, a better donor by resonance than most halogens and exerts a stronger inductive effect (Table 4.1). Due to its high hydrophobicity, the trifluoromethoxy group can be used to replace halogens and increase the lipophilicity of a molecule.
Contrarily to anisole that adopts a planar conformation, trifluoromethoxybenzene prefers an out-of-plane conformation with a C—O—CF₃ angle of 90° (Figure 4.1). Evidence of this conformation was provided by NMR studies and X-ray spectroscopy. The planar conformation of anisole is required for the efficient delocalization of the oxygen’s lone pairs into the aromatic ring (n→π*). Dipole moment analysis and molecular photoelectron spectroscopy revealed, however, that very little delocalization occurs in trifluoromethoxybenzene. This limited delocalization is claimed to result from the low electron density in the trifluoromethoxybenzene oxygen’s non-bonding orbitals, due to electronegativity of the CF₃ group and the delocalization by hyperconjugation in the σ*C–F. This poor delocalization of the oxygen’s lone pair in the aryl ring allows a free rotation of the OCF₃ group. The orthogonal orientation is favored over the planar orientation by 0.5 kcal/mol (barrier of rotation = 0.2 kcal/mol), due to stereoelectronic effects and minimized steric interactions. This orthogonal orientation contributes to the increase in lipophilicity observed for trifluoromethyl aryl ethers, because of the partial shielding of the π face of the ring. This out-of-plane conformation is valuable in medicinal chemistry as it can also induce valuable spatial interactions with receptors.

Table 4.1 Inductive and resonance substituent constants for halogens and OCF₃

<table>
<thead>
<tr>
<th>Halogen</th>
<th>Inductive substituent constant</th>
<th>Resonance substituent constant</th>
</tr>
</thead>
<tbody>
<tr>
<td>OCF₃</td>
<td>0.51 – 0.53</td>
<td>−0.13 – −0.18</td>
</tr>
<tr>
<td>F</td>
<td>0.45 – 0.52</td>
<td>−0.35 – −0.40</td>
</tr>
<tr>
<td>Cl</td>
<td>0.42 – 0.47</td>
<td>−0.20</td>
</tr>
<tr>
<td>Br</td>
<td>0.45</td>
<td>−0.19</td>
</tr>
<tr>
<td>I</td>
<td>0.39</td>
<td>−0.12</td>
</tr>
</tbody>
</table>

Figure 4.1 Conformation of anisole and trifluoromethoxybenzene
Due to the influence of the trifluoromethoxy moiety on the conformation of a molecule, as well as the effect of fluorine on its physicochemical properties (see Chapter 1), new pharmaceuticals and agrochemicals are emerging that contain trifluoromethyl aryl ethers (Figure 4.2).\textsuperscript{133a,134a,171,172,173} Riluzole (4.1, Figure 4.2) is to date the only approved drug for the treatment of amyotrophic lateral sclerosis. Jimonet et al. synthesized Riluzole and two series of its analogs (benzothiazolamines derivatives) and their structure-activity studies showed that the highest “antiglutamate” activity was recorded for Riluzole and analogs bearing a fluorinated group at the 6-position.\textsuperscript{174} The trifluoromethoxy group has also been used as methoxy group analog to improve the metabolic stability of NK-1 receptor antagonist CP-122,721 (4.3, Figure 4.2, not commercialized).\textsuperscript{175} In agrochemicals, the trifluoromethoxy group is typically introduced because its high lipophilicity allows a better permeability of the compound in a plant’s membrane.\textsuperscript{134a}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{commercial_trifluoromethoxy_compounds.png}
\caption{Commercial trifluoromethoxy containing agrochemical and pharmaceutical compounds}
\end{figure}
Trifluoromethoxy-containing compounds have proven to be valuable components of liquid crystal displays (LCD).\textsuperscript{11a,176} Trifluoromethyl aryl ethers usually exhibit interesting properties such as a low viscosity, a high stability, and a favorable mesophase (liquid crystal) behavior.\textsuperscript{177,178} Materials containing terminal trifluoromethoxybenzenes also have a higher clearing temperature (temperature at which the liquid crystal becomes an isotropic liquid and, therefore, lose its desired anisotropic properties). Increasing the clearing temperature allows notably the use of a higher processing temperature range during the fabrication of the device.\textsuperscript{179} The dipole moment induced by the trifluoromethoxy group can also impact the dielectric anisotropy ($\Delta\varepsilon$) of the liquid crystals.\textsuperscript{178,179} This results in a better response to the electric current applied to the material.

### 4.2 Current methods for the synthesis of trifluoromethyl aryl ethers

#### 4.2.1 Halogen/fluorine exchange

Trifluoromethyl aryl ethers were first synthesized by Yagupol’skii from anisole derivatives via the formation of trichloromethyl aryl ethers (4.10, Scheme 4.1).\textsuperscript{180} The displacement of chlorine by fluorine can be achieved through the use of HF or antimony trifluoride,\textsuperscript{180,181} and is currently used on an industrial scale for the synthesis of trifluoromethoxylated building blocks.\textsuperscript{164} The addition of Lewis acids such as SbCl$_5$, MoCl$_5$, TaCl$_5$ and NbCl$_5$ have been shown to catalyze the reaction with HF.\textsuperscript{182} Alternative methods for the synthesis of the trichloromethoxybenzene derivatives were later developed. Anisole derivatives can be chlorinated by irradiation in CCl$_4$ in presence of Cl$_2$, but this reaction can only be applied to electron-poor substrates.\textsuperscript{183} Trichloromethyl aryl ethers have also been synthesized from the corresponding phenols via thionochloroformates (4.12, Scheme 4.2, a)).\textsuperscript{181a} Mathey and Bensoam later reported that the thionochloroformates could be directly converted to the trifluoromethyl aryl ethers by treatment with MoF$_6$ (b), Scheme 4.2).\textsuperscript{184} Application of this methodology has been limited due to the high toxicity of thionochloroformates.\textsuperscript{134a}
A simplified procedure was reported by Feiring in 1979, in which phenol derivatives could be directly converted to the trifluoromethyl aryl ethers when reacted with CCl₄ and HF (Scheme 4.3). Preliminary mechanistic studies suggest that the trichloromethoxy derivatives are formed in-situ, followed by halogen exchange. Only electron-poor substrates could undergo efficient trifluoromethoxylation. "ortho"-Substituents capable of hydrogen bonding were not compatible with the reaction conditions.

Scheme 4.3 Feiring’s synthesis of trifluoromethoxybenzene derivatives
In 2015, Gouverneur et al. reported the synthesis of $^{18}$F-labelled trifluoromethyl aryl ethers by bromine/fluorine exchange (Scheme 4.4).\textsuperscript{186} Superstoichiometric amounts of Ag$^+$ salt are necessary for the reaction to proceed. Only radiochemical yields (RCY) were reported and no comments were made on the applicability of this method for the synthesis non-radiolabelled of trifluoromethyl aryl ethers.

4.2.2 Deoxygenation/desulfurization

Trifluoromethoxybenzene derivatives can be synthesized by deoxofluorination of fluoroformates (4.16, Scheme 4.5).\textsuperscript{163a,187} The fluoroformates are synthesized by reaction of phenols with fluorophosgene (4.15) and reacted with SF$_4$ without further purification.\textsuperscript{187} The presence of HF, liberated during the fluoroformate formation, is essential for the success of the deoxofluorination reaction.\textsuperscript{187} The high toxicity of fluorophosgene and SF$_4$ constitutes a major drawback of this methodology.\textsuperscript{164}
Hiyama et al. developed a desulfurization-fluorination method for the synthesis of trifluoromethyl aryl ethers (Scheme 4.6). Treatment of methyl xanthates (4.17) with HF/pyridine in presence of an electrophilic brominating agent (4.18, 1,3-dibromo-5,5-dimethylhydantoin, DHB) affords the trifluoromethoxybenzene derivatives in good yields. N-Bromosuccinimide can also be used, albeit with reduced efficiency. Substrates bearing alkoxy substituents underwent ring bromination along with desulfurization-fluorination. Difluoro(methylthio)methyl ethers (4.19) have been identified as intermediates in the reaction; therefore, the mechanism described in Scheme 4.6 has been proposed for the desulfurization-fluorination reaction. This method was later employed by Leroux et al. for the synthesis of trifluoromethoxylated pyridines. For such substrates, the presence of a chlorine substituent on the pyridine was essential for the reaction to proceed.

Scheme 4.6 Synthesis of trifluoromethyl aryl ethers by fluorodesulfurization
4.2.3 Electrophilic trifluoromethylation

The electrophilic trifluoromethylation of phenol is a challenging transformation due to the competing C-trifluoromethylation. The reaction of Togni’s reagent (4.20, Figure 4.3), arguably the most widely used reagent for electrophilic trifluoromethylation, with phenols mostly affords products of C-trifluoromethylation at the most electron-rich positions (Scheme 4.7, a). Blocking those positions with alkyl substituents allowed the trifluoromethoxybenzene derivative to be formed (3.24b, Scheme 4.7, b), albeit in low yield, along with oxidized products.

Figure 4.3 Togni’s reagent

Scheme 4.7 Trifluoromethylation of phenols using Togni’s reagent

Electrophilic trifluoromethylating reagents based on chalcogenium salts (S⁺, Se⁺, Te⁺) have been developed by Yagupolskii and Umemoto, however, none of those have been successfully used for the trifluoromethylation of phenols due to competing C-alkylation. More electrophilic O-based reagents developed by Umemoto et al. (4.26, Scheme 4.8) have allowed the direct trifluoromethylation of phenols (Scheme 4.8). Those trifluoromethylating agents need to be
generated *in-situ* by photolysis of diazonium salts using a high-pressure mercury lamp (Scheme 4.8) Electron-poor and electron-rich phenols could be trifluoromethylated in good yields. The specialized equipment necessary for the generation of 4.26 (irradiation using a high pressure mercury lamp while maintaining a temperature of -100 °C) can limit the applicability of this methodology.165

**Scheme 4.8 Umemoto’s trifluoromethylation of phenols**190

An alternative strategy for the trifluoromethylation of phenols that employs the Ruppert-Prakash reagent 4.27, a nucleophilic trifluoromethylating agent, has recently been reported by Qing *et al.* (Scheme 4.9).197 A wide range of functional groups were tolerated under the reaction conditions. The applicability of the reaction to late stage synthesis was demonstrated on a medicinally relevant β-lactam. The nucleophilic nature of the trifluoromethyl source prevented the formation of side products from C-alkylation. The formation of Ag(I)CF₃ generated in presence 4.27, AgOTf, CsF and 2-fluoropyridine was observed by ¹⁹F NMR. Addition of starting material, NFSI and Selectfluor® to a solution of preformed Ag(I)CF₃ in toluene furnished the trifluoromethyl aryl ether, indicating that the Ag(I)CF₃ complex is indeed an intermediate in the reaction. The presence of both NFSI and Selectfluor® was necessary to achieve good yields of the trifluoromethyl aryl ethers.
4.2.4 Direct trifluoromethoxylation

The development of methods allowing the direct introduction of the OCF₃ moiety has been limited in the past due to the instability of the trifluoromethoxy anion (Scheme 4.10).¹⁹⁸

\[
\begin{align*}
\text{F} & \quad \text{F} \\
\text{O}^- & \quad \text{F} \quad \text{F} \\
\end{align*}
\]

Scheme 4.10 Decomposition of the trifluoromethoxy anion

One early example of direct trifluoromethoxylation was reported by Kitazume and Shreeve (Scheme 4.11).¹⁹⁹ Treatment of phenols with trifluoromethoxy sulfurane ⁴.₂₈ (Scheme 4.11) affords the corresponding trifluoromethyl aryl ethers. The reaction was proposed to proceed through an ipso-substitution rather than a direct trifluoromethylation of the oxygen (Scheme 4.11).
while a series of stable trifluoromethanolate salts have been synthesized by kolomeitsev et al. (figure 4.4),\textsuperscript{198} efforts to use those salts for the aromatic nucleophilic substitution (-sn-ar) of electron-poor aryl rings have been unsuccessful.\textsuperscript{198} decomposition of the trifluoromethoxy anion yielded fluoride and ring fluorination was exclusively observed. generation of benzyne in presence of salt 4.31 could afford trifluoromethoxybenzene, along with fluorobenzene (scheme 4.12).\textsuperscript{198}

\[ \text{Si(CF}_3\text{)}_2 + \text{F}_3\text{COCl} \rightarrow \text{hv} \rightarrow \text{F}_3\text{C} = \text{CF}_2\text{OCF}_3 \]

\[ \text{R} = \text{H} \quad \text{Me} \quad \text{53 %} \quad \text{67%} \]

**Scheme 4.11 Trifluoromethoxy sulfurane as trifluoromethoxylating agent\textsuperscript{199}**

\[ \text{R} = \text{H} \quad \text{Me} \quad \text{53 %} \quad \text{67%} \]
Trifluormethoxy salt 4.33 (Figure 4.4) was later used by Ritter et al. in a cross-coupling reaction with aryl stannanes and aryl boronic acids (Scheme 4.13).200 Electron-rich substrates did not suffer from competitive ring fluorination, and the reaction could be applied on complex substrates. In the case of boronic acids, a two-steps one-pot procedure is necessary to generate a reactive aryl silver complex that then undergo trifluromethoxylation.200 The use of super-stoichiometric amounts of silver is a limitation of this methodology.

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**Scheme 4.12 Trifluromethoxylation of benzyne**198

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**Scheme 4.13 Silver-mediated trifluromethoxylation**200

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Selected examples:
An approach to \( o \)-trifluoromethoxylated aniline derivatives has recently been reported by Ngai \textit{et al.} (Scheme 4.14).\textsuperscript{201} Reaction of the \( N \)-hydroxyanilines with Togni's reagent (4.22, Figure 4.3) affords \( N \)-trifluoromethoxyanilines, which upon heating undergo trifluoromethoxy migration. The reaction can be performed in a two-step, one-pot sequence, with a slightly reduced efficiency. Electron-donating and electron-withdrawing groups are tolerated under the reaction conditions. When the two \textit{ortho} positions were available, low regioselectivity was observed. The authors postulated that the OCF\(_3\) migration occurred through a dissociated ion pair. Mechanistic experiments ruled out the presence of radical intermediates.\textsuperscript{201}

\[
\text{Scheme 4.14} \quad \text{\( o \)-Trifluoromethoxy aniline derivatives synthesis}\textsuperscript{201}
\]

### 4.2.5 Radical trifluoromethoxylation

One example of radical trifluoromethoxylation has been reported to date, which utilizes trifluoromethoxy hypofluorite (1.40, Scheme 4.15).\textsuperscript{202} The radical reactivity of trifluoromethoxy hypofluorite has been discussed in the introductory chapter of this thesis (see 1.3.2). Alison, Cady and Kollonitsch had previously reported the formation of trifluoromethoxybenzene as a side product of the fluorination of benzene using 1.40.\textsuperscript{62,63} To promote the formation and the addition of trifluoromethoxy radicals, Navarrini \textit{et al.} used trifluoromethyl-trifluorovinyl ether 4.42 as a radical initiator (Scheme 4.15). The trifluoromethoxylated products were, however, obtained as inseparable mixtures of regioisomers along with fluorination products, limiting the synthetic utility of this methodology. Highly activated and highly deactivated aryls were not suitable substrates for the reaction. Furthermore, the fluorinating agent used, trifluoromethoxy hypofluorite, is a highly corrosive and potentially explosive gas.\textsuperscript{28,72}
4.3 Results and discussion

4.3.1 Synthesis of trifluoromethyl aryl ethers by photo-fluorodecarboxylation

Despite recent advances, only a limited number of methodologies are available for the trifluoromethyl aryl ethers synthesis, which require the use of super-stoichiometric amounts of metals, toxic reagents or specialized equipment (mercury arc lamp). No synthetically relevant radical methods for the synthesis of trifluoromethoxybenzene derivatives have been reported to date. We envisioned that our previously developed photo-fluorodecarboxylation method (See Chapter 3) could provide an attractive alternative for the synthesis of trifluoromethyl aryl ethers. Thus, the synthesis of trifluoromethyl aryl ethers by fluorodecarboxylation of difluorophenoxy acetic acid derivatives was investigated. This study involved: a) the synthesis of the difluorophenoxyacetic acid derivatives, postulated to be the radical precursors for the fluorodecarboxylation; b) the development of an analytic method using $^{19}$F NMR for the quantitative analysis of the fluorodecarboxylation reaction; c) an investigation of the scope and limitations of the fluorodecarboxylation of difluorophenoxyacetic acid derivatives.
4.3.1.1 Synthesis of the difluorophenoxyacetic acid derivatives

Difluorophenoxyacetic acid derivatives 4.44 were obtained in two steps from the corresponding phenols using an alkylation-saponification sequence (Scheme 4.16). The conditions initially developed for the synthesis of fluorophenoxyacetic acid derivatives (see 3.3.1), however, only afforded the desired compounds in low yields (10% overall yield).

The low yields obtained for the esterification step can be explained by a slower rate of nucleophilic addition, allowing side reactions such as trans-esterification or difluorocarbene\textsuperscript{203} insertion to occur. Indeed, it has been shown that the presence of α-halogens reduces the rate of nucleophilic substitution.\textsuperscript{204} Lorenzo Frassoni, an undergraduate student under my supervision, optimized the synthesis of the ethyl difluorophenoxyacetate derivatives 4.43. He found that using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base, and using more diluted reaction conditions (0.16 M vs. 0.5 M, see 4.5.1), the desired esters could be obtained in higher yields.

Saponification of those esters only afforded the corresponding difluorophenoxyacetic acid derivatives 4.44 in low yields (10-30%). Surprisingly, the remaining mass balance could be recovered as the sodium salts of the corresponding carboxylic acids in the organic washes of the crude reaction mixture. The purification method was modified, and the crude saponification mixture was directly acidified and extracted with organic solvents upon completion. For this reason, a careful purification of the esters 4.43 is necessary prior to saponification.

\begin{center}
\textbf{Scheme 4.16 Synthesis of the difluorophenoxyacetic acid derivatives}
\end{center}
4.3.1.2 Quantification of the reaction mixture using $^{19}$F NMR analysis

In Chapter 3, the use of $^1$H NMR for the analysis of the crude photofluorodecarboxylation reaction mixture was described (see 3.3.1). Both mono- and difluoromethyl aryl ethers possess characteristic hydrogen atoms that can be used for the determination of NMR yield using $^1$H NMR. Such a handle is not available in trifluoromethyl aryl ethers. Those compounds only bear aromatic protons, which signals overlap with the signals from the starting material and the eventual side products (see Figure 4.5). The trifluoromethoxy group has a distinctive signal in $^{19}$F NMR ($\delta \approx -58$ ppm, Figure 4.5) that is very different from the fluorine signal of the starting material ($\delta \approx -76$ ppm, Figure 4.5). $^{19}$F NMR was, therefore, used for the determination of the NMR yield (see Figure 4.5). Fluorobenzene ($\delta \approx -113.2$ ppm, Figure 4.5) or ethyl trifluoroacetate ($\delta \approx -76$ ppm) were used as internal standard.

![Figure 4.5 Representative examples of crude $^1$H and $^{19}$F NMR spectra for the fluorodecarboxylation of difluorophenoxyacetic acids using fluorobenzene as internal standard.](image_url)
The longitudinal relaxation time ($T_1$) of the $^{19}$F nucleus, however, can vary greatly depending on its electronic environment. For nuclei with a long longitudinal relaxation time, the standard relaxation delay (d1) used to record the NMR spectra can be too short to allow the complete relaxation of the nucleus before the next pulse. The intensity of the signals produced would, therefore, not accurately represent the number of nuclei present in the sample.

To accurately measure the NMR yield, it is necessary to ensure that all nuclei have relaxed completely before each pulse, a condition met when $d1 \geq 5T_1$. The $T_1$ value for each $^{19}$F nucleus of interest was determined using the inversion recovery method; the values obtained are presented in Table 4.2. The relaxation delay (d1) was, therefore, set to 30 s for all NMR yield determination using $^{19}$F NMR to ensure complete relaxation of all nuclei.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Fluorinated compound</th>
<th>$^{19}$F δ (ppm)</th>
<th>$\tau_{1/2}$ (s)</th>
<th>$T_1$ (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CF$_3$CO$_2$Et</td>
<td>-75.6</td>
<td>1.7</td>
<td>2.4</td>
</tr>
<tr>
<td>2</td>
<td>C$_6$H$_5$OCF$_3$</td>
<td>-57.6</td>
<td>1.9</td>
<td>2.7</td>
</tr>
<tr>
<td>3</td>
<td>$p$-C$_4$H$_3$C$_6$H$_4$OCF$_2$C(O)OH (4.44a)</td>
<td>-76.5</td>
<td>0.8</td>
<td>1.2</td>
</tr>
<tr>
<td>4</td>
<td>C$_6$H$_7$F</td>
<td>-113.2</td>
<td>1.5</td>
<td>2.2</td>
</tr>
</tbody>
</table>

$\tau_{1/2}$: time at which the relaxation has returned halfway to equilibrium: $T_1 = \tau_{1/2}/\ln2$.

4.3.1.3 Fluorodecarboxylation induced by the direct excitation of the substrate

Difluorophenoxyacetic acid derivative 4.44a was subjected to the reaction conditions developed for the synthesis of mono- and difluoromethyl aryl ethers (Scheme 4.17). Only traces of the expected product were detected, and most of the starting material was unreacted.
UV-visible spectroscopy revealed that substrate 4.44a does not absorb light at 300 nm, but that its maximum absorption is centered around 254 nm (Figure 4.6). While phenoxyacetic acid and fluorophenoxyacetic acid derivatives both absorb light around 300 nm,\textsuperscript{92a} the presence of a second fluorine led to a shift of the absorbance to a lower wavelength. The irradiation wavelength was, therefore, switched to 254 nm. Since the cut-off wavelength of regular laboratory (borosilicate) glassware is at 275 nm,\textsuperscript{207} quartz cuvettes (cut-off 170 nm\textsuperscript{207}) were used.
After 24 h of irradiation at 254 nm, only 50% of the starting material remained in the crude mixture, while product 1.83a was only detected by NMR in 3% yield (Scheme 4.18). The reaction mixture was analyzed by \(^{1}\text{H}\), \(^{19}\text{F}\), \(^{13}\text{C}\) NMR as well as IR and GC-MS, but the fate of the remaining mass balance could not be identified. When NFSI was used as the fluorine source, no conversion was observed.

As electron-poor substrates gave better results for the fluorodecarboxylative fluorination described in Chapter 3, substrate 4.44c was also submitted to irradiation at 254 nm (Scheme 4.19). Furthermore, the aromatic fluorine might provide a handle for analysis of the \(^{19}\text{F}\) NMR spectra. Product 1.83c was detected in 8% yield, and no starting material remained in the reaction mixture. No side products could be identified. Only traces of other aromatic fluorinated compounds were observed in \(^{19}\text{F}\) NMR. Shorter reaction time (3 h) led to similar yields with only less than 5% starting material remaining. To probe whether the high volatility of the ether was impacting the yield of the reaction, a substrate with a higher molecular weight was investigated (1.83d, Scheme 4.19). While most of the starting material was consumed, no fluorinated product was detected.
Degassing D$_2$O prior to the experiment had no effect on the yield (Table 4.3, entry 2). When acetonitrile was added as co-solvent no starting material remained after irradiation but product 1.83a was only detected in 6% yield (Table 4.3, entry 3). Similar results were obtained using acetone as co-solvent (Table 4.3, entry 4). Many fluorinated side products were detected by $^{19}$F NMR, but could not be identified. Increasing the ratio D$_2$O/d$_6$-acetone did not affect the yield or reduce the amount of impurities formed. More unreacted starting material was detected when the reaction was run in a 1:1 CD$_3$OD/D$_2$O mixture (Table 4.3, entry 5), most likely due to the poor solubility of Selectfluor®. Using a 2:1 mixture of CD$_3$OD/D$_2$O, a better conversion of the starting material was observed, without significantly impacting the yield (Table 4.3, entry 6). Using d$_6$-DMSO as co-solvent completely inhibited the reaction (Table 4.3, entry 7).
Table 4.3 Influence of the co-solvent on the light-mediated fluorodecarboxylation of difluorophenoxyacetic acid derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield[a]</th>
<th>Conversion[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>D$_2$O</td>
<td>3%</td>
<td>47%</td>
</tr>
<tr>
<td>2</td>
<td>D$_2$O[b]</td>
<td>5%</td>
<td>50%</td>
</tr>
<tr>
<td>3</td>
<td>D$_2$O/CD$_3$CN 1:1</td>
<td>6%</td>
<td>100%</td>
</tr>
<tr>
<td>4</td>
<td>D$_2$O/d$_6$-acetone 1:1</td>
<td>9%</td>
<td>100%</td>
</tr>
<tr>
<td>5</td>
<td>D$_2$O/CD$_3$OD 1:1</td>
<td>5%</td>
<td>76%</td>
</tr>
<tr>
<td>6</td>
<td>D$_2$O/CD$_3$OD 2:1</td>
<td>5%</td>
<td>57%</td>
</tr>
<tr>
<td>7</td>
<td>D$_2$O/d$_6$-DMSO</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Conditions: 0.1 mmol of substrate, 0.15 mmol of NaOH (5.0 M solution in H$_2$O), 0.35 mmol of Selectfluor®, irradiated at 254 nm for 24 h in a quartz test tube.

[a] Determined by $^{19}$F NMR using fluorobenzene or ethyl trifluoroacetate as internal standard. [b] Degassed with Argon.

Other bases were investigated (Table 4.4). Using LiOH as a base decreased the solubility of the reagents and little conversion was observed (Table 4.4, entry 2). More unidentified side products were detected when using KOH, without any improvement on the yield (Table 4.4, entry 3). Carbonates (K$_2$CO$_3$ and Cs$_2$CO$_3$) led to similar results. No starting material remained after irradiation when an organic base was used, while product 1.83a was detected in similar yields (Table 4.4, entry 6). Regardless of the base employed, the reaction mixture was found to be acidic (pH < 2) after irradiation. It has been reported that Selectfluor® decomposes in alkaline solutions to produce HF, reducing the pH of the media. The acidification of the reaction mixture possibly causes the carboxylate to be reprotonated and prevents the fluorodecarboxylation. This is consistent with the higher amount of starting material detected after irradiation when using methanol as co-solvent (Table 4.3, entries 5 and 6). Indeed, the decomposition of Selectfluor® in alkaline media has been reported to be faster in polar solvent such as methanol. To maintain a basic pH throughout the reaction, the reaction was run using 10 equivalents of base (Table 4.4, entry 7), but no conversion was observed. Additionally, attempts to add Selectfluor® as a solution in D$_2$O dropwise through a syringe pump under constant irradiation to prevent decomposition in solution did not provide the
product. When the carboxylate salt of 4.45 was used (Scheme 4.20), less starting material was detected after irradiation, but the yield of product 1.83a remained low.

### Table 4.4 Influence of the base on the light-mediated fluorodecarboxylation of difluorophenoxy acetic acid derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Yield[a]</th>
<th>Conversion[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaOH</td>
<td>3%</td>
<td>47%</td>
</tr>
<tr>
<td>2</td>
<td>LiOH</td>
<td>2%</td>
<td>20%</td>
</tr>
<tr>
<td>3</td>
<td>KOH</td>
<td>2%</td>
<td>37%</td>
</tr>
<tr>
<td>4</td>
<td>K₂CO₃</td>
<td>traces</td>
<td>44%</td>
</tr>
<tr>
<td>5</td>
<td>Cs₂CO₃</td>
<td>2%</td>
<td>50%</td>
</tr>
<tr>
<td>6[b]</td>
<td>2,6-di-t-butyl-4-methylpyridine</td>
<td>2%</td>
<td>100%</td>
</tr>
<tr>
<td>7</td>
<td>K₂CO₃ (10 equiv.)</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

**Conditions:** 0.1 mmol of substrate, 0.15 mmol of base, 0.35 mmol of Selectfluor®, irradiated at 254 nm for 24 h in a quartz test tube. [a]: Determined by ¹⁹F NMR using fluorobenzene or ethyl trifluoroacetate as internal standard. [b]: in CD₃CN.

### Scheme 4.20 Fluorodecarboxylation of carboxylate salt 4.45

No improvement in yield could be achieved, despite the improvement in starting material conversion. The trapping of the reactive intermediate might be impacted by the decomposition of Selectfluor® in solution. The reaction was thus run using 10 equivalents of the fluorinating agent (Scheme 4.21). Gratifyingly, product 1.83a was obtained in 38% yield. No remaining
starting material could be detected. The crude reaction mixture was analyzed by $^1$H, $^{19}$F and $^{13}$C NMR, GC-MS and IR spectroscopy. No side product could, however, be identified and the fate of the remaining mass balance could not be determined.

Finally, irradiation of trifluoromethoxybenzene **1.83** using 254 nm light led to the disappearance of the ether. No other compounds were detected by NMR. UV-visible spectroscopy revealed that **1.83** absorbs light around 254 nm (Figure 4.7). While the fate of the ether could not be identified, it is possible that UV-light excitation triggers its decomposition under the reaction conditions. The development of an alternative approach that does not required 254 nm irradiation would, therefore, be desirable.

![Diagram](image)

**Scheme 4.21 Fluorodecarboxylation of 4.44a using 10 equivalents of fluorine source**

*Figure 4.7 Absorption spectra of trifluoromethoxybenzene between 200 and 400 nm in CD$_3$CN [0.001M]*
4.3.1.4 Photocatalyzed fluorodecarboxylation

The instability of the trifluoromethyl aryl ethers under a 254 nm irradiation entailed the development of an alternative method for the excitation of the substrate. The use of a photoactive compound could allow to switch the irradiation to wavelength compatible with the trifluoromethyl aryl ethers. Photoactive compounds have the potential to act in two ways (Scheme 4.22).\textsuperscript{209} In a photosensitization mechanism, the excited state of the sensitizer transfers its energy to the substrate. The substrate in its excited state is then oxidized by an external oxidant (Selectfluor\textsuperscript{®} or NFSI), inducing the decarboxylation, similarly to the direct excitation (see Chapter 3 and 4.3.1.3). In this case, the energy of the sensitizer’s excited state (triplet or singlet energy, \(E_T\) or \(E_S\)) must be greater than the energy required for the substrate’s excitation. Alternatively, in a photooxidation mechanism, the excited state of the sensitizer itself can act as an oxidant. The reduction potential of the sensitizer in its excited state (\(E_{\text{red}}\)) must be high enough to allow oxidation of the substrate. Davidson \textit{et al.} reported that phenoxyacetic acid derivatives are prone to radical decarboxylation in presence of photosensitizers,\textsuperscript{210} following a photoexcitation mechanism as depicted in Scheme 4.22. Various sensitzers can be used, such as benzophenone and quinones,\textsuperscript{210a} aromatic ketones,\textsuperscript{210b} heterocycles,\textsuperscript{210e} or flavins.\textsuperscript{211} The presence of radical intermediates was demonstrated by ESR experiments.\textsuperscript{212} Dr. Joe C.T. Leung also reported that acetone and benzophenone could act as photoactive reagents for the fluorodecarboxylation of phenoxyacetic acid derivatives.\textsuperscript{92b}

\begin{equation}
\text{Scheme 4.22 Possible pathways for the radical decarboxylation using photoactive compounds}
\end{equation}
Various photosensitizers were evaluated (Table 4.5). Rose Bengal$^{213}$ did not provide any product, regardless of the fluorine source used (Table 4.5, entries 1 and 2). Using acetophenone as the photoactive compound and NFSI as the fluorine source, no fluorodecarboxylation was observed (Table 4.5, entry 3). Switching the fluorine source to Selectfluor®, a stronger oxidant than NFSI,$^{92b}$ product 1.83a could be detected in 3% yield (Table 4.5, entry 4). Those results suggest that acetophenone does not act as the oxidant, but rather as a sensitizer. Increasing the amount of Selectfluor® to 10 equivalents allowed to achieve 14% yield (Table 4.5, entry 5). Running the reaction in a d$_6$-acetone/D$_2$O mixture improved the yield to 30% (Table 4.5, entry 6). No reaction was observed using NFSI when benzophenone was used as the photoactive compound (Table 4.5, entry 7), similarly to what was observed with acetophenone (Table 4.5, entry 3). When Selectfluor® was used as the fluorine source, product 1.83a was detected in 10% yield (Table 4.5, entry 8). The higher yield obtained with benzophenone compared to acetophenone could be explained by a more efficient excitation of the substrate. Increasing the amount of Selectfluor® led to an increase in yield (Table 4.5, entry 9), as did switching the co-solvent to acetone (Table 4.5, entry 10). Since acetone is also a sensitizer with a high triplet energy,$^{214}$ the reaction was performed in d$_6$-acetone/D$_2$O without addition of a sensitizer, furnishing product 1.83a in 40% yield (Table 4.5, entry 11).
Table 4.5 Evaluation of different photoactive compounds

<table>
<thead>
<tr>
<th>Entry</th>
<th>Photosensitizer</th>
<th>λ_{max} (nm)</th>
<th>E°_{red} (eV)</th>
<th>E_r (eV)</th>
<th>Fluorine source (equiv.)</th>
<th>Solvent [0.1 M]</th>
<th>Yield[^a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rose Bengal</td>
<td>550</td>
<td>0.99</td>
<td>1.77</td>
<td>NFSI (3.5)</td>
<td>CD-CN</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>Rose Bengal</td>
<td></td>
<td></td>
<td></td>
<td>Selectfluor® (3.5)</td>
<td>CD-CN/D_2O</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>Acetophenone</td>
<td>311</td>
<td>1.35</td>
<td>2.64</td>
<td>NFSI (3.5)</td>
<td>CD-CN</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>Acetophenone</td>
<td></td>
<td></td>
<td></td>
<td>Selectfluor® (10)</td>
<td>CD-CN/D_2O</td>
<td>3%</td>
</tr>
<tr>
<td>5</td>
<td>Acetophenone</td>
<td></td>
<td></td>
<td></td>
<td>Selectfluor® (10)</td>
<td>d_6-acetone/D_2O</td>
<td>14%</td>
</tr>
<tr>
<td>6</td>
<td>Acetophenone</td>
<td></td>
<td></td>
<td></td>
<td>Selectfluor® (10)</td>
<td>d_6-acetone/D_2O</td>
<td>30%</td>
</tr>
<tr>
<td>7</td>
<td>Benzophenone</td>
<td>384</td>
<td>1.32</td>
<td>3.00</td>
<td>NFSI (3.5)</td>
<td>CD-CN</td>
<td>0%</td>
</tr>
<tr>
<td>8</td>
<td>Benzophenone</td>
<td></td>
<td></td>
<td></td>
<td>Selectfluor® (3.5)</td>
<td>CD-CN/D_2O</td>
<td>10%</td>
</tr>
<tr>
<td>9</td>
<td>Benzophenone</td>
<td></td>
<td></td>
<td></td>
<td>Selectfluor® (10)</td>
<td>CD-CN/D_2O</td>
<td>21%</td>
</tr>
<tr>
<td>10</td>
<td>Benzophenone</td>
<td></td>
<td></td>
<td></td>
<td>Selectfluor® (10)</td>
<td>d_6-acetone/D_2O</td>
<td>38%</td>
</tr>
<tr>
<td>11</td>
<td>Acetone (solvent)</td>
<td>330</td>
<td>0.49</td>
<td>3.49</td>
<td>Selectfluor® (10)</td>
<td>d_6-acetone/D_2O</td>
<td>40%</td>
</tr>
</tbody>
</table>

[^a]: Determined by \(^{19}\text{F}\)NMR using fluorobenzene or ethyl trifluoroacetate as internal standard.

Full conversion of the starting material was observed regardless of the sensitizer used, while a maximum of 40% yield was achieved (Table 4.5, entry 11) using acetone. No side products could be identified using the typical analysis techniques (thin layer chromatography, \(^1\text{H}, \(^{13}\text{C}\) and \(^{19}\text{F}\) NMR, mass spectrometry, gas and liquid chromatography/mass-spectrometry, infrared spectroscopy).

The addition of 1.5 equiv. of NaOH did not impact the yield of the reaction. Using a large excess of base led to complete degradation of the starting material and no desired product was observed. Addition of fluoride salts (CsF or KF) led to a decrease in yield to 10% and 26% respectively. Lowering the temperature to 5 °C to slow down an eventual decomposition did not impact the yield.

To gain more insight on the decomposition pathways, an hydrogen source (tris(trimethylsilyl)silane (TTMSS), D_{SiH}: 83.7 kcal/mol)\(^{113}\) was added to trap possible radical intermediates (Scheme 4.23). Hydrogen abstraction from TTMSS is a relatively fast process (k \approx 2.5 \times 10^5 \text{ mol}^{-1} \text{s}^{-1})\(^{215}\) yet, no significant change in yield was observed, and only 6% of the
reduced product 3.39a was detected. No other products were observed. Using a faster hydrogen transfer agent, triphenyltin hydride (\(D_{\text{salt}}: 78.0 \text{ kcal/mol, } k \approx 5 \times 10^6 \text{ mol}^{-1}\text{s}^{-1}\)),\(^{113,216}\) 10% of product 1.83a were detected, along with 19% of reduced product 3.39a, but no other side products were identified. Substrate 4.44a might be decomposing via non-radical pathways, or processes faster than intermolecular hydrogen abstraction.

An intramolecular radical trap was also synthesized (Scheme 4.24). Substrate 4.44e is capable of undergoing an intramolecular 5-exo-cyclization (\(k \approx 2.2 \times 10^5 \text{ mol}^{-1}\text{s}^{-1}\))\(^{217}\), which would lead to product 4.51. When 4.44e was submitted to the reaction conditions, full conversion of the starting material was observed but neither product 1.83e nor 4.51 were detected in the reaction mixture. Traces amounts of fluorinated compounds could be detected by NMR but could not be identified. Product 4.44e most likely underwent side reactions under the reaction conditions (e.g. polymerization of the styrene moiety under UV-irradiation or fluorination of the double bond by the electrophilic fluorine source).

The impact of the electron-density of the ring on the reaction outcome was next evaluated (Table 4.6). Increasing the electron-density led to complete decomposition of the starting material, and no product was detected (Table 4.6, entry 2). As observed in Chapter 3,
electron-rich substrates are not compatible with the fluorodecarboxylation conditions. Decreasing the electron-density resulted in decrease in yield (Table 4.6, entries 3 and 4). The fluorine abstraction might be slower for electron-poor substrates. No product was detected when the electron-density of the ring was further decreased (Table 4.6, entry 5) and 25% of the starting material was detected in the reaction mixture, indicating that substrate 4.44h possibly relaxes to its ground state faster than it is being oxidized.

Varying the electron-density of the ring did not improve the yield of the reaction, and the fate of the remaining mass balance could not be determined using standard analysis technique. It was hypothesized that the presence of excess acetone in its excited state might have led to side reactions. Benzophenone also was shown to efficiently promote the fluorodecarboxylation reaction (Table 4.5, entry 9). The possibility of using benzophenone as a photocatalyst was therefore investigated.

When 30 mol% of benzophenone were used, product 1.83a was obtained in similar yields as when stoichiometric amounts of benzophenone were used (Table 4.7, entry 1). Addition of NaOH had no influence on the yield (Table 4.7, entry 2). Reducing the equivalents of

<table>
<thead>
<tr>
<th>Entry</th>
<th>R =</th>
<th>Yield[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>t-Bu (1.83a)</td>
<td>40%</td>
</tr>
<tr>
<td>2</td>
<td>OMe (1.83f)</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>F (1.83c)</td>
<td>20%</td>
</tr>
<tr>
<td>4</td>
<td>Br (1.83g)</td>
<td>6%</td>
</tr>
<tr>
<td>5</td>
<td>CF₃ (1.83h)</td>
<td>0%</td>
</tr>
</tbody>
</table>

Conditions: 0.1 mmol of substrate, 0.15 mmol of NaOH (5.0 M solution in H₂O), 1.0 mmol of Selectfluor®, irradiated at 350 nm for 24 h. [a]: Determined by ¹⁹F NMR using fluorobenzene or ethyl trifluoroacetate as internal standard.
Selectfluor® led to a decrease in yield (Table 4.7, entry 3). The amount of benzophenone could be reduced to 10 mol% without impacting significantly the yield of 1.83a (Table 4.7, entry 4).

### Table 4.7 Benzophenone equivalents screening

<table>
<thead>
<tr>
<th>Entry</th>
<th>Benzophenone equivalent</th>
<th>NaOH equiv.</th>
<th>Selectfluor® equiv.</th>
<th>Yield [a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30 mol%</td>
<td>0</td>
<td>10</td>
<td>30%</td>
</tr>
<tr>
<td>2</td>
<td>30 mol%</td>
<td>1.5</td>
<td>10</td>
<td>30%</td>
</tr>
<tr>
<td>3</td>
<td>30 mol%</td>
<td>1.5</td>
<td>5</td>
<td>19%</td>
</tr>
<tr>
<td>4</td>
<td>10 mol%</td>
<td>0</td>
<td>10</td>
<td>28%</td>
</tr>
</tbody>
</table>

[a] Conditions: 0.1 mmol of substrate, 0.15 mmol of NaOH (5.0 M solution in H2O), benzophenone, Selectfluor®, irradiated at 350 nm for 24 h. [a]: Determined by 19F NMR using fluorobenzene or ethyl trifluoroacetate as internal standard.

The beneficial effect of high concentration in Selectfluor® had previously been observed (Table 4.5, entry 8 vs. entry 9). The influence of the reaction concentration was, therefore, investigated. Because of the poor solubility of Selectfluor® at high concentration, 3.5 equivalents were used for those studies. A reaction was run using 3.5 equivalents of Selectfluor® in a 0.1 M solution for comparison, and product 1.83a was detected in 16% yield (Table 4.8, entry 2). As expected, decreasing the concentration led to a decrease in yield (Table 4.8, entry 3). Increasing the concentration to 0.6 M allowed product 1.83a to be formed in 54% (Table 4.8, entry 4). Further increase in concentration was detrimental to the reaction as Selectfluor® was not completely soluble in the reaction mixture (Table 4.8, entry 5). Increasing the amount of Selectfluor® at 0.6 M allowed to reach 61% yield (Table 4.8, entry 6).
Table 4.8 Influence of the concentration on the benzophenone-sensitized fluorodecarboxylation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Selectfluor® equiv.</th>
<th>([c]) (mol.L(^{-1}))</th>
<th>Yield(^{[a]})</th>
<th>Conversion(^{[a]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>0.1</td>
<td>28%</td>
<td>100%</td>
</tr>
<tr>
<td>2</td>
<td>3.5</td>
<td>0.1</td>
<td>16%</td>
<td>100%</td>
</tr>
<tr>
<td>3</td>
<td>3.5</td>
<td>0.03</td>
<td>11%</td>
<td>100%</td>
</tr>
<tr>
<td>4</td>
<td>3.5</td>
<td>0.6</td>
<td>54%</td>
<td>75%</td>
</tr>
<tr>
<td>5</td>
<td>3.5</td>
<td>1.0</td>
<td>29%</td>
<td>78%</td>
</tr>
<tr>
<td><strong>6</strong></td>
<td><strong>5</strong></td>
<td><strong>0.6</strong></td>
<td><strong>61%</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

Conditions: 0.1 mmol of substrate, 0.01 mmol of benzophenone, Selectfluor®, irradiated at 350 nm for 24 h. \([a]\): Determined by \(^{19}\)F NMR using fluorobenzene or ethyl trifluoroacetate as internal standard.

Those optimized conditions (Table 4.8, entry 6) were then tested on substrate 4.44g (Scheme 4.25). The trifluoromethyl aryl ether 1.83g was only detected in 3% yield along with 20% of remaining starting material. Full conversion was observed after 48 h without any improvement of the yield. This result further suggests that the fluorine transfer step might be too slow to compete with side reactions, particularly for electron-poor substrates.

Scheme 4.25 Fluorodecarboxylation of substrate 4.44g using catalytic amounts of benzophenone
4.3.1.5 Conclusion on the light-mediated fluorodecarboxylation using Selectfluor®
Difluorophenoxy acetic acid derivatives undergo fluorodecarboxylation under direct excitation at 254 nm in presence of Selectfluor®. Trifluoromethyl aryl ethers, however, proved to be unstable under the 254 nm irradiation. The use of acetone as a photosensitizer and solvent allowed the desired products to be formed in better yields using a 350 nm irradiation. A maximum of 40% yield and full conversion of the starting material were observed but the fate of the remaining mass balance could not be determined. Catalytic amounts of benzophenone can also be used to promote the reaction with similar efficiency. Increasing the concentration of the reaction allowed the conversion of test substrate 4.44a to the trifluoromethyl aryl ether in 60% yield. The reaction was substrate-dependent and very low yields were obtained for a more electron-poor substrate. The results obtained seem to indicate that side reactions occur faster than fluorine abstraction. The use of a faster fluorine transfer agent should, therefore, be investigated to increase the substrate scope of the fluorodecarboxylation of difluorophenoxyacetic acid derivatives.

4.3.2 Fluorodecarboxylation using XeF₂
The slow rate of the fluorine abstraction has been identified as a possible limitation of the photosensitized fluorodecarboxylation to the synthesis of trifluoromethyl aryl ethers. Atomic fluorine transfer from XeF₂ has been shown by Patrick et al. to occur rapidly, with a rate constant of $k = 1.1 \times 10^6 \text{ M}^{-1}/\text{s}$. The fluorodecarboxylation reaction was, therefore, performed using XeF₂ as the fluorine source (Scheme 4.26). Investigation focused on substrate 4.44g in order to improve the yield obtained using the photosensitized conditions. Upon addition of the fluorinating agent, gas evolution was observed. Analysis of the reaction mixture prior to irradiation showed that product 1.83g was formed in 16% yield. The high reduction potential of XeF₂ (2.64 V) might be high enough to allow oxidation of the difluorophenoxyacetic acid derivatives without prior excitation of the substrate. No benzophenone was, therefore, used for the following investigations on the XeF₂-mediated fluorodecarboxylation of difluorophenoxyacetic acid derivatives.
4.3.2.1 Development of GC quantification method

A limitation of the previously described $^{19}$F NMR yield measurement method (see 4.3.1.2) is the long acquisition time required to obtain accurate $^{19}$F NMR spectra ($\approx 6$ min/sample to obtain both $^1$H and $^{19}$F NMR spectra). Gas chromatography (GC) would allow a faster yield determination. Commercial trifluoromethyl aryl ether 1.83g was therefore used to establish a GC quantification method that was used for the following studies (see 4.5 for details). In some cases, $^{19}$F NMR yield was also determined and was in agreement with the yield obtained by GC.

4.3.2.2 Optimization of the reaction conditions

The impact of the solvent on the reaction was first studied (Table 4.9). In the absence of benzophenone, no product was detected when CD$_3$CN was used as solvent (Table 4.9, entry 1). Using acetone, comparable results to the reaction with catalytic benzophenone (Scheme 4.26) were obtained (Table 4.9, entry 2), indicating that the ketone might play a role in the reaction process. In benzene, a common solvent for XeF$_2$-mediated reactions, a slight increase in yield was observed (Table 4.9, entry 3). Other aromatic solvents were investigated (Table 4.9, entries 4 to 6), with the best results being observed in toluene (Table 4.9, entry 5). When the reaction was run in more polar solvents, no trifluoromethyl aryl ether was detected, and most of the starting material was still present in the reaction mixture (Table 4.9, entries 7 and 8). Higher yields were obtained using chlorinated solvents (Table 4.9, entries 9 to 11). Using deuterated chloroform, product 1.83g could be obtained in 52% yield (Table 4.9, entry 10). No other products were detected by $^1$H or $^{19}$F NMR. When a mixture of acetone and CDCl$_3$ were used, full conversion of the starting material was observed but no product was detected. CDCl$_3$ was, therefore, chosen for further studies.

Scheme 4.26 Xenon difluoride as fluorine source

![Scheme 4.26](attachment:image.png)
Table 4.9 Solvent screen for the XeF$_2$-mediated fluorodecarboxylation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Yield$^{[a]}$</th>
<th>Conversion$^{[b]}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CD$_3$CN</td>
<td>0%</td>
<td>65%</td>
</tr>
<tr>
<td>2</td>
<td>d$_6$-acetone</td>
<td>14%</td>
<td>36%</td>
</tr>
<tr>
<td>3</td>
<td>d$_6$-benzene</td>
<td>17%</td>
<td>60%</td>
</tr>
<tr>
<td>4</td>
<td>d$_5$-nitrobenzene</td>
<td>14%</td>
<td>Not determined</td>
</tr>
<tr>
<td>5</td>
<td>d$_8$-toluene</td>
<td>24%</td>
<td>75%</td>
</tr>
<tr>
<td>6</td>
<td>Hexafluorobenzene</td>
<td>7%</td>
<td>100%</td>
</tr>
<tr>
<td>7</td>
<td>d$_4$-methanol</td>
<td>0%</td>
<td>20%</td>
</tr>
<tr>
<td>8</td>
<td>d$_6$-DMSO</td>
<td>0%</td>
<td>25%</td>
</tr>
<tr>
<td>9</td>
<td>CD$_2$Cl$_2$</td>
<td>30%</td>
<td>80%</td>
</tr>
<tr>
<td>10</td>
<td>CDCl$_3$</td>
<td>52%</td>
<td>88%</td>
</tr>
<tr>
<td>11</td>
<td>CHCl$_3$</td>
<td>46%</td>
<td>Not determined</td>
</tr>
<tr>
<td>12</td>
<td>d$_6$-acetone/CDCl$_3$</td>
<td>0%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Conditions: 0.1 mmol of substrate, 0.2 mmol of XeF$_2$ stirred until gas evolution stopped.

$^{[a]}$: Determined by $^{19}$F NMR and/or GC using ethyl trifluoroacetate and/or bromobenzene respectively as internal standard.

$^{[b]}$: Determined by $^{19}$F NMR using ethyl trifluoroacetate as internal standard.

Decreasing the amount of XeF$_2$ used led to a decrease in yield (Table 4.10, entries 1 and 2). Using more than two equivalents allowed the full conversion of the starting material but no increase in yield was observed (Table 4.9, entry 4). Furthermore, when 4 equivalents of XeF$_2$ were used, product 1.83g was detected in lower yields (Table 4.9, entry 5).
Table 4.10 Influence of XeF$_2$ equivalents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv.</th>
<th>Yield$^a$</th>
<th>Conversion$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>27%</td>
<td>56%</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>33%</td>
<td>54%</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>52%</td>
<td>88%</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>51%</td>
<td>100%</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>14%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Conditions: 0.1 mmol of substrate, XeF$_2$, stirred until gas evolution stopped.

$^a$: Determined by $^{19}$F NMR and/or GC using ethyl trifluoroacetate and/or bromobenzene respectively as internal standard. $^b$: Determined by $^{19}$F NMR using ethyl trifluoroacetate as internal standard.

As observed for the photosensitized fluorodecarboxylation, the concentration had a great impact on the reaction outcome (Table 4.11). In more dilute solutions, both the conversion and the yield were lower (Table 4.11, entries 1 to 3). Increasing the concentration led to the full conversion of the starting material and afforded a slight increase in yield (Table 4.11, entries 5 and 6). At high concentration, the poor solubility of the reagents had a detrimental effect on the yield (Table 4.11, entry 7). When the reaction was run without solvent, conversion still occurred and product 1.83g was detected in 19% (Table 4.11, entry 8).


### Table 4.11 Effect of concentration on the XeF₂-mediated fluorodecarboxylation

<table>
<thead>
<tr>
<th>Entry</th>
<th>[c] (mol/L)</th>
<th>Yield</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.05</td>
<td>24%</td>
<td>69%</td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
<td>28%</td>
<td>76%</td>
</tr>
<tr>
<td>3</td>
<td>0.2</td>
<td>35%</td>
<td>83%</td>
</tr>
<tr>
<td>4</td>
<td>0.5</td>
<td>52%</td>
<td>88%</td>
</tr>
<tr>
<td>5</td>
<td>1.0</td>
<td>55%</td>
<td>&gt; 98%</td>
</tr>
<tr>
<td>6</td>
<td>2.0</td>
<td>57%</td>
<td>100%</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>32%</td>
<td>100%</td>
</tr>
<tr>
<td>8</td>
<td>Neat</td>
<td>19%</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Conditions:** 0.1 mmol of substrate, 0.2 mmol of XeF₂, stirred until gas evolution stopped.

[a]: Determined by $^{19}$F NMR and/or GC using ethyl trifluoroacetate and/or bromobenzene respectively as internal standard. [b]: Determined by $^{19}$F NMR using ethyl trifluoroacetate as internal standard.

When substrate **4.44g** was added portionwise to a 2 M solution of XeF₂ in CDCl₃, more starting material was recovered, and product **1.83g** was only formed in 20% yield. Portionwise addition of XeF₂ to a 2.0 M of substrate **1.83g** in CDCl₃ also led to lower yield (30%).

Xenon difluoride is known to react slowly with chlorinated solvents, producing hydrofluoric acid (HF). HF has the ability to polarize the Xe–F bond of XeF₂ favoring ionic reactivity (see: 1.3.3) and has been shown to catalyze some XeF₂-mediated reactions. Therefore, the presence of hydrofluoric acid in the reaction might, therefore, influence the formation of the trifluoromethyl aryl ethers. To assess whether HF is favoring the trifluoromethyl aryl ethers, XeF₂ was led to react in CDCl₃ for 30 min before adding substrate **4.44g**. No decarboxylation was observed. XeF₂ likely decomposed in CDCl₃ prior to the addition of the acid.

The effect of a base was next investigated (Table 4.12). Using Na₂CO₃ in super-stoichiometric amount caused the yield to decrease significantly (Table 4.12, entry 2). When NaHCO₃ was used, a slight erosion of the yield was observed (Table 4.12, entry 3). Decreasing the amount of
NaHCO₃ to 0.5 equivalents (Table 4.12, entry 4), or using solvent stored on NaHCO₃ (Table 4.12, entry 5) had no influence on the yield.

**Table 4.12 Effect of base on the XeF₂-mediated fluorodecarboxylation**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv.)</th>
<th>Yield[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>57%</td>
</tr>
<tr>
<td>2</td>
<td>Na₂CO₃ (1.2)</td>
<td>20%</td>
</tr>
<tr>
<td>3</td>
<td>NaHCO₃ (1.2)</td>
<td>48%</td>
</tr>
<tr>
<td>4</td>
<td>NaHCO₃ (0.5)</td>
<td>55%</td>
</tr>
<tr>
<td>5</td>
<td>NaHCO₃[b]</td>
<td>56%</td>
</tr>
</tbody>
</table>

Conditions: 0.1 mmol of substrate, base, 0.2 mmol of XeF₂, stirred until gas evolution stopped. [a]: Determined by ¹⁸F NMR and/or GC using ethyl trifluoroacetate and/or bromobenzene respectively as internal standard. [b]: CDCl₃ was basified with NaHCO₃.

Patrick *et al.* reported that some XeF₂-mediated reaction proceed via carbocation intermediates, arising from the oxidation of radical intermediates.⁸³ᵃ ¹⁸F incorporation was observed when the reaction was run in presence of [¹⁸F]F⁻ source.⁸³ᵇ The impact of nucleophilic sources of fluorine on the XeF₂-mediated fluorodecarboxylation of difluorophenoxyacetic acid derivatives was therefore studied (Table 4.13). When tetrabutylammonium fluoride (TBAF) was used, almost no product was detected (Table 4.13, entry 2). The presence of water from TBAF might have been detrimental to the reaction. The use of CsF led to similarly low yield (Table 4.13, entry 3). While dry CsF was used, it is possible that the salt absorbed enough water during weighing and transfer to affect the reaction. Better yields were obtained using the less hygroscopic KF (Table 4.13, entry 4) and tosyl fluoride (Table 4.13, entry 5), but no improvement were observed compared to the reaction in the absence of nucleophilic fluorine sources (Table 4.13, entry 1).
Table 4.13 Influence of fluoride on the XeF₂-mediated fluorodecarboxylation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Fluoride source</th>
<th>Yield[a]</th>
<th>Conversion[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>57%</td>
<td>100%</td>
</tr>
<tr>
<td>2</td>
<td>TBAF-3H₂O</td>
<td>2%</td>
<td>50%</td>
</tr>
<tr>
<td>3</td>
<td>CsF</td>
<td>&lt;5%</td>
<td>100%</td>
</tr>
<tr>
<td>4</td>
<td>KF, dried</td>
<td>20%</td>
<td>100%</td>
</tr>
<tr>
<td>5</td>
<td>TsF, dried</td>
<td>40%</td>
<td>75%</td>
</tr>
</tbody>
</table>

Conditions: 0.1 mmol of substrate, 0.1 mmol fluoride, 0.2 mmol of XeF₂, stirred until gas evolution stopped. [a]: Determined by ¹⁹F NMR and/or GC using ethyl trifluoroacetate and/or bromobenzene respectively as internal standard. [b]: Determined by ¹⁹F NMR using ethyl trifluoroacetate as internal standard.

At 0 °C, product 1.83g was only detected in 5% yield while less of the starting material remained in the reaction mixture (Scheme 4.27). No increase in yield was observed when the reaction was run at 50 °C (Scheme 4.27).

Scheme 4.27 Effect of temperature of the XeF₂-mediated fluorodecarboxylation

Ramsden et al. have commented on the influence of the reaction vial on the outcome of XeF₂-mediated reactions. Ionic reactions are promoted in glass apparatus, while plastic flasks favor radical pathways. The fluorodecarboxylation was, therefore, performed in a falcon tube made of polypropylene. Full conversion was observed, and product 1.83g was detected in
similar yield as when using a glass vial (Table 4.14, entry 1) along with unreacted XeF$_2$. Decreasing the amount of XeF$_2$ to 1.5 equivalents had little influence on the reaction (Table 4.14, entry 2), but further lowering was overall beneficial (Table 4.14, entries 3 and 4). Using exactly one equivalent was essential to obtain the highest yields of the product (Table 4.14, entry 4). The excess XeF$_2$ might be leading to over-oxidation of the radical intermediate or reacting with the product 1.83g, resulting in lower yields. When less than one equivalent was used, the reaction did not go to completion (Table 4.14, entry 5).

### Table 4.14 Influence of XeF$_2$ equivalents on the fluorodecarboxylation in polypropylene vials

<table>
<thead>
<tr>
<th>Entry</th>
<th>XeF$_2$ equiv.</th>
<th>Yield$^a$</th>
<th>Conversion$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>58%</td>
<td>100%</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>56%</td>
<td>100%</td>
</tr>
<tr>
<td>3</td>
<td>1.19</td>
<td>67%</td>
<td>100%</td>
</tr>
<tr>
<td><strong>4</strong></td>
<td><strong>1.05</strong></td>
<td><strong>73%</strong></td>
<td><strong>100%</strong></td>
</tr>
<tr>
<td>5</td>
<td>0.77</td>
<td>57%</td>
<td>87%</td>
</tr>
</tbody>
</table>

Conditions: 0.1 mmol of substrate, dissolved in a polypropylene vial. XeF$_2$ added in one portion. Reaction stirred until gas evolution stopped. $^a$: Determined by $^{19}$F NMR using ethyl trifluoroacetate as internal standard.

#### 4.3.2.3 Synthesis of trifluoromethyl aryl ethers by XeF$_2$-mediated fluorodecarboxylation

Using the optimized conditions established above (Table 4.14, entry 4), the scope of trifluoromethyl aryl ethers accessible using this methodology was explored (Scheme 4.28). CHCl$_3$ was first used as solvent for larger scale reactions. Difluoromethyl aryl ether 3.33b, however, was detected in the crude reaction mixture in about 10% yield. The difluoromethoxy benzene derivative most likely arises from hydrogen abstraction from the solvent. CDCl$_3$ was, therefore, chosen as solvent for both NMR scale and larger scale reactions. The reaction proceeded extremely rapidly. Gas evolution (Xe and CO$_2$) started within a few seconds of XeF$_2$ addition and ceased within 5 minutes indicating completion of the reaction. The trifluoromethyl aryl ethers are highly non-polar and could be easily purified on a silica plug using pentanes. The isolation of some trifluoromethyl aryl ethers (1.83 and 1.83c, Scheme 4.28) proved to be
challenging due to their high volatility. Fluorine introduction tends to increase the volatility of organic compounds, despite the added molecular weight, due to the low polarizability of fluorine and few intermolecular interactions.\textsuperscript{17a,134a} The boiling point of aryl ether in particular has been shown to follow the trend anisol $>$ difluoromethoxybenzene $>$ trifluoromethoxybenzene.\textsuperscript{134a} A highly volatile solvent (pentane) was therefore chosen for the purification. Careful monitoring of the evaporation under reduced pressure was necessary, as well as the use of a cold water bath.

When difluorophenoxyacetic acid \textsuperscript{4.44} was subjected to the XeF\textsubscript{2}-mediated fluorodecarboxylation, trifluoromethoxybenzene \textsuperscript{1.83} was detected in 79\% yield by \textsuperscript{19}F and isolated in 39\% yield due to its high volatility. Trifluoromethyl aryl ether \textsuperscript{1.83a} was isolated in 66\% yield, a higher yield than previously obtained using the photo-mediated fluorodecarboxylation method (61\%. See: 4.3.1.4, Table 4.8, entry 6). Increasing the electron-density on the substrate led to decomposition of the starting material and/or product. Only 2\% of product \textsuperscript{1.83f} were detected by NMR, along with 20\% remaining starting material and some unidentified, non-fluorinated impurities. Electron-poor substrates were obtained in very good yield (\textsuperscript{1.83c}, \textsuperscript{1.83g}, \textsuperscript{1.83i} and \textsuperscript{1.83j}, Scheme 4.28). While product \textsuperscript{1.83c} could not be isolated due to its high volatility, heavier substrates could be accessed in good yields (\textsuperscript{1.83g}, \textsuperscript{1.83i}, and \textsuperscript{1.83j}, Scheme 4.28). Substitution at the meta- position did not impact significantly the yield of the reaction (\textsuperscript{1.83j}, Scheme 4.28). When another electron-withdrawing substituent was added in the ortho- position the yield dropped to 38\%. The decrease in electron-density might lead to a slower rate of fluorine abstraction, allowing the reactive intermediate to decompose faster via other pathway. The proximity of the otho-substituent to the reactive alkyl radical might also have led to side reactions. Similarly, low yields were obtained for substrate \textsuperscript{1.83l}, bearing a \textit{t}-butyl group in the ortho- position. About 20\% remaining starting material were detected, and traces of impurities were observed both in \textsuperscript{1}H and \textsuperscript{19}F NMR that could not be assigned. Again, the proximity of the otho-substituent might have allowed side reactions to occur. It is also possible that the added electron-density due to the presence of a second alkyl group led to degradation as observed for substrate \textsuperscript{4.44l}. Finally, when the radical-trap \textsuperscript{1.83e} was subjected to the reaction conditions, no trifluoromethoxylated or cyclized products were detected. Alkenes are known to react with XeF\textsubscript{2} and substrate \textsuperscript{4.44e} might have decomposed via other pathways.
As discussed in the introductory chapter (see 1.3.3), XeF$_2$-mediated fluorodecarboxylation can proceed via a radical mechanism, or a SET/ionic mechanism. No conclusion on the nature of the mechanism could be drawn from the reaction of radical clock 4.44. The influence of the reaction vessel on the reaction outcome supports a radical mechanism. Indeed, formation of the trifluoromethyl aryl ethers was favored when plastic vials were used, conditions that have been shown to favor radical pathways.\textsuperscript{31} Based on previous reports on fluorodecarboxylation (see 1.3.3), the following mechanism is proposed (Scheme 4.29). Formation of xenon esters from the reaction of carboxylic acids with XeF$_2$ has previously been observed\textsuperscript{84} and proposed as initial step of the fluorodecarboxylation by Patrick \textit{et al.}\textsuperscript{83b} Homolytic cleavage of this ester, followed by radical decarboxylation affords a radical intermediate. Atomic fluorine transfer most likely
occur from the xenon radical and not XeF₂, as one equivalent of xenon difluoride only was needed for the reaction to occur.

Scheme 4.29 Proposed mechanism for the XeF₂-mediated fluorodecarboxylation of difluorophenoxyacetic acids

4.3.2.5 Comparison with the currently available methods
The fluorodecarboxylation of difluorophenoxyacetic acid derivatives using xenon difluoride offers a synthetically relevant radical approach to the synthesis of trifluoromethyl aryl ethers. Similarly to the halogen/fluorine exchange and the fluorodeoxygenation and fluorodesulfurization methods, this fluorodecarboxylation method requires the installation of a more complex functional group that will be converted to the trifluoromethyl ether. Contrarily to those methods, the fluorodecarboxylation reaction does not require the use of toxic reagents (SF₄) or the highly corrosive HF. The “two-step process” from readily available starting material can be considered less atom-efficient than the direct utilization of phenols¹⁹⁷ or aryl stannanes and aryl boronic acids.²⁰⁰ Those methodologies, however, both require large amount of fluorinating agents, oxidants, as well as superstoichiometric amounts of silver salts. Furthermore, both experimental procedures are relatively complex. The fluorodecarboxylation method reported in this chapter allows access to trifluoromethyl aryl ethers using only one reagent, following a simple experimental procedure requiring no transition metals or tin derivatives.

A promising preliminary substrate scope was presented, and the reaction seems applicable to the synthesis of electron-poor substrates. This methodology appears limited for the synthesis of more electron-rich substrates, due to the competitive side reactions. This limitation might be
overcome by the use of more electron-withdrawing oxygenated-substituents (mesylate or esters). Other trifluoromethoxylation methods are still more efficient for the direct access to electron-rich trifluoromethyl aryl ethers.

### 4.4 Conclusion and future work

The synthesis of trifluoromethyl aryl ethers by fluorodecarboxylation of difluorophenoxyacetic acid derivatives was investigated. The UV-light mediated photofluorodecarboxylation described in Chapter 3 was first employed. A 254 nm irradiation was necessary to induce the excitation of the difluorophenoxyacetic acid derivatives. The desired products proved, however, to be unstable under those reaction conditions. A photosensitized fluorodecarboxylation was developed utilizing benzophenone as sensitizer allowing the use of a 350 nm irradiation.

Using a photosensitizer, better yields of the trifluoromethyl aryl ethers could be obtained. The scope of the reaction, however, was limited. The slow rate of fluorine transfer compared to side reactions was identified as one of the main challenges of this methodology. Using a faster fluorine transfer agent, XeF$_2$, fluorodecarboxylation proceeded smoothly without the need for light-irradiation. A broader scope of difluorophenoxyacetic acids was tolerated, and various trifluoromethyl aryl ethers were obtained in good yields. The full scope of the reaction, including heteroaryl substrates is currently under investigation by Meruyert Binayeva and Maxim Epifanov in the group of Prof. Sammis. The influence of the electron-density of the aryl ring and the position of the substituents will be further studied.

This reaction has the potential to be applied for PET-tracers synthesis. Radiolabelled $[^{18}\text{F}]XeF_2$ is easily accessible from XeF$_2$ and $[^{18}\text{F}]F$. The short reaction time of the fluorodecarboxylation and the easy purification of the products (see 4.5.3) allow rapid access to trifluoromethyl aryl ethers, compatible with the $^{18}\text{F}$ half-life (110 min.). Due to the potential application in medical imaging, a patent application has been filed at the University of British Columbia.

### 4.5 Experimentals

All reactions were performed under nitrogen atmosphere in flame-dried glassware unless otherwise noted. A KD-Scientific KDS100 syringe pump was used for all slow additions. All
Chapter 4 Synthesis of trifluoromethyl aryl ethers by fluorodecarboxylation

Chemicals were purchased from commercial sources and used as received. N,N-Dimethylformamide (DMF) was dried on 4Å molecular sieves, distilled under reduced pressure and stored on 4Å molecular sieves under N₂. All other solvents were used without further purification.

Reactions were monitored using Macherey-Nagel SIL G-25 UV₂54+366 aluminium backed plates. TLC's were visualized by UV fluorescence (254 nm) then one of the following stains: KMnO₄, p-anisaldehyde, vanillin. Flash column chromatography was performed using Silicycle P60 silica: 230-400 mesh (40-63 μm) silica.

Ultraviolet-visible (UV/VIS) spectra were obtained using a Varian Cary 5000 spectrophotometer. Melting points were performed using a Mel-Temp II apparatus (Lab devices USA) and are uncorrected. Infrared (IR) spectra were obtained using a Thermo Nicolet 4700 FT-IR spectrometer or a Perkin Elmer Frontier FT-IR. High resolution mass spectra (HRMS) were recorded on either a Waters or Micromass LCT spectrometer. NMR spectra were recorded using a Bruker AV-300 or AV-400 spectrometer. ¹H frequency is at 400.13 MHz, ¹³C frequency is at 100.62 MHz, ¹⁹F frequency is at 316.50 MHz. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual solvent peaks rounded to the nearest 0.01 for proton and 0.1 for carbon (ref: CHCl₃ [¹H: 7.26, ¹³C: 77.0], CH₂Cl₂ [¹H: 5.32, ¹³C 53.8]). Coupling constants (J) are reported in Hz to the nearest 0.1 Hz. Peaks multiplicity is indicated as follows s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). GC analysis were performed on a Bruker 450 GC equipped with an autosampler (5 μL syringe, 0.1 μL injection). GC-FID analysis: 50 to 250 ºC temperature gradient at 15 ºC/min

### 4.5.1 Synthesis of ethyl 2-aryloxy-2,2-difluoroacetate (4.43)

![Reaction Scheme]

To a 0.16 M solution of phenol derivative (1 equiv.) in dry DMF was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 2.5 equiv.) and the reaction was heated to 70 ºC. Ethyl bromodifluoroacetate (2.5 equiv.) was added via a syringe pump at 8.0 mL/h and the
reaction was stirred at 70 °C for 16 h. The crude mixture was cooled to room temperature, diluted with H2O (the amount of DMF used), and extracted with Et2O (5x half the amount of DMF used). The combined organic layers were washed with water (2x half the amount of DMF used) and brine (1x half the amount of DMF used), dried with Na2SO4, filtered and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography to afford the pure ester.

**Ethyl 2-(4-(t-butyl)phenoxy)-2,2-difluoroacetate (4.43a)**

![Chemical Structure](image)

4-(t-Butyl)phenol (3.00 g, 20.0 mmol) was subjected to the general ethyl 2-aryloxy-2,2-difluoroacetate synthesis procedure. Purification by flash column chromatography 7:1 hexanes/EtOAc afforded 3.61 g of compound 4.43a (13.3 mmol, 66% yield) as a colorless oil. 1H NMR (400 MHz; CDCl3): δ 7.40-37 (m, 2H), 7.18-7.14 (m, 2H), 4.39 (d, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H), 1.33 (s, 9H). 19F NMR (282 MHz; CDCl3): δ -76.6. 13C NMR (101 MHz; CDCl3): δ 160.1 (t, J = 41.4 Hz), 149.4, 147.1, 126.4, 121.1, 114.0 (t, J = 272.7 Hz), 63.6, 34.5, 31.3, 13.8. IR (neat): 3677, 2969, 1776, 1509, 1394, 1173, 1105, 1077 cm⁻¹. HRMS-EI (m/z) [M]+ calcd for C14H18O3F2: 272.12244. Found: 272.12240.

**Ethyl 2-(4-fluorophenoxy)-2,2-difluoroacetate (4.44c)**

![Chemical Structure](image)

4-Fluorophenol (1.12 g, 10.0 mmol) was subjected to the general ethyl 2-aryloxy-2,2-difluoroacetate synthesis procedure. Purification by flash column chromatography 10:1 hexanes/EtOAc afforded 1.49 g of compound 4.44c (6.36 mmol, 64% yield) as a colorless oil. 1H NMR (400 MHz; CDCl3): δ 7.23-7.18 (m, 2H), 7.09-7.03 (m, 2H), 4.40 (d, J = 7.2 Hz, 2H), 1.38 (t, J = 7.2 Hz, 3H). 19F NMR (282 MHz; CDCl3): δ -77.1, -116.3 (m). 13C NMR (101 MHz; CDCl3): δ 160.6 (d, J = 246.4 Hz), 159.6 (t, J = 41.4 Hz), 145.1, 123.4 (d, J = 8.5 Hz), 116.2 (d, J = 23.6 Hz), 113.9 (t, J = 272.7 Hz), 63.7, 13.6. IR (neat): 2990, 1775, 1503, 1379, 1342, 1184, 1133, 1088, 1013, 850, 780 cm⁻¹. HRMS-EI (m/z) [M]+ calcd for C10H9O3F3: 234.05038. Found: 234.05025.
Ethyl 2,2-difluoro-2-(2-vinylphenoxy)acetate (4.43e)

2-Vinyl phenol (1.24 g, 4.66 mmol) was subjected to the general ethyl 2-aryloxy-2,2-difluoroacetate synthesis procedure. Purification by flash column chromatography 5:1 hexanes/EtOAc afforded 1.12 g of compound 4.43e (4.60 mmol, 90% yield) as a colorless oil. \(^1\)H NMR (400 MHz; CDCl\(_3\)): \(\delta\) 7.62-7.59 (m, 1H), 7.27-7.21 (m, 3H), 7.00 (dd, \(J = 17.7, 11.1\) Hz, 1H), 5.79 (d, \(J = 17.7\) Hz, 1H), 5.36 (d, \(J = 11.1\) Hz, 1H), 4.39 (q, \(J = 7.2\) Hz, 2H), 1.36 (t, \(J = 7.2\) Hz, 3H). \(^19\)F NMR (282 MHz; CDCl\(_3\)): \(\delta\) -76.1. \(^{13}\)C NMR (101 MHz; CDCl\(_3\)): \(\delta\) 159.9 (t, \(J = 41.4\) Hz), 146.8, 131.4, 130.5, 128.8, 126.5, 122.3, 116.4, 114.2 (t, \(J = 102.7\) Hz), 63.8, 31.1, 14.0. IR (neat): 3378, 2979, 2914, 2884, 1649, 1504, 1475, 1393, 1218, 1116 cm\(^{-1}\). HRMS-EI (m/z) [M]+ calcd for C\(_{12}\)H\(_{12}\)O\(_3\)F\(_2\): 242.0754. Found: 242.0752.

Ethyl 2,2-difluoro-2-(4-methoxyphenoxy)acetate (4.43f)

4-Methoxy phenol (1.86 g, 15.0 mmol) was subjected to the general ethyl 2-aryloxy-2,2-difluoroacetate synthesis procedure. Purification by flash column chromatography 5:1 hexanes/EtOAc afforded 1.85 g of compound 4.43f (7.50 mmol, 50% yield) as a colorless oil. \(^1\)H NMR (400 MHz; CDCl\(_3\)): \(\delta\) 7.16-7.13 (m, 2H), 6.88-6.85 (m, 2H), 4.38 (q, \(J = 7.1\) Hz, 2H), 3.80 (s, 3H), 1.37 (t, \(J = 7.1\) Hz, 3H). \(^19\)F NMR (282 MHz; CDCl\(_3\)): \(\delta\) -76.9.

Ethyl 2-(4-bromophenoxy)-2,2-difluoroacetate (4.43g)

4-Bromophenol (3.46 g, 20.0 mmol) was subjected to the general ethyl 2-aryloxy-2,2-difluoroacetate synthesis procedure. Purification by flash column chromatography 15:1 hexanes/EtOAc afforded 5.42 g of compound 4.43g (18.4 mmol, 92% yield) as a colorless oil. \(^1\)H NMR (400 MHz; CDCl\(_3\)): \(\delta\) 7.51-7.49 (m, 2H), 7.13-7.11 (m, 2H), 4.40
(d,  J = 7.1 Hz,  2H),  1.38 (t,  J = 7.1 Hz,  3H).  \(^{19}\)F NMR (282 MHz; CDCl\(_3\)):  δ -77.0.  
\(^{13}\)C NMR (101 MHz; CDCl\(_3\)):  δ 159.5 (t,  J = 40.9 Hz),  148.5,  132.7,  123.4,  119.6,  113.7 (t,  J = 274.7 Hz),  63.8,  13.8.  IR (neat):  3445,  2987,  1779,  1486,  1342,  1205,  1139,  1012 cm\(^{-1}\).  
HRMS-EI (m/z) [M]+ calcd for C\(_{10}\)H\(_{9}\)O\(_3\)F\(_2\)Br:  293.97031.  Found:  293.97009.

**Ethyl 2,2-difluoro-2-phenoxyacetate (4.43)**

![Chemical Formula: C\(_{10}\)H\(_{10}\)F\(_2\)O\(_3\)  Molecular Weight: 216.18](image)

Phenol (1.88 g, 20.0 mmol) was subjected to the general ethyl 2-aryloxy-2,2-difluoroacetate synthesis procedure. Purification by flash column chromatography 15:1 hexanes/EtOAc afforded 3.14 g of compound 4.43 (14.5 mmol, 73% yield) as a colorless oil.  \(^1\)H NMR (300 MHz; CDCl\(_3\)):  δ 7.40-7.36 (m, 2H),  7.28-7.22 (m, 3H),  4.49 (d,  J = 7.1 Hz,  2H),  1.37 (t,  J = 7.1 Hz,  3H).  \(^{19}\)F NMR (282 MHz; CDCl\(_3\)):  δ -76.6.  
\(^{13}\)C NMR (101 MHz; CDCl\(_3\)):  δ 159.8 (t,  J = 41.5 Hz),  149.4,  129.6,  126.3,  121.7,  114.0 (t,  J = 272.7 Hz),  63.6,  13.8.  IR (neat):  3074,  2989,  2939,  1783,  1591,  1491,  1378,  1343,  1200 cm\(^{-1}\).  
HRMS-EI (m/z) [M]+ calcd for C\(_{10}\)H\(_{10}\)O\(_3\)F\(_2\):  216.05980.  Found:  216.05988.

**Ethyl 2-(4-chlorophenoxy)-2,2-difluoroacetate (4.43i)**

![Chemical Formula: C\(_{10}\)H\(_{9}\)ClF\(_2\)O\(_3\)  Molecular Weight: 250.63](image)

4-Chlorophenol (2.57 g, 20.0 mmol) was subjected to the general ethyl 2-aryloxy-2,2-difluoroacetate synthesis procedure. Purification by flash column chromatography 5:1 hexanes/EtOAc afforded 3.54 g of compound 4.43i (14.1 mmol, 71% yield) as a colorless oil.  \(^1\)H NMR (400 MHz; CDCl\(_3\)):  δ 7.37-7.32 (m, 2H),  7.21-7.13 (m, 2H),  4.40 (d,  J = 7.1 Hz,  2H),  1.38 (t,  J = 7.1 Hz,  3H).  \(^{19}\)F NMR (282 MHz; CDCl\(_3\)):  δ -76.9.  
\(^{13}\)C NMR (101 MHz; CDCl\(_3\)):  δ 159.8 (t,  J = 41.5 Hz),  147.9,  131.9,  129.7,  123.1,  113.8 (t,  J = 273.7 Hz),  63.8,  13.8.  IR (neat):  2989,  1775,  1487,  1378,  1342,  1197,  1166,  1132,  1088 cm\(^{-1}\).  
HRMS-EI (m/z) [M]+ calcd for C\(_{10}\)H\(_{9}\)O\(_3\)F\(_2\)Cl:  250.02083.  Found:  250.02052.

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Ethyl 2-(3-bromophenoxy)-2,2-difluoroacetate (4.43j)

3-Bromophenol (1.06 mL, 1.73 g, 10.0 mmol) was subjected to the general ethyl 2-aryloxy-2,2-difluoroacetate synthesis procedure. Purification by flash column chromatography 10:1 hexanes/EtOAc afforded 2.61 g of compound 4.43j (8.84 mmol, 88% yield) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.44-7.41 (m, 2H), 7.29-7.18 (m, 2H), 4.41 (d, $J$ = 7.1 Hz, 2H), 1.39 (t, $J$ = 7.1 Hz, 3H). $^{19}$F NMR (282 MHz; CDCl$_3$): $\delta$ -76.9. $^{13}$C NMR (101 MHz; CDCl$_3$): $\delta$ 159.4, 144.6, 132.4, 130.5, 128.7, 127.9, 124.2, 113.8 (t, $J$ = 276.7 Hz), 63.8, 13.8. IR (neat): 2988, 1777, 1585, 1473, 1342, 1197, 1137 cm$^{-1}$. HRMS-EI (m/z) [M]$^+$ calcd for C$_{10}$H$_9$BrF$_2$O$_3$: 293.97031. Found: 293.97001.

Ethyl 2-(2,4-dichlorophenoxy)-2,2-difluoroacetate (4.43k)

2,4-Dichlorophenol (3.26 g, 20.0 mmol) was subjected to the general ethyl 2-aryloxy-2,2-difluoroacetate synthesis procedure. Purification by flash column chromatography 15:1 hexanes/EtOAc afforded 4.36 g of compound 4.43k (15.3 mmol, 76% yield) as a colorless oil. $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.48 (d, $J$ = 2.3 Hz, 1H), 7.32-7.24 (m, 2H), 4.43 (d, $J$ = 7.1 Hz, 2H), 1.40 (t, $J$ = 7.1 Hz, 3H). $^{19}$F NMR (282 MHz; CDCl$_3$): $\delta$ -76.9. $^{13}$C NMR (101 MHz; CDCl$_3$): $\delta$ 159.1 (t, $J$ = 40.5 Hz), 144.6, 132.4, 130.5, 128.7, 127.9, 124.2, 113.8 (t, $J$ = 276.7 Hz), 63.8, 13.8. IR (neat): 3100 (w), 2988 (w), 1780 (s), 1583 (w), 1476 (s), 1379 (m), 1342 (m), 1221 (s), 1139 (s) cm$^{-1}$. HRMS-EI (m/z) [M]$^+$ calcd for C$_{10}$H$_8$O$_3$F$_2$Cl$_2$: 283.98186. Found: 283.98164.

Ethyl 2-(2,4-di-t-butylphenoxy)-2,2-difluoroacetate (4.43l)

2,4-Di-t-butylphenol (4.13 g, 20.0 mmol) was subjected to the general ethyl 2-aryloxy-2,2-difluoroacetate synthesis procedure. Purification by flash column
chromatography 15:1 hexanes/EtOAc afforded 1.72 g of compound 4.431 (5.23 mmol, 26% yield) as a colorless oil. $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.40-7.38 (m, 1H), 7.21-7.15 (m, 2H), 4.38 (q, $J = 7.2$ Hz, 2H), 1.39 (s, 9H), 1.32 (t, $J = 7.2$ Hz, 3H), 1.31 (s, 9H). $^{19}$F NMR (282 MHz; CDCl$_3$): $\delta$ -74.2. $^{13}$C NMR (101 MHz; CDCl$_3$) $\delta$ 160.1 (t, $J = 34.3$ Hz), 147.7, 147.1, 139.6, 124.8, 123.9, 118.6, 114.4 (t, $J = 272.7$ Hz), 63.6, 35.1, 34.7, 31.6, 30.3, 13.9. IR (neat): 3676, 2963, 2901, 1777, 1497, 1364, 1192, 1122, 1083 cm$^{-1}$. HRMS-ESI (m/z) [M$-$H]$^+$ calcd for C$_{18}$H$_{26}$O$_3$F$_2$: 328.1850. Found: 328.1853.

4.5.2 Synthesis of 2-aryloxy-2,2-difluoroacetic acids (4.44)

The ester 4.43 was dissolved in a 2:1 mixture of MeOH/THF (0.35 M). A 3.0 M solution of NaOH$_{aq}$ (3 equiv.) was added in one portion and the reaction was stirred at room temperature until completion was observed by TLC (1 to 16 h). The reaction mixture was concentrated under reduced pressure, acidified to pH = 2 with 1.0 M HCl$_{aq}$ and extracted with DCM (3x half the amount of solvent used for the reaction). The combined organic layers were dried with Na$_2$SO$_4$, filtered and concentrated under reduced pressure to afford the acid 4.44.

2-(4-(tert-butyl)phenoxy)-2,2-difluoroacetic acid (4.44a)

Ester 4.43a (3.61 g, 13.2 mmol) was subjected to the general 2-aryloxy-2,2-difluoroacetic acid synthesis procedure. After evaporation under reduced pressure, 1.85 g of acid 4.44a were obtained as a pale pink solid (7.58 mmol, 57% yield). m.p. 70-73 °C. $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 11.55 (s, 1H), 7.44-7.42 (m, 2H), 7.22-7.20 (m, 2H), 1.36 (s, 9H). $^{19}$F NMR (282 MHz; CDCl$_3$): $\delta$ -76.5. $^{13}$C NMR (101 MHz; CDCl$_3$): $\delta$ 164.0 (t, $J = 42.7$ Hz), 149.6, 146.7, 126.6, 121.1, 113.6 (t, $J = 271.6$ Hz), 34.5, 31.3. IR (neat): 3476, 2965, 2872, 1766, 1509, 1211, 1149, 1017 cm$^{-1}$. HRMS-ESI (m/z) [M-H]$^+$ calcd for C$_{12}$H$_{13}$O$_3$F$_2$: 243.0833. Found: 243.0832.
**2,2-difluoro-2-(4-fluorophenoxy)acetic acid (4.44c)**

![Chemical Structure](image)

Ester **4.43c** (1.49 g, 6.36 mmol) was subjected to the general 2-aryloxy-2,2-difluoroacetic acid synthesis procedure. After evaporation under reduced pressure, 895 mg of acid **4.44c** were obtained as brown oil (4.34 mmol, 68% yield). \(^1\)H NMR (400 MHz; CDCl\(_3\)): \(\delta\) 10.02 (s, 1H), 7.25-7.20 (m, 2H), 7.12-7.06 (m, 2H). \(^{19}\)F NMR (282 MHz; CDCl\(_3\)): \(\delta\) -77.3, -115.6 (m). \(^{13}\)C NMR (101 MHz; CDCl\(_3\)): \(\delta\) 162.9 (t, \(J = 42.3\) Hz), 160.8 (d, \(J = 245.8\) Hz), 144.8, 123.5 (d, \(J = 8.6\) Hz), 116.4 (d, \(J = 23.6\) Hz), 113.5 (t, \(J = 272.7\) Hz). IR (neat): 3676, 2990, 2902, 1768, 1486, 1453, 1176, 1145 cm\(^{-1}\). HRMS-ESI (m/z) [M-H] \text{calcld for C}_{8}H_{7}F_{3}O_{3}: 205.0113. Found: 205.0118.

**2,2-difluoro-2-(2-vinylphenoxy)acetic acid (4.44e)**

![Chemical Structure](image)

Ester **4.43e** (1.18 g, 4.87 mmol) was subjected to the general 2-aryloxy-2,2-difluoroacetic acid synthesis procedure. After evaporation under reduced pressure, 869 mg of acid **4.44e** were obtained as a pale yellow oil (4.05 mmol, 83% yield). \(^1\)H NMR (400 MHz; CDCl\(_3\)): \(\delta\) 7.63-7.61 (m, 1H), 7.29-7.26 (m, 3H), 7.00 (dd, \(J = 17.7, 11.1\) Hz, 1H), 5.80 (d, \(J = 17.7\) Hz, 1H), 5.38 (d, \(J = 11.1\) Hz, 1H). \(^{19}\)F NMR (282 MHz; CDCl\(_3\)): \(\delta\) -97.6. \(^{13}\)C NMR (101 MHz; CDCl\(_3\)): \(\delta\) 163.5 (t, \(J = 42.6\) Hz), 146.4, 131.5, 130.3, 128.9, 126.9, 126.6, 122.3, 116.7, 113.9 (t, \(J = 274.7\) Hz). IR (neat): 3070, 2572, 1765, 1486, 1453, 1176, 1145 cm\(^{-1}\). HRMS-ESI (m/z) [M-H] \text{calcld for C}_{10}H_{7}O_{3}F_{2}: 213.0363. Found: 213.0364.

**2,2-difluoro-2-(4-methoxyphenoxy)acetic acid (4.44f)**

![Chemical Structure](image)

Ester **4.43f** (1.85 g, 7.50 mmol) was subjected to the general 2-aryloxy-2,2-difluoroacetic acid synthesis procedure. After evaporation under reduced pressure and recrystallization from pentanes/EtOAc, 956 mg of acid **4.44f** were obtained as a white solid (4.38 mmol, 58% yield). m.p. 72-76 °C. \(^1\)H NMR (400 MHz; CDCl\(_3\)): \(\delta\) 8.24 (s, 1H), 7.16 (d, \(J = 9.0\) Hz, 2H), 6.89 (d,
$J = 9.0 \text{ Hz, 2H}$, 3.81 (s, 3H). $^{19}$F NMR (282 MHz; CDCl$_3$): $\delta$ -77.4. $^{13}$C NMR (101 MHz; CDCl$_3$): $\delta$ 163.3 (t, $J = 42.4 \text{ Hz}$), 158.0, 142.6, 123.2, 116.5, 113.8 (t, $J = 271.7 \text{ Hz}$), 55.8. IR (neat): 3491, 2983, 1722, 1504, 1352, 1148, 1081 cm$^{-1}$. HRMS-ESI (m/z) [M-H]$^-$ calcd for C$_9$H$_7$O$_4$F$_2$: 217.0312. Found: 217.0310.

2-(4-bromophenoxy)-2,2-difluoroacetic acid (4.44g)

Ester 4.43g (5.42 g, 18.4 mmol) was subjected to the general 2-aryloxy-2,2-difluoroacetic acid synthesis procedure. After evaporation under reduced pressure, 4.27 g of acid 4.44g were obtained as a pale beige solid (16.0 mmol, 87% yield). m.p. 40-44 °C. $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 11.44 (s, 1H), 7.53-7.51 (m, 2H), 7.14-7.12 (m, 2H). $^{19}$F NMR (282 MHz; CDCl$_3$): $\delta$ -77.4.

2,2-difluoro-2-phenoxyacetic acid (4.44)

Ester 4.43 (3.67 g, 17.0 mmol) was subjected to the general 2-aryloxy-2,2-difluoroacetic acid synthesis procedure. After evaporation under reduced pressure, 1.76 g of acid 4.44 were obtained as a brown oil (9.38 mmol, 55% yield). $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 10.62 (s, 1H), 7.45-7.40 (m, 2H), 7.34-7.26 (m, 3H). $^{19}$F NMR (282 MHz; CDCl$_3$): $\delta$ -77.0.

13C NMR (101 MHz; CDCl$_3$): $\delta$ 163.8 (t, $J = 42.4 \text{ Hz}$), 149.1, 129.7, 126.6, 121.6, 113.6 (t, $J = 272.1 \text{ Hz}$). IR (neat): 3077, 1765, 1591, 1491, 1189 cm$^{-1}$. HRMS-ESI (m/z) [M-H]$^-$ calcd for C$_8$H$_5$O$_3$F$_2$: 187.0207. Found: 187.0203.
2-(4-chlorophenoxy)-2,2-difluoroacetic acid (4.44i)

Ester 4.43i (3.54 g, 14.1 mmol) was subjected to the general 2-aryloxy-2,2-difluoroacetic acid synthesis procedure. After evaporation under reduced pressure, 2.93 g of acid 4.44i were obtained as a pale beige solid (13.2 mmol, 94% yield). m.p. 33-35 °C. \(^1\)H NMR (400 MHz; CDCl\(_3\)): \(\delta\) 10.65 (s, 1H), 7.38-7.35 (m, 2H), 7.20-7.17 (m, 2H). \(^19\)F NMR (282 MHz; CDCl\(_3\)) \(\delta\) -77.5. \(^13\)C NMR (101 MHz; CDCl\(_3\)): \(\delta\) 163.4 (t, \(J = 41.8\) Hz), 147.7, 132.4, 129.9, 123.2, 113.6 (t, \(J = 273.1\) Hz). IR (neat): 2877, 1759, 1487, 1303, 1189, 1141, 1076, 1015 cm\(^{-1}\). HRMS-ESI (m/z) [M-H]: calcld for C\(_8\)H\(_7\)ClF\(_2\): 220.9817. Found: 220.9808.

2-(3-bromophenoxy)-2,2-difluoroacetic acid (4.44j)

Ester 4.43j (2.61 g, 8.85 mmol) was subjected to the general 2-aryloxy-2,2-difluoroacetic acid synthesis procedure. After evaporation under reduced pressure, 1.88 g of acid 4.44j were obtained as a brown oil that partially solidifies at room temperature (7.04 mmol, 80% yield). \(^1\)H NMR (400 MHz; CDCl\(_3\)): \(\delta\) 8.50 (s, 1H), 7.44-7.42 (m, 2H), 7.28-7.18 (m, 2H). \(^19\)F NMR (282 MHz; CDCl\(_3\)) \(\delta\) -77.2. \(^13\)C NMR (101 MHz; CDCl\(_3\)): \(\delta\) 163.0 (t, \(J = 41.5\) Hz), 149.5, 130.7, 129.8, 125.1, 122.6, 120.3, 113.5 (t, \(J = 275.7\) Hz). IR (neat): 3075, 2567, 1767, 1584, 1472, 1188, 1143 cm\(^{-1}\). HRMS-ESI (m/z) [M-H]: calcld for C\(_8\)H\(_7\)BrF\(_2\): 264.9312. Found: 264.9315.

2-(2,4-dichlorophenoxy)-2,2-difluoroacetic acid (4.44k)

Ester 4.43k (4.90 g, 17.2 mmol) was subjected to the general 2-aryloxy-2,2-difluoroacetic acid synthesis procedure. After evaporation under reduced pressure, 2.62 g of acid 4.44k were obtained as a pale brown solid (10.2 mmol, 58% yield). m.p. 51-61 °C. \(^1\)H NMR (400 MHz; CDCl\(_3\)): \(\delta\) 10.33 (s, 1H), 7.50-7.49 (m, 1H), 7.33-7.26 (m, 2H). \(^19\)F NMR (282 MHz; CDCl\(_3\)) \(\delta\) -77.4. \(^13\)C NMR (101 MHz; CDCl\(_3\)): \(\delta\) 163.1 (t, \(J = 41.4\) Hz), 143.8, 132.8, 130.7, 128.8, 128.0,
124.3, 113.4 (t, J = 276.7 Hz). IR (neat): 3098, 2556, 1767, 1475, 1138, 1094 cm⁻¹. HRMS-ESI (m/z) [M-H]- calcd for C₈H₃O₃F₂Cl₂: 254.9427. Found: 254.9430.

2-(2,4-di-t-butylphenoxy)-2,2-difluoroacetic acid (4.44l)

Ester 4.43l (1.55 g, 4.75 mmol) was subjected to the general 2-aryloxy-2,2-difluoroacetic acid synthesis procedure. After evaporation under reduced pressure, 1.03 g of acid 4.44l were obtained as a white solid (3.43 mmol, 73% yield). m.p. 121-123 °C. ¹H NMR (400 MHz; CDCl₃): δ 9.12 (s, 1H), 7.41 (d, J = 2.2 Hz, 1H), 7.25-7.18 (m, 2H), 1.40 (s, 3H), 1.32 (s, 3H). ¹⁹F NMR (282 MHz; CDCl₃): δ -74.5. ¹³C NMR (101 MHz; CDCl₃): δ 164.7 (t, J = 42.4 Hz), 148.0, 146.8, 139.8, 124.9, 124.0, 118.8 (t, J = 3.0 Hz), 114.1 (t, J = 273.7 Hz), 35.1, 34.8, 31.6, 30.3. IR (neat): 2959, 2908, 2872, 1757, 1498, 1210, 1193, 1079 cm⁻¹. HRMS-ESI (m/z) [M-H]- calcd for C₁₆H₂₁O₃F₂: 299.1459. Found: 299.1460.

4.5.3 Xenon difluoride-mediated decarboxylative fluorination

Warning: Because of the production of Xenon and CO₂ over the course of the reaction, pressure can build up in the reaction vessel. We advise to choose a polypropylene vial with a screw cap and enough headspace to accommodate for the gas release. Furthermore, HF is most likely produced over the course of the reaction. Particular care is required when working up the reaction. Washing the reaction mixture with a saturated solution of NaHCO₃(aq.) is advised for large scale-ups.

Quantification using gas chromatography:

A calibration curve was built for substrate 1.83g using bromobenzene as the internal standard. 6 samples were prepared with concentration of analyte varying from 0.00125 M to 0.02 M and constant concentration in internal standard (0.01 M). A correlation factor of R² = 0.9995 was obtained.
In a 15 mL polypropylene vial, 0.1 mmol of the 2-aryloxy-2,2-difluoroacetic acid was dissolved in CDCl₃ (2.0 M). XeF₂ (17 mg, 0.1 mmol, 1 equiv.) was added in one portion and the vial was sealed. When gas evolution was no longer observed, the reaction was stirred for an additional minute, and bromobenzene (10 μL, 1 equiv.) was added as internal standard. An aliquot (≈ 100 μL) was added to a GC-vial and dissolved in methanol (≈ 1 mL). The concentration in trifluoromethyl aryl ether 1.83g was calculated using the regression equation obtained from the calibration curve.

**Determination of NMR yield:**
In a 15 mL polypropylene vial, 0.1 mmol of the 2-aryloxy-2,2-difluoroacetic acid was dissolved in CDCl₃ (2.0 M). XeF₂ (17 mg, 0.1 mmol, 1 equiv.) was added in one portion and the vial was sealed. When gas evolution was no longer observed, the reaction was stirred for an additional minute, and ethyl trifluoroacetate (12 μL, 1 equiv.) was added as internal standard. NMR yield were determined by ¹⁹F NMR using a relaxation delay (or recycle delay) of 30 seconds to ensure complete relaxation of all fluorine nuclei. Reported NMR yields are averaged over a minimum of three trials. Sample NMR spectra are given for substates 1.83c and 1.83l.

**Decarboxylative fluorination of 2-aryloxy-2,2-difluoroacetic acids using XeF₂:**
In a 15 mL polypropylene vial, 0.5 mmol of 2-aryloxy-2,2-difluoroacetic acid was dissolved in CDCl₃ (2.0 M). XeF₂ (0.5 mmol, 1 equiv.) was added in one portion and the vial was sealed. When gas evolution was no longer observed, the reaction was stirred for an additional minute. The reaction mixture was diluted with 2 mL of pentanes. The crude mixture was purified as such on a silica plug using pentanes. The solvent was removed at 5 °C under reduced pressure to minimize evaporation of the product.

**(trifluoromethoxy)benzene (1.83)**

Acid 4.44 was subjected to the NMR scale general procedure. ¹H and ¹⁹F NMR spectroscopy analysis of the crude reaction mixture confirmed the presence of (trifluoromethoxy)benzene 1.83. The reaction was repeated 3 times and the yield was determined by comparing the
integration of the fluorine signal of trifluoromethoxybenzene (-58.3 ppm) with that of ethyl trifluoroacetate (-75.7 ppm) to give 79%, 82% and 76% yield, or an average of 79% NMR yield.

In parallel, 196 mg (1.04 mmol) of acid 4.44 were subjected to the general decarboxylative fluorination procedure. After evaporation under reduced pressure, 65 mg of product 1.83 were obtained as a colorless oil (0.40 mmol, 39% yield). The characterization data matched with those of the commercially available compound (CAS: 456-55-3, TCI T1617). ¹H NMR (400 MHz; CD₂Cl₂): δ 7.45-7.40 (m, 2H), 7.35-7.29 (m, 1H), 7.26-7.22 (m, 2H). ¹³F NMR (282 MHz; CD₂Cl₂): δ -58.3 ppm. ¹³C NMR (101 MHz; CD₂Cl₂): δ 149.8 (m), 130.4, 127.5, 121.5, 121.1 (q, J = 257.6 Hz).

1-(t-butyl)-4-(trifluoromethoxy)benzene (1.83a)

![Chemical structure of 1.83a]

Acid 4.44a (246 mg, 1.01 mmol) was subjected to the general decarboxylative fluorination procedure. After evaporation under reduced pressure, 136 mg of product 1.83a were obtained as a colorless oil (0.623 mmol, 62% yield). ¹H NMR (400 MHz; CD₂Cl₂): δ 7.45-7.40 (m, 2H), 7.35-7.30 (m, 1H), 7.26-7.22 (m, 2H). ¹⁹F NMR (282 MHz; CD₂Cl₂): δ -56.7 ppm. ¹³C NMR (101 MHz; CD₂Cl₂): δ 149.8 (m), 130.4, 127.5, 121.5, 121.1 (q, J = 257.6 Hz).

IR (neat): 2967, 1512, 1256, 1212, 1158, 1110, 1019 cm⁻¹. HRMS-EI (m/z) [M]+ calcd for C₁₁H₁₃OF₃: 218.0918. Found: 218.0917.

1-fluoro-4-(trifluoromethoxy)benzene (1.83c)

![Chemical structure of 1.83c]

Acid 4.44c was subjected to the NMR scale general procedure. ¹H and ¹⁹F NMR spectroscopy analysis of the crude reaction mixture confirmed the presence of 1-fluoro-4-(trifluoromethoxy)benzene 1.83c (Figure 4.8). The reaction was repeated 3 times and the yield was determined by comparing the integration of the fluorine signal of 1-fluoro-4-(trifluoromethoxy)benzene (-58.9 ppm and -115.6 ppm) with that of ethyl trifluoroacetate (-75.7 ppm) to give 72%, 77% and 74% yield, or an average of 74% NMR yield.
1-bromo-4-(trifluoromethoxy)benzene (1.83g)

Acid **4.44g** (128 mg, 0.479 mmol) was subjected to the general decarboxylative fluorination procedure. After evaporation under reduced pressure, 77 mg of product **1.83g** were obtained as a colorless oil (0.32 mmol, 67% yield). The characterization data matched with those of the commercially available compound (CAS: 407-14-7, TCI B1772). **1H NMR** (400 MHz, CDCl3): δ 7.56-7.50 (m, 2H), 7.16-7.10 (m, 2H). **19F NMR** (282 MHz; CDCl3): δ -58.5. **13C NMR** (101 MHz; CDCl3): δ 148.3 (q, J = 2.0 Hz), 132.9, 122.7, 120.4 (q, J = 258.6 Hz), 120.1. IR (neat): 1487, 1255, 1209, 1068, 1013 cm⁻¹. HRMS-El (m/z) [M]+ calcd for C₇H₄OF₃⁷⁹Br: 239.9398. Found: 239.9399.

![NMR Spectra](image)
1-chloro-4-(trifluoromethoxy)benzene (1.83i)

Acid 4.44i was subjected to the NMR scale general procedure. $^1$H and $^{19}$F NMR spectroscopy analysis of the crude reaction mixture confirmed the presence of 1-chloro-4-(trifluoromethoxy)benzene 1.83i. The reaction was repeated 3 times and the yield was determined by comparing the integration of the fluorine signal of 1-chloro-4-(trifluoromethoxy)benzene (-58.5 ppm) with that of ethyl trifluoroacetate (-75.7 ppm) to give 70%, 71% and 76% yield, or an average of 72% NMR yield.

In parallel, 224.1 mg (1.14 mmol) of acid 4.44i were subjected to the general decarboxylative fluorination procedure. After evaporation under reduced pressure, 107 mg of product 1.83i were obtained as a colorless oil (0.544 mmol, 54% yield). $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.40-7.36 (m, 2H), 7.18-7.16 (m, 2H). $^{19}$F NMR (282 MHz; CDCl$_3$): $\delta$ -58.5. $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 147.7 (q, $J = 3.0$ Hz), 129.9, 124.2, 122.4, 120.3 (q, $J = 258.6$ Hz). IR (neat): 2967, 1489, 1260, 1215, 1166, 1071, 1018 cm$^{-1}$.

1-bromo-3-(trifluoromethoxy)benzene (1.83j)

Acid 4.44j was subjected to the NMR scale general procedure. $^1$H and $^{19}$F NMR spectroscopy analysis of the crude reaction mixture confirmed the presence of 1-bromo-3-(trifluoromethoxy)benzene 1.83j. The reaction was repeated 3 times and the yield was determined by comparing integration of the peak of 1-bromo-3-(trifluoromethoxy)benzene (-58.4 ppm) with that of ethyl trifluoroacetate (-75.7 ppm), to give 60%, 64% and 67% yield, or an average of 64% NMR yield.

In parallel, 323.5 mg (1.21 mmol) of acid 4.44j were subjected to the general decarboxylative fluorination procedure. After evaporation under reduced pressure, 173 mg of product 1.83j were obtained as a colorless oil (0.720 mmol, 59% yield). $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.43-7.38 (m, 2H), 7.27-7.23 (m, 1H), 7.16-7.13 (m, 1H). $^{19}$F NMR (282 MHz; CDCl$_3$): $\delta$ -58.4.
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$^{13}$C NMR (101 MHz; CDCl$_3$): $\delta$ 149.6 (m), 130.9, 130.1, 124.4, 122.7, 119.6, 120.3 (q, $J$ = 259.6 Hz). HRMS-EI (m/z) [M]$^+$ calcd for C$_7$H$_4$OF$_3$Br: 239.9398. Found: 239.9399.

2,4-dichloro-1-(trifluoromethoxy)benzene (1.83k)

Acid 4.44k was subjected to the NMR scale general procedure. $^1$H and $^{19}$F NMR spectroscopy analysis of the crude reaction mixture confirmed the presence of product 1.83k. The reaction was repeated 5 times and the yield was determined by comparing integration of the peak of 2,4-dichloro-1-(trifluoromethoxy)benzene (-58.4 ppm) with that of ethyl trifluoroacetate (-75.7 ppm), to give 35%, 34%, 39%, 37% and 32% yield, or an average of 35 % NMR yield.

In parallel, 254 mg (0.989 mmol) of acid 4.44k were subjected to the general decarboxylative fluorination procedure. After evaporation under reduced pressure, 88 mg of 2,4-dichloro-1-(trifluoromethoxy)benzene 1.83k were obtained as a colorless oil. (0.38 mmol, 38% yield). $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.52-7.51 (m, 1H), 7.29-7.28 (m, 2H). $^{19}$F NMR (282 MHz; CDCl$_3$): $\delta$ -58.4. $^{13}$C NMR (101 MHz; CDCl$_3$): $\delta$ 143.9, 133.0, 130.8, 128.5, 128.1, 123.5, 120.4 (q, $J$ = 260.6 Hz). IR (neat): 2932, 1489, 1260, 1211, 1162, 1071 cm$^{-1}$. HRMS-EI (m/z) [M]$^+$ calcd for C$_7$H$_3$OF$_3$Cl$_2$: 229.9513. Found: 229.9514.

2,4-di-t-butyl-1-(trifluoromethoxy)benzene (1.83l)

Acid 4.44l was subjected to the NMR scale general procedure. $^1$H and $^{19}$F NMR spectroscopy analysis of the crude reaction mixture confirmed the presence of 2,4-di-t-butyl-1-(trifluoromethoxy)benzene 1.83l. The reaction was repeated 3 times and the yield was determined by comparing the integration of the fluorine signal of 2,4-di-t-butyl-1-(trifluoromethoxy)benzene (-54.5 ppm) with that of ethyl trifluoroacetate (-75.7 ppm), to give 6%, 8%, and 7%, or an average of 64 % NMR yield.
Figure 4.9 Sample $^{19}$F NMR yield determination for substrate 1.831 and $^1$H NMR crude NMR spectra.
Chapter 5 Copper-catalyzed intermolecular carboetherification of unactivated alkenes using alkyl nitriles

Synthetic procedures enabling the rapid building of molecular complexity from readily available starting material are highly desirable. In this chapter, the development of a copper-catalyzed three-component carboetherification of alkenes using unfunctionalized alkyl nitriles will be described. An overview of the currently available methods for the three-component carboetherification of alkenes will first be provided. The development of a carboetherification reaction of unactivated alkenes using methanol as solvent and nucleophile will then be presented. Finally, the mechanistic aspect of the reaction will be discussed.

5.1 Introduction

The difunctionalization of alkenes (Scheme 5.1) is a powerful method for the rapid building of molecular complexity from readily available starting material.\(^{224}\) The formation of two bonds in a one-pot procedure allows the faster synthesis of molecules by reducing the number of synthetic steps and purification procedures.\(^{225}\) Metal-catalyzed difunctionalization of alkenes has been extensively studied in recent years, and numerous methods have been developed for the addition of various functional groups across alkenes.\(^{226}\) Among those methods, the carboetherification reaction focuses on the one step formation of a $\text{C}(\text{sp}^3)-\text{O}$ bond and a $\text{C}(\text{sp}^3)-\text{C}$ bond. The metal-catalyzed intramolecular carboetherification of alkenes has been thoroughly investigated and has found a wide application notably for the synthesis of heterocyclic compounds.\(^{225,226}\) The three-component intermolecular variant of this reaction would allow a faster access to a diversity of compounds by allowing to vary a third reagent. However, only a few examples of three-component carboetherification of alkenes have been reported. Those methodologies mainly focus on the oxy-trifluoromethylation and the oxy-arylation of alkenes, while a few allow the introduction of more synthetically versatile handles.
5.1.1 Intermolecular oxy-trifluoromethylation

The oxy-trifluoromethylation of alkenes has been one of the most heavily investigated of the intermolecular carboetherification reactions. The majority of the methodologies developed involves the formation of trifluoromethyl radicals from trifluoromethylating agents.\textsuperscript{228} Nagano \textit{et al.} first reported the oxy-trifluoromethylation of \(\alpha,\beta\)-unsaturated esters using CF\(_3\)I as the trifluoromethyl radical source and triethyl borane as radical initiator (Scheme 5.2).\textsuperscript{229} Experimental evidence supports a chain propagation mechanism, affording the iodo-trifluoromethylated product that subsequently undergoes hydrolysis to the oxy-trifluoromethylated product 5.2. Low to good yields were obtained and a low diastereoselectivity was observed. The substrate scope of the reaction was later expanded, and the reaction applied to longer perfluorinated alkyl iodides, an \(\alpha\)-iodoester and iodoalkanes.\textsuperscript{229b}
The possibility of using Togni’s reagent (4.20, Scheme 5.3) for the intermolecular carboetherification of alkenes was first demonstrated by Szabó et al. (Scheme 5.3). The addition of the trifluoromethyl and benzoic acid moieties occurred in high regioselectivity and the difunctionalized compounds were obtained in good yields. The rate acceleration observed for substrates bearing electron-donating substituents supports an electrophilic mechanism. Sodeoka et al. later reported a similar method using milder reaction conditions. A broader substrate scope was presented, and the reaction could be extended to dienes. The oxy-trifluoromethylated products were obtained in generally excellent yields with good regioselectivity. When alcohols were used as solvents, the authors observed the formation of the solvent addition products.

Scheme 5.3 Oxy-trifluoromethylation using Togni’s reagent

A copper-catalyzed oxy-trifluoromethylation of enamides using Togni’s reagent was developed by Loh et al. (Scheme 5.4). Methanol was used as solvent and nucleophile. The choice of the copper source impacted the reaction outcome: when CuCl was used, the difunctionalized compounds 5.7 were obtained, but the more Lewis acidic Cu(CH₃CN)₄PF₆ favored an elimination and the formation of trifluoromethylenamides. While the authors could not rule out the presence of radical intermediates, an ionic mechanism was proposed.
Studer et al. developed a transition metal-free oxy-trifluoromethylation of alkenes (Scheme 5.5). Trifluoromethyl radicals and TEMPO were generated by reaction of sodium aminoalkoxide 5.9 with Togni’s reagent 4.20. Radical addition of the trifluoromethyl moiety to the alkene generates an alkyl radical that recombines with TEMPO to afford the oxy-trifluoromethylated product. Styrene derivatives and aliphatic terminal alkenes were difunctionalized in good to excellent yields, while lower yields were obtained for electron-poor substrates such as methylacrylates. When internal alkenes were used, excellent trans-diastereoselectivity was observed. The N—O bond can subsequently be cleaved by reaction with Zn in presence of AcOH. One example of introduction of pentafluoroethane was also presented.

Scheme 5.5 Transition metal-free oxy-trifluoromethylation of alkenes
Akita et al. reported the first use of photocatalysis to promote the oxy-trifluoromethylation of alkenes (Scheme 5.6). The Umemoto reagent (5.11, Scheme 5.6) was used as the trifluoromethyl source. Togni's reagent 4.20 could also be employed, albeit in lower yields. The reaction was applicable to a wide range of styrene derivatives and gem-disubstituted alkenes. When internal alkenes were used, products were obtained in good yields but generally low diastereoselectivity. Various alcohols and carboxylic acids could be used as nucleophiles. A radical mechanism was proposed for this transformation (Scheme 5.6). Reaction of the photocatalyst in its excited state with the Umemoto reagent furnishes a trifluoromethyl radical that adds to the alkene. The higher yields obtained for electron-rich alkenes are consistent with the reactivity of the electrophilic trifluoromethyl radical. The resulting alkyl radical is then oxidized to a carbocation that traps the oxygen nucleophile, affording the difunctionalized product.

\[
\begin{align*}
\text{Scheme 5.6 Photocatalyzed oxy-trifluoromethylation of alkenes}^{234}
\end{align*}
\]

A photocatalyzed approach to the oxy-trifluoromethylation of ene-carbamates was later reported by Magnier, Masson et al. In this study, Togni's reagent was used as the trifluoromethylating agent. Various internal alkenes were subjected to the reaction conditions
affording the difunctionalized compounds in good to excellent yields with low diastereoselectivity. Methanol, ethanol, isopropanol could be used as solvent and nucleophile in the reaction, as well as water using a 1:1 THF/water mixture. Benzylthiourea, benzylthiocarbamate and t-butylcarbamates were also compatible with the reaction conditions.

![Scheme 5.7](image)

Scheme 5.7 Photocatalyzed oxy-trifluoromethylation of ene-carbamates

Qing et al. used the Langlois' reagent (5.14, Scheme 5.8) as trifluoromethyl source for the oxy-trifluoromethylation of alkenes. Hydroxamic acid 5.13 was used as oxygen source. Trifluoromethyl radicals and amidoxyl radicals were generated from 5.14 and 5.13 respectively using copper-catalysis (Scheme 5.8). The reaction was applied to aromatic and aliphatic substituted alkenes and showed a wide functional group tolerance, including esters, amides, free alcohols and halogens.
Some methods for the oxy-trifluoromethylation of alkenes have been developed that allow the formation of \( \alpha \)-trifluoromethyl ketones. Xiao et al. reported the use of trifluoromethylsulfonium 5.17 as the trifluoromethylationating agent for the formation of \( \alpha \)-trifluoromethyl ketones from styrenes (Scheme 5.9).\(^{237}\) The generation of trifluoromethyl radicals from the reaction of 5.17 with the reducing agent 5.18 and their subsequent addition to the styrene was proposed as working mechanism. Control experiments support the role of \( \text{O}_2 \) as the oxygen source for the ketone formation.
An alternative procedure utilizing Langlois’ reagent 5.21 as trifluoromethyl source was later reported by Maiti et al. (Scheme 5.10). A broader substrate scope was presented and a wide range of functional groups were tolerated on the styrene derivatives. The presence of trifluoromethyl radicals was supported by a trapping experiment using TEMPO. Labeling studies revealed that both O₂ and K₂S₂O₈ can act as the oxygen source. The use of benzoquinone and t-butyl hydroperoxide for the radical generation was later reported by Luo et al. However, products were obtained as a mixture with the corresponding alcohols.

\[ \text{Scheme 5.10 \( \alpha \)-trifluoromethyl ketones synthesis by oxy-trifluoromethylation using Langlois' reagent}^{238} \]

5.1.2 Intermolecular oxy-arylation

Similarly to the oxy-trifluoromethylation reactions (see 5.1.1), most of the intermolecular oxy-arylation of alkenes involve the presence of radical intermediates. The use of Meerwein-type reactions for the difunctionalization of alkenes has recently been reviewed. Heinrich et al. demonstrated that a combination of aryl diazonium salts (5.23) and TEMPO could be used for the intermolecular oxy-arylation of alkenes (Scheme 5.11). Aryl radicals, generated from the diazonium salts, add to the alkenes to form alkyl radicals. Subsequent trapping with TEMPO affords the corresponding difunctionalized products. The reaction is not sensitive to the electron density of the aryl diazonium salt. Both electron-rich and electron-poor
alkenes could be used. Studer et al. later reported a transition metal-free variant of this reaction.\textsuperscript{242} Aryl radicals and TEMPO were generated from the reaction of TEMPONa and aryl diazonium salts. The scope of the reaction was extended to gem-disubstituted and trisubstituted alkenes. Excellent diastereoselectivity was observed when internal alkenes were used, but no rationalization was provided for this observation.

\textbf{Scheme 5.11 Meerwein-type three-component oxy-arylation of alkenes}\textsuperscript{241,242}

More recently, an oxy-arylation reaction that utilizes of [Ru(bpy)\textsubscript{3}]Cl\textsubscript{2}(H\textsubscript{2}O)\textsubscript{6} for the generation of aryl radicals from aryl diazonium salts was reported by König et al. (Scheme 5.12).\textsuperscript{243} DMF was used both as solvent and reagent, affording the formyloxyarylated product after hydrolysis. A wide range of aryl diazonium salts, including heteroaryls, were amenable to the reaction conditions.

\textbf{Scheme 5.12 Photocatalyzed oxy-arylation of styrene derivatives using aryl diazonium salts}\textsuperscript{243}

Another oxy-arylation of styrenes utilizing iodonium salts as radical precursors has been reported by Greany et al. (Scheme 5.13).\textsuperscript{244} Photoredox catalysis was used to generate the aryl
radical and oxidize the alkyl radical resulting from the aryl radical addition to the alkene. A wide range of functional groups was compatible on both the aryl iodonium salts and styrene derivatives. Different alcohols could be used as solvent and nucleophile, as well as water when used in a 1:1 mixture with THF. Two examples of the use of diazonium salts as radical precursors were also reported.

Scheme 5.13 Photocatalyzed oxy-arylation of styrene derivatives using aryl iodonium salts

Phenyl hydrazines (5.29) have also been used as aryl radical precursors for the oxy-arylation of alkenes by Taniguchi et al. (Scheme 5.14). The reaction was run in the presence of oxygen and afforded the corresponding peroxides, which can be subsequently converted to the alcohols. Mono-, di- and trisubstituted alkenes were amenable to the reaction conditions. No diastereoselectivity was observed when internal alkenes were used. Both electron-donating and electron-withdrawing groups were tolerated on the aryl hydrazine. Low yields were obtained when the substrate was substituted in the ortho position, possibly due to steric effects. A method using MnO₂ as oxidant was later described, but the products were obtained in overall lower yields.

Scheme 5.14 Oxy-arylation of alkenes using phenyl hydrazines

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Jiao et al. later reported a transition metal-free oxy-arylation of alkenes using hydrazines 5.29 (Scheme 5.15).247 The authors showed that the choice of oxidant allows accessing the corresponding ketones or alcohols selectively.

![Scheme 5.15 Transition metal-free oxy-arylation of alkenes using phenyl hydrazines247](image)

Aryl boronic acids can also be used as radical precursors for the oxy-arylation of alkenes. Studer et al. reported that aryl radicals, generated by reaction with Mn(OAc)3, could add to the alkene and furnish the oxy-arylated product when the reaction was run in presence of oxygen.248 Electron-rich and electron-poor aryl boronic acids could be used. The scope of alkene was, however, limited to methacrylate, acrylonitrile, and dimethyl maleate.

![Scheme 5.16 Mn-promoted oxy-arylation of alkenes using aryl boronic acids248](image)

Several metal-catalyzed methods have additionally been reported for the oxy-arylation of alkenes using boronic acids that do not involve radical intermediates. Studer et al. reported the
oxy-arylation of indene using palladium catalysis (Scheme 5.17). The reaction was proposed to proceed via an oxidative addition, and insertion of the palladium complex to the alkene. The impact of the electron-density of the indene indicates that the reaction most likely proceed via a cationic intermediate. TEMPO derivatives 5.34 were employed as oxidant to generate the active palladium species, and as the oxygen source. The reaction showed excellent regio- and diastereoselectivity.

![Scheme 5.17 Palladium-catalyzed oxy-arylation of indenes](image)

A gold-catalyzed method for the oxyarylation of alkenes that utilizes aryl boronic acids was reported by Toste et al. (Scheme 5.18). Activation of the alkene by a cationic Au(III) species allowed the oxy-auration of the double bond. Reaction of the gold complex with the boronic acid then affords the difunctionalized compound. Various oxygen nucleophiles could be used including water, alcohols and carboxylic acids, although bulkier alcohols led to lower yields. A wide range of functional groups was tolerated under the reaction conditions, and the difunctionalized products were obtained in good yields. The authors later expanded their methodology to aryl silanes, with comparable efficiency. In both methodologies, Selectfluor® was used as oxidant to generate the active gold species. Russel et al. later reported that hypervalent iodine could be used as oxidant. This allowed expanding the alkene scope to styrenes and gem-disubstituted olefins, which otherwise underwent fluorination under the previously developed conditions.
A dual gold-photocatalysis approach for the oxy-arylation of alkenes was reported by Glorius et al. (Scheme 5.19). Aryl diazonium and aryl iodonium salts were used as aryl sources. The mechanism proposed by the authors differs from the other methods described previously (Scheme 5.11 and Scheme 5.13). Coordination of the gold catalyst to the alkene, followed by the nucleophilic addition of methanol leading to the formation of a Au(I) complex has been proposed. Addition of the aryl radical, generated by the photocatalyst, to Au(I) followed by oxidation from the photocatalyst would generate a Au(III) complex that undergoes reductive elimination to afford the difunctionalized product. Using this tandem gold/photocatalysis, the scope of alkenes was expanded to non-activated substrates. While yields were generally good, lower yields were obtained for aryl diazonium and aryl iodonium salts bearing electron-donating substituents in the para-position.
Finally, Heinrich et al. demonstrated that aryl radicals can be generated by treating aryl azocarboxylates with triflic acid. The authors reported a few examples of oxy-arylation using those conditions; however, products were only obtained in moderate yields.

### 5.1.3 Oxy-carbonylation

Fewer intermolecular carboetherification methods allow the introduction of more versatile synthetic handles. Only three examples have been reported for the introduction of a carbonyl group. Taniguchi et al. reported the synthesis of various β-hydroxy esters by oxy-carbonylation of alkenes (Scheme 5.20). An iron catalyst was used to generate acyl radicals from carbazates 5.32 that subsequently add to unsaturated C—C bonds. Molecular oxygen acted as oxidant and oxygen source in the reaction. Various activated and unactivated alkenes could be efficiently difunctionalized. Carbazates susceptible of leading to stable alkyl radicals by decarbonylation (e.g. R^3 = t-Bu or Bn) were not amenable to the oxy-carbonylation. For such substates, the difunctionalized products were only detected in trace amounts due to the rapid decomposition of the acyl radical.
Aldehydes have also been used as acyl radical precursors for the oxy-carbonylation of alkenes. Li et al. reported a synthesis of β-peroxide ketones using acyl radicals and hydroperoxide (Scheme 5.21). A combination of hydroperoxide and an iron catalyst were used for the generation of the acyl radicals. When pivaldehyde was used (R³ = t-Bu), the acyl radical underwent rapid decarbonylation to the t-butyl radical and the oxy-alkylation product was obtained as the sole product. Trapping experiments using TEMPO confirmed the presence of acyl radicals. The use of vanadium catalysis for the generation of the acyl radicals was later reported by Weng, Chen et al. By carefully tuning the electron density of the vanadium complex, it was possible to access selectively the hydroxylation or peroxidation product.

The enantioselective carboetherification of styrenes reported by MacMillan et al. allows the introduction of an aldehyde moiety, while not being formally an oxy-carbonylation reaction (Scheme 5.22). Alkyl radicals were generated by oxidation of the chiral enamine 5.40 formed
in-situ by ceric ammonium nitrate (CAN). The steric bulk on the intermediate led to the selective addition to the re-face of the styrene. Subsequent oxidation of the resulting benzylic radical followed by trapping by nitrate ions, arising from the reduction of the ceric ammonium nitrate, afforded the difunctionalized products in an anti: syn ratio of 3:1. Several examples of heterocycle synthesis from the oxy-alkylated products were also presented.

Scheme 5.22 Enantioselective carboetherification of styrenes\textsuperscript{258}

5.1.4 Oxy-alkylation using bromonitriles

Lei \textit{et al.} developed a method for the carboetherification of alkenes allowing the introduction of a cyanomethyl group (Scheme 5.23).\textsuperscript{259} Photocatalysis was used to generate an alkyl radical from \(\alpha\)-bromoacetonitrile, which subsequently added to the alkene. Oxidation of the resulting
radical, followed by trapping by the nucleophilic solvent afforded the difunctionalized product. Various alcohols could be used as solvent or co-solvent and nucleophile. A wide range of functional groups was tolerated, however, substrates bearing strongly electron-withdrawing substituents did not furnish the desired products. The authors later reported that copper catalysis could also be used to generate the radical from the \( \alpha \)-bromonitrile. A similar scope of styrenes and alcohols was presented.

The carboetherification method developed by Lei et al. is particularly interesting as it allows the introduction of a cyano group, which is a robust and versatile functional group that can easily be converted to other functional groups. A similar transformation using non-functionalized alkyl nitriles would be desirable to engage readily available starting material without the need for a pre-functionalization.
5.2 Carboetherification of alkenes using unfunctionalized alkyl nitriles

Carboetherification methods allowing the introduction of alkyl nitriles are particularly valuable transformations due to versatility of the nitrile functional group. Nitriles can be further transformed in a variety of functional groups (Scheme 5.24) allowing the rapid building of molecular complexity and access to a wide library of compounds. The use of α-bromonitriles has previously been reported for this transformation (see 5.1.4). We sought to develop an approach allowing the direct use of readily available alkyl nitriles through C-H functionalization, preventing the need for pre-functionalization.

![Scheme 5.24 Possible transformation of the nitrile group](image)

5.2.1 C–H functionalization of alkyl nitriles

Early examples of C—H bond activation of alkyl nitriles have been reported in the context of organometallic complex formation. Synthetic methods for the α-C—H functionalization of nitriles have mainly focused on the use of their enolate form. Due to the high pK_a of alkyl nitriles (pK_a(CH_3CN) ≈ 31 in DMSO) however, the use of strong bases or activated nitriles (e.g. β-cyanocarbonyls) was required to achieve the desired reactivity. Recently, milder metal-catalyzed methods have emerged for the α-C—H functionalization of alkyl nitriles. Kanai, Shibasaki et al. reported the C—H activation of alkyl nitriles in a copper-catalyzed enantioselective aldol-type reaction. The authors postulated that activation of the nitrile due to the Lewis acidity of the copper catalyst allowed the deprotonation by the t-butoxide ligand (Scheme 5.25), as the use t-BuOK alone was not enough to deprotonated the alpha proton. Shibasaki et al. also reported the use of ruthenium catalysis for the aldol-type reaction of alkyl
nitriles. The activation of the alkyl nitriles by the catalyst allowed their deprotonation using a mild base, DBU. A similar method utilizing a nickel catalyst was later developed by Guan et al. 268

\[ \text{Scheme 5.25 Copper-catalyzed C—H activation of alkyl nitriles} \]

A palladium-catalyzed method for the carboarylation of alkenes that involves the C—H functionalization of acetonitrile was reported by Liu et al. (Scheme 5.26). The reaction allows access to various indolinones 269 in good yields. The addition of PhI(OPiv)2 and AgF were key to activate acetonitrile, but the authors did not provide any insight on the mechanism of the C—H activation step. Other methodologies were later developed for the synthesis of indolinones via C—H functionalization of acetonitrile. In those reactions, the proposed mechanism involves the formation of alkyl radicals from acetonitrile and their addition to the alkenes.

\[ \text{Scheme 5.26 Metal-catalyzed synthesis of indolinones using C—H functionalization of acetonitrile} \]

Unfunctionalized alkyl nitriles have been used in a copper-catalyzed intramolecular carboetherification of alkenes by Zhu et al. (Scheme 5.27). A possible mechanism proposed by the authors involves the formation of an alkyl radical from the unactivated nitrile and its addition to the alkene. Oxidation of the newly formed radical affords a carbocation that is then trapped by the intramolecular nucleophile (Scheme 5.27). Amides could also be used as starting material for the synthesis of the lactones (Scheme 5.27) when water was added to the reaction mixture. Two equivalents of copper were necessary, however, for the reaction to proceed in good yields.
Previous work on three-component intermolecular carboetherification involving the formation and oxidation of alkyl radicals has shown that the carbocation intermediate can efficiently be trapped using a nucleophilic solvent (see 5.1.4). We, therefore, hypothesized that it would be possible to merge this type of reactivity with the copper-catalyzed C—H functionalization of alkyl nitriles previously reported in the group of Prof. Zhu to develop a intermolecular carboetherification of alkenes using unfunctionalized nitriles (Scheme 5.28).

Scheme 5.27 Copper-catalyzed intramolecular carboetherification of alkenes using alkyl nitriles

Scheme 5.28 Strategy for the intermolecular carboetherification of alkenes using unfunctionalized nitriles

10 examples
44-77%
5.2.2 Results and discussion

1,1-Diphenylethylene 5.25a (Scheme 5.29) was chosen as a test substrate for the initial investigation as the two phenyl rings have the ability to stabilize both the alkyl radical and the carbocation and might favor their formation over some side reactions. The reaction was quantified using $^1$H NMR (see 5.5.1 for more details). Preliminary studies focused on the use of methanol as nucleophile. We had previously observed$^{272}$ that the reaction of 5.25a under similar reaction conditions in the presence of oxygen led to the formation of significant amounts of benzophenone.$^{273}$ The reaction was thus run in a glovebox using thoroughly degassed solvents.

To test the feasibility of the reaction, the initial screening was performed using the conditions previously developed by Zhu et al. for the intramolecular carboetherification of alkenes.$^{271}$ Gratifyingly, using 2 equivalents of copper and 11 equivalents of methanol, product 5.42a was detected in 55% yield along with unreacted starting material (Table 5.1, entry 1). Increasing the amount of methanol to 20 equivalents increased the yield to 62% (Table 5.1, entry 2). When 50 equivalents of methanol were used (a 4:1 ratio of CH$_3$CN to CH$_3$OH) almost quantitative conversion was observed, and product 5.42a was detected in 94% yield. (Table 5.1, entry 3). Using a larger amount of methanol, the product was detected in slightly lower yield (87%, Table 5.1, entry 4), which led to the use of a 4:1 CH$_3$CN/CH$_3$OH ratio for further optimization studies.
Table 5.1 Influence of the equivalents of methanol on the carboetherification of 5.25a

<table>
<thead>
<tr>
<th>Entry</th>
<th>MeOH equiv.</th>
<th>Conversion[a]</th>
<th>Yield[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11</td>
<td>86%</td>
<td>55%</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>82%</td>
<td>62%</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>100%</td>
<td>94%</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>100%</td>
<td>87%</td>
</tr>
</tbody>
</table>

Conditions: 0.05 mmol of 5.25a, 0.1 mmol of DTBP, 0.1 mmol of Cu(OTf)$_2$, 0.05 mmol bipyridine, 0.1 mmol of K$_3$PO$_4$ in a sealed tube in 0.1 M CH$_3$CN/CH$_3$OH. Stirred for 16 h at 120 °C. [a]: Determined by $^1$H using trimethoxybenzene as internal standard.

The possibility of using a catalytic amount of copper was then investigated (Table 5.2). Lowering the copper loading to 50 mol% led to a decrease in the yield of product 5.42a to 24% (Table 5.2, entry 1). In addition, the hydrogen-abstraction product 5.47 was detected in 29% yield in the reaction mixture. Both methanol and acetonitrile could be acting as hydrogen source for the formation of product 5.47. Other promising copper sources were surveyed. When Cu(OTf) was used, only the product of hydrogen-abstraction 5.47 could be detected in the crude reaction mixture (Table 5.2, entry 2). The formation of 5.42a could be observed when using Cu(CH$_3$CN)$_4$BF$_4$, albeit only in 16% yield along with product 5.47 (Table 5.2, entry 3). Cu(CH$_3$CN)$_4$PF$_6$ only favored the formation of product 5.47 and the desired compound 5.42a was not detected (Table 5.2, entry 4).
### Table 5.2 Carboetherification of 5.25a using catalytic amounts of copper

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cu (0.5 equiv)</th>
<th>Conversion[^a]</th>
<th>Yield 5.42a[^a]</th>
<th>Yield 5.47[^a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OTf)$_2$</td>
<td>85%</td>
<td>24%</td>
<td>29%</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OTf)</td>
<td>80%</td>
<td>0%</td>
<td>30%</td>
</tr>
<tr>
<td>3</td>
<td>Cu(CH$_3$CN)$_4$BF$_4$</td>
<td>91%</td>
<td>16%</td>
<td>30%</td>
</tr>
<tr>
<td>4</td>
<td>Cu(CH$_3$CN)$_4$PF$_6$</td>
<td>36%</td>
<td>0</td>
<td>26%</td>
</tr>
</tbody>
</table>

[^a]: Determined by $^1$H NMR using trimethoxybenzene as internal standard.

Conditions: 0.05 mmol of 5.25a, 0.1 mmol of DTBP, 0.025 mmol of Cu(OTf)$_2$, 0.05 mmol bipyridine, 0.1 mmol K$_3$PO$_4$ in a sealed tube in 0.1 M 4:1 CH$_3$CN/CH$_3$OH. Stirred for 16 h at 120 °C.

Various ligands were tested to improve the yield and selectivity of the reaction (Table 5.3). The use of oxazoline only led to the formation of the reduced product 5.47 but the desired product 5.42a was not detected (Table 5.3, entry 2). Using 2,2-dimethylpyrimidine, only some unreacted starting material could be detected by $^1$H NMR (Table 5.3, entry 3). The use of phenanthroline favored the formation of the desired product 5.42a, which was detected in 29% yield in 3.6:1 ratio with the reduced product 5.47 (Table 5.3, entry 4). Lowering the ligand loading to 50 mol% led to a decrease in yield of product 5.42a to 18% using either bipyridine and phenanthroline (Table 5.3, entries 5 and 6). The ratio 5.42a/5.47 decreased in both cases. Further decreasing of the phenanthroline loading did not impact the yield of the reaction (Table 5.3, entry 7). 4,4'-Dimethoxy-2,2'-bipyridine can be used as ligand with a similar efficiency as phenanthroline (Table 5.3, entry 8). When (±)-trans-1,2-diaminocyclohexane was used, only the reduced product 5.47 was detected (Table 5.3, entry 9).
Table 5.3 Influence of the ligand on the carboetherification of 5.25a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand (equiv.)</th>
<th>Conversion[a]</th>
<th>Yield 5.42a[a]</th>
<th>Yield 5.47[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bipyridine (1)</td>
<td>85%</td>
<td>24%</td>
<td>29%</td>
</tr>
<tr>
<td>2</td>
<td>Oxazoline (1)</td>
<td>80%</td>
<td>0%</td>
<td>17%</td>
</tr>
<tr>
<td>3</td>
<td>2,2-dimethylpyrimidine (1)</td>
<td>87%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>Phenanthroline (1)</td>
<td>84%</td>
<td>29%</td>
<td>8%</td>
</tr>
<tr>
<td>5</td>
<td>Bipyridine (0.5)</td>
<td>79%</td>
<td>18%</td>
<td>37%</td>
</tr>
<tr>
<td>6</td>
<td>Phenanthroline (0.5)</td>
<td>92%</td>
<td>18%</td>
<td>16%</td>
</tr>
<tr>
<td>7</td>
<td>Phenanthroline (0.25)</td>
<td>91%</td>
<td>16%</td>
<td>19%</td>
</tr>
<tr>
<td>8</td>
<td>p-OMe-bipyridine (0.5)</td>
<td>84%</td>
<td>18%</td>
<td>13%</td>
</tr>
<tr>
<td>9</td>
<td>Diaminocyclohexane (0.5)</td>
<td>83%</td>
<td>0%</td>
<td>18%</td>
</tr>
</tbody>
</table>

Conditions: 0.05 mmol of substrate, 0.1 mmol of DTBP, 0.025 mmol of Cu(OTf)$_2$, ligand, 0.1 mmol of K$_3$PO$_4$ in a sealed tube in 0.1 M 4:1 CH$_3$CN/CH$_3$OH. Stirred for 16 h at 120 °C. [a]: Determined by $^1$H using trimethoxybenzene as internal standard.

The intramolecular carboetherification of alkenes developed by Zhu et al. requires different bases (K$_3$PO$_4$ and K$_2$CO$_3$) depending on the substrate and reaction conditions. Switching from K$_3$PO$_4$ to K$_2$CO$_3$ did not impact the yield of product 5.42a but lowered the amount of reduced product 5.47 formed from 29% to 21% (Table 5.4, entry 1 vs. entry 2). Decreasing the amount of base allowed the formation of product 5.42a in 31% yield while lowering the amount of reduced product 5.47 formed (Table 5.4, entry 3). The absence of base was beneficial for the reaction and led to the formation of product 5.42a in 60% yield (Table 5.4, entry 4). No reduced product was detected. The reaction was also performed using phenanthroline, which was previously identified as a promising ligand for the reaction (Table 5.3, entry 4). Gratifyingly product 5.42a was detected in 80% yield (Table 5.4, entry 6). Further optimization studies were performed in the absence of base using phenanthroline as a ligand.
Table 5.4 Influence of the base on the reaction outcome

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Base (equiv.)</th>
<th>Conversion[^{[a]}]</th>
<th>Yield[^{[b]}]</th>
<th>Yield[^{[b]}] (H)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bipyridine</td>
<td>K(_3)PO(_4) (2)</td>
<td>85%</td>
<td>18%</td>
<td>29%</td>
</tr>
<tr>
<td>2</td>
<td>K(_2)CO(_3) (2)</td>
<td>96%</td>
<td>17%</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>K(_2)CO(_3) (0.5)</td>
<td>96%</td>
<td>32%</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>No base</td>
<td>100%</td>
<td>60%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Phenanthroline</td>
<td>K(_3)PO(_4) (2)</td>
<td>84%</td>
<td>29%</td>
<td>18%</td>
</tr>
<tr>
<td>6</td>
<td>No base</td>
<td>100%</td>
<td>80%</td>
<td>0%</td>
<td></td>
</tr>
</tbody>
</table>

\[^{[a]}\]: Determined by \(^1\)H using trimethoxybenzene as internal standard.

The use of an even lower catalyst loading would be desirable. The carboetherification was thus performed using lower catalyst amounts, keeping a constant ratio of ligand to copper (Table 5.5, entries 2 to 5). Reducing the catalyst loading to 30 mol% did not impact the yield and product 5.42a was detected in 84% yield (Table 5.5, entry 2). Further decreasing the catalyst loading to 20 mol%, 10 mol% or 5 mol% led to a decrease in yield to 72%, 60% and 41% respectively (Table 5.5, entries 3 to 5). When a 5 mol% loading was used, unreacted starting material was detected in the crude reaction mixture (Table 5.5, entry 5). We chose to further optimize the reactions conditions using a 20 mol% catalyst loading, starting with an investigation of the influence of the ligand loading. In previous work on the intramolecular carboetherification of alkene\(^{271}\) different ratios of ligand to catalyst have indeed been used depending on the reaction conditions: a 1:2 ratio of ligand to catalyst has been used for the copper-mediated process, while a 1:1 ratio was used for the copper-catalyzed process. Using a large amount (1 equivalent) of ligand was detrimental for the reaction and product 5.42a was only detected in traces amount (Table 5.5, entry 6). Lowering the ligand loading to 30 mol% lead to a decrease in yield to 63% (Table 5.5, entry 8). When a 1:1 ratio was used, product 5.42a was detected in lower yield along with unreacted starting material (Table 5.5, entry 8).
Further decreasing the amount of ligand used only lead to a decrease in yield and conversion (Table 5.5, entry 9). A 2:1 ratio of ligand to catalyst was therefore used in the following studies.

### Table 5.5 Influence of the catalyst and ligand loadings

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst loading</th>
<th>Ligand loading</th>
<th>Conversion[a]</th>
<th>Yield[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50 mol%</td>
<td>100 mol%</td>
<td>100%</td>
<td>80%</td>
</tr>
<tr>
<td>2</td>
<td>30 mol%</td>
<td>60 mol%</td>
<td>100%</td>
<td>84%</td>
</tr>
<tr>
<td>3</td>
<td><strong>20 mol%</strong></td>
<td><strong>40 mol%</strong></td>
<td><strong>100%</strong></td>
<td><strong>72%</strong></td>
</tr>
<tr>
<td>4</td>
<td>10 mol%</td>
<td>20 mol%</td>
<td>100%</td>
<td>60%</td>
</tr>
<tr>
<td>5</td>
<td>5 mol%</td>
<td>10 mol%</td>
<td>90%</td>
<td>41%</td>
</tr>
<tr>
<td>6</td>
<td>20 mol%</td>
<td>100 mol%</td>
<td>100%</td>
<td>Traces</td>
</tr>
<tr>
<td>7</td>
<td>20 mol%</td>
<td>30 mol%</td>
<td>100%</td>
<td>63%</td>
</tr>
<tr>
<td>8</td>
<td>20 mol%</td>
<td>20 mol%</td>
<td>&gt; 95%</td>
<td>65%</td>
</tr>
<tr>
<td>9</td>
<td>20 mol%</td>
<td>15 mol%</td>
<td>69%</td>
<td>31%</td>
</tr>
</tbody>
</table>

**Conditions:** 0.05 mmol of substrate, 0.1 mmol of DTBP, Cu(OTf)$_2$, phenanthroline, in a sealed tube in 0.1 M 4:1 CH$_3$CN/CH$_3$OH. Stirred for 16 h at 120 °C. [a]: Determined by $^1$H using trimethoxybenzene as internal standard.

A lower conversion was observed when the reaction was run at 100 °C (Table 5.6, entry 1). The corrected yield, based on the conversion of starting material, was similar to the one obtained when the reaction was run at 120 °C (75% vs. 72%, Table 5.6, entry 2). Full conversion was observed when the reaction was run at 140 °C, but product 5.42a was only detected in 55% yield (Table 5.6, entry 3).
Chapter 5 Copper-catalyzed three-component carboetherification of alkenes

Table 5.6 Impact of the temperature on the carboetherification of 5.25a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Conversion</th>
<th>Yield[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>72%</td>
<td>54%</td>
</tr>
<tr>
<td>2</td>
<td>120</td>
<td>100%</td>
<td>72%</td>
</tr>
<tr>
<td>3</td>
<td>140</td>
<td>100%</td>
<td>55%</td>
</tr>
</tbody>
</table>

Conditions: 0.05 mmol of substrate, 0.1 mmol of DTBP, 0.01 mmol of Cu(OTf)$_2$, 0.02 mmol phenanthroline, in a sealed tube in 0.1 M 4:1 CH$_3$CN/CH$_3$OH. Stirred for 16 h.

[a]: Determined by $^1$H using trimethoxybenzene as internal standard.

Finally, various solvent ratios were investigated (Table 5.7). When the reaction was run in methanol using 1 equivalent of acetonitrile, partial conversion of the starting material was observed but no desired product was detected (Table 5.7, entry 1). The yield of product 5.42a increased with the increasing CH$_3$CN/CH$_3$OH ratio (Table 5.7, entries 2 to 6) with a maximum of 88% being reached using a 1:1 ratio of CH$_3$CN/CH$_3$OH (Table 5.7, entry 6). Further increasing of the ratio led to lower yields of product 5.42a (Table 5.7, entries 7 and 8).
5.2.3 Evaluation of the reaction scope

Using the previously established reaction conditions (Table 5.7, entry 6), the scope of the reaction was investigated. The influence of the aryl substituents was first studied (Scheme 5.30). Unsubstituted substrate 5.42a could be isolated in 77% yield. The addition of electron-donating substituents on the aryl ring had no impact on the yield; substrates bearing a methyl (5.42b) or a methoxy group (5.42c) in the para-position were obtained in 77% and 76% yield respectively. Similarly good yields were obtained for halogen-substituted substrates. p-Fluorosubstituted substrate 5.42d was obtained in 67% yield. p-Chloro (5.42e) and p-bromosubstituted (5.42f) product were obtained respectively in 81% and 80% yield. Product 5.42g, bearing a cyano substituent, could be obtained in 60% yield. Substitution in the meta-position was tolerated, although products were obtained in slightly lower yields that the
corresponding para-substituted substrates. Substrates bearing a m-methyl (5.42h) and a m-chloro (5.42i) substituent were obtained in 62% and 60% respectively. When a stronger electron-withdrawing group, CF$_3$, was present in the meta-position, product 5.42j was obtained in a comparable 61% yield. When a methyl group was present in the ortho-position, the reaction was much slower. A longer reaction time and 40 mol% of copper were necessary to obtain product 5.42k in 57% yield. The steric bulk around the alkene might be hindering the carboetherification reaction, as observed for similar methodologies.\textsuperscript{245, 275} Di-substituted substrates were also investigated and the corresponding products were obtained in similarly high yields. The dimethyl-substituted product 5.42l could be isolated in 81% yield. When stronger electron-donating groups were present, the reaction was slower and 30 mol% of copper were necessary to drive the reaction to completion and to obtained product 5.42m in 71% yield. Using a “push-pull” substrate, in which the electron-donating methoxy group was counterbalanced with an electron-withdrawing trifluoromethyl group, the desired product (5.42n) could be accessed in 80% yield using the regular reaction conditions. Difluorinated substrate 5.42o was obtained in slightly higher yield that its monofluorinated counter part (75% vs. 67%) while the opposite trend was observed for the chlorinated substrate 5.42p (73% vs. 81%).
Scheme 5.30 Carboetherification of gem-biaryl substituted alkenes

[a]: 40 mol% Cu, 80 mol% ligand, run for 24h. [b]: 30 mol% Cu, 60 %mol ligand
α-Alkylstyrene derivatives were next investigated under our optimized reaction conditions (Scheme 5.31). α-Methylstyrene was efficiently difunctionalized and product 5.42q was obtained in 88% yield. When a more electron-rich substrate was submitted to the reaction conditions, full conversion was observed; however, the expected product (5.42r) was isolated in 6% yield. The remaining of the mass balance was not detected in the crude reaction mixture. The reaction might be sensitive to the extra electron-density added to the substrate. Indeed, a lower conversion was observed for the electron-rich substrate 5.42c (Scheme 5.30). Substrate 5.25r might be undergoing side reactions, such as thermal or peroxide mediated polymerization, more readily that it can be difunctionalized. The presence of an electron-withdrawing group in the para-position was found to be compatible with the reaction condition and product 5.42s was detected in 85% by 1H NMR and isolated in 58% yield. The presence of a methyl group in the ortho-position did not impact the yield as significantly as it did for gem-biaryl substrates and product 5.42t could be isolated in 61% yield. For this substrate, the added steric bulk of the ortho-methyl group might be less hindering as only phenyl group is present. When the methyl group was substituted by bromine, however, product 5.42u was only detected in 19% by 1H NMR. Since electron-withdrawing groups were shown to be tolerated under the reaction conditions (see 5.42d, 5.42e and 5.42f, Scheme 5.30 and 5.42s, Scheme 5.31), the large size of the bromine substituent might be responsible for the decrease in yield. The more sterically hindered mesityl derivatives 5.42v bearing three methyl groups could not, indeed, be synthesized under the reaction conditions. The influence of other alkyl groups in the α-position was next investigated. Substrates bearing secondary and tertiary carbons in the α-position were amenable to the reaction conditions: Bicyclic substrate 5.42w was isolated in 77% and a cyclohexyl-substituted alkene underwent difunctionalization in 60% yield (5.42x). The conversion was more sluggish when the bulkier t-butyl was present in the α-position. When the reaction was run under the regular reaction conditions, product 5.42y was only detected in traces amount with remaining starting material. A maximum of 13% 1H NMR yield could be achieved when the reaction was run for 48 h using 50 mol% of copper. The fate of the remaining mass balance could not be identified. This result further suggests that the carboetherification reaction is sensitive to the steric bulk around the alkene. A slower rate of difunctionalization for such substrates might allow for faster side reactions to occur.
The carboetherification reaction was also applied to some heteroaryl-containing substrates. Thiophene was compatible with the reaction condition and product 5.42z was obtained in 61%. Substrates 5.42aa and 5.42ab bearing a pyridine could be accessed only in low yields (26% and 20% yield respectively), which is most likely explained by the coordination of the catalyst to the substrate rather than the ligand.
Chapter 5 Copper-catalyzed three-component carboetherification of alkenes

5.25 - Cu(OTf)$_2$ (20 mol%) + (hetero)Aryl + DTBP (2 equiv.) + Phenanthroline (40 mol%) → 5.42

MeCN/MeOH 120 °C

Scope:

- 5.42z (hetero)Aryl OMe CN 61%
- 5.42aa (hetero)Aryl OMe CN 26%
- 5.42ab (hetero)Aryl OMe CN 20%

Scheme 5.32 Carboetherification of heteroaryl containing substrates

Low conversion of the internal alkene 5.25ac (Scheme 5.33) was observed when it was submitted to the general reaction conditions, further supporting the influence of the steric on the reaction outcome. The use of 30 mol% of copper and longer reaction time were necessary to achieve full conversion. Using those conditions, product 5.42ac was isolated in 56% yield.

5.25ac → DTBP 2 equiv. Cu(OTf)$_2$ 30 mol% Phenanthroline 60 mol% → 5.42ac

CH$_3$CN/CH$_3$OH 1:1 [0.1 M] 120 °C, 24 h

56%

Scheme 5.33 Carboetherification of internal alkene 5.25ac

It is noteworthy that when styrene was submitted to the reaction conditions, no difunctionalized product or remaining starting material were detected. The high reaction temperature and the presence of radical intermediates might have led to the polymerization of styrene.$^{276}$

Several nitriles were amenable to the reaction conditions (Scheme 5.34). Propionitrile could be used as solvent in a 1:1 mixture with methanol and the corresponding product 5.48a was obtained using only 20 mol% catalyst loading. Butyronitrile could also be used as solvent, but product 5.48b could only be obtained in 45% yield. When the bulkier isobutyronitrile was used product 5.48c was not detected. No remaining starting material or other side products were
detected, and alkene 5.25a might have decomposed via other paths. 3-Methoxypropionitrile could be engaged in the carboetherification reaction. 11 equivalents of the nitrile were used to obtain product 5.48d in 75% isolated yield. No product was detected when 3-bromopropionitrile was used (5.48e).

A 30 mol% catalyst loading was necessary to obtained good yield of difunctionalized using ethanol as solvent and nucleophile (Scheme 5.35). The reaction was applied to both 1,1-diphenylethylene and α-methylstyrene and the corresponding compounds 5.42ad and 5.42ae were obtained in 37% and 36% yield respectively. Increasing the amount of DTBP to 3 equivalents allowed the formation of 5.42ad in 47% yield. The low yield and slower conversion observed can be due to a less efficient nucleophilic trapping of the carbocation due to the more important steric bulk of ethanol. The solvent could also be acting as ligand in the copper complex, and ethanol might be less efficient at stabilizing it than the less bulky methanol.
5.3 Proposed mechanism

To get more insight on the reaction mechanism, some control and mechanistic experiments were run. In the absence of copper, no desired product was detected. No remaining starting material was observed, indicating that in the absence of copper the alkene undergoes side reactions, which could not be identified. When no peroxide was used, the product was detected in 10% yield, along with 50% remaining starting material. The peroxide is, therefore, not directly involved in the product formation, but most likely used to regenerate the catalyst.

Significantly, when the radical clock 5.25af was subjected to the reaction conditions, product 5.49 could be isolated in 57% yield (Scheme 5.36). No difunctionalized product was detected in the crude reaction mixture. The formation of product 5.49 can be rationalized by the presence of radical intermediates (Scheme 5.36). Formation of a radical α to the cyclopropane (5.50) would lead to ring opening to afford the homoallylic radical 5.51. Cyclization of 5.51 followed by rearomatization would afford product 5.49. A similar rearrangement was observed by Chemler et al. when product 5.25af was reacted in presence of nitrogen-centered radicals.275
Based on the above-mentioned observations, we proposed the mechanism outlined in Scheme 5.37 for the carboetherification reaction. Complexation of the copper with 1,10-phenanthroline followed by ligand exchange with the alcohol affords the complex A. Activation of the nitrile by the catalyst allows the deprotonation by one of the ligand, and the formation of complex C. Cuprate C can undergo homolytic cleavage, yielding an alkyl radical that subsequently adds to 5.25a to form intermediate F. Alternatively, carbocupration of alkene 5.25a by C can afford complex D, which upon homolytic cleavage leads to F. The presence of intermediate F is supported by the radical clock experiment described in Scheme 5.36. Oxidation of the radical F to G by CuII followed by trapping by the nucleophile affords the difunctionalized product 5.42a. Finally, the CuII catalyst is regenerated by oxidation of complex E with DTBP.
5.4 Conclusion

Unactivated alkyl nitriles have been successfully engaged in the carboetherification of α-substituted styrenes. This reaction allows the concomitant formation of a C(sp^3)—C(sp^3) bond and a C(sp^3)—O bond. Methanol was used as co-solvent and nucleophile. By carefully optimizing the reaction conditions, the catalyst loading could be decreased to 20 mol%. Those reaction conditions were applied to a broad scope of α-substituted styrenes. Both electron-donating and electron-withdrawing substituents were tolerated on the aryl ring. Substrates bearing strongly electron-withdrawing groups (CN, CF_3), which could not be difunctionalized using the previously described carboetherification using α-bromonitriles,^259,260^ were amenable to the reaction conditions. Heterocycle-containing substrates could also be difunctionalized. The reaction was sensitive to the steric bulk around the alkene. Substrates substituted in the ortho-position or bearing a bulky α-group on the alkene underwent a slower difunctionalization, which allowed the decomposition of the starting material via other pathways. Preliminary results indicated that other alkyl nitriles could be used in this reaction.
The possibility of using ethanol as co-solvent and nucleophile was also demonstrated. Optimization of the reaction conditions for other alcohols is currently undergoing in the group of Prof. Zhu. Furthermore, current investigations are focusing on the use of other types of nucleophiles.

### 5.5 Experimental section

All chemicals were purchased from commercial sources and used as received. All reactions were performed under nitrogen atmosphere in flame-dried glassware unless otherwise noted. When solvents are indicated as dry they were either purchased as such, distilled prior to use or were dried by a passage through a column of anhydrous alumina or copper using a Puresolv MD 5 from Innovative Technology Inc. For reactions in oxygen-free conditions, solvents were degassed by a minimum of three freeze-pump-thaw cycles using classic Schlenk techniques. The reactions requiring inert and dry atmosphere were carried out in a PureLab HE 4GB 2500 Glovebox System from Innovative Technologies Inc.

Reactions were monitored using Macherey-Nagel SIL G-25 UV$_{254+366}$ aluminium backed plates. TLC's were visualized by UV fluorescence (254 nm) then one of the following stains: KMnO$_4$, $p$-anisaldehyde, vanillin. Flash column chromatography was performed using Silicycle P60 silica: 230-400 mesh (40-63 μm) silica.

Melting points were measured on a Stuart SMP30 melting point apparatus using open glass capillaries (uncorrected). IR spectra were recorded on a Jasco FT/IR-4100 spectrometer outfitted with a PIKE technology MIRacleTM ATR accessory as neat films compressed onto a Zinc Selenide window. High resolution mass spectra (HRMS) were recorded on either a Waters or Micromass LCT spectrometer. NMR spectra were recorded using a Brüker AvanceIII-400, Brüker Avance-400 or Brüker DPX-400 spectrometer. $^1$H frequency is at 400.13 MHz, $^{13}$C frequency is at 100.62 MHz, $^{19}$F frequency is at 316.50 MHz. Chemical shifts (δ) are reported in parts per million (ppm) relative to the residual solvent peaks rounded to the nearest 0.01 for proton and 0.1 for carbon (ref: CHCl$_3$ [ $^1$H: 7.26, $^{13}$C: 77.0], C$_6$D$_6$ [ $^1$H: 7.16, $^{13}$C 128.1]). Coupling constants (J) are reported in Hz to the nearest 0.1 Hz. Peaks multiplicity is indicated as follows s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet).
5.5.1 Method for the yield determination using $^1$H NMR.

Sample $^1$H analysis for the conversion of 5.25a:
Figure 5.1 shows the singlet at 6.02 ppm corresponding to the 3 aromatic protons of the internal standard 3.41 and the singlet at 5.39 ppm corresponding to the 2 alkene protons of product 5.25a. From the integration of those signals, we can calculate the molar ratio of product 5.25a to internal standard, which is 0.31:1. The conversion of product 5.25a can then be measured using the following equation:

$$Conversion \text{ of } 5.25a = \frac{n_{5.25a} - n_{3.41} \times 0.62}{n_{5.25a}} \times 100,$$

where $n_{3.41}$ is the number of moles of internal standard used and $n_{5.25a}$ the number of moles of starting material initially used.

Sample $^1$H analysis for the yield of product 5.42a:
Figure 5.1 shows the singlet at 6.02 ppm corresponding to the 3 aromatic protons of the internal standard 3.41 and the two multiplets at 2.62 ppm and 2.02 ppm corresponding to the 2 methylene protons of product 5.42a. From the integration of those signals, we can calculate the molar ratio of product to internal standard, which is 0.63:1. The yield of product 5.42a can then be measured using the following equation:

$$Yield \text{ 5.42a} = \frac{n_{3.41}}{n_{5.25a}} \times \frac{1.25}{2} \times 100,$$

where $n_{3.41}$ is the number of moles of internal standard used and $n_{5.25a}$ the number of moles of starting material initially used.
Figure 5.1 Sample crude $^1$H NMR spectra for the carboetherification of 5.25a using methanol
5.5.2 Synthesis of starting materials

**General procedure A:**

Methyltriphenylphosphonium bromide (3 equiv.) was suspended in dry THF (0.2 M) and cooled to 0 °C. t-BuOK (3 equiv) was added in one portion and the reaction was stirred at 0 °C for 30 min. Ketone (1 equiv.) was added and the reaction was let to warm to r.t. and stirred until completion was observed by TLC (2 to 16 h). The reaction was quenched with H₂O (2x the amount of THF initially used) and extracted with EtOAc (3x with half the volume of H₂O). The combined organic layers were washed with water (2x with the amount of EtOAC used) and dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give alkene 3.25.

**General procedure B:**

Phenyl magnesium bromide (1.0 M in THF, 2.2 equiv) was added to a solution of the acetophenone (1 equiv) in dry THF (0.083 M). The reaction was stirred at r.t. for 30 min. Diethyl phosphite (1.2 equiv) was added to the reaction, which was let to stir at r.t. for 16 h. The reaction was quenched with H₂O (2x the amount of THF initially used) and extracted with EtOAc (3x with half the volume of H₂O). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give alkene 3.25.
General procedure C:\(^{281}\)

\[
\begin{align*}
\text{Acetophenone derivatives (1 equiv) were added to a solution of } & p\text{-toluenesulfonyl hydrazide (1 equiv) in MeOH (0.66 M). The reaction was refluxed until product precipitated (30 min to 2 h). The crude product S6 was filtered off, washed thoroughly with hexanes, dried and used as such.} \\
\text{Tosylhydrazone S6 (1.5 equiv), PdCl}_2(PPh_3)_2 (2.5 mol%), bromobenzene S7 (1 equiv) were dissolved in 1,4-dioxane (0.13 M) under N\textsubscript{2} and heated to 100 °C. To this hot solution was added t-BuOLi (2.5 equiv). The reaction was stirred at 100 °C until completion was observed by TLC (1 to 3 h). The reaction was cooled to r.t., diluted with EtOAc (3x the amount of 1,4-dioxane used), filtered through celite and rinced with EtOAc. The solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography.}
\end{align*}
\]

1-methyl-4-(1-phenylvinyl)benzene (5.25b)

\[
\text{4'-Methylacetophenone (530 μL, 4.00 mmol) was submitted to the general procedure B. Purification by flash column chromatography (100% PE) provided 582 mg of compound 5.25b (2.99 mmol, 75% yield) as a colorless oil. Spectroscopic data was consistent with that previously reported.}^{282} \text{ }^1H NMR (400 MHz; CDCl}_3: \delta 7.36-7.30 (m, 5H), 7.26-7.24 (m, 2H), 7.16-7.14 (m, 2H), 5.44 (d, J = 1.1 Hz, 1H), 5.41 (d, J = 1.2 Hz, 1H), 2.38 (s, 3H). \text{ }^{13}C NMR (101 MHz; CDCl}_3: \delta 150.0, 141.8, 138.7, 137.7, 129.0, 128.4, 128.3, 128.3, 127.8, 113.8, 21.3.
\]

1-methoxy-4-(1-phenylvinyl)benzene (5.25c)
4'-Methoxybenzophenone (840 mg, 3.96 mmol) was submitted to the general procedure A. Purification by flash column chromatography (10:1 PE/EtOAc) provided 452 mg of compound 5.25c (2.14 mmol, 54% yield) as a colorless oil. Spectroscopic data was consistent with that previously reported.\textsuperscript{283} \textsuperscript{1}H NMR (400 MHz; CDCl\textsubscript{3}): \(\delta\) 7.36-7.27 (m, 7H), 6.89-6.87 (m, 2H), 5.41 \((d, J = 1.0\text{ Hz}, 1H), 5.37 \((d, J = 1.3\text{ Hz}, 1H), 3.84 \((s, 3H). \textsuperscript{13}C\text{ NMR} (101 MHz; CDCl\textsubscript{3}): \delta 159.3, 149.5, 141.8, 134.0, 129.4, 128.1, 127.6, 113.5, 112.9, 55.3.

1-fluoro-4-(1-phenylvinyl)benzene (5.25d)

4'-Fluoroacetophenone (370 \(\mu\)L, 4.00 mmol) was submitted to the general procedure B. Purification by flash column chromatography (20:1 PE/EtOAc) provided 703 mg of compound 5.25d (3.50 mmol, 89% yield) as a colorless oil. Spectroscopic data was consistent with that previously reported.\textsuperscript{282} \textsuperscript{1}H NMR (400 MHz; CDCl\textsubscript{3}): \(\delta\) 7.36 - 7.28 (m, 7H), 7.06-6.99 (m, 2H), 5.44 \((d, J = 1.1\text{ Hz}, 1H), 5.42 \((d, J = 1.1\text{ Hz}, 1H). \textsuperscript{13}C\text{ NMR} (101 MHz; CDCl\textsubscript{3}): \delta 162.7 \((d, J = 246.7\text{ Hz}), 149.2, 141.4, 137.7 \((d, J = 3.3\text{ Hz}), 130.0 \((d, J = 7.9\text{ Hz}), 128.4, 128.3, 128.0, 115.2 \((d, J = 21.4\text{ Hz}), 114.4.\) As the literature characterization data did not include \textsuperscript{19}F NMR, the information is provided below: \textsuperscript{19}F NMR (376 MHz, CDCl\textsubscript{3}): \(\delta\) -114.7.

1-bromo-4-(1-phenylvinyl)benzene (5.25f)

4'-Bromoacetophenone (530 \(\mu\)L, 4.00 mmol) was submitted to the general procedure B. Purification by flash column chromatography (100% PE) provided 855 mg of compound 5.25f (3.30 mmol, 82% yield) as a white solid. Spectroscopic data was consistent with that previously reported.\textsuperscript{282} \textsuperscript{1}H NMR (400 MHz; CDCl\textsubscript{3}): \(\delta\) 7.48-7.46 (m, 2H), 7.36-7.31 (m, 5H), 7.23-7.21 (m, 2H), 5.48 \((d, J = 1.0\text{ Hz}, 1H), 5.46 \((d, J = 1.0\text{ Hz}, 1H). \textsuperscript{13}C\text{ NMR} (101 MHz; CDCl\textsubscript{3}): \delta 149.0, 140.9, 140.4, 131.3, 129.9, 128.3, 128.2, 127.9, 121.8, 114.7.
4-(1-phenylvinyl)benzonitrile (5.25g)

Chemical Formula: \(C_{15}H_{14}N\)
Molecular Weight: 205.25

4-Acetylbenzonitrile (726 mg, 5.00 mmol) was submitted to the general procedure B. Purification by flash column chromatography (30:1 PE/EtOAc) provided 426 mg of compound 5.25g (2.07 mmol, 41% yield) as a colorless oil. Spectroscopic data was consistent with that previously reported.\(^{284}\) \(^1\)H NMR (400 MHz; CDCl\(_3\)): \(\delta\) 7.65-7.63 (m, 2H), 7.46-7.44 (m, 2H), 7.38-7.36 (m, 3H), 7.30-7.28 (m, 2H), 5.60 (d, \(J = 0.6\) Hz, 1H), 5.55 (d, \(J = 0.6\) Hz, 1H). \(^{13}\)C NMR (101 MHz; CDCl\(_3\)): \(\delta\) 148.7, 146.1, 140.2, 132.1, 128.8, 128.5, 128.4, 128.2, 118.9, 116.7, 111.3.

1-methyl-3-(1-phenylvinyl)benzene (5.25h)

Chemical Formula: \(C_{15}H_{14}\)
Molecular Weight: 194.27

3-Methylbenzophenone (715 μL, 4.00 mmol) was submitted to the general procedure A. Purification by flash column chromatography (10:1 PE/EtOAc) provided 698 mg of compound 5.25h (3.59 mmol, 90% yield) as a colorless oil. Spectroscopic data was consistent with that previously reported.\(^{285}\) \(^1\)H NMR (400 MHz; CDCl\(_3\)): \(\delta\) 7.42-7.37 (m, 5H), 7.31-7.19 (m, 4H), 5.51 (s, 2H), 2.41 (s, 3H). \(^{13}\)C NMR (101 MHz; CDCl\(_3\)): \(\delta\) 150.1, 141.6, 141.5, 137.7, 128.9, 128.5, 128.2, 128.1, 128.0, 127.6, 125.4, 114.1, 21.4.

1-(1-phenylvinyl)-3-(trifluoromethyl)benzene (5.25j)

Chemical Formula: \(C_{15}H_{14}F_3\)
Molecular Weight: 248.24

3-Acetylbenzotrifluoride (640 μL, 4.97 mmol) was submitted to the general procedure B. Purification by flash column chromatography (100% PE) provided 791 mg of compound 5.25j (3.18 mmol, 64% yield) as a colorless oil. \(^1\)H NMR (400 MHz; CDCl\(_3\)): \(\delta\) 7.63 (s, 1H), 7.59 (d, \(J = 7.8\) Hz, 1H), 7.53-7.51 (m, 1H), 7.48-7.46 (m, 1H), 7.38-7.31 (m, 5H), 5.57 (s, 1H), 5.52 (s, 1H). \(^{13}\)C NMR (101 MHz; CDCl\(_3\)): \(\delta\) 148.9, 142.3, 140.6, 131.6, 130.7 (q, \(J = 32.3\) Hz), 128.8, 128.4, 128.1, 128.0, 124.9 (q, \(J = 4.2\) Hz), 124.4 (q, \(J = 3.7\) Hz), 124.1 (q, \(J = 272.0\) Hz), 115.7. \(^{19}\)F NMR
(376 MHz; CDCl₃); δ -62.57. IR 3084, 3026, 1615, 1494, 1469, 1431, 1325, 1026 cm⁻¹. HRMS (ESI) calcd for C₁₅H₁₁F₃⁺ [M⁺] 248.0813; found 248.0805.

1-methyl-2-(1-phenylvinyl)benzene (5.25k)

2-Methylbenzophenone (715 μL, 4.00 mmol) was submitted to the general procedure A. Purification by flash column chromatography (10:1 PE/EtOAc) provided 530 mg of compound 5.25k (2.73 mmol, 68% yield) as a colorless oil. Spectroscopic data was consistent with that previously reported.²⁸⁶ As the literature characterization data did not include IR, the information is provided below: IR 3058, 3020, 2922, 1496, 1445, 1029, 902 cm⁻¹. ¹H NMR (400 MHz; CDCl₃): δ 7.31-7.22 (m, 9H), 5.81 (d, J = 1.4 Hz, 1H), 5.24 (d, J = 1.4 Hz, 1H), 2.09 (s, 3H). ¹³C NMR (101 MHz; CDCl₃): δ 149.4, 141.6, 140.6, 136.1, 130.0, 130.0, 128.3, 127.5, 127.5, 126.4, 125.6, 114.8, 20.1.

4,4’-(ethene-1,1-diyl)bis(methoxybenzene) (5.25m)

4,4’-Dimethoxybenzophenone (605 mg, 2.50 mmol) was submitted to the general procedure A. Purification by flash column chromatography (100% PE) provided 496 mg of compound 5.25m (2.06 mmol, 83% yield) as a white solid. Spectroscopic data was consistent with that previously reported.²⁸⁴ ¹H NMR (400 MHz; CDCl₃): δ 7.31-7.27 (m, 4H), 6.89-6.87 (m, 4H), 5.31 (s, 2H), 3.84 (s, 6H). ¹³C NMR (101 MHz; CDCl₃): δ 159.3, 148.9, 134.3, 129.4, 113.4, 111.6, 55.3.

1-methoxy-4-(1-(4-(trifluoromethyl)phenyl)vinyl)benzene (5.25n)

4’-Methoxyacetophenone (750 mg, 5.00 mmol) was submitted to the general procedure C and reacted with 4-bromobenzyltrifluoride. Purification by flash column chromatography (15:1 PE/EtOAc) provided 552 mg of compound 5.25n (1.98 mmol, 40% yield) as a white solid.
Spectroscopic data was consistent with that previously reported.\(^{284}\) \(^1\)H NMR (400 MHz; CDCl\(_3\)): \(\delta\) 7.60 (d, \(J = 8.0\) Hz, 2H), 7.46 (d, \(J = 8.0\) Hz, 2H), 7.26-7.24 (m, 2H), 6.90-6.88 (m, 2H), 5.50 (s, 1H), 5.41 (s, 1H), 3.84 (s, 3H). \(^{13}\)C NMR (101 MHz; CDCl\(_3\)): \(\delta\) 159.6, 148.4, 145.4, 133.1, 129.7 (q, \(J = 32.0\) Hz), 129.3, 128.6, 125.1 (q, \(J = 3.7\) Hz), 124.3 (q, \(J = 272.7\) Hz), 114.5, 113.7, 55.3.

\(4,4'\)-{(ethene-1,1-diyl)bis(fluorobenzene) (5.25o)}

\(4,4'\)-Difluorobenzophenone (654 mg, 3.00 mg) was submitted to the general procedure A. Purification by flash column chromatography (100% PE) provided 511 mg of compound 5.25o (2.36 mmol, 79% yield) as a white solid. Spectroscopic data was consistent with that previously reported.\(^{282}\) \(^1\)H NMR (400 MHz; CDCl\(_3\)): \(\delta\) 7.35-7.29 (m, 4H), 7.08-7.04 (m, 4H), 5.42 (s, 2H). \(^{13}\)C NMR (101 MHz; CDCl\(_3\)): \(\delta\) 162.6 (d, \(J = 246.5\) Hz), 148.0, 137.4 (d, \(J = 3.7\) Hz), 129.8 (d, \(J = 8.1\) Hz), 115.1 (d, \(J = 21.3\) Hz), 114.1. As the literature characterization data did not include \(^{19}\)F NMR, the information is provided below: \(^{19}\)F NMR (376 MHz; CDCl\(_3\)): \(\delta\) -114.5.

\(4,4'\)-{(ethene-1,1-diyl)bis(chlorobenzene) (5.25p)}

\(4,4'\)-Dichlorobenzophenone (251 mg, 1.00 mmol) was submitted to the general procedure A. Purification by flash column chromatography (50:1 Pentanes/Et\(_2\)O) provided 130 mg of compound 5.25p (0.52 mmol, 52% yield) as a white solid. Spectroscopic data was consistent with that previously reported.\(^{282}\) \(^1\)H NMR (400 MHz; CDCl\(_3\)): \(\delta\) 7.33-7.30 (m, 4H), 7.27-7.24 (m, 4H), 5.46 (s, 2H). \(^{13}\)C NMR (101 MHz; CDCl\(_3\)): \(\delta\) 147.9, 139.5, 133.8, 129.5, 126.5, 115.1.

\(1,3,5\)-trimethyl-2-{(prop-1-en-2-yl)benzene (5.25v)}

\(4\)-Methoxyacetophenone (420 \(\mu\)L, 2.52 mmol) was submitted to the general procedure A. Purification by flash column chromatography (30:1 Pentanes/Et\(_2\)O) provided 201 mg of
compound 5.25v (1.25 mmol, 50% yield). Spectroscopic data was consistent with that previously reported.\textsuperscript{287} \textsuperscript{1}H NMR (400 MHz; CDCl\textsubscript{3}): δ 6.90-6.89 (m, 2H), 5.27-5.26 (m, 1H), 4.78-4.76 (m, 1H), 2.29 (s, 3H), 2.25 (s, 6H), 1.98-1.96 (m, 3H). \textsuperscript{13}C NMR (101 MHz; CDCl\textsubscript{3}): δ 144.8, 140.5, 136.0, 134.8, 128.1, 114.9, 23.9, 21.1, 19.7.

5-methylene-6,7,8,9-tetrahydro-5H-benzo[7]annulene (5.25w)

\begin{center}
\includegraphics[width=1cm]{5.25w}\text{Chemical Formula: }\text{C}_{12}\text{H}_{14} \\
\text{Molecular Weight: } 185.24
\end{center}

1-Benzosuberone (390 μL, 2.60 mmol) was submitted to the general procedure A. Purification by flash column chromatography (30:1 Pentanes/Et2O) provided 410 mg of compound 5.25w (2.59 mmol, 98% yield) as a colorless oil. \textsuperscript{1}H NMR (400 MHz; CDCl\textsubscript{3}): δ 7.16-6.98 (m, 4H), 5.02-5.00 (m, 1H), 4.89 (d, J = 2.3 Hz, 1H), 2.69-2.66 (m, 2H), 2.31-2.28 (m, 2H), 1.76-1.72 (m, 2H), 1.67-1.63 (m, 2H). \textsuperscript{13}C NMR (101 MHz; CDCl\textsubscript{3}): δ 152.8, 144.2, 140.2, 128.9, 128.1, 127.1, 126.1, 113.7, 36.5, 36.3, 31.5, 27.3. IR 3067, 3015, 2922, 2849, 1629, 1489, 1441, 1043 cm\textsuperscript{-1}. HRMS (ESI) calcd for C\textsubscript{12}H\textsubscript{14}[M]+ 158.1096; found 158.1091.

(1-cyclohexylvinyl)benzene (5.25x)

\begin{center}
\includegraphics[width=1cm]{5.25x}\text{Chemical Formula: }\text{C}_{14}\text{H}_{18} \\
\text{Molecular Weight: } 186.29
\end{center}

Cyclohexylphenylketone (470 mg, 2.50 mmol) was submitted to the general procedure A. Purification by flash column chromatography (30:1 PE/EtOAc) provided 443 mg of compound 5.25x (2.38 mmol, 95%) as a colorless oil. Spectroscopic data was consistent with that previously reported.\textsuperscript{288} As the literature characterization data did not include IR, the information is provided below: IR 3079, 3020, 2924, 2852, 1625, 1493, 1446, 1027 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (400 MHz; CDCl\textsubscript{3}): δ 7.36-7.24 (m, 5H), 5.14 (d, J = 1.4 Hz, 1H), 5.02 (t, J = 1.4 Hz, 1H), 2.46-2.40 (m, 1H), 1.87-1.74 (m, 5H), 1.38-1.32 (m, 2H), 1.25-1.16 (m, 3H). \textsuperscript{13}C NMR (101 MHz; CDCl\textsubscript{3}): δ 155.2, 143.1, 128.2, 127.1, 126.8, 110.5, 42.7, 32.9, 27.0, 26.6.
(3,3-dimethylbut-1-en-2-yl)benzene (5.25y)

2,2-Dimethylpropiophenone (502 µL, 3.00 mmol) was submitted to the general procedure A. Purification by flash column chromatography (100% PE) provided 323 mg of compound **5.25y** (2.00 mmol, 67%) as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.31-7.25 (m, 3H), 7.16-7.14 (m, 2H), 5.19 (s, 1H), 4.78 (s, 1H), 1.13 (s, 9H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 159.8, 143.5, 129.0, 127.3, 126.2, 111.5, 36.1, 29.6. IR 3081, 2956, 1626, 1492, 1482, 1385, 1361, 1361, 1206, 1094, 1073 cm$^{-1}$. HRMS (ESI) calcd for C$_{12}$H$_{16}$ [M$^+$] 160.1252; found 160.1256.

2-(prop-1-en-2-yl)thiophene (5.25z)

2-Acetylthiophene (272 µL, 2.50 mmol) was submitted to the general procedure A. Purification by flash column chromatography (20:1 PE/EtOAc) provided 250 mg of compound **5.25z** (2.01 mmol, 80% yield) as a colorless oil. $^1$H NMR (400 MHz; CDCl$_3$): δ 7.18 (dd, $J$ = 5.1, 0.9 Hz, 1H), 7.04 (dd, $J$ = 3.5, 1.0 Hz, 1H), 6.99 (dd, $J$ = 5.0, 3.5 Hz, 1H), 5.39 (s, 1H), 4.98-4.96 (m, 1H), 2.18-2.16 (m, 3H). $^{13}$C NMR (101 MHz; CDCl$_3$): δ 145.8, 137.2, 127.3, 124.2, 123.5, 111.2, 21.8. IR 3085, 2921, 1623, 1436, 1374, 1298, 1228, 1068, 1044 cm$^{-1}$. HRMS (ESI) calcd for C$_7$H$_8$S $^+$ 124.0347; found 124.0340.

2-(prop-1-en-2-yl)pyridine (5.25aa)

2-Acetylpyridine (280 µL, 2.50 mmol) was submitted to the general procedure A. Purification by flash column chromatography (10:1 Pentanes/Et2O) provided 219 mg of compound **5.25aa** (1.84 mmol, 73% yield) as a colorless oil. $^1$H NMR (400 MHz; CDCl$_3$): δ 8.60 (d, $J$ = 4.5 Hz, 1H), 7.66 (t, $J$ = 7.8 Hz, 1H), 7.49 (d, $J$ = 7.9 Hz, 1H), 7.17 (t, $J$ = 5.8 Hz, 1H), 5.87 (s, 1H), 5.32 (s, 1H), 2.23 (s, 3H). $^{13}$C NMR (101 MHz; CDCl$_3$): δ 158.2, 148.8, 143.1, 136.3, 122.1, 119.8, 115.7, 20.5. IR 3089, 3007, 2922, 1632, 1585, 1563, 1468, 1432, 1373, 1155, 1137 cm$^{-1}$. HRMS (ESI) calcd for C$_8$H$_9$N $^+$ [M+H$^+$] 120.0808; found 120.0814.
prop-1-ene-1,1-diyldibenzene (5.25ac)

Ethyltriphenylphosphonium bromide (2.78 g, 7.49 mmol, 3 equiv.) was suspended in dry THF (0.2 M) and cooled to 0 °C. 841 mg of t-BuOK (7.50 mmol, 3 equiv.) were added in one portion and the reaction was stirred at 0 °C for 30 min. 455 mg of benzophenone (2.50 mmol, 1 equiv.) was added and the reaction was let to warm to r.t. and stirred for 16 h. The reaction was quenched with H2O (25 mL) and extracted with EtOAc (3x 15 mL). The combined organic layers were washed with water and dried over Na2SO4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (30:1 PE/EtOAc) yielded 481 mg of compound 5.25ac (2.47 mmol, 98% yield) as a white solid. Spectroscopic data was consistent with that previously reported.\(^{284}\) 1H NMR (400 MHz; CDCl3): δ 7.39 (t, J = 7.0 Hz, 2H), 7.34-7.20 (m, 8H), 6.20 (q, J = 7.0 Hz, 1H), 1.78 (d, J = 7.0 Hz, 3H). \(^{13}\)C NMR (101 MHz; CDCl3) δ 142.9, 142.4, 140.0, 130.0, 128.1, 128.0, 127.2, 126.8, 126.7, 124.1, 15.7.

(1-cyclopropylvinyl)benzene (5.25af)

Cyclopropylphenylketone (691 μL, 5.00 mmol) was submitted to the general procedure A. Purification by flash column chromatography (30:1 PE/EtOAc) provided 694 mg of compound 5.25af (4.81 mmol, 96% yield) as a colorless oil. Spectroscopic data was consistent with that previously reported.\(^{289}\) As the literature characterization data did not include IR, the information is provided below: IR 3082, 3000, 1624, 1574, 1495, 1445, 1383, 1261, 1021 cm\(^{-1}\). 1H NMR (400 MHz; CDCl3): δ 7.63-7.61 (m, 2H), 7.36-7.28 (m, 3H), 5.30 (brs, 1H), 4.96 (brs, 1H), 1.71-1.64 (m, 1H), 0.88-0.84 (m, 2H), 0.64-0.60 (m, 2H). \(^{13}\)C NMR (101 MHz; CDCl3): δ 149.3, 141.61, 128.1, 127.4, 126.1, 109.0, 15.6, 6.7.
3.3.1 Copper-catalyzed intermolecular carboetherification of unactivated alkenes:

**General procedure:**

In the glovebox, the alkene (1 equiv.), Cu(OTf)₂ (20 mol%) and phenanthroline (40 mol%) were dissolved in a sealed tube in a 1:1 v:v mixture of dry and degassed MeOH and CH₃CN (0.1 M). DTBP (2 equiv.) was added. The tube was sealed and heated to 120 °C for 16 h. The reaction mixture was diluted with EtOAc (an amount equivalent to amount of MeOH/CH₃CN initially used) and washed with an aqueous solution of 1:1 v:v of NH₃(aq.)/NH₄Cl(aq.). (3x with the amount of EtOAc used). The combined aqueous layers were extracted 3x with EtOAc (3x with the amount of EtOAc previously used). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica.

**4-methoxy-4,4-diphenylbutanenitrile (5.42a)**

Alkene 5.25a (88 μL, 0.50 mmol) was submitted to the general reaction conditions. Purification by flash chromatography (7:1 Pentanes/Et20) afforded 97 mg of compound 5.42a (0.38 mmol, 77% yield) as a pale yellow solid. m.p. 92.8-93.7 °C. ¹H NMR (400 MHz; CDCl₃): δ 7.32-7.23 (m, 10H), 3.05 (s, 3H), 2.72-2.68 (m, 2H), 2.15-2.11 (m, 2H). ¹³C NMR (101 MHz; CDCl₃) δ 143.5, 128.4, 127.5, 126.8, 120.18, 81.5, 50.5, 31.4, 11.6. IR 3087, 3026, 2930, 2247, 1489, 1447, 1266, 1184, 1085, 1074 cm⁻¹. HRMS (ESI) calcd for C₁₇H₁₅NO⁺ [M+H]⁺ 252.1383; found 252.1387.
4-methoxy-4-phenyl-4-(p-tolyl)butanenitrile (5.42b)

Chemical Formula: C_{18}H_{19}NO
Molecular Weight: 265.35

Alkene 5.25b (99 mg, 0.51 mmol) was submitted to the general reaction conditions. Purification by flash chromatography (15:1 PE/EtOAc) afforded 104 mg of compound 5.42b (0.392 mmol, 77% yield) as a yellow solid. m.p. 80.7-83.7 °C. {^1}H NMR (400 MHz; CDCl\textsubscript{3}): δ 7.28-7.08 (m, 9H), 3.02 (s, 3H), 2.66-2.62 (m, 2H), 2.29 (s, 3H), 2.13-2.09 (m, 2H). {^{13}}C NMR (101 MHz; CDCl\textsubscript{3}): δ 143.6, 140.3, 137.0, 129.0, 128.2, 127.2, 126.7, 120.2, 81.3, 50.3, 31.4, 21.0, 11.5. IR 3090, 3061, 2948, 2245, 1514, 1446, 1185, 1093, 1082, 1036 cm\textsuperscript{-1}. HRMS (ESI) calcd for C_{18}H_{19}NNaO\textsuperscript{+} [M+Na]\textsuperscript{+} 288.1359; found 288.1367.

4-methoxy-4-(4-methoxyphenyl)-4-phenylbutanenitrile (5.42c)

Chemical Formula: C_{18}H_{19}NO\textsubscript{2}
Molecular Weight: 281.35

Alkene 5.25c (106 mg, 0.500 mmol) was submitted to the general reaction conditions. Purification by flash chromatography (15:1 PE/EtOAc) afforded 107 mg of compound 5.42c (0.380 mmol, 76% yield) as a yellow oil. {^1}H NMR (400 MHz; CDCl\textsubscript{3}): δ 7.31-7.20 (m, 7H), 6.85-6.83 (m, 2H), 3.80 (s, 3H), 3.05 (s, 3H), 2.74-2.60 (m, 2H), 2.22-2.05 (m, 2H). {^{13}}C NMR (101 MHz; CDCl\textsubscript{3}): δ 158.7, 143.7, 135.3, 128.2, 128.1, 127.2, 126.6, 120.2, 113.6, 81.2, 55.2, 50.2, 31.5, 11.5. IR 3056, 2936, 2248, 1607, 1510, 1444, 1294, 1247, 1179, 1078 cm\textsuperscript{-1}. HRMS (ESI) calcd for C_{18}H_{19}NNaO\textsubscript{2}\textsuperscript{+} [M+Na]\textsuperscript{+} 304.1308; found 304.1318.
4-(4-fluorophenyl)-4-methoxy-4-phenylbutanenitrile (5.42d)

Chemical Formula: C_{17}H_{16}FNO
Molecular Weight: 269.31

Alkene 5.25d (100 mg, 0.504 mmol) was submitted to the general reaction conditions. Purification by flash chromatography (15:1 PE/EtOAc) afforded 92 mg of compound 5.42d (0.34 mmol, 67% yield) as a pale yellow solid. m.p. 89.8-92.4 °C. \(^1\)H NMR (400 MHz; CDCl\(_3\)): \(\delta\) 7.34-7.25 (m, 7H), 7.02-6.98 (m, 2H), 3.04 (s, 3H), 2.69-2.65 (m, 2H), 2.14-2.10 (m, 2H). \(^{13}\)C NMR (101 MHz; CDCl\(_3\)): \(\delta\) 162.0 (d, \(J = 246.6\) Hz), 143.3, 139.4 (d, \(J = 3.2\) Hz), 128.7 (d, \(J = 8.1\) Hz), 128.6, 127.7, 126.8, 120.1, 115.3 (d, \(J = 21.3\) Hz), 81.2, 50.5, 31.5, 11.6. IR 3065, 2957, 2250, 1608, 1509, 1447, 1222, 1158, 1079 cm\(^{-1}\). HRMS (ESI) calcd for C\(_{17}\)H\(_{16}\)FNNaO\(^+\) [M+Na]\(^+\) 292.1108; found 292.1109.

4-(4-chlorophenyl)-4-methoxy-4-phenylbutanenitrile (5.42e)

Chemical Formula: C_{17}H_{16}ClNO
Molecular Weight: 285.77

4-chlorobenzophenone (106 mg, 0.489 mmol) was submitted to the general reaction conditions. Purification by flash chromatography (10:1 PE/EtOAc) afforded 114 mg of compound (0.400 mmol, 81% yield) as a yellow solid. m.p. 128.8-131.0 °C. \(^1\)H NMR (400 MHz; CDCl\(_3\)): \(\delta\) 7.33-7.24 (m, 9H), 3.06 (s, 3H), 2.74-2.62 (m, 2H), 2.18-2.11 (m, 2H). \(^{13}\)C NMR (101 MHz; CDCl\(_3\)): \(\delta\) 142.8, 142.1, 133.3, 128.5, 128.4, 128.1, 127.6, 126.7, 119.8, 81.1, 50.4, 31.1, 11.5. IR 3069, 2955, 2248, 1490, 1446, 1190, 1082, 1035, 1013 cm\(^{-1}\). HRMS (ESI) calcd for C\(_{17}\)H\(_{16}\)ClNNaO\(^+\) [M+Na]\(^+\) 308.0813; found 308.0819.
4-(4-bromophenyl)-4-methoxy-4-phenylbutanenitrile (5.42f)

Alkene 5.25f (120 mg, 0.463 mmol) was submitted to the general reaction conditions. Purification by flash chromatography (15:1 PE/EtOAc) afforded 122 mg of compound 5.42f (0.369 mmol, 80% yield) as a pale yellow solid. m.p. 117.6-120.4 °C. $^{1}$H NMR (400 MHz; CDCl$_3$): δ 7.45 (d, $J = 8.5$ Hz, 2H), 7.35-7.27 (m, 5H), 7.19 (d, $J = 8.5$ Hz, 2H), 3.06 (s, 3H), 2.71-2.65 (m, 2H), 2.15-2.11 (m, 2H). $^{13}$C NMR (101 MHz; CDCl$_3$) δ 142.9, 142.8, 131.6, 128.6, 128.6, 127.8, 126.8, 121.7, 120.0, 81.1, 50.4, 31.1, 11.5. IR 3065, 2942, 2246, 1487, 1446, 1396, 1190, 1082, 1034, 1009 cm$^{-1}$. HRMS (ESI) calcd for C$_{17}$H$_{16}$BrNO$^+$ [M+Na]$^+$ 352.0307; found 352.0311.

4-(3-cyano-1-methoxy-1-phenylpropyl)benzonitrile (5.42g)

Alkene 5.25g (104 mg, 0.507 mmol) was submitted to the general reaction conditions. Purification by flash chromatography (10:1 PE/EtOAc) afforded 82 mg of compound 5.42g (0.30 mmol, 60% yield) as a yellow oil. $^{1}$H NMR (400 MHz; CDCl$_3$): δ 7.62 (d, $J = 8.5$ Hz, 2H), 7.46 (d, $J = 8.5$ Hz, 2H), 7.37-7.26 (m, 5H), 3.08 (s, 3H), 2.81-2.74 (m, 1H), 2.70-2.63 (m, 1H), 2.24-2.16 (m, 1H), 2.11-2.02 (m, 1H). $^{13}$C NMR (101 MHz; CDCl$_3$): δ 149.1, 141.9, 132.2, 128.7, 128.0, 127.3, 126.7, 119.4, 118.5, 111.4, 81.2, 50.5, 30.7, 11.4. IR 3062, 2228, 1607, 1494, 1447, 1406, 1269, 1238, 1096, 1080 cm$^{-1}$. HRMS (ESI) calcd for C$_{18}$H$_{17}$N$_2$O$^+$ [M+H]$^+$ 277.1335; found 277.1331.
4-methoxy-4-phenyl-4-(m-tolyl)butanenitrile (5.42h)

![Chemical Formula: C_{18}H_{19}NO
Molecular Weight: 265.35](5.42h)

Alkene **5.25h** (97 mg, 0.50 mmol) was submitted to the general reaction conditions. Purification by flash chromatography (10:1 PE/EtOAc) afforded 83 mg of compound **5.42h** (0.31 mmol, 62% yield) as a yellow oil. \(^1H\) NMR (400 MHz; CDCl\(_3\)): \(\delta\) 7.30-7.28 (m, 4H), 7.24-7.16 (m, 2H), 7.10-7.02 (m, 3H), 3.03 (s, 3H), 2.69-2.65 (m, 2H), 2.30 (s, 3H), 2.13-2.09 (m, 2H). \(^13C\) NMR (101 MHz; CDCl\(_3\)): \(\delta\) 143.4, 143.3, 137.8, 128.2, 128.1, 128.0, 127.2, 127.2, 126.6, 123.8, 120.1, 81.3, 50.2, 31.2, 21.6, 11.5. IR 3061, 2944, 2828, 2247, 1605, 1489, 1447, 1194, 1078, 1035 cm\(^{-1}\). HRMS (ESI) calcd for C\(_{18}\)H\(_{19}\)NNaO\(^+\) [M+Na\(^+\)] 288.1359; found 288.1370.

4-(3-chlorophenyl)-4-methoxy-4-phenylbutanenitrile (5.42i)

![Chemical Formula: C_{17}H_{16}ClNO
Molecular Weight: 285.77](5.42i)

3-Chlorobenzophenone (108 mg, 0.498 mmol) was submitted to the general reaction conditions. Purification by flash chromatography (15:1 PE/EtOAc) afforded 87 mg of compound **5.242i** (0.30 mmol, 60% yield) as a pale yellow oil. \(^1H\) NMR (400 MHz; CDCl\(_3\)): \(\delta\) 7.35-7.12 (m, 9H), 3.04 (s, 3H), 2.73-2.60 (m, 2H), 2.14-2.09 (m, 2H). \(^13C\) NMR (101 MHz; CDCl\(_3\)): \(\delta\) 145.8, 142.5, 134.4, 129.6, 128.4, 127.6, 127.5, 126.7, 126.6, 124.8, 119.7, 81.0, 50.3, 30.9, 11.4. IR 3060, 2944, 2248, 1595, 1573, 1475, 1447, 1268, 1196, 1078 cm\(^{-1}\). HRMS (ESI) calcd for C\(_{17}\)H\(_{16}\)ClNaO\(^+\) [M+Na\(^+\)] 308.0818; found 308.0822.

4-methoxy-4-phenyl-4-(3-(trifluoromethyl)phenyl)butanenitrile (5.42j)

![Chemical Formula: C_{18}H_{16}F\(_3\)NO
Molecular Weight: 319.32](5.42j)

Alkene **5.25j** (124 mg, 0.500 mmol) was submitted to the general reaction conditions. Purification by flash chromatography (15:1 PE/EtOAc) afforded 97 mg of compound **5.42j**
(0.30 mmol, 61% yield) as a pale yellow oil. \( ^1H \) NMR (400 MHz; CDCl\(_3\)): \( \delta \) 7.67 (s, 1H), 7.54-7.50 (m, 1H), 7.44-7.42 (m, 2H), 7.37-7.28 (m, 5H), 3.08 (s, 3H), 2.72 (ddd, \( J = 19.1, 10.5, 5.5 \) Hz, 2H), 2.23-2.03 (m, 2H). \( ^{13}C \) NMR (101 MHz; CDCl\(_3\)): \( \delta \) 145.0, 142.5, 130.8 (q, \( J = 32.3 \) Hz), 130.3, 129.0, 128.6, 127.9, 126.8, 124.4 (q, \( J = 3.7 \) Hz), 124.1 (q, \( J = 273.2 \) Hz), 123.2 (q, \( J = 4.2 \) Hz), 119.8, 81.2, 50.5, 31.1, 11.5. \( ^{19}F \) NMR (376 MHz; CDCl\(_3\)) \( \delta \) -62.50.

IR 3063, 2948, 2249, 1490, 1446, 1329, 1269, 1162, 1121 cm\(^{-1}\). HRMS (ESI) calcd for C\(_{18}\)F\(_3\)H\(_{17}\)NO\(^+\) [M+H]\(^+\) 320.1257; found 320.1262.

4-methoxy-4-phenyl-4-(o-tolyl)butanenitrile (5.42k)

In the glovebox, 100 mg of alkene \( 5.25k \) (0.515 mmol, 1 equiv.), Cu(OTf)\(_2\) (40 mol\%) and phenanthroline (80 mol\%) were dissolved in a sealed tube in a 1:1 v:v mixture of dry and degassed MeOH and CH\(_3\)CN (0.1 M). DTBP (2 equiv.) was added. The tube was sealed and heated to 120 °C for 24 h. The reaction mixture was diluted with EtOAc (5 mL) and washed with an aqueous solution 1:1 v:v of NH\(_3\)(aq.)/NH\(_4\)Cl(aq.) (3x 5 mL). The combined aqueous layers were extracted with EtOAc (3x 5 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\), filtered and concentrated under reduced pressure. Purification by flash chromatography (15:1 PE/EtOAc) afforded 76 mg of compound 5.42k (0.28 mmol, 57% yield) as a pale yellow solid. \( ^1H \) NMR (400 MHz; CDCl\(_3\)): \( \delta \) 7.56 (dd, \( J = 7.7, 1.4 \) Hz, 1H), 7.29-7.22 (m, 7H), 7.08 (dd, \( J = 6.9, 1.1 \) Hz), 3.05 (s, 3H), 2.89 (ddd, \( J = 13.3, 10.8, 5.0 \) Hz, 1H), 2.45 (ddd, \( J = 13.4, 11.0, 5.0 \) Hz, 1H), 2.30 (m, 1H), 1.98 (ddd, \( J = 16.9, 10.9, 5.0 \) Hz, 1H), 1.90 (s, 3H). \( ^{13}C \) NMR (101 MHz; CDCl\(_3\)): \( \delta \) 143.3, 139.9, 138.2, 132.6, 128.1, 127.9, 127.0, 126.5, 125.4, 120.3, 81.1, 49.9, 32.3, 20.7, 11.5. IR 3065, 2930, 2246, 1590, 1489, 1448, 1091 cm\(^{-1}\). HRMS (ESI) calcd for C\(_{18}\)H\(_{20}\)NO\(^+\) [M+H]\(^+\) 266.1539; found 266.1544.
4-methoxy-4,4-di-p-tolylbutanenitrile (5.42l)

![Chemical Structure]

4,4'-Dimethylbenzophenone (104 mg, 0.495 mmol) was submitted to the general reaction conditions. Purification by flash chromatography (7:1 PE/EtOAc) afforded 113 mg of compound 5.42l (0.404 mmol, 81% yield) as a yellow oil. $^1$H NMR (400 MHz; CDCl$_3$): δ 7.17-7.08 (m, 8H), 3.03 (s, 3H), 2.66-2.62 (m, 2H), 2.32 (s, 6H), 2.13-2.09 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 140.7, 137.1, 129.1, 126.8, 120.4, 81.4, 50.4, 31.6, 21.1, 11.7. IR 3024, 2943, 2828, 2247, 1510, 1449, 1185, 1089 cm$^{-1}$. HRMS (ESI) calcd for C$_{19}$H$_{21}$NNaO$^+$ [M+Na]$^+$ 302.1515; found 302.1520.

4-methoxy-4,4-bis(4-methoxyphenyl)butanenitrile (5.42m)

![Chemical Structure]

In the glovebox, 120 mg (0.500 mmol) of alkene 5.25m, Cu(OTf)$_2$ (30 mol%) and phenanthroline (60 mol%) were dissolved in a sealed tube in a 1:1 v:v mixture of dry and degassed MeOH and CH$_3$CN (0.1 M). DTBP (2 equiv.) was added. The tube was sealed and heated to 120 °C for 24 h. The reaction mixture was diluted with EtOAc (5 mL) and washed with an aqueous solution 1:1 v:v of NH$_3$(aq.)/NH$_4$Cl(aq.) (3x 5 mL). The combined aqueous layers were extracted with EtOAc (3x 5 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (20:1 PE/EtOAc) afforded 110 mg of compound 5.42m (0.353 mmol, 71% yield) as a yellow oil. $^1$H NMR (400 MHz; C$_6$D$_6$): δ 7.21 (d, $J = 8.8$ Hz, 4H), 6.84 (d, $J = 8.8$ Hz, 4H), 3.39 (s, 6H), 2.79 (s, 3H), 2.26-2.22 (m, 2H), 1.79-1.73 (m, 2H). $^{13}$C NMR (101 MHz; C$_6$D$_6$): δ 158.8, 136.1, 128.02, 119.5, 113.4, 80.8, 54.4, 49.4, 31.2, 11.0. IR 3059, 2937, 2247, 1609, 1582, 1509, 1462, 1303, 1247, 1176 cm$^{-1}$. HRMS (ESI) calcd for C$_{19}$H$_{21}$NNaO$_3$ [M+Na]$^+$ 334.1414; found 334.1423.
Chapter 5 Copper-catalyzed three-component carboetherification of alkenes

4-methoxy-4-(4-methoxyphenyl)-4-(4-(trifluoromethyl)phenyl)butanenitrile (5.42n)

[Chemical Structure Image]

Alkene 5.25n (140 mg, 0.503 mmol) was submitted to the general reaction conditions. Purification by flash chromatography (7:1 Pentanes/Et2O) afforded 135 mg of compound 5.42n (0.386 mmol, 77% yield) as a yellow oil. 1H NMR (400 MHz; CDCl3): δ 7.56 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 8.9 Hz, 2H), 6.85 (d, J = 8.9 Hz, 2H), 3.80 (s, 3H), 3.05 (s, 3H), 2.75 (dd, J = 13.9, 10.9, 5.3 Hz, 1H), 2.62 (dd, J = 13.9, 10.7, 5.3 Hz, 1H), 2.20 (ddd, J = 17.1, 10.7, 5.3 Hz, 1H), 2.03 (ddd, J = 17.1, 10.8, 5.3 Hz, 1H). 13C NMR (101 MHz; CDCl3): δ 159.2, 148.2, 134.5, 129.6 (q, J = 32.5 Hz), 128.2, 127.0, 125.4 (q, J = 2.9 Hz), 124.1 (q, J = 273.2 Hz), 119.9, 114.0, 81.1, 55.4, 50.5, 31.3, 11.6. 19F NMR (376 MHz; CDCl3): δ -62.6. IR 3062, 2934, 2249, 2107, 1612, 1511, 1326, 1252, 1165, 1121 cm⁻¹. HRMS (ESI) calcd for C19H18F3NO2⁺ [M+Na]⁺ 372.1182; found 372.1187.

4,4-bis(4-fluorophenyl)-4-methoxybutanenitrile (5.42o)

[Chemical Structure Image]

Alkene 5.25o (113 mg, 0.522 mmol) was submitted to the general reaction conditions. Purification by flash chromatography (7:1 Pentanes/Et2O) afforded 113 mg of compound 5.42o (0.393 mmol, 75% yield) as a pale yellow solid. m.p.: 75.4-76.6 °C. 1H NMR (400 MHz; CDCl3): δ 7.47-7.17 (m, 4H), 7.14-6.77 (m, 4H), 3.04 (s, 3H), 2.68-2.64 (m, 2H), 2.14-2.10 (m, 2H). 13C NMR (101 MHz; CDCl3): δ 162.1 (d, J = 248.0 Hz), 139.2 (d, J = 2.5 Hz), 128.6 (d, J = 8.2 Hz), 119.9, 115.4 (d, J = 21.4 Hz), 80.9, 50.5, 31.5, 11.6. 19F NMR (376 MHz; CDCl3): δ -114.7. IR 3068, 2990, 2954, 2832, 2253, 1604, 1508, 1222, 1161, 1086 cm⁻¹. HRMS (ESI) calcd for C17H15F2NO⁺ [M+Na]⁺ 310.1014; found 310.1013.
4,4-bis(4-chlorophenyl)-4-methoxybutanenitrile (5.42p)

![Chemical Structure](image)

Alkene 5.25p (124 mg, 0.498 mmol) was submitted to the general reaction conditions. Purification by flash chromatography (10:1 PE/EtOAc) afforded 117 mg of compound 5.42p (0.37 mmol, 73% yield) as a yellow oil. $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.30-7.28 (m, 4H), 7.23-7.21 (m, 4H), 3.05 (s, 3H), 2.67-2.61 (m, 2H), 2.13-2.09 (m, 2H). $^{13}$C NMR (101 MHz; CDCl$_3$): $\delta$ 141.5, 133.5, 128.6, 128.0, 119.5, 80.7, 50.3, 30.8, 11.3. IR 3059, 2944, 2249, 1595, 1489, 1402, 1267, 1195, 1088, 1013 cm$^{-1}$. HRMS (ESI) calcd for C$_{17}$H$_{15}$Cl$_2$NO$^+$ [M+Na]$^+$ 342.0423; found 342.0428.

4-methoxy-4-phenylpentanenitrile (5.42q)

![Chemical Structure](image)

$\alpha$-Methylstyrene (65 µL, 0.50 mmol) was submitted to the general reaction conditions. Purification by flash chromatography (7:1 Pentanes/Et2O) afforded 83.1 mg of compound 5.42q (0.39 mmol, 88% yield) as a colorless oil. $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.42-7.26 (m, 5H), 3.13 (s, 3H), 2.40-2.27 (m, 1H), 2.22-1.99 (m, 3H), 1.58 (s, 3H). $^{13}$C NMR (101 MHz; CDCl$_3$): $\delta$ 143.3, 128.7, 127.6, 126.0, 120.3, 77.8, 50.6, 38.7, 23.1, 12.1. IR 2981, 2938, 2247, 1490, 1399, 1162, 1093, 1064 cm$^{-1}$. HRMS (ESI) calcd for C$_{12}$H$_{16}$NO$^+$ [M+H]$^+$ 190.1226; found 190.1227.

4-(4-chlorophenyl)-4-methoxypentanenitrile (5.42s)

![Chemical Structure](image)

4-Chloro-$\alpha$-methylstyrene (72 µL, 0.50 mmol) was submitted to the general reaction conditions. Purification by flash chromatography (7:1 Pentanes/Et2O) afforded 65 mg of compound 5.42s (0.29 mmol, 58% yield) as a colorless oil. $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.39-7.36 (m, 2H), 7.31-7.29 (m, 2H), 3.12 (s, 3H), 2.34 (ddd, $J$ = 14.9, 10.2, 5.0 Hz, 1H), 2.23-1.96 (m, 3H), 1.56 (s, 3H). $^{13}$C NMR (101 MHz; CDCl$_3$): $\delta$ 142.0, 133.5, 128.9, 127.5, 120.0, 77.4, 50.6, 38.5, 23.0, 12.1. IR
2981, 2938, 2829, 2247, 1490, 1399, 1162, 1093, 1064, 1012 cm⁻¹. HRMS (ESI) calcd for C₁₂H₁₄AgClNO⁺ [M+Ag]⁺ 329.9809; found 329.9817.

4-methoxy-4-((o-tolyl)pentanenitrile (5.42t)

2-Methyl-α-methylstyrene (66 mg, 0.50 mmol) was submitted to the general reaction conditions. Purification by flash chromatography (7:1 PE/EtOAc) afforded 61 mg of compound 5.42t (0.30 mmol, 61% yield) as a colorless oil. ¹H NMR (400 MHz; CDCl₃): δ 7.23-7.19 (m, 4H), 3.06 (s, 3H), 2.52 (s, 3H), 2.42-2.28 (m, 3H), 2.17-2.12 (m, 1H), 1.64 (s, 3H). ¹³C NMR (101 MHz; CDCl₃): δ 140.1, 136.6, 132.9, 127.7, 127.5, 125.9, 120.2, 79.1, 50.1, 36.1, 23.2, 21.3, 12.3. IR 3061, 2982, 2938, 2247, 1473, 1451, 1377, 1166, 1098, 1069 cm⁻¹. HRMS (ESI) calcd for C₁₃H₁₈NO⁺ [M+H]⁺ 204.1383; found 204.1386.

3-(5-methoxy-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-yl)propanenitrile (5.42w)

Alkene 5.25w (78 mg, 0.49 mmol) was submitted to the general reaction conditions. Purification by flash chromatography (15:1 PE/EtOAc) afforded 87 mg of compound 5.42w (0.38 mmol, 77% yield) as a pale yellow oil. ¹H NMR (400 MHz; CDCl₃): δ 7.35 (dd, J = 7.5, 1.5 Hz, 1H), 7.23-7.15 (m, 2H), 7.14-7.10 (m, 1H), 3.16 (s, 3H), 2.89-2.73 (m, 2H), 2.50-2.42 (m, 1H), 2.33-2.05 (m, 4H), 1.86-1.65 (m, 5H). ¹³C NMR (101 MHz; CDCl₃): δ 140.5, 140.3, 131.4, 128.4, 127.6, 126.1, 120.5, 80.6, 50.1, 35.6, 35.1, 34.9, 27.4, 24.2, 11.7. IR 3060, 2935, 2247, 1481, 1445, 1097, 1066 cm⁻¹. HRMS (ESI) calcd for C₁₅H₁₉NNaO⁺ [M+Na]⁺ 252.1359; found 252.1368.
4-cyclohexyl-4-methoxy-4-phenylbutanenitrile (5.42x)

Alkene 5.25x (93 mg, 0.50 mmol) was submitted to the general reaction conditions. Purification by flash chromatography (7:1 Pentanes/Et₂O) afforded 78 mg of compound 5.42x (0.30 mmol, 60% yield) as a pale yellow oil. ¹H NMR (400 MHz; CDCl₃): δ 7.36-7.26 (m, 5H), 3.21 (s, 3H), 2.48-2.20 (m, 4H), 1.91-1.88 (m, 1H), 1.72-1.59 (m, 1H), 1.59-1.56 (m, 1H), 1.26-1.17 (m, 2H), 0.87 (qt, J = 13.1, 3.8 Hz, 1H), 0.73 (qd, J = 12.5, 3.3 Hz, 1H), 0.51-0.47 (m, 1H). ¹³C NMR (101 MHz; CDCl₃): δ 139.6, 127.6, 127.2, 127.0, 120.4, 82.3, 49.4, 44.0, 28.2, 26.7, 26.3, 26.1, 11.3. IR 2931, 2246, 1493, 1446, 1184, 1101, 1071 cm⁻¹. HRMS (ESI) calcd for C₁₇H₂₃NO⁺ [M+H]⁺ 258.1852; found 258.1853.

4-methoxy-4-(thiophen-2-yl)pentanenitrile (5.42z)

Alkene 5.25z (63 mg, 0.51 mmol) was submitted to the general reaction conditions. Purification by flash chromatography (15:1 PE/EtOAc) afforded 61 mg of compound 5.42z (0.31 mmol, 61% yield) as a pale yellow oil. ¹H NMR (400 MHz; CDCl₃): δ 7.29 (dd, J = 5.0, 1.3 Hz, 1H), 6.99 (dd, J = 5.0, 1.3 Hz, 1H), 6.92 (dd, J = 3.5, 1.0 Hz, 1H), 3.17 (s, 3H), 2.44-2.28 (m, 2H), 2.22-2.18 (m, 2H), 1.62 (s, 3H). ¹³C NMR (101 MHz; CDCl₃): δ 148.0, 126.7, 125.2, 124.7, 119.9, 76.6, 50.6, 38.8, 23.7, 12.2. IR 3109, 2982, 2247, 1623, 1531, 1467, 1436, 1378, 1200, 1166, 1152, 1106, 1066 cm⁻¹. HRMS (ESI) calcd for C₁₀H₁₄NOS⁺ [M+H]⁺ 196.0791; found 196.0789.

4-methoxy-4-(pyridin-2-yl)pentanenitrile (5.42aa)

Alkene 5.25aa (61 mg, 0.51 mmol) was submitted to the general reaction conditions. Purification by flash chromatography (3:1 PE/EtOAc + Et₃N) afforded 25 mg of compound 5.42aa (0.13 mmol, 25% yield) as a pale yellow oil. ¹H NMR (400 MHz; CDCl₃): δ 8.57 (d, J = 4.5 Hz, 1H), 7.70 (t, J = 7.7 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.19 (t, J = 5.8 Hz, 1H), 3.25 (s, 3H),
2.33-2.03 (m, 4H), 1.57 (s, 3H). $^{13}$C NMR (101 MHz; CDCl$_3$): δ 162.7, 149.0, 136.5, 122.2, 120.4, 120.0, 79.4, 50.5, 35.0, 23.0, 11.8. IR 3059, 2937, 2246, 1589, 1470, 1433, 1371, 1201, 1169, 1119 cm$^{-1}$. HRMS (ESI) calcd for C$_{11}$H$_{15}$N$_2$O $^{[M+H]^+}$ 191.1179; found 191.1177.

4-methoxy-4-(pyridin-3-yl)pentanenitrile (5.42ab)

Alkene 5.25ab (59 mg, 0.50 mmol) was submitted to the general reaction conditions. Purification by flash chromatography (3:1 PE/EtOAc + Et$_3$N) afforded 20 mg of compound 5.42ab (0.10 mmol, 20% yield) as a pale yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.61 (d, $J$ = 2.3 Hz, 1H), 8.56 (dd, $J$ = 4.8 Hz, 1.5 Hz, 1H), 7.69 (dt, $J$ = 8.0 Hz, 2.0 Hz, 1H), 7.33 (dd, $J$ = 8.0 Hz, 4.8 Hz, 1H), 3.16 (s, 3H), 2.21 (m 4H), 1.61 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 148.7, 147.5, 138.9, 133.8, 123.4, 119.6, 76.5, 50.5, 38.2, 22.7, 11.8. IR 3046, 2981, 2362, 2247, 1575, 1476, 1417, 1380, 1168, 1096, 1023 cm$^{-1}$. HRMS (ESI) calcd for C$_{11}$H$_{15}$N$_2$O $^{[M+H]^+}$ 191.1179; found 191.1186.

4-methoxy-3-methyl-4,4-diphenylbutanenitrile (5.42ac)

Alkene 5.25ac (97 mg, 0.50 mmol) was submitted to the general reaction conditions. The reaction was stirred for 48 h. Purification by flash chromatography (15:1 PE/EtOAc) afforded 75 mg of compound 5.42ac (0.28 mmol, 56% yield) as a pale yellow oil. $^1$H NMR (400 MHz; CDCl$_3$): δ 7.38-7.24 (m, 10H), 3.15 (dq, $J$ = 10.6, 7.0, 3.4 Hz, 1H), 2.86 (s, 3H), 2.80 (dd, $J$ = 16.6, 3.3 Hz, 1H), 1.64 (dd, $J$ = 16.7, 10.9 Hz, 1H), 1.05 (d, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (101 MHz; CDCl$_3$): δ 139.1, 138.2, 129.3, 129.1, 128.0, 127.9, 127.6, 127.5, 119.7, 85.6, 51.2, 36.4, 20.2, 15.8. IR 3059, 2977, 2359, 2341, 2247, 1493, 1446, 1384, 1287, 1202 cm$^{-1}$. HRMS (ESI) calcd for C$_{18}$H$_{20}$NO $^{[M+H]^+}$ 266.1539; found 266.1545.
4-methoxy-2-methyl-4,4-diphenylbutanenitrile (5.48a)

![Structure](5.48a)

In the glovebox, 88 μL of 1,1-diphenylethylene (0.50 mmol, 1 equiv.), Cu(OTf)$_2$ (20 mol%) and phenanthroline (40 mol%) were dissolved in a sealed tube in a 1:1 v:v mixture of dry and degassed MeOH and EtCN (0.1 M). DTBP (2 equiv.) was added. The tube was sealed and heated to 120 °C for 24 h. The reaction mixture was diluted with EtOAc (5 mL) and washed with an aqueous solution of 1:1 v:v of NH$_3$(aq)/NH$_4$Cl(aq) (3x 5 mL). The combined aqueous layers were extracted with EtOAc (3x 5 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (15:1 PE/EtOAc) afforded 81 mg of compound 5.48a (0.31 mmol, 61% yield) as a white solid. m.p. 87.4-90.1 °C. $^1$H NMR (400 MHz; CDCl$_3$): δ 7.36-7.22 (m, 10H), 3.10 (s, 3H), 2.94-2.88 (m, 1H), 2.51-2.43 (m, 1H), 2.37-2.33 (m, 1H), 1.22 (d, J = 7.3 Hz, 3H). $^{13}$C NMR (101 MHz; CDCl$_3$): δ 144.5, 143.4, 128.3, 128.2, 127.5, 127.2, 127.1, 126.6, 123.3, 81.7, 50.8, 39.3, 20.1, 19.7. IR 3084, 2939, 2240, 1491, 1447, 1262, 1205, 1100, 1074 cm$^{-1}$. HRMS (ESI) calcd for C$_{18}$H$_{19}$NNaO$_2$ [M+Na]$^+$ 288.1359; found 288.1371.

2-ethyl-4-methoxy-4,4-diphenylbutanenitrile (5.48b)

![Structure](5.48b)

In the glovebox, 88 μL of 1,1-diphenylethylene (0.50 mmol, 1 equiv.), Cu(OTf)$_2$ (30 mol%) and phenanthroline (60 mol%) were dissolved in a sealed tube in a 1:1 v:v mixture of dry and degassed MeOH and butyronitrile (0.1 M). DTBP (2 equiv.) was added. The tube was sealed and heated to 120 °C for 36 h. The reaction mixture was diluted with EtOAc (5 mL) and washed with an aqueous solution of 1:1 v:v of NH$_3$(aq)/NH$_4$Cl(aq) (3x 5 mL). The combined aqueous layers were extracted with EtOAc (3x 5 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography (15:1 PE/EtOAc) afforded 62 mg of compound 5.48b (0.22 mmol, 45% yield) as a colorless oil. $^1$H NMR (400 MHz; CDCl$_3$): δ 7.36-7.21 (m, 10H), 3.10 (s, 3H), 2.92-2.86 (m, 1H), 2.38-2.33 (m, 2H), 1.60-1.42 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H). $^{13}$C NMR (101 MHz; CDCl$_3$): δ 144.5, 143.5, 128.3,
128.2, 127.5, 127.2, 127.1, 126.6, 122.3, 81.7, 50.8, 37.4, 27.4, 26.9, 11.4. IR 3050, 2967, 2878, 2237, 1493, 1447, 1101, 1076 cm⁻¹. HRMS (ESI) calcd for C₁₉H₂₁NO⁺ [M]⁺ 279.1623; found 279.1622.

4-methoxy-2-(methoxymethyl)-4,4-diphenylbutanenitrile (5.48d)

In the glovebox, 88 μL of 1,1-diphenylethylene (0.50 mmol, 1 equiv.), Cu(OTf)₂ (30 mol%) and phenanthroline (60 mol%) were dissolved in a sealed tube in 4.5 mL of dry and degassed MeOH. 3-Methoxypropionitrile (11 equiv.) and DTBP (2 equiv.) were added. The tube was sealed and heated to 120 °C for 36 h. The reaction mixture was diluted with EtOAc (5 mL) and washed with an aqueous solution of 1:1 v:v of NH₃(aq.)/NH₄Cl(aq.) (3x 5 mL). The combined aqueous layers were extracted with EtOAc (3x 5 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash chromatography (10:1 PE/EtOAc) afforded 111 mg of compound 5.48d (0.37 mmol, 75% yield) as a colorless oil. ¹H NMR (400 MHz; CDCl₃): δ 7.37-7.21 (m, 10H), 3.37-3.30 (m, 2H), 3.26 (s, 3H), 3.11 (s, 3H), 2.87-2.81 (m, 1H), 2.72-2.66 (m, 1H), 2.63-2.58 (m, 1H). ¹³C NMR (101 MHz; CDCl₃): δ 144.3, 143.4, 128.3, 128.2, 127.5 (2C), 127.1 (2C), 126.6, 120.8, 81.5, 72.3, 58.8, 50.7, 34.1, 26.7. IR 3058, 2937, 2830, 2242, 1493, 1447, 1121, 1076 cm⁻¹.

4-ethoxy-4-phenylpentanenitrile (5.42ad)

In the glovebox, 65 μL of α-methylstyrene (0.50 mmol, 1 equiv.), Cu(OTf)₂ (30 mol%) and phenanthroline (60 mol%) were dissolved in a sealed tube in a 1:1 v:v mixture of dry and degassed EtOH and CH₃CN (0.1 M). DTBP (2 equiv.) was added. The tube was sealed and heated to 120 °C for 36 h. The reaction mixture was diluted with EtOAc (5 mL) and washed with an aqueous solution 1:1 v:v of NH₃(aq.)/NH₄Cl(aq.) (3x 5 mL). The combined aqueous layers were extracted with EtOAc (3x 5 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash chromatography (15:1 Hexanes/EtOAc) afforded 37 mg of compound 5.42ad (0.18 mmol, 37% yield) as a colorless oil.
1H NMR (400 MHz; CDCl3): δ 7.39-7.29 (m, 5H), 3.41-3.33 (m, 1H), 3.24-3.17 (m, 1H), 2.42-2.34 (m, 1H), 2.24-2.01 (m, 3H), 1.60 (s, 3H), 1.21 (t, J = 7.0 Hz, 3H). 13C NMR (101 MHz; CDCl3): δ 144.0, 128.6, 127.5, 125.9, 120.4, 77.4, 58.1, 39.1, 23.7, 15.7, 12.6. IR 3061, 2978, 2930, 2243, 1491, 1448, 1387, 1104, 1070 cm⁻¹.

4-ethoxy-4,4-diphenylbutanenitrile (5.42ae)

\[
\text{Chemical Formula: C}_{18}H_{19}NO} \\
\text{Molecular Weight: 265.35}
\]

In the glovebox, 88 μL of 1,1-diphenylethylene (0.50 mmol, 1 equiv.), Cu(OTf)₂ (30 mol%) and phenanthroline (60 mol%) were dissolved in a sealed tube in a 1:1 v:v mixture of dry and degassed MeOH and CH₂CN (0.1 M). DTBP (2 equiv.) was added. The tube was sealed and heated to 120 °C for 24 h. The reaction mixture was diluted with EtOAc (5 mL) and washed with an aqueous solution 1:1 v:v of NH₃(aq.)/NH₄Cl(aq.) (3x 5 mL) The combined aqueous layers were extracted with EtOAc (3x 5 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash chromatography (20:1 PE/EtOAc) afforded 48 mg of compound 5.42ae (0.18 mmol, 36% yield) as a yellow oil. 1H NMR (400 MHz; CDCl3): δ 7.34-7.23 (m, 10H), 3.16 (q, J = 6.9 Hz, 2H), 2.73-2.69 (m, 2H), 2.16-2.12 (m, 2H), 1.22 (t, J = 6.9 Hz, 3H). 13C NMR (101 MHz; CDCl3): δ 143.9, 128.2, 127.3, 126.6, 120.2, 81.1, 57.8, 32.0, 15.4, 11.6. IR 3088, 3059, 3026, 2973, 2928, 2247, 1491, 1447, 1101 cm⁻¹. HRMS (ESI) calcd for C₁₈H₁₉NNaO⁺ [M+Na⁺] 288.1359; found 288.1359.

3-(3,4-dihydrornaphthalen-1-yl)propanenitrile (5.49)

\[
\text{Chemical Formula: C}_{13}H_{12}N} \\
\text{Molecular Weight: 183.25}
\]

Alkene 5.25af (70.2 mg, 0.48 mmol) was submitted to the general reaction conditions. Purification by flash chromatography (15:1 PE/EtOAc) afforded 50 mg of compound 5.49 (0.27 mmol, 57% yield) as a pale yellow oil. 1H NMR (400 MHz; C₆D₆): δ 7.03-7.00 (m, 2H), 6.96-6.93 (m, 1H), 6.68-6.64 (m, 1H), 5.50 (t, J = 4.5 Hz, 1H), 2.45 (t, J = 7.9 Hz, 2H), 2.15-2.11 (m, 2H), 1.92-1.87 (m, 2H), 1.66 (t, J = 7.4 Hz, 2H). 13C NMR (101 MHz; CDCl₃): δ 137.0, 133.6, 133.5, 128.2, 127.4, 127.0, 126.8, 122.3, 119.0, 28.6, 28.3, 23.2, 16.2. IR 3058, 3018, 2937, 2830,
2246, 1489, 1448, 1427, 1080, 1024 cm\(^{-1}\). HRMS (ESI) calcd for C\(_{13}\)H\(_{14}\)N\(^+\) [M+H]\(^+\) 184.1121; found 184.1119.
Chapter 6  Conclusion

In this thesis, the development of new synthetic methods involving radical intermediates has been described (Scheme 6.1). In Chapters 2 to 4, new radical methods for the synthesis of fluorinated compounds have been presented. A copper-catalyzed method for three-component etherification of alkenes using alkyl nitriles and methanol was detailed in Chapter 5.

Scheme 6.1 Methodologies presented in the dissertation
6.1 Radical fluorination

The work presented in this thesis mainly focuses on the development of new methods for radical fluorination. In Chapter 2, the ability of two traditionally electrophilic fluorinating agents, NFSI and Selectfluor®, to transfer fluorine to alkyl radicals was demonstrated. Initial DFT calculations performed by Prof. Kennepohl and Dr. Okbinoglu, revealed that N—F bond strength of those reagents, 63.4 kcal/mol and 61.0 kcal/mol respectively, was sufficiently weak to allow fluorine abstraction by radicals. Experimental verification was performed by Dr. Rueda-Becerril, by independently generating alkyl radicals in presence of a fluorinating agent. Thermal and photochemical homolysis of lauroyl peroxide in the presence of NFSI afforded the corresponding fluorinated products. Easier to handle radical precursors, t-butyl peresters, were synthesized by Dr. Rueda-Becerril, Dr. Leung and myself to study the scope of the radical fluorination reaction using NFSI. Primary, secondary, tertiary and benzylic radicals were fluorinated by Dr. Rueda-Becerril using NFSI (Scheme 6.2). I personally demonstrated that this radical fluorination method could be used on a radical α to a nitrogen atom. The ability of Selectfluor® to transfer fluorine to alkyl radicals was also demonstrated by Dr. Leung. I developed a one-pot procedure for the synthesis and fluorination of peresters that avoids having to purify the more thermally unstable radical precursors. The one-pot procedure proved to be less efficient than the two-step procedure for stable peresters. Higher yields were obtained using the one-pot procedure than the sequential method when applied to an unstable perester.

\[
\begin{align*}
\text{R} = \text{1°, 2°, 3°, benzyl} \\
\alpha\text{-heteroatom} \\
\end{align*}
\]

A new radical fluorination method that utilizes Selectfluor® as atomic fluorine source was subsequently developed and was described in Chapter 3. Dr. Leung showed that phenoxyacetic
acid derivatives undergo fluorodecarboxylation when exposed to UV-light in an alkaline solution in presence of Selectfluor® (Scheme 6.3). Experimental evidence support the mechanism depicted in Scheme 6.3; under UV irradiation, the phenoxyacetic acid derivative is promoted to an excited state, which can be oxidized by Selectfluor®. The resulting intermediate undergoes a fast decarboxylation to afford a radical intermediate that is subsequently fluorinated.

\[
\begin{align*}
\text{Scheme 6.3 Proposed mechanism for the photofluorodecarboxylation reaction}
\end{align*}
\]

The light mediated fluorodecarboxylation method developed by Dr. Leung has been applied to the synthesis of monomethyl aryl ethers (Scheme 6.4) by Dr. Leung, Julian West and myself. My contribution to the fluorodecarboxylation method began with the investigation of the effects of the substituents on the phenoxy moiety on the reaction outcome. Electron-withdrawing and alkyl substituents were both tolerated. Electron-rich substrates suffered from competitive side reactions with Selectfluor® and substrates bearing weak C—H bonds were not compatible under the reaction conditions. I then demonstrated the possibility of applying this methodology to the synthesis of difluoromethyl aryl ethers (Scheme 6.4). Similar substituent effects were observed for this reaction. Furthermore, two examples of fluorodecarboxylation of 2-aryl acetic acid derivatives have been presented.
The application of the photofluorodecarboxylation method presented in Chapter 3 to the synthesis of trifluoromethyl aryl ethers was described in Chapter 4. Difluorophenoxyacetic acid derivatives were used as radical precursors. Under the previously developed conditions, no decarboxylation was observed. A shift in the maximum absorbance of phenoxyacetic acids from 300 nm to 254 nm was indeed observed using UV-visible spectroscopy. Switching the irradiation wavelength to 254 nm allowed the fluorodecarboxylation to occur. The trifluoromethyl aryl ethers, however, proved to be unstable under irradiation at this wavelength. An alternative method was developed using benzophenone to induce the decarboxylation using a 350 nm irradiation. Benzophenone was proposed to act as a sensitizer rather than a photooxidant since no fluorodecarboxylation was observed using NFSI (a milder oxidant than Selectfluor®) as fluorine source. The photosensitized fluorodecarboxylation was shown to be very sensitive to the substitution on the substrate; electron-rich substrates underwent side reactions with Selectfluor® and electron-poor trifluoromethyl aryl ethers were only obtained in low yields.

We hypothesized that the low yields observed for electron-deficient substrates might be due to a slow fluorine transfer step to the radical intermediate, allowing side reactions to occur. XeF₂, a faster atomic fluorine transfer agent, was therefore used as fluorine source for the fluorodecarboxylation of difluorophenoxyacetic acid derivatives (Scheme 6.5). Due to the high reduction potential of XeF₂ (2.64 V)²¹⁹, no excitation of the substrate was required to induce the decarboxylation. Using XeF₂, a wider range of trifluoromethyl aryl ethers could be synthesized. Halogen-substituted and alkyl-substituted substrates were obtained in high yields. Electron-rich and alkene-substituted substrates were not compatible with the reaction conditions and underwent side reactions with XeF₂.
6.2 Copper-catalyzed carboetherification of alkenes

A copper-catalyzed method for the intermolecular carboetherification of alkenes was described in Chapter 5. This reaction allows the rapid building of molecular complexity by the one-step formation of a C(sp³)—C(sp³) and a C(sp³)—O bond, using readily available starting materials. Unfunctionalized alkyl nitriles were directly added to the alkenes via direct C—H functionalization. Methanol was used as solvent and nucleophile. This methodology was applied to a wide range of α-substituted styrenes (Scheme 6.6). Both electron-rich and electron-poor substrates were amenable to the reaction conditions. Substrates bearing bulky substituents around the alkene were only difunctionalized in low yields, indicating that steric bulk probably impedes the reaction. The applicability of the reaction to other linear alkyl nitriles was demonstrated. Ethanol could also be used as solvent and nucleophile, albeit with a reduced efficiency.

Mechanistic experiments showed that the reaction did not proceed in the absence of copper. Furthermore, the presence of DTPB was not necessary for the formation of the product, but is
most likely necessary to regenerate the catalyst. More importantly, a radical clock experiment confirmed the presence of radical intermediates. The mechanism depicted in Scheme 6.7 was, therefore, proposed for the reaction.

Scheme 6.7 Proposed mechanism for the intermolecular carboetherification of alkenes
Bibliography


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36 Hutchinson, J.; Sandford, G. In *Elemental Fluorine in Organic Chemistry; Topics in Current Chemistry* 193; Springer-Verlag New-York, **1997**.


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85 Obtained from Matrix Scientific


By analogy with previous perester synthesis. The new spot of TLC appeared dark blue using p-anisaldehyde, similarly to what had been previously observed for other t-butyl perester.


Criegee, R. Chem. Ber. 1944, 77, 722


Synthesized by Dr. Joe C. T. Leung using the general phenoxyacetic acid derivatives synthesis procedure


214 Ramamurthy, V.; Schanze, K. Organic Photochemistry and Photophysics. Taylor & Francis Group, LLC; Boca Raton, 2006


218 Fluorodecarboxylation could be induced using the silver-catalyzed conditions developed by Li et al. A similar loss in mass balance was observed: 5% of the desired product was detected while only 40% of substrate \[4.44a\] remained in the reaction mixture.


221 The C—H bond of halocarbons is about 2 kcal/mol weaker that the C—D bond.


For a recent review see; Alonso, C.; Martínez de Marigorta, E.; Rubiales, G.; Palacios, F. Chem. Rev. 2015, 115, 1847.


Yao, C.-J.; Sun, Q.; Rastogi, N.; König, B. ACS Catalysis 2015, 5, 2935.


272 Unpublished results no discussed in this thesis.


274 Cu(OTf)₂, Cu(OTf)₂, Cu(CH₃CN)₄BF₄ and Cu(CH₃CN)₄PF₆ were identified as promising copper sources in a related study on difunctionalization, currently unpublished, which is not discussed in this thesis.


Appendix A.

Selected spectra for Chapter 2
Methyl 2-methyl-4-phenylbutanoate (S1):
Methyl 2,2-dimethyl-4-phenylbutanoate (S2):
2,2-Dimethyl-4-phenylbutanoic acid (2.35):
*t*-Butyl 2,2-dimethyl-4-phenylbutaneperoxoate (2.20):
Appendix A: Selected spectra for Chapter 2

\textit{t-Butyl 2-phenylpropaneperoxyate (2.21):}

\begin{center}
\includegraphics[width=\textwidth]{t-butyl_2-phenylpropaneperoxyate_spectra}
\end{center}
t-Butyl 2-((tert-butoxycarbonyl)amino)ethaneperoxoate (2.28):
t-Butyl 2-(1,3-dioxoisindolin-2-yl)ethaneperoxoate (2.30):
(1R,4R)-t-Butyl 4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboperoxoate (2.33):
2-(Fluoromethyl)isoindoline-1,3-dione (2.31):
Appendix A: Selected spectra for Chapter 2

![Selected spectra diagram]
Appendix B.

Selected spectra for Chapter 3
2-(4-Acetyl-2-methoxyphenoxy)acetic acid \((3.14l)\):

\[
\begin{align*}
\text{OMe} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{3.14l}
\end{align*}
\]

2-(4-((Methylsulfonyl)oxy)phenoxy)acetic acid \((3.14d)\):

\[
\begin{align*}
\text{MsO} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{3.14d}
\end{align*}
\]
Appendix B: Selected spectra for Chapter 3

(E)-2-(2-Methoxy-5-((8-methylene-6-enamido)methyl)phenoxy)acetic acid (3.14q):

(E)-2-(2-Methoxy-5-((8-methylene-6-enamido)methyl)phenoxy)acetic acid (3.14q):
Appendix B: Selected spectra for Chapter 3

2-((Trimethylsilyl)ethyl 2-bromoacetate (S4):

![Diagram of S4]

2-((trimethylsilyl)ethyl 2-(3-acetoxyphenoxy)acetate (S5)

![Diagram of S5]
2-(3-acetoxyphenoxy)acetic acid (3.14m)

\[
\text{3.14m}
\]

1-bromo-4-(fluoromethoxy)benzene (3.15h)

\[
\text{3.15h}
\]
Appendix B: Selected spectra for Chapter 3
1-bromo-3-(fluoromethoxy)benzene (3.15i)
2,4-dichloro-1-(fluoromethoxy)benzene (3.15c)
Appendix B: Selected spectra for Chapter 3

3.15c

[Diagram of a chemical structure with labeled peaks]

3.15c

[Diagram of another chemical structure with labeled peaks]
2-fluoro-2-phenoxyacetic acid (3.42b)
Appendix B: Selected spectra for Chapter 3

2-fluoro-2-(4-fluorophenoxy)acetic acid (3.42c)
Appendix B: Selected spectra for Chapter 3
2-(4-bromophenoxy)-2-fluoroacetic acid (3.42d)
Appendix B: Selected spectra for Chapter 3

2-(3-bromophenoxy)-2-fluoroacetic acid (3.42e)
Appendix B: Selected spectra for Chapter 3

Br\(\text{O}\)\(\text{OF}\)\(\text{OH}\)

3.42e

\[\begin{align*}
\text{f1 (ppm)} & : -168.22, -164.24, 13.18, 12.14, 12.19, 11.63, 10.32, 10.089 \\
\end{align*}\]
difluoromethoxybenzene (3.33b)
1-(difluoromethoxy)-4-fluorobenzene (3.33c)
1-bromo-4-(difluoromethoxy)benzene (3.33d)
Appendix B: Selected spectra for Chapter 3

1-bromo-3-(difluoromethoxy)benzene (3.33e)
Appendix B: Selected spectra for Chapter 3

3.33e

3.33e
Appendix C.

Selected spectra for Chapter 4
Appendix C: Selected spectra for Chapter 4

Ethyl 2-(4-(t-butyl)phenoxy)-2,2-difluoroacetate (4.43a)
Appendix C: Selected spectra for Chapter 4

Ethyl 2-(4-fluorophenoxy)-2,2-difluoroacetate (4.43c)
Appendix C: Selected spectra for Chapter 4

4.43c
Appendix C: Selected spectra for Chapter 4

Ethyl 2,2-difluoro-2-(2-vinylphenoxy)acetate (4.43e)
Ethyl 2,2-difluoro-2-(4-methoxyphenoxy)acetate (4.43f)
Ethyl 2-(4-bromophenoxy)-2,2-difluoroacetate (4.43g)
Appendix C: Selected spectra for Chapter 4

Ethyl 2,2-difluoro-2-phenoxyacetate (4.43)
Appendix C: Selected spectra for Chapter 4

Ethyl 2-(4-chlorophenoxy)-2,2-difluoroacetate (4.43i)
Appendix C: Selected spectra for Chapter 4

Ethyl 2-(3-bromophenoxy)-2,2-difluoroacetate (*4.43j*)

![Ethyl 2-(3-bromophenoxy)-2,2-difluoroacetate (*4.43j*)](image)
Appendix C: Selected spectra for Chapter 4

Ethyl 2-(2,4-dichlorophenoxy)-2,2-difluoroacetate (4.43k)
Appendix C: Selected spectra for Chapter 4
Ethyl 2-(2,4-di-t-butylphenoxy)-2,2-difluoroacetate (4.43I)
Appendix C: Selected spectra for Chapter 4

2-(4-(tert-butyl)phenoxy)-2,2-difluoroacetic acid (4.44a)
2,2-difluoro-2-(4-fluorophenoxy)acetic acid (4.44c)
2,2-difluoro-2-(2-vinylphenoxy)acetic acid (4.44e)
Appendix C: Selected spectra for Chapter 4

4.44e

[Chemical structure image]

4.44e
2,2-difluoro-2-(4-methoxyphenoxy)acetic acid (4.44f)
Appendix C: Selected spectra for Chapter 4

2-(4-bromophenoxy)-2,2-difluoroacetic acid (4.44g)
Appendix C: Selected spectra for Chapter 4

4.44g

164.34
163.50
148.03
132.82
123.40
116.06
113.35
110.63

4.44g

-77.32

-100 -80 -60 -40 -20 0 20 40 60 80 100 120 140 160 180 200
f1 (ppm)
2,2-difluoro-2-phenoxyacetic acid (4.44)
Appendix C: Selected spectra for Chapter 4

2-(4-chlorophenoxy)-2,2-difluoroacetic acid (4.44i)
Appendix C: Selected spectra for Chapter 4

4.44i
2-(3-bromophenoxy)-2,2-difluoroacetic acid (4.44j)
2-(2,4-dichlorophenoxy)-2,2-difluoroacetic acid (4.44k)
Appendix C: Selected spectra for Chapter 4

4.44k

[Diagram of chemical structure with spectra peaks labeled: 163.06, 162.05, 143.84, 132.79, 129.68, 129.53, 128.01, 127.98, 124.29, 113.40, 110.66]
2-(2,4-di-t-butylphenoxy)-2,2-difluoroacetic acid (4.44I)
Appendix C: Selected spectra for Chapter 4

(trifluoromethoxy)benzene (1.83)
Appendix C: Selected spectra for Chapter 4

OCF$_3$ 1.83

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

f1 (ppm)

-56.68

OCF$_3$ 1.83

60 40 20 0 -20 -40 -60 -80 -100 -120 -140 -160 -180 -200

f1 (ppm)
1-(t-butyl)-4-(trifluoromethoxy)benzene (1.83a)
1-bromo-4-(trifluoromethoxy)benzene (1.83g)
Appendix C: Selected spectra for Chapter 4

\[
\text{Br-OCF}_3
\]

1.83g
1-chloro-4-(trifluoromethoxy)benzene (1.83i)

[Chemical structure and spectra image]
1-bromo-3-(trifluoromethoxy)benzene (1.83j)
Appendix C: Selected spectra for Chapter 4

1.83j

Br\(\text{OCF}_3\)

1.83j

Br\(\text{OCF}_3\)
2,4-dichloro-1-(trifluoromethoxy)benzene (1.83k)
Appendix C: Selected spectra for Chapter 4

[Chemical structure image]

1.83k

[Graph with ppm scale]
Appendix D.

Selected spectra for Chapter 5
1-methyl-4-(1-phenylvinyl)benzene (5.25b)
1-methoxy-4-(1-phenylvinyl)benzene (5.25c)
1-fluoro-4-(1-phenylvinyl)benzene (5.25d)
Chemical Formula: C\textsubscript{14}H\textsubscript{11}F

Molecular Weight: 198.24
1-bromo-4-(1-phenylvinyl)benzene (5.25f)
4-(1-phenylvinyl)benzonitrile (5.25g)
1-methyl-3-(1-phenylvinyl)benzene (5.25h)
1-(1-phenylvinyl)-3-(trifluoromethyl)benzene (5.25j)
Chemical Formula: $\text{C}_{15}\text{H}_{11}\text{F}_3$

Molecular Weight: 248.24
1-methyl-2-(1-phenylvinyl)benzene **(5.25k)**
4,4’-(ethene-1,1-diyl)bis(methoxybenzene) (5.25m)
1-methoxy-4-(1-(4-(trifluoromethyl)phenyl)vinyl)benzene (5.25n)
4,4'-{ethene-1,1-diy}bis{fluorobenzene} (5.25o)
Chemical Formula: C_{14}H_{10}F_{2}

Molecular Weight: 216.23
4,4’-(ethene-1,1-diyl)bis(chlorobenzene) (5.25p)
1,3,5-trimethyl-2-(prop-1-en-2-yl)benzene (5.25v)

Chemical Formula: C_{12}H_{16}

Molecular Weight: 160.26
5-methylene-6,7,8,9-tetrahydro-5H-benzo[7]annulene (5.25w)
Appendix D: Selected spectra for Chapter 5

(1-cyclohexylvinyl)benzene (5.25x)
(3,3-dimethylbut-1-en-2-yl)benzene (5.25y)

Chemical Formula: $C_{12}H_{16}$
Molecular Weight: 160.26

5.25y
2-(prop-1-en-2-yl)thiophene (5.25z)
2-(prop-1-en-2-yl)pyridine (5.25aa)

Chemical Formula: C₈H₉N

Molecular Weight: 119.16
prop-1-ene-1,1-diyl dibenzene (5.25ac)
(1-cyclopropylvinyl)benzene (5.25af)
4-methoxy-4,4-diphenylbutanenitrile (5.42a)
4-methoxy-4-phenyl-4-(p-tolyl)butanenitrile (5.42b)
4-methoxy-4-(4-methoxyphenyl)-4-phenylbutanenitrile (5.42c)
4-(4-fluorophenyl)-4-methoxy-4-phenylbutanenitrile (5.42d)
4-(4-chlorophenyl)-4-methoxy-4-phenylbutanenitrile (5.42e)
4-(4-bromophenyl)-4-methoxy-4-phenylbutanenitrile (5.42f)
4-(3-cyano-1-methoxy-1-phenylpropyl)benzonitrile (5.42g)
Appendix D: Selected spectra for Chapter 5

4-methoxy-4-phenyl-4-(m-tolyl)butanenitrile (5.42h)
Appendix D: Selected spectra for Chapter 5

4-(3-chlorophenyl)-4-methoxy-4-phenylbutanenitrile (5.42i)

Chemical Formula: \(C_{17}H_{16}ClNO\)
Molecular Weight: 285.77
4-methoxy-4-phenyl-4-(3-(trifluoromethyl)phenyl)butanenitrile (5.42j)
Chemical Formula: C\textsubscript{18}H\textsubscript{16}F\textsubscript{3}NO

Molecular Weight: 319.32
4-methoxy-4-phenyl-4-(o-tolyl)butanenitrile (5.42k)
4-methoxy-4-di-p-tolylbutanenitrile (5.42I)
4-methoxy-4,4-bis(4-methoxyphenyl)butanenitrile (5.42m)
4-methoxy-4-(4-methoxyphenyl)-4-(4-(trifluoromethyl)phenyl)butanenitrile (5.42n)
Appendix D: Selected spectra for Chapter 5

Chemical Formula: C_{19}H_{18}F_{3}NO_{2}

Molecular Weight: 349.35
4,4-bis(4-fluorophenyl)-4-methoxybutanenitrile (5.42o)

Chemical Formula: $\text{C}_{17}\text{H}_{15}\text{F}_2\text{NO}$

Molecular Weight: 287.30
4,4-bis(4-chlorophenyl)-4-methoxybutanenitrile (5.42p)
4-methoxy-4-phenylpentanenitrile (5.42q)
4-(4-chlorophenyl)-4-methoxypentanenitrile (5.42s)

Chemical Formula: C\textsubscript{12}H\textsubscript{14}ClNO

Molecular Weight: 223.70
4-methoxy-4-(o-tolyl)pentanenitrile (5.42t)

Chemical Formula: C_{13}H_{17}NO

Molecular Weight: 203.28
3-(5-methoxy-6,7,8,9-tetrahydro-5H-benzo[7]annulen-5-yl)propanenitrile (5.42w)

Chemical Formula: \( \text{C}_{15}\text{H}_{19}\text{NO} \)

Molecular Weight: 229.32
4-cyclohexyl-4-methoxy-4-phenylbutanenitrile (5.42x)
4-methoxy-4-(thiophen-2-yl)pentanenitrile (5.42z)
Appendix D: Selected spectra for Chapter 5

4-methoxy-4-(pyridin-2-yl)pentanenitrile (5.42aa)

Chemical Formula: $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}$

Molecular Weight: 190.24
4-methoxy-4-(pyridin-3-yl)pentanenitrile (5.42ab)
4-methoxy-3-methyl-4,4-diphenylbutanenitrile (5.42ac)

Chemical Formula: \( \text{C}_{18}\text{H}_{19}\text{NO} \)
Molecular Weight: 265.35
4-methoxy-2-methyl-4,4-diphenylbutanenitrile (5.48a)

Chemical Formula: C_{18}H_{19}NO
Molecular Weight: 265.35
2-ethyl-4-methoxy-4,4-diphenylbutanenitrile (5.48b)
4-methoxy-2-(methoxymethyl)-4,4-diphenylbutanenitrile (5.48d)
4-ethoxy-4-phenylpentanenitrile \((5.42\text{ad})\)
4-ethoxy-4,4-diphenylbutanenitrile (5.42ae)

Chemical Formula: C_{18}H_{19}NO
Molecular Weight: 265.35
3-(3,4-dihyronaphthalen-1-yl)propanenitrile (5.49)