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Preparation of Organofluorine Compounds: Exploring Mono-, Di-, and Tri-fluorination

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Preparation of Organofluorine Compounds: Exploring Mono-, Di-, and Tri-fluorination

DiAndra Marie Rudzinski,

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Master of Science
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2013
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Preparation of Organofluorine Compounds:
Exploring Mono-, Di-, and Tri-fluorination

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University of Connecticut
2013
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I would not be here today if I was not backed by the love and support of my mom, Lucy, my dad Bob, and my brother Craig. Each day you push me to do better and grow. I am truly blessed to have the best family that I can depend on. I love you all.

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<thead>
<tr>
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<th>Description</th>
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<tbody>
<tr>
<td>PPM</td>
<td>parts per million</td>
</tr>
<tr>
<td>PLP</td>
<td>pyridoxal phosphate</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>DAST</td>
<td>diethylaminosulfur trifluoride</td>
</tr>
<tr>
<td>EWG</td>
<td>electron-withdrawing group</td>
</tr>
<tr>
<td>Halex</td>
<td>halogen exchange</td>
</tr>
<tr>
<td>MW</td>
<td>microwave</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>NMP</td>
<td>n-methyl pyrrolidone</td>
</tr>
<tr>
<td>MeCN</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>PEG</td>
<td>polyethylene glycol</td>
</tr>
<tr>
<td>TBAB</td>
<td>tetrabutylammonium bromide</td>
</tr>
<tr>
<td>EDA</td>
<td>ethylenediamine</td>
</tr>
<tr>
<td>DMA</td>
<td>dimethylacetamide</td>
</tr>
<tr>
<td>TBAT</td>
<td>tetrabutylammonium difluorotrip phenylsilicate</td>
</tr>
<tr>
<td>BMIM</td>
<td>1-butyl-3-methylimidaz ole</td>
</tr>
<tr>
<td>TFKM</td>
<td>trifluoromethyl ketone</td>
</tr>
<tr>
<td>SARS</td>
<td>severe acute respiratory syndrome</td>
</tr>
<tr>
<td>AIDS</td>
<td>acquired immune deficiency syndrome</td>
</tr>
<tr>
<td>TMS-CF₃</td>
<td>(trifluoromethyl)trimethylsilane</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>Equiv</td>
<td>equivalents</td>
</tr>
<tr>
<td>Temp</td>
<td>temperature</td>
</tr>
<tr>
<td>KOʻBu</td>
<td>potassium tert-butox ide</td>
</tr>
<tr>
<td>DMF</td>
<td>dimethylformamide</td>
</tr>
<tr>
<td>DFMK</td>
<td>difluoromethyl ketone</td>
</tr>
<tr>
<td>DME</td>
<td>dimethoxyethane</td>
</tr>
<tr>
<td>TMEDA</td>
<td>tetramethylene diam ine</td>
</tr>
<tr>
<td>Dppf</td>
<td>1′1′-Bis(diphenylphosphino)ferrocene</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>psi</td>
<td>pounds per square inch</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>DART</td>
<td>direct analysis in real time</td>
</tr>
<tr>
<td>DCM</td>
<td>dichloromethane</td>
</tr>
<tr>
<td>TMS-CHF₂</td>
<td>(difluoromethyl)trimethylsilane</td>
</tr>
<tr>
<td>CDI</td>
<td>1,1′-Car bonyldiimidazole</td>
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The Properties of Organofluorine Compounds

Chapter 1

“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.”

-M. Schlosser¹
Elemental fluorine is the thirteenth most abundant element in the earth’s crust;\(^2\) however, organofluorine compounds are essentially absent in nature.\(^3\) The reason for the scarcity of natural occurring fluorinated organic molecules is three-fold. Firstly, the most common fluoride, mineral fluorite (CaF\(_2\)), has limited solubility in water.\(^4\) The concentration of fluoride in seawater is 1.3 ppm compared to 19,000 ppm of chloride.\(^3\) Secondly, fluoride is easily solvated in aqueous media rendering it a poor nucleophile for displacement reactions.\(^3\) Lastly, the haloperoxidase reaction that is responsible for forming other organo-halides cannot incorporate fluorine into organic molecules.\(^3\) This is a result of a higher redox potential for the oxidation of fluorine as compared to the potential for the reduction of peroxide.\(^3\)

Due to their chemical and biological properties, the demand for fluorinated molecules as pharmaceuticals and agro-chemicals has boomed since the late 1950’s.\(^5\) Today, about 25% of pharmaceutical drugs on the market consist of at least one fluorine atom, driving the development for new chemical syntheses and methodologies for these organic molecules.\(^6\) Discussed below are the advantageous properties of fluorinated compounds.

**Chemical and Molecular Properties:**

Organofluorine compounds possess multiple properties beneficial for pharmaceutical drug design. These include electronic effects, conformational changes, and their lipophilic nature. Fluorine is the most electronegative of all atoms. Therefore, the exchange of hydrogen for fluorine alters the electronic properties of a molecule
As a bioisostere, fluorine can mimic the electronic properties of certain other functional groups, such as an alcohol without producing an encumbering steric effect. The C-F bond has a Van der Waals radius of 1.47 Å, when compared to the 1.20 Å radius of a C-H bond. If steric bulk is desired, a trifluoromethyl group may be used. This represents the size of an ethyl group while maintaining its electron withdrawing nature.

Fluorine not only alters the electronics of a molecule, it can also influence conformation. The electronegativity and lone pairs of fluorine may result in conformational changes of a fluorinated analogue. This is exemplified in Figure 1.1 between methoxyphenyl and trifluoromethoxyphenyl groups. The methoxy group is arranged planar to the phenyl ring. Here the oxygen is sp² hybridized. Its p-orbitals are aligned with the π-bonds of the aryl ring, allowing for conjugation. Replacing the methoxy with a trifluoromethoxy group creates an anti-periplanar arrangement. Electron density is shifted from the aryl ring to the C-F bond creating an sp³ hybridized oxygen. Its lone pairs are pulled away from the aryl ring eliminating planarity. The difference in methoxybenzene and trifluoromethoxybenzene conformations have strategically been used in inhibitors of cholesteryl ester transfer proteins, which are linked to coronary artery disease. A tetrafluoroethyl compound had an 8-fold increase in potency for the target protein due to the loss of planarity when examined against its ethoxy counterpart.
Hydrogen bonds with fluorine may also affect the conformation of a molecule. This is a weak interaction when compared to hydrogen bonds with oxygen or nitrogen. The carbon-fluorine bond is strong and therefore exhibits low polarizability. This is responsible for the weakening effect of hydrogen-fluorine bonds.\textsuperscript{6} Figure 1.2 illustrates conformational changes with F-H interactions between regioisomers of 2- and 6-fluoronorepinephrine. Compound 1 partakes in hydrogen bonding allowing for a conformation in which it is an $\alpha$-adrenergic agonist, whereas the isomer 2 hydrogen bonds in a way to be a $\beta$-adrenergic agonist.\textsuperscript{9}

During drug design, medicinal chemists must take into account how the molecule will get through biological barriers to get to its target. The compound must be polar
enough to exhibit solubility in water, yet lipophilic enough to pass through cell membranes without getting trapped in the bilayer. As a general trend, fluorination increases lipophilicity when compared to its hydrogen counterpart. Exceptions are with monofluorinated or trifluoromethylated saturated alkyl systems. Overlap occurs between the 2s or 2p orbitals of the fluorine and the orbitals of the neighboring carbon, resulting in a strong, non-polarizable C-F bond. Consequently, lipophilic character is increased. One calculation used to measure the lipophilic nature of a molecule is logP or log([solute octanol]/[solute water]). This partition coefficient measures the likeliness of a molecule to exist in an organic solvent (octanol) over water. A higher logP correlates to a greater lipophilic nature of the molecule. This was exploited while studying a series of amide compounds for the treatment of asthma. Figure 1.3 shows a range of the substrates screened. In order for the compounds to be delivered to the target a greater lipophilic moiety was needed. Lengthening the alkyl chain increased lipophilicity but potency suffered. Insertion of fluorine into the series not only increased the logP, it also had a ten-fold favor in binding affinity shown in the in vivo studies.  

Figure 1.3: Fluorine and Lipophilicity

![Figure 1.3: Fluorine and Lipophilicity](image)

<table>
<thead>
<tr>
<th>R</th>
<th>Log P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃CH₂CH(CH₃)</td>
<td>5.85</td>
</tr>
<tr>
<td>CF₂CH₂CH(CH₃)</td>
<td>6.18</td>
</tr>
<tr>
<td>(CH₃CH₂)₂CHCH₂</td>
<td>6.29</td>
</tr>
<tr>
<td>CF₃CH₂CH(CH₃CH₂)CH₂</td>
<td>6.45</td>
</tr>
<tr>
<td>CF₃CH(CH₃)CH₂CH₂</td>
<td>6.30</td>
</tr>
<tr>
<td>CF₃CH(CH₃)CH₂</td>
<td>5.89</td>
</tr>
</tbody>
</table>
Effects of Fluorine in Medicinal Chemistry:

Understanding key transformations and metabolic processes in the body is an important factor to drug design. The presence of a fluorine atom in a molecule can stop metabolic processes and change the reactivity.\textsuperscript{13} As such, the orthogonal differences between a fluorine and a hydrogen atom have been exploited for biological activity.\textsuperscript{13}

One of the major differences between fluorine and hydrogen atoms is the ability to form a cation. The production of $\text{F}^+$ is impossible due to the highly electronegative nature of fluorine. Contrastingly, many biological and metabolic processes produce the $\text{H}^+$ ion through heterolytic cleavage.\textsuperscript{13} The exchange of fluorine for hydrogen is exploited in drug development to alter biological activity. This technique is exemplified through the design of the anti-cancer agent 5-fluorouracil (8). Figure 1.4 illustrates the mechanistic action of this mechanism-based inhibitor. Fluorine in the 5-position halts the synthesis of thymidylate (7), a compound involved in cancer development. Biologically, thymidylate is synthesized through a complex with substrate (4), enzyme, and the methylene tetrahydrofolic acid cofactor (CH$_2$FAH$_4$).\textsuperscript{14} A Michael-addition from a cysteine residue of the enzyme onto the substrate, followed by subsequent attack onto the methylene tetrahydrofolic acid forms intermediate (5).\textsuperscript{14} A key transformation towards thymidylate production is through an abstraction of a proton followed by β-elimination of tetrahydrofolic acid. 5-fluorouracil (8) was designed to mimic the substrate. However, a fluorine in the 5 position blocks the beta-elimination. The $\text{F}^+$ cation is not formed resulting in a trapped and inactive enzyme-substrate complex (9).\textsuperscript{14}
Although fluorine will not form a cation, the anion is easily produced. Elimination reactions of the fluoride ion have been exploited in medicinal development. Eflornithine (10), a drug used in the treatment of African sleeping sickness was designed as an irreversible mechanism based inhibitor. This mechanism is classified as a pyridoxal phosphate (PLP) dependent enzyme-catalyzed reaction. Generally, the PLP complexes to an enzyme through a Schiff-base linkage. This complex can then undergo tautomerization releasing the enzyme to continue its function. However, as Figure 1.5 illustrates, fluorine was incorporated in Eflornithine (10) to form an irreversible substrate-enzyme complex. Elimination of a fluorine results in compound 13 prone to nucleophilic attack. The nucleophilic enzyme irreversibly binds to the substrate rendering it inactive (14).
Not only are irreversible substrate-enzyme complexes formed through elimination pathways, they can also form through nucleophilic displacements. **Figure 1.5** illustrates compound 16 irreversibly bound to the cysteine (15) of tubulin. This process releases H-F to form 17, which was found to be responsible for anti-cancer activity.
Another concern of the medicinal chemist is metabolic stability. A drug must have a long enough half-life in the body to perform its desired action. However, harsh environments and metabolizing agents/mechanisms within the body may increase the clearance time resulting in decreased drug efficiency. When a compound is transported through the stomach it is subjected to extreme acidic conditions. If the compound has an acid labile group it may become protonated, and potentially, deactivate through rearrangements or side reactions. A fluorine in the β-position of such group redirects the electron density back into the system, creating a weaker nucleophile. As contrasts to prostacyclins 18, prostacyclins 19 and 20 are stabilized by β-fluorination to remain active even within the stomach (Figure 1.6). \(^{15}\)

Fluorine may be utilized to block the oxidative activity of the cytochrome P450 enzyme class. An example of this strategy is shown with the cholesterol inhibitor, Ezetimib (Figure 1.7, compound 22). Introductory studies in rats suggested that disfavored metabolic reactions were occurring. Oxidation and de-methylation were two transformations that occurred to the precursor 21. Fluorination of 21 not only blocked

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these metabolic processes, potency was also favored. Ezetimib was found to have a 40-fold increase in potency compared to its hydrogen-containing analog.\textsuperscript{16}

![Figure 1.7: Optimization of Ezetimib](image)

**Summary:**

In summary, utilization of fluorine in drug design is of great importance. The addition of a fluorine into potential pharmacophores may increase lipophilicity, hinder unwanted metabolic eliminations, alter conformation, as well as change reactivity. One complication in this design is the scarcity of organofluorines in nature. Therefore there is a high demand for new synthetic methodologies of fluorinated intermediates and compounds.
References:


Methodologies for Preparing Fluorinated Organic Molecules

Chapter 2
The high demands to incorporate fluorine into drug design have sparked interest for new synthetic methods. Currently, fluorine may be introduced to molecules through electrophilic and nucleophilic reagents. Although an exhaustive list of these reagents will not be given, the most important developments in the synthesis of organofluorines will be highlighted.

**Electrophilic Fluorination:**

The ideal process for electrophilic fluorination is through the attack of a nucleophilic site onto an “electron poor” or “F⁺” species. However, the production of a lone “F⁺” is not achievable due to its instability. Therefore, fluorinating agents are strategically developed to mimic an electron-poor fluorine. Initially, elemental fluorine was the only source for this type of transformation. Liberation of the fluoride ion is the driving force for a nucleophilic attack onto $F_2$. This produces the $[(\text{He})2s^22p^6]$ configuration to completely fill its valence shell.¹ Utilizing $F_2$ for electrophilic fluorination leads to complications in handling. Elemental fluorine is highly reactive, toxic, potentially explosive, and poorly selective. It is possible to hinder the reactivity through the dilution of $F_2$ with inert gases such as nitrogen or argon. However, safer reagents, with a greater tolerance of substrate scope are desired. As a result, much attention has been placed on designing alternative electrophilic fluorinating agents.¹
Efforts to find new electrophilic fluorine sources began with nucleophilic displacement reactions as exemplified by $\text{F}_2$. Fluoroxytrifluoromethane ($\text{CF}_3\text{OF}$) responsible for the transformation from $\text{23}$ to $\text{24}$, and acetyl hypofluorite ($\text{AcOF}$) exemplified by reaction $\text{25}$ to $\text{26}$, are two examples of these reagents as shown in Scheme 2.1. Fluorination of steroids, olefins, enolates, and certain carboxylic acid derivatives have been reported with these compounds.\textsuperscript{2,3,4,5}

Although organofluoroxy reagents were developed as alternatives to elemental fluorine they are also highly reactive species and can be difficult to handle. One major contribution to the field of electrophilic fluorination was the emergence of reagents bearing an N-F bond, which are less reactive and used with ease.\textsuperscript{1} Reactivity is decreased due to a lower electronegativity of nitrogen resulting in a stronger N-F bond. Many N-F derivatives have been developed as an electrophilic source; of the most popular is the commercially available Selectfluor (27).\textsuperscript{6} This versatile reagent is involved in the fluorination of aryl groups, steroids, organometallics, and nucleosides.\textsuperscript{1} Selectfluor and its N-fluoroquinuclidine derivatives electrophilic strength may be adjusted by altering groups on the non-fluorinated nitrogen. ($\text{CH}_3$, $\text{C}_8\text{H}_7 < \text{CH}_2\text{Cl} < \text{CF}_3\text{CH}_2$). Other N-F fluorinating sources include $N$-fluoropyridinium salts (28), $N$-fluoro-$N$-
alkylsulfonamides (29), perfluoroalkylsulfonamides (30), and \( N \)-fluorobenzenesulfonimide (31) (Figure 2.1.2).\(^7,8,9,10\)

![Figure 2.2: Electrophilic Fluorination Reagents](image)

**Nucleophilic Fluorination:**

Nucleophilic fluorination reagents have been widely developed.\(^1\) Solvent effects are extremely important for their success.\(^1\) Protic solvents should be avoided, as the fluoride ion is easily solvated. In aprotic solvents, tight ion pairing must be overcome before the reactivity of the nucleophilic fluoride is advantageous.\(^1\) This can be accomplished with large, steric cations such as tetrabutylammonium fluoride (TBAF) (Figure 2.3, 32). The bulky steric groups, as well as a delocalizing effect by the alkyl chains help to reduce counter ion interactions.\(^1\)

![Figure 2.3: TBAF](image)

The simplest reagent to deliver a fluoride ion is hydrofluoric acid. In practicality, HF is a dangerous and corrosive material, which should be handled carefully. However, the reactivity may be suppressed through the dilution of H-F with amines. An example is compound 33 termed Olah’s reagent (pyridinium poly(hydrogen

![Figure 2.4: Olah’s Reagent](image)
fluoride). These mixtures slightly weaken the nucleophilicity of the fluoride and more activated substrates are needed to achieve fluorination.\(^1\)

Another approach towards nucleophilic fluorination is combining the fluoride ion with a soft Lewis base. These may be different transition metals such as Pd, Sn, or Hg. Also non-transition metals have been used such as S-F.\(^1\) One of the most popular reagents is diethylaminosulfur trifluoride (34) (DAST)\(^{12}\) and its dimethoxy counterpart Deoxo-fluor (35)\(^{13}\) (Figure 2.5). The latter reagent has a greater thermal stability and may be used as safe alternative to DAST as it is reported to detonate above 90 °C.\(^1\)

Fluorodeoxygenation of alcohols (36 to 37)\(^{14}\) and the addition of difluoromethylene to carbonyls (38 to 39)\(^{13}\) are examples of fluorination reactions involving these reagents (Scheme 2.2).

**Summary:**

In summary, without the emergence of electrophilic and nucleophilic fluorine reagents, new synthetic methods for fluorinated organic molecules would be scarce. These contributions are essential for the discovery of new chemical entities. Therefore, much attention is placed on using these and other reagents for the production of mono, di, and tri-fluorinated molecules.
References:


Methodologies for Preparing Aryl Fluorides

Chapter 3
The unique and advantageous properties of fluorinated compounds have driven the development for new reactions. Although a large number of organofluorine compounds have been prepared, remarkably little effort has been focused on aryl fluorides. The three conventional methods for preparing aryl fluorides have drawbacks of harsh conditions and low substrate scope. Therefore, new synthetic routes to these compounds are desired.

A common approach to fluoroarenes is the Balz-Schiemann reaction developed in 1927. Aniline precursors (40) are converted to the corresponding fluoride (41) in the presence of tetrafluoroboric acid and sodium nitrite (Scheme 3.1). The reaction occurs through a diazo intermediate, which presents potential hazards. The substrate scope is limited as a result of the acidic reagent needed. The risk of explosion and toxic chemicals used create a liability for industrial application, and is therefore discouraged.

Another pathway for aryl fluorination is through nucleophilic aromatic substitution (S$_{\text{NAr}}$) (Scheme 3.2). The method involves direct formation of the fluoroarene (43) from aryl chlorides (42) or nitroarenes in the presence of a fluoride salt. One caveat is the necessity of an electron-withdrawing group on the arene. This deactivates the ring and increases the susceptibility for nucleophilic attack. Even with these substituents, temperatures as high as 450 °C have been needed. Therefore, only a restricted amount of substrates are tolerated.
Lastly, aryl fluorides can be prepared using transition metal complexes. Nucleophilic and electrophilic fluorination sources have been used for these processes. Palladium-catalyzed transformations of aryl triflates to 41 have been reported with cesium fluoride. High reaction yields are limited to substrates with electron-withdrawing substituents. Electrophilic fluorination of aryl rings is also synthesized via transition metal catalysis. Typically an aryl stannane, silane or boronic acid is converted with palladium or silver and an electrophilic fluorine source. Although a wide range of substrates can be used, metal complexes such as 44 are usually synthesized from aryl halides. Therefore, a direct approach of aryl halides to the corresponding fluoroarene (41) is widely desired.

Our Attempts Towards Aryl Fluorination:

We became interested in halide exchange (halex) reactions due to the demand for a safe and general method to aryl fluorides. Many copper and nickel-mediated processes have been published for the exchange of iodides, bromides and chlorides. However, the lack of literature precedent deems fluorination via a halex reaction a challenging task. In theory the reactions should favor the fluorinated product due to a strong C-F bond. Yet, the highly electronegative character of fluorine impedes product formation. The reaction proceeds with oxidative addition of the metal source into the aryl halide, resulting in intermediate 46 as shown in Scheme 3.4. The metal-fluorine bond of 46 is strong and difficult to break. For halex reactions with bromine and chlorine reagents, a stronger aryl-halide bond of the bromide or chloride drives the reductive
elimination towards the production of 47 and M-I. Yet, in fluorination attempts the M-F complex of is too strong for reductive elimination to occur. Therefore the M-F is eliminated, and starting material 45 is observed.\textsuperscript{9}

![Scheme 3.4: Halex Reaction](image)

It was proposed that high heat associated with microwave technology may help facilitate halex reactions towards fluorination. The advantage of these microwave units is the ability to reach high temperatures in a controlled fashion. A pressure locking mechanism allows up to 300 psi of autogenic pressure within the vessel without failure. Previously, Leadbeater and Arvela reported nickel-mediated halide exchange protocols using microwave heating.\textsuperscript{10} Aryl iodides, bromides, and chlorides were all used as starting materials in conjunction with nickel (II) halide salts. A generic representation of exchange from 47 to 48 is depicted in Scheme 3.5. Substrates with electron-withdrawing and donating substituents in the ortho and para positions were successful
for the halide exchange. One disadvantage reported was the inability to produce aryl iodides from aryl bromide starting materials.\textsuperscript{10} Fluorination was not reported.

**Halogen Exchange with Cu (II) Salts:**

The developed method for halogen exchange reactions using microwave heating and Ni (II) salts drove interest towards the utilization of Cu (II) salts. Our goal was to attempt the reaction with CuF\textsubscript{2} to produce various aryl fluorides. In order to begin our investigation, we first desired to optimize a method for the halide exchange of aryl iodides to bromides. Aryl iodides are the most reactive starting materials in halex reactions. The C-I bond is relatively weak and is likely to undergo oxidative addition. If the halex transformation from aryl iodides were unsuccessful, most likely the other reactions would be as well. We chose 4-iodoanisole (49) as a test substrate due to the electron donating nature of the substituent. Initial attempts focused on using a stoichiometric amount of CuBr\textsubscript{2} as both the bromine source and metal mediator of the reaction. Once complete, an ether extraction and water wash allowed for the isolation of the crude product. We monitored product yield via \textsuperscript{1}H NMR, with an internal standard 1,2,4,5-tetramethylbenzene. This allows for quick analysis of results without performing further purification.

Initial reaction screenings were successful in polar solvents such as n-methyl pyrrolidone and acetonitrile; which were chosen due to the greater solubility of the copper salts when compared to non-polar solvents. Observed conversions were 80\% (Table 3.1, entry 1) in NMP, and near quantitative with acetonitrile (Table 3.1, entry 2).
We found that slightly longer reaction times were needed than the 5 minutes of the nickel mediated protocol. Starting material 4-iodoanisole was converted to 50 in 15 minutes at 170 °C with CuBr₂. The highest NMR yield observed was 70% (Table 3.1, entry 2).

Subsequent trials were performed with a catalytic amount of CuBr₂ and external bromide source (NaBr). This allows for a cheaper and greener reaction. Unfortunately, low conversions were observed with acetonitrile (Table 3.1, entry 3). We then focused on water as solvent with a phase transfer agent. This increases the solubility of the sodium bromide, which we hypothesized would increase the catalytic reaction conversion. Phase transfer agents polyethylene glycol and tetrabutylammonium bromide resulted in minimal conversions of 14% and 8% respectively (Table 3.1, entries 4-5). The highest conversion observed was with ethylenediamine of 64%, but the resulting 14% recovery of the brominated product was not an acceptable yield. A longer reaction time of 30 minutes and a higher temperature of 180 °C was needed for this higher conversion (Table 3.1, entry 6).
With optimized halogen exchange conditions in hand for preparing 4-bromoanisole, we next turned our attention towards the fluorination of 49. The reaction was repeated with stoichiometric CuF$_2$ in acetonitrile at 170 °C for 15 minutes. Product 51 was not observed. Thinking that the lower solubility of CuF$_2$ could be a limitation to the halide exchange we then screened other polar solvents such as acetonitrile/water, DMA, DMA/water, and methanol. Again no reaction was observed.
One disadvantage to microwave reactors is that moderately polar reagents or solvents are needed for advantageous heating. Non-polar solvents with low dielectric constants are not the most suitable solvents for microwave-assisted reactions. Ionic liquids have been used in microwave reactors as heating aids. These are made up of organic cations and various anions. Therefore, we attempted the halex reaction in various 1-butyl-3-methylimidazolium [BMIM] ionic liquids. [BMIM]+ Br−, [BMIM]+ I−, and [BMIM]+ PF6− were screened and each time the reaction was unsuccessful. Consequently, we decided to move to alternative projects.

The goal for our halide exchange attempts was to develop a facile method compatible with all halides, especially fluorine. Efforts in ligand and catalysis design were not the focus of these attempts. However, it is important to note that since our initial trials the Hartwig group published a method for aryl fluorination from aryl iodides. The metal source and ligands were key for a successful transformation. This method focuses on the use of Cu1 + and nitrile ligands as key components for the reaction. Scheme 3.7 summarizes this work, which allows for the reaction of electron-rich, neutral, and poor aryl iodides as acceptable starting materials.
Summary:

There is an ongoing interest for the halide exchange reactions of aryl halides to the corresponding fluoride. We focused on halex reactions using microwave reactors towards copper mediated fluorination. Although initial halex reactions of 4-iodoanisole to 4-bromoanisole were successful, this method was not comparable to fluorinations. Our efforts were then focused towards other projects.
References:


10. Arvela, R. K; Leadbeater, N. E. Synlett, 2003, 8, 1145.

Preparation of Trifluoromethyl Ketones

Chapter 4
Recently the trifluoromethyl ketone (TFMK) has been exploited for its biological and chemical properties. They exhibit biological activity and have been used as inhibitors in the study of disorders such as severe acute respiratory syndrome (SARS)\(^1\) and cystic fibrosis.\(^2\) Secondly, TFMKs are intermediates for the production of many trifluoromethylated heterocycles, which are synthetically useful in drug design.

**TFMKs as Biologically Active Molecules:**

One significant property of TFMKs is the readiness to form a hydrate in aqueous conditions. This is mimicked with a serine or cysteine of an enzyme to form a hemiketal (52) or hemithioketal. The trifluoromethyl ketone is a competitive inhibitor of the enzyme, which stops its biological function.\(^3\) This has been exploited for certain viruses, diseases, and complications caused by serine and cysteine proteases.\(^2\) The mechanism of action is through a nucleophilic attack by the active site of these proteases onto the electron-poor carbonyl carbon. Hemiketals and hemithioketals are formed from the nucleophilic attack of serine and cysteine proteases respectively rendering them inactive.\(^2\)

Proteases, which contain serine and cysteine active sites, are inhibited by aldehydes. Hemiacetals are readily formed with serine or cysteine as a result of a hydrated aldehyde to the enzyme. This mimics the intermediate of hydrolyzed peptides and may be noted as “transition state analogue inhibitors.”\(^4\) However, aldehydes are limited to the carboxyl terminus of peptides and therefore may only be effective for a
smaller amount of proteases. Ketones may also be inhibitors but are not easily hydrated, this can be circumvented with the introduction of fluorine. Functionalities readily hydrated have been exploited in drug discovery. Trifluoromethyl ketones have been used as inhibitors for diseases such as cystic fibrosis, severe acute respiratory syndrome (SARS), and inflammatory disorders.

**TFMKs as Intermediates in Drug Design:**

The trifluoromethyl ketone is not only a biological inhibitor, it is also used as a building block for the incorporation of the trifluoromethyl group into many cyclic and heterocyclic compounds. Heterocycles are often cores in many biologically active compounds due to an increase of solubility and other drug-like properties. **Scheme 4.1** shows a selection of the compound classes that can be derived from TFMK starting materials (54-59).
The synthesis of the blockbuster AIDS medication Sustiva (62) produced by Bristol-Myers Squibb involves the introduction of the trifluoromethyl group to the molecule through a TFMK intermediate. This pathway is depicted in Scheme 4.2.\(^7\)
Previous Methods for Synthesis of Trifluoromethyl Ketones:

The major methods for TFMK synthesis can be categorized into three different classes: acetylation of trifluoromethyl esters, oxidation, and nucleophilic addition via ( trifluoromethyl )trimethylsilane (TMS-CF$_3$). Although each pathway is effective for specific substrates, they all have disadvantages. Since the original work in the 1950’s,$^8$ the most preferred method was acetylation of trifluoroacetic acid derivatives.$^9$ However, yields and reaction scope may be limited. The range of trifluoromethylated compounds produced depends upon the availability of the organometallic reagents. Also, yields can be diminished through double-alkylation by-products. This may be hindered by careful addition of the organometallic reagent. Grignard,$^8$ organo lithiums,$^8$ zinc,$^{10}$ cadmium,$^8$ and manganese$^{11}$ reagents all have been reported as suitable alkylating agents for a variety of trifluoromethyl starting materials such as: alkylfluoroacetates,$^8$ anhydrides,$^{12}$ amides,$^{13}$ and trifluoroacetonitriles.$^{10}$

Another method is the oxidation of $\alpha$-trifluoromethyl alcohols. The first apparent disadvantage is that it is a two-step process to the ketone. Secondary CF$_3$ carbinols
must first be synthesized from an aldehyde precursor followed by subsequent oxidation. Usually this oxidation requires harsh conditions.\textsuperscript{14} Traditional methods of oxidation have been reported, however these are substrate specific and there may be complications with reproducibility.\textsuperscript{15} Dess-Martin periodinane is a reliable oxidant tolerant to a broad range of functionality but is quite costly and caution must be used when dealing with this shock-sensitive reagent.\textsuperscript{14} Recently, the Leadbeater group has published an alternative route utilizing a recyclable, green oxidation of CF\textsubscript{3} carbinols (63) with an oxoammonium salt (64) as shown in Scheme 4.3.\textsuperscript{16}

![Scheme 4.3: Oxidation of CF\textsubscript{3} Carbinols](image)

(Trifluoromethyl)trimethylsilane:

The production of trifluoromethyl ketones through nucleophilic attack by the trifluoromethyl anion has boomed since the early 1990’s with the utilization of (trifluoromethyl)trimethylsilane (TMS-CF\textsubscript{3}) (70). This is commonly known as the Ruppert-Prakash reagent. Ingo Ruppert first synthesized TMS-CF\textsubscript{3} in 1984 from
trimethylsilyl chloride and trifluoromethyl bromide in the presence of hexaethyl phosphorus triamide (Scheme 4.4). Surya Prakash, and George Olah applied it to a range of aldehydes and ketones in 1989.

Initiation of the reaction occurs with a catalytic amount of tetrabutylammonium fluoride (TBAF); a fluoride source for the production of the trifluoromethide ion. Nucleophilic attack of the CF$_3$ group onto the carbonyl carbon produces an alkoxide. The alkoxide acts as a nucleophile towards TMS-CF$_3$ for the liberation of another trifluoromethide ion resulting in a silylated ether. Hydrolysis of the ether with acid generates the desired CF$_3$ carbinol. This significant finding was of great importance for the field of trifluoromethylation. Previously, Lewis acid catalyzed reactions from carbonyl species were not possible with trifluoromethide-metal complexes. The catalyst would form a M-F bond, decomposing the CF$_3$ anion into a difluorocarbene without product formation. Scheme 4.5 illustrates the range of alcohols (72) that are formed by Prakash’s method. Since 1989, reports of trifluoromethylation via TMS-CF$_3$ have been shown to add at carbon, nitrogen, phosphorus, and sulfur centers.
Prakash reported the synthesis of trifluoromethyl ketones through CF$_3$ initiation in 1998. Starting methyl esters (73) were converted to product (74) with 2.5% TBAF and TMS-CF$_3$ at -78 °C (Scheme 4.6). Reaction yields were moderate to excellent (68-95%). Disadvantages to this method include the need for an inert atmosphere and rigorously dried solvents. Also, the temperature must be carefully controlled. When charging the flask with the initiator, the reaction mixture must be cooled to -78 °C. Reactions conducted with greater temperatures produced the desired ketone as well as a bis-trifluoromethylated by-product. This method was tolerant of aliphatic, aromatic, and α-β unsaturated systems. Alkynes were unreactive. \(^{20}\)

Realizing the limitations of the TFMK synthesis via the Prakash route, the Shreeve lab had sought to create a more facile transformation. \(^{21}\) They suggested that rigorous drying of the reactants and

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**Scheme 4.6: Prakash’s Synthesis of TFMK**

![Diagram](image1)

**Scheme 4.7: Shreeves’s Synthesis of TFMK**

![Diagram](image2)
solvent was needed due to a competing reaction of water with TMS-CF$_3$ producing CF$_3$H. As a control experiment they mimicked Prakash’s procedure in the presence of TBAF with <5% water by weight. The TMS-CF$_3$ had quantitatively reacted to form HCF$_3$ and HOSi(CH$_3$)$_3$ which confirmed their hypothesis. Ketones and aldehydes are more reactive than esters. Therefore, anhydrous conditions were not necessary when Prakash reported the synthesis of trifluoromethyl alcohols. Upon many initiators screened, cesium fluoride was chosen as the best fluoride source for the trifluoromethylation of esters (Scheme 4.7). Most reactions were performed neat and at room temperature. For the cases of solid starting materials such as 74m, glyme was used as a solvent. Neat reaction conditions may cause complications during scale-up.

The mechanism for the transformation to TFMKs via TMS-CF$_3$ occurs through initiation by a catalytic amount of fluoride, propagation, and hydrolysis to the ketone. Prakash suggests that a CF$_3$ transfer to the ester first occurs from a direct reaction of the fluoride source with TMS-CF$_3$. The initiation step most likely

Figure 4.2: Prakash’s Suggested Mechanistic Pathway$^{19}$
occurs in a concerted fashion rather than liberating the trifluoromethide ion, producing alkoxide 77. Propagation of the reaction occurs through a trifluoromethyl transfer to another starting ester. The silylated ether (78) can then be cleaved by acid to the desired trifluoromethyl ketone (Figure 4.2).19

A Weinreb Amide Approach:

Given the advantages of trifluoromethyl ketones, this functionality has become a subject of great interest in our laboratory. Of the three main approaches to TFMK synthesis we have explored in detail the use of TMS-CF₃ as the trifluoromethyl source. Although it has been reported to act as a trifluoromethylating agent for many carbonyl compounds, the only productive starting functionality for TFMK synthesis is an ester. The methods reported by Prakash and Shreeve do contain limitations of over-addition and possible solubility and scalability complications.20,21 Therefore, our intentions were to investigate the use of other starting materials to produce trifluoromethyl ketones in a controlled fashion.

The Weinreb amide became a functionality of interest for our study. Weinreb and co-workers exploited these N-methoxy-N-methyl amides for the production of ketones via alkylation reactions in 1981.23 Previous to Weinreb’s research, organo lithium, and Grignard
reagents were used for alkylation reactions of carbonyl compounds containing leaving group functionalities (79). Unfortunately, with esters, only double-alkylated products were formed (80). Scheme 4.8 depicts how using the Weinreb amide forced the reaction pathway towards the desired ketone. Nucleophilic attack of the alkyl reagent results in the tetrahedral intermediate 82, which is coordinated by the metal. This is a stable species, and can be hydrolyzed to produce the desired ketone (83). Since the intermediate cannot be further alkylated, double-addition by-products were not observed. 23

Our hypothesis was that we could utilize Weinreb amides for the production of trifluoromethyl ketones without producing the corresponding bis-trifluoromethyl alcohol. Previous reports suggested

<table>
<thead>
<tr>
<th>Starting Materials</th>
<th>Trifluoromethylated Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Image" /> 84</td>
<td><img src="image2" alt="Image" /> 89</td>
<td>40%</td>
</tr>
<tr>
<td><img src="image3" alt="Image" /> 85</td>
<td><img src="image4" alt="Image" /> 90</td>
<td>88%</td>
</tr>
<tr>
<td><img src="image5" alt="Image" /> 86</td>
<td><img src="image6" alt="Image" /> 91</td>
<td>78%</td>
</tr>
<tr>
<td><img src="image7" alt="Image" /> 87</td>
<td><img src="image8" alt="Image" /> 92</td>
<td>68%</td>
</tr>
<tr>
<td><img src="image9" alt="Image" /> 88</td>
<td><img src="image10" alt="Image" /> 93</td>
<td>87%</td>
</tr>
</tbody>
</table>

Table 4.1: Activated Imides and Amides
that amides were not prone to nucleophilic attack of the trifluoromethide group. Simple amides were unreactive with TMS-CF$_3$ even when a stoichiometric amount of initiator was used.$^{24}$ The carbonyl is deactivated through the lone pair of electrons on nitrogen. Susceptibility for attack can be increased if an electron-withdrawing substituent is added to the amide or a more activated system is used. Table 4.1 depicts an activated amide (84) and imides (85-88) that did react with trifluoromethyl trimethylsilane.$^{25}$ Shreeve and co-workers reported another promising discovery. They had witnessed an exothermic reaction when $N,N$-dimethylbenzamide and dimethylacetamide were treated with TMS-CF$_3$ and CsF. No results were ever published on this finding suggesting the reaction could not be controlled.$^{22}$

We believed Weinreb amides would be suitable starting materials for trifluoromethylation reactions. Pre-coordination of the TMS-CF$_3$ could facilitate reactivity, by moving electron density away from the carbonyl. The intermediate could then be exploited for a single trifluoromethyl addition.

Results and Discussion for a Weinreb Amide Approach:

Our initial reaction conditions mimicked the standard procedure of trifluoromethylation from aldehyde and ketone precursors.$^{26}$ Prakash’s method reacted the starting materials with TMS-CF$_3$, TBAF as initiator, and THF as solvent. Our reactions were tested on a 1 mmol scale with 1.3 equivalents of TMS-CF$_3$ and 20 mol% of initiator at 0 °C. Potassium fluoride, sodium fluoride, cesium fluoride, and TBAF were all screened as initiators (Table 4.2, entries1-4). In the case of TBAF, only 5 mol% was
used as it is a soluble fluoride source. We had believed that the reaction would proceed in a one-pot, two-step fashion to first produce a silylated intermediate, which could be further cleaved to the ketone. No reaction was observed with potassium or sodium fluorides (Table 4.2, entries 1-2). This is most likely due to low solubility of the salts in organic solvents. Low conversions of 12% and 55% to the trifluoromethyl ketone respectively were observed with TBAF and CsF as initiators (Table 4.2, entries 3-4). Thinking that low solubility of CsF may be impeding the reaction, other polar solvents such as acetonitrile and dichloromethane were screened (Table 4.2, entries 5-6). Unfortunately, inferior conversions were observed. Cesium fluoride was deemed the best initiator however much progress was needed to optimize reaction conditions to quantitative conversions. 

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Initiator</th>
<th>TMS-CF$_3$ (equiv.)</th>
<th>Solvent (0.7M)</th>
<th>Time</th>
<th>94</th>
<th>95</th>
<th>96</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaF</td>
<td>1.3</td>
<td>THF</td>
<td>17 h</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>KF</td>
<td>1.3</td>
<td>THF</td>
<td>17 h</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>TBAF</td>
<td>1.3</td>
<td>THF</td>
<td>17 h</td>
<td>88%</td>
<td>0%</td>
<td>12%</td>
</tr>
<tr>
<td>4</td>
<td>CsF</td>
<td>1.3</td>
<td>THF</td>
<td>17 h</td>
<td>45%</td>
<td>0%</td>
<td>55%</td>
</tr>
<tr>
<td>5</td>
<td>CsF</td>
<td>1.3</td>
<td>MeCN</td>
<td>17 h</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>6</td>
<td>CsF</td>
<td>1.3</td>
<td>DCM</td>
<td>17 h</td>
<td>89%</td>
<td>11%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Table 4.2: Initial Trials

To understand further the reactivity in THF, we screened other substrates. It was determined that the reactivity differed. Over time amide 94 converted to the TFMK (Table 4.2, entry 4). Yet with amide 97 only the intermediate was detected (Table 4.3).
For this substrate the reaction was reversible, as after time it would revert back to starting material. The reaction was monitored for conversion over time. The highest conversion of intermediate 98 observed was 33% after 10 minutes (Table 4.3, entry 3). When monitored hours later, only starting material was present (Table 4.3, entry 5). We believed that polar solvents were stabilizing the CF$_3$ ion, and therefore a reverse reaction to liberate the trifluoromethide was possible.

Understanding that polar solvents were not ideal for the reaction, we next looked at solvent-free conditions. The Shreeve group successfully produced TFMKs from esters under neat reaction conditions.$^{21}$ We believed that an excess of TMS-CF$_3$ in the absence of a polar solvent would facilitate product formation. Six equivalents of the reagent was chosen as a starting point on a 1.0 mmol scale, allowing enough volume to stir the reaction. To our delight, there was complete conversion to the tetrahedral intermediate. However, an uncontrollable exotherm was observed. Various approaches were taken to control the reaction. Lowering the temperature to -10 to -78 °C, and slow addition of 5-15 minutes of TMS-CF$_3$ to the starting amides, were unsuccessful. Low temperatures of -78 °C were not productive and gradually warming up the reaction mixture resulted in an exotherm. Further optimization was needed.$^{26}$

---

### Table 4.3: Timed Trials

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time</th>
<th>97</th>
<th>98</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0 min</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>5 min</td>
<td>&gt;100%</td>
<td>Trace</td>
</tr>
<tr>
<td>3</td>
<td>10 min</td>
<td>66%</td>
<td>33%</td>
</tr>
<tr>
<td>4</td>
<td>20 min</td>
<td>70%</td>
<td>30%</td>
</tr>
<tr>
<td>5</td>
<td>4 h</td>
<td>100%</td>
<td>0%</td>
</tr>
</tbody>
</table>

---

[Diagram of reaction]
Our next efforts were focused on selecting a co-solvent to dilute the reaction and act as a heat-sink. From previous experiments we knew that a polar solvent may be problematic and reversible. Therefore, we chose to screen non-polar solvents. Our primary attempts screened pentane, hexanes, and toluene as co-solvents on a 1-mmol scale at room temperature. Near quantitative conversion to the intermediate was observed. However, complications arose upon scale-up to 5 mmol. We were encouraged to find that cooling the contents to 0 °C before addition of TMS-CF₃ resulted in an easily handled reaction without intense exothermic activity.²⁶

With the ability to contain the exotherm, we went on to examine loadings of initiator and TMS-CF₃. Initially we were running the reaction in 6 equiv. of trifluoromethyl trimethylsilane. This is not desired as larger scale reactions could become quite expensive. Table 4.4 summarizes the trials. Lowering the amount to 3 equiv. was just as effective (Table 4.4, entry 3), and 2 equiv. resulted in acceptable conversion of 84% (Table 4.4, entry 2). Further reducing the loading resulted in incomplete reactions (Table 4.4, entry 1). A decrease to 10 mol% CsF resulted in sub-optimal conversion to 95 of 67%. After longer reaction times of 24 hours, we were able to charge 2 equivalents of TMS-CF₃ and 20 mol% CsF to produce optimized conditions, which resulted in near quantitative conversions to the tetrahedral intermediate (Table 4.4, entry 5).²⁶
Our next objective was to transform the silylated ether to the desired trifluoromethyl ketone. Prakash and Shreeve’s methods cleaved the intermediate with acid. To our surprise, the intermediate was quite robust in acidic conditions. We then attempted to use a fluoride reagent, TBAF, as a cleavage source. Initially, the cleavage step was performed at room temperature with a stoichiometric amount of TBAF. An equal amount of water to TBAF was added to act as a proton source for the liberated N-methoxy-N-methyl amine. Due to cost of the reagent, we also attempted using a catalytic amount of TBAF. Although it was successful for some substrates (Table 4.5, entry 3), it was not compatible with all (Table 4.5, entry 6). Some substrates were even resistant to cleavage with a stoichiometric amount of TBAF (Table 4.5, entry 4). Stirring the reaction for 2 hours at 50 °C allowed for optimal conversion of each intermediate produced to the trifluoromethyl ketone (Table 4.5, entry 5).
Optimized conditions to perform the trifluoromethylation reaction involve a one-pot two-step process. The Weinreb amide (5.0 mmol) in toluene (2.5 mL) is cooled to 0 oC. To the flask are added 20 mol% of CsF followed by 2.0 equivalents of TMS-CF₃. The reaction is stirred overnight (18-24 hours) and monitored by ¹H NMR for completeness. Once a quantitative conversion to the intermediate is confirmed, a stoichiometric amount of TBAF and equal volume of water is added directly to the reaction flask and the resultant mixture heated to 50 oC for 2 h. A simple ether extraction and water wash allowed for the crude product. The pure products were isolated by column chromatography or distillation.²⁶
<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>TBAF (equiv.)</th>
<th>Time</th>
<th>Temp.</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>1.0</td>
<td>2 h</td>
<td>23 °C</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>0.5</td>
<td>2 h</td>
<td>23 °C</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>0.1</td>
<td>2 h</td>
<td>23 °C</td>
<td>85%</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>1.0</td>
<td>18 h</td>
<td>23 °C</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>1.0</td>
<td>2 h</td>
<td>50 °C</td>
<td>&gt;99%</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>0.1</td>
<td>2 h</td>
<td>23 °C</td>
<td>30%</td>
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<tr>
<td>7</td>
<td></td>
<td>1.0</td>
<td>2 h</td>
<td>50 °C</td>
<td>&gt;99%</td>
</tr>
</tbody>
</table>

Table 4.5: Optimized Cleavage
With optimal conditions at hand, we then probed the substrate scope of the reaction. As shown in Table 4.6 we were able to produce a variety of aryl, alkyl, and heterocyclic trifluoromethyl ketones with yields as high as 99% (Table 4.6, TFMK 115). Our methodology was tolerant of electron donating (Table 4.6, TFMK 96, 112) and electron withdrawing substituents (Table 4.6, TFMK 101-102) on the meta and para positions of aryl compounds. Heterocycles such as thiophenes, pyridines, and furans, are also compatible with this methodology (Table 4.6, TFMK 113, 114, 119). However, pure hydrate rather than the TFMK was isolated from the 4-pyridyl system due to an electron withdrawing nature of the system (Table 4.6, TFMK 114).  

To continue our investigation of reaction scope, we turned to substituted and unsubstituted aliphatic compounds (Table 4.6, TFMK 104-111, 116-118). Initial complications of this methodology became apparent in the isolation and purification steps. Addition of the trifluoromethyl group generally increases the volatility of the ketone products compromising reaction yield. Therefore, larger alkyl chains and phenyl substituted aliphatic compounds were preferred. Due to a lack of chromophores, many of the alkyl systems had little or no UV activity. Products were also unreactive to stains limiting the purification process to distillation.

Originally the reactions were run on a 5 mmol scale, however scale-up was required for a fruitful distillation. When reactions were increased to 10-15 mmol, an exotherm was observed after the TMS-CF$_3$ was added. We were delighted to find that diluting the reaction from 2.0 M to 0.5 M controlled the exotherm, even when conducted at room temperature. The increased volume of toluene, slowed the cleavage step from 2
h to overnight. Therefore, the toluene was removed in *vacuo* prior to TBAF addition. As mentioned for some of the lighter aliphatic systems, reaction yield was diminished due to high volatility. A greater percent of TFMK could be observed if all of the toluene was removed prior to the cleavage step. Ether or hexanes may be used as a replacement solvent. The alkyl substrates were converted to the desired ketones in 49-76% yields (Table 4.6, TFMK 104-111, 116-118). Slightly lower reaction yields were due to isolation processes.\(^{26}\)

<table>
<thead>
<tr>
<th>TFMK</th>
<th>Product</th>
<th>Yield</th>
<th>TFMK</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>96</td>
<td><img src="image1.png" alt="Image" /></td>
<td>81%</td>
<td>112</td>
<td><img src="image2.png" alt="Image" /></td>
<td>84%</td>
</tr>
<tr>
<td>101</td>
<td><img src="image3.png" alt="Image" /></td>
<td>78%</td>
<td>113</td>
<td><img src="image4.png" alt="Image" /></td>
<td>63%</td>
</tr>
<tr>
<td>102</td>
<td><img src="image5.png" alt="Image" /></td>
<td>72%</td>
<td>114</td>
<td><img src="image6.png" alt="Image" /></td>
<td>90%</td>
</tr>
<tr>
<td>103</td>
<td><img src="image7.png" alt="Image" /></td>
<td>88%</td>
<td>115</td>
<td><img src="image8.png" alt="Image" /></td>
<td>99%</td>
</tr>
<tr>
<td>104</td>
<td><img src="image9.png" alt="Image" /></td>
<td>75%</td>
<td>116</td>
<td><img src="image10.png" alt="Image" /></td>
<td>59%</td>
</tr>
<tr>
<td>105</td>
<td><img src="image11.png" alt="Image" /></td>
<td>66%</td>
<td>117</td>
<td><img src="image12.png" alt="Image" /></td>
<td>61%</td>
</tr>
</tbody>
</table>
We also performed our method with α,β-unsaturated amides (Table 4.6, TFMK 120-123). Diminished yields of the trifluoromethyl ketones were observed due to the production of a side-product. Mass spectrometry and NMR analyses confirmed a 1,4-Michael addition of the N-methoxy-N-methyl amine to the trifluoromethyl ketone (Table 4.7, compound 126). This was first observed with the unsubstituted cinnamic acid derivative 120 when a low TFMK yield of 22% was acquired. The Michael adduct was isolated in 63%, with a ratio of TFMK to by-product of 25:75 (Table 4.7, TFMK 120). The weakened olefin is susceptible to 1,4 addition of the amine produced.26

It was thought that adding acid to the cleavage step could hinder by-product formation. In theory, the nitrogen of the N-methoxy-N-methyl amine liberated could be
protonated and inhabit the aqueous phase. To our surprise, a biphasic TBAF/ 6 N HCl did not affect 1,4-addition. We then attempted to skew product ratio through an electronic effect. Systems with an electron withdrawing substituent should weaken the double bond favoring amine attack. Contrastingly, an electron-donating group will increase electron density to the olefin, reducing the probability of Michael addition. We investigated this hypothesis with different electron donating and withdrawing functionalities as shown in Table 4.7. Initially, we believed that the presence of an electronegative fluorine in the para-position would favor the 1,4 addition product. However, the ratio of TFMK to Michael adduct was 41:59 (Table 4.7, TFMK 122). This is not surprising as fluorine may also have a donating effect from its lone pairs of electrons. Increasing the electron donating power onto the alkene resulted in a greater percentage of TFMK to side product as expected. The para-methoxy substrate produced a ratio of 55:45 TFMK to 1,4 adduct (Table 4.7, TFMK 121), and the furyl substrate resulted in a ratio of 71:29 in favor of the trifluoromethyl ketone (Table 4.7, TFMK 123). It is important to note that all of the 1,4-adducts isolated existed as part ketone and part hydrate that were inseparable by chromatography. The ratios calculated are of the desired TFMK to combined 1,4 adduct and its hydrate. 26
Unfortunately, the α,β-unsaturated amides were not the only incompatible substrates with our method. Table 4.8 summarizes the problematic compounds. Ortho-substituents on aryl rings were not tolerated. This was first discovered with the o-methoxy amide (Table 4.8, amide 128). Conversion to the intermediate was minimal, which over time would self-cleave to the TFMK. As with any complication of organic chemistry this low reactivity could either be contributed by a steric or electronic effect. We initially hypothesized the former based on the 88% isolated yield obtained with the chemically similar para-methoxy substrate. In order to support our theory, we conducted an experiment with the ortho nitro amide 129 as a contrasting electron-withdrawing group. No reaction occurred suggesting that electronics was not hindering the reactivity (Table 4.8, amide 129). We then sought to see if any ortho substituent would be
tolerated with the 2-methyl amide (Table 4.8, amide 127). Again, little or no product was generated. Even this small steric interaction dramatically decreased the reactivity.\textsuperscript{26}

Steric issues were again apparent with branched aliphatic substrates. The presence of a substituent alpha to the carbonyl was not accepted as can be shown with the branched ethyl chain of substrate (Table 4.8, amide 132). In comparison, the straight octyl chain led to a high conversion of the intermediate (85-90\%) and the TFMK product (58\% yield). We then attempted reactions with differing groups beta to the carbonyl. The branched phenyl derivative was not reactive (Table 4.8, amide 134), compared to the de-branched, which generated a 68\% yield of TFMK 110. It was not until we decreased the steric hindrance to a methyl group in this position was conversion to the intermediate observed. Even then, only partial

<table>
<thead>
<tr>
<th>Amide</th>
<th>Substrate</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>127</td>
<td><img src="image.png" alt="Amide 127" /></td>
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</tr>
<tr>
<td>128</td>
<td><img src="image.png" alt="Amide 128" /></td>
<td>25%</td>
</tr>
<tr>
<td>129</td>
<td><img src="image.png" alt="Amide 129" /></td>
<td>0%</td>
</tr>
<tr>
<td>130</td>
<td><img src="image.png" alt="Amide 130" /></td>
<td>0%</td>
</tr>
<tr>
<td>131</td>
<td><img src="image.png" alt="Amide 131" /></td>
<td>0%</td>
</tr>
<tr>
<td>132</td>
<td><img src="image.png" alt="Amide 132" /></td>
<td>0%</td>
</tr>
<tr>
<td>133</td>
<td><img src="image.png" alt="Amide 133" /></td>
<td>0%</td>
</tr>
<tr>
<td>134</td>
<td><img src="image.png" alt="Amide 134" /></td>
<td>0%</td>
</tr>
</tbody>
</table>

Table 4.8: Problematic Substrates
transformation to the intermediate of 55-60% occurred, resulting in a compromised yield of TFMK 118 in 48%.\textsuperscript{26}

The steric limitation of the reaction hints towards the mechanism. In our method we believed that either one of two initiation pathways are plausible. Initially we suggested that the cesium fluoride activated this reaction. This reagent would act as a dual contributor to the reaction as an initiator, and chelator. This chelation would result in the 5-membered transition state, increasing the electrophilicity of the carbonyl. However, evidence from our studies points away from this theory.

When screening initiators, we did see some conversion with TBAF as an initiating source. Literature precedent suggests that amides must be activated in order to react with TMS-CF\textsubscript{3}.\textsuperscript{24,25} If chelation really was as important for this reaction as believed, there would be no conversion with TBAF due to a lack of metal or chelating source. In addition, this does not explain the steric limitations of the reaction. The Shreeve group had suggested that TMS-CF\textsubscript{3} was responsible for precoordination with starting esters even in the presence of CsF. Our results can be explained by this theory. \textbf{Figure 4.3} illustrates this precoordinated transition state (135 or 136). Just as a chelation effect, the TMS-CF\textsubscript{3} could allow for amide activation. Therefore, conversion to the intermediate would be possible when using a non-metal fluoride source such as TBAF. The transition state also contributes a large steric bulk around the electrophilic carbon. Increasing density around this site with an ortho substituent, or alpha branching would result in a dramatic decrease in reactivity as observed.
Once precoordination occurs, the fluoride ion then reacts with TMS-CF$_3$ for the liberation of the trifluoromethyl group. Shreeve suggests that this occurs in a concerted like fashion, where the nucleophilic attack onto the carbonyl occurs instantaneously to generate an alkoxide ion 137.$^{22}$ This further propagates the reaction by interacting with another TMS-CF$_3$ to produce a silylated ether. The resulting intermediate is an isolatable, stable moiety as confirmed with our $p$-tBu substrate (138). After conversion to the intermediate, we then filtered the reaction and removed the solvent to produce an 86% yield of the silylated ether. The compound was stable at room temperature without any noticeable degradation even when monitored months later. Nonetheless, once
converted to the intermediate the substrates were immediately introduced to a stoichiometric amount of fluoride to form the desired TFMK in a one-pot fashion.26

**Summary:**

In summary, this methodology is a novel way for the production of trifluoromethyl ketones. It is the first report for the introduction of the CF₃ group into an amide to form a TFMK. Over trifluoromethylation was never detected. The reaction may be performed at room temperature under dilute conditions without the need for anhydrous conditions or an inert atmosphere. Although the methodology is limited to less-hindered substrates, we have demonstrated a successful method with aryl, aliphatic, and heterocyclic starting amides with up to quantitative yields.
References:


Synthesis of Difluorinated Compounds

Chapter 5
(Difluoromethyl)trimethylsilane:

Trifluoromethyl trimethylsilane has been a dependable trifluoromethylating reagent since its synthesis in 1984.\(^1\) The difluorinated analogue, TMS-CHF\(_2\) (140), however has seen little use as a difluoromethylating reagent. It was not until 1995, that TMS-CHF\(_2\) was applied towards fluoroalkylation reactions.\(^2\) Hagiwara and Fuchikami were pioneers for the difluoromethylation of aldehydes to CF\(_2\) alcohols (Scheme 5.1).\(^2\)

Hagiwara and Fuchikami began their work repeating the procedure for trifluoromethylation with TMS-CHF\(_2\).\(^1b\) Benzaldehyde and TBAF (0.6 mol %) were added to THF and the reaction mixture stirred at room temperature for 24 h.\(^2\) No reaction was noted using this procedure. Molecular orbital calculations (MOPAC) were employed to understand the reactivity differences between each fluoroalkylating reagent. The nucleophilic attack of a fluoride onto the silicon forms pentavalent silicate intermediates (142). The bond order between the silicon and carbon intermediates were calculated for TMS-CHF\(_2\) (0.436) and TMS-CF\(_3\). (0.222).\(^2\) This increase in bond character of the TMS-CHF\(_2\) intermediate explains why the Si-C bond is more difficult to break. This means that harsher reaction conditions were necessary for difluoromethylation to occur.

\[\text{Scheme 5.1. Fuchikami's Difluoromethylation}\]

\[\text{Figure 5.1: Silicate Intermediates}\]
Benzaldehyde and KF (5-50 mol%) were added to DMF and heated to 100 °C for 6 h. The CF$_2$ alcohol was isolated in an 82% yield. Ketones were also employed as starting materials but poor yields of 20-35% were reported.$^2$

Since the original report in 1995, limited attention has been focused on using (difluoromethyl)trimethylsilane as a fluoroalkylating reagent. However, in 2011, Hu et. al. reported alternative reaction conditions for the difluoromethylation of aldehydes and ketones.$^3$ Different solvents, initiators, and temperatures were screened for the reaction of aldehydes with TMS-CHF$_2$. In DMF, suitable initiators were CsF, KF/18-crown-6, and tetrabutylammonium difluorotriphenylsilicate (TBAT). Interestingly, when the solvent was changed to THF, potassium tert-butoxide (KO$_t$Bu) was a successful initiator, whereas TBAT was not. This is attributed to the greater solubility of KO$_t$Bu in THF than the other initiators screened. Nonetheless, the CsF/DMF system was chosen as it exhibited the best reaction conversions (Scheme 5.2).$^3$ Aryl, aliphatic, and conjugated aldehydes were isolated in 50-96% yields.$^3$

The Hu group then sought to perform the difluoromethylation of ketones. When conducted using CsF and DMF (conditions developed for aldehydes) low yields of 30-40% were reported.$^3$ Reaction monitoring had suggested that an irreversible, nucleophilic difluoromethylation occurred with DMF compromising yields. Since the solvent was not ideal, they next screened THF and alkoxide initiators. Interestingly, non-enolizable ketones proceeded to the CF$_2$ alcohol with 2 equivalents of KO$_t$Bu at -78 °C.
A stoichiometric amount of the initiator was crucial for the reaction to occur. This suggests that the mechanism is not auto-catalyzed by the alkoxide produced after addition of the CF₂. Excellent yields of 95-97% of the CF₂ carbinols were generated, as shown with ketone 144.³

**The Difluoromethyl Ketone:**

Since Hu’s breakthrough, DFMKs have notably not been synthesized via TMS-CHF₂.³ Hence, we have embarked upon the synthesis of DFMKs via a Weinreb amide approach. Initial screenings for DFMKs were accomplished prior to the optimization of trifluoromethyl ketones from Weinreb amides. (Difluoromethyl)trimethylsilane was freshly prepared from the reduction of TMS-CF₃ with sodium borohydride.⁴ We hypothesized the difluorination would occur through the silyl-intermediate 145 (Scheme 5.4). A range of amides were screened with the following: THF, DME and DMF as potential solvents. The reaction was unsuccessful with catalytic amounts of CsF (20 mol%) or KO'Bu (20 mol%). Reaction times of 24 hours were employed with no conversion (Table 5.1, entries 1-4). This was discouraging as our trifluoromethylation
attempts exhibited minor conversions under these conditions. Nonetheless, we next mimicked conditions reported by Hu for difluoromethylation of ketones with the remaining TMS-CHF₂ in hand. Amide 146 (1.0 mmol), TMS-CHF₂ (1.3 equiv.), and KO₂Bu (2.0 equiv.) were added to THF. The reaction was cooled to 0 °C and left to stir overnight. To our delight, we observed near quantitative conversion to the difluoromethyl ketone (Table 5.1, entry 5). Due to time constraints the product was never isolated.

![Chemical structure diagram]

Table 5.1: Experimental Attempts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amide</th>
<th>R</th>
<th>Solvent</th>
<th>Initiator</th>
<th>Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>148</td>
<td></td>
<td>DME</td>
<td>20 mol% CsF</td>
<td>0%</td>
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<tr>
<td>2</td>
<td>146</td>
<td></td>
<td>DMF</td>
<td>20 mol% CsF</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>149</td>
<td></td>
<td>THF</td>
<td>20 mol% KO₂Bu</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>146</td>
<td></td>
<td>DMF</td>
<td>20 mol% KO₂Bu</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>146</td>
<td></td>
<td>DMF</td>
<td>200 mol% KO₂Bu</td>
<td>&gt;99% TFMK</td>
</tr>
</tbody>
</table>
**TMS-CHF₂ for 1,1-difluoro Alkenes:**

We were interested in exploiting TMS-CHF₂ for the synthesis of other difluorinated functionalities. One reaction of interest was the Petersen olefination for the production of 1,1-difluoroalkenes. This method reacts ketones and aldehydes with α-silylcarbanions (150) to form substituted olefins (Scheme 5.5). Currently, this reaction has not been reported with TMS-CHF₂ to yield 1,1-difluoroalkenes. With no literature precedent on this transformation, we sought to investigate the reactivity of TMS-CHF₂ for a Peterson-like reaction (Scheme 5.5). The silylated reagent could be deprotonated to form intermediate 156. In theory, this would then eliminate to form the desired CF₂ alkene (157).

To begin our investigation, we needed to find an appropriate base to deprotonate the TMS-CHF₂. We hypothesized n-BuLi would be sufficient for this purpose. THF (1 mL) was cooled to -78 °C. (Difluoromethyl)trimethylsilane (1.25 mmol) was added followed by the base (1 mmol). We waited for a period of 5 min for the deprotonation to occur. The aldehyde (158, 0.25 mmol) was then added to the flask in attempts to form the difluoro alkene. However, the desired product (159) was not observed. Instead, butyl addition into the aldehyde occurred (Table 5.2, entry 1). These results suggest that the
silylated reagent was not deprotonated. It is important to note that the solvent was dried, and base titrated before conducting the reaction. We next hypothesized that a stronger base may be needed for a successful reaction, so t-BuLi was tested. Again, the t-Bu group reacted with the aldehyde rather than the desired reagent (Table 5.2, entry 2).

We next turned to tetramethylethylenediamine (TMEDA) as an additive. The TMEDA increases reactivity through disruption of the hexameric aggregation of n-BuLi. Unfortunately, only starting material was observed (Table 5.2, entry 3). In this instance, the TMEDA increases a steric bulk into the system, which may have hindered alkyl addition.

![Chemical reaction image]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Equiv.</th>
<th>Time</th>
<th>Temperature</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-BuLi</td>
<td>1.0</td>
<td>5 min</td>
<td>-78 °C</td>
<td>n-Bu addition</td>
</tr>
<tr>
<td>2</td>
<td>t-BuLi</td>
<td>1.0</td>
<td>5 min</td>
<td>-78 °C</td>
<td>t-Bu addition</td>
</tr>
<tr>
<td>3</td>
<td>n-BuLi/TMEDA</td>
<td>1.0</td>
<td>1.5 h</td>
<td>-10 °C-78 °C</td>
<td>NR</td>
</tr>
</tbody>
</table>

Table 5.2: The Peterson Olefination Attempts

We initially believed that deprotonation of a hydrogen on TMS-CHF₂ would be facile because of the electronegative nature of fluorine. However, the literature explains why this proton abstraction did not occur. A carbon alpha to a difluoromethyl group may
easily be deprotonated. However, deprotonation of a carbon directly attached to two fluorines is not. Repulsion of the lone pairs of electrons on the fluorine extremely destabilizes the carbanion.\textsuperscript{7} As a result, it is not known to deprotonate.\textsuperscript{7}

**Summary:**

Difluorination of organic molecules has been a challenging task for synthetic chemists. A few of the significant breakthroughs have been accomplished with TMS-CHF$_2$ as a difluorinating reagent. We have attempted the synthesis of 1,1-difluoroalkenes, and difluoromethyl ketones with TMS-CHF$_2$. A Weinreb amide approach to DFMK seems promising, although more optimization is needed.
References:


Experimental Procedures

Chapter 6
General Considerations:

All chemical transformations requiring inert atmospheric conditions or vacuum distillation utilized Schlenk line techniques with a 3- or 4-port dual-bank manifold. Nitrogen was used to provide such an atmosphere. NMR Spectra ($^1$H, $^{13}$C, $^{19}$F) were performed at 298 K on either a Brüker Avance Ultra Shield 300 MHz NMR, Brüker DRX-400 400 MHz NMR, or Brüker Avance 500 MHz NMR. $^1$H-NMR Spectra obtained in CDCl$_3$ were referenced to residual non-deutered chloroform (7.26 ppm) in the deuterated solvent or in deuterated methanol referenced to TMS (0.00 ppm). $^{13}$C-NMR Spectra obtained in CDCl$_3$ were referenced to chloroform (77.3 ppm) or to deuterated acetone (29.84 ppm). $^{19}$F-NMR spectra were referenced to hexafluorobenzene (−164.9 ppm). Reactions were monitored by an Agilent Technologies 7820A Gas Chromatograph attached to a 5975 Mass Spectrometer, $^1$H-NMR, and/or by TLC on silica gel plates (60Å porosity, 250 µm thickness). High-resolution mass spectra were obtained using a JEOL AccuTOF-DART SVP 100 in positive direct analysis in real time (DART) ionization method, using PEG as the internal standard. TLC analysis was performed using hexanes/ethyl acetate as the eluent and visualized using permanganate stain, p-anisaldehyde stain, Seebach’s Stain, and/or UV light. Flash chromatography and silica plugs utilized Dynamic Adsorbants Inc. Flash Silica Gel (60Å porosity, 32-63 µm).
Attempts towards Fluoroarenes:

4-Bromoanisole from 4-iodoanisole\(^2\):

To a 10 mL microwave tube equipped with a stir bar was added 4-iodoanisole (41, 0.235g, 1.0 mmol, 1.0 equiv.), followed by copper (II) bromide (0.246 g, 1.1 mmol, 1.1 equiv.), and acetonitrile (1 mL). The tube was then capped and placed into the microwave cavity. The contents were ramped to 170 °C and let stir at temperature for 15 minutes. Upon cooling, the reaction mixture was transferred to a separatory funnel and diluted with diethyl ether (20 mL). The mixture was washed twice with a brine solution (2 x 20 mL). The organics were collected and the aqueous layer was extracted with a third portion of diethyl ether (20 mL). The combined organics were dried with magnesium sulfate and filtered. Internal standard 1,2,4,5-tetramethylbenzene (.0680g, 0.5 mmol, 0.5 equiv.) was added to the flask and the solvent was removed in vacuo. \(^1\)H-NMR yield suggested full conversion to 4-bromoanisole (50) with 70% recovery by internal standard. \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) ppm 3.83 (s, 3H), 6.84 (d, \(J = 9.00\) Hz, 2 H), 7.44 (d, \(J = 9.00\) Hz, 2 H).
A Weinreb Amide Approach to Trifluoromethyl Ketones:

Synthesis of Weinreb Amide Substrates:

**General Procedure A: Weinreb Amides From Acid Chlorides:**

To a 250 mL round bottom flask equipped with a stir bar was added 4-t-butylbenzoyl chloride (7.867 g, 40 mmol, 1.0 equiv.), DCM (80 mL, 0.5 M in the acid chloride), followed by N-0-dimethylhydroxylamine hydrochloride (4.098 g, 42 mmol, 1.05 equiv.). The flask was cooled to 0 °C in an ice bath for 10 minutes. Pyridine (6.638 g, 84 mmol, 2.1 equiv.) was added drop-wise to the flask over a period of 10 minutes. The reaction flask was taken out of the ice bath and upon warming, a white precipitate formed. The reaction was allowed to stir overnight. The reaction mixture was then diluted with DCM (200 mL) and was transferred into a separatory funnel. The organic layer was washed with 2 x 120 mL of 1 M HCl, 2 x 140 mL of a saturated sodium bicarbonate solution, and 1 x 120 mL of brine. The resulting organic solution was dried over Na₂SO₄, decanted, and the solvent was removed in vacuo by rotary evaporation to yield the pure Weinreb amide (7.91 g, 89%).

\(^1\)H NMR (CDCl₃, 500 MHz) δ ppm 1.30 (s, 9 H) 3.32 (s, 3 H) 3.54 (s, 3 H) 160
(s, 3 H) 7.38 (d, J=8.83 Hz, 2 H) 7.60 (d, J=8.20 Hz, 2 H) \(^{13}\text{C} \ \text{NMR} \) (CDCl\(_3\), 125 MHz) \(\delta\) ppm 31.32 (CH\(_3\)) 34.06 (CH\(_3\)) 34.97 (C) 61.13 (CH\(_3\)) 125.07 (CH) 128.25 (CH) 131.24 (C) 154.06 (C) 170.10 (C) \text{GC-MS (EI)} 221 ([M]\(^+\), .01%), 161 (100%), 146 (14%), 118 (14%), 115 (8%), 91 (10%), 77 (6%).

\[ \text{N-methoxy-N-methyl-3-nitrobenzamide} \]\(^5\) (161) (5.83 g, 69%) was prepared according to the representative procedure from 3-nitrobenzoyl chloride (7.423 g, 40 mmol) giving the pure Weinreb amide as an off-white solid. \(^1\text{H} \ \text{NMR} \) (CDCl\(_3\), 400 MHz) \(\delta\) ppm 3.41 (s, 3 H) 3.56 (s, 3 H) 7.61 (t, J=7.95 Hz, 1 H) 8.04 (d, J=7.58 Hz, 1 H) 8.33 (d, J=9.29 Hz, 1 H) 8.58 (s, 1 H) \(^{13}\text{C} \ \text{NMR} \) (CDCl\(_3\), 125 MHz) \(\delta\) ppm 33.48 (CH\(_3\)) 61.60 (CH\(_3\)) 123.75 (CH) 125.48 (CH) 129.46 (CH) 134.58 (CH) 135.75 (C) 148.00 (C) 167.39 (C) \text{GC-MS (EI)} 210 ([M]\(^+\), 2%), 150 (100%), 104 (39%), 92 (4%), 76 (33%), 75 (9%), 50 (11%), 43 (6%).

\[ N\text{-methoxy-N-methyl-3-nitrobenzamide} \]\(^6\) (162) (3.26 g, 67%) was prepared according to the representative procedure from 3-bromobenzoyl chloride (4.389 g, 20 mmol) giving the pure Weinreb amide as a colorless oil. \(^1\text{H} \ \text{NMR} \) (CDCl\(_3\), 500 MHz) \(\delta\) ppm 3.35 (s, 3 H) 3.55 (s, 3 H) 7.28 (t, J=7.88 Hz, 1 H) 7.59 (m apparent overlapping doublets, 2 H) 7.82 (s, 1 H) \(^{13}\text{C} \ \text{NMR} \) (CDCl\(_3\), 125 MHz) \(\delta\) ppm 33.71 (CH\(_3\)) 61.37 (CH\(_3\)) 122.17 (C) 126.97 (CH) 129.81 (CH) 131.38 (CH) 133.72 (CH) 136.14 (C) 168.33 (C) \text{GC-MS (EI)} 245 ([M]\(^{+2}\), 4%), 243
([M]$^+$, 4%), 185 (97%), 183 (100%), 157 (38%), 155 (39%) 76 (27%), 75 (22%), 74 (9%), 50 (14%).

$N_4$-dimethoxy-$N$-methylbenzamide$^5$ (163) (7.05 g, 90%) was prepared according to the representative procedure from 4-methoxybenzoyl chloride (6.824 g, 40 mmol) giving the pure Weinreb amide as a colorless oil. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ ppm 3.34 (s, 3 H) 3.55 (s, 3 H) 3.83 (s, 3 H) 6.89 (d, $J$=9.05 Hz, 2 H) 7.72 (d, $J$=9.05 Hz, 2 H) $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ ppm 34.14 (CH$_3$) 55.56 (CH$_3$) 61.13 (CH$_3$) 113.49 (CH) 126.27 (C) 130.79 (CH) 161.77 (C) 169.63 (C) GC-MS (EI) 195 ([M]$^+$, 1%), 135 (100%), 107 (8%), 92 (12%), 77 (15%), 64 (6%).

$N$-methoxy-$N$,2-dimethylbenzamide$^7$ (127) (4.42g, 75%) was prepared according to the representative procedure from 2-nitrobenzoyl chloride (10.0 g, 60 mmol) giving the pure Weinreb amide as a clear colorless oil. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ ppm 2.27 (s, 3 H) 3.23 (br. s., 3 H) 3.43 (br. s., 3 H) 7.09 - 7.16 (m, 2 H) 7.16 - 7.25 (m, 2 H) $^{13}$C NMR (CDCl$_3$, 125 MHz) $\delta$ ppm 19.04 (CH$_3$) 33.19 (broad, CH$_3$) 61.00 (CH$_3$) 125.38 (CH) 126.15 (CH) 129.16 (CH) 130.11 (CH) 134.75 (C) 135.25 (C) 170.81 (C) GC-MS (EI) 179 ([M]$^+$, 1 %), 119 (100%), 91 (60%), 65 (19%) 51 (3%)
**N-methoxy-N-methyl-2-nitrobenzamide** (129) (3.41 g, 85%) was prepared according to the representative procedure from 2-nitrobenzoyl chloride (3.45 g, 22.17 mmol) giving the pure Weinreb amide as a yellow solid. \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) ppm 3.26 (br. s., 3 H) 3.27 (br. s., 3 H) 7.46 (d, \(J=7.57\) Hz, 1 H) 7.53 (t, \(J=8.20\) Hz, 1 H) 7.66 (t, \(J=7.60\) Hz, 1 H) 8.06 (d, \(J=8.20\) Hz, 1 H) \(^1^3\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) ppm 33.41 (CH\(_3\)) 61.39 (CH\(_3\)) 123.93 (C) 128.50 (CH) 130.19 (CH) 131.56 (CH) 134.14 (CH) 145.84 (C) 168.85 (C) GC–MS (El) 210 ([M]+, 0.1%), 163 (1%), 150 (100%), 121 (17%), 104 (25%), 92 (10%), 78 (18%), 77 (14%), 76 (70%), 75 (15%), 74 (15%), 63 (10%), 51 (53%)  

**N,O-dimethoxy-N-methylbenzamide** (128) (6.27 g, 80%) was prepared according to the representative procedure from 2-methoxybenzoyl chloride (6.82 g, 40 mmol) giving the pure Weinreb amide as an off-yellow solid. \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) ppm 3.26 (br. s., 3 H) 3.36 - 3.71 (m, 3 H) 3.79 (s, 3 H) 6.88 (d, \(J=8.20\) Hz, 1 H) 6.92 (t, \(J=7.88\) Hz, 1 H) 7.22 (d, \(J=6.94\) Hz, 1 H) 7.30 (td, \(J=7.88, 1.70\) Hz, 1 H) \(^1^3\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) ppm 32.59 (CH\(_3\)) 55.82 (CH\(_3\)) 61.10 (CH\(_3\)) 111.24 (CH) 120.54 (CH) 125.37 (C) 127.74 (CH) 130.71 (CH) 155.89 (C) 169.66 (C) GC–MS (El) 195 ([M]+, 1%), 135 (100%), 120 (4%), 92 (18%), 77 (26%), 51 (4%).
**N-methoxy-3-(2-methoxyphenyl)-N-methylpropanamide (164)** (7.78 g, 87%) was prepared according to the representative procedure from 3-(2-methoxyphenyl)propanoyl chloride (7.946 g, 40 mmol) giving the pure Weinreb amide as a colorless oil. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ ppm 2.71 (t, $J$=7.25 Hz, 2 H) 2.95 (t, $J$=8.20 Hz, 2 H) 3.17 (s, 3 H) 3.61 (s, 3 H) 3.82 (s, 3 H) 6.84 (d, $J$=7.57 Hz, 1 H) 6.88 (t, $J$=7.88 Hz, 1 H) 7.14 - 7.23 (m, 2 H) $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ ppm 26.00 (CH$_2$) 32.18 (CH$_2$) 32.20 (CH$_3$) 55.30 (CH$_3$) 61.25 (CH$_3$) 110.33 (CH) 120.58 (CH) 127.57 (CH) 129.69 (CH) 130.22 (CH) 157.65 (C) 174.41 (C) GC-MS (EI) 223 ([M]$^+$, 11%), 163 (27%), 135 (17%), 121 (100%), 105 (7%), 91 (40%), 77 (11%), 65 (7%), 44 (7%). HRMS (ESI+), calcd for C$_{12}$H$_{17}$NO$_3$ [M+H]$^+$ 224.1287, found: 224.1278

**N-methoxy-N-methyl-3-(o-tolyl)propanamide (165)** (2.31 g, 68%) was prepared according to the representative procedure from 3-(o-tolyl)propanoyl chloride (3.00 g, 16.43 mmol) giving the pure Weinreb amide as a colorless oil. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ ppm 2.35 (s, 3 H) 2.70 (apparent triplet, $J$=8.10 Hz, 2 H) 2.96 (apparent triplet, $J$=8.00 Hz, 2 H) 3.20 (s, 3 H) 3.62 (s, 3 H) 7.06 - 7.22 (m, 4 H) $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ ppm 19.44 (CH$_3$) 28.32 (CH$_2$) 32.39 (CH$_3$) 32.73 (CH$_2$) 61.39 (CH$_3$) 126.30 (CH) 126.48 (CH) 128.96 (CH) 130.45 (CH) 136.20 (C) 139.62 (C) 173.98 (C) GC-MS (EI) 207 ([M]$^+$, 0.1%), 147 (6%), 119 (41%), 105 (100%), 91 (17%), 77 (14%), 61 (32%), 39 (3%). HRMS (ESI+), calcd for C$_{12}$H$_{17}$NO$_2$ [M+H]$^+$ 208.1338, found: 208.1313
**N-methoxy-3-(3-methoxyphenyl)-N-methylpropanamide**

(166) (3.11 g, 60%) was prepared according to the representative procedure from 3-(3-methoxyphenyl)propanoyl chloride (4.86 g, 23.31 mmol) giving the pure Weinreb amide as a colorless oil. **¹H NMR** (CDCl₃, 400 MHz) δ ppm 2.73 (apparent triplet, J=7.60 Hz, 2 H) 2.93 (apparent triplet, J=8.30 Hz, 2 H) 3.17 (s, 3 H) 3.60 (s, 3 H) 3.78 (s, 3 H) 6.74 (d, J=8.07 Hz, 1 H) 6.77 (s, 1 H) 6.81 (d, J=7.58 Hz, 1 H) 7.19 (t, J=7.82 Hz, 1 H) **¹³C NMR** (CDCl₃, 100 MHz) δ ppm 30.89 (CH₂) 32.36 (CH₃) 33.85 (CH₂) 55.30 (CH₃) 61.38 (CH₃) 111.57 (CH) 114.36 (CH) 120.94 (CH) 129.61 (CH) 143.14 (C) 159.86 (C) 173.84 (C) **GC-MS** (El) 223 ([M]⁺, 25%), 163 (44%), 135 (61%), 121 (100%), 105 (14%), 91 (32%), 77 (16%), 65 (10%).

**3-(4-fluorophenyl)-N-methoxy-N-methylpropanamide**

(167) (2.46 g, 66%) was prepared according to the representative procedure from 3-(4-fluorophenyl)propanoyl chloride (3.50 g, 18.75 mmol) giving the pure Weinreb amide as a colorless oil. **¹H NMR** (CDCl₃, 400 MHz) δ ppm 2.70 (apparent triplet, J=7.30 Hz, 2 H) 2.92 (apparent triplet, J=8.60 Hz, 2 H) 3.16 (s, 3 H) 3.59 (s, 3 H) 6.95 (t, J=8.68 Hz, 2 H) 7.17 (dd, J=8.31, 5.62 Hz, 2 H) **¹³C NMR** (CDCl₃, 100 MHz) δ ppm 30.02 (CH₂) 32.36 (CH₃) 33.98 (CH₂) 55.30 (CH₃) 61.41 (CH₃) 115.36 (d, J_C-C-F =20.54 Hz, CH) 130.06 (d, J_C-C-C-F =8.07 Hz, CH) 137.18 (d, J_C-C-C-C-F =3.67 Hz, C) 161.60 (d, J_C-F J=243.55 Hz, C-F) 173.66 (C) **¹⁹F NMR** (CDCl₃, 377 MHz) δ ppm -
119.41 - -119.31 (m, 160 F) -82.35 (s, 202 F) \textbf{GC-MS} (El) 211 ([M]^{+}, 14\%), 151 (8\%), 123 (36\%), 109 (100\%), 103 (14\%), 83 (9\%), 75 (6\%), 61 (18\%), 57 (3\%). \textbf{HRMS} (ESI+), calcd for C_{11}H_{14}FNO_2 [M+H]^+ 212.1087 found: 212.1099

\textbf{N-methoxy-3-(p-tolyl)-N-methylpropanamide} (168) (3.94 g, 62\%) was prepared according to the representative procedure from 3-(p-tolyl)propanoyl chloride (5.60 g, 30.7 mmol) giving the pure Weinreb amide as a colorless oil. \textbf{\textsuperscript{1}H NMR} (CDCl_3, 400 MHz) \(\delta\) ppm 2.32 (s, 3 H) 2.73 (\textit{apparent triplet}, \(J=7.60\) Hz, 2 H) 2.93 (\textit{apparent triplet}, \(J=8.10\) Hz, 2 H) 3.18 (s, 3 H) 3.61 (s, 3 H) 6.97 - 7.21 (m, 4 H) \textbf{\textsuperscript{13}C NMR} (CDCl_3, 100 MHz) \(\delta\) ppm 21.26 (CH_3) 30.51 (CH_2) 32.44 (CH_3) 34.20 (CH_2) 61.46 (CH_3) 128.56 (CH) 129.39 (CH) 135.82 (C) 138.51 (C) 174.08 (C) \textbf{GC-MS} (El) 207 ([M]^{+}, 15\%), 147 (11\%), 119 (29\%), 105 (100\%), 91 (16\%), 77 (12\%), 65 (6\%), 61 (9\%), 39 (3\%). \textbf{HRMS} (ESI+), calcd for C_{12}H_{17}NO_2 [M+H]^+ 208.1338, found: 208.1343

\textbf{N-methoxy-3-(4-methoxyphenyl)-N-methylpropanamide}^{10} (169) (5.11 g, 61\%) was prepared according to the representative procedure from 3-(4-methoxyphenyl)propanoyl chloride (7.45 g, 37.5 mmol) giving the pure Weinreb amide as a colorless oil. \textbf{\textsuperscript{1}H NMR} (CDCl_3, 400 MHz) \(\delta\) ppm 2.70 (\textit{apparent triplet}, \(J=7.80\) Hz, 2 H) 2.89 (\textit{apparent triplet}, \(J=8.10\) Hz, 2 H) 3.16 (s, 3 H) 3.59 (s, 3 H) 3.77 (s, 3 H) 6.82 (d, \(J=8.07\) Hz, 2 H) 7.14 (d, \(J=8.31\) Hz, 2 H) \textbf{\textsuperscript{13}C NMR} (CDCl_3, 100 MHz) \(\delta\) ppm 30.01 (CH_2) 32.38 (CH_3) 34.22 (CH_2) 55.45 (CH_3) 61.41 (CH_3)
N-methoxy-N-methyl-3-phenylpropanamide\textsuperscript{10} (170) (10.74 g, 93\%) was prepared according to the representative procedure from 3-phenylpropanoyl chloride (10.1172 g, 60 mmol) giving the pure Weinreb amide as a yellow oil. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \( \delta \) ppm 2.77 (t, \( J=7.60 \) Hz, 12 H) 2.99 (t, \( J=8.30 \) Hz, 2 H) 3.20 (s, 3 H) 3.61 (s, 3 H) 7.04 - 7.47 (m, 5 H) \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz) \( \delta \) ppm 30.50 (CH\textsubscript{2}) 31.92 (CH\textsubscript{3}) 33.56 (CH\textsubscript{2}) 60.93 (CH\textsubscript{3}) 125.91 (CH) 128.25 (2 x CH) 141.17 (C) 173.35 (C) \textbf{GC-MS} (EI) 193 ([M]\textsuperscript{+}, 24\%), 133 (20\%), 105 (100\%), 103 (16\%), 91 (95\%), 77 (24\%), 65 (12\%), 61 (18\%), 51 (11\%), 39 (5\%).

N-methoxy-N-methylnaphthalene-1-carboxamide\textsuperscript{5} (149) (8.17 g, 95\%) was prepared according to the representative procedure from naphthalene-1-carbonyl chloride (7.625 g, 40 mmol) giving the pure Weinreb amide as a white solid. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \( \delta \) ppm 2.81 - 3.78 (overlapping s br, 6 H) 7.44 - 7.57 (m, 4 H) 7.82 - 7.95 (m, 3 H) \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz) \( \delta \) ppm 33.06 (CH\textsubscript{3}) 61.06 (CH\textsubscript{3}) 124.13 (CH) 124.64 (CH) 124.74 (CH) 126.11 (CH) 126.71 (CH) 128.17 (CH) 129.39 (CH) 129.55 (C) 133.05 (C) 133.15 (C) 169.70 (C) \textbf{GC-MS} (EI) 215 ([M]\textsuperscript{+}, 3\%), 155 (100\%), 127 (84\%), 101 (5\%), 77 (9\%), 44 (8\%).
5-bromo-N-methoxy-N-methylthiophene-2-carboxamide (171) (4.77 g, 38% over two steps\(^1\)) was prepared according to the representative procedure from 5-bromothiophene-2-carboxylic acid (50 mmol) giving the pure Weinreb amide as a yellow oil. \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) ppm 3.25 (s, 3 H) 3.68 (s, 3 H) 6.99 (d, \(J=4.21\) Hz, 1 H) 7.63 (d, \(J=4.21\) Hz, 1 H) \(^13\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) ppm 32.86 (CH\(_3\)) 61.69 (CH\(_3\)) 120.55 (C) 129.73 (CH) 133.53 (C) 134.64 (CH) 160.98 (C) GC-MS (El) 251 ([M]+, 9%), 250 ([M]+, 1%), 191 (100%), 189 (98%), 119 (7%), 117 (7%), 82 (28%), 44 (5%). HRMS (ESI+), calcd for C\(_{17}\)H\(_9\)BrNO\(_2\)S [M + H]+ 249.9537, found: 249.9528

\(N,3,5\)-trimethoxy-\(N\)-methylbenzamide\(^{11}\) (172) (3.84 g, 69%) was prepared according to the representative procedure from 3,5-dimethoxybenzoyl chloride (5.016 g, 25 mmol) giving the pure Weinreb amide as a yellow oil. \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) ppm 3.28 (s, 1 H) 3.54 (s, 3 H) 3.75 (s, 3 H) 6.49 (s, 1 H) 6.74 (s, 2 H) \(^13\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) ppm 34.14 (CH\(_3\)) 55.60 (CH\(_3\)) 61.26 (CH\(_3\)) 102.87 (CH) 106.04 (CH) 136.16 (C) 160.52 (C) 169.73 (C) GC-MS (El) 225 ([M]+, 9%), 165 (100%), 137 (27%), 122 (24%), 107 (11%), 79 (6%), 77 (8%).

\(^1\) Note that in the case of this substrate the acid chloride was prepared \textit{in situ} in the reaction flask just prior to use.
N-methoxy-N-methyloctanamide\textsuperscript{12} (97) (7.22 g, 96\%) was prepared according to the representative procedure from octanoyl chloride (6.506 g, 40 mmol) giving the pure Weinreb amide as a colorless oil.  

\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz) \(\delta\) ppm 0.81 (t, \(J=6.90\) Hz, 3 H) 1.16 - 1.32 (m, 8 H) 1.56 (quin, \(J=7.25\) Hz, 2 H) 2.35 (t, \(J=7.25\) Hz, 2 H) 3.11 (s, 3 H) 3.62 (s, 3 H) \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz) \(\delta\) ppm 14.07 (CH\textsubscript{3}) 22.63 (CH\textsubscript{2}) 24.67 (CH\textsubscript{2}) 29.11 (CH\textsubscript{2}) 29.42 (CH\textsubscript{2}) 31.74 (CH\textsubscript{2}) 31.90 (CH\textsubscript{2}) 32.12 (CH\textsubscript{3}) 61.16 (CH\textsubscript{3}) 174.76 (C) GC-MS (EI) 187 ([M]+, 1\%), 127 (60\%), 109 (7\%), 103 (11\%), 61 (53\%), 57 (100\%), 55 (18\%), 43 (25\%), 41 (21\%).

2-ethyl-N-methoxy-N-methylhexanamide\textsuperscript{13} (132) (7.14 g, 95\%) was prepared according to the representative procedure from 2-ethylhexanoyl chloride (6.51 g, 40 mmol) giving the pure Weinreb amide as a colorless oil.  

\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 500 MHz) \(\delta\) ppm 0.83 (t, \(J=7.80\) Hz, 6 H) 1.13 - 1.33 (m, 4 H) 1.33 - 1.51 (m, 2 H) 1.53 - 1.66 (m, 2 H) 2.62 - 2.82 (broad s, 1 H) 3.16 (s, 3 H) 3.64 (s, 3 H) \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz) \(\delta\) ppm 12.29 (CH\textsubscript{3}) 14.15 (CH\textsubscript{3}) 23.05 (CH\textsubscript{2}) 25.88 (CH\textsubscript{2}) 30.09 (CH\textsubscript{2}) 32.37 (CH\textsubscript{2}) 42.58 (CH\textsubscript{3}) 47.23 (CH) 61.55 (CH\textsubscript{3}) 178.20 (C) GC-MS (EI) 187 ([M]+, 0.1\%), 127 (21\%), 99 (12\%), 57 (100\%), 55 (15\%), 43 (15\%), 40 (54\%).

2-cyclohexyl-N-methoxy-N-methylacetamide \textsuperscript{14} (173) (6.40 g, 86\%) was prepared according to the representative procedure from 2-cyclohexylethanoyl chloride (6.426 g, 40 mmol) giving the
Weinreb amide as a colorless oil. $^1$H NMR (CDCl$_3$, 500 MHz) δ ppm 0.87 (qd, $J$=12.19, 3.15 Hz, 2 H) 1.05 (apparent q, 1 H) 1.19 (apparent q, 2 H) 1.53 - 1.69 (m, 5 H) 1.69 - 1.81 (m, 1 H) 2.20 (d, $J$=6.94 Hz, 2 H) 3.08 (s, 3 H) 3.58 (s, 3 H) $^{13}$C NMR (CDCl$_3$, 100 MHz) δ ppm 26.18 (CH$_2$) 26.32 (CH$_2$) 32.05 (CH$_3$) 33.39 (CH$_2$) 34.52 (CH$_2$) 39.36 (CH) 61.18 (CH$_3$) 174.04 (C) GC-MS (EI) 185 ([M]$^+$, 2%), 125 (76%), 103 (22%), 97 (98%), 83 (22%), 73 (13%), 61 (35%), 55 (100%), 41 (24%), 39 (12%).

![N-methoxy-N-methyl-2-phenylacetamide](image)

$N$-methoxy-$N$-methyl-2-phenylacetamide$^{15}$ (130) (6.25 g, 87%) was prepared according to the representative procedure from 2-phenylacetyl chloride (6.184 g, 40 mmol) giving the pure Weinreb amide as a yellow oil. $^1$H NMR (CDCl$_3$, 500 MHz) δ ppm 3.14 (s, 3 H) 3.55 (s, 3 H) 3.73 (s, 2 H) 7.17 - 7.22 (m, 1 H) 7.24 - 7.31 (m, 4 H) $^{13}$C NMR (CDCl$_3$, 125 MHz) δ ppm 32.30 (CH$_3$) 39.46 (CH$_2$) 61.34 (CH$_3$) 126.84 (CH) 128.56 (CH) 129.38 (CH) 135.05 (C) 172.53 (C) GC-MS (EI) 179 ([M]$^+$, 3%), 119 (4%), 118 (32%), 91 (100%), 65 (14%), 61 (10%), 40 (28%).

![N-methoxy-N,2-dimethyl-2-phenylpropanamide](image)

$N$-methoxy-$N$,2-dimethyl-2-phenylpropanamide (131) (7.03 g, 88%) was prepared according to the representative procedure from 2-methyl-2-phenylpropanoyl chloride (7.08 g, 39 mmol) giving the pure Weinreb amide as a yellow oil. $^1$H NMR (CDCl$_3$, 500 MHz) δ ppm 1.54 (s, 6 H) 2.64 (s, 3 H) 3.09 (s, 3 H) 7.19 (apparent $tt$, $J$=7.20, 1.30 Hz, 1 H) 7.25 - 7.28 (m, 2 H) 7.29 - 7.34 (m, 2 H) $^{13}$C NMR (CDCl$_3$, 125 MHz) δ ppm 26.81 (CH$_3$) 33.60 (CH$_2$) 47.01 (C) 59.08 (CH$_3$) 125.72 (CH) 126.26 (CH) 128.46 (C) 146.28 (C) 177.91 (C) GC-MS (EI) 207 ([M]$^+$, 3%), 147
(8%), 119 (100%), 103 (8%), 91 (43%), 77 (10%), 40 (12%). **HRMS** (ESI+), calcd for C_{12}H_{17}NO_{2} [M+H]^+ 208.1338, found: 208.1334

**N-methoxy-N-methylcinnamamide**

16 (146) (3.46 g, 91%) was prepared according to the representative procedure from trans-cinnamoyl chloride (3.332 g, 20 mmol) giving the pure Weinreb amide as a white solid. **1H NMR** (CDCl$_3$, 400 MHz) δ ppm 3.31 (s, 3 H) 3.77 (s, 3 H) 7.04 (d, $J$=15.89 Hz, 1 H) 7.35 - 7.40 (m, 3 H) 7.57 (apparent d, $J$=7.58 Hz, 2 H) 7.74 (d, $J$=15.89 Hz, 1 H) **13C NMR** (CDCl$_3$, 100 MHz) δ ppm 32.79 (CH$_3$) 62.16 (CH$_3$) 116.06 (CH) 128.32 (CH) 129.07 (CH) 130.11 (CH) 135.45 (C) 143.73 (CH) 167.24 (C) **GC-MS** (EI) 191 ([M]$^+$, 5%), 131 (100%), 103 (47%), 77 (27%), 51 (10%), 44 (42%), 40 (4%).

**(E)-N-methoxy-3-(4-methoxyphenyl)-N-methylacrylamide**

17 (174) (1.90 g, 86%) was prepared according to the representative procedure from 4-methoxycinnamoyl chloride (1.966 g, 10 mmol) giving the Weinreb amide as a colorless oil. **1H NMR** (CDCl$_3$, 400 MHz) δ ppm 3.24 (s, 3 H) 3.69 (s, 3 H) 3.75 (s, 3 H) 6.80 - 6.89 (m, 3 H) 7.46 (d, $J$=8.80 Hz, 2 H) 7.64 (d, $J$=15.65 Hz, 1 H) **13C NMR** (CDCl$_3$, 100 MHz) δ ppm 32.55 (CH$_3$) 55.37 (CH$_3$) 61.85 (CH$_3$) 113.40 (CH) 114.28 (CH) 127.91 (C) 129.69 (CH) 143.09 (CH) 161.10 (C) 167.37 (C) **GC-MS** (EI) 221 ([M]$^+$, 3%), 161 (100%), 133 (20%), 118 (8%), 103 (4%), 89 (8%), 77 (6%).
(E)-3-(4-fluorophenyl)-N-methoxy-N-methylacrylamide \(^{18}\)

(175) (4.06 g, 65\%) was prepared according to the representative procedure from 4-fluorocinnamoyl chloride (5.538 g, 30 mmol) giving the pure Weinreb amide as a white solid. \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) ppm 3.27 (s, 3 H) 3.73 (s, 3 H) 6.93 (d, \(J=15.76\) Hz, 1 H) 7.03 (t, \(J=8.51\) Hz, 2 H) 7.47 - 7.56 (m, 2 H) 7.66 (d, \(J=15.76\) Hz, 1 H) \(^1^3\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) ppm 32.66 (CH\(_3\)) 62.05 (CH\(_3\)) 115.73 (CH) 116.04 (d, \(J_{C-C-F}=21.08\) Hz, CH) 130.03 (d, \(J_{C-C-C-F}=8.20\) Hz, CH) 131.58 (d, \(J_{C-C-C-F}=3.70\) Hz, C) 142.29 (CH) 163.79 (d, \(J_{C-F}=250.20\) Hz, C-F) 166.96 (C) \(^1^9\)F NMR (CDCl\(_3\), 377 MHz) -113.64 GC-MS (EI) 209 ([M]\(^+\), 2\%), 207 (9\%), 149 (100\%), 121 (35\%), 101 (30\%), 95 (5\%), 75 (10\%), 44 (23\%).

(E)-3-(furan-2-yl)-N-methoxy-N-methylprop-2-enamide \(^ {19} \)

(176) (1.15 g, 80\%) was prepared according to the representative procedure from (E)-3-(furan-2-yl)prop-2-enoyl chloride (1.266 g, 8 mmol) giving the pure Weinreb amide as a brown oil. \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) ppm 3.22 (s, 3 H) 3.69 (s, 3 H) 6.46 (apparent doublet, \(J=54.30\) Hz, 2 H) 6.86 (apparent d, \(J=15.41\) Hz, 1 H) 7.35 - 7.50 (m, 2 H) \(^1^3\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) ppm 32.61 (CH\(_3\)) 61.98 (CH\(_3\)) 112.32 (CH) 113.72 (CH) 114.39 (CH) 129.96 (CH) 144.26 (CH) 151.76 (C) 167.05 (C) GC-MS (EI) 181 ([M]\(^+\), 7\%), 121 (100\%), 93 (4\%), 65 (24\%), 63 (4\%), 39 (9\%).
(E)-N-methoxy-N-methyldec-2-enamide\(^{20}\) (133) (6.94 g, 82\%) was prepared according to the representative procedure from (E)-dec-2-enoxy chloride (7.54 g, 40 mmol) giving the pure Weinreb amide as a yellow oil. \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) ppm 0.87 (t, \(J=6.94\) Hz, 3 H) 1.21 - 1.32 (m, 8 H) 1.46 (quin, \(J=6.90\) Hz, 2 H) 2.22 (q, \(J=7.15\) Hz, 2 H) 3.23 (s, 3 H) 3.69 (s, 3 H) 6.38 (d, \(J=15.13\) Hz, 1 H) 6.97 (dt, \(J=15.76, 6.90\) Hz, 1 H) \(^{13}\)C NMR (CDCl\(_3\), 125 MHz) \(\delta\) ppm 14.24 (CH\(_3\)) 22.81 (CH\(_2\)) 28.50 (CH\(_2\)) 29.25 (CH\(_2\)) 29.33 (CH\(_2\)) 31.95 (CH\(_2\)) 32.56 (CH\(_3\)) 32.69 (CH\(_2\)) 61.81 (CH\(_3\)) 118.78 (CH) 148.27 (CH) 167.34 (C) GC-MS (EI) 213 ([M]\(^+\), 3\%), 153 (100\%), 83 (24\%), 81 (15\%), 69 (47\%), 55 (82\%), 43 (16\%), 41 (23\%).
General Procedure B: Weinreb Amides from Carboxylic Acid via CDI Activation:

\[
\begin{align*}
\text{N-methoxy-N,3,7-trimethyloct-6-enamide}^{21} \ (178)
\end{align*}
\]

To a 250 mL round bottom flask equipped with stir bar was added (±)-citronellic acid (4.01 g, 23.5 mmol, 1 equiv.) and DCM (80 mL ≈ 0.3M). To this stirred solution was added 1,1'-carbonyl diimidazole (4.19 g, 25.8 mmol, 1.1 equiv.) in one portion, turning the solution yellow and resulting in the evolution of CO\textsubscript{2} gas. The now yellow solution was allowed to stir for 45 minutes. At this time, N-O-dimethylhydroxylamine hydrochloride (2.52 g, 25.8 mmol, 1.1 equiv.) was added all at once and the reaction mixture was stirred overnight. The reaction mixture was then quenched with 30 mL of 1 M HCl and stirred vigorously for 10 minutes. After this time, the solution was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with DCM (2 X 100 mL). The combine organic layers were washed with 1 M HCl (50 mL), deionized water (50 mL) and a 1:1 mixture of brine and a saturated sodium bicarbonate solution (100 mL). The organic layer was dried with Na\textsubscript{2}SO\textsubscript{4} and the solvent was removed \textit{in vacuo} by rotary evaporation to afford the pure amide (3.98 g, 79.4%).
**1H NMR** (CDCl₃, 400 MHz) δ ppm 0.90 (d, J=6.60 Hz, 3 H) 1.09 - 1.23 (m, 1 H) 1.29 - 1.40 (m, 1 H) 1.55 (s, 3 H) 1.63 (s, 3 H) 1.86 - 2.05 (m, 3 H) 2.15 - 2.29 (m, 1 H) 2.29 - 2.44 (m, 1 H) 3.14 (s, 3 H) 3.63 (s, 3 H) 5.06 (t, J=6.97 Hz, 1 H) **13C NMR** (CDCl₃, 100 MHz) δ ppm 17.81 (CH₃) 19.99 (CH₂) 25.73 (CH₂) 25.88 (CH₃) 29.73 (CH) 32.27 (CH₃) 37.30 (CH₂) 39.29 (CH₂) 61.33 (CH₃) 124.70 (CH) 131.44 (C) 174.51 (C) **GC-MS** (El) 213 ([M]⁺, 1%), 153 (35%), 135 (6%), 130 (6%), 109 (62%), 83 (16%), 81 (18%), 73 (10%), 69 (100%), 67 (17%), 61 (62%), 55 (24%), 43 (14%), 41 (43%).

3-(furan-2-yl)-N-methoxy-N-methylpropanamide (179) (3.40 g, 79%) was prepared according to the representative procedure from 3-(furan-2-yl)propanoic acid²² (3.29 g, 23.5 mmol) giving the pure Weinreb amide as a clear light brown oil. **1H NMR** (CDCl₃, 400 MHz) δ ppm 2.77 (t, J=7.60 Hz, 2 H) 2.98 (t, J=8.30 Hz, 2 H) 3.18 (s, 3 H) 3.65 (s, 3 H) 6.03 (apparent dd, J=2.20, 1.00 Hz, 1 H) 6.27 (dd, J=3.18, 1.96 Hz, 1 H) 7.30 (dd, J=1.83, 0.86 Hz, 1 H) **13C NMR** (CDCl₃, 100 MHz) δ ppm 23.21 (C₇H₂) 30.55 (CH₂) 32.35 (CH₃) 61.38 (CH₃) 105.38 (CH) 110.36 (CH) 141.18 (CH) 155.03 (C) 173.35 (C) **GC-MS** (El) 183 ([M]⁺, 20%), 123 (13%), 94 (12%), 81 (100%), 67 (10%), 61 (19%), 53 (10%). **HRMS** (ESI+), calcd for C₉H₁₃NO₃ [M + H]⁺ 184.0973, found: 184.0975.

**N-methoxy-N-methylisonicotinamide**²³ (180) (5.23 g, 78%) was prepared according to the representative procedure from isonicotinic acid (4.924 g, 40 mmol) with the following modifications²⁴:
a) The reaction was stirred for 150 min; b) After the reaction was complete, the reaction was quenched with 225 mL of a \( \approx 1 \) M NaOH solution. The aqueous layer was extracted with DCM (2 X 200 mL) washed with brine (1 X 100 mL), dried with Na\(_2\)SO\(_4\) and the solvent was removed \textit{in vacuo} via rotary evaporation to give the pure Weinreb amide as a yellow oil.  

\(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) ppm 3.13 (s, 3 H) 3.32 (s, 3 H) 7.30 (d, \( J=4.65 \) Hz, 2 H) 8.48 (d, \( J=4.65 \) Hz, 2 H) \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) ppm 32.83 (CH\(_3\)) 61.11 (CH\(_3\)) 121.69 (CH) 141.48 (C) 149.63 (CH) 167.24 (C) GC-MS (El) 166 ([M]+, 5%), 135 (12%), 106 (100%), 78 (71%), 51 (31%), 50 (11%).

\[\text{5-bromo-N-methoxy-N-methylfuran-2-carboxamide} \quad 25 \quad (181)\]

(5.70 g, 70%) was prepared according to the representative procedure from 5-bromo-2-furanoic acid (6.69 g, 35 mmol) with the following modifications: a) The reaction was worked up six hours after addition of the \( N-O \)-dimethylhydroxylamine hydrochloride. The pure Weinreb amide was obtained as a clear yellow oil \(^1\)H NMR (CDCl\(_3\), 400 MHz) \( \delta \) ppm 3.17 (s, 3 H) 3.62 (s, 3 H) 6.32 (d, \( J=3.42 \) Hz, 1 H) 6.94 (d, \( J=3.67 \) Hz, 1 H) \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \( \delta \) ppm 32.98 (CH\(_3\)) 61.34 (CH\(_3\)) 113.54 (CH) 119.64 (CH) 126.31 (C) 147.57 (C) 157.75 (C) GC-MS (El) 235 ([M]+, \(^{81}\)Br 7%), 233([M]+, \(^{79}\)Br 7%), 175 (\(^{81}\)Br 98%), 173 (\(^{79}\)Br 100%), 119 (\(^{81}\)Br 24%), 117 (\(^{79}\)Br 24%) 66 (16%) 38 (19%).
General Procedure for Trifluoromethyl Ketone Synthesis:

General Procedure A: Small Scale Synthesis of TFMKs:

1-(4-(t-butyl)phenyl)-2,2,2-trifluoroethanone\textsuperscript{26} (96)

To a 50 mL round bottom flask equipped with a stir bar was added CsF (0.1512 g, 1.0 mmol, 0.2 equiv.). Toluene (2.5 mL) was added to the flask, followed by 4-(tert-butyl)-N-methoxy-N-methylbenzamide (1.11 g, 5.0 mmol, 1 equiv.) (94). The flask was sealed with a septum equipped with a inlet needle as an exit valve. The flask was cooled to 0 °C for 10 minutes. Once cooled, TMS-CF\textsubscript{3} (1.42 g, 10.0 mmol, 2 equiv.) was added to the reaction mixture drop wise over a period of \(\approx 10\) minutes. After completion of addition, the reaction mixture was allowed to stir at 0 °C for 10 minutes. The cooling bath was removed and the reaction mixture was allowed to stir at room temperature. **CAUTION:** Upon reaching room temperature, the reaction occurs and is mildly exothermic and gas is evolved. After completion of addition, the reaction mixture was allowed to stir at room temperature overnight. Reaction progress was monitored by \(^1\text{H}\)
NMR. Note: Over this time period the solution became dark yellow to dark brown in color.

Once complete conversion to the silylated intermediate was confirmed, water (5 mL) followed by TBAF (5 mL, 1 M in THF, 1 equiv.) were added to the reaction flask. The flask was equipped with a reflux condenser, open to air. The contents were then heated to 50 °C by either conventional or microwave methods, and allowed to stir at that temperature for 2 hours. Once cooled to room temperature, the reaction mixture were diluted with Et₂O (= 30 mL), and transferred to a separatory funnel. The organic layer was washed with deionized water (3 X 30 mL), followed with a brine solution (1 X 30 mL). The organic layer was dried with Na₂SO₄ and the solvent was removed in vacuo by rotary evaporation to yield crude trifluoromethyl ketone. Further purification was accomplished by flash chromatography (8:2 Hex:EtOAc) produced the pure CF₃ ketone as an orange solid (0.935 g, 81%).

^1H NMR (CDCl₃, 400 MHz) δ ppm 1.36 (s, 9 H) 7.56 (d, J=8.80 Hz, 2 H) 8.02 (d, J=8.07 Hz, 2 H) ^13C NMR (CDCl₃, 100 MHz) δ ppm  31.15 (CH₃) 35.73 (C) 117.10 (q, J_C-C-F = 289.80 Hz, CF₃) 126.42 (CH) 127.64 (C) 130.45 (q, J_C-C-C-C-F = 2.20 Hz, CH) 160.13 (C) 180.37 (q, J_C-C-F = 34.50 Hz, C) ^19F NMR (CDCl₃, 377 MHz) δ ppm -74.73. GC-MS (El) 230 ([M]^+, 15%), 215 (100%), 187 (32%), 161 (56%), 159 (11%), 146 (10%), 118 (24%), 115 (14%), 91 (12%), 77 (8%), 69 (3%), 57 (3%).

^2 Most, if not all, substrates converted near quantitatively after stirring for 24 h.
Synthesis of TFMK Procedure B (Large Scale):

1,1,1-trifluoro-4-phenylbutan-2-one\(^{27}\) (110)

To a 250 mL round bottom flask equipped with a stir bar was added CsF (0.820 g, 5.4 mmol, 0.2 equiv.). Toluene (54 mL, 0.5 M in the Weinreb amide) was added to the flask, followed by \(N\)-methoxy-\(N\)-methyl-3-phenylpropanamide (5.30 g, 27 mmol, 1 equiv.) (171). The flask was sealed with a septum equipped with a inlet needle as an exit valve. The flask was cooled to 0 °C for 10 minutes. TMS-CF\(_3\) (7.82 g, 55 mmol, 2 equiv.) was added to the reaction mixture drop wise over a period of \(\approx\) 10 minutes. After completion of addition, the reaction mixture was allowed to stir for 10 minutes. The cooling bath was removed and the reaction mixture was allowed to stir at room temperature. **CAUTION:** Upon reaching room temperature, the reaction occurs and is mildly exothermic and gas is evolved. After completion of addition, the reaction mixture was allowed to stir at room temperature overnight. Reaction progress was monitored by \(^1\)H NMR\(^3\). *Note:* Over this time period the solution became dark yellow to dark brown in color.

\(^3\) Most, if not all, substrates converted near quantitativelly after stirring for 24 h.
Once complete conversion to the silylated intermediate was confirmed, the toluene was removed in vacuo by rotary evaporation. Hexanes (20 mL), followed by Water (27 mL) followed by 1M solution of TBAF in THF (27 mL, 27 mmol, 1 equiv.) were added to the reaction flask. The flask was equipped with a reflux condenser, open to air. The reaction mixture was then heated to 50 °C in an oil bath and allowed to stir 2 hours. Once cooled to room temperature, the reaction mixture were diluted with Et₂O (≈ 120 mL), and transferred to a separatory funnel. The organic layer was washed with deionized water (3 X 120 mL), followed with a brine solution (1 X 120 mL). The organic layer was dried with Na₂SO₄ and the solvent was removed in vacuo by rotary evaporation to yield crude trifluoromethyl ketone. Further purification was accomplished Vacuum distillation (b.p. 77-80 °C @ 6 mmHg) afforded the pure CF₃ ketone as a clear colorless oil (4.16 g, 76%). 

**¹H NMR** (CDCl₃, 400 MHz) δ ppm 2.99 - 3.23 (m, 4 H) 7.28 - 7.38 (m, 3 H) 7.38 - 7.48 (m, 2 H) ¹³C NMR (CDCl₃, 100 MHz) δ ppm 28.49 (CH₂) 38.24 (CH₂) 115.83 (q, J_C-F = 292.00 Hz, CF₃) 126.89 (CH) 128.50 (CH) 128.94 (CH) 139.55 (C) 190.87 (q, J_C-C-F = 35.20 Hz, C) ¹⁹F NMR (CDCl₃, 377 MHz) δ ppm -82.01 GC-MS (El) 202 ([M]+, 38%), 133 (42%), 105 (37%), 103 (11%), 91 (100%), 77 (17%), 69 (6%), 65 (12%), 51 (11%), 39 (5%).

**N-(1-(4-(tert-butyl)phenyl)-2,2,2-trifluoro-1-(((trimethylsilyl)oxy)ethyl)-N,O-dimethylhydroxylamine (183)** (1.56 g, 86%) was prepared according to the representative procedure A from 4-(tert-butyl)-N-methoxy-N-methylbenzamide (1.11 g, 5 mmol) (94) with the
**following modifications:** prior to the cleavage step the contents were filtered and the toluene removed *in vacuo* to produce the intermediate as a brown oil. \(^1\)H NMR (CDCl\(_3\), 300 MHz) δ ppm 0.30 (s, 9 H) 1.34 (s, 9 H) 2.32 (s, 3 H) 3.60 (s, 3 H) 7.37 (d, J=8.48 Hz, 2 H) 7.55 (d, J=8.48 Hz, 2 H) \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) δ ppm 2.27 (CH\(_3\)) 31.61 (CH\(_3\)) 34.82 (C) 36.94 (q, J\(_{C-N-C-C-F}\) = 1.50 Hz, CH\(_3\)) 59.66 (CH\(_3\)) 93.49 (q, J\(_{C-C-F}\) = 29.30 Hz, C) 123.99 (q, J\(_{C-F}\) = 291.20 Hz, CF\(_3\)) 125.11 (CH) 127.54 (CH) 134.86 (C) 152.09 (C) \(^{19}\)F NMR (CDCl\(_3\), 377 MHz) δ ppm -76.60 GC-MS (EI) 303 ([M]\(^{60}\), 39%), 174 (5%), 161 (100%), 73 (23%). HRMS (ESI+), calcd for C\(_{17}\)H\(_{28}\)F\(_3\)NO\(_2\)Si [M- C\(_2\)H\(_6\)NO]+ 303.1392, found: 303.1409.

\[ \text{2,2,2-trifluoro-1-(3-nitrophenyl)ethanone}^{28} (101) \] (0.865 g, 78%) was prepared according to the representative procedure A from N-methoxy-N-methyl-3-nitrobenzamide (1.05 g, 5 mmol) (161). Flash chromatography on deactivated silica (8:2 hexanes/EtOAc, 10% NEt\(_3\)) afforded the pure CF\(_3\) ketone as a yellow solid. \(^1\)H NMR (CDCl\(_3\), 400 MHz) δ ppm 7.82 (t, J=8.07 Hz, 1 H) 8.40 (d, J=7.82 Hz, 1 H) 8.57 (dd, J=8.19, 0.86 Hz, 1 H) 8.88 (s, 1 H) \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) δ ppm 116.47 (q, J\(_{C-F}\) = 287.60 Hz, 6 CF\(_3\)) 125.11 (m, CH) 129.86 (CH) 130.90 (CH) 131.33 (C) 135.54 (CH) 148.85 (C) 179.09 (q, J\(_{C-C-F}\) = 35.90 Hz, C) \(^{19}\)F NMR (CDCl\(_3\), 377 MHz) δ ppm -74.89 GC-MS (EI) 150 (100%), 123 (10%), 104 (36%), 95 (10%), 76 (31%), 69 (5%), 50 (12%).
1-(3-bromophenyl)-2,2,2-trifluoroethanone\textsuperscript{29} (102) (0.908 g, 72%) was prepared according to the representative procedure A from 3-bromo-\textit{N}-methoxy-\textit{N}-methylbenzamide (1.220 g, 5 mmol) (162). Flash chromatography (8:2 Hex/EtOAc) afforded the pure \textit{CF}_3 ketone as a yellow oil. $^1$H NMR (CDCl\textsubscript{3}, 400 MHz) δ ppm 7.45 (t, $J$=7.95 Hz, 1 H) 7.85 (d, $J$=9.05 Hz, 1 H) 8.01 (s, 1 H) 8.20 (s, 1 H) $^{13}$C NMR (CDCl\textsubscript{3}, 100 MHz) δ ppm 116.65 (q, $J_{C-F}$ =291.20 Hz, CF\textsubscript{3}) 123.64 (C) 128.79 (CH) 130.88 (CH) 131.81 (C) 133.08 (CH) 138.66 (CH) 179.60 (q, $J_{C-C}$ 35.90 Hz, C) $^{19}$F NMR (CDCl\textsubscript{3}, 377 MHz) δ ppm -74.59 GC-MS (EI) 254 ([M]$^+$, 24%), 252 ([M]$^+$, 25%), 185 (97%), 183 (100%), 157 (61%), 155 (63%), 76 (37%), 75 (34%), 74 (20%), 69 (9%), 50 (26%).

2,2,2-trifluoro-1-(4-methoxyphenyl)ethanone\textsuperscript{30} (103) (0.90 g, 88%) was prepared according to the representative procedure A from \textit{N},4-dimethoxy-\textit{N}-methylbenzamide (0.976 g, 5 mmol) (163). Flash chromatography (8:2 Hex/ EtOAc) afforded the pure \textit{CF}_3 ketone as a yellow oil. $^1$H NMR (CDCl\textsubscript{3}, 400 MHz) δ ppm 3.89 (s, 3 H) 6.98 (dd, $J$=9.05, 2.45 Hz, 2 H) 8.02 (d, $J$=8.07 Hz, 2 H) $^{13}$C NMR (CDCl\textsubscript{3}, 100 MHz) δ ppm 55.84 (CH\textsubscript{3}) 114.68 (CH) 117.21 (q, $J_{C-C}$ =291.20 Hz, CF\textsubscript{3}) 122.98 (C) 132.95 (CH) 165.73 (C) 179.13 (q, $J_{C-C}$ = 34.50 Hz, C) $^{19}$F NMR (CDCl\textsubscript{3}, 377 MHz) δ ppm -73.82 GC-MS (EI) 204 ([M]$^+$, 21%), 135 (100%), 107 (13%), 92 (24%), 77 (29%), 69 (4%), 64 (11%).
1,1,1-trifluoro-4-(2-methoxyphenyl)butan-2-one (104) (3.46 g, 75%) was prepared according to the representative procedure B from N-methoxy-3-(2-methoxyphenyl)-N-methylpropanamide (4.425 g, 20 mmol) (164). Vacuum distillation (b.p. 56-57 °C @ 0.3 mmHg) afforded the pure CF₃ ketone as a clear colorless oil. ¹H NMR (CDCl₃, 400 MHz) δ ppm 2.74 - 3.22 (m, 4 H) 3.83 (s, 3 H) 6.85-6.91 (m, 2H) 7.15 (d, J=7.34 Hz, 1 H) 7.23 (t, J=7.30 Hz, 1 H) ¹³C NMR (CDCl₃, 100 MHz) δ ppm 24.27 (CH₂) 36.75 (CH₂) 55.29 (CH₃) 110.53 (CH) 115.88 (q, J_C-F = 292.00 Hz, CF₃) 120.82 (CH) 127.79 (C) 128.33 (CH) 130.37 (CH) 157.68 (C) 191.42 (q, J_C-C-F =35.20 Hz, C) ¹⁹F NMR (CDCl₃, 377 MHz) δ ppm -82.11 GC-MS (EI) 232 ([M⁺, 51]), 163 (9%), 121 (100%), 108 (12%), 91 (100%), 77 (13%), 69 (4%), 65 (13%), 51 (7%). HRMS (ESI+), calcd for C₁₁H₁₁F₃O₂ [M+H]⁺ 233.0789, found: 233.0777

1,1,1-trifluoro-4-(o-tolyl)butan-2-one (105) (1.51 g, 66%) was prepared according to the representative procedure B from N-methoxy-3-(o-tolyl)-N-methylpropanamide (2.2 g, 10.62 mmol) (165) giving the pure Weinreb amide as a colorless oil. Vacuum distillation (b.p. 74-76 °C @ 2.5 mmHg) afforded the pure CF₃ ketone as a clear colorless oil. ¹H NMR (CDCl₃, 500 MHz) δ ppm 2.36 (s, 3 H) 2.83 - 3.14 (m, 4 H) 7.14 - 7.23 (m, 4 H) ¹³C NMR (CDCl₃, 125 MHz) δ ppm 19.45 (CH₃) 25.97 (CH₂) 37.06 (CH₂) 115.85 (q, J_C-F =292.30 Hz, CF₃) 126.62 (CH) 127.12 (CH) 128.76 (CH) 130.80 (CH) 136.15 (C) 137.62 (C) 191.02 (q, J_C-C-F =34.80 Hz, C) ¹⁹F NMR (CDCl₃, 377 MHz) δ ppm -82.24 GC-MS (EI) 216 ([M⁺, 30]),
147 (19%), 129 (17%), 119 (13%), 105 (100%), 91 (21%), 77 (17%), 69 (8%), 65 (8%).

HRMS (ESI+), calcd for C₁₁H₁₁F₃O [M + H – H₂O]⁺ 199.0735, found:199.0730

1,1,1-trifluoro-4-(3-methoxyphenyl)butan-2-one (106) (6.07 g, 81%) was prepared according to the representative procedure B from N-methoxy-3-(3-methoxyphenyl)-N-methylpropanamide (7.20 g, 32.24 mmol) (166). Vacuum distillation (b.p. 56-59 °C @ 0.1 mmHg) afforded the pure CF₃ ketone as a clear colorless oil. 

1H NMR (CDCl₃, 500 MHz) 3.00 (apparent triplet, J=6.50 Hz, 2 H) 3.08 (apparent triplet, J=6.50 Hz, 2 H) 3.83 (s, 3 H) 6.76 - 6.84 (m, 3 H) 7.23 - 7.30 (m, 1 H) 13C NMR (CDCl₃, 125 MHz) δ ppm 28.59 (CH₂) 38.26 (CH₂) 55.44 (CH₃) 112.18 (CH) 115.82 (q, J_C-F = 289.90 Hz, CF₃) 114.43 (CH) 120.80 (CH) 130.02 (CH) 141.12 (C) 160.15 (C) 190.89 (q, J_C-C-F =33.90 Hz, C) 19F NMR (CDCl₃, 377 MHz) δ ppm -82.33 GC-MS (EI) 232 ([M]+, 78 %), 163 (14%), 135 (88%), 121 (100%), 105 (15%), 91 (56%), 77 (21%), 69 (10%). HRMS (ESI+), calcd for C₁₁H₁₁F₃O₂ [M + H]+ 233.0789, found: 233.0798

1,1,1-trifluoro-4-(4-fluorophenyl)butan-2-one (107) (1.46 g, 61%) was prepared according to the representative procedure B from N-methoxy-3-(4-fluorophenyl)-N-methylpropanamide (2.30 g, 10.89 mmol) (167). Vacuum distillation (b.p. 68-70 °C @ 3.0 mmHg) afforded the pure CF₃ ketone as a clear colorless oil. 

1H NMR (CDCl₃, 400 MHz) δ ppm 2.97 (t, J=6.40 Hz, 2 H) 3.03 (t, J=6.10 Hz, 2 H) 6.99 (t, J=8.56 Hz, 2 H) 7.17 (dd, J=8.19, 5.50 Hz, 2 H) 13C NMR
(CDCl₃, 100 MHz) δ ppm 27.78 (CH₂) 38.37 (CH₂) 115.77 (q, J_C-F = 291.20 Hz, CF₃)
115.78 (d, J_C-C-F = 21.27 Hz, CH) 130.05 (d, J_C-C-C-F = 7.34 Hz, CH) 135.18 (d, J_C-C-C-C-F = 2.93 Hz, C)
161.96 (d, J_C-F = 245.02 Hz, C-F) 190.78 (J_C-C-F, J = 35.90 Hz, C) 19F NMR
(CDCl₃, 377 MHz) δ ppm -119.41 -119.31 (m, 1 F) -82.35 (s, 3 F)
GC-MS (EI) 220 ([M]⁺, 23%), 151 (28%), 123 (10%), 109 (100%), 96 (9%), 83 (10%), 69 (8%), 63 (3%).
HRMS (ESI+), calcd for C₁₀H₈F₄O [M + H - H₂O]⁺ 203.0484, found: 203.0489

1,1,1-trifluoro-4-(p-tolyl)butan-2-one (108) (3.97 g, 78%) was prepared according to the representative procedure B from N-methoxy-3-(p-tolyl)-N-methylpropanamide (6.70 g, 47.1 mmol) (168). Vacuum distillation (b.p. 68-71 °C @ 1.2 mmHg) afforded the pure CF₃ ketone as a clear colorless oil. ¹H NMR (CDCl₃, 400 MHz) δ ppm 22.34 (s, 3 H) 2.97 (apparent triplet, J = 6.80 Hz, 2 H) 3.04 (apparent triplet, J = 6.60 Hz, 2 H) 7.08 - 7.16 (m, 4 H) ¹³C NMR (CDCl₃, 100 MHz) δ ppm 21.18 (CH₃) 28.13 (CH₂) 38.44 (CH₂) 115.83 (q, J_C-F = 292.00 Hz, CF₃) 128.40 (CH) 129.64 (CH) 136.46 (C) 136.50 (C) 190.97 (q, J_C-C-F = 35.20 Hz, CF₃) ¹⁹F NMR (CDCl₃, 377 MHz) δ ppm -82.24 GC-MS (EI) 216 ([M]⁺, 35%), 147 (22%), 119 (9%), 105 (100%), 91 (16%), 77 (14%), 69 (7%), 65 (6%).

1,1,1-trifluoro-4-(4-methoxyphenyl)butan-2-one (109) (9.28 g, 73%) was prepared according to the representative procedure B from N-methoxy-3-(4-methoxyphenyl)-N-methylpropanamide (12.27 g,
54.96 mmol) (169). Vacuum distillation (b.p. 68-71 °C @ 0.2 mmHg) afforded the pure CF₃ ketone as a clear colorless oil. **¹H NMR** (CDCl₃, 500 MHz) δ ppm 2.94 (apparent triplet, J=6.80 Hz, 2 H) 3.02 (apparent triplet, J=6.60 Hz, 2 H) 3.79 (s, 3 H) 6.85 (d, J=8.56 Hz, 2 H) 7.12 (d, J=8.56 Hz, 2 H) **¹³C NMR** (CDCl₃, 100 MHz) δ ppm 27.73 (CH₂) 38.61 (CH₂) 55.49 (CH₃) 115.77 (q, J_C-F =292.00 Hz, CF₃) 114.36 (CH) 129.51 (CH) 131.53 (C) 158.62 (C) 191.00 (q, J_C-C-F =35.90 Hz, C) **¹⁹F NMR** (CDCl₃, 377 MHz) δ ppm -82.34 δ ppm **GC-MS** (El) 232 ([M]⁺, 19%), 121(100%), 91 (13%), 77 (10%), 69 (4%), 65 (5%).

1,1,1-trifluoro-4-(furan-2-yl)butan-2-one (111) (1.01 g, 52%) was according to the representative procedure B from 3-(furan-2-yl)-N-methoxy-N-methylpropanamide (1.86 g, 0.01015) (179) with the following modification: Flash chromatography (Gradient Hex to 8:2 Hex:EtOAc) afforded the pure CF₃ ketone as a clear light brown oil. **¹H NMR** (CDCl₃) δ ppm 3.03 (apparent t, J=6.90 Hz, 2 H) 3.09 (apparent t, J=6.30 Hz, 2 H) 6.05 (d, J=2.52 Hz, 11 H) 6.29 (t, J=2.50 Hz, 12 H) 7.31 (d, J=1.26 Hz, 11 H) **¹³C NMR** (CDCl₃) δ ppm 21.17 (CH₂) 35.11 (CH₂) 106.17 (CH) 110.58 (CH) 115.81 (q, J_C-F =290.50 Hz, CF₃) 141.83 (CH) 152.90 (C) 190.50 (q, J_C-C-F =35.90 Hz, C) **¹⁹F NMR** (CDCl₃, 377 MHz) δ ppm -82.21 **GC-MS** (El) 192 ([M]⁺, 29%), 123 (24%), 95 (8%), 81 (100%), 69 (10%), 53 (21%), 39 (10%). **HRMS** (ESI+), calcd for C₈H₇F₃O₂ [M+H]⁺193.0476, found: 193.0486
2,2,2-trifluoro-1-(naphthalen-1-yl)ethanone\textsuperscript{32} (112) (0.941 g, 84\%) was prepared according to the representative procedure A from N-methoxy-N-methylnaphthalene-1-carboxamide (1.076 g, 5 mmol) (149). Flash chromatography (8:2 hexanes/CH\textsubscript{2}Cl\textsubscript{2}) produced the pure CF\textsubscript{3} ketone as a brown solid. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) $\delta$ ppm 7.55 (t, $J$=7.83 Hz, 1 H) 7.60 (t, $J$=7.60 Hz, 1 H) 7.70 (t, $J$=8.30 Hz, 1 H) 7.91 (d, $J$=8.31 Hz, 1 H) 8.13 (d, $J$=8.07 Hz, 1 H) 8.21 (d, $J$=7.58 Hz, 1 H) 8.87 (s, 1 H) \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz) $\delta$ ppm 116.94 (q, $J_{C-F}$ = 293.40 Hz, CF\textsubscript{3}) 124.38 (CH) 125.44 (CH) 126.54 (C) 127.38 (CH) 129.25 (CH) 129.74 (CH) 131.44 (C) 131.95 (q, $J_{C-C-C-F}$ = 3.67 Hz,) 134.21 (C) 136.45 (CH) 182.54 (q, $J_{C-C-F}$ = 34.50 Hz, C) \textsuperscript{19}F NMR (CDCl\textsubscript{3}, 377 MHz) $\delta$ ppm -73.01 GC-MS (El) 224 ([M]\textsuperscript{+}, 31\%), 155 (87\%), 127 (100\%), 101 (7\%), 77 (11\%), 69 (3\%), 63 (10\%).

1-(5-bromothiophen-2-yl)-2,2,2-trifluoroethanone\textsuperscript{33} (113) (0.785 g, 63\%) was prepared according to the representative procedure A from 5-bromo-N-methoxy-N-methylthiophene-2-carboxamide (1.251 g, 5 mmol) (171). Flash chromatography (100 % Hex) afforded the pure CF\textsubscript{3} ketone as a yellow oil. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) $\delta$ ppm 7.21 (d, $J$=4.16 Hz, 1 H) 7.69 (m, 1 H) \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz) $\delta$ ppm 116.42 (q, $J_{C-F}$ = 292.00 Hz, CF\textsubscript{3}) 128.21 (C) 132.69 (CH) 137.10 (q, $J_{C-C-C-F}$ =2.90 Hz, CH) 138.00 (C) 172.76 (q, $J_{C-F}$ =36.70 Hz, C) \textsuperscript{19}F NMR (CDCl\textsubscript{3}, 377 MHz) $\delta$ ppm -75.33 GC-MS (El) 260 ([M]\textsuperscript{+}, 31\%), 258 ([M]\textsuperscript{-1}, 30\%), 191 (100\%), 189 (99\%), 163 (11\%), 161 (11\%), 119 (11\%), 117 (11\%), 82 (47\%), 69 (14\%), 57 (10\%).
2,2, 2-trifluoro-1-(pyridin-4-yl)ethane-1,1-diol\textsuperscript{34} (114) (0.865 g, 80\%) was prepared according to the representative procedure A from N-methoxy-N-methylisonicotinamide (0.831 g, 5 mmol) (180) \textit{with the following modifications to the cleavage step}: Prior to the addition of TBAF/H\textsubscript{2}O, the reaction mixture was cooled to 0 °C. At this time 5 mL of deionized H\textsubscript{2}O was added to the flask followed by drop wise addition of 20 mL of a 0.25M solution of TBAF \textbf{CAUTION}: The first few drops induce a violent reaction and evolved gas therefore slow addition over 10 minutes is recommended. The remained of the cleavage and subsequent workup was carried out as detailed in Procedure A. This afforded the pure CF\textsubscript{3} ketone in its hydrated form as a tan solid. \textbf{\textsuperscript{1}H NMR} (Acetone-\textit{d\textsubscript{6}}, 400 MHz) δ ppm 7.09 (br. s., 2 H) 7.66 (d, \textit{J}=4.65 Hz, 2 H) 8.64 (d, \textit{J}=4.65 Hz, 2 H) \textbf{\textsuperscript{13}C NMR} (Acetone-\textit{d\textsubscript{6}}, 100 MHz) δ ppm 93.34 (q, \textit{J}_{C-C-F}=32.30 Hz, C) 124.11 (q, \textit{J}_{C-F}=287.60 Hz, CF\textsubscript{3}) 123.00 (CH) 147.66 (C) 150.40 (CH) \textbf{\textsuperscript{19}F NMR} (Acetone-\textit{d\textsubscript{6}}, 377 MHz) δ ppm - 84.13 \textbf{GC-MS} (EI) 175 ([M]\textsuperscript{+}, 38\%), 106 (95\%), 78 (100\%), 69 (12\%), 59 (12\%), 51 (52\%), 50 (20\%), 44 (28\%).

1-(3,5-dimethoxyphenyl)-2,2,2-trifluoroethanone (115) (1.16 g, 99\%) was prepared according to the representative procedure A from N,3,5-trimethoxy-N-methylbenzamide (1.113 g, 5 mmol) (172) giving the pure CF\textsubscript{3} ketone as a light brown oil. No further purification was required. \textbf{\textsuperscript{1}H NMR} (CDCl\textsubscript{3}, 400 MHz) δ ppm 3.82 (s, 6 H) 6.75 (s, 1 H) 7.15 (s, 2 H) \textbf{\textsuperscript{13}C NMR} (CDCl\textsubscript{3}, 100 MHz) δ ppm 55.83 (CH\textsubscript{3}) 107.91 (CH) 108.16 (CH) 116.86 (q, \textit{J}_{C-F}=291.20 Hz, CF\textsubscript{3})
131.66 (C) 161.31 (C) 180.46 (q, J_{C-C-F} = 35.20 \text{ Hz}, C) ^{19}\text{F NMR} (\text{CDCl}_3, 377 \text{ MHz}) \delta ppm -73.91 \text{ GC-MS (EI)} 234 ([M]^+, 69%), 165 (100%), 137 (35%), 122 (49%), 107 (20%), 79 (11%), 77 (16%), 69 (11%), 63 (16%). \text{HRMS (ESI+)} calcd for C_{10}H_{9}F_{3}O_{3} [M+H]^+ \text{235.0582, found: 235.0582}

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=2cm]{116}};
\end{tikzpicture}
\end{center}

\text{1,1,1-trifluorononan-2-one}^{35} \text{ (116)} \text{ (1.84 g, 59%)} \text{ was prepared according to the representative procedure B from N-methoxy-N-methyloctanamide (3.00 g, 16 mmol) (97). Vacuum distillation (b.p. 67-70 °C @ 12 mmHg) afforded the pure CF}_3 \text{ ketone as a pale yellow oil.} \ ^{1}\text{H NMR (CDCl}_3, 400 \text{ MHz}) \delta \text{ ppm 0.87 (t, } J=6.60 \text{ Hz, 3 H}) 1.22 - 1.33 \text{ (m, 8 H}) 1.66 \text{ (quin, } J=6.97 \text{ Hz, 2 H}) 2.69 \text{ (t, } J=7.21 \text{ Hz, 2 H}) \text{^{13}\text{C NMR (CDCl}_3, 100 \text{ MHz}) \delta \text{ ppm 14.22 (CH}_3\text{) 22.68 (CH}_2\text{) 22.83 (CH}_2\text{) 29.00 (CH}_2\text{) 29.15 (CH}_2\text{) 31.85 (CH}_2\text{) 36.62 (CH}_2\text{) 115.92 (q, } J_{C-F} = 292.00 \text{ Hz, CF}_3\text{) 191.88 (q, } J_{C-C-F} = 33.70 \text{ Hz, C}) ^{19}\text{F NMR (CDCl}_3, 377 \text{ MHz}) \delta \text{ ppm -82.51 \text{ GC-MS (EI)} 127 (92%), 109 (7%), 84 (17%), 69 (41%), 57 (100%), 55 (43%), 43 (49%), 41 (50%), 39 (15%).}

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\includegraphics[width=2cm]{117}};
\end{tikzpicture}
\end{center}

\text{3-cyclohexyl-1,1,1-trifluoropropan-2-one}^{35} \text{ (117)} \text{ (1.82 g, 61%)} \text{ was prepared according to the representative procedure B from 2-cyclohexyl-N-methoxy-N-methylacetamide (3.000 g, 16 mmol) (173). Vacuum distillation (b.p. 55-57 °C @ 7 mmHg) afforded the pure CF}_3 \text{ ketone as a pale yellow oil.} \ ^{1}\text{H NMR (CDCl}_3, 400 \text{ MHz}) \delta \text{ ppm 0.98 (apparent q, } J=10.80 \text{ Hz, 2 H}) 1.15 \text{ (apparent q, } J=12.00 \text{ Hz, 1 H}) 1.29 \text{ (apparent q, } J=12.00 \text{ Hz, 2 H}) 1.61 - 1.76 \text{ (m, 5 H}) 1.86-1.99 \text{ (m, 1 H}) 2.56
(d, J=6.85 Hz, 2 H) $^{13}$C NMR (CDCl$_3$, 100 MHz) δ ppm 26.16 (CH$_2$) 26.26 (CH$_2$) 33.13 (CH$_2$) 33.16 (CH) 44.04 (CH$_2$) 115.82 (q, J$_{C-F}$ = 292.70 Hz, CF$_3$) 191.32 (q, J$_{C-F}$ = 34.50 Hz, C) $^{19}$F NMR (CDCl$_3$, 377 MHz) δ ppm -82.51 GC-MS (EI) 194 ([M]+, 0.1%), 125 (73%), 97 (72%), 82 (87%), 69 (24%), 67 (51%), 55 (100%), 41 (37%), 39 (20%).

1,1,1-trifluoro-4,8-dimethylnon-7-en-2-one$^{36}$ (118) (0.538 g, 48%) was prepared according to the representative procedure A from N-methoxy-N,3,7-trimethyloct-6-enamide (1.067 g, 5 mmol) (178) $^1$H NMR (CDCl$_3$, 500 MHz) δ ppm 0.96 (d, J=6.94 Hz, 3 H) 1.22 - 1.42 (m, 2 H) 1.60 (s, 3 H) 1.69 (d, J=1.26 Hz, 3 H) 1.91 - 2.07 (m, 2 H) 2.12 (sxt, J=6.30 Hz, 1 H) 2.48 - 2.58 (m, 1 H) 2.70 (dd, J=17.97, 5.36 Hz, 1 H) 5.07 (t, J=7.40 Hz, 1 H) $^{13}$C NMR (CDCl$_3$, 100 MHz) δ ppm 17.81 (CH$_3$) 19.68 (CH$_3$) 25.61 (CH$_2$) 25.88 (CH$_3$) 28.29 (CH) 36.86 (CH$_2$) 43.72 (CH$_2$) 115.83 (q, J$_{C-F}$=291.00 Hz, CF$_3$) 124.06 (CH) 132.24 (C) 191.43 (q, J$_{C-C-F}$ = 34.50 Hz, C) $^{19}$F NMR (CDCl$_3$, 377 MHz) δ ppm -82.59 GC-MS (EI) 222 ([M]+, 20%), 153 (7%), 109 (26%), 95 (26%), 83 (12%), 69 (100%), 67 (12%), 55 (35%), 43 (7%), 41 (53%), 39 (10%).

1-(5-bromofuran-2-yl)-2,2,2-trifluoroethanone$^{37}$ (119) (2.75 g, 66%) was prepared according to the representative procedure B from 5-bromo-N-methoxy-N-methylfuran-2-carboxamide (4.00 g, 17.09 mmol) (181). Vacuum distillation (b.p. 73-75 °C @ 8 mmHg) afforded the pure CF$_3$ ketone as a bright yellow oil. $^1$H NMR (CDCl$_3$, 500 MHz) δ ppm 6.64 (d, J=3.78 Hz, 1 H) 7.41 - 7.45 (m, 1 H) $^{13}$C
NMR (CDCl₃, 125 MHz) δ ppm 116.28 (q, Jₔ-F = 289.10 Hz, 3 C) 115.75 (CH) 126.29 (CH) 134.26 (C) 148.86 (C) 167.47 (q, Jₔ-C ≈ 38.10 Hz, 4 C) ²⁹F NMR (CDCl₃, 377 MHz) δ ppm -76.54 GC-MS (EI) 245 ([M]+, 81Br 7%), 243([M]+, ⁷⁹Br 7%), 175 (⁸¹Br 97%), 173 (⁷⁹Br 100%), 147 (⁸¹Br 6%), 147 (⁷⁹Br 6%) 119 (⁸¹Br 35%), 117 (⁷⁹Br 36%) 94 (8%) 69 (33%) 66 (19%) 38 (30%)

(E)-1,1,1-trifluoro-4-phenylbut-3-en-2-one (120) was prepared according to the representative procedure A from N-methoxy-N-methylcinnamide (0.956 g, 5 mmol) (146) with the following modification: The cleavage was conducted at room temperature rather than heating at 50 °C. Flash chromatography (8:2 Hex/EtOAc) afforded the pure CF₃ ketone as a yellow oil. ¹H NMR (CDCl₃, 400 MHz) δ ppm 7.03 (d, J=15.89 Hz, 1 H) 7.42 - 7.54 (m, 3 H) 7.65 (d, J=7.58 Hz, 2 H) 7.98 (d, J=15.89 Hz, 1 H) ¹³C NMR (CDCl₃, 100 MHz) δ ppm 116.69 (q, Jₔ-C = 291.20 Hz, CF₃) 116.89 (CH) 129.51 (2 X CH) 132.60 (CH) 133.59 (C) 150.44 (CH) 180.28 (q, Jₔ-C = 35.20 Hz, C) ²⁹F NMR δ ppm (CDCl₃, 377 MHz) -80.73 GC-MS (EI) 200 ([M]+, 50%), 131 (100%), 103 (85%), 77 (34%), 69 (6%), 51 (24%).

(E)-1,1,1-trifluoro-4-(4-methoxyphenyl)but-3-en-2-one (121) (0.535 g, 46%) was prepared according to the representative procedure A from (E)-N-methoxy-3-(4-methoxyphenyl)-N-methylacrylamide (1.106 g, 5 mmol) (174) with the following modification: The cleavage was conducted at room temperature rather than heating at 50 °C. Flash chromatography (8:2 Hex/EtOAc) afforded the pure CF₃ ketone as a yellow oil. ¹H NMR (CDCl₃, 400 MHz) δ ppm 7.03 (d, J=15.89 Hz, 1 H) 7.42 - 7.54 (m, 3 H) 7.65 (d, J=7.58 Hz, 2 H) 7.98 (d, J=15.89 Hz, 1 H) ¹³C NMR (CDCl₃, 100 MHz) δ ppm 116.69 (q, Jₔ-C = 291.20 Hz, CF₃) 116.89 (CH) 129.51 (2 X CH) 132.60 (CH) 133.59 (C) 150.44 (CH) 180.28 (q, Jₔ-C = 35.20 Hz, C) ²⁹F NMR δ ppm (CDCl₃, 377 MHz) -80.73 GC-MS (EI) 200 ([M]+, 50%), 131 (100%), 103 (85%), 77 (34%), 69 (6%), 51 (24%).

⁴ Heating leads to decreased yield of the desired α,β-unsaturated CF₃ ketone and an increase in the undesired 1,4-addition product.
was conducted at room temperature\textsuperscript{4} rather than heating at 50 °C. Flash chromatography (8:2 Hex/EtOAc) afforded pure CF\textsubscript{3} ketone as a yellow solid. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) δ ppm 3.87 (s, 3 H) 6.88 (d, \textit{J}=15.89 Hz, 1 H) 6.95 (d, \textit{J}=8.80 Hz, 2 H) 7.60 (d, \textit{J}=8.07 Hz, 2 H) 7.93 (d, \textit{J}=15.89 Hz, 1 H) \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz) δ ppm 55.77 (CH\textsubscript{3}) 114.28 (CH) 115.02 (CH) 116.84 (q, \textit{J}_{C-F}=291.02 Hz, CF\textsubscript{3}) 126.43 (C) 131.66 (CH) 150.23 (CH) 163.48 (C) 180.15 (q, \textit{J}_{C-C-F}=32.30 Hz, C) \textsuperscript{19}F NMR (CDCl\textsubscript{3}, 377 MHz) δ ppm -80.58 GC-MS (EI) 230 ([M]\textsuperscript{+}, 37%), 161 (100%), 133 (34%), 118 (16%), 89 (16%), 69 (4%), 63 (10%).

(E)-1,1,1-trifluoro-4-(4-fluorophenyl)but-3-en-2-one 40 (122) (0.450 g, 41%) was prepared according to the representative procedure A from (E)-3-(4-fluorophenyl)-N-methoxy-N-methylacrylamide (1.046 g, 5 mmol) (175) with the following modification: The cleavage was conducted at room temperature rather than heating at 50 °C. Flash chromatography (9:1 Hex/EtOAc) afforded the pure CF\textsubscript{3} ketone as a yellow solid. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) δ ppm 6.95 (d, \textit{J}=15.89 Hz, 1 H) 7.15 (t, \textit{J}=8.44 Hz, 2 H) 7.66 (dd, \textit{J}=8.56, 5.62 Hz, 2 H) 7.93 (d, \textit{J}=15.89 Hz, 1 H) \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 125 MHz) δ ppm 116.65 (q, \textit{J}_{C-F}=289.80 Hz, CF\textsubscript{3}) 116.62 (CH) 116.84 (d, \textit{J}_{C-C-F}=22.01 Hz, CH) 129.96 (d, \textit{J}_{C-C-C-C-F}=2.94 Hz, C) 131.68 (d, \textit{J}_{C-C-C-F}=8.80 Hz, CH) 148.99 (CH) 165.40 (d, \textit{J}=255.29 Hz, C-F) 180.14 (q, \textit{J}_{C-C-F}=35.20 Hz, C) \textsuperscript{19}F NMR (CDCl\textsubscript{3}, 377 MHz) δ ppm -80.70 (s, 3 F) -108.71 -108.59 (m, 1 F) GC-MS (EI) 218 ([M]\textsuperscript{+}, 30%), 149 (100%), 121 (51%), 101 (55%), 95 (10%), 75 (18%), 69 (8%).
(E)-1,1,1-trifluoro-4-(furan-2-yl)but-3-en-2-one\(^{40}\) (123) (0.482 g, 51\%) was prepared according to the representative procedure A from (E)-3-(furan-2-yl)-N-methoxy-N-methylprop-2-enamide (0.906 g, 5 mmol) (176) with the following modification: The cleavage was conducted at room temperature\(^4\) rather than heating at 50 °C. Flash chromatography (Gradient 9:1 to 8:2 Hex:EtOAc) afforded the pure CF\(_3\) ketone as a brown oil. \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\) ppm 6.57 (dd, \(J=3.42, 1.71\) Hz, 1 H) 6.85 - 6.93 (m, 2 H) 7.60 (d, \(J=0.49\) Hz, 1 H) 7.68 (d, \(J=15.65\) Hz, 1 H) \(^{13}\)C NMR (CDCl\(_3\), 100 MHz) \(\delta\) ppm 116.72 (q, \(J_{C-F}=290.50\) Hz, CF\(_3\)) 113.71 (CH) 114.15 (CH) 120.21 (CH) 135.02 (CH) 147.26 (CH) 150.84 (C) 180.13 (J\(_{C-C-F}=35.20\) Hz, C) \(^{19}\)F NMR (CDCl\(_3\), 377 MHz) \(\delta\) ppm -80.69 GC-MS (EI) 190 ([M]+, 36\%), 121 (100\%), 93 (7\%), 69 (9\%), 65 (56\%), 63 (12\%), 39 (20\%).

A Weinreb Amide Approach to Difluoromethyl Ketones:

\[
\begin{align*}
\begin{array}{c}
\text{O} \\
\text{N} \text{O} \\
\text{Me} \\
\text{Me}_3 \text{Si} \\
\text{F} \\
\text{F} \\
\text{O} \\
\end{array}
\end{align*}
\]

1,1-Difluoro-4-phenyl-3-buten-2-one\(^{41}\) (147)

To a round bottom flask equipped with a stir bar was added \(N\)-methoxy-\(N\)-methylcinnamamide (0.192 g, 1.0 mmol, 1.0 equiv.). THF (1.4 mL) was added, the flask
was sealed with a septum and the contents were cooled to 0 °C. Freshly prepared (difluoromethyl)trimethylsilane\textsuperscript{42} (0.1863 g, 1.5 mmol, 1.5 equiv.) was then added drop wise to the reaction mixture via a syringe. Lastly, KO\textsuperscript{t}Bu  (0.224 g, 2.0 mmol, 2.0 equiv.) was added in one portion to the reaction mixture. The contents were allowed to stir overnight. Progress of the reaction was monitored through dilution of an aliquot with diethyl ether (2 mL). The organics were washed with H\textsubscript{2}O (2 mL), dried with sodium sulfate, and removed in vacuo. \textsuperscript{1}H NMR suggested quantitative conversion to (E)-1,1-difluoro-4-phenylbut-3-en-2-one. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \( \delta \) 5.92 (t, \( J = 54.0 \) Hz, 1 H), 7.04 (d, \( J = 16.1 \) Hz, 1H), 7.33-7.63 (m, 5 H), 7.89 (d, \( J = 16.1 \), 1H).

**General Procedure for Attempts Towards 1,1-difluoroalkenes:**

\textit{n}-BuLi and \textit{t}-BuLi Attempts without Additives:

![Chemical Diagram]

Freshly distilled THF (1 mL) was added to a sealed flame-dried flask under nitrogen. The contents were cooled to -78 °C and (difluoromethyl)trimethylsilane\textsuperscript{42} (0.155 g, 1.25 mmol, 5.0 equiv.) was added to the flask. Then butyl lithium (1.0 mmol, 4.0 equiv.) was added drop wise to the reaction mixture. Contents were stirred for 5 minutes. Benzo[1,3]dioxole-5-carbaldehyde (0.0375g, 0.25 mmol, 1.0 equiv.) was diluted in THF (0.5 mL) and was added drop wise to the reaction. Progress of the reaction was assayed after 30 minutes by dilution of an aliquot with diethyl ether (2 mL). The organics
were washed with a solution of NH₄Cl (2 mL), dried with sodium sulfate, and removed in \textit{vacuo}. $^1$H NMR suggested butyl addition into the aldehyde.

\textit{n}-BuLi and Attempts with TMEDA:

Freshly distilled THF (2 mL) was added to a sealed flame-dried flask under nitrogen. The contents were cooled to -30 °C and (difluoromethyl)trimethylsilane\textsuperscript{42} (0.228 g, 2.0 mmol, 1.0 equiv.) was added to the flask, followed by TMEDA (0.328 mL, 2.2 mmol, 1.1 equiv.). Then \textit{n}-butyl lithium (2.0 mmol, 1.0 equiv.) was added drop wise to the reaction mixture. Contents were stirred for 90 minutes, and then cooled to -78 °C. Benzo[1,3]dioxole-5-carbaldehyde (0.3302g, 2.2 mmol, 1.1 equiv.) was diluted in THF (4.0 mL) and was added drop wise to the reaction. Progress of the reaction was assayed after 30 minutes through a quench with a solution of NH₄Cl (6mL), and extraction with diethyl ether (6 mL). Organics were dried with sodium sulfate, and removed in \textit{vacuo}. $^1$H NMR suggested no reaction.
References:


Appendices
Appendix 1 (A.1): Exploring New Methods for Aryl Nitriles:

The Evolution of Cyanation Reactions:

Cyanation of aryl halides has been a significant area of study since the early 1900s.\(^1\) Aryl nitriles are found in many natural products, used in dyes, herbicides, agrochemicals, and pharmaceuticals.\(^2\) These compounds are also extremely useful intermediates for organic synthesis, mainly the formation of heterocycles.\(^2\) Many modifications have been made to the original synthetic methodologies due to toxic cyanide salts and harsh conditions. A major goal of the Leadbeater group is to transform this method to a quicker, and greener process through risk-free reagents and microwave technology.\(^3\)

Conversion of aryl halides to nitriles was first introduced via the Rosenmund-von Braun reaction in the early 1900s. In 1919 Rosenmund had developed a protocol for the production of aryl esters from bromide precursors (Compounds \textbf{A1} to \textbf{A2}).\(^4\) The reaction was completed in water with potassium cyanide, potassium hydroxide, and copper (I) cyanide. Although it was not isolated, Rosenmund suggested the reaction proceeded through a nitrile intermediate.\(^4\) In 1931, Von Braun developed the cyanation
of 4-bromofluoranthenone (A3) to nitrile A4. The reaction was conducted at 260 °C for 6 hours, solvent-free with copper (I) cyanide. This synthetic breakthrough was deemed the Rosenmund-Von Braun reaction.\textsuperscript{4,5}

As the use for aryl nitriles became popularized, so did the demand for a safer, greener method. New protocols for transition metal-catalyzed reactions were developed. Some early transformations involved the use of palladium catalysts with an MCN source to eradicate the use of stoichiometric CuCN. Tagaki et al. reported a synthesis of aryl nitriles from haloarenes utilizing Pd (II) salts, including Pd(CN)\textsubscript{2} and Pd(OAc)\textsubscript{2}. The catalysts were combined with KCN in DMF to produce high conversions of the aryl nitriles.\textsuperscript{6} Later, Pd(PPh\textsubscript{3})\textsubscript{4} was also studied as a suitable catalyst for these reactions.\textsuperscript{7,8}

The use of palladium catalysts with cyanide salts resulted in disadvantages of poisoned or deactivated catalysts, limited substrate scope, and low reaction yields. These drawbacks were circumvented with the emergence of K\textsubscript{4}Fe(CN)\textsubscript{6} as a cyanide source.\textsuperscript{9} Potassium hexacyanoferrate is a safe and mild oxygen-transfer agent commercially used in red wines to improve color through the precipitation of iron ions.\textsuperscript{10} The use of this salt for cyanation reactions greatly reduces the toxic effects of previous methodologies, and can be used without any precaution. Schareina, Zapf, and Beller first employed this cyanide source in 2004 using aryl bromides and chlorides with palladium catalysts (Scheme A.2).\textsuperscript{9,11}
New technologies to perform cyanation reactions have evolved with the emergence of greener reagents. Microwave reactors have been used as a tool for the quick conversion of aryl halides to the corresponding nitriles. Deblase and Leadbeater had optimized the potassium hexacyanoferrate reactions with microwave irradiation.\textsuperscript{12} Aryl iodides were converted in water using K\textsubscript{4}Fe(CN)\textsubscript{6}, CuI as catalyst, and TEG as a phase transfer agent. The reactions were held at 175 °C for 30 minutes to yield up to 79% of the cyanides. Aryl bromides were not tolerant of this methodology.\textsuperscript{12}

Deblase and Leadbeater made a significant discovery with further studies of K\textsubscript{4}Fe(CN)\textsubscript{6} and copper catalysts. When catalyst CuO was used, a change of color from black to purple occurred to the reaction mixture.\textsuperscript{13} This color change was found to be a resultant of Cu\textsubscript{2}Fe(CN)\textsubscript{6} formed. Copper hexacyanoferrate was synthesized and screened. This acts as both a cyanide source and catalyst. Only 30 mol\% of Cu\textsubscript{2}Fe(CN)\textsubscript{6} is needed for the reaction. The conversions of aryl iodides were reported with water and a phase transfer agent (Scheme A.4). Aryl bromides were not reported for this methodology.\textsuperscript{13}
Our Work Towards the Cyanation of Aryl Bromides:

We had sought to develop a method for the production of aryl nitriles from their corresponding bromides. Table A.1 summarizes the attempted reactions with substrate A8. Since aryl bromides were not reported as starting materials in Deblase’s and Leadbeater’s cyanation attempts in water, we began with altering solvent. Acetonitrile and ionic liquid [BMIM]+ I- were employed for transformation of A8 to A9 (Table A.1, entries 1-3). Heating the reaction to 200 °C for 30 minutes with a catalytic amount of Cu₂Fe(CN)₆ (30 mol%) resulted in 23% conversion to A9 (Table A.1, entry 1). Employing a stoichiometric amount of Cu₂Fe(CN)₆ resulted in a greater conversion of 61% (Table A.1, entry 2). The reaction time was lengthened to 60 minutes, and to our delight a 93% conversion was observed (Table A.1, entry 3). A water wash of the reaction mixture followed by an ethyl acetate extraction resulted in crude product. The recovery was measured via ¹H NMR with internal standard 1,2,4,5-tetramethylbenzene. Unfortunately, only 39% of A9 was recovered (Table A.1, entry 3). We hypothesized that the product was not fully extracted from the ionic liquid, compromising yield. The reaction was then completed in the absence of [BMIM]+ I-. Both a stoichiometric and catalytic amount of Cu₂Fe(CN)₆ were used, each resulting in about 80% conversion (Table A.1, entries 4-5). The highest yield observed was 49% (Table A.1, entry 5). When attempting the reaction with K₄Fe(CN)₆ and Cu₂O only starting material was observed.
We further conducted trials to understand why the conversion of the reaction was high but the recovery was low. One idea was the temperature was too high and decomposing the reaction contents. It was reduced from 200 °C to 150 °C. However, only 2% conversion of A9 was observed. To further disprove our theory we combined a known amount of 4-bromobenzonitrile, 4-bromoanisole, internal standard, and acetonitrile in a microwave vessel. The contents were heated to 200 °C for 1 hour and then measured via ¹H NMR. Quantitative amounts of each were recovered. This suggests that the starting material and product did not decompose at high temperatures.

We believe the contents are lost upon work-up. Subsequent to the end of the reaction the contents were diluted in ethyl acetate, and washed with water. The water is then extracted multiple times with ethyl acetate. A viscous polymeric-like material was observed, which also created emulsions upon work up. The highest recovery of 49% occurred when the reaction mixture was stirred in ethyl acetate over the course of 1-2 hours. This method was not feasible to continue due to the low reaction yields.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cu₂Fe(CN)₆ Equiv.</th>
<th>Solvent</th>
<th>Time</th>
<th>Temp.</th>
<th>Conv.</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.3</td>
<td>MeCN/[BMIM]+ I-</td>
<td>30 min</td>
<td>200 °C</td>
<td>23%</td>
<td>N/A</td>
</tr>
<tr>
<td>2</td>
<td>1.0</td>
<td>MeCN/[BMIM]+ I-</td>
<td>30 min</td>
<td>200 °C</td>
<td>61%</td>
<td>N/A</td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td>MeCN/[BMIM]+ I-</td>
<td>1 h</td>
<td>200 °C</td>
<td>93%</td>
<td>39%</td>
</tr>
<tr>
<td>4</td>
<td>1.0</td>
<td>MeCN</td>
<td>1 h</td>
<td>200 °C</td>
<td>83%</td>
<td>36%</td>
</tr>
<tr>
<td>5</td>
<td>0.3</td>
<td>MeCN</td>
<td>1 h</td>
<td>200 °C</td>
<td>81%</td>
<td>49%</td>
</tr>
</tbody>
</table>

Table A.1: Cyanation Attempts
Representative Procedure for Cyanation:

To a 10-mL microwave vessel equipped with a stir bar was added 4-bromoanisole (0.122 g, 1.0 mmol, 1 equiv.), acetonitrile (1 mL) and Cu$_2$Fe(CN)$_6$ (0.3-1.0 mmol, 0.3-1.0 equiv.). The vessel was sealed and placed in the cavity of a CEM Discover microwave. The temperature was ramped to 200 °C and stirred for 1 h holding temperature. Once cooled, the contents were diluted in EtOAc (10 mL) and washed with water (5 mL). The aqueous layer was extracted with EtOAc (3 x 10mL). Organics were collected, dried with sodium sulfate, and filtered. Internal standard 1,2,4,5-tetramethylbenzene (0.0671 g, 0.5 mmol, 0.5 equiv.) was added and the solvent was removed in vacuo. Conversion was measured by $^1$H NMR.
Appendix 2 (A.2): Utilizing Flow Technology for the Decarboxylative Heck Coupling:

Microwave and Continuous Flow Technologies:

A significant theme of the New Synthetic Methods Group is the utilization of new technologies for quicker, cleaner, and greener chemistries. Microwave and continuous flow reactors are the tools exploited for these goals. Many literature protocols involve small-scale reactions to explore the scope and limitation of the methodology. Our goal is to improve upon the reaction times through microwave heating and transition the method for scale-up in the continuous flow reactor.

One of the common misconceptions of microwave heating is it employs a “microwave effect” to break bonds and therefore force reactivity. However, this is not the case. Microwave reactors are tools for controlled super heating that only agitate bonds. Round bottom flasks that are placed upon a heat source are warmed through contact. Contrastingly, microwave sources allow for homogenous heating throughout the reaction mixture, resulting in a steadied and controlled warming process. A pressure locking system is
one of the capabilities of the CEM Discover microwave unit the lab is equipped with. The reaction vessels are built to withstand pressures of up to 300 psi. This is advantageous for a quicker reaction time as temperatures much higher than the boiling point of the solvent are tolerated. The greater temperatures, and consequently higher pressures are accountable for the shorter reaction times.

Once a method is transitioned from batch to microwave protocols, attention can then be focused on reaction scale-up. Although larger microwaves may be employed, another useful technology is the continuous flow reactor. The concept behind the flow reactor is a series of small-scale reactions allowing for safer and controlled chemistry. This is possible by small reaction coils that are wrapped around a heat source. The reactor employs conventional heating, however, the small diameter of the long coil allows for a larger contact surface area by the heat source than a round bottom flask. Reactions that may be dangerous and explosive especially upon scale-up may safely be run in a flow reactor due to a series of continuously flowing mini-reactions.
One system that the lab is equipped with is the Vapourtec flow system, which has low
temperature, high temperature, and gas loading capabilities.

The Decarboxylative Heck Reaction:

The Leadbeater lab is continuously searching for conventional reaction methods
that would benefit from microwave and flow technologies. One reaction targeted was the
decarboxylative Heck coupling. The Myers’s group first reported this chemistry with the
coupling of various benzoic acids (A10) and substituted alkenes (A11) in the presence
of a palladium catalyst and a silver salt to yield compounds A12 (Scheme A.5).\textsuperscript{15}
Recently, many variations of this reaction have been studied.\textsuperscript{16} It was thought that the
silver salt is key for decarboxylation.\textsuperscript{17} However, Su et. al recently found that dioxygen
may be replaced as the terminal oxidant allowing for a greener process.\textsuperscript{18} Electron rich
aromatic carboxylic acids were coupled to methyl acrylate with Pd(OAc)$_2$, and O$_2$, in a
5% DMSO-DMF solution. Reactions were run in 10 hours at 120 °C with 23-
91% yields.
Our CEM discover and Vapourtec systems are both equipped with gas loading capabilities. Therefore, we embarked on transitioning the reaction from batch protocols to microwave and flow methods. We believed we could reduce the 10 h reaction time. Substrate A13 was chosen due to low cost and reported high reaction yield (Table A.2).¹⁸ Reaction yields were determined by integration of the internal standard 1,2,4,5-tetramethylbenzene by ¹H NMR. Initial trials were screened on a 0.2 mmol scale with 10 mol% Pd(OAc)₂, and 2 equivalents of methyl acrylate (A14). Su reported that higher yields were accomplished with a greater pressure of oxygen.¹⁸ Therefore, 200 psi of oxygen was employed as a contrast to 1 atm (~ 15 psi) used by the Su group. The reaction was heated to 150 °C for 1 h, resulting in a 74% yield of A15 (Table A.2, entry 1). To our delight a 90% yield was observed when reducing catalyst loading to 5 mol% (Table A.2, entry 2). Lowering the temperature to 140 °C did not effect the yield (Table A.2, entry 3). An optimized reaction time of 30 minutes was observed (Table A.2, entry 4). Reducing the time to 15 minutes or reducing catalyst loading (1 mol%) resulted in sub-optimal yields (Table A.2, entries 5-6). The use of O₂ was essential as no conversion was reported when dioxygen was not employed (Table A.2, entry 7). Pure product was isolated in a 67% yield when optimized conditions were used (Table A.2, entry 4).
With microwave conditions optimized we next sought to transition the method to a continuous flow protocol. We began mimicking the reaction at 140 °C with a resonance time of 30 min in 1 coil with a flow rate of 0.5 mL/min. A pressure of 250 psi of oxygen was needed in order to maintain homogeneous gas bubbles in the reaction coil. Only partial conversion was observed (Table A.3, entry 1). Table A.3 summarizes the reaction optimization. We next attempted increasing the resonance time to 1 hour by slowing the flow rate to 0.25 mL/min. A 70% yield was determined via internal standard (Table A.3, entry 2). A second coil was added to increase the resonance time to 2 h. Product A15 was collected and passed through a pad of silica gel. Pure product was isolated in an 86% yield (Table A.3, entry 3). Other alkenes such as acrylonitrile were employed however decomposition was observed. When 2,4,5-trimethoxybenzoic acid was used as starting material with methyl acrylate only 70% conversion to the

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd(OAc)$_2$</th>
<th>O$_2$</th>
<th>Temperature</th>
<th>Time</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 mol%</td>
<td>200 psi</td>
<td>150 °C</td>
<td>1.0 h</td>
<td>74%</td>
</tr>
<tr>
<td>2</td>
<td>5 mol%</td>
<td>200 psi</td>
<td>150 °C</td>
<td>1.0 h</td>
<td>90%</td>
</tr>
<tr>
<td>3</td>
<td>5 mol%</td>
<td>200 psi</td>
<td>140 °C</td>
<td>1.0 h</td>
<td>90%</td>
</tr>
<tr>
<td>4</td>
<td>5 mol%</td>
<td>200 psi</td>
<td>140 °C</td>
<td>0.5 h</td>
<td>90%(67)</td>
</tr>
<tr>
<td>5</td>
<td>5 mol%</td>
<td>200 psi</td>
<td>140 °C</td>
<td>15 min</td>
<td>63%</td>
</tr>
<tr>
<td>6</td>
<td>1 mol%</td>
<td>200 psi</td>
<td>140 °C</td>
<td>0.5 h</td>
<td>40%</td>
</tr>
<tr>
<td>7</td>
<td>5 mol%</td>
<td>0 psi</td>
<td>140 °C</td>
<td>0.5 h</td>
<td>0%</td>
</tr>
</tbody>
</table>

Table A.2.: Microwave Optimization
corresponding product was observed. Therefore more optimization is needed for a broader substrate scope.

Microwave Procedure for Decarboxylative Heck Coupling:

\[
\text{MeO}COOH + \text{MeO}COMe \xrightarrow{\text{Pd(OAc)}_2, O_2, 20:1 \text{ DMF/DMSO}} \text{OMe}\text{OME}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd(OAc)$_2$</th>
<th>O$_2$</th>
<th>Temperature</th>
<th>Rate/Coils</th>
<th>Time</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 mol%</td>
<td>250 psi</td>
<td>140 °C</td>
<td>0.5 mL/min 1</td>
<td>0.5 h</td>
<td>partial Conv.</td>
</tr>
<tr>
<td>2</td>
<td>5 mol%</td>
<td>250 psi</td>
<td>140 °C</td>
<td>0.25 mL/min 1</td>
<td>1.0 h</td>
<td>70% yield</td>
</tr>
<tr>
<td>3</td>
<td>5 mol%</td>
<td>250 psi</td>
<td>140 °C</td>
<td>0.25 mL/min 2</td>
<td>2.0 h</td>
<td>86% yield</td>
</tr>
</tbody>
</table>

Table A.3: Flow Optimization

\[(E)\text{-methyl 3-(2,6-dimethoxyphenyl)prop-2-enoate:}\]

\[
\text{MeO}COOH + \text{MeO}COMe \xrightarrow{\text{Pd(OAc)}_2, O_2, 20:1 \text{ DMF/DMSO}} \text{OMe}\text{OME}
\]

2,6-dimethoxybenzoic acid (0.0364g, 0.2 mmol, 1.0 equiv.) was weighed out and added to a microwave vessel equipped with a stir bar. Methyl acrylate (36 μL, 0.4 mmol, 2.0 equiv.) was added to the vessel, which was then and purged with nitrogen. Dry DMF (2mL) was added via a syringe followed by 0.1 mL of a stock solution of 5% Pd(OAc)$_2$ (.01 mmol) in DMSO. The reaction vessel was uncapped and the gas loading
apparatus introduced 200 psi of dioxygen. It was heated to 140 °C and held for 30 minutes. Once cooled the contents were diluted in diethyl ether (10 mL), filtered through a small layer of silica gel, and extracted with diethyl ether (4 x 10 mL). The organics were transferred into a separatory funnel, and washed with a brine solution (2 x 20 mL). The organic layer was dried with sodium sulfate, and evaporated to dryness resulting in pure product (0.29 g, 67%). $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ ppm 3.79 (s, 3H), 3.87 (s, 6H), 6.55 (d, $J = 8.37$ Hz, 2 H), 6.88 (d, $J = 16.26$ Hz), 7.26 (t, $J = 8.37$ Hz), 8.13 (d, $J = 16.26$ Hz)

**Continuous Flow Procedure for Decarboxylative Heck Coupling:**

![Chemical Reaction Diagram]

(E)-methyl 3-(2,6-dimethoxyphenyl)prop-2-enoate:

2,6-dimethoxybenzoic acid (0.9109g, 5.0 mmol, 1.0 equiv.) was weighed out and added an Erlenmeyer flask and dissolved in dry DMF (50 mL). Methyl acrylate (0.900 mL, 10.0 mmol, 2.0 equiv.) was added to the flask followed by 2.5 mL of a stock solution of 5% Pd(OAc)$_2$ (.01 mmol) in DMSO. The Vapourtec flow apparatus was primed, flushed, with DMF, introduced to a continuous flow of 250 psi O$_2$, and heated to 140 °C. The reaction mixture was passed through 2 coils at a flow rate of 0.25 mL/min, and collected. Once cooled the contents were diluted in ether (100 mL), filtered through a small layer of silica gel, and extracted with diethyl ether (3 x 50 mL). The organics were transferred
into a separatory funnel, and washed with a brine solution (3 x 50 mL). The organic
layer was dried with sodium sulfate, and evaporated to dryness resulting in pure product
(0.957 g, 86%). \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 400 MHz) \( \delta \) ppm 3.79 (s, 3H), 3.87 (s, 6H), 6.55 (d, \( J = 8.37 \) Hz, 2 H), 6.88 (d, \( J = 16.26 \) Hz), 7.26 (t, \( J = 8.37 \) Hz), 8.13 (d, \( J = 16.26 \) Hz).
References:

