

Direct Synthesis of (Fluoro)ketones from Carboxylic Acids and Organozincs via Acyloxyphosphonium Ions

By

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ABSTRACT

The thesis presented herein delineates a straightforward approach for the generation of ketones directly from carboxylic acids through the intermediacy of acyloxyphosphonium ions. The work presented herein builds upon research findings performed in the laboratory of my thesis advisor, Prof. Socrates B. Munoz that have been published as a pre-print dealing with the synthesis of both α,α -difluoro as well as non-fluorinated ketones; the latter being the main focus of my work. However, an introduction on the significance of fluorine, Fluoroketones and non-fluorinated ketones in organic chemistry is also provided. Importantly, my work is focused on the application of the previously found method for Fluoroketones synthesis and its expansion to the synthesis of benzophenones, and a manuscript delineating the preparation of both types of ketones (fluorinated and non-fluorinated benzophenones) is currently under preparation for submission to peer-review in which I am a listed co-author along with various members of the Munoz lab.

Of note, these electrophiles (i.e. acyloxyphosphonium ions) are easily accessible commodity chemicals which renders their use in synthetic organic chemistry as highly practical. The work delineated herein establishes the use of these electrophiles in Cu-catalyzed cross-coupling reactions with easy-to-generate organozinc reagents as carbon nucleophiles. These transformations lead to the efficient production of ketones in a facile and practical manner. The transformations take place under mild reaction conditions (ranging from 0°C to room temperature), allowing for the generation of target compounds in brief reaction intervals. In addition, the approach demonstrates remarkable chemoselectivity and compatibility with various functional groups, highlighting its effectiveness and versatility. In the case of benzophenones, several FDA-approved active pharmaceutical ingredients (APIs) have been established as suitable substrates and have been successfully derivatized into their corresponding ketones.

Finally, this thesis concludes with our group's collaborative efforts to elucidate the nature of active electrophiles in these transformations. Accordingly, the mechanistic investigations using both fluorinated as well as non-fluorinated benzoic acids through NMR spectroscopic studies are presented and discussed.

Table of Contents

List of Figures.....	v
List of Tables.....	vi
List of Schemes.....	vii
Acknowledgments.....	viii
Chapter 1 – Introduction.....	1
1.1. Organofluorine Compounds and Their Significance.....	1
1.1.1 Brief Remarks on The Fluorine Atom Supply Chain	2
1.2. (Fluoro)ketones: Significance, Synthesis, and Applications.....	3
1.3. Acyloxyphosphonium ions in Synthetic Organic Chemistry	9
Chapter 2 Copper-Catalyzed Cross-Coupling of Organozincs with α,α-Difluorocarboxylic Acids via Acyloxyphosphonium Ions	11
2.1. Introductory Remarks	11
2.1.1 Previous Work: Di/trifluoroalkylation of Acyloxyphosphonium Ions.....	11
2.1.2 Remarks on Organozinc Reagents vs Other Carbon Nucleophiles.....	12
2.2. Current Work: Difluoroacylation of Organozincs.....	14
2.2.1 Introductory Remarks	14
2.2.2 Aryldifluoromethyl Ketones from Aryldifluoroacetic Acids.....	16
2.2.3 Difluoromethyl Ketones from Difluoroacetic Acid.....	19
Chapter 3 - Copper-Catalyzed Cross-Coupling of Organozincs with Benzoic Acids via Acyloxyphosphonium Ions	22
3.1. Introductory Remarks	22
3.2. Optimization of the Reaction Conditions.....	23
3.3. Copper Catalyzed Synthesis of Benzophenones via Acyloxyphosphonium Ions	25
3.4. Remarks on Atom Economy and Triphenylphosphine Oxide	27
Chapter 4 – Mechanistic Considerations.....	30
4.1 Control Experiments using ^{19}F and ^{31}P NMR Spectroscopy	30
4.2 Experimental Section.....	40
4.3 Conclusions	50
Appendix – ^1H and ^{13}C NMR spectra of synthesized molecules.....	52
References.....	69

List of Figures

Figure 1 Naturally occurring organofluorine compounds known to date	1
Figure 2 X-Ray Crystal Structure of Fluorinase Enzyme Discovered by O'Hagan	1
Figure 3 Biologically relevant α,α -Difluoroketones.....	7
Figure 4 Representative examples of phosphonium-based reagents for peptide coupling	9
Figure 5 Organozinc reagents: uses and superior functional group compatibility	13
Figure 6 Naturally occurring and Synthetic bioactive Benzophenones	23
Figure 7a ^{31}P -NMR of the species obtained from PPh_3 and NCS reaction in CDCl_3	31
Figure 7b ^{31}P -NMR of the species obtained from PPh_3 and NBS reaction in CDCl_3	32
Figure 7c. ^{31}P -NMR obtained from the reaction of PhCF_2COOH with PPh_3 and NCS reaction after 10 min	33
Figure 8a. ^{19}F -NMR obtained from the reaction of PhCF_2COOH with PPh_3 and NCS reaction after 10 min.	33
Figure 8b. ^{31}P -NMR of the reaction of PhCF_2COOH with PPh_3 and NCS reaction after 30 min..	34
Figure 9a. ^{31}P -NMR of the reaction 4-fluorobenzoic acid with NBS and PPh_3 in CDCl_3	35
Figure 9b. ^{19}F -NMR of the reaction 4F-benzoic acid with NBS and PPh_3 in CDCl_3	35
Figure 9c. ^{19}F -NMR of the reaction 4F-benzoic acid with NBS and PPh_3 in CDCl_3 spiked with authentic acyl bromide.	36
Figure 9d. ^{31}P -NMR of the reaction between PPh_3 , NBS and 4-trifluoromethylbenzoic acid after 10min.	37
Figure 9e. ^{19}F -NMR of the reaction between PPh_3 , NBS and 4-trifluoromethylbenzoic acid after 10min (before adding authentic 4-(trifluoromethyl)benzoyl bromide	37
Figure 9f. ^{19}F -NMR-after adding authentic 4-(trifluoromethyl)benzoyl bromide	38
Figure 10a. ^{31}P -NMR spectrum of the reaction mixture of DFA, PPh_3 , and NBS in CDCl_3 (8 min)	39
Figure 10b ^{19}F NMR spectrum of the reaction mixture of DFA, PPh_3 , and NBS in CDCl_3 (10min)	39

List of Tables

Table 1 Effect of Cu-catalyst for Benzophenone Synthesis Using PhZnCl.....	24
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List of Schemes

Scheme 1 Sources of fluorine and reagents to install fluorine or fluoroalkyl groups through synthetic organic chemistry	3
Scheme 2 Key tetrahedral intermediate enables ketone synthesis using Weinreb amides.....	4
Scheme 3 Generally accepted catalytic redox cycle for a Negishi acylation.....	5
Scheme 4 Two commonly used name reactions for ketone synthesis - Pd and Cu as catalysts...	6
Scheme 5 Representative routes to α,α -Difluoro ketones from acyl electrophiles.....	8
Scheme 6 Di/trifluoromethyl ketones through a Cu-mediated process via acyloxyphosphonium ions.....	11
Scheme 7 α,α -Difluoroacyloxyphosphonium ions from α,α -difluorocarboxylic acids	15
Scheme 8 Difluoroacylation of organozinc reagents directly from difluoro acids	16
Scheme 9 Copper-Catalyzed Synthesis of Difluorophenyl Ketones	18
Scheme 10 Synthesis of Difluoromethyl Ketones Under Cu-Free conditions.....	20
Scheme 11 Synthesis of Benzophenones Under Cu conditions	26
Scheme 12 Current Limitation of the present method	27
Scheme 13 Examples of O=PPh_3 generated routinely in multikilogram scale in industrial settings.....	28
Scheme 14 Versatility O=PPh_3 as reagent, catalyst, ligand and further derivatizations.....	28

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My experience at Kansas State University has not only equipped me with a robust skillset in Chemistry but has also enriched my life with meaningful relationships and experiences. I am grateful for the opportunity to have been part of this vibrant academic community.

Chapter 1. Introduction

1.1 Organofluorine Compounds and Their Significance

In spite of the fact that fluorine is the thirteenth most abundant element in the earth's crust¹ naturally occurring organofluorine compounds are very rare and only a handful have been found and isolated (**Figure 1**).^{1c} In this context, O'Hagan and coworkers isolated the only known Fluorinase enzyme capable of making C–F bonds in 2004². This enzyme was isolated from the bacteria *Streptomyces cattleya*, and a single-crystal X-ray structure was successfully disclosed by O'Hagan's team.² This represented a significant discovery in the whole field of fluorine chemistry. (**Figure 2**)

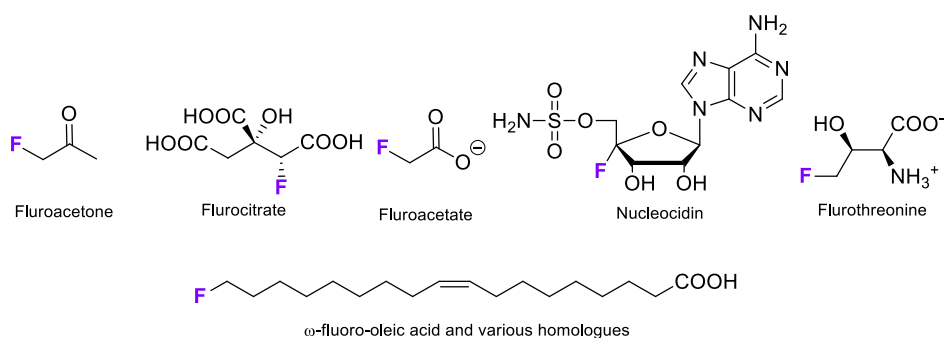


Figure 1. Naturally occurring organofluorine compounds known to date



Figure 2. X-ray crystal structure of Fluorinase discovered by O'Hagan <https://doi.org/10.2210/pdb1RQP/pdb>

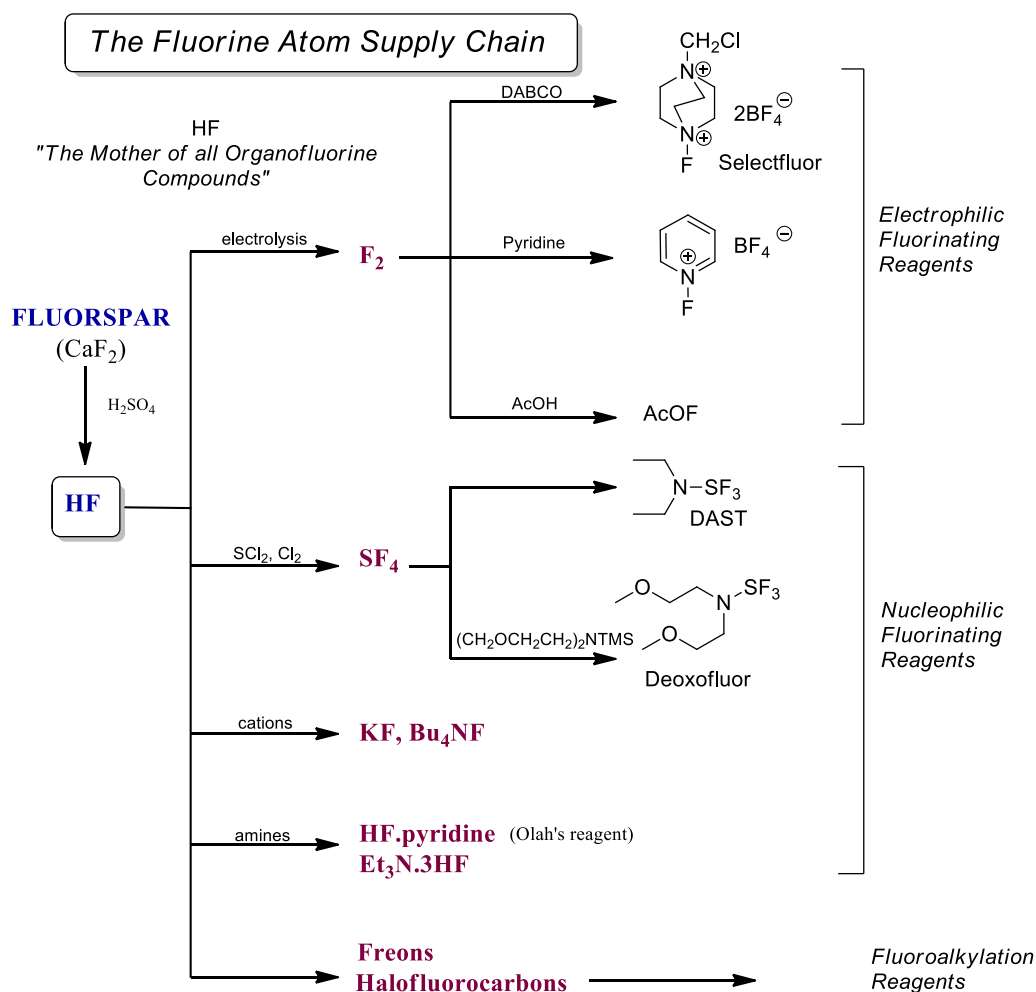
Because of the limited number of naturally occurring compounds, one can argue that most organofluorine compounds are man-made, and as such, their synthesis relies on the availability of synthetic methods that enable the installation of fluorine atom or fluorinated motifs (e.g., fluoroalkyl groups, fluoroacyl groups, etc.) into organic molecules. Furthermore, organofluorine compounds are increasingly being utilized in a variety of areas, including medicine,³ material science,⁴ and agrochemical development.⁵ In the context of pharmaceuticals, the high prevalence of fluorine is due

to the properties imparted by the strong C–F bond, which has been dubbed as *the strongest bond in organic chemistry*^{3c} (BDE = 115 kcal/mol⁻¹ for C–F bond in CH₃–F)⁶ This *usually* results in enhanced lipophilicity,^{3j} increased membrane permeability, as well as increased resistance to metabolism^{7,3e} (i.e. metabolic stability). However, it must be noted that it is difficult to predict precisely the properties imparted to a molecule upon fluorination. As an example, as delineated by Gouverneur^{3e} and others,^{3k} adding fluorine atoms into a molecule does not always result in an enhanced lipophilicity, and a variety of structural factors must be considered. In fact, adding a single fluorine atom or trifluoromethyl group to a saturated alkyl chain can, in some cases, reduce lipophilicity. As a consequence, a so-called “fluorine screen” is commonly practiced amongst medicinal chemists during drug design.^{3j} This topic has thoroughly been reviewed, and a great body of literature exists³ that aids medicinal chemists in their efforts to optimize a bioactive lead.

In light of the significance that fluorine plays in medicine, the pharmaceutical industry has issued a call-to-action⁸ to develop effective methods or reagent systems for the preparation of organofluorine compounds. It has been recognized however, that such methods must be designed with the fluorine atom supply chain in mind. In order to better understand the fluorine atom supply chain a brief discussion is provided below.

1.1.1 Brief Remarks on The Fluorine Atom Supply Chain

The primary source of fluorine on earth is CaF₂ (a mineral also known as fluorspar)⁹, a compound from which hydrofluoric acid (HF) is made at industrial scale upon treatment with concentrated sulfuric acid (CaF₂+H₂SO₄→ 2HF+CaSO₄), a process first reported by C. W. Scheele in 1771^{10a} and later improved.^{10b} From here, HF is then transformed into several compounds, such as alkali metal fluorides, HF-amine complexes (such as Olah’s reagent),¹¹ Sulfur/Fluorine Reagents,¹² and elemental fluorine (F₂) through electrolysis^{13a-b} or as elegantly described by Christe^{13c} through chemical means from the reaction of K₂MnF₆ and SbF₅. Historically, strong fluorination reagents like F₂, HF, and SF₄ played a significant role in creating fluoroalkyl compounds through multi-fluorination or deoxyfluorination of various starting materials. However, due to the highly toxic nature of these reagents, several alternative fluorinating reagents, derivatives of SF₄ such as DAST (diethylamino sulfur trifluoride) or Deoxofluor[®], were later developed.^{14a} Still, these reagents are explosive, highly sensitive to moisture, and/or extremely toxic, requiring careful and strict handling procedures.^{15a} Gaseous elemental fluorine (F₂) is then used to access a variety of solid and easy-to-handle electrophilic fluorine sources typically having an N–F bond (such as Selectfluor[®] invented by Banks^{14b} and coworkers). (**Scheme 1**)



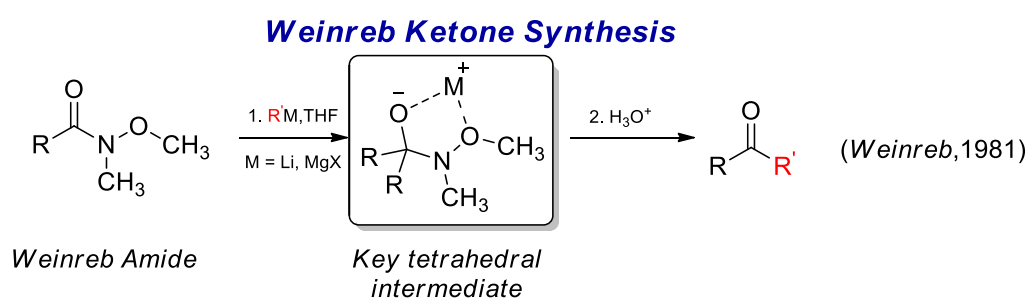
Scheme 1. Sources of fluorine and reagents to install fluorine or fluoroalkyl groups through synthetic organic chemistry

It is important to note that, until recently (*vide infra*) all fluorinating agents can be ultimately traced back to hydrofluoric acid (HF) and thus, to mined fluorspar (CaF₂). In this context, a major breakthrough in organofluorine chemistry has been very recently delineated by Gouverneur^{15b} in which CaF₂ itself was used to generate an inorganic mixture upon ball-milling with K₂HPO₄ ("Fluoromix", K₃(HPO₄)F), which upon further ball milling with CaHPO₄ afforded a new material, presumably, an inorganic crystal with the formula K_{2-x}Ca_y(PO₃F)_a(PO₄)_b. Notably, both of these inorganic materials were successfully utilized as fluorination reagents in the solution phase.

1.2 (Fluoro)ketones: Significance, Synthesis and Applications

Carbonyl compounds are highly important in organic chemistry and are found in a variety of naturally occurring molecules as well as (Active Pharmaceutical Ingredients)API's.¹⁶ Particularly, the keto- functionality plays a central role in organic chemistry and its importance is underscored by the use of ketones as a handle for a wide range of chemical elaborations¹⁷ including the total synthesis of natural products^{16c} and active pharmaceutical ingredients (APIs).¹⁶

In this context, a reaction between a carbon nucleophile and an acyl electrophile would, in principle, be suitable to forge a desired carbon–carbon bond for ketone formation. At first glance, one would surmise that a reaction between well-established carbon nucleophiles such as a Grignard¹⁸ reagents organolithiums¹⁹ or other organometallic reagents,²⁰ and an acyl electrophile (e.g. acyl chloride) would be a useful way to generate ketones.²¹ However, this process is plagued with many drawbacks and limitations, all of which have been well documented in the scientific literature.²⁰⁻²¹ In fact, the reaction of a Grignard reagent (or any other highly nucleophilic organometallic reagent such as organolithiums) with an acyl halide can, in select cases, afford the target ketones. However, a more common scenario is a double addition of this strongly nucleophilic organometallic reagent to generate carbinols. To avoid this highly common side reaction, the reaction conditions must be strictly controlled. For example, at cryogenic temperatures, the rate and order of addition of reagents, (reverse addition, i.e. nucleophile added to electrophile) are some of the factors that must be controlled if one aspires to get appreciable amounts of the target ketones. This stands as a major synthetic issue to be solved. Accordingly, several procedures have been ingeniously developed to mitigate this problem. For example, in 1981 Weinreb and co-workers²² devised a new protocol in which, instead of an acyl halide, another acylating agent, namely *N*-methoxy-*N*-methanilamides (now known as Weinreb Amides) are employed as the acyl electrophiles in reactions with either organomagnesium or organolithium reagents. This transformation has come to be known as the “*Weinreb Ketone Synthesis*.” Key to the success of this reaction is the formation of a stable tetrahedral intermediate, which is unmasked upon mild aqueous acidic workup into the target ketones. It is through this stable tetrahedral intermediate that this reaction effectively prevents the formation of double-addition carbinol by-products (**Scheme 2**).

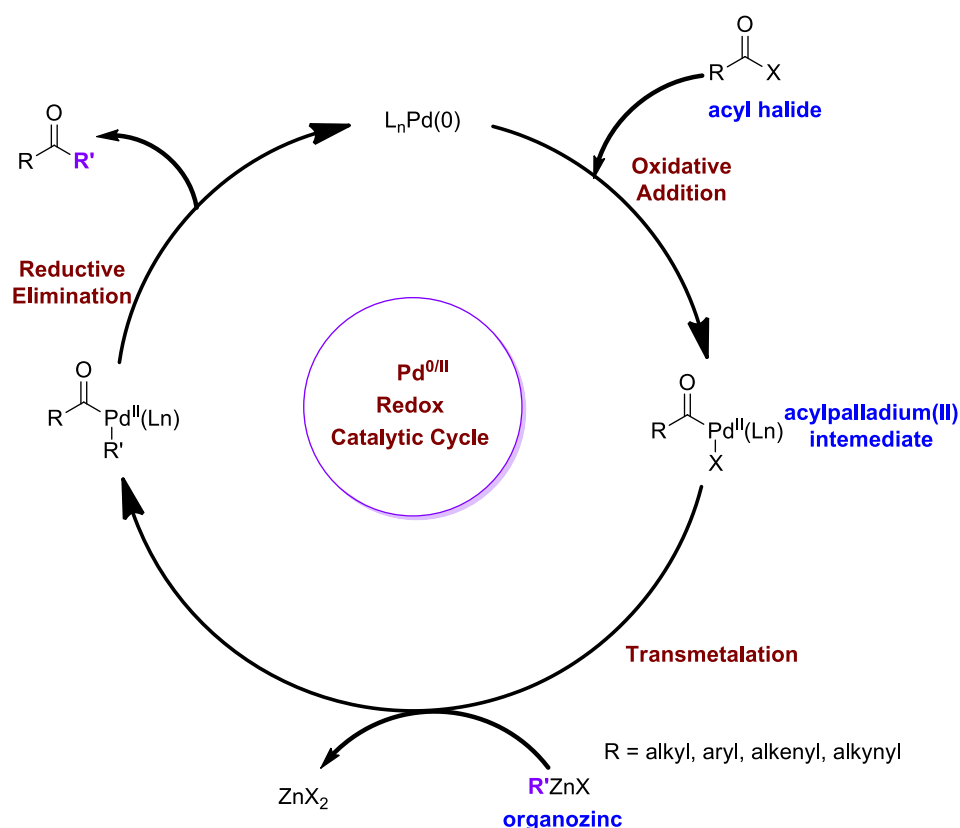


Scheme 2. Key tetrahedral intermediate enables ketone synthesis using Weinreb amides

For decades, the *Weinreb Ketone Synthesis* was the method of choice for synthetic organic chemists. However, over the years, more modern transformations showcasing a better functional group

compatibility profile were developed (*vide-infra*). A further limitation of this process is the fact that Weinreb amides must be synthesized from acyl halides and isolated prior to their utilization.

With the advent of cross-coupling reactions through transition metal catalysis, Negishi and coworkers disclosed a procedure in 1983, to cross-couple an organozinc reagent as a carbon nucleophile with an acyl chloride to smoothly afford ketones in the presence of a [Pd] catalyst.²³ This transformation represents a variation of the well-known nickel-catalyzed Negishi Coupling, for which Negishi was awarded the Nobel Prize in 2010.²⁴ In some reports, this variant for ketone synthesis, has been also referred to as Negishi coupling however, it should be noted this named reaction (i.e. Negishi coupling) should be reserved for transformations that afford biaryls through a metal-catalyzed process using organozinc nucleophiles. Instead, this ketone synthesis method should be referred to as *Negishi Acylation*. The pathway for ketone synthesis using this approach with acyl fluorides^{25a} and chlorides^{25b} has been well studied and the following mechanism has been postulated to be operative (**Scheme 3**). This commonly accepted mechanism proceeds through a Pd^{0/II} redox catalytic cycle and is described as follows: initially, an electron-rich, phosphine-ligated zero-valent palladium species undergoes oxidative addition to an acyl electrophile furnishing a square planar acylpalladium(II) complex.

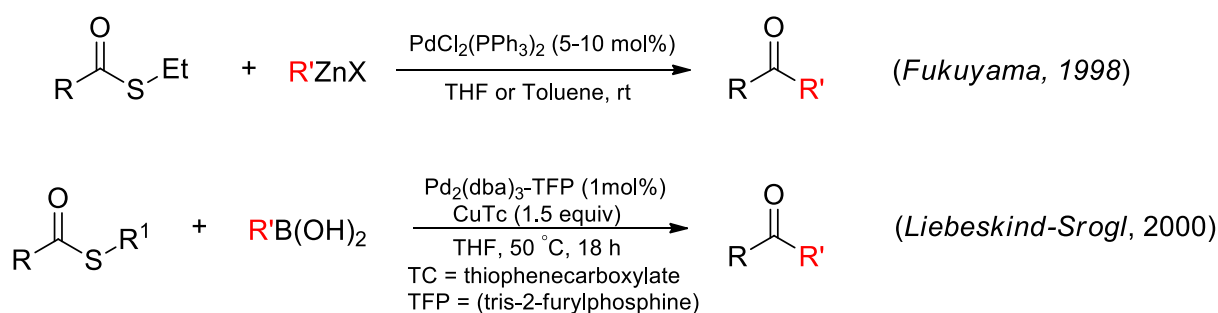


Scheme 3. Generally accepted catalytic redox cycle for a Negishi acylation

Upon transmetalation of an organozinc reagent, the newly formed acylpalladium^(II) containing the carbon chain (R group) undergoes a reductive elimination to afford the target ketone while regenerating the Pd⁽⁰⁾ catalyst, thereby, closing the catalytic cycle.

Ever since, many more synthetic protocols have been developed to access ketones through either direct uncatalyzed or transition-metal-catalyzed acylation with acyl electrophiles. Examples of acyl electrophiles used in ketone synthesis include acyl halides,²⁶ (thio)esters,²⁷ activated amides,²⁸ or anhydrides.²⁹ Notably, some of these are now known as named reactions, of which the Pd-Catalyzed *Fukuyama Coupling*^{27a} and the Pd/Cu co-catalyzed *Liebeskind-Srogl Coupling*,^{27b-d} stand as landmark reactions for ketone synthesis. (**Scheme 4**)

Landmark Reactions for Ketone Synthesis



Scheme 4. Two commonly used name reactions for ketone synthesis - Pd and Cu as catalysts.

In spite of these advances, all of these processes necessitate additional preparative steps for the synthesis and purification of the required acyl electrophiles (amides, (thio)esters, anhydrides, etc.), most of which are typically derived from their parent carboxylic acids via acyl chlorides. Thus, a simplified and direct access to ketones from easily available carboxylic acids or through their *in-situ* (pre)activation³⁰ remains highly sought-after.

On the other hand, α,α -difluoroketones play a significant role in medicinal chemistry, as synthetic precursors, and intermediates in organic synthesis.³¹ In the area of medicinal chemistry, α,α -difluoroketones have been found useful as HMG (Human menopausal gonadotropins) CoA Reductase inhibitors,^{32a} AMPAR (α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid Receptor) Allosteric modulator,^{32b} Inhibitor of AgAChE^{32c}, and Antimalarial Plasmepsin inhibitor.^{32d} (**Figure 3**) Historically, the majority of methods employed for the production of α,α -difluoroketones involve electrophilic α -difluorination of (di)carbonyl compounds or their derivatives (like imines or enamines),³³ the electrophilic fluorination of alkynes,³⁴ the modification of *gem*-difluorinated

(silyl)enolates through transition metal-catalyzed,^{35a-d} metal-free,^{35e-f} or visible photoredox-catalyzed modifications,³⁶ oxidation of fluoroalkyl carbinols^{37a} and various other methods.^{37b-g}

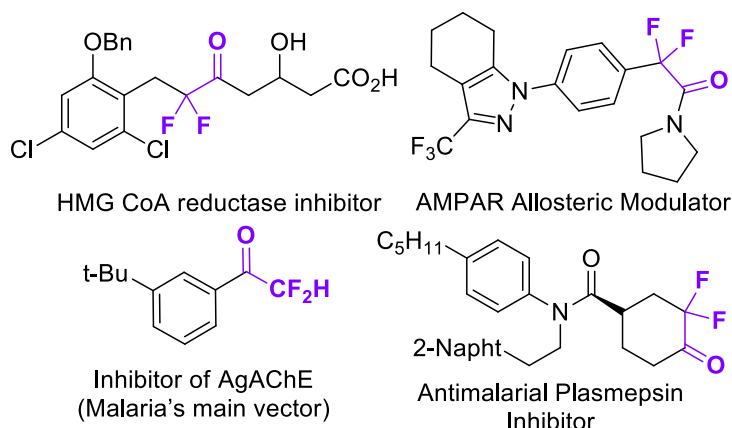


Figure 3. Biologically relevant α,α -difluoroketones

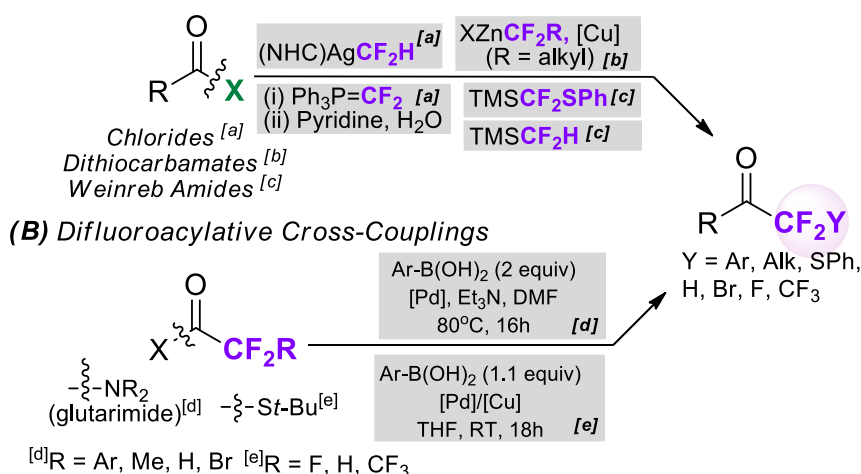
The development of a synthetic approach that *directly* utilizes α,α -difluorinated acids under mild and practical conditions would represent a significant addition to the synthetic chemists' current toolbox. However, despite their apparent simplicity, contemporary reports using this approach suffer severe flaws. For example, 2.4 equiv. of BuLi must be added to difluoroacetic acid (DFA) at $-78\text{ }^{\circ}\text{C}$ to yield only 48% of the desired CF_2H ketone after 3 hours under these cryogenic conditions.^{38a} RLi or RMgX addition to α,α -difluoro esters^{38b} or amides^{38c-e} requires similar cryogenic temperatures. The highly reactive nature of these organometallic reagents calls for precise control of the reaction conditions to prevent the formation of by-products arising from double addition. Naturally, the use of cryogenic conditions limits the synthetic utility of the method, especially for large-scale applications.

To overcome these constraints, significant attempts have been made in recent years that rely on difluoroalkylations of acyl electrophiles. Dilman and coworkers,^{39a} reported a Cu-catalyzed cross-coupling between dithiocarbamates and *gem*-difluorinated organozinc compounds, along with the reaction of acyl chlorides with $\text{Ph}_3\text{P}=\text{CF}_2$.^{39b} Likewise, an NHC-ligated (NHC = *N*-heterocyclic carbene) $\text{Ag}^{(\text{I})}\text{CF}_2\text{H}$ complex,^{39c} PhSCF_2TMS ,^{39d} and TMSCF_2H ^{39e} have been used to difluoromethylate acyl chlorides^{39(a-c)} or Weinreb amides.^{39(d-e)} However, these techniques require the generation and separation of acyl electrophiles, and the employment of costly and/or difficult-to-generate difluoroalkylation reagents. (**Scheme 5A**) A recent report by Munoz and coworkers⁴⁰ can be classified in a similar category however, this method employs carboxylic acids *directly* in a deoxydi/trifluoromethylation protocol using $(\text{DMPU})_2\text{Zn}(\text{CF}_2\text{H})_2$ or CuCF_3 to afford di- and trifluoromethyl ketones (see **Scheme 6, Chapter 2**).

On the other hand, difluoroacylative approaches (**Scheme 5B**) using non-fluorinated carbon nucleophiles and difluorinated acyl electrophiles stands as an attractive alternative to the previously described nucleophilic difluoroalkylation protocols of acyl electrophiles.

A. Difluoroalkylations of Acyl Electrophiles

-Many reports from pre-synthesized acyl electrophiles



Scheme 5. Representative routes to α,α -Difluoro ketones from acyl electrophiles

In this context, Amgoune and coworkers^{41a} recently reported a significant breakthrough in which a Pd-catalyzed cross-coupling of N-(difluoroacyl)-glutarimides with arylboronic acids, $Ar-B(OH)_2$, as carbon nucleophiles resulted in the desired products. However, though this is a step in the right direction, this procedure calls for elevated temperatures ($80^\circ C$) and prolonged reaction times (16 h), which makes this procedure less attractive. Nevertheless, this is the first report on the catalytic installation of the $RCF_2C(O)-$ ($R = Ar, H$) motif into carbon nucleophiles. In stark contrast, a direct installation of a $CF_3C(O)-$ functionality had been reported by Yamamoto and coworkers^{41b} in the early 2000's. This work uses phenyltrifluoroacetates as acyl electrophiles under palladium catalysis. In the case of Amgoune's work, though mechanistically novel, significant disadvantages still persist. For example, the required N-(difluoroacyl)-glutarimides are prepared from the parent α,α -difluorocarboxylic acids in low to moderate yields (44-75%).^{41a} More recently, Ban, Dai, and coworkers^{41c} reported a similar approach in which fluorinated thioesters were cross-coupled with $Ar-B(OH)_2$ under *Liebeskind-Strogl* coupling conditions.^{27b-d} In this case, after 18 hours of reaction time, CF_2H- , CF_3- , and CF_3CF_2- ketones were obtained from $Ar-B(OH)_2$ using Pd/Cu co-catalyzed conditions at room temperature. In this example, no information regarding the yield or the synthetic

route for the required thioester electrophiles was provided. Still, it is naturally expected that these electrophiles were also prepared from the parent fluorinated carboxylic acids.

In spite of the previously described advancements in synthetic methods to access α,α -difluoroketones, the *synthesis of these compounds directly from α,α -difluorocarboxylic acids under mild and practical conditions remains a critical unmet need.*

1.3 Acyloxyphosphonium ions in Synthetic Organic Chemistry

Acyloxyphosphonium ions are well established acylating agents in organic chemistry and they have found widespread applications for the acylation of N -^{42a} and O -based^{42b} nucleophiles. In fact, several commercially available $P^{(V)}$ reagents are commonly used in peptide coupling chemistry. Surprisingly, these electrophilic acyl intermediates have mostly been engaged by N -, O -, or S -based nucleophiles. Along these lines, it is notable that C–C bond formations using these reactive intermediates are extremely rare.^{42c} These phosphorus^(V) reagents are used to activate carboxylic acids for subsequent amidation, (thio)esterification or dehydration reactions, and currently, these reagents are now commonplace in most synthetic laboratories. Selected phosphonium-based coupling reagents are shown in **(Figure 4)**. It is important to note that though commercially available, these reagents are expensive and, *in some cases*, must be kept under cryogenic conditions for long-term storage.

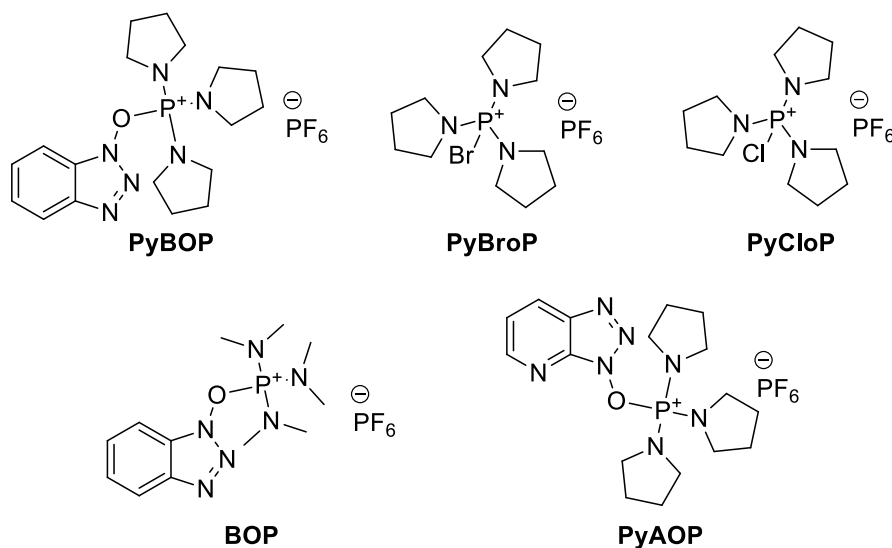


Figure 4. Representative examples of phosphonium-based reagents for peptide coupling or esterification reactions

Recognizing the ample synthetic versatility displayed by oxyphosphonium⁴³ and acyloxyphosphonium^{42,44} ions in peptide coupling,^{45a-b} Mitsunobu⁴⁶, and Appel⁴⁷ reactions, Munoz and coworkers⁴⁸ recently delineated the use of these intermediates for the synthesis of acyl fluorides. This transformation represented a significant discovery in the field as previously reported nucleophilic reactions with acyloxyphosphonium only involved *N*-, *O*-, *S*- nucleophiles.^{42,44,45} Key to the success of this transformation was the utilization of acidic fluoride source (Et₃N·3HF) while basic fluoride sources such as CsF, KF, NMe₄F all gave triphenyldifluorophosphorane (PPh₃F₂) due to fluoride attack at the phosphorus center.⁴⁸ As previously mentioned, a similar system was subsequently developed also by Munoz and coworkers⁴⁰ for the synthesis of di- and trifluoromethyl ketones (*vide infra*).

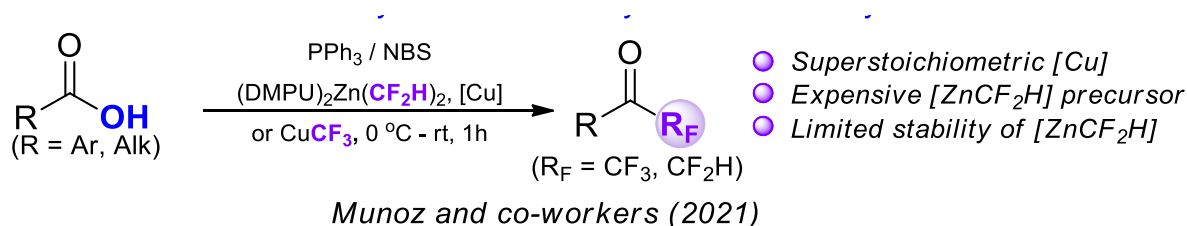
Chapter 2. Copper-Catalyzed Cross-Coupling of Organozincs with α,α -Difluorocarboxylic Acids via Acyloxyphosphonium Ions

2.1 Introductory Remarks

As previously mentioned, the scientific community is actively working towards achieving efficient and direct access to α,α -difluoroketones from readily available and inexpensive starting materials and reagents. Because carboxylic acids are ubiquitous in organic chemistry as well as naturally occurring compounds, these compounds meet this criterion and their utilization as starting materials for the synthesis of difluorinated ketones is highly sought-after. Therefore, methods that directly utilize carboxylic acids for this purpose, as opposed to pre-assembled acyl electrophiles,^{39,41} which, in turn, are derived from the carboxylic acids themselves (see **Scheme 5**) can be considered as more convenient and practical given that unnecessary synthetic and purification steps are avoided. In principle, utilization of carboxylic acids for difluoroketones synthesis can be done either by their direct conversion into the target compounds (only one isolated example using organolithiums has been reported³⁸), or alternatively, by activating them *in-situ* for subsequent functionalization. Accordingly, a lot of attention has been paid into developing novel synthetic protocols for α,α -difluoroketone synthesis using carboxylic acids directly as substrates by several research groups, including our own.

2.1.1 Previous Work: Di/trifluoroalkylation of Acyloxyphosphonium Ions

As previously mentioned, recently, Munoz and co-workers⁴⁰ disclosed a practical and operationally simple method to access di- and trifluoromethyl ketones directly from readily accessible benzoic acids via acyloxyphosphonium ions. In this protocol, acyloxyphosphonium ions were conveniently accessed from a series of substituted benzoic acids, PPh_3 and NBS and subsequently, without any isolation, they were engaged in a Cu-mediated cross-coupling process with both $(\text{DMPU})_2\text{Zn}(\text{CF}_2\text{H})_2$ and $[\text{CuCF}_3]$. (**Scheme 6**)



Scheme 6. Di/trifluoromethyl ketones through a Cu-mediated process via acyloxyphosphonium ions (**ref 40**)

Even though this method directly furnishes α,α -difluoroketones from benzoic acids in short reaction times, it is certainly not free from limitations. For example, it relies on the use of Vicic's Reagent,⁴⁹ $(\text{DMPU})_2\text{Zn}(\text{CF}_2\text{H})_2$ as a source of nucleophilic CF_2H^- and it requires superstoichiometric amounts of [Cu] reagent. In this context, it should be noted that $(\text{DMPU})_2\text{Zn}(\text{CF}_2\text{H})_2$ is easy to prepare and is a free-flowing solid that has found widespread applications in difluoroalkylation chemistry.⁵⁰ Vicic's reagent certainly exhibits superior properties when compared Burton's⁵¹ ligand-free difluoromethylzinc reagent. However, this nucleophilic $[\text{CF}_2\text{H}]$ source is prepared from pyrophoric diethylzinc (Et_2Zn) and expensive HCF_2I , which is a potentially ozone-depleting substance and a difficult-to-handle compound, usually sold in gas cylinders (b.p. = 21.6 °C). Furthermore, this nucleophilic $[\text{CF}_2\text{H}]$ source is rather unstable and must be stored in a glovebox under strictly anhydrous conditions. Munoz and coworkers have noted that best results are obtained when this reagent is used shortly after its preparation to avoid its decomposition and afford high yields of difluoromethyl ketones.⁴⁰ Taken together it was deemed essential to develop an alternative, more convenient approach. The results of our group's investigations in this endeavor will be discussed in the next section. However, before delving into the details of this chemistry, a discussion on the nature, properties, and versatility of organozinc reagents, the carbon nucleophiles used throughout our work, is presented.

2.1.2 Remarks on Organozinc Reagents vs Other Carbon Nucleophiles

In recent years significant advances in organozinc chemistry have been made therefore, key remarks on their properties and reactivity are highly warranted. Thus, the following paragraphs will address this topic in some detail.

Historically, insertion of zinc metal into $\text{C}(\text{sp}^3)\text{-X}$ bonds required highly reactive zinc obtained through the activation by TMSCl (trimethylsilyl chloride) and 1,2-dibromoethane as reported by Gaudemar.⁵² This protocol, however, only works for activated benzylic halides and requires the use of polar solvents. Subsequently, other methods to activate zero-valent Zn powder, such as the use of catalytic amounts of I_2 as disclosed by Huo and coworkers⁵³ were developed. However, a significant breakthrough came when Knochel and coworkers⁵⁴ delineated an enhanced approach, in which the utilization of LiCl promoted a smooth formation of highly functionalized organozinc reagents. Since then, Knochel's group has remained at the forefront of organozinc chemistry and has continued to enhance the practicality and enable the preparation of these types of organozinc nucleophiles with

great facility. As a testament of this fact, the preparation of solid, *air-stable* organozinc pivalates (RZnOPiv) is now possible.⁵⁵⁻⁵⁶ Furthermore, Knochel has also employed TMPZnOPiv-LiCl as a strong base (TMP = tetramethylpiperidine) to directly perform zincation of C-H bonds of heterocyclic compounds.⁵⁶ Furthermore, these reagents enjoy a functional group compatibility which can only be described as being vastly superior and unrivaled, especially when compared to Grignard⁵⁷ and organolithium reagents.¹⁹ Organozinc reagents are for example compatible with esters, aldehydes, ketones, cyano, and amide functionalities with which organomagnesium or organolithium reagents are incompatible. (**Figure 5**)

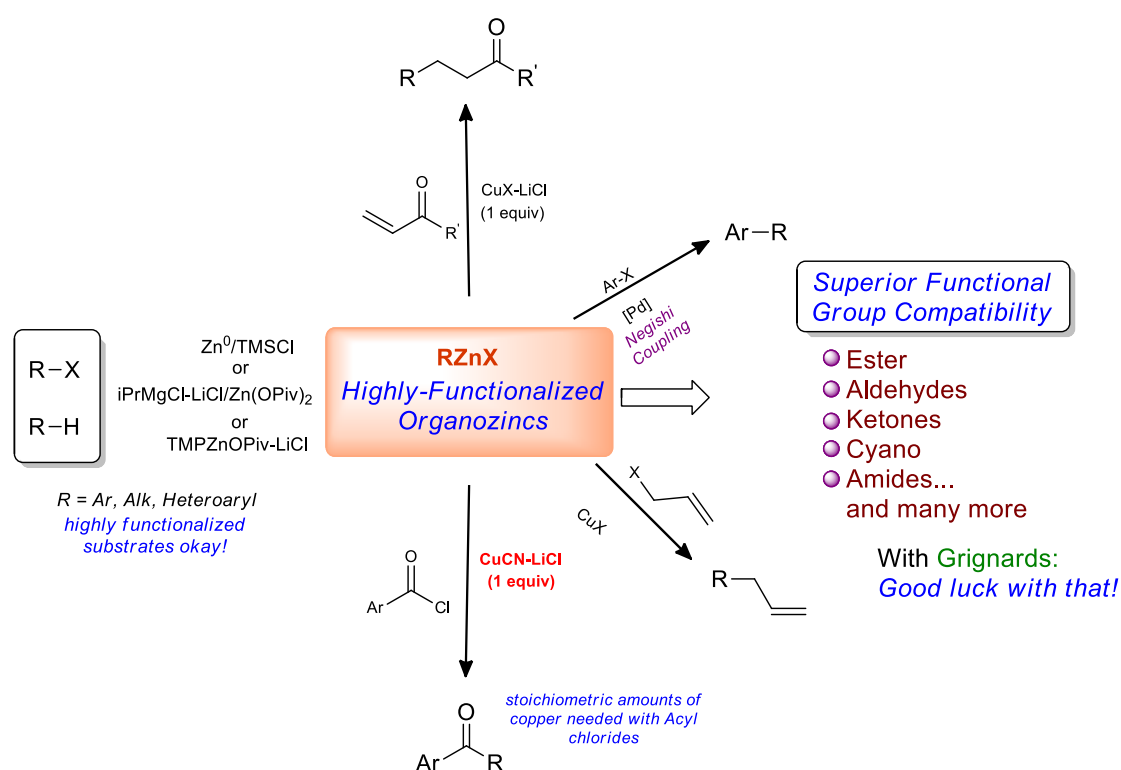


Figure 5. Organozinc reagents: uses and superior functional group compatibility

Taken together, all these new developments for accessing organozinc reagents⁵⁸ render them the reagents of choice over highly reactive organolithiums and organomagnesium compounds. Thus, Knochel's contributions⁵⁴⁻⁵⁸ in the field of organozinc chemistry stand as a major breakthrough, and they are beyond any doubt a fascinating and enabling technology for the synthetic organic chemistry community.

On the other hand, organoboron reagents (boronic acids and esters) could, at first glance seem as more convenient alternatives to organozincs. This can be true if is seen only through the prism of their chemical stability and commercial availability, which is indeed their major advantage. However, their reactivity profile is lower compared to organozincs as they require activation by a

Lewis base. Furthermore, recent investigations have led the pharmaceutical industry to start shifting away from using boronic acids, due to recent findings about their mutagenicity.⁵⁹ This is especially true at industrial scale applications where the risk of exposure is increased. As a result, the trained eye can recognize organozinc reagents, with their balanced stability, ease of preparation, and *vastly superior functional group tolerance*, as much more advantageous. In addition to the above-mentioned properties, organozinc reagents also enjoy a good nucleophilicity profile, and lack the mutagenic effects observed in boronic acids.⁵⁹ Notably, organozinc reagents have been used for ketone synthesis mostly through a *copper-mediated* processes, in which stoichiometric amounts of CuCN-2LiCl must be employed.^{54,56} Cross-coupling reactions of organozinc nucleophiles using catalytic amounts of copper as the sole catalyst are, to the best of our knowledge unprecedented, and often these reactions require small amounts of a Pd as a co-catalyst.^{54,60}

2.2 Current Work: Difluoroacylation of Organozincs

2.2.1 Introductory Remarks

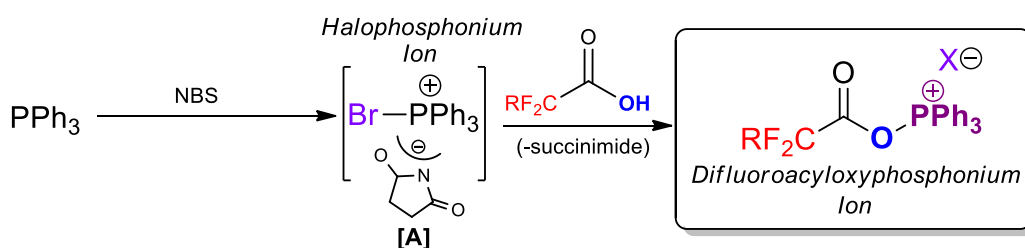
Considering the above-mentioned limitations exhibited by Munoz's previously reported deoxydifluoromethylation protocol using Vicic's difluoromethylzinc reagent (**Scheme 6, ref 40**), and with the advent and significant developments in organozinc chemistry as demonstrated by Knochel,⁵⁴⁻⁵⁸ our group set out to develop an improved method to access α,α -difluoroketones. In this context, our group's attention was focused in developing a protocol that avoids the use of either expensive or unstable reagents such as CF₂HI, or (DMPU)₂ZnCF₂H, respectively.

Furthermore, we considered that an optimal method to prepare α,α -difluoroketones should enjoy the following features:

- (i) Avoid the isolation of any acyl electrophiles
- (ii) Take advantage of the wide availability of α,α -difluoro acids
- (iii) Take advantage of the improved stability, superior functional group compatibility, and balanced reactivity, of non-fluorinated organozinc reagents.

Toward this goal, we surmised that α,α -difluoroacyloxyphosphonium ions could be generated from inexpensive *gem*-difluoro acids, using conditions similar to the ones previously reported ⁴⁰ i.e. via the reaction of difluorocarboxylic acids with PPh₃/NXS (X = Cl or Br) reagent system. (**Scheme 7**)

Collaborative efforts within our group found that these highly reactive intermediates can be accessed within minutes under very mild conditions (0°C-RT) by the reaction of triphenylphosphine and an oxidant, usually an *N*-halosuccinimide, NXS (NCS or NBS), in the presence of a difluorinated carboxylic acid. This process occurs via the intermediacy of a halophosphonium ion, which is rapidly converted into the acyloxyphosphonium ion, with concomitant extrusion of succinimide. (**Scheme 7**)



Scheme 7. α,α -Difluoroacyloxyphosphonium ions from α,α -difluorocarboxylic acids

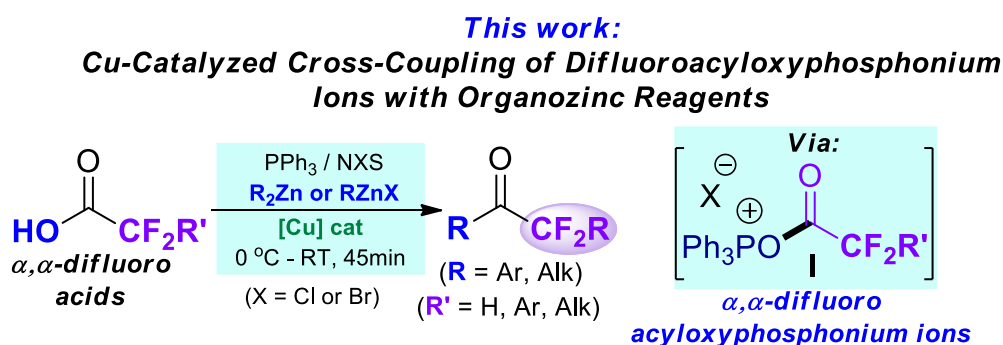
Accordingly, inspired by our two previous protocols using carboxylic acids for deoxyfluorination⁴⁸ and deoxyfluoroalkylation⁴⁰ via acyloxyphosphonium ions, we surmised that α,α -difluorocarboxylic acids could be directly converted into the corresponding α,α -difluoroketones via the intermediacy of α,α -difluoroacyloxyphosphonium ions. Notably, these fluorinated phosphonium species had not been synthesized nor characterized before.

Importantly, it should be noted that the work on difluorinated ketones shown below was conducted by various members of the Munoz group, mainly by Dr. Md. Nirshad Alam. However, for completeness, and due to the fact that a single publication⁶¹ delineates the preparation of both *gem*-difluoro as well as benzophenones, the results of the investigations using both types of carboxylic acids (α,α -difluoro and benzoic acids) will be presented and discussed in this work. It should be emphasized however, that the main focus of this thesis will be centered on the work I have conducted, which entailed the utilization of non-fluorinated carboxylic acid (benzoic acids) for the synthesis of benzophenones (**Chapter 3**) which is part of the same publication.⁶¹

Implementation of a synthetic methodology utilizing α,α -difluorinated acids under mild conditions stands as a highly important advance in the field, due in part to the disadvantages that the other current methodologies present, such as the need of cryogenic temperatures with highly reactive organometallics (RLi or RMgX), prolonged reaction times, use of precious metal catalysts (Pd),^{41a,c} amongst other limitations. Furthermore, most existing reports to date all have a pressing limitation

namely, the requirement of a pre-assembled acyl electrophile, thereby severely restricting their practicality, particularly when it comes to industrial settings. Though efficient for laboratory scale applications, arguably the protocols that employ highly reactive organometallic reagents like RMgX or RLi in combination with α,α -difluoro acyl electrophiles such as amides^{38d} or esters^{38b}, as reported by Hartwig and coworkers can be regarded by some as unpractical due to the required strict control of reaction conditions and the need for cryogenic temperatures.

The work presented here on *difluoroacylation of organozincs*, enabled us to achieve a *direct* installation of the $-(CO)CF_2R$ ($R = Ar, Alk, H$) motif in the form of a difluoroacyl electrophile. This represents a complementary, yet more practical and operationally simple protocol when compared to the one reported by Amgoune^{41a} or Ban and Dai^{41c} using pre-assembled acyl electrophiles (see Scheme 5 above). This effectively results in enhanced overall practicality, cost-efficiency, and simplicity. Notably, it was found that the nature of the carboxylic acid determined whether or not Cu-catalysis was necessary (*vide infra*) (**Scheme 8**).



Scheme 8. Difluoroacylation of organozinc reagents directly from difluoro acids

2.2.2 Aryldifluoromethyl Ketones from Aryldifluoroacetic Acids

Optimization of the reaction conditions

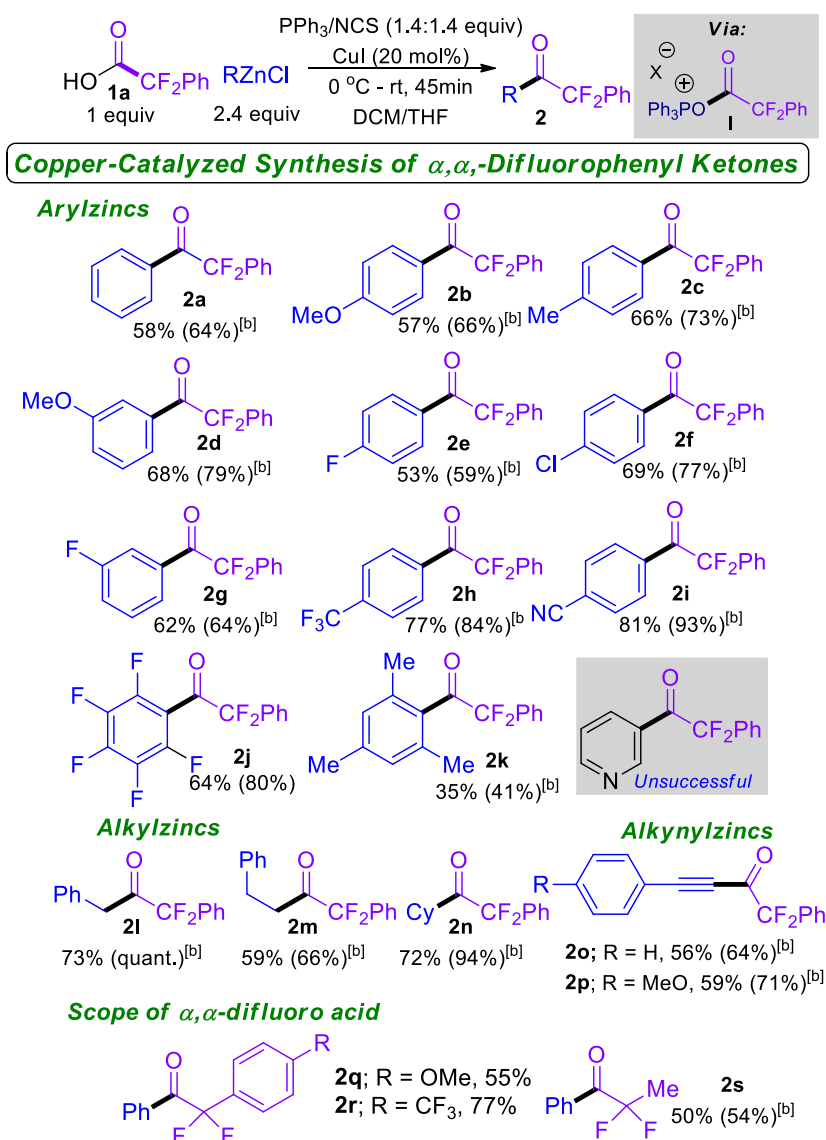
Initial efforts for difluoroketone synthesis using difluorocarboxylic acids were focused on the use of PhMgBr (and other Grignard reagents) as carbon nucleophiles. However, as discovered by Prof. Munoz and some of our group members, this reaction yields a complex mixture, and no target ketones were obtained. Instead, attack at the P-center yields a mixture of tetraphenylphosphonium salt, anhydrides and starting material carboxylic acids.

In light of the well-established balanced reactivity and superior functional group compatibility of organozinc reagents as highlighted above, our attention was thus focused on their use. Preliminary experiments for the synthesis of phenyldifluoromethyl ketone, PhCF₂(CO)Ph **2a** were carried out primarily by Dr. Md Nirshad Alam and by other group members during early stages

of the project. This was done using commercially available α,α -difluorophenylacetic acid **1a** as a model substrate. Under our previously optimized conditions for deoxydifluoromethylation of benzoic acids⁴⁰ (PPh₃/NBS; 1.4 equiv each); the target product **2a** was obtained in a meager 39% yield (as determined by ¹⁹F NMR analysis) upon reaction with Ph₂Zn (1.2 equiv) as a carbon nucleophile and *in the absence* of Cu-catalyst. After *extensive optimization studies*, optimal results were obtained by treatment of **1a** with *N*-chlorosuccinimide (PPh₃/NCS; 1.4 equiv each) in dichloromethane as solvent (DCM; 0.1M) at 0°C for 10-15min, followed by addition (reverse addition mode) of a THF solution (~1M) of organozinc chloride, PhZnCl (2.4 equiv) in the presence of catalytic amounts of CuI (20 mol%). Notably, in these cases, arylzinc chlorides proved superior to diorganozinc reagents, and NCS performed better when compared to NBS. We hypothesize the larger amounts of Zn^(II), present when ArZnCl are used, is likely to promote product formation by serving as a Lewis acid, further activating the electrophilic species. As far as the better performance of NCS vs NBS, the reader is referred to **Chapter 4** where a detailed discussion on the NMR spectroscopic investigations revealed the nature of electrophilic species formed and its relationship with the nature of the oxidant used (NBS vs NCS).

Under the optimized conditions mentioned above, **2a** was smoothly and rapidly (45 min) generated in 64% yield as determined by ¹⁹F NMR spectroscopy under exceedingly mild conditions (0°C to room temperature). With these conditions in hand, we explored the generality and scope of this Cu-catalyzed procedure and the results are shown in (**Scheme 9**). First, the scope of arylzinc chlorides was studied using **1a** as the model substrate and pro-electrophile. ArZnCl nucleophiles bearing electron-donating, electron-neutral and electron-withdrawing groups all afforded the target ketones **2a-2k** in satisfactory yields in fast reaction times. Methyl and methoxy substituents afforded **2b-2d** in good yields. Chloro- and Fluoro-substituted ArZnCl at different positions all cleanly afforded the corresponding ketones **2e-2g** in good yields. Electron-deficient arylzincs were also well tolerated and 4-CF₃, 4-CN-, and pentafluorophenylzinc chlorides gave the target products **2h**, **2i**, **2j** in 80-93% yields as determined by ¹⁹F NMR.

Scheme 9 Copper-Catalyzed Synthesis of Difluorophenyl Ketones



^[a] Conditions: 0.25 mmol (1 equiv) of α,α -difluoro acid **1**, PPh_3 (1.4 equiv), NCS (1.4 equiv), PhZnCl (1.2 equiv) and CuI (0.05 mmol); Isolated yields. ^[b] Yields in parenthesis as determined by ^{19}F NMR using PhOCF_3 as internal standard. See *Experimental Section* for full details.

In some cases, product loss during purification could not be avoided (**2j**, 64% isolated yield vs 80% by ^{19}F NMR). Though a modest isolated yield of **2j** was obtained, this result is notable as it is in stark contrast with the results described by Amgoune and Monteiro^{41a} in which attempts to prepare **2j** using *N*-difluoroacyl glutarimides, $\text{C}_6\text{F}_5\text{-B(OH)}_2$ under Pd-catalysis were completely unsuccessful. As expected, the bulkier mesityl group led to low yields of **2k** presumably due to steric factors. Gratifyingly, more reactive alkylzincs (benzyl, phenethyl and cyclohexyl) were also well tolerated under our reaction conditions and in these cases, excellent yields of **2l** and **2n** were obtained, albeit phenethyl derivative **2m** was obtained in slightly lower yield (59% isolated). Importantly, in all these

cases, no double addition by-products (a common side reaction when electrophilic ketones are involved) was detected. This was also true even in the case of more nucleophilic aliphatic organozincs (**2l-2n**). Notably, cyclohexyl-substituted ketone **2n**, was obtained in 94% by ^{19}F NMR, whereas this product was not obtained in Amgoune's report.^{41a} Nevertheless, it is important to acknowledge that the existing approach does not support the inclusion of the 3-pyridylzinc chloride, which stands as a current constraint and limitation of our protocol. The reasons for these unsuccessful results are yet unclear and investigations to understand the origin of these unsuccessful results are currently underway in our laboratory.

Alkynes are a versatile functionality for the synthesis of valuable organic compounds, serving as useful handles for further chemical elaborations.⁶² Thus, motivated by the success of different types of aryl- and alkylzinc nucleophiles, we were eager to explore the generality of our protocol using zinc acetylides as nucleophilic coupling partners. Accordingly, propargyl ketones **2o** and **2p** derived from alkynylzinc reagents were smoothly formed. Subsequently, other α,α -difluoro acids were screened and 4-OMe and 4-CF₃ substituted difluoroarylacetic acids, smoothly afforded good yields of the target products, **2q** and **2r**, respectively. Finally, α,α -difluoropropanoic acid **1s** furnished ketone **2s** in synthetically useful isolated yield of 54% (**Scheme 9**).

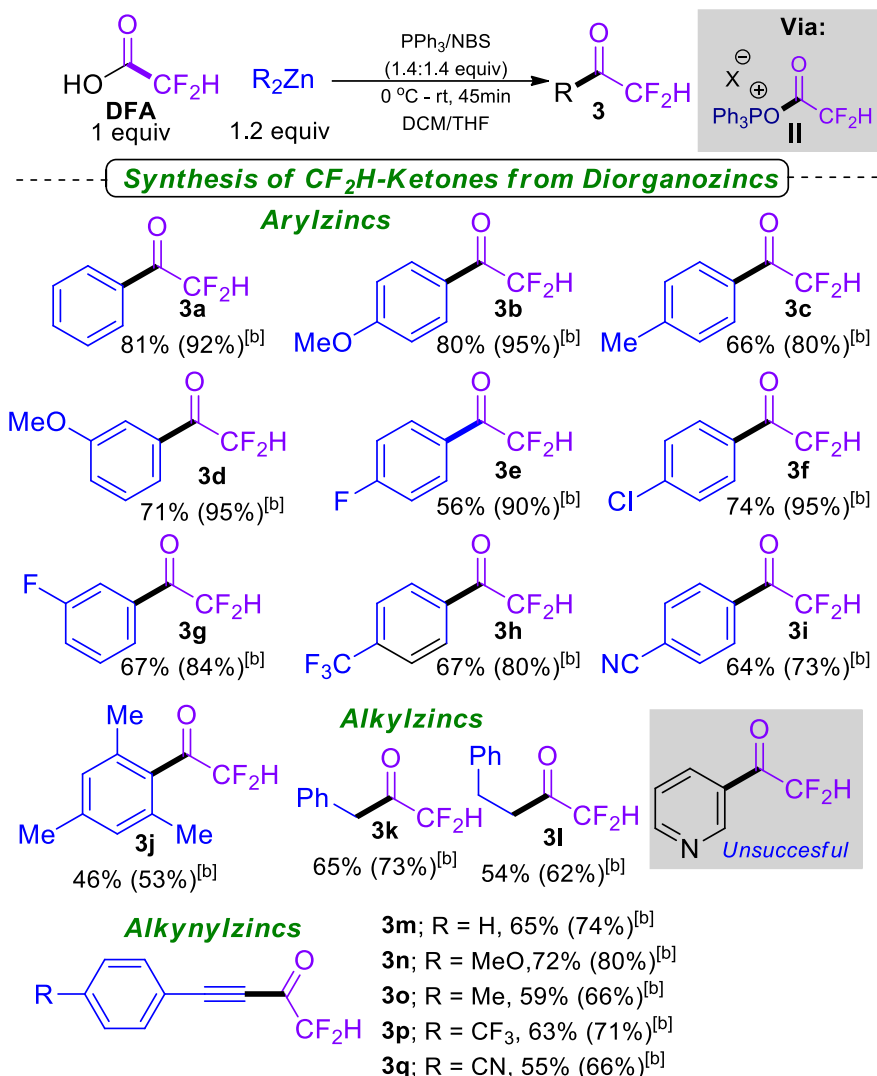
2.2.3 Difluoromethyl Ketones from Difluoroacetic Acid

By employing a similar procedure with difluoroacetic acid (DFA) as the most convenient produce of the difluoroacetyl functionality, our group successfully obtained difluoromethyl ketones **3** in a fast and efficient manner under mild reaction conditions (0°C to RT, in 45 min) (**Scheme 10**). In this specific case, the fact that the reaction is effective *even in the absence of a copper catalyst* warrants special mention. We surmise that this is likely due to a higher electrophilicity of the α,α -difluoroacyloxyphosphonium species **[II]** formed. This contrasts with the need for Cu-catalysis to effectively prepare aryl difluoromethyl (ArCF₂) ketones **2**. Intriguingly, in this case (using DFA) diorganozinc reagents (1.2 equiv), as opposed to organozinc chlorides were found to yield the best results, in combination with NBS as the optimal oxidant. We surmised that a likely higher electrophilicity of **[II]** obviates the need for Cu-catalysis and higher loadings of Lewis acidic Zn^(II) as required in the case of ArCF₂COOH substrates **1**, where ArZnCl (2.4 equiv) were required.

With the optimized conditions in hand, the generality and scope of this transformation was subsequently studied using a variety of diorganozinc, R₂Zn nucleophiles (R = aryl and alkyl). The results of this investigation are shown in **Scheme 10**. Organozinc reagents featuring electron-

donating, electron-neutral, and electron-withdrawing groups, all yielded the desired ketones **3a-3j** efficiently, with short reaction times.

Scheme 10 Synthesis of Difluoromethyl Ketones Under Cu-Free conditions



^[a] Conditions: 0.25 mmol of DFA (1 equiv), PPh_3 (1.4 equiv), NBS (1.4 equiv), Ph_2Zn (1.2 equiv); isolated yields shown.

^[b] Yields in parenthesis as determined by ¹⁹F NMR using $PhOCF_3$ as internal standard.

The target products **3k** and **3l** were successfully obtained using more reactive dialkylzinc reagents, and notably, formation of double addition by-products was not observed at all. This is particularly noteworthy as difluoromethyl ketones **3** are electrophilic and known to undergo subsequent addition reactions with carbon nucleophiles (especially $RMgX$ or RLi),³¹ which highlights the key nature of organozinc reagents for the success of this protocol. Just like the synthetic procedure towards products **2**, this approach also has a limitation where 3-Pyridyl-substituted organozincs were found to be unsuccessful in the generation of the desired products. The causes behind these subpar outcomes

hitherto remain unclear. In contrast, propargyl CF₂H ketones **3m-3q** were obtained in high yields using dialkynylzinc reagents. Notably, electron-deficient zinc diacetylides produced **3p** and **3q** in synthetically useful isolated yields (63% and 55%, respectively). It should be mentioned that in certain cases, such as in **3e**, the high volatility of the target compounds prevented us from obtaining high isolated yields however, yields as determined by ¹⁹F NMR spectroscopy were determined to be high (90%).

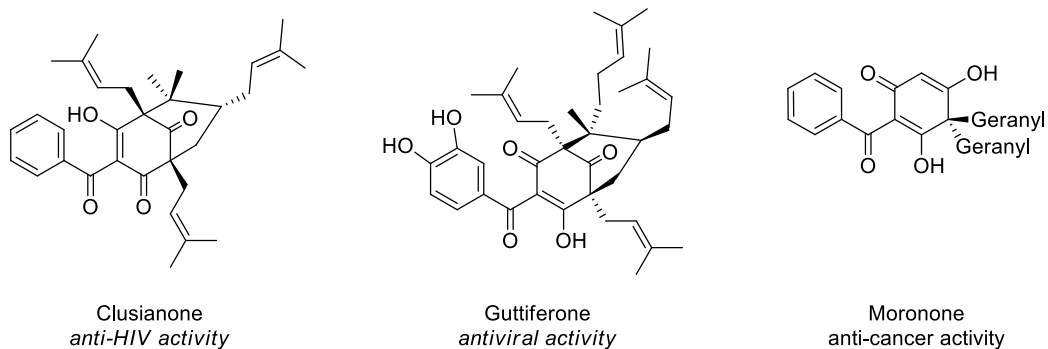
Chapter 3. Copper-Catalyzed Cross-Coupling of Organozincs with Benzoic Acids via Acyloxyphosphonium Ions

3.1. Introductory Remarks

Benzophenones are highly significant scaffolds, and they occupy a central role in organic chemistry. They are present in numerous active pharmaceutical ingredients, and moreover, the keto-functionality serves as a versatile handle for synthetic chemical elaborations. In addition, this motif is widely prevalent in a variety of naturally occurring compounds and in some cases, they have found to exhibit diverse biological activities (*vide infra*).^{63a}

It has been estimated that around 77% of known naturally occurring benzophenones come from plants in the *Clusiaceae* family.^{63b} These compounds have been reported to have various biological activities, including antifungal, anti-HIV, antimicrobial, antiviral, and antioxidant properties.⁶⁴ For instance, Clusianone, a prenylated benzophenone, has been shown to exhibit anti-HIV activity,⁶⁵ similarly, Guttiferone is shown to exhibit antiviral activity.⁶⁶ Another important naturally occurring benzophenone is the compound Moronone, (**Figure 6-top**) isolated from *Moronobea coccinea*, which exhibits anti-cancer activity.⁶⁷ Furthermore, several synthetic benzophenones are utilized as active pharmaceutical ingredients and sun-protective agents (**Figure 6-bottom**). For instance, ketoprofen⁶⁸ is a potent anti-inflammatory drug known for its analgesic and antipyretic properties. Tolcapone (marketed as Tasmar), a dihydroxy derivative of benzophenone, is prescribed for Parkinson's disease.⁶⁹ Fenofibrate (Tricor) is primarily used to reduce cholesterol levels in humans at risk of cardiovascular disease.⁷⁰

Naturally-occurring benzophenone compounds



Benzophenones- as API's

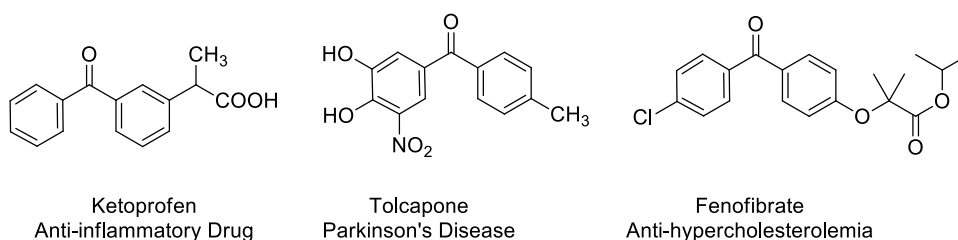


Figure 6: Naturally occurring (Top), and synthetic bioactive Benzophenones (Bottom)

In pursuit of a simple strategy for ketone synthesis and seeking a direct method for benzophenone synthesis, we found inspiration in the successful preparation of α,α -difluoroketones **2** and **3** described in the previous chapter. Thus, we were prompted to interrogate the hypothesis of whether benzoic acids **4** would also be amenable substrates under the current strategy. If successful, such a transformation would provide a quick and efficient access to the corresponding benzophenones and would offer a complementary, perhaps more convenient approach than the commonly used Pd-catalyzed Fukuyama ketone synthesis, Weinreb ketone synthesis, Liebeskind-Srogl coupling, and other conventional methods for producing ketones from acyl electrophiles.²²⁻²⁹ This investigation not only expands our range of synthetic possibilities but also offers a simplified and effective route to various ketone structures.

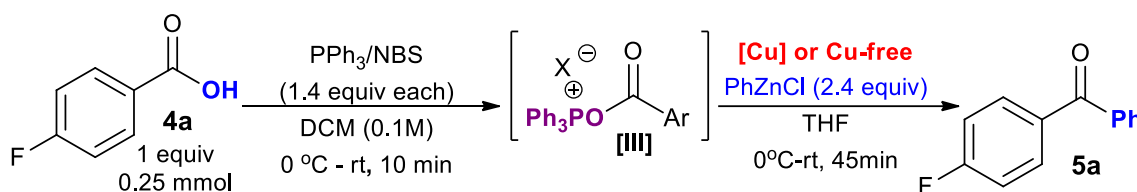
3.2 Optimization of the Reaction Conditions

Previous reports by Munoz and coworkers on deoxyfluoroalkylation^{40a} and deoxyfluorination⁴⁸ of benzoic acids had established the formation of acyloxyphosphonium species **[III]** derived from benzoic acids upon treatment with PPh_3/NBS in DCM solvent at 0°C to RT for 15 min. Toward the synthesis of benzophenones, our optimization efforts were conducted using 4-fluorobenzoic acid **4a** as the model substrate and PhZnCl as the carbon nucleophile (2.4 equiv). This

substrate **4a** was selected because its fluorine tag enabled us to rapidly assess the outcome of the reaction by quantitative ^{19}F NMR analysis.

It was anticipated that less electrophilic species **[III]**, derived from benzoic acids would require a Cu^{I} catalyst to promote ketone formation. To interrogate this hypothesis, we conducted control experiments with and without copper catalyst. Indeed, it was found that in the absence of the Cu catalyst formation of the desired ketone could not be observed. In contrast, and as expected, when the reaction was conducted in the presence of catalytic amounts of a Cu^{I} salt (CuI ; 20 mol%) the target benzophenones **5** were smoothly prepared after 45min from 0°C to room temperature. Notably, protodemetalation products were the main products detected in the absence of Cu-catalyst and no benzophenone product was observed. (**Table 1**)

Table 1. Effect of Cu-catalyst for Benzophenone Synthesis Using PhZnCl



Entry	[Cu] Source	5a %Yield (^{19}F NMR)
1	none	n.d.
2	CuI (20 mol%)	69

^[a] Conditions: 0.25 mmol of **4a** (1 equiv), PPh_3 (1.4 equiv), NBS (1.4 equiv) were stirred in DCM from 0°C -RT, followed by addition of a PhZnCl (2.4 equiv in THF); Entry 1: no copper; Entry 2: electrophile **[III]**, was transferred to a vial containing CuI (20mol%) prior to addition of PhZnCl in THF ^[b] Yields as determined by ^{19}F NMR using PhOCF_3 as internal standard.

These results employing inexpensive copper salts as the sole catalyst contrast with previous reports in which coupling of organozinc reagents with acyl halides require either stoichiometric amounts of $[\text{Cu}]$ or the presence of precious $[\text{Pd}]$ co-catalyst.⁵⁴⁻⁶⁰ Thus, the present method stands as a significant addition to the current toolbox for benzophenone synthesis.

Effect of Organozinc Nucleophile Stoichiometry.

Optimal results were obtained using PhZnCl (2.4 equiv) as the carbon nucleophile. Previous investigations using fluorinated acids showed that utilization of smaller amounts of organozinc nucleophile afforded lower yields of the target fluoroketones. It was surmised that these

unsatisfactory results are likely due to the fact that at least 1 equiv of active carbon nucleophile can be effectively quenched by succinimide released after formation of acyloxyphosphonium electrophile. Similarly, NBS was found to be a convenient oxidant which outperformed NCS in the case of products **3**. Thus, our subsequent investigations were focused on using this optimized procedure with the only exception being that organozinc halides (ArZnCl , 2.4 equiv) were employed instead of diorganozinc reagents (Ar_2Zn ; 1.2 equiv). It should be clarified that in either case, 2.4 equiv of active carbon nucleophile would be available to engage the electrophilic species **[III]**. This said, efforts to decrease the amounts of organozinc nucleophile were not pursued on the basis of said previous experimentation.

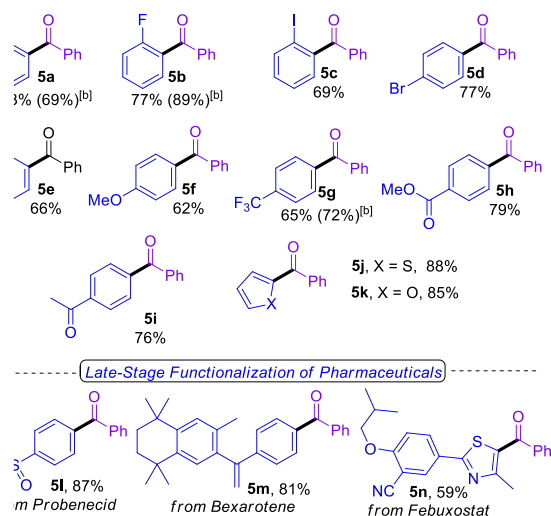
In summary, optimal results for benzophenone synthesis were found when benzoic acids **4** (1 equiv), were pre-activated with PPh_3/NBS (1.4 equiv each) in DCM from 0°C to RT for 15 min, followed by dropwise addition of a THF solution ($\sim 1\text{M}$) of PhZnCl (2.4 equiv) at 0°C and further stirring of this mixture for 45 min while allowing it to slowly warm up to room temperature.

3.3 Copper Catalyzed Synthesis of Benzophenones via Acyloxyphosphonium Ions

In order to test the generality of our method using the optimized conditions mentioned above for **4a**, several other substituted benzoic acids were tested, and the results are shown in **Scheme 11**. Gratifyingly, acyloxyphosphonium ions **[III]**, derived from halo-substituted benzoic acids, 4-fluoro, 2-fluoro, 4-iodo, 4-bromo show a remarkable ability to yield the desired benzophenone products **5b-5d**. Other electron-withdrawing groups such as 4-trifluoromethyl benzoic acid, satisfactorily furnished **5g** in 65% isolated yield within 45 minutes. These results showcase the ability of our method to tolerate electron-withdrawing functionalities at both at the ortho- and para- positions in the aromatic ring of benzoic acids. Moreover, the reaction demonstrated good tolerance towards electron-donating and electron-neutral functionalities and the target ketones **5e** and **5f** were obtained in moderate yields (62-66%). Noteworthy, our approach exhibited excellent chemoselectivity, since methyl ester motifs as well as acetyl-substituted benzoic acids were well tolerated and ketones **5h** and **5i** were successfully prepared in high yields without any signs of undesired addition to the carbonyl motifs of these substrates.

Next, carboxylic acid substrates containing heterocyclic groups such as thiophene and furan were evaluated, and it was noted that our method exhibited a high level of compatibility with said heterocycles, giving rise to ketones **5j** and **5k** in 88% and 85% yield, respectively.

Scheme 11 Synthesis of Benzophenones Under Cu conditions^[a]



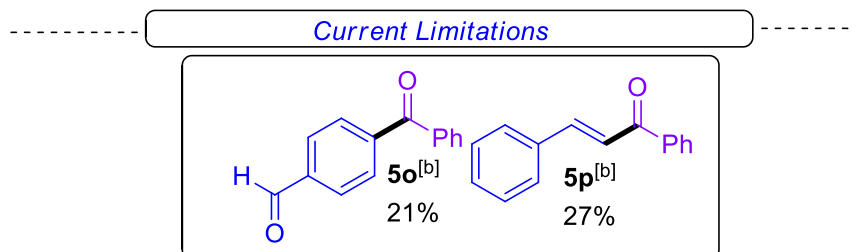
^[a] Reaction conditions: 0.25 mmol of benzoic acid **4** (1 equiv), PPh₃ (1.4 equiv), NBS (1.4 equiv), PhZnCl (2.4 equiv) and CuI (0.05 mmol); Isolated yields shown. ^[b] Yields in parenthesis as determined by ¹⁹F NMR using PhOCF₃ as internal standard.

In pursuit of medicinally active compounds, we conducted a late-stage functionalization of several FDA-approved drugs that contain the carboxylic acid functionality. Pleasingly, we were able to demonstrate the applicability of our protocol, to probenecid, bexarotene, and febuxostat, all of which were smoothly converted into their respective ketone derivatives **5l–5n**, between 59% and 87% yields. These results highlight the ability of our approach to work effectively with many functional groups, including nitriles, sulfonamides, exocyclic olefins, ether as well as heterocyclic functionalities like thiazole.

The method presented herein is not free from limitations. A drawback of the present method is highlighted by the fact the ketone **5o** containing the formyl functionality was only isolated in 21% yield. The major side product in this case is the corresponding alcohol which results from the addition of organozinc nucleophile to the aldehyde moiety. Similarly, when employing trans-cinnamic acid, the resultant product **5p** was obtained in low yield (27%), (Scheme 12) likely due to a

competing 1,4-addition process. This is likely due to both Cu^(I) and Zn^(II) salts which can act as Lewis Acids and promote this unproductive side reaction.⁷¹

Scheme 12 Current Limitations of the present method^[a]

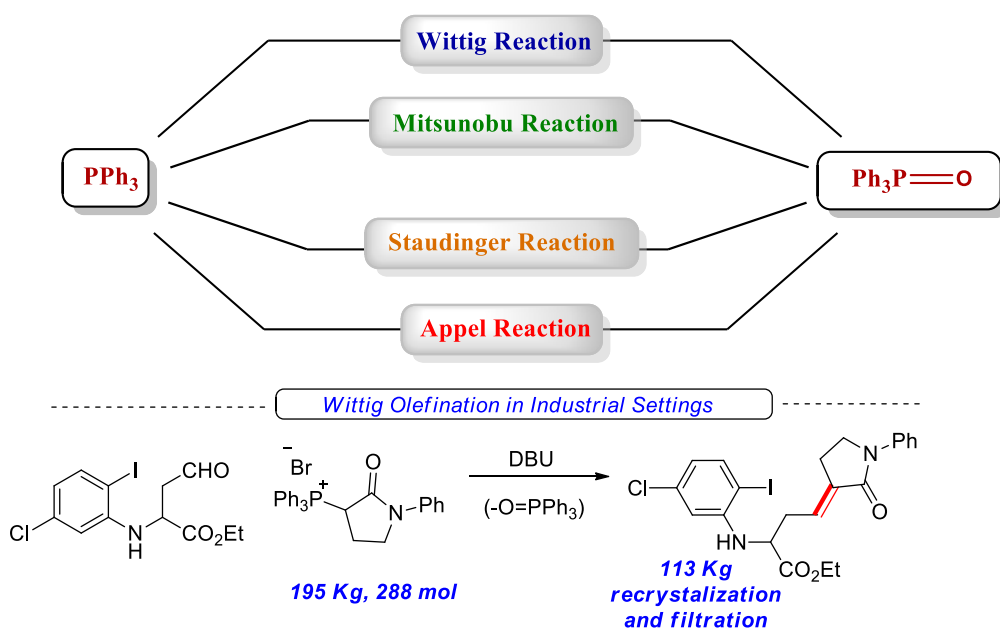


^[a] Reaction conditions: 0.25 mmol of benzoic acid **4** (1 equiv), PPh₃ (1.4 equiv), NBS (1.4 equiv), PhZnCl (2.4 equiv) and CuI (0.05 mmol); Isolated yields shown. ^[b] Yields in parenthesis as determined by ¹⁹F NMR using PhOCF₃ as internal standard.

3.4 Remarks on Atom Economy and Triphenylphosphine Oxide

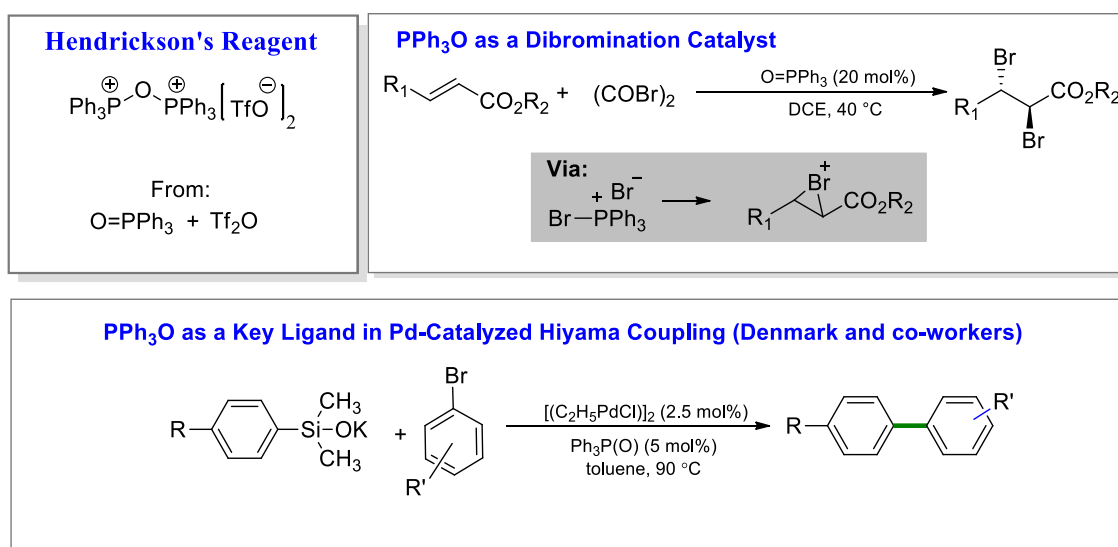
In 1991, Trost⁷² brought the concept of "atom economy" to the forefront of synthetic chemistry, emphasizing that every atom from the reagents should ideally end up in the final product. While this concept effectively tackles the problem of waste from reaction byproducts, it does not consider the waste generated from solvents or purification procedures such as work-up or chromatography.

While our approach may initially appear to have a less favorable atom economy due to the formation of 1 equiv of triphenylphosphine oxide, this aspect must be viewed through the prism of practicality, utility, and advantage of the method at hand. For example, there are numerous instances in the pharmaceutical and other industries where triphenylphosphine oxide is produced as a by-product of several reactions (**Scheme 13-top**) such as Appel,⁷³ and Wittig reactions.⁷⁴ In spite of this, these reactions are routinely conducted on a large scale. One of many examples of a Wittig olefination conducted at a scale of 195 Kg⁷⁵ is shown below. In this case, the product is isolated, phosphine oxide produced is separated and not wasted by simple recrystallization and filtration(**Scheme 13-bottom**).



Scheme 13 Reactions that generate OPPh_3 routinely in multikilogram scale in industrial settings (top); One example of a Wittig Olefination conducted at 195 Kg scale. O=PPh_3 is generated as a by-product and easily separated (see ref. 75)

In cases where O=PPh_3 is generated as a by-product, naturally, the compound separated is isolated and utilized. In this fashion, instead of being wasted, it becomes a valuable commodity chemical, which is also utilized as a reagent in various transformations⁷⁶ as a catalyst⁷⁷ and ligand⁷⁸ for several transition metals (*vide-infra*). For example, O=PPh_3 is a crucial component of the Hendrickson Reagent⁷⁹ (triphenylphosphine oxide ditriflate), which has been widely employed in amide and acid anhydride synthesis.⁸⁰



Scheme 14. Versatility O=PPh_3 as reagent, catalyst and key ligand in Hiyama Couplings see **ref 77-80**

Furthermore, O=PPh_3 also serves as a catalyst in the dibromination of α,β -unsaturated esters,⁷⁷ (**Scheme 14**) and it functions as a promoter in the diastereoselective synthesis of α -ribofuranosides,⁸¹ just to name a few examples. In addition, a recent monograph showcases a wide range of derivatizations that can be performed on triphenylphosphine oxide, beyond the reduction back to triphenylphosphine.⁷⁶ It is well-established that these kinds of reactions are conducted almost routinely in industrial settings at very large scale.

4. Mechanistic Considerations

4.1 Control Experiments using ^{19}F and ^{31}P NMR Spectroscopy

Prior studies conducted by the Munoz research team suggested that unsubstituted benzoic acid does not produce benzoyl bromide upon treatment with PPh_3/NBS in DCM from 0°C to RT and that acyloxyphosphonium ion of type **[III]** is really the active electrophilic species.^{40a} Notably, in addition to our previous findings, it has also been reported that benzoic acids afford appreciable amounts of acyl bromides upon reaction with PPh_3/NBS **only** under refluxing dioxane conditions⁸² but not in DCM at 0°C (our reaction conditions). However, a study outlining substituent effects on benzoic acids or using α,α -difluorinated carboxylic acids has not been reported.

With this in mind and with the goal of increasing our mechanistic understanding a series of control experiments were conducted. The experiments were designed to shine light into the structural nature of the acyl electrophile species responsible for the successful acylation of organozincs, and to have certainty of the active electrophile generated under our reaction conditions. Accordingly, we conducted several NMR spectroscopic investigations with each kind of acid (PhCF_2COOH , HCF_2COOH , 4-fluoro- and 4-trifluoromethylbenzoic acid). We utilized conditions identical to the ones used as optimal for each family of ketones **2**, **3** and **5**. Namely, we used NBS for DFA and benzoic acids, while NCS was used in the experiments with PhCF_2COOH , **1a**.

Reaction Between NCS and PPh_3 (1:1) - Figure 7a

In a 4 mL vial, PPh_3 (0.14 mmol, 1 equiv) was charged with a stir bar and CDCl_3 (1 mL, 0.14 M) was added at room temperature. This reaction mixture was cooled to 0°C -rt (ice-bath) and then solid *N*-chlorosuccinimide (0.14 mmol, 1 equiv) was added in one portion quickly. The vial was further stirred at 0°C (ice-bath) for 2 min then transferred to the *J*-Young NMR tube under N_2 balloon. The ^{31}P NMR spectrum of this reaction showed two species resonating at δ 64.93 and δ 32.14 which correspond to the known chlorophosphonium ion **[A]**⁸³ and imidophosphonium⁸⁴ chloride **[B]**, respectively (**Figure 7a**). Interestingly, species **[B]** was the major component in this case.

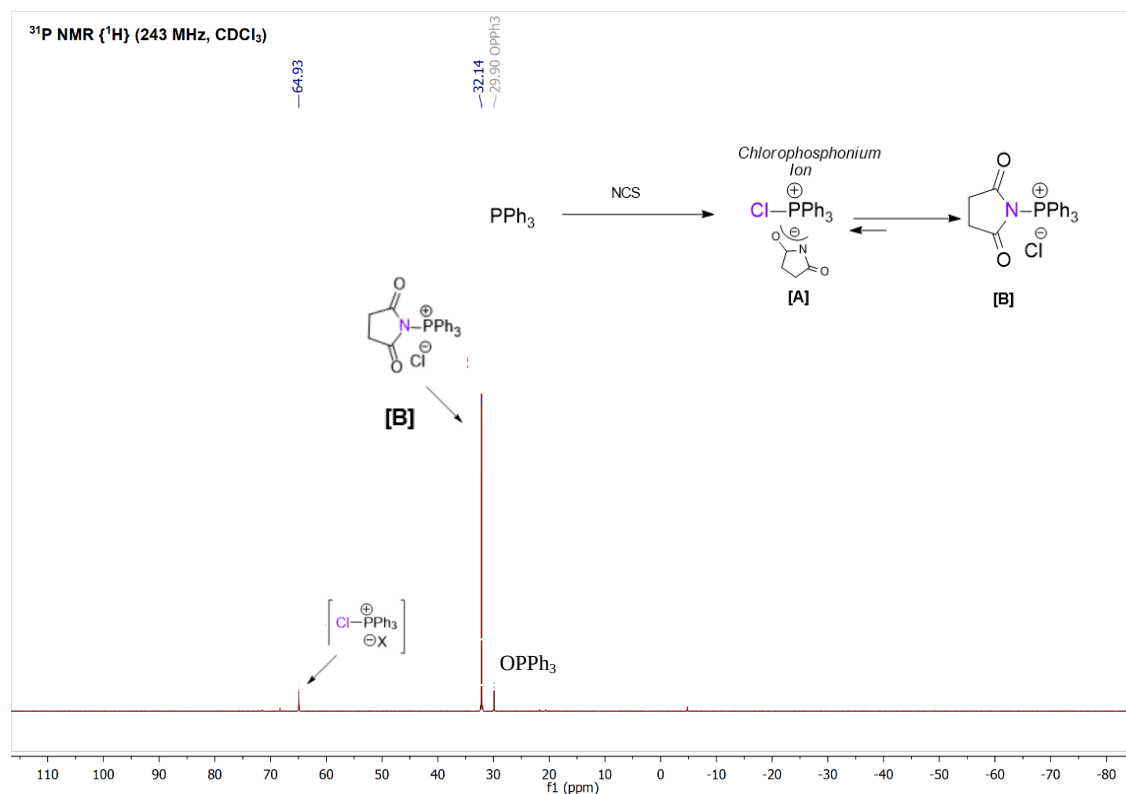


Figure 7a. ^{31}P -NMR observation of the species obtained from PPh_3 and NCS reaction in 1 mL CDCl_3 .

Reaction Between NBS and PPh_3 (1:1) – (Figure 7b).

In a similar way, we studied the reaction between NBS and PPh_3 . In a 4 mL vial, PPh_3 (0.14 mmol, 1 equiv) was charged with a stir bar and CDCl_3 (0.7 mL, 0.1M) was added at room temperature. This reaction mixture was cooled to 0°C -rt (ice-bath) and then solid NBS (0.14 mmol, 1 equiv) was added in one portion quickly. The vial was further stirred 0°C (ice-bath) for 2 min then transferred to the *J*-Young NMR tube under N_2 balloon. The ^{31}P -NMR spectrum of this mixture showed bromophosphonium⁸⁵ ion [C] at δ 70.11 and a new species at δ 33.73 ppm which was assigned to imidophosphonium bromide [D] (Figure 7b). As expected, OPPh_3 (δ 29.90) was always present in both cases, likely due to hydrolysis of these highly electrophilic species by adventitious water.

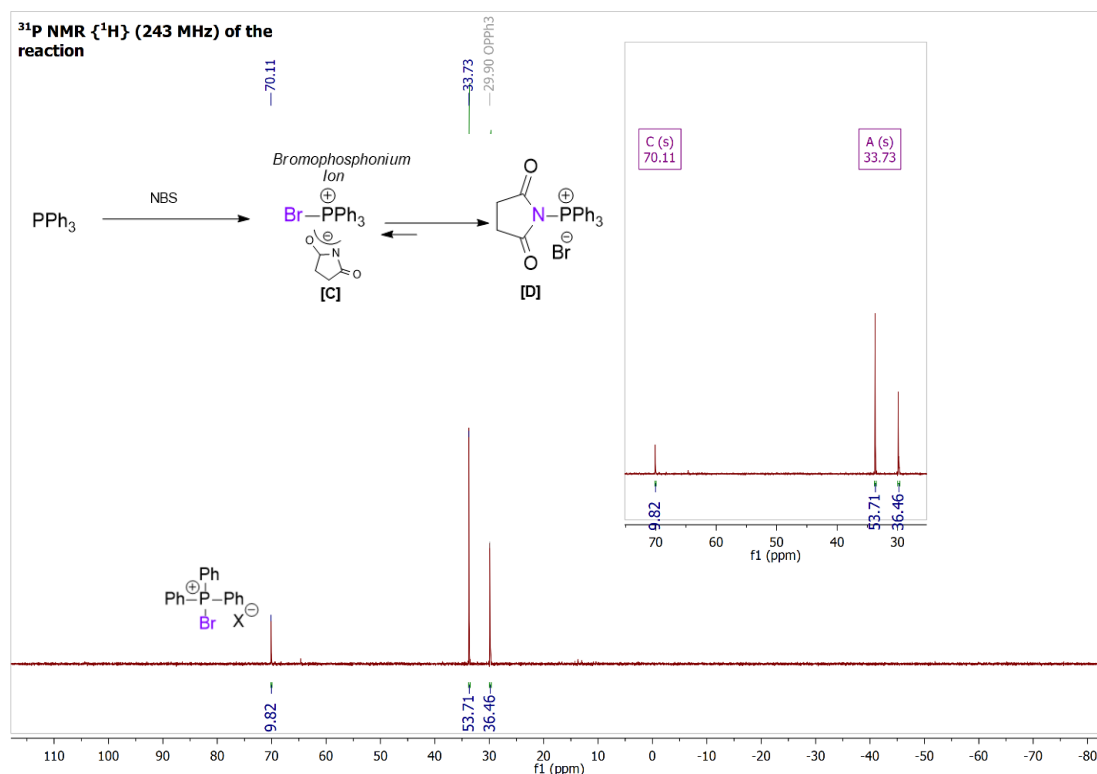


Figure 7b. ³¹P-NMR observation of the species obtained from PPh₃ and NBS reaction in 1 mL DCM.

Identification of the Acyl Electrophile Using PhCF₂COOH

In a glovebox, a 7 mL vial was charged with PhCF₂COOH (0.1 mmol, 1 equiv) and was then brought outside of the glovebox. Subsequently, PPh₃ (0.14 mmol, 1.4 equiv) was quickly added. To this vial anhydrous CDCl₃ (1 mL, 0.1 M) was then added under N₂ balloon and this mixture was cooled to 0 °C (ice-bath) for 2 min. Next, in one portion solid *N*-chlorosuccinimide (0.14 mmol, 1.4 equiv) was added to the vial, the vial was quickly recapped, and allowed to stir for 2 min at 0 °C (ice-bath). After this time, the vial was removed from the ice-bath and stirred for further 10 min while allowing it to warm up to room temperature. After this, the reaction mixture transferred to a *J*-Young NMR tube under a stream of N₂. The ³¹P-NMR spectrum of this mixture showed two signals resonating at δ 31.71 and δ 63.85. The peak at δ 31.71 can be either assigned to imidophosphonium ion [A] or to α,α-difluorophenylacetoxyphosphonium ion [I], further investigations are needed. The signal at δ 63.85 was assigned to the previously observed chlorophosphonium ion (minor shift observed).⁸³ **(Figure 7c)** Next, we recorded the ¹⁹F-NMR spectrum of this mixture and two signals resonating at δ -100.92 which matched the one of authentic α,α-difluoro-2-phenylacetyl chloride [E] made from oxalyl chloride and **1a**. This result suggest that the signal at δ 31.71 the ³¹P NMR is not ion [I], and that such species rapidly transforms into the corresponding acyl chloride. **(Figure 8a)**. Still, this mixture showed acyl chloride [E] as the sole species upon standing for 30 min at room temperature.

In this case, further experimentation is needed to clarify this fact. (**Figure 8b**). As expected, triphenylphosphine oxide (δ 29.90 ppm) was also present.

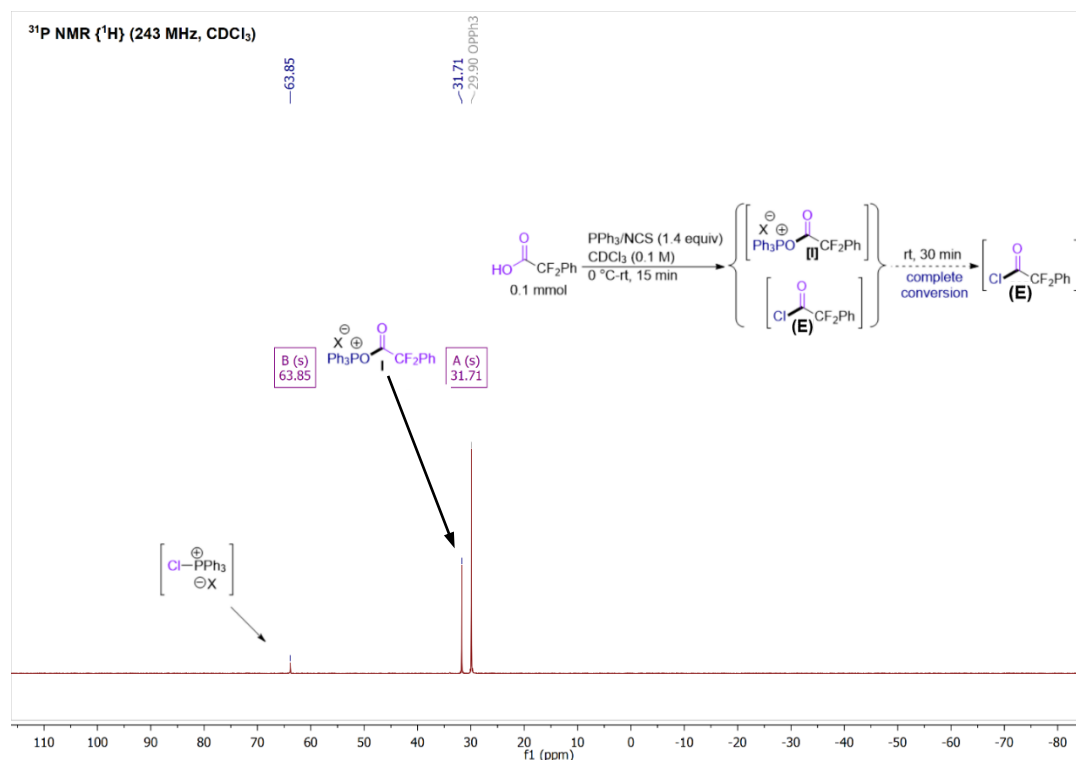


Figure 7c. ^{31}P -NMR obtained from the reaction of PhCF_2COOH with PPh_3 and NCS reaction after 15 min.

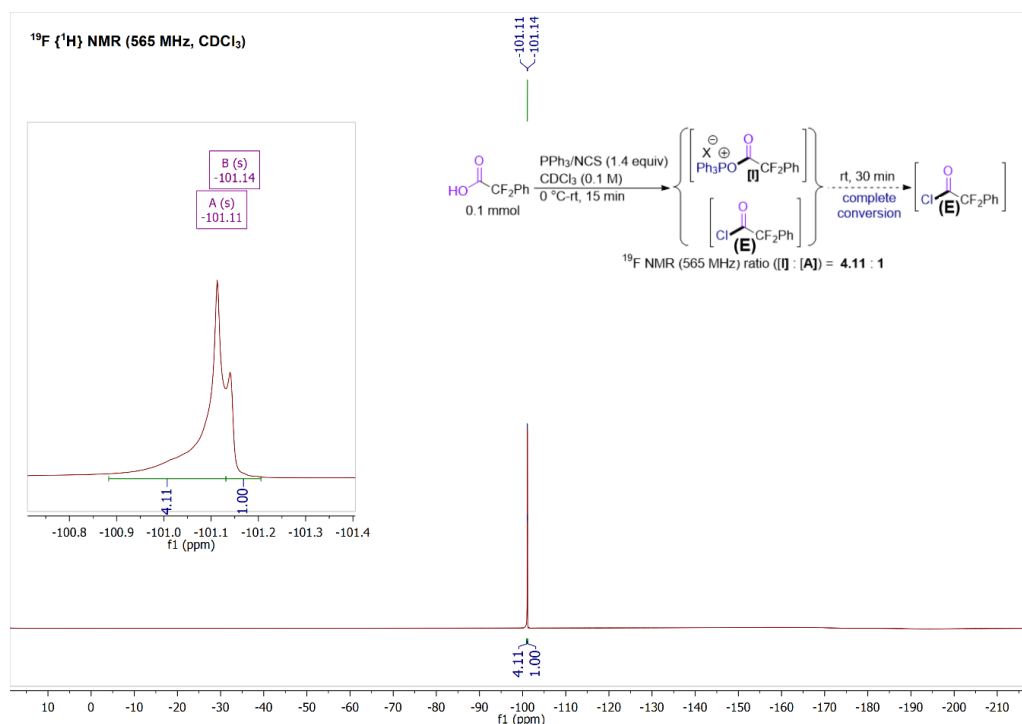


Figure 8a. ^{19}F -NMR obtained from the reaction of PhCF_2COOH with PPh_3 and NCS reaction after 15 min.

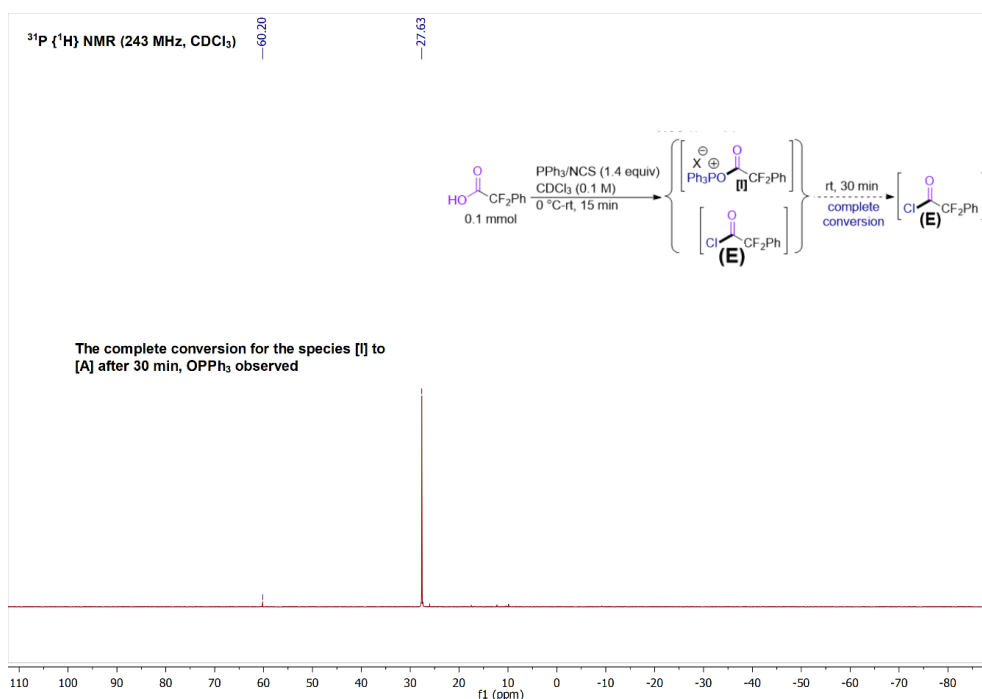


Figure 8b. ^{31}P { ^1H } NMR of the reaction of PhCF_2COOH with PPh_3 and NCS reaction after 30 min.

Identification of the Active Acyl Electrophile Using 4-Fluorobenzoic Acid.

Next, we conducted similar studies with 4-fluorobenzoic acid. A 4 mL vial equipped stir bar was charged with a 4-fluorobenzoic acid (0.1 mmol, 1 equiv) and PPh_3 (0.14 mmol, 1 equiv). Subsequently, CDCl_3 (1 mL, 0.14 M) was added at room temperature. This mixture was pre-cooled to 0°C (ice-bath) for 2 min, before adding *N*-bromosuccinimide (0.14 mmol, 1 equiv) as a solid in one portion. The vial was then recapped, and the reaction mixture was stirred for 2 min at 0°C -rt (ice-bath) followed by 8 min at rt. The mixture was then transferred to a *J*-Young NMR tube under a stream of N_2 (balloon). In this case, the ^{31}P NMR spectrum showed only two resonances at δ 31.26 and δ 29.90, with the latter corresponding to OPPh_3 and the former being assigned to acyloxyphosphonium ion **[III-F]** (**Figure 9a**). Next, ^{19}F -NMR spectroscopy was also employed to determine the extent of acyl bromide formation and it was found that 4-fluorobenzoyl bromide (compared vs an authentic sample at δ -102.15) was not detected (**Figure 9b-c**). This observations helped us in corroborating that the signal observed in the ^{31}P NMR at δ 31.26 and the one in ^{19}F -NMR at δ -100.54 indeed corresponds to species **[III-F]**. The ^{19}F -NMR showed a yet unidentified species at δ -100.98.

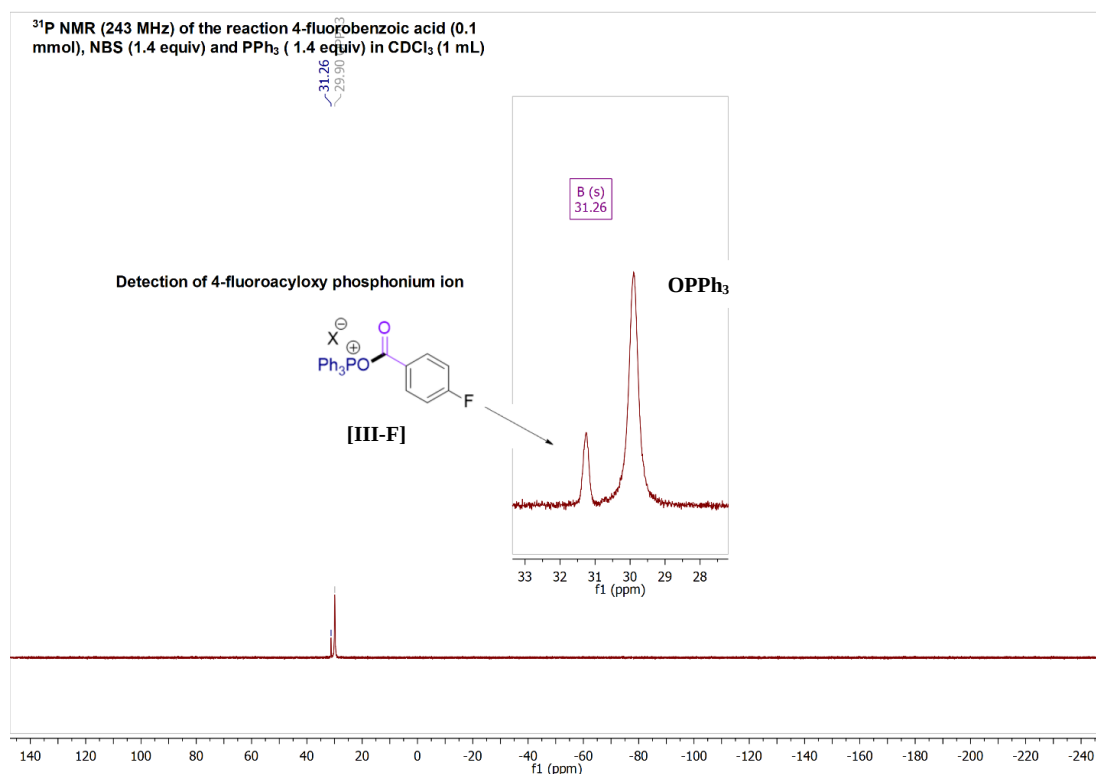


Figure 9a. ³¹P-NMR of the reaction 4-fluorobenzoic acid with NBS and PPh₃ in CDCl₃

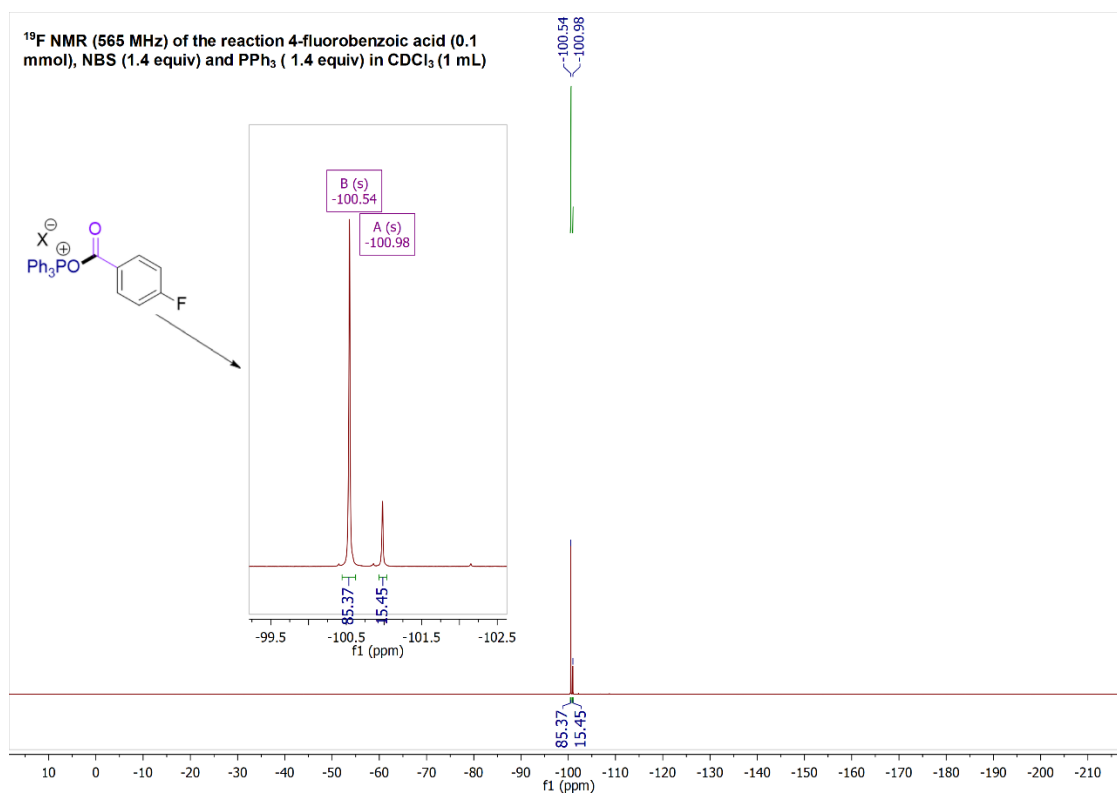


Figure 9b. ¹⁹F-NMR of the reaction 4F-benzoic acid with NBS and PPh₃ in CDCl₃

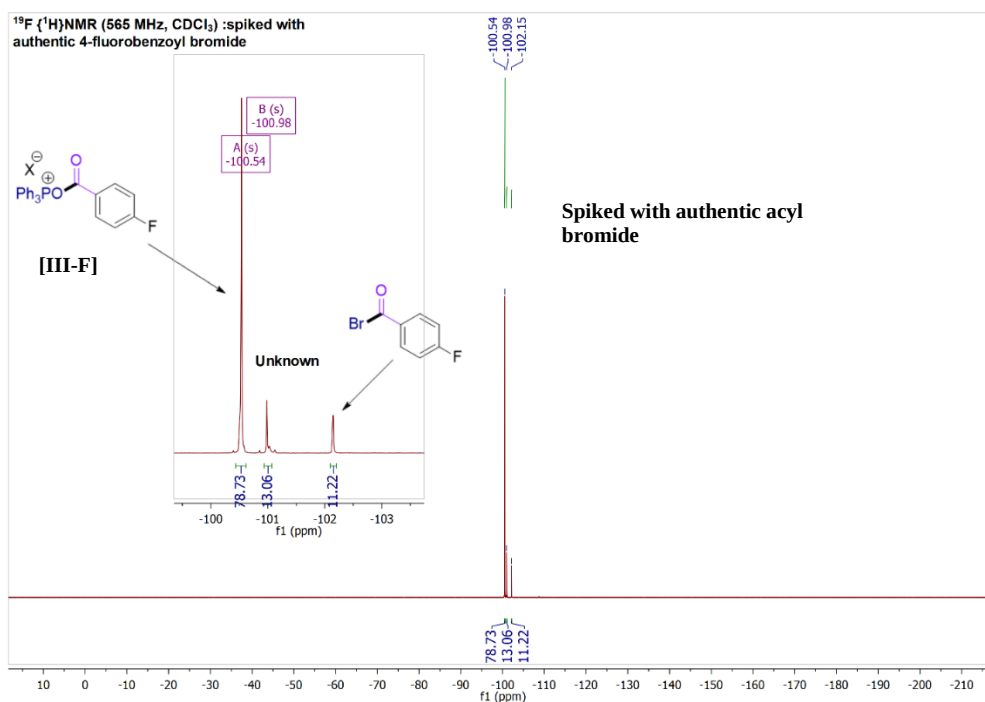


Figure 9c. ¹⁹F-NMR of the reaction 4F-benzoic acid with NBS and PPh₃ in CDCl₃ spiked with authentic acyl bromide.

Identification of the Active Acyl Electrophile Using 4-trifluoromethylbenzoic Acid.

Next, a similar control experiment was performed using 4-trifluoromethylbenzoic acid. A 7 mL vial equipped with a stir bar, was charged with PPh₃ (0.14 mmol, 1 equiv) and anhydrous DCM (1 mL, 0.1 M) was added at room temperature. This reaction mixture was cooled to 0 °C (ice-bath) for 2 min. After this, *N*-bromosuccinimide (0.14 mmol, 1 equiv) was added in one portion as a solid and the vial was recapped. The mixture was stirred for 2 min at 0 °C (ice-bath) then 4-(trifluoromethyl)benzoic acid (0.1 mmol, 1 equiv) was added in one-portion and further stirred for 8 min at rt before transferring to a *J*-Young NMR tube under a stream of N₂. In this case, the ³¹P-NMR spectrum showed a resonance at δ 66.02, corresponding to the previously observed bromophosphonium ion [C], and one signal at δ 36.39 (in addition to the usual OPPh₃ at δ 29.9). Next, the ¹⁹F-NMR spectrum was recorded and two signals at peaks at δ -63.45 and δ -63.89 in a ratio of 1.53:1 were observed. The same *J*-Young NMR tube was spiked with authentic 4-(trifluoromethyl)benzoyl bromide, and we observed a new ratio 0.96:1 of the same signals. With this result we can assign the ¹⁹F resonance at δ -63.89 to 4-(trifluoromethyl)benzoyl bromide, and the one at δ -63.45 was thus assigned to ion [III]-CF₃ (Figure 9d-f). The signal at δ 36.39 was assigned to acyloxyphosphonium ion

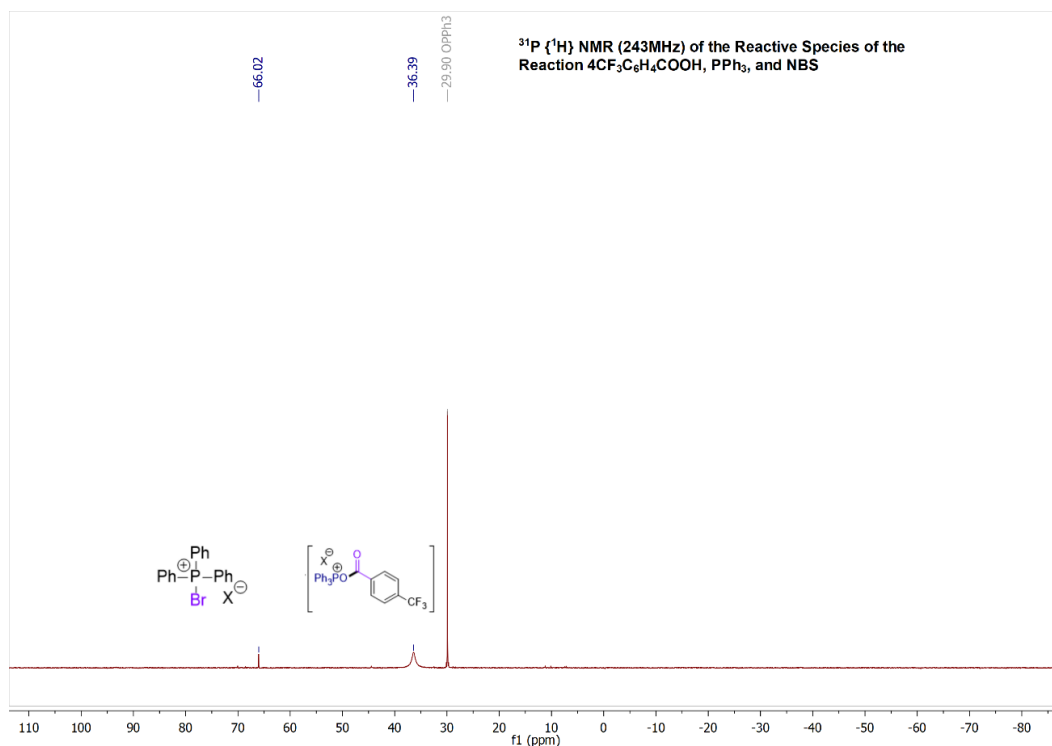


Figure 9d. ³¹P-NMR of the reaction between PPh₃, NBS and 4-trifluoromethylbenzoic acid after 10min.

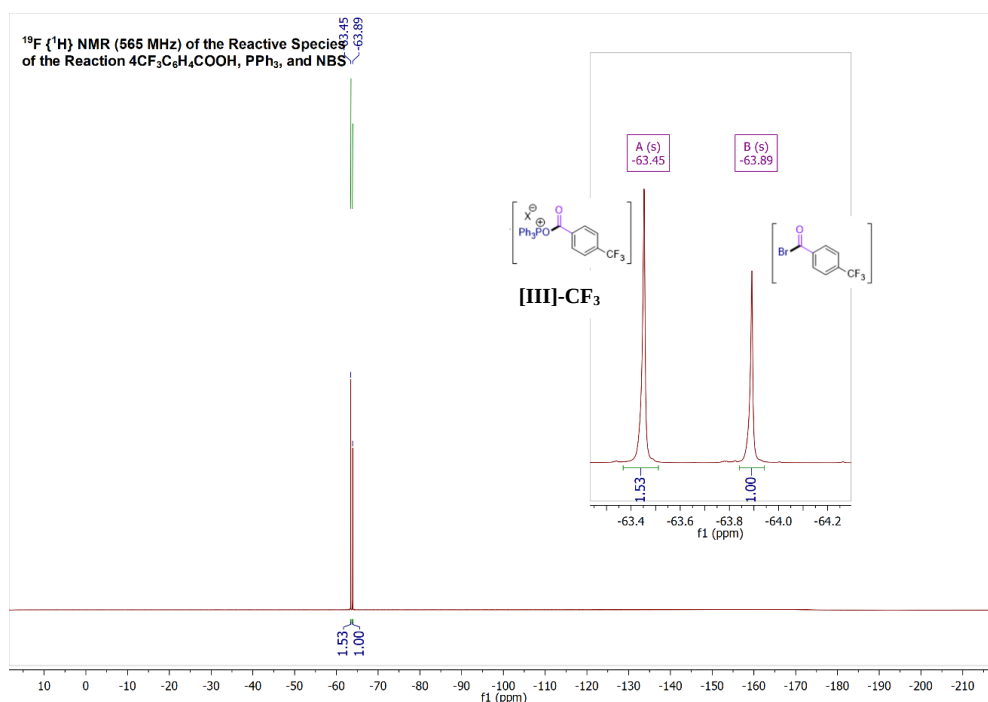


Figure 9e. ¹⁹F-NMR of the reaction between PPh₃, NBS and 4-trifluoromethylbenzoic acid after 10min (before adding authentic 4-(trifluoromethyl)benzoyl bromide).

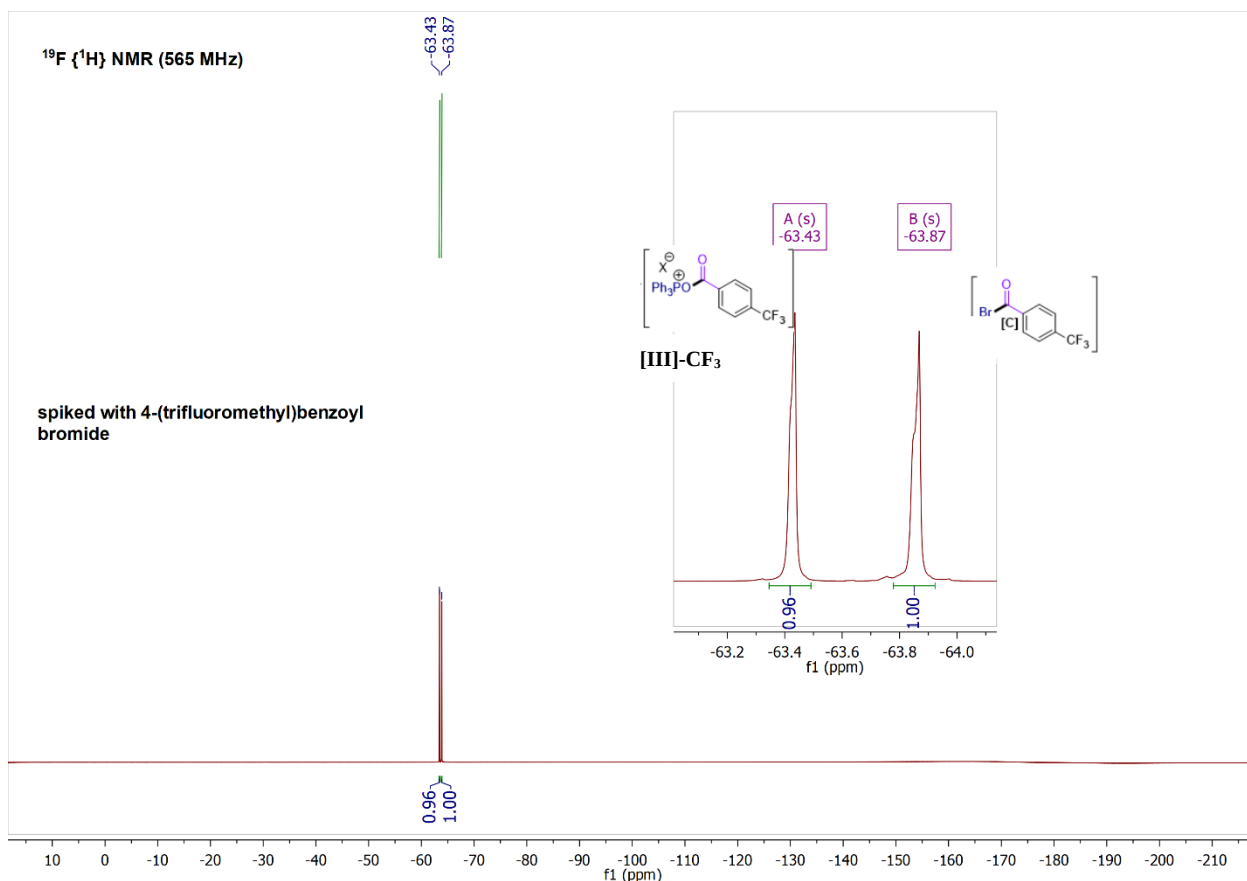


Figure 9f. ¹⁹F-NMR-after adding authentic 4-(trifluoromethyl)benzoyl bromide.

Identification of the Active Acyl Electrophile Using Difluoroacetic Acid (DFA)

We then used difluoroacetic acid in place of benzoic acids in similar experiments.

Into a 4 mL vial PPh₃ (0.098 mmol, 1 equiv) was charged followed by addition of CDCl₃ (0.7 mL, 0.1M) at room temperature. This reaction mixture vial was pre-cooled to 0 °C (ice-bath) for 2 min before addition of solid NBS (1.4 equiv) was added in one portion. The vial was further stirred 0 °C (ice-bath) for 5 min then transferred to the *J*-Young NMR tube under a stream of N₂. The *J*-Young NMR tube was kept at 0 °C (ice-bath), while DFA (4.4 μL, 1 equiv) was added via microsyringe under the stream of N₂ (balloon). This mixture was stirred using a vortex and NMR analysis was quickly conducted.

In the ³¹P NMR spectrum a species resonating at δ 38.95 was observed, along with OPPh₃ (δ 29.9) and minute amounts of what appears to be bromophosphonium ion [C] at around 67ppm. Interestingly, ¹⁹F NMR, showed the presence of two resonances at δ -120.73 (d, J = 53.5 Hz) and δ -127.04 (d, J = 53.8 Hz) in a ratio of 1: 3.76. Independently prepared difluoroacetyl bromide appeared

at δ -120.73 (d, J = 53.5 Hz). Therefore, the peak at δ -127.05 (d, J = 53.8 Hz) was assigned to the difluoroacyloxyphosphonium ion species **[II]** (Figure 10a-b).

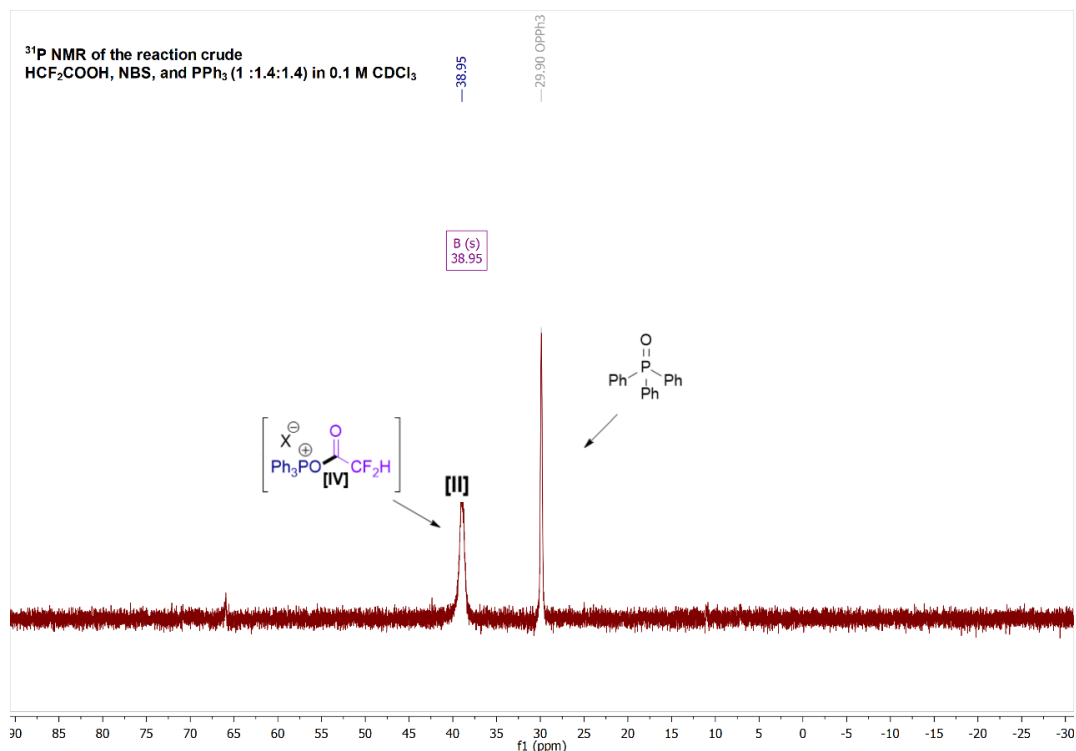


Figure 10a. ³¹P-NMR spectrum of the reaction mixture of DFA, PPh₃, and NBS in CDCl₃ (8 min)

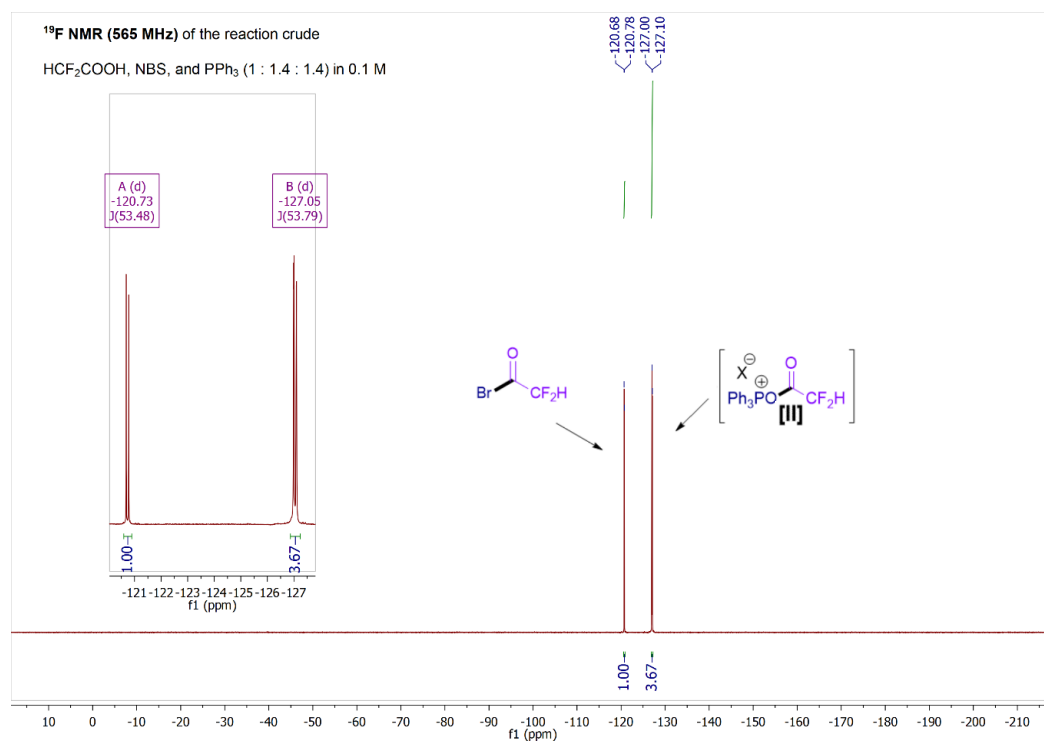


Figure 10b: ¹⁹F NMR spectrum of the reaction mixture of DFA, PPh₃, and NBS in CDCl₃ (10min)

Summary of Control Experiments

From the NMR spectroscopic studies of both nuclei, ^{31}P and ^{19}F conducted with the fluorine tagged carboxylic acids **1a**, **4a**, **4g** and DFA, we can reach the following conclusions:

- The use of NCS/ PPh_3 and **1a** likely produces an initial mixture of **[I]** and acyl chloride, which rapidly forms acyl chloride. However, we are still investigating the identity of peak observed in the ^{31}P NMR. Still upon standing for 30 min, the sole species observed corresponds to the acyl chloride **[E]**. This result can be expected from the enhanced nucleophilicity of chloride ion in non-protic media.
- The use of NBS/ PPh_3 with DFA produces acyloxyphosphonium ions **[II]**, **[III]-F** exclusively without any acyl bromide being observed. However, when an electron-poor benzoic acid is used, a mixture of **[III]-CF₃** and the corresponding acyl bromide in a 1.5:1 ratio with the acyloxyphosphonium ion as the major species. Importantly, both types of electrophilic species are expected to be capable of engaging the organozinc reagent to produce the target ketones.

4.2 Experimental Section

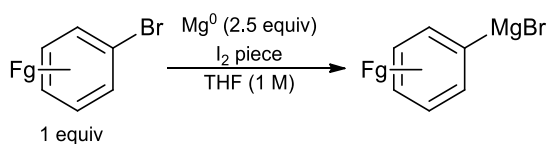
Note: For full details on the optimization of the reaction conditions and NMR spectra of fluorinated ketones, the reader is referred to the pre-print published⁶¹. It is important to note that the experimental details mentioned below are exclusively dealing with the work I have conducted on benzophenone synthesis as well as my collaboration with Dr. Alam, Dr. Kimura and Dr. Munoz on the NMR mechanistic investigations with all types of carboxylic acids.

4.2.1 General

Unless otherwise mentioned, all the chemicals were purchased from commercial sources and used without further purification. *N*-bromosuccinimide (NBS) was recrystallized from water and dried over P_2O_5 under high vacuum. Commercially available PPh_3 was used without further recrystallization. Anhydrous dichloromethane (DCM) was purchased from EMD (dry solvent) and further dried by distillation from CaH_2 . For moisture-and/or air sensitive reactions, the flask were flame dried by heat gun under vacuum, cooled to room temperature, and reactions were carried out under nitrogen atmosphere using standard Schlenk techniques. Anhydrous tetrahydrofuran (THF) was purchased from EMD (dry solv) and further dried by distillation from sodium (Na)/benzophenone and was kept under inert atmosphere over activated molecular sieves (3Å) in a

Strauss flask. In the cases indicated, flash column chromatography was performed using silica gel (230-400 mesh) purchased from Silicycle to isolate products with suitable eluent as determined by TLC. For 0.25 mmol scale reactions, 10g columns were used in Biotage Isolera flash column chromatography automated system. ^1H , ^{13}C , and ^{19}F spectra were recorded on 400 MHz or 600 MHz Varian NMR spectrometers at room temperature. ^1H NMR chemical shifts given in parts per million (ppm) were determined relative to CDCl_3 as the internal standard at δ 7.26 ppm. ^{13}C NMR shifts were determined relative to CDCl_3 at δ 77.16 ppm. ^{19}F NMR chemical shifts were determined relative to PhOCF_3 at δ -58.00 ppm or the corresponding standard for NMR yield (PhCF_3 or PhOCF_3). High-resolution mass spectra were recorded on Cary 630 (Agilent) mass spectrometer, EI or ESI mode. The mass spectrometric data were obtained at the Mass Spectrometry Laboratory at the University of Illinois. FT-IR were recorded on Cary 630 (Agilent) and the absorptions peaks are given in wave numbers (cm^{-1}). GS-MS were performed on a Shimadzu GCMS-QP2020

General Procedure for Grignard reagent preparation.

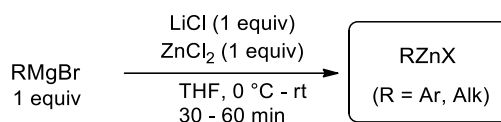


Scheme E1 Formation of Grignard Reagents

Unless otherwise mentioned, the following procedure to synthesize Aryl Grignard reagents was adapted from literature reports.⁸⁶ In a flame dried 15 ml vial charged with Mg turnings (2.5 equiv.) and a small piece of iodine. Then dry THF (1M) was added in presence of N_2 balloon. The neat Aryl bromide or iodide (1 equiv.) was added dropwise to the solution at 0 °C. The formation of Grignard was initiated in 1-3 mins (which was confirmed by generation of the heat) then the remaining aryl halide was added slowly at 0 °C. After addition of the aryl halide, the reaction mixture was stirred for 2-6 h at room temperature and the completion of the Br/Mg exchange was confirmed by GC-analysis in which aryl halide was not observed. Iodometric titration⁸⁷ of these resulting Grignard reagents was performed immediately prior to generation of organozinc reagents.

Preparation of Organozinc Reagents

General Procedure (GP1) for the Preparation of Aryl/Alkyl Organozinc Halides



Scheme E2 Formation of Organozinc Halides

Unless otherwise specified, aryl/alkylorganozinc reagents were prepared using the following general procedure (see individual examples for specific conditions). Inside an N₂-filled glovebox, a flame-dried 4 mL vial with a stir bar, anhydrous ZnCl₂ (0.6 mmol, 82 mg, 2.4 equiv.), and LiCl (0.6 mmol, 25.4 mg, 2.4 equiv.) was charged, recapped, and brought outside the glovebox. Subsequently, the vial was placed under high vacuum and dried with a heat gun (low flame) for 1-2 min. After cooling to room temperature, anhydrous THF was added (THF volume was adjusted so that the total volume of the resulting organozinc reagent solution is 1 mL; this amount varies depending on the concentration of Grignard reagent used). The reaction mixture was cooled to 0 °C (ice bath) and ArMgBr (0.6 mmol, 2.4 equiv.) was added dropwise using an oven-dried microsyringe under the stream of N₂ balloon. The puncture hole was sealed with electrical tape, the mixture was taken off the ice-bath, and the reaction mixture was continued to stir at ambient temperature for 30 min. The resulting suspension or solution (see each case) was directly used in the next step without further titration. **Note:* Unless otherwise stated, Grignard reagents used were obtained from commercial sources and were *titrated shortly before* use using the method described by Knochel and coworkers.⁸⁷

Phenylzinc (II) chloride

By following the **GP1** reaction procedure, the phenylzinc(II) chloride solution (2.4 equiv., 0.60 mmol) was prepared by adding phenylmagnesium bromide (0.89 M THF, 674 μL, 2.4 equiv.) to ZnCl₂ (0.60 mmol, 2.4 equiv., 82mg) and LiCl (0.60 mmol, 2.4 equiv., 25.6 mg) in 0.326 mL THF with cooling in ice-bath. After addition, this solution was stirred at ambient temperature for 30 min and was used without further titration.

(4-methoxyphenyl)zinc (II) chloride

By following the **GP1** reaction procedure, the (4-methoxyphenyl)zinc(II) chloride solution (2.4 equiv., 0.60 mmol) was prepared by adding 4-methoxyphenylmagnesium bromide (0.75 M THF, 800 μ L, 2.4 equiv.) to ZnCl_2 (0.60 mmol, 2.4 equiv., 82 mg) and LiCl (0.60 mmol, 2.4 equiv., 25.4 mg) in 0.200 mL with cooling in ice-bath. After addition, this solution was stirred at ambient temperature for 30 min and was used without further titration.

p-tolylzinc (II) chloride

By following the **GP1** reaction procedure, the p-tolylzinc(II) chloride solution (2.4 equiv., 0.60 mmol) was prepared by adding p-tolylmagnesium bromide (0.75 M THF, 800 μ L, 2.4 equiv.) to ZnCl_2 (0.60 mmol, 2.4 equiv., 82 mg) and LiCl (0.60 mmol, 2.4 equiv., 25.4 mg) in 0.200 mL THF with cooling in ice-bath. After addition, this solution was stirred at ambient temperature for 30 min and was used without further titration.

(3-methoxyphenyl)zinc (II) chloride

By following the **GP1** reaction procedure, the (3-methoxyphenyl)zinc(II) chloride solution (2.4 equiv., 0.60 mmol) was prepared by adding (3-methoxyphenyl)magnesium bromide (0.79 M THF, 760 μ L, 2.4 equiv.) to ZnCl_2 (0.60 mmol, 2.4 equiv., 82 mg) and LiCl (0.60 mmol, 2.4 equiv., 25.4 mg) in 0.240 mL THF with cooling in ice-bath. After addition, this solution was stirred at ambient temperature for 30 min and was used without further titration.

(4-fluorophenyl)zinc (II) chloride

By following the **GP1** reaction procedure, the (4-fluorophenyl)zinc(II) bromide solution (2.4 equiv., 0.60 mmol) was prepared by adding (4-fluorophenyl)magnesium bromide (0.92 M THF, 650 μ L, 2.4 equiv.) to ZnCl_2 (0.60 mmol, 2.4 equiv., 82 mg) and LiCl (0.60 mmol, 2.4 equiv., 25.4 mg) in 0.350 mL THF with cooling in ice-bath. After addition, this solution was stirred at ambient temperature for 30 min and was used without further titration.

(4-chlorophenyl)zinc (II) chloride

By following the **GP1** reaction procedure, the (4-chlorophenyl)zinc(II) chloride solution (2.4 equiv., 0.60 mmol) was prepared by adding (4-chlorophenyl)magnesium bromide (0.78 M THF, 769 μ L, 2.4 equiv.) to ZnCl_2 (0.60 mmol, 2.4 equiv., 82 mg) and LiCl (0.60 mmol, 2.4 equiv., 25.4 mg) in 0.230

mL THF with cooling in ice-bath. After addition, this solution was stirred at ambient temperature for 30 min and was used without further titration.

(3-fluorophenyl)zinc (II) chloride

By following the **GP1** reaction procedure, the (3-fluorophenyl)zinc(II) chloride solution (2.4 equiv., 0.60 mmol) was prepared by adding (3-fluorophenyl)magnesium bromide (0.65 M THF, 925 μ L, 2.4 equiv.) to ZnCl_2 (0.60 mmol, 2.4 equiv., 82 mg) and LiCl (0.60 mmol, 2.4 equiv., 25.4 mg) in 0.075 mL THF with cooling in ice-bath. After addition, this solution was stirred at ambient temperature for 30 min and was used without further titration.

(4-(trifluoromethyl)phenyl)zinc (II) chloride

By following the **GP1** reaction procedure, the (4-(trifluoromethyl)phenyl)zinc(II) chloride solution (2.4 equiv., 0.60 mmol) was prepared by adding (4-(trifluoromethyl)phenyl)magnesium bromide (0.80 M THF, 750 μ L, 2.4 equiv.) to ZnCl_2 (0.60 mmol, 2.4 equiv., 82 mg) and LiCl (0.60 mmol, 2.4 equiv., 25.4 mg) in 0.250 mL THF with cooling in ice-bath. After addition, this solution was stirred at ambient temperature for 30 min and was used without further titration.

(4-cyanophenyl)zinc (II) chloride

By following the **GP1** reaction procedure, the (4-cyanophenyl)zinc(II) chloride solution (2.4 equiv., 0.60 mmol) was prepared by adding 4-Cyanophenylmagnesium halide LiCl complex (0.64 M THF, 932 μ L, 2.4 equiv.) to ZnCl_2 (0.60 mmol, 2.4 equiv., 82 mg) and LiCl (0.60 mmol, 2.4 equiv., 25.4 mg) in 0.07 mL THF with cooling in ice-bath. After addition, this solution was stirred at 0 °C for 30 min and was used without further titration.

(perfluorophenyl)zinc (II) chloride

By following the **GP1** reaction procedure, the perfluorophenylzinc chloride solution (2.4 equiv., 0.60 mmol) was prepared by adding (perfluorophenyl)magnesium bromide (0.67 M THF, 895 μ L, 2.4 equiv.) to solid ZnCl_2 (0.60 mmol, 2.4 equiv., 82mg) and LiCl (0.60 mmol, 2.4 equiv., 25.4 mg) in 0.1 mL THF with cooling in ice-bath. After addition, this solution stirred at ambient temperature for 2 h and was used without further titration.

Mesitylzinc (II) chloride

By following the **GP1** reaction procedure, the mesitylzinc(II) chloride solution (2.4 equiv., 0.60 mmol) was prepared by adding mesitylmagnesium bromide (0.95 M THF, 631 μ L, 2.4 equiv.) to ZnCl_2 (0.60 mmol, 2.4 equiv., 82 mg) and LiCl (0.60 mmol, 2.4 equiv., 25.4 mg) in 0.369 mL THF with cooling in ice-bath. After addition, this solution was stirred at ambient temperature for 45 min and was used without further titration.

Benzylzinc (II) chloride

By following the **GP1** reaction procedure, the benzylzinc(II) chloride solution (2.4 equiv., 0.60 mmol) was prepared by adding benzylmagnesium bromide (2 M THF, 300 μ L, 2.4 equiv.) to ZnCl_2 (0.60 mmol, 2.4 equiv., 82 mg) and LiCl (0.60 mmol, 2.4 equiv., 25.4 mg) in 0.7 mL THF with cooling in ice-bath. After addition, this solution was stirred at ambient temperature for 60 min and was used without further titration.

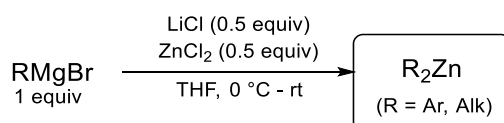
Phenethylzinc (II) chloride

By following the **GP1** reaction procedure, the phenethylzinc(II) chloride solution (2.4 equiv., 0.60 mmol) was prepared by adding phenethylmagnesium bromide (0.94 M THF, 638 μ L, 2.4 equiv.) to ZnCl_2 (0.60 mmol, 2.4 equiv., 82 mg) and LiCl (0.60 mmol, 2.4 equiv., 25.4 mg) in 0.362 mL THF with cooling in ice-bath. After addition, this solution was stirred at ambient temperature for 60 min and was used without further titration.

Cyclohexylzinc (II) chloride

By following the **GP1** reaction procedure, the cyclohexylzinc(II) chloride solution (2.4 equiv., 0.60 mmol) was prepared by adding cyclohexyl magnesium bromide (0.95 M THF, 630 μ L, 2.4 equiv.) to ZnCl_2 (0.60 mmol, 2.4 equiv., 82 mg) and LiCl (0.60 mmol, 2.4 equiv., 25.4 mg) in 0.370 mL THF with cooling in ice-bath. After addition, this solution was stirred at ambient temperature for 60 min and was used without further titration.

General Procedure (GP2) for the Preparation of Diorganozinc Reagents



Scheme E3 Formation of Diarylzincs/Dialkylzincs Halides

Unless otherwise specified, diorganozincs were prepared using the following general procedure (see individual examples for specific conditions). Inside an N₂-filled glovebox, a flame-dried 4 mL vial with a stir bar, anhydrous ZnCl₂ (0.3 mmol, 41 mg, 1.2 equiv.), and LiCl (0.3 mmol, 12.7 mg, 1.2 equiv.) was charged, recapped, and brought outside the glovebox. Subsequently, the vial was placed under high vacuum and dried with a heat gun (low flame) for 1-2 min. After cooling to room temperature anhydrous THF was added (THF volume was adjusted so that the total volume of the resulting organozinc reagent solution is 1 mL; this amount varies depending on the concentration or Grignard reagent used). The reaction mixture was cooled to 0 °C (ice bath) and ArMgBr (0.6 mmol, 2.4 equiv.) was added dropwise using an oven-dried microsyringe under the stream of Ar balloon. The puncture hole was sealed with electrical tape, the mixture was taken off the ice-bath, and the reaction mixture was continued to stir at ambient temperature for 30 min. The resulting suspension or solution (see each case) was directly used in the next step without further titration.

Diphenylzinc

By following the **GP2** reaction procedure, the Diphenylzinc solution (1.2 equiv., 0.30 mmol) was prepared by adding freshly titrated phenylmagnesium bromide (0.6 mmol, 0.85M in THF, 705 µL, 2.4 equiv.) added to ZnCl₂ (0.30 mmol, 1.2 equiv., 41mg) and LiCl (0.30 mmol, 1.2 equiv., 12.7 mg) in enough THF to afford a total of 1 mL (0.3 mL THF in this case) with cooling in ice-bath. After addition, this mixture was stirred at ambient temperature for 30 min resulting in a grey suspension which was used without further titration in the following step.

Bis(4-methoxyphenyl)zinc

By following the **GP2** reaction procedure, the Bis(4-methoxyphenyl)zinc solution (1.2 equiv., 0.30 mmol) was prepared by adding 4-methoxyphenylmagnesium bromide (0.7M THF, 857 µL, 2.4 equiv.) added to ZnCl₂ (0.30 mmol, 1.2 equiv., 41 mg) and LiCl (0.30 mmol, 1.2 equiv., 12.7 mg) in 0.150 mL with cooling in ice-bath. After addition, this solution was stirred at ambient temperature for 30 min and was used without further titration.

Di-*p*-tolylzinc

By following the **GP2** reaction procedure, the Di-*p*-tolylzinc solution (1.2 equiv., 0.30 mmol) was prepared by adding *p*-tolylmagnesium bromide (0.8M THF, 750 µL, 2.4 equiv.) added to ZnCl₂ (0.30

mmol, 1.2 equiv., 41mg) and LiCl (0.30 mmol, 1.2 equiv., 12.7 mg) in 0.250 mL THF with cooling in ice-bath. After addition, this solution was stirred at ambient temperature for 30 min and was used without further titration.

Bis(3-methoxyphenyl)zinc and 3-methoxyphenyl zinc halide

By following the **GP2** reaction procedure, the Bis(3-methoxyphenyl)zinc solution (1.2 equiv., 0.30 mmol) was prepared by adding 3-methoxyphenylmagnesium bromide (0.83M THF, 720 μ L, 2.4 equiv.) added to ZnCl₂ (0.30 mmol, 1.2 equiv., 41mg) and LiCl (0.30 mmol, 1.2 equiv., 12.7 mg) in 0.28 mL with cooling in ice-bath. After addition, this solution stirred at ambient temperature for 30 min and was used without further titration.

Bis(4-fluorophenyl)zinc

By following the **GP2** reaction procedure, the Bis(4-fluorophenyl)zinc solution (1.2 equiv., 0.30 mmol) was prepared by adding 4-fluorophenylmagnesium bromide (0.94M THF, 638 μ L, 2.4 equiv.) added to ZnCl₂ (0.30 mmol, 1.2 equiv., 41 mg) and LiCl (0.30 mmol, 1.2 equiv., 12.7 mg) in 0.24 mL THF with cooling in ice-bath. After addition, this solution stirred at ambient temperature for 30 min and was used without further titration.

Bis(4-Chlorophenyl)zinc

By following the **GP2** reaction procedure, the Bis(4-Chlorophenyl)zinc solution (1.2 equiv., 0.30 mmol) was prepared by adding 4-chlorophenylmagnesium bromide (0.80M Et₂O, 750 μ L, 2.4 equiv.) added to ZnCl₂ (0.30 mmol, 1.2 equiv., 41 mg) and LiCl (0.30 mmol, 1.2 equiv., 12.7 mg) in 0.25 mL THF with cooling in ice-bath. After addition, this solution stirred at ambient temperature for 30 min and was used without further titration.

Bis(3-fluorophenyl)zinc

By following the **GP2** reaction procedure, the Bis(3-fluorophenyl)zinc solution (1.2 equiv., 0.30 mmol) was prepared by adding 3-fluorophenylmagnesium bromide (0.67M THF, 900 μ L, 2.4 equiv.) to ZnCl₂ (0.30 mmol, 1.2 equiv., 41 mg) and LiCl (0.30 mmol, 1.2 equiv., 12.7 mg) in 0.1 mL THF with cooling in ice-bath. After addition, this solution stirred at ambient temperature for 30 min, and was used without further titration.

Bis(4-trifluoromethylphenyl)zinc

By following the **GP2** reaction procedure, the Bis(4-trifluoromethylphenyl)zinc solution (1.2 equiv., 0.30 mmol) was prepared by adding 4-trifluoromethylphenyl magnesium bromide (0.80M THF, 750 μ L, 2.4 equiv.) added to solid ZnCl_2 (0.30 mmol, 1.2 equiv., 41 mg) and LiCl (0.30 mmol, 1.2 equiv., 12.7 mg) in 0.25 mL THF with cooling in ice-bath. After addition, this solution stirred at ambient temperature for 30 min and was used without further titration.

Bis(4-cyanophenyl)zinc

By following the **GP2** reaction procedure, the Bis(4-cyanophenyl)zinc solution (1.2 equiv., 0.30 mmol) was prepared by adding 4-trifluoromethylphenyl magnesium bromide (0.66M THF, 900 μ L, 2.4 equiv.) added to solid ZnCl_2 (0.30 mmol, 1.2 equiv., 41 mg) and LiCl (0.30 mmol, 1.2 equiv., 12.7 mg) in 0.1 mL THF with cooling in ice-bath. After addition, this solution stirred at ambient temperature for 30 min and was used without further titration.

Bis(benzyl)zinc

By following the **GP2** reaction procedure, the Bis(benzyl)zinc solution (1.2 equiv., 0.30 mmol) was prepared by adding benzylmagnesium bromide (2M THF, 300 μ L, 2.4 equiv.) to ZnCl_2 (0.30 mmol, 1.2 equiv., 41mg) and LiCl (0.30 mmol, 1.2 equiv., 12.7 mg) in 0.7 mL THF with cooling in ice-bath. After addition, this solution stirred at ambient temperature for 30 min, and was used without further titration.

Bis(phenethyl)zinc

By following the **GP2** reaction procedure, the Bis(phenethyl)zinc solution (1.2 equiv., 0.30 mmol) was prepared by adding phenethylmagnesium bromide (0.94M THF, 638 μ L, 2.4 equiv.) to ZnCl_2 (0.3mmol, 1.2 equiv., 41 mg) and LiCl (0.30 mmol, 1.2 equiv., 12.7 mg) in 0.361 mL THF with cooling in ice-bath. After addition, this solution stirred at ambient temperature for 30 min, and was used without further titration.

Bis(phenylethynyl)zinc

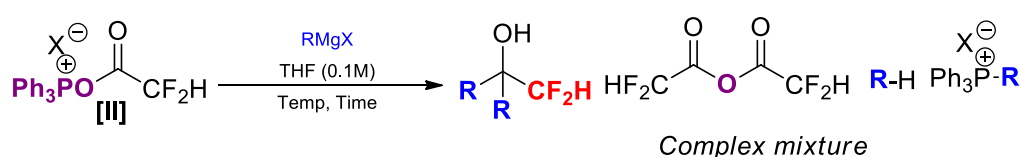
By following the **GP2** reaction procedure, the Bis(phenylethynyl)zinc solution (1.2 equiv., 0.30 mmol) was prepared by adding phenylethynylmagnesium bromide (1.0M THF, 600 μ L, 2.4 equiv.) added to ZnCl₂ (0.30 mmol, 1.2 equiv., 41 mg) and LiCl (0.30 mmol, 1.2 equiv., 12.7 mg) in 0.4 mL THF with cooling in ice-bath. After addition, this solution stirred at ambient temperature for 30 min, and was used without further titration.

Graphical Procedure for the preparation of RZnCl and R₂Zn



Figure E1: (Left) flame dried ZnCl₂ and LiCl under vacuum by heat gun (Right) dropwise addition of Grignard to ZnCl₂ and LiCl in THF under N₂ balloon.

Remarks using Grignard reagents as nucleophiles:



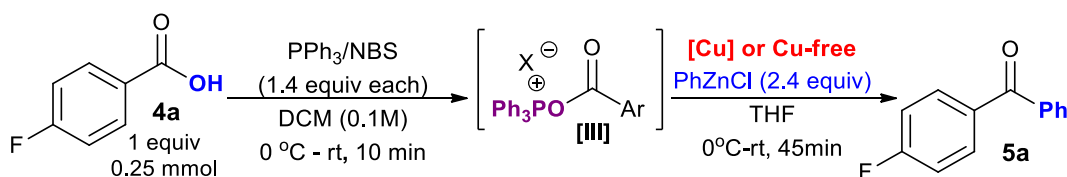
Scheme E5 Products using Grignard reagents as nucleophiles.

Reaction of **II** with Grignard reagents is capricious. Only protodemetalation product (R–H) and double addition CF₂H carbinol was detected as major products in both GC and ¹⁹F NMR analysis. Varying amounts of difluoroacetic acid anhydride were also observed. Attempts to control the reaction outcome and prevent double addition or proton abstraction by cooling down to -78 °C were unsuccessful. This highlights the superior nature of organozinc reagents with less basicity, a property required for a successful outcome of this transformation. During the first step of the reaction, all DFA is consumed and succinimide is liberated which could be the H⁺ source that leads to

unproductive protodemetallation of Grignard reagents. We surmise that other non-fluorinated by-products that arise from RMgBr addition to phosphonium center of **II**.

General Procedure (GP3) for the Synthesis of Benzophenones **5** from Benzoic acids

In all cases, a ‘reverse addition’ mode (i.e. nucleophile added to electrophile) was implemented. On the bench-top, **4a** (0.25 mmol), PPh₃ (1.4 equiv.), were charged into a screw-cap vial. Anhydrous DCM (2.5 ml, 0.1 M) was added, the mixture was cooled to 0 °C (ice-bath) and subsequently, solid NBS (1.4 equiv.) was quickly added. The vial was recapped and stirred for 2 min at 0 °C then removed from the ice-bath and stirring was continued for 6 min while slowly warming up to RT. If applicable (entry 2,), this solution was then transferred to a vial containing CuI (0.2 equiv.) under a stream of Argon and the mixture of **III** and CuI stirred for additional 2 minutes at rt. This mixture was cooled down to 0 °C before addition of PhZnCl (2.4 equiv.). After addition, the vial was removed from the ice-bath and stirring was continued for 45 min at rt. Upon completion of this time, PhOCF₃ (20 uL) was added as internal standard and the yield of **5a** δ = -106.6 (m) was determined by comparing the integration values with that of PhOCF₃ (δ = -58.0 ppm).



Scheme E6 Synthesis of Benzophenones via Acyloxyphosphonium Ions

****NOTE:** Experimental procedures listed herein are limited to the ones conducted during my research. The reader is referred to our published procedure⁶¹ and supporting information for full experimental details on the synthesis of difluoromethyl (**3**) and aryldifluoromethyl ketones (**2**).

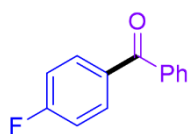
4.3 Conclusions

In conclusion, building upon findings by our group to generate difluoroketones, a new method for the synthesis of non-fluorinated diaryl ketones (benzophenones) directly from the parent benzoic acids has been established. The method reported here is a fast and effective way to synthesize ketones. It is an advantageous upgrade to the existing methods that use different acyl electrophiles. The crucial reactive intermediates, acyloxyphosphonium ions **III**, are efficiently generated in situ from the original carboxylic acids and readily available chemicals (PPh₃, NBS). Furthermore, a salient aspect of these procedures is their rapid reaction times (30-45 minutes) and the

mild reaction conditions. Significantly, the utilization of organozinc reagents, which exhibit superior compatibility with various functional groups compared to other reactive organometallics such as RMgX and RLi, results in an overall improvement in practicality and compatibility with functional groups. We anticipate that the incorporation of these methods will serve as a valuable addition to the repertoire of synthetic chemists.

– Appendix –
NMR Spectra of Synthesized Compounds

(4-fluorophenyl)(phenyl)methanone (5a)

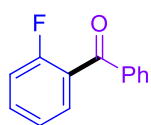


Product **5a** was synthesized using 4-fluorobenzoic acid (0.25 mmol, 1 equiv., 35 mg) and triphenyl phosphine, PPh₃ (0.35 mmol, 1.4 equiv., 91.8 mg), DCM (0.1M, 2.5 mL), NBS (0.35 mmol, 1.4 equiv., 62.3 mg), CuI (20 mol%, 9.5 mg), and phenylzinc chloride solution (2.4 equiv.). Internal standard, PhOCF₃ (0.151 mmol, 20 μ L). **Crude reaction mixture** ¹⁹F NMR (376 MHz) δ -106.60 (m, CF). ¹⁹F NMR yield: 69%

The title compound was isolated via flash column chromatography using 3-5% EtOAc/Hexane as eluent and obtained as an oil. Isolated yield: (63%, 32 mg). ¹H NMR (400 MHz, CDCl₃) δ 7.85 (t, J = 7.4 Hz, 2H), 7.77 (d, J = 7.5 Hz, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 7.17 (t, J = 7.9 Hz, 2H). ¹⁹F NMR (376 MHz, CDCl₃) δ -106.11 (m, Ar-F). GC-MS: 200 m/z. The spectral data match the previously reported structure.⁸⁸

1 mmol scale reaction: For the 1 mmol scale reaction, the product **6a** was obtained following the GP-10 using 4-fluorobenzoic acid (1 mmol, 1 equiv., 140 mg) and triphenyl phosphine, PPh₃ (1.4 mmol, 1.4 equiv., 367.2 mg), DCM (0.1M, 10 mL), NBS (1.4 mmol, 1.4 equiv., 249.2 mg), CuI (20 mol%, 38 mg), and phenylzinc halide solution (2.4 equiv.). Internal standard, PhOCF₃ (0.302 mmol, 40 μ L). **Crude reaction mixture** ¹⁹F NMR (376 MHz) δ -106.60 (m, CF). ¹⁹F NMR yield: 71%. Isolated yield: (68%, 136 mg)

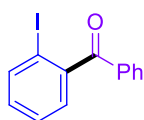
(2-fluorophenyl)(phenyl)methanone (5b)



Product **5b** was synthesized using 2-fluorobenzoic acid (0.25 mmol, 1 equiv., 35 mg) and triphenyl phosphine, PPh₃ (0.35 mmol, 1.4 equiv., 91.8 mg), DCM (0.1M, 2.5 mL), NBS (0.35 mmol, 1.4 equiv., 62.3 mg), CuI (20 mol%, 9.5 mg), and phenylzinc chloride solution (2.4 equiv.). Internal standard, PhOCF₃ (0.151 mmol, 20 μ L). **Crude reaction mixture** ¹⁹F NMR (376 MHz) δ -112.09 (m, CF). ¹⁹F NMR yield: 89%

The title compound was isolated via flash column chromatography using 3-5% EtOAc/Hexane as eluent and obtained as an oil. Isolated yield: (77%, 39 mg). ¹H NMR (400 MHz, CDCl₃) δ 7.84 (d, J = 7.6 Hz, 2H), 7.59 (t, J = 7.7 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.47 (t, J = 7.7 Hz, 2H), 7.26 (t, J = 7.7 Hz, 1H), 7.15 (t, J = 9.1 Hz, 1H). ¹⁹F NMR (376 MHz, CDCl₃) δ -111.18 (m, CF). GC-MS: 200 m/z. The spectral data match the previously reported structure.⁸⁸

(2-iodophenyl)(phenyl)methanone (5c)

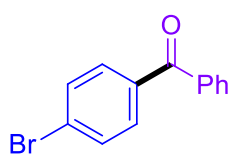


Product **5c** was synthesized using 2-iodobenzoic acid (0.25 mmol, 1 equiv., 62 mg) and triphenyl phosphine, PPh₃ (0.35 mmol, 1.4 equiv., 91.8 mg), DCM (0.1M, 2.5

mL), NBS (0.35 mmol, 1.4 equiv., 62.3 mg), CuI (20 mol%, 9.5 mg), and phenylzinc chloride solution (2.4 equiv.).

The title compound was isolated via flash column chromatography using 3-5% EtOAc/Hexane as eluent and obtained as a yellowish oil. Isolated yield: (69%, 53 mg). **¹H NMR (600 MHz, CDCl₃)** δ 7.93 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.81 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.65 – 7.57 (m, 1H), 7.51 – 7.41 (m, 3H), 7.30 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.19 (td, *J* = 7.7, 1.7 Hz, 1H). **GC-MS:** 308 m/z. The spectral data match the previously reported structure.⁸⁹

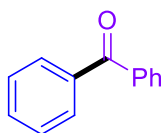
(4-bromophenyl)(phenyl)methanone (5d)



Product **5d** was synthesized using 4-bromobenzoic acid (0.25 mmol, 1 equiv., 50.25 mg) and triphenyl phosphine, PPh₃ (0.35 mmol, 1.4 equiv., 91.8 mg), DCM (0.1M, 2.5 mL), NBS (0.35 mmol, 1.4 equiv., 62.3 mg), CuI (20 mol%, 9.5 mg), and phenylzinc chloride solution (2.4 equiv.).

The title compound was isolated via flash column chromatography using 3-5% EtOAc/Hexane as eluent and obtained as a white solid. Isolated yield: (77%, 50 mg). **¹H NMR (600 MHz, CDCl₃)** δ 7.78 (d, *J* = 6.8 Hz, 2H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.66 – 7.58 (m, 3H), 7.49 (t, *J* = 7.7 Hz, 2H). **GC-MS:** 261 m/z. The spectral data match the previously reported structure.⁸⁸

benzophenone (5e)

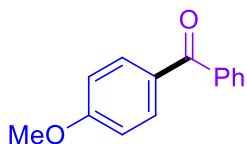


Product **5e** was synthesized using benzoic acid (0.25 mmol, 1 equiv., 30.53 mg) and triphenylphosphine, PPh₃ (0.35 mmol, 1.4 equiv., 91.8 mg), DCM (0.1M, 2.5 mL), NBS (0.35 mmol, 1.4 equiv., 62.3 mg), CuI (20 mol%, 9.5 mg), and phenylzinc chloride solution (2.4 equiv.).

chloride solution (2.4 equiv.).

The title compound was isolated via flash column chromatography using 3-5% EtOAc/Hexane as eluent and obtained as a white solid. Isolated yield: (66%, 30 mg). **¹H NMR (600 MHz, CDCl₃)** δ 7.81 (d, *J* = 6.8 Hz, 4H), 7.59 (t, *J* = 7.4 Hz, 2H), 7.48 (t, *J* = 7.7 Hz, 4H). **GC-MS:** 182 m/z. The spectral data match the previously reported structure.⁸⁸

(4-methoxyphenyl)(phenyl)methanone (5f)

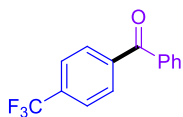


Product **5f** was synthesized using 4-methoxybenzoic acid (0.25 mmol, 1 equiv., 38.03 mg) and triphenyl phosphine, PPh₃ (0.35 mmol, 1.4 equiv., 91.8 mg), DCM (0.1M, 2.5 mL), NBS (0.35 mmol, 1.4 equiv., 62.3 mg), CuI (20 mol%, 9.5 mg), and phenylzinc chloride solution (2.4 equiv.).

The title compound was isolated via flash column chromatography using 5-7% EtOAc/Hexane as eluent and obtained as a white solid. Isolated yield: (62%, 33 mg). **¹H NMR (600 MHz, CDCl₃)** δ 7.83 (d, *J* = 8.8 Hz, 2H), 7.76 (d, *J* = 6.8 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H),

6.97 (d, $J = 8.8$ Hz, 2H), 3.89 (s, 3H). **GC-MS**: 212 m/z. The spectral data match the previously reported structure.⁸⁸

phenyl(4-(trifluoromethyl)phenyl)methanone (5g)

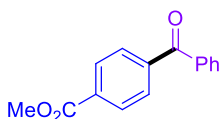


Product **5g** was synthesized using 4-(trifluoromethyl)benzoic acid (0.25 mmol, 1 equiv., 47.5 mg) and triphenylphosphine, PPh₃ (0.35 mmol, 1.4 equiv., 91.8 mg), DCM (0.1M, 2.5 mL), NBS (0.35 mmol, 1.4 equiv., 62.3 mg), CuI (20 mol%, 9.5 mg), and phenylzinc chloride solution (2.4 equiv.). Internal standard, PhOCF₃ (0.151 mmol, 20 μ L).

Crude reaction mixture ¹⁹F NMR (376 MHz) δ -63.08 (m, CF₃). ¹⁹F NMR yield: 72%

The title compound was isolated via flash column chromatography using 3-5% EtOAc/Hexane as eluent and obtained as an oil. Isolated yield: (65%, 41 mg). **¹H NMR (400 MHz, CDCl₃)** δ 7.90 (d, $J = 8.0$ Hz, 2H), 7.81 (d, $J = 7.8$ Hz, 2H), 7.76 (d, $J = 8.1$ Hz, 2H), 7.63 (t, $J = 7.4$ Hz, 1H), 7.51 (t, $J = 7.6$ Hz, 2H). **¹⁹F NMR (376 MHz, CDCl₃)** δ -63.15 (m, CF). **GC-MS**: 250 m/z. The spectral data match the previously reported structure.⁸⁸

methyl 4-benzoylbenzoate (5h)

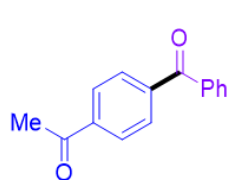


Product **5** was synthesized using 4-(methoxycarbonyl)benzoic acid (0.25 mmol, 1 equiv., 45.04 mg) and triphenyl phosphine, PPh₃ (0.35 mmol, 1.4 equiv., 91.8 mg), DCM (0.1M, 2.5 mL), NBS (0.35 mmol, 1.4 equiv., 62.3 mg), CuI (20

mol%, 9.5 mg), and phenylzinc chloride solution (2.4 equiv.).

The title compound was isolated via flash column chromatography using 5-7% EtOAc/Hexane as eluent and obtained as a white solid. Isolated yield: (79%, 48 mg). **¹H NMR (400 MHz, CDCl₃)** δ 8.15 (d, $J = 8.4$ Hz, 2H), 7.82 (dd, $J = 14.5, 7.9$ Hz, 4H), 7.62 (t, $J = 7.4$ Hz, 1H), 7.50 (t, $J = 7.7$ Hz, 2H), 3.96 (s, 3H). **GC-MS**: 240 m/z. The spectral data match the previously reported structure.⁹⁰

methyl 4-benzoylbenzoate (5i)

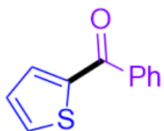


Product **5** was synthesized using 4-acetylbenzoic acid (0.25 mmol, 1 equiv., 41.04 mg) and triphenyl phosphine, PPh₃ (0.35 mmol, 1.4 equiv., 91.8 mg), DCM (0.1M, 2.5 mL), NBS (0.35 mmol, 1.4 equiv., 62.3 mg), CuI (20 mol%, 9.5 mg), and phenylzinc chloride solution (2.4 equiv.).

The title compound was isolated via flash column chromatography using 5-7% EtOAc/Hexane as eluent and obtained as a white solid. Isolated yield: (76%, 43 mg). **¹H NMR (400 MHz, CDCl₃)** δ 8.08 (d, $J = 8.1$ Hz, 2H), 7.88 (d, $J = 8.2$ Hz, 2H), 7.82 (d, $J = 7.3$ Hz, 2H), 7.64 (t, $J = 7.4$ Hz, 1H),

7.52 (t, $J = 7.6$ Hz, 2H), 2.69 (s, 3H). **GC-MS**: 224 m/z. The spectral data match the previously reported structure.⁹⁰

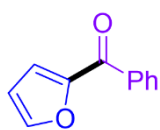
phenyl(thiophen-2-yl)methanone (5j)



Product **5j** was synthesized using thiophene-2-carboxylic acid (0.25 mmol, 1 equiv., 32.03 mg) and triphenyl phosphine, PPh₃ (0.35 mmol, 1.4 equiv., 91.8 mg), DCM (0.1M, 2.5 mL), NBS (0.35 mmol, 1.4 equiv., 62.3 mg), CuI (20 mol%, 9.5 mg), and phenylzinc chloride solution (2.4 equiv.).

The title compound was isolated via flash column chromatography using 3-5% EtOAc/Hexane as eluent and obtained as a white solid. Isolated yield: (85%, 40 mg). **¹H NMR (600 MHz, CDCl₃)** δ 7.87 (d, $J = 6.9$ Hz, 2H), 7.72 (dd, $J = 5.0, 1.1$ Hz, 1H), 7.65 (dd, $J = 3.8, 1.2$ Hz, 1H), 7.59 (t, $J = 7.4$ Hz, 1H), 7.50 (t, $J = 7.7$ Hz, 2H), 7.17 (dd, $J = 5.0, 3.7$ Hz, 1H). **GC-MS**: 188 m/z. The spectral data match the previously reported structure.⁸⁸

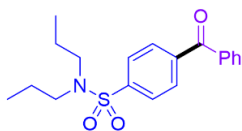
furan-2-yl(phenyl)methanone (5k)



Product **5k** was synthesized using furan-2-carboxylic acid (0.25 mmol, 1 equiv., 28.02 mg) and triphenyl phosphine, PPh₃ (0.35 mmol, 1.4 equiv., 91.8 mg), DCM (0.1M, 2.5 mL), NBS (0.35 mmol, 1.4 equiv., 62.3 mg), CuI (20 mol%, 9.5 mg), and phenylzinc chloride solution (2.4 equiv.).

The title compound was isolated via flash column chromatography using 3-5% EtOAc/Hexane as eluent and obtained as a white solid. Isolated yield: (88%, 38 mg). **¹H NMR (600 MHz, CDCl₃)** δ 7.97 (d, $J = 6.8$ Hz, 2H), 7.71 (d, $J = 1.6$ Hz, 1H), 7.59 (t, $J = 7.5$ Hz, 1H), 7.50 (t, $J = 7.7$ Hz, 2H), 7.24 (d, $J = 3.5$ Hz, 1H), 6.60 (dd, $J = 3.6, 1.7$ Hz, 1H). **GC-MS**: 172 m/z. The spectral data match the previously reported structure.⁸⁸

4-benzoyl-*N,N*-dipropylbenzenesulfonamide (5l)

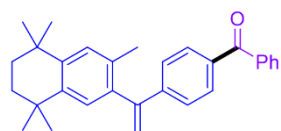


Product **5l** was synthesized using 4-(*N,N*-dipropylsulfamoyl)benzoic acid (0.25 mmol, 1 equiv., 71.36 mg) and triphenylphosphine, PPh₃ (0.35 mmol, 1.4 equiv., 91.8 mg), DCM (0.1M, 2.5 mL), NBS (0.35 mmol, 1.4 equiv., 62.3 mg), CuI (20 mol%, 9.5 mg), and phenylzinc chloride solution (2.4 equiv.).

The title compound was isolated via flash column chromatography using 4-6% EtOAc/Hexane as eluent and obtained as a white solid. Isolated yield: (87%, 75 mg). **¹H NMR (600 MHz, CDCl₃)** δ 7.92 (d, $J = 8.5$ Hz, 2H), 7.89 (d, $J = 8.5$ Hz, 2H), 7.79 (d, $J = 6.9$ Hz, 2H), 7.64 (t, $J = 7.5$ Hz, 1H),

7.51 (t, $J = 7.8$ Hz, 2H), 3.24 – 3.02 (m, 4H), 1.58 (h, $J = 7.5$ Hz, 4H), 0.88 (t, $J = 7.4$ Hz, 6H). The spectral data match the previously reported structure.⁹¹

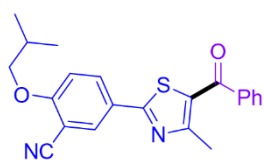
(4-(1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)vinyl)phenyl)(phenyl)methanone (5m)



Product **5m** was synthesized using 4-(1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydronaphthalen-2-yl)vinyl)benzoic acid (0.25 mmol, 1 equiv., 87.12 mg) and triphenyl phosphine, PPh₃ (0.35 mmol, 1.4 equiv., 91.8 mg), DCM (0.1M, 2.5 mL), NBS (0.35 mmol, 1.4 equiv., 62.3 mg), CuI (20 mol%, 9.5 mg), and phenylzinc chloride solution (2.4 equiv.).

The title compound was isolated via flash column chromatography using 4-6% EtOAc/Hexane as eluent and obtained as a white solid. Isolated yield: (81%, 83 mg). **¹H NMR (600 MHz, CDCl₃)** δ 7.84 (d, $J = 8.2$ Hz, 2H), 7.79 (d, $J = 8.4$ Hz, 2H), 7.61 (t, $J = 7.4$ Hz, 1H), 7.51 (t, $J = 7.8$ Hz, 2H), 7.43 (d, $J = 8.4$ Hz, 2H), 7.19 (s, 1H), 7.14 (s, 1H), 5.89 (d, $J = 1.3$ Hz, 1H), 5.39 (d, $J = 1.4$ Hz, 1H), 2.03 (s, 3H), 1.74 (s, 4H), 1.35 (s, 6H), 1.33 (s, 6H). **¹³C NMR (151 MHz, CDCl₃)** δ 196.4, 149.2, 145.2, 144.5, 142.5, 138.1, 137.9, 136.5, 132.9, 132.4, 130.5, 130.1, 128.4, 128.2, 128.1, 126.6, 117.0, 35.3, 34.2, 34.0, 32.1, 32.0, 20.1. **HRMS (ESI):** C₃₀H₃₃O [M+H]⁺ calc: 409.2531; found: 409.2539. **FTIR (cm⁻¹):** 2963, 2921, 2857, 1647, 1597, 1494, 1445, 1275, 1075, 939, 856. **GC-MS:** 408 m/z.

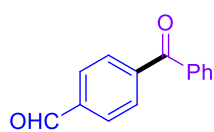
5-(5-benzoyl-4-methylthiazol-2-yl)-2-isobutoxybenzonitrile (5n)



Product **5n** was synthesized using 2-(3-cyano-4-isobutoxyphenyl)-4-methylthiazole-5-carboxylic acid (0.25 mmol, 1 equiv., 79.09 mg) and triphenyl phosphine, PPh₃ (0.35 mmol, 1.4 equiv., 91.8 mg), DCM (0.1M, 2.5 mL), NBS (0.35 mmol, 1.4 equiv., 62.3 mg), CuI (20 mol%, 9.5 mg), and phenylzinc chloride solution (2.4 equiv.).

The title compound was isolated via flash column chromatography using 10-12% EtOAc/Hexane as eluent and obtained as a white solid. Isolated yield: (59%, 55 mg). **¹H NMR (400 MHz, CDCl₃)** δ 8.23 (d, $J = 2.3$ Hz, 1H), 8.14 (dd, $J = 8.9, 2.3$ Hz, 1H), 7.86 (d, $J = 7.0$ Hz, 2H), 7.64 (t, $J = 7.5$ Hz, 1H), 7.53 (t, $J = 7.6$ Hz, 2H), 7.04 (d, $J = 8.9$ Hz, 1H), 3.93 (d, $J = 6.5$ Hz, 2H), 2.67 (s, 3H), 2.34 – 2.14 (m, 1H), 1.12 (d, $J = 6.7$ Hz, 6H). **GC-MS:** 376 m/z. The spectral data match the previously reported structure.⁹¹

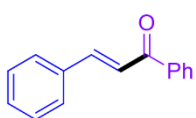
4-benzoylbenzaldehyde (5o)



Product **5o** was synthesized using 4-formylbenzoic acid (0.25 mmol, 1 equiv., 37.53 mg) and triphenyl phosphine, PPh₃ (0.35 mmol, 1.4 equiv., 91.8 mg), DCM (0.1M, 2.5 mL), NBS (0.35 mmol, 1.4 equiv., 62.3 mg), CuI (20 mol%, 9.5 mg), and phenylzinc chloride solution (2.4 equiv.).

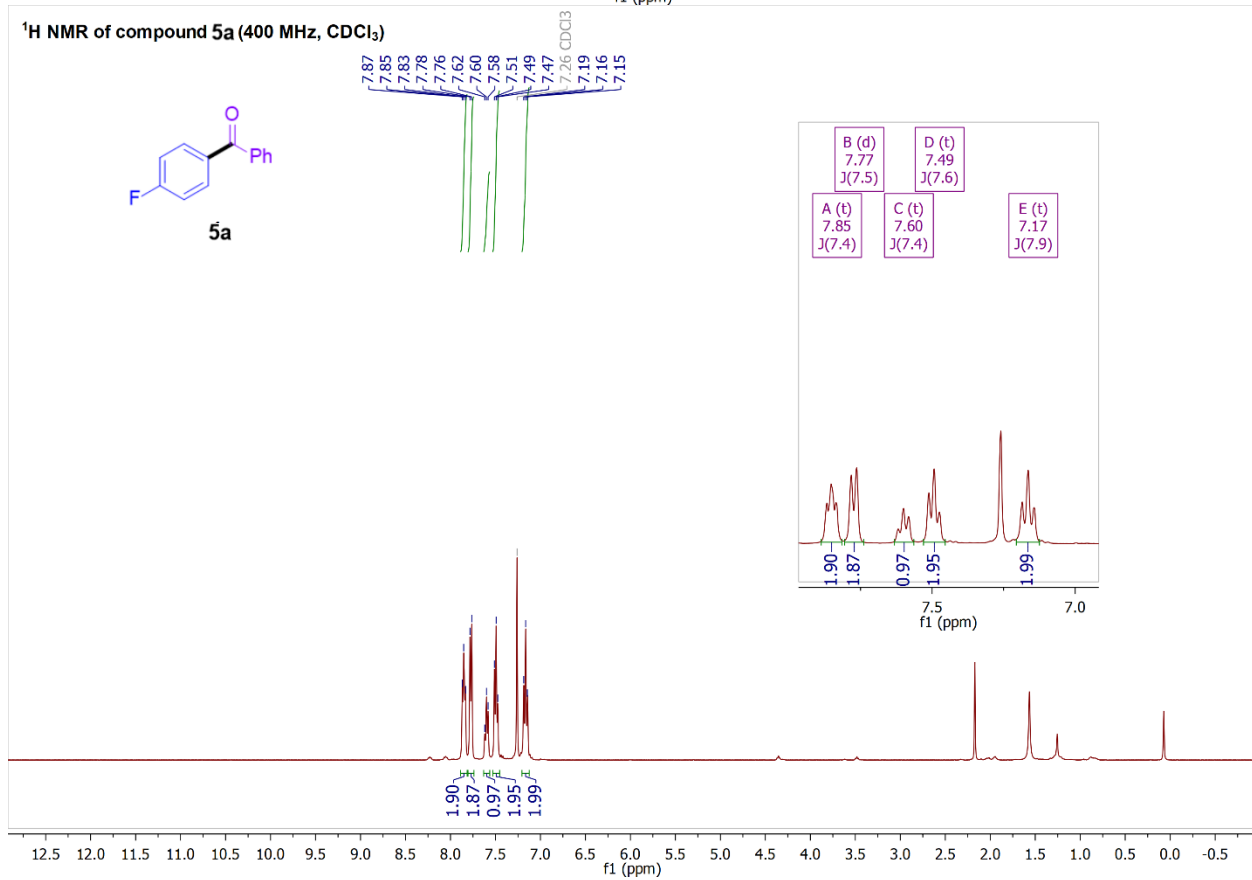
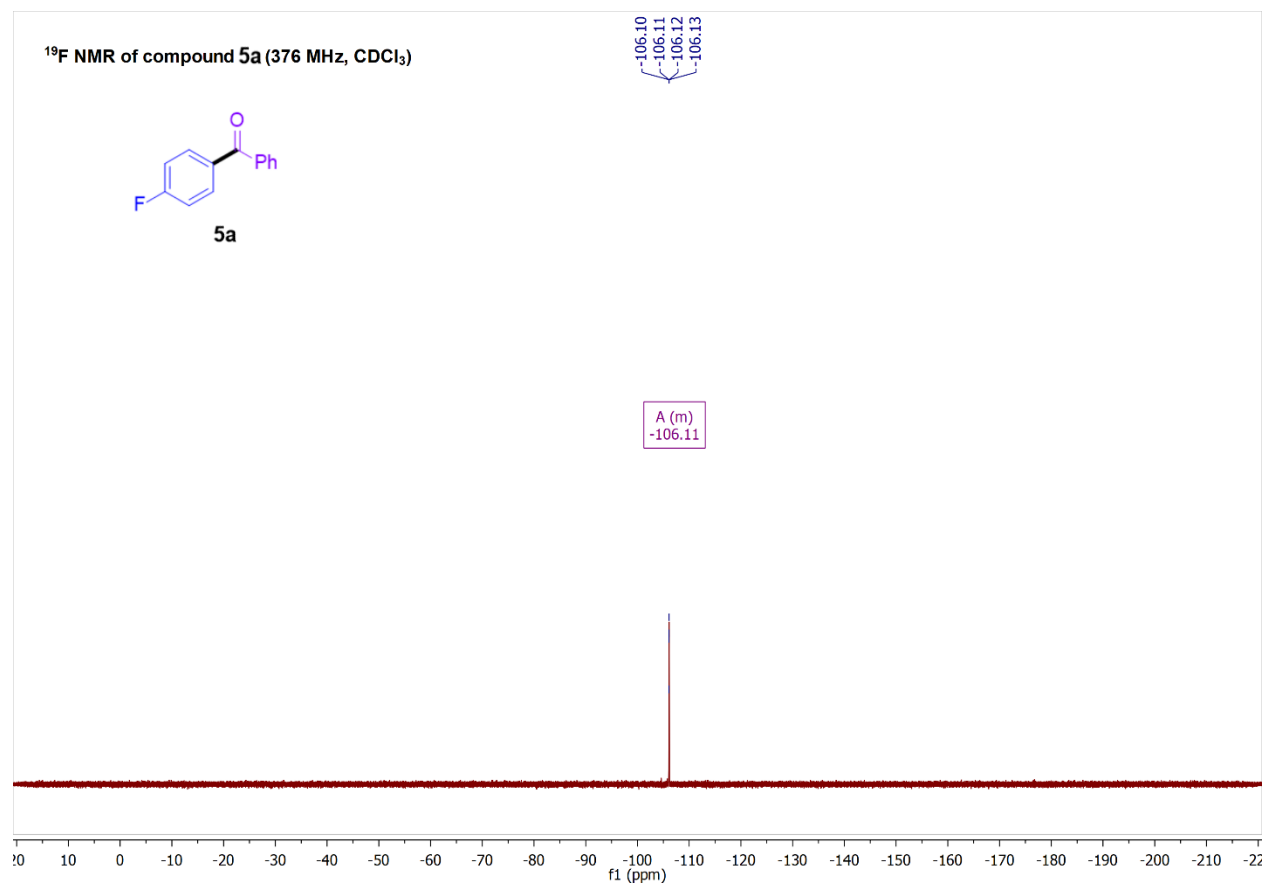
The title compound was isolated via flash column chromatography using 3-5% EtOAc/Hexane as eluent and obtained as a white solid. Isolated yield: (21%, 11 mg). **¹H NMR (400 MHz, CDCl₃)** δ 10.14 (s, 1H), 8.01 (d, J = 8.1 Hz, 2H), 7.93 (d, J = 8.2 Hz, 2H), 7.81 (d, J = 8.4 Hz, 2H), 7.64 (t, J = 7.5 Hz, 1H), 7.51 (t, J = 7.9 Hz, 2H). **GC-MS:** 210 m/z. The spectral data match the previously reported structure.⁹⁰

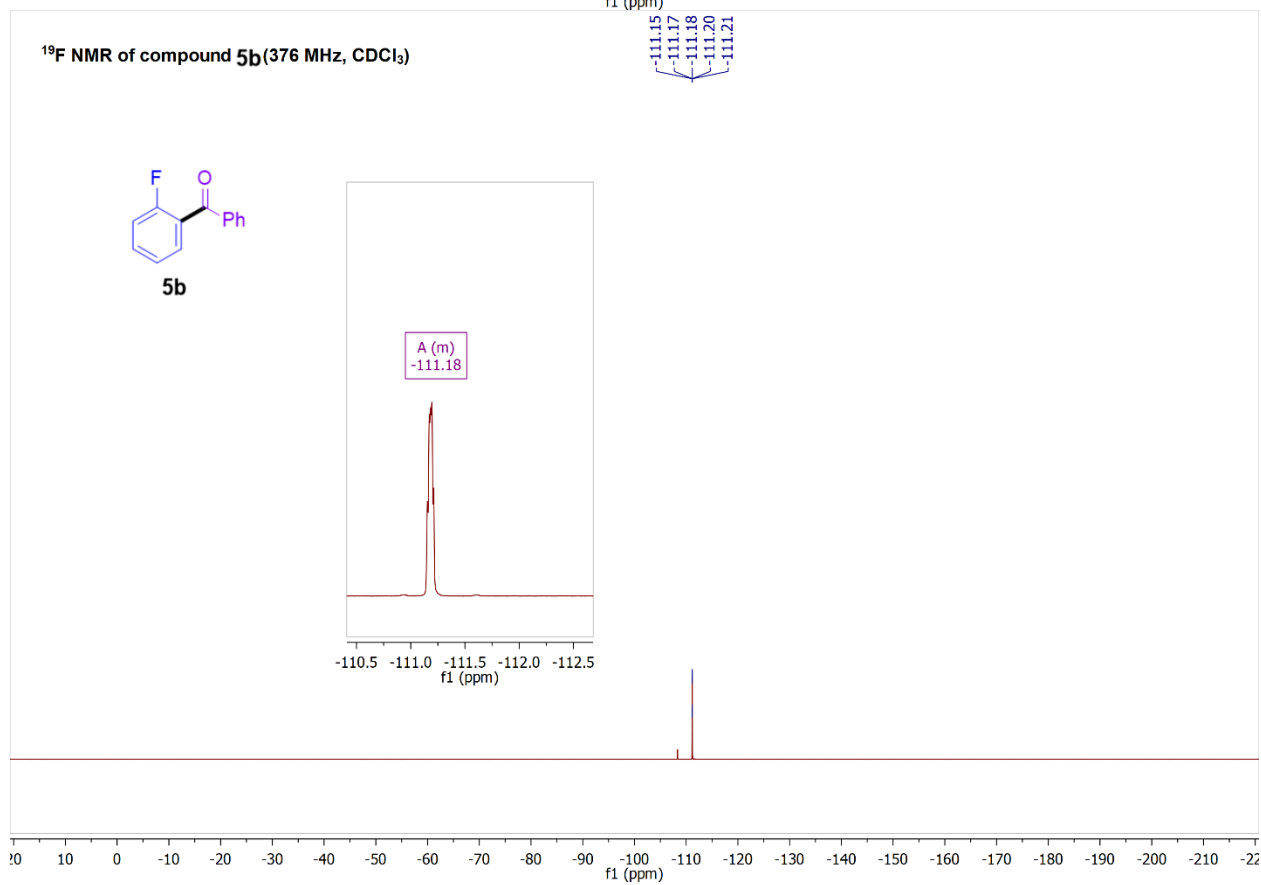
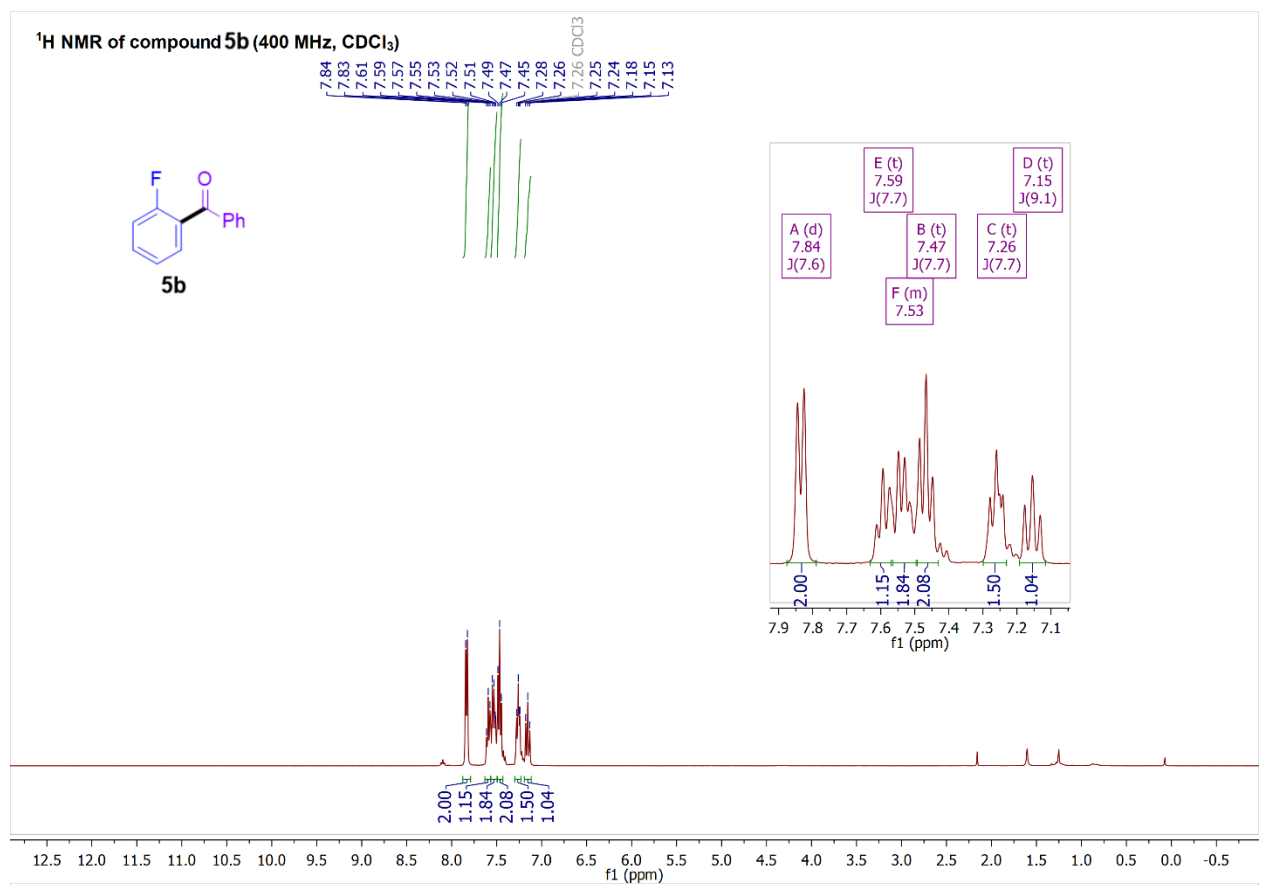
(E)-chalcone (5p)

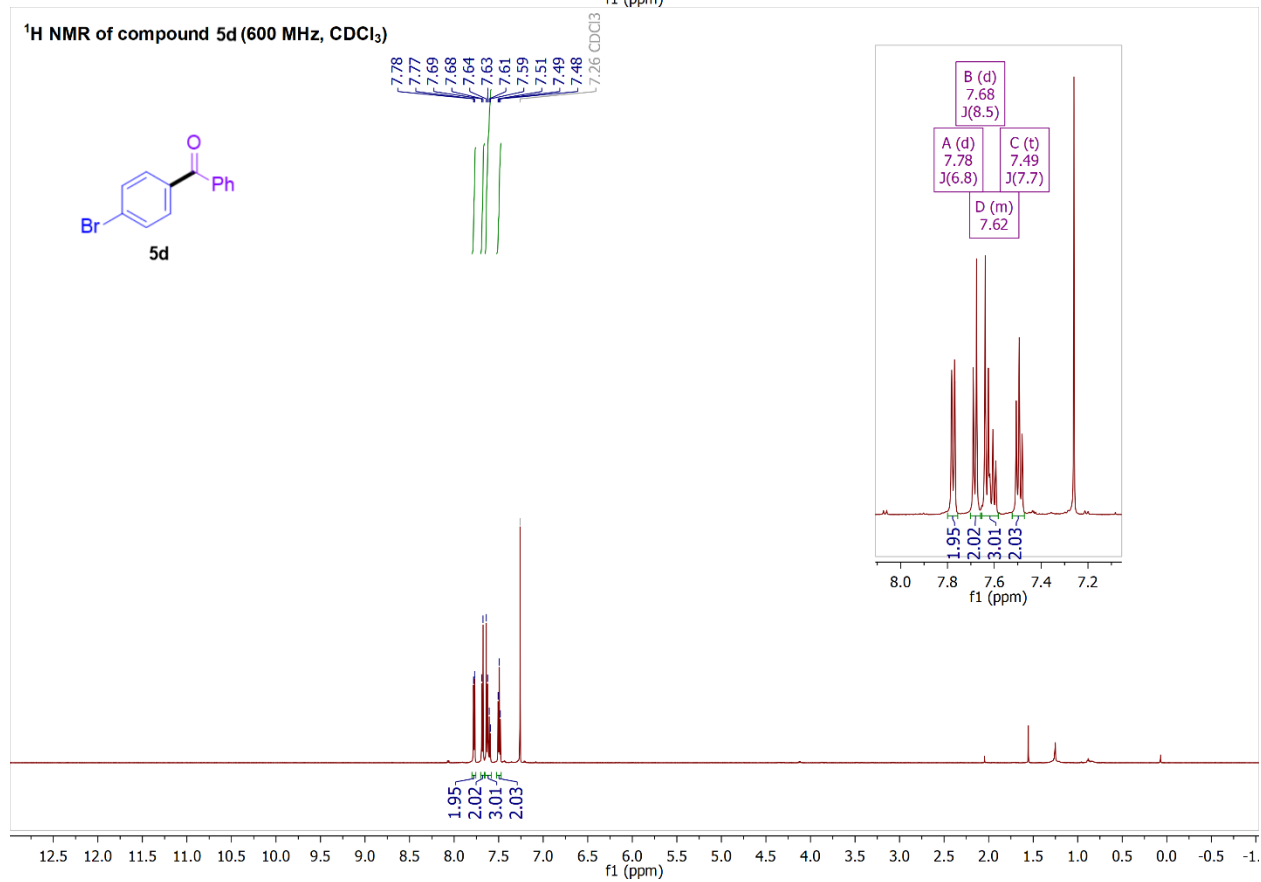
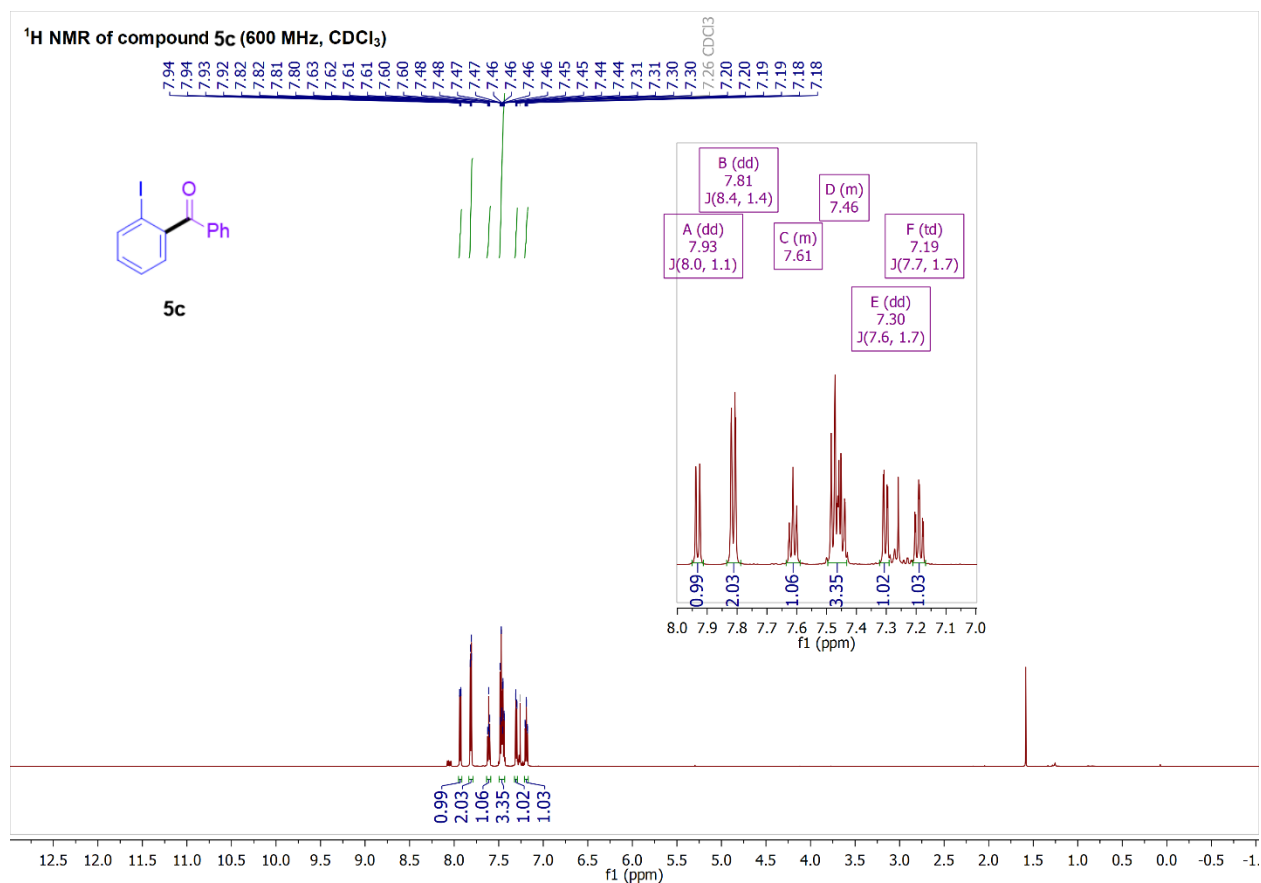


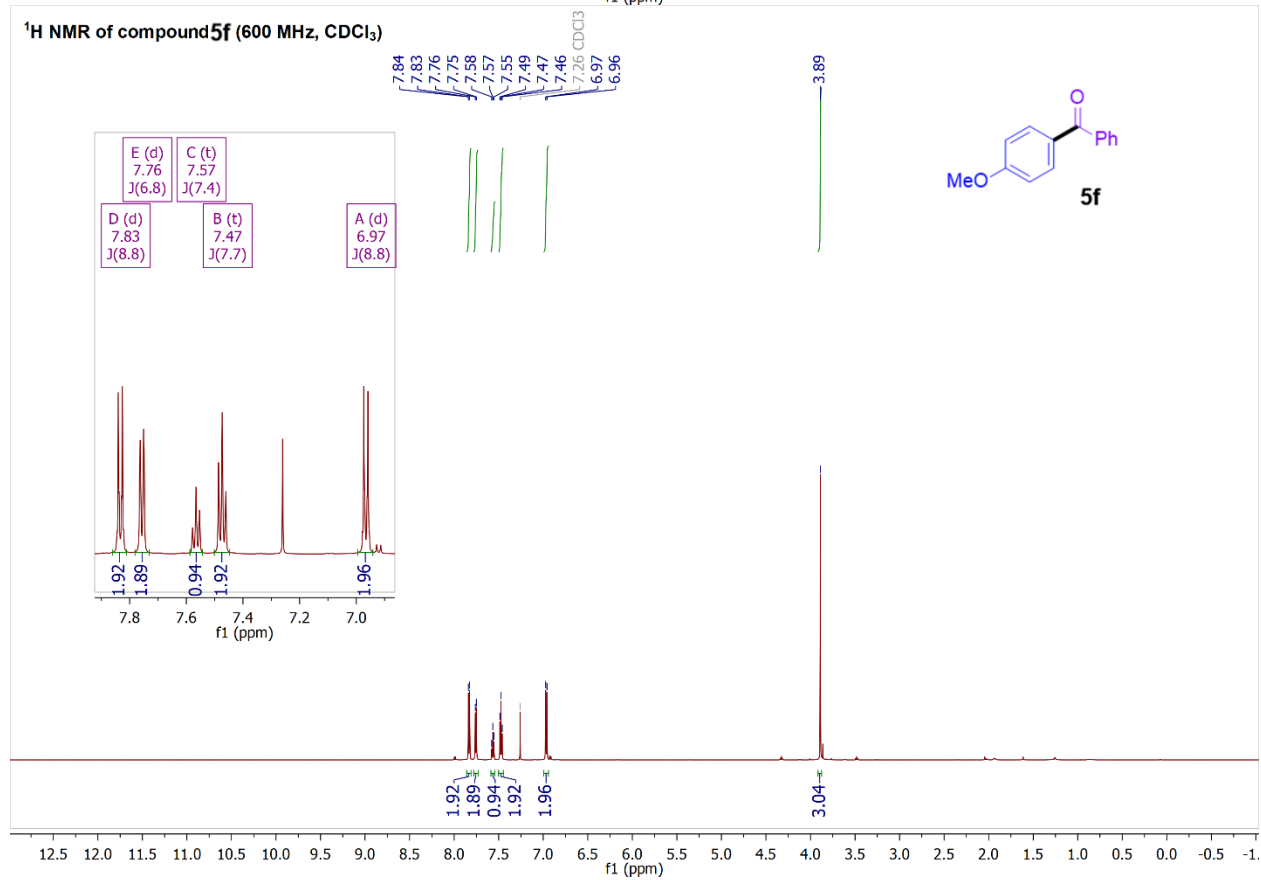
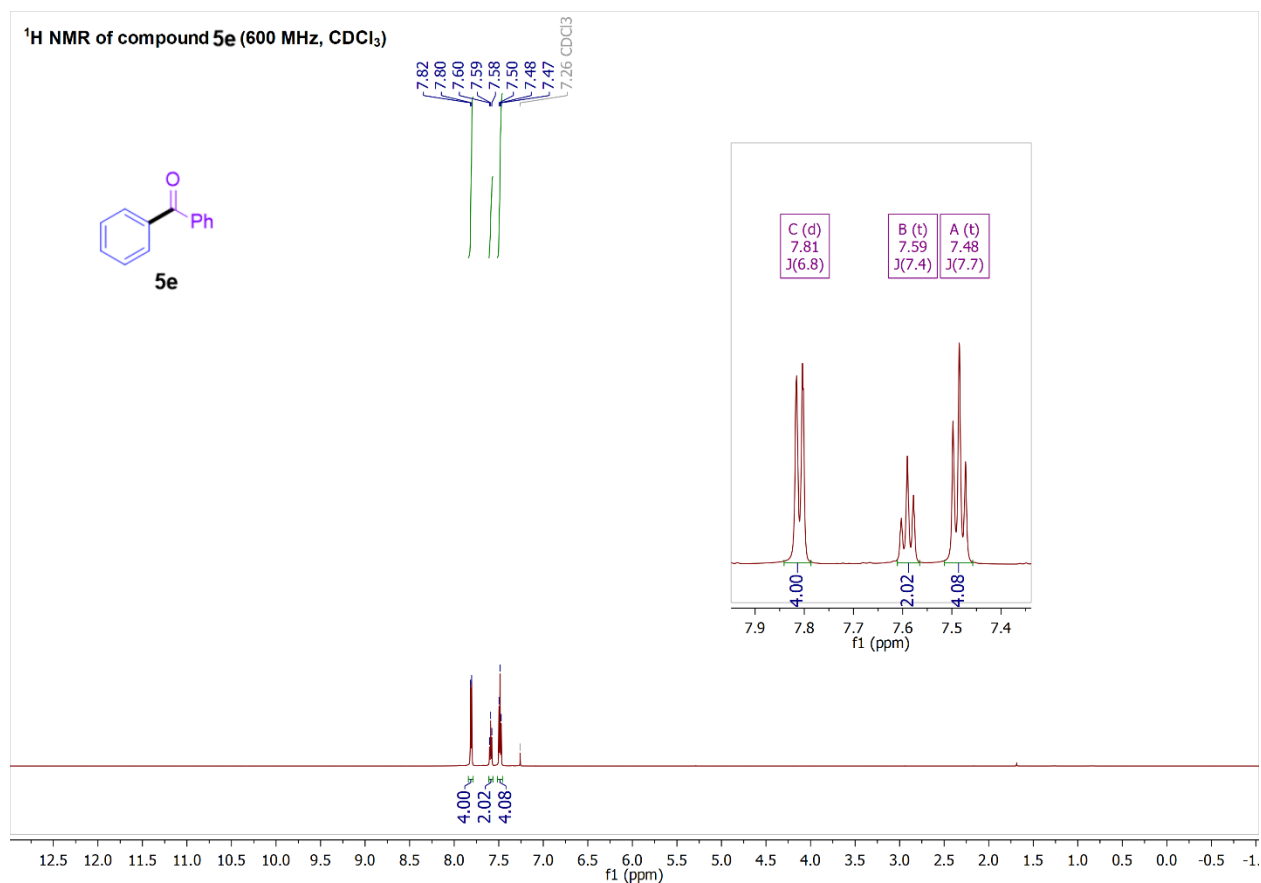
Product **5p** was synthesized using cinnamic acid (0.25 mmol, 1 equiv., 41.04 mg) and triphenylphosphine, PPh₃ (0.35 mmol, 1.4 equiv., 91.8 mg), DCM (0.1M, 2.5 mL), NBS (0.35 mmol, 1.4 equiv., 62.3 mg), CuI (20 mol%, 9.5 mg), and phenylzinc chloride solution (2.4 equiv.).

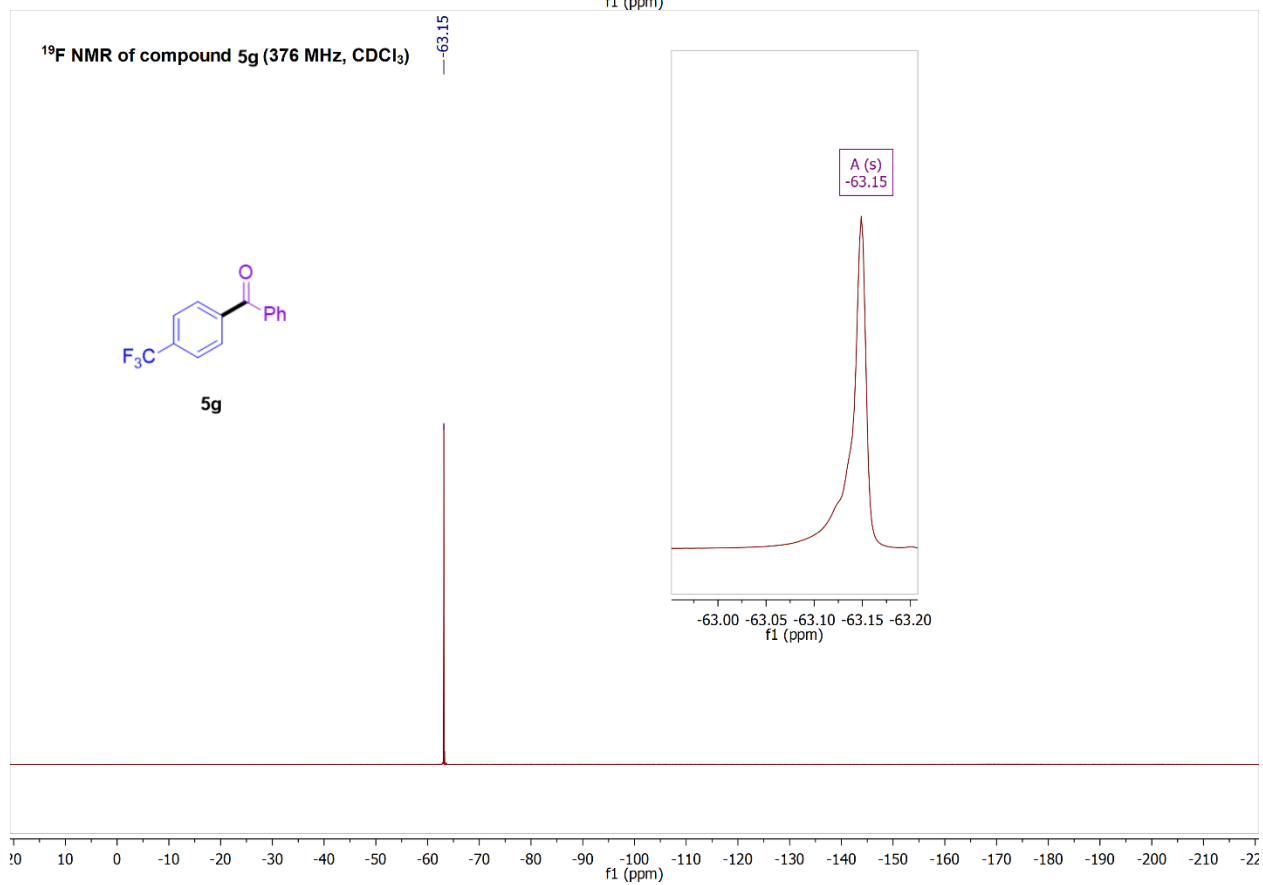
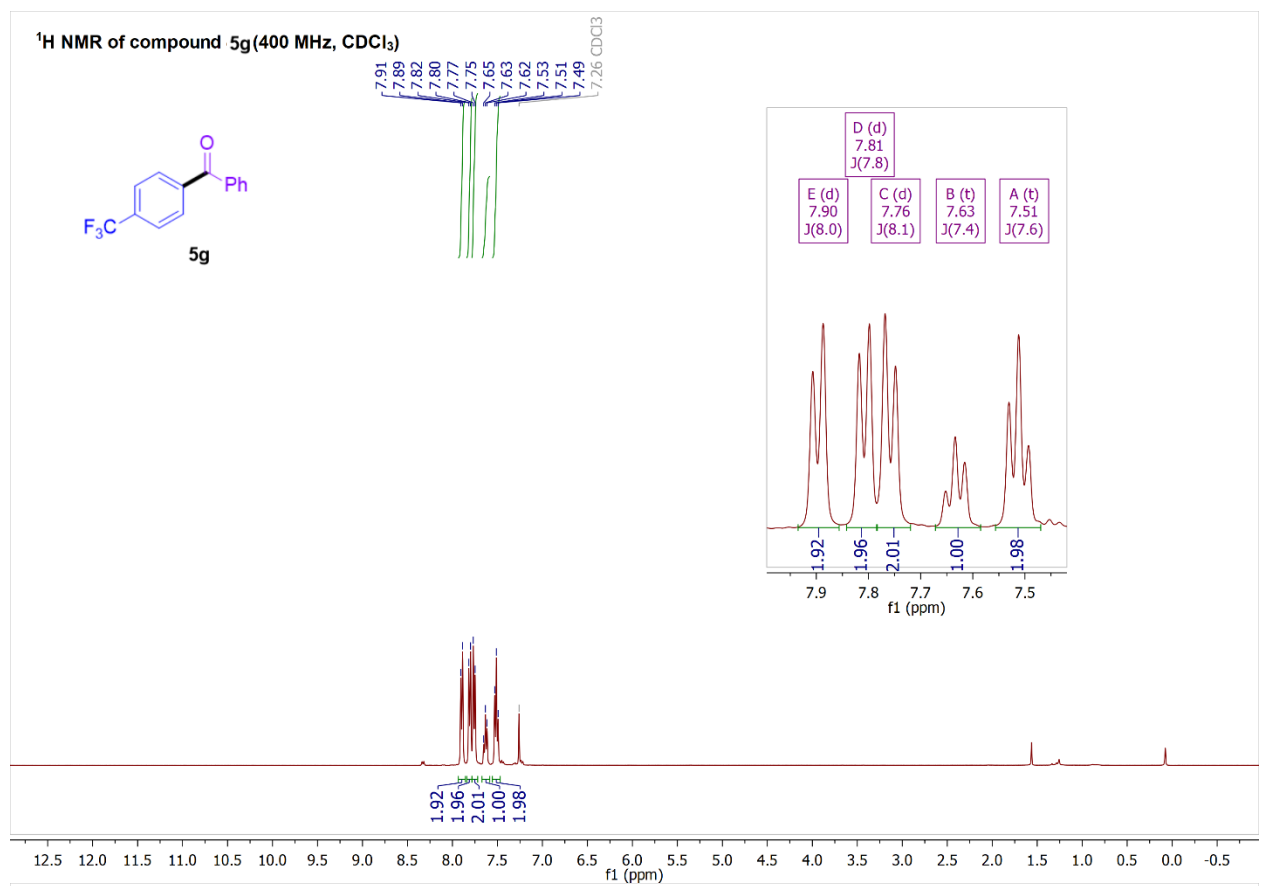
The title compound was isolated via flash column chromatography using 3-5% EtOAc/Hexane as eluent and obtained as a white solid. Isolated yield: (27%, 14 mg). **¹H NMR (400 MHz, CDCl₃)** δ 8.03 (d, J = 6.9 Hz, 2H), 7.82 (d, J = 15.7 Hz, 1H), 7.68 – 7.64 (m, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.55 (d, J = 15.8 Hz, 1H), 7.51 (t, J = 7.7 Hz, 2H), 7.43 (dd, J = 5.0, 2.0 Hz, 3H). **GC-MS:** 208 m/z. The spectral data match the previously reported structure.⁹⁰

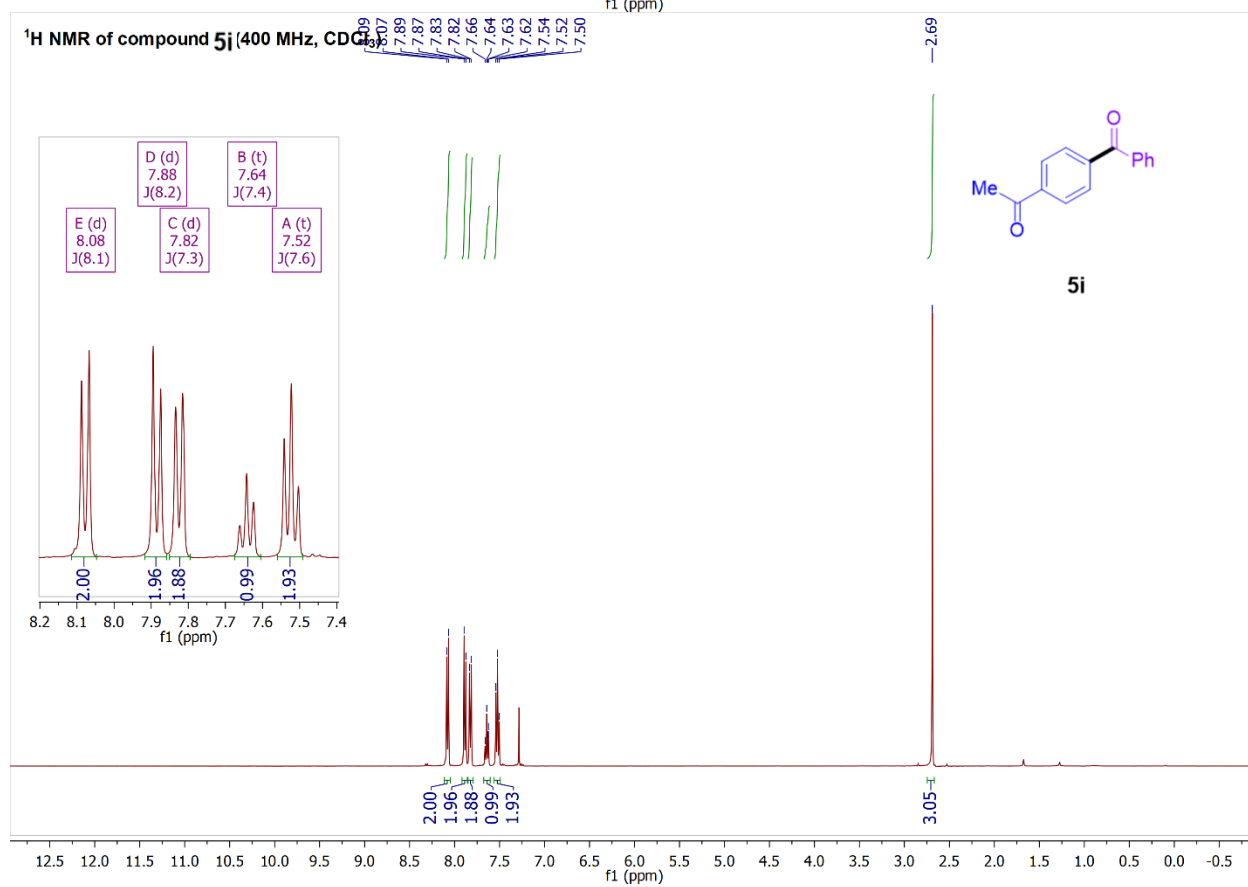
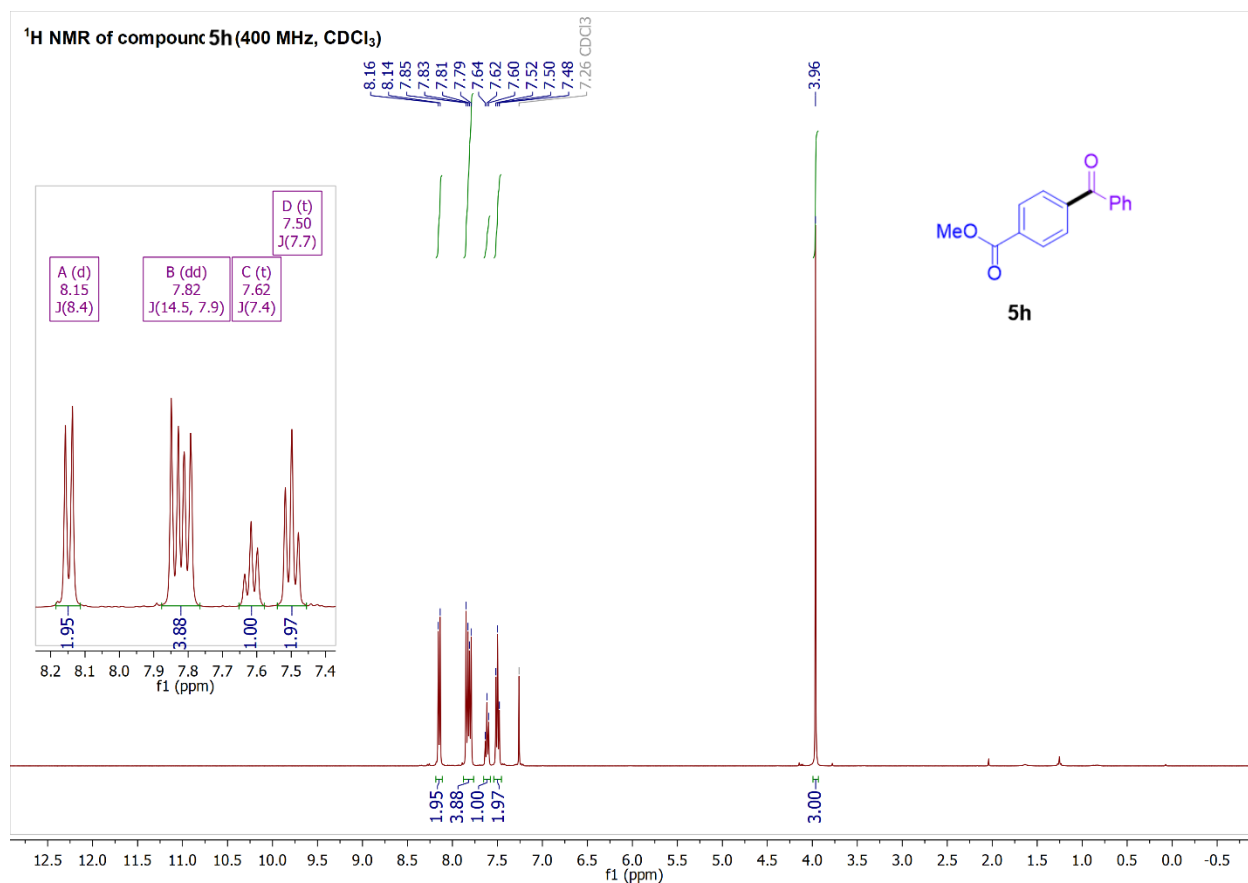


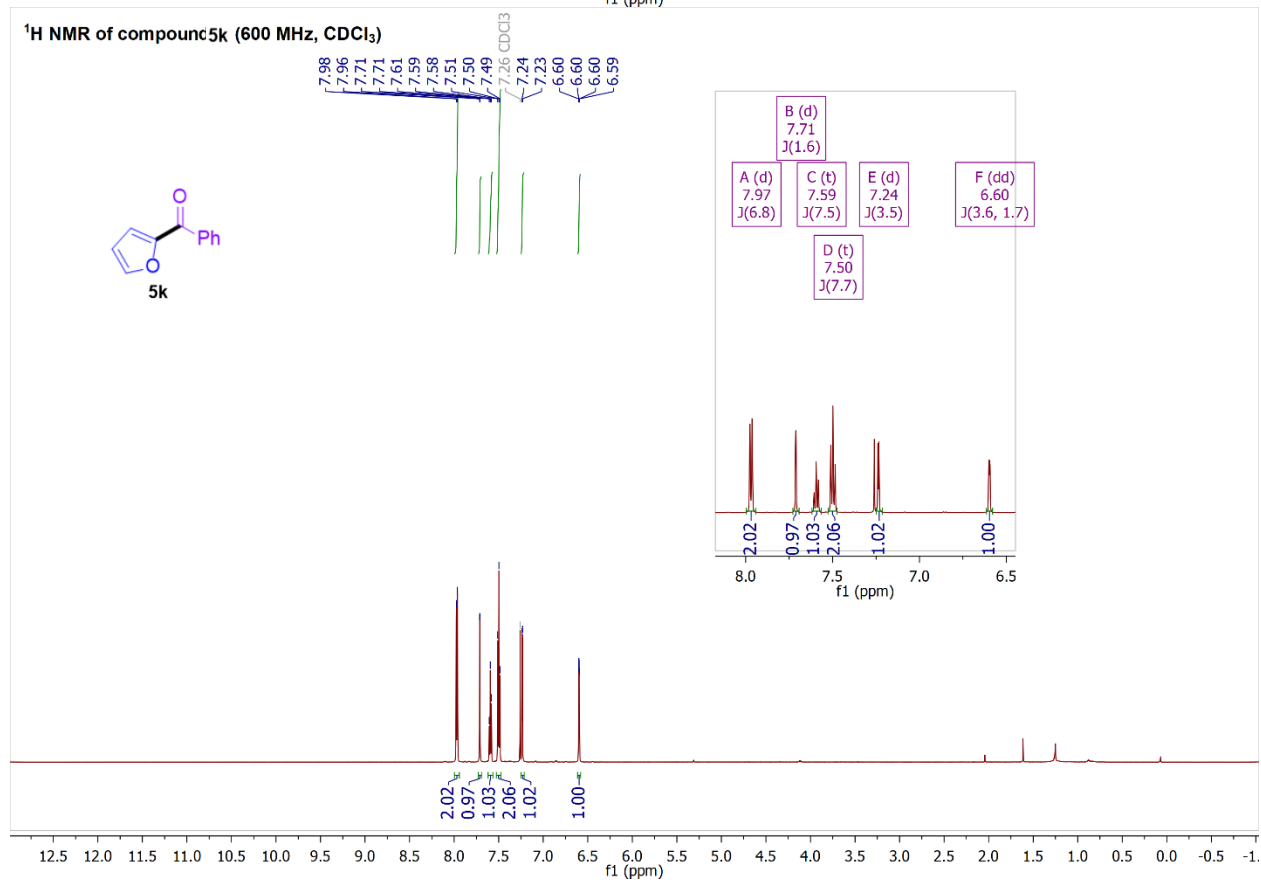
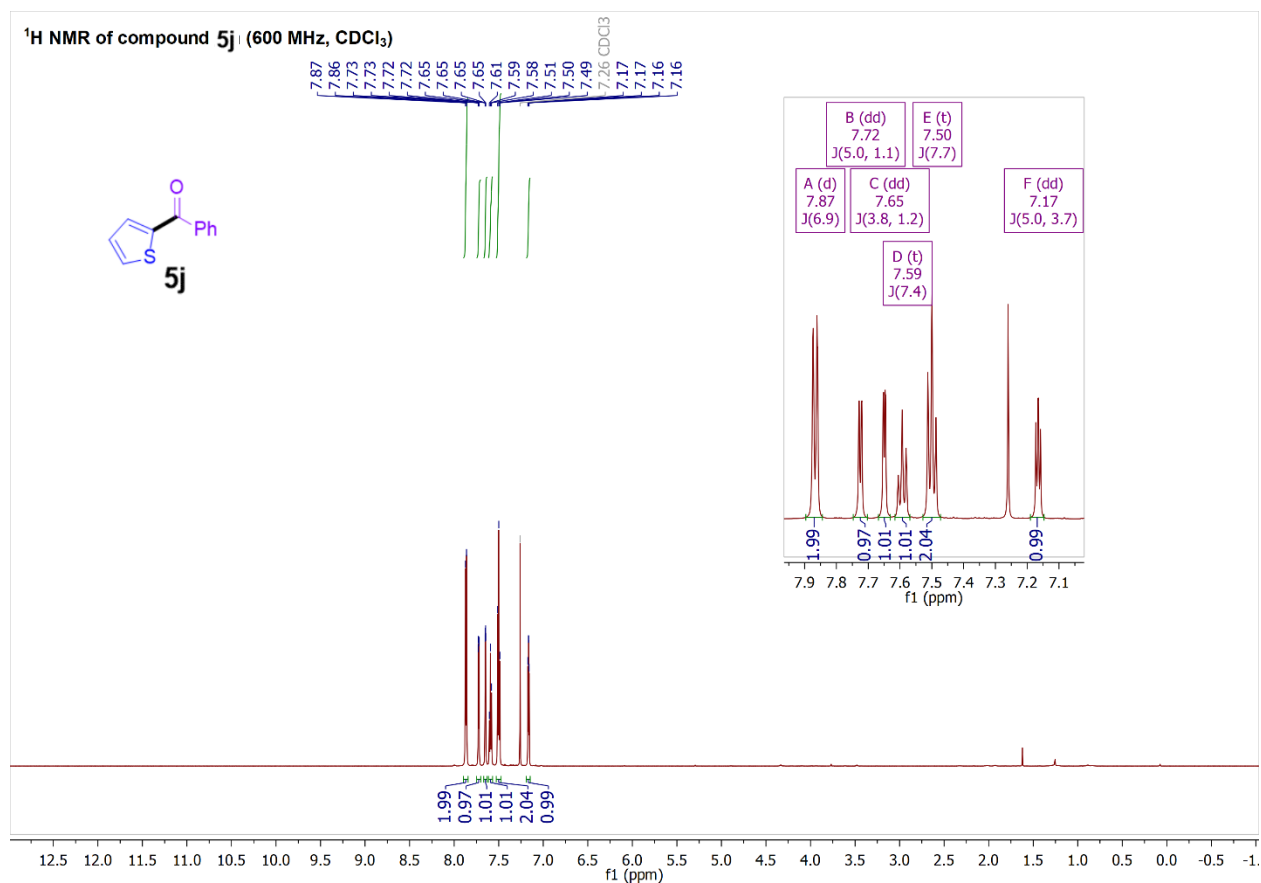


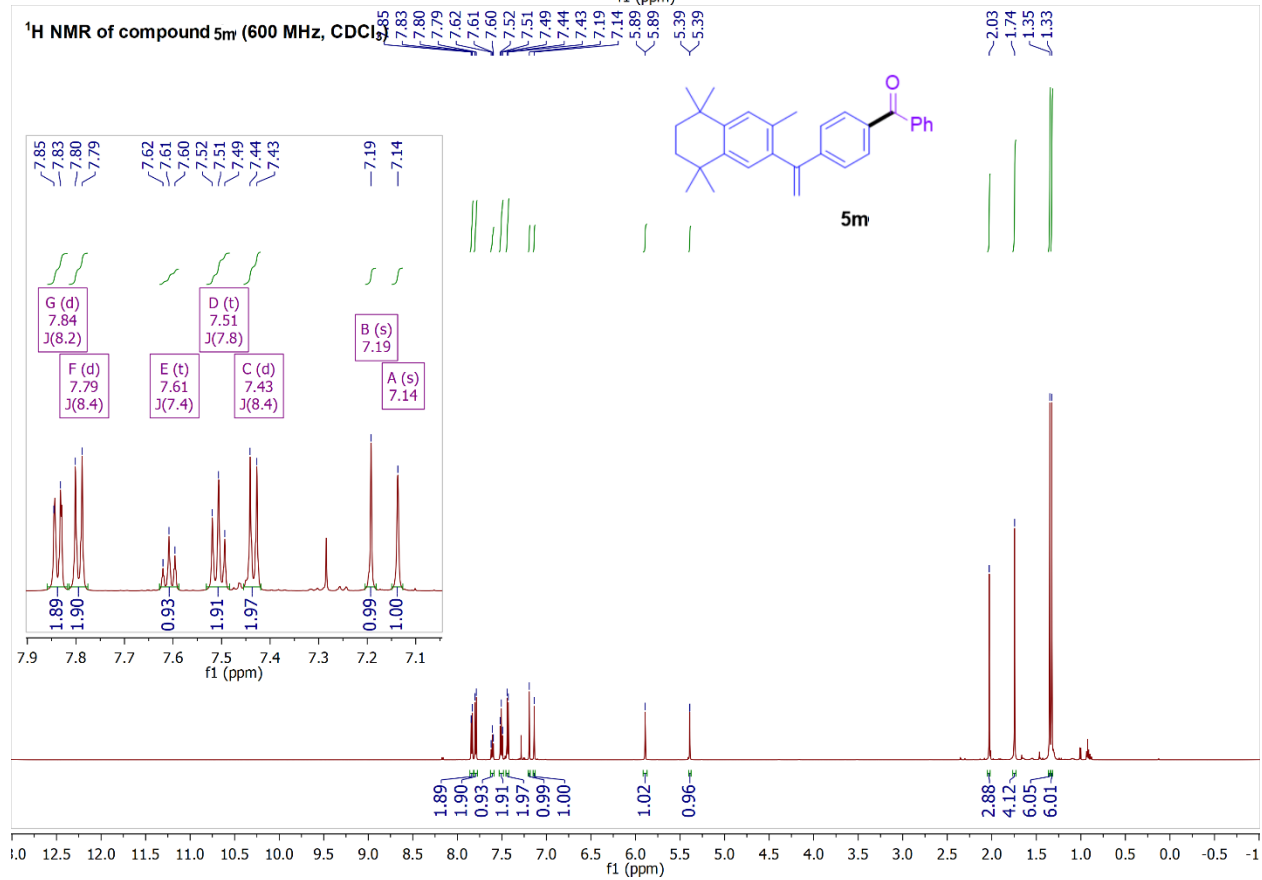
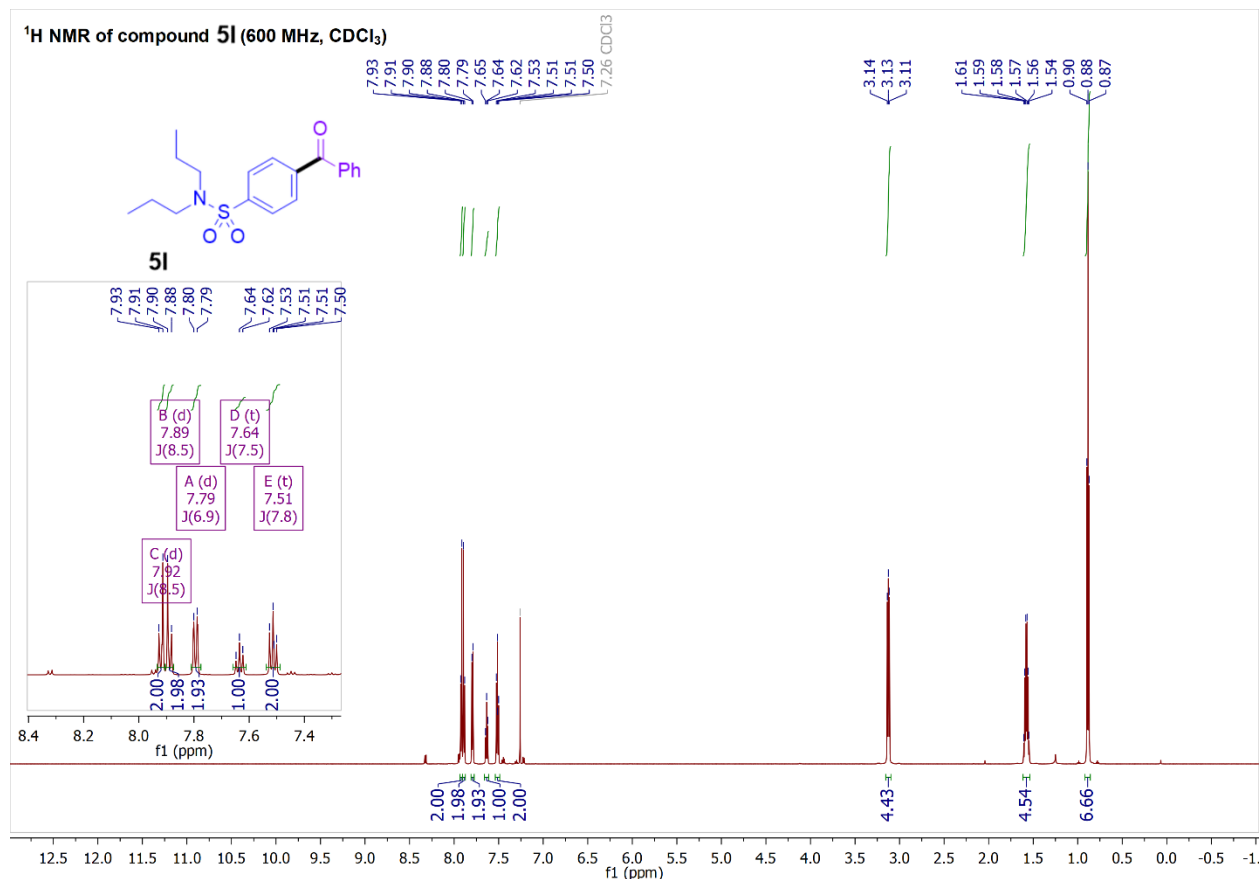


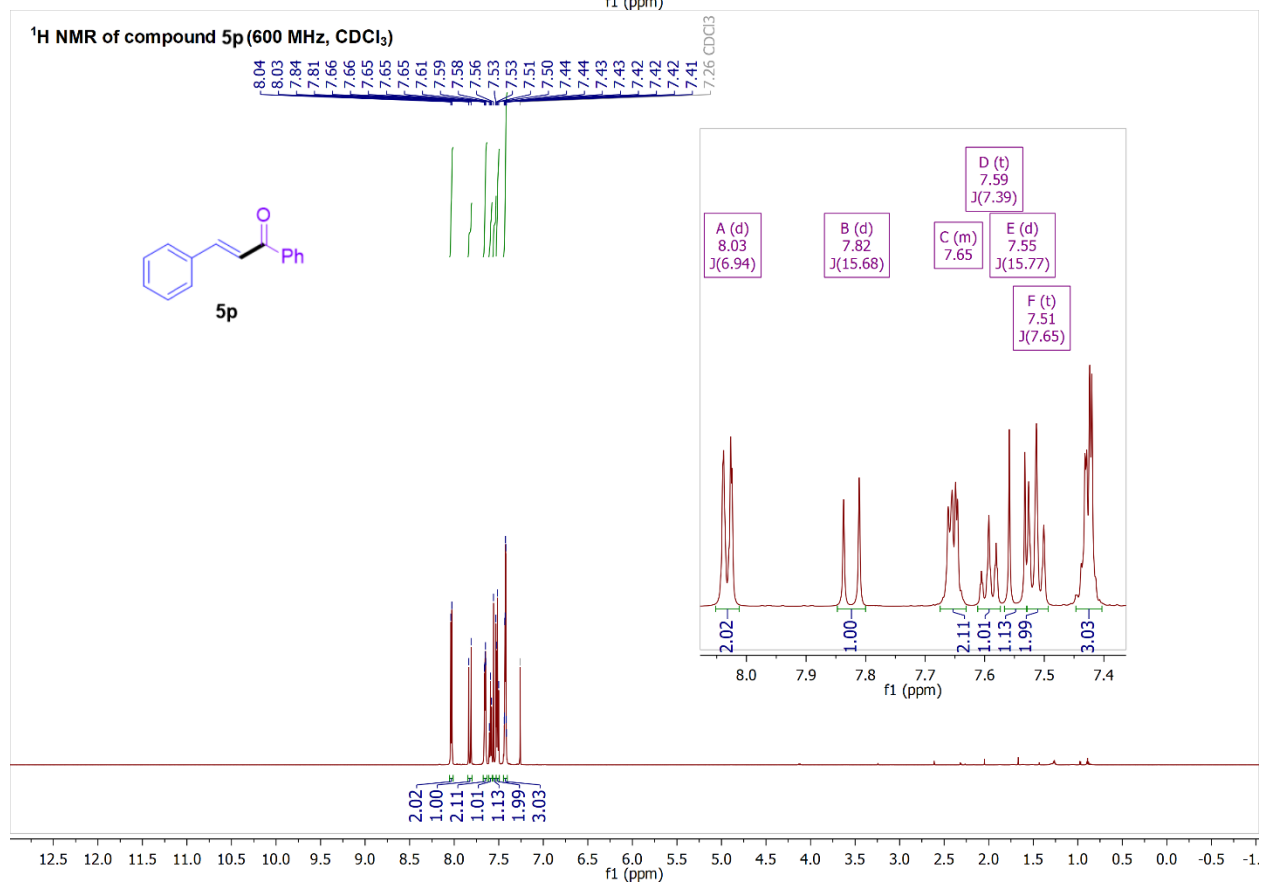
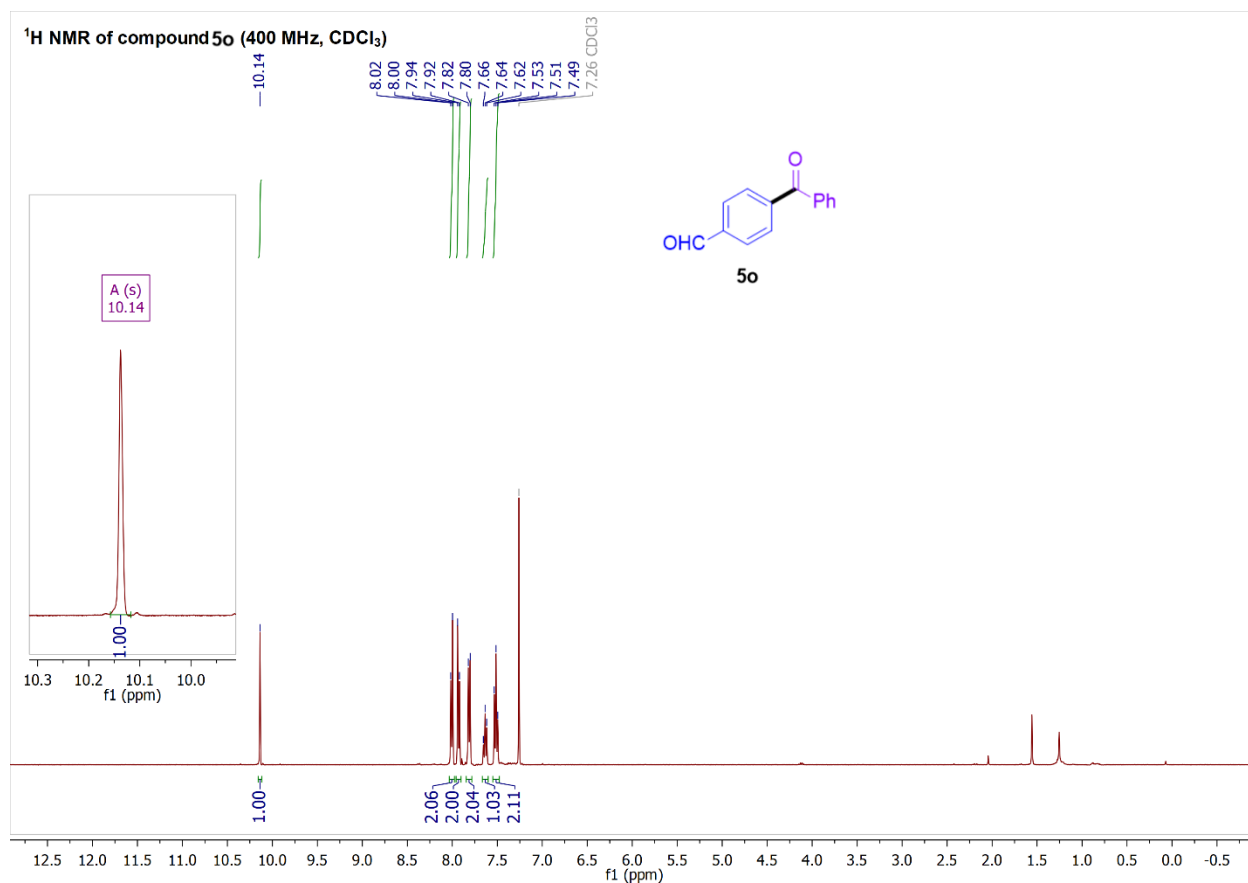












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