Design of Transition-Metal-Catalyzed and Mediated Carbonylative Routes to Acyl Electrophiles

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Abstract

Friedel-Crafts acylations represent one of the most heavily utilized platforms for the synthesis of ketones from aromatic hydrocarbons. This reaction is dependent upon the availability of reactive acyl electrophiles, which are classically generated from the combination of high energy, synthetic, and often corrosive organic electrophiles with Bronsted or Lewis acid catalysts. This thesis describes the development of alternative, metal-mediated routes to access these electrophiles from carbon monoxide, which is a stable, abundant C1 building block. The product of these reactions, aroyl triflate electrophiles, are directly used in the functionalization of arenes. In addition, applications of this concept to radiolabeling pharmaceuticals are explored.

Chapter 2 describes the development of the palladium catalyzed carbonylative C-H functionalization of arenes to form ketones. This research addressed a long-standing challenge in palladium-catalyzed C-H functionalization, in which the incorporation of carbon monoxide to form ketones was not typically viable due to intrinsic limitations in reaction design. An alternative approach was developed in which potent aroyl triflate electrophiles are generated in catalysis and reacted with arenes to form ketones. This led to the first general platform to preform carbonylative C-H functionalization to synthesize ketones, and employs simply aryl iodides, CO and arenes as reagents. Mechanistic studies revealed the key to this transformation is the generation of an electron poor, CO-ligated palladium catalyst from which reductive elimination of reactive acyl electrophiles becomes viable.

Chapter 3 describes an extension of the work in chapter 2, in which aryl iodides can be replaced by much more readily available carboxylic acids to generate aroyl triflates without a palladium catalyst. This represents a rare example of a mild transition-metal-free activation of carbon monoxide. While typical routes to acyl electrophiles require the use of highly energetic chlorinating reagents, this platform allows direct access to aroyl triflates from bench stable reagents (CO, aryl carboxylic acids, I_2, and AgOTf), which can be trapped with arenes under mild conditions to form ketones. It is postulated that an *in situ* generated acyl hypoiodite is trapped with carbon monoxide to promote decarboxylation and form the aroyl triflate.

Chapter 4 describes a collaborative project initiated by Merck, in which the concepts of reversible acyl electrophile formation under palladium catalysis are applied to the radiolabeling of

pharmaceuticals. Because of this reversibility, the carbonyl units of acyl electrophiles can exchange, which provides an efficient strategy for the incorporation of carbon isotopes into pharmaceuticals. Palladium catalysts were initially investigated and found to be highly effective for exchange of C(sp^2) acid chlorides, but much less efficient for C(sp^3) acid chlorides due to β-hydride elimination. Nickel was employed as a solution, and gave high levels of exchange with a variety of aryl and alkyl acid chlorides. Coupling this catalytic reaction with the *in situ* formation of acid chlorides can allow the one pot exchange of carbon isotopes on pharmaceutically relevant carboxylic acids with readily available carbon isotope donors (e.g. ^{13}C-benzoic acid derivatives)

Résumé

Les acylations de Friedel-Crafts représentent l'une des plateformes les plus utilisées dans la synthèse de cétone à partir d'hydrocarbure aromatique. Cette réaction est dépendante de la génération d'électrophiles acyles réactifs, qui sont habituellement générés à partir d'une combinaison d'électrophiles organiques hauts en énergie, qui doivent être synthétisés et qui parfois sont corrosifs, ainsi qu'un catalyseur de type acide de Bronsted ou Lewis. Cette thèse décrit le développement de voies de synthèse alternatives pour accéder à ces électrophiles à partir de monoxyde de carbone, un outil de synthèse C1 stable et abondant, pour la génération d'électrophiles puissants de type triflate d'aroyle à partir de réactifs stables médiés par des métaux de transition. De plus, cette thèse présente une exploration des applications de ce concept avec des produits pharmaceutiques de radiomarquage.

Le chapitre 2 décrit le développement de la fonctionnalisation C-H carbonylative d'arènes catalysées au palladium pour dans le but de former des cétones. Cette recherche a résolu un défi de longue date dans la fonctionnalisation C-H catalysée au palladium, dans lequel l'incorporation de monoxyde de carbone pour la synthèse de cétone n'est typiquement pas viable en raison des limitations intrinsèques du modèle réactionnel. Une approche alternative a été développée dans laquelle de puissants électrophiles de type triflate d'aroyle sont générés de manière catalytique et réagissent avec des composés aromatiques pour former des cétones. Ceci a mené à la première plateforme générale pour la fonctionnalisation C-H carbonylative dans la synthèse de cétones à partir de simples iodures d'aryle, CO et de composés aromatiques. Des études mécanistiques ont révélé que la clé de cette transformation est la génération d'un catalyseur de palladium hautement électron pauvre CO-lié duquel l'élimination réductrice d'électrophiles réactifs acyles devient possible.

Le chapitre 3 décrit une extension du travail fait dans le chapitre 2, dans lequel les iodures d'aryle peuvent ultimement être remplacés par des acides carboxyliques davantage disponibles pour générer des triflates d'aroyle sans catalyseur de palladium. Cela représente un rare exemple d'activation de monoxyde de carbone de façon douce et sans métaux de transition. Alors que les voies typiques vers les électrophiles acyles requièrent l'utilisation d'agents de chloration hautement énergétiques, cette plateforme permet l'accès direct vers les triflates d'aroyle à partir

de composés stables (CO, acides carboxyliques aromatiques, I_2, et AgOTf), pouvant être piégés par des composés aromatiques dans des conditions douces pour former des cétones. Un postulat suggère qu'un hypoiodite d'acyle généré in situ est piégé par le monoxyde de carbone pour promouvoir la décarboxylation et former le triflate d'aroyle.

Le chapitre 4 présente un projet collaboratif initié par Merck, dans lequel les concepts de formation réversible d'électrophiles acyles sous catalyse au palladium sont appliqués pour le radiomarquage de produits pharmaceutiques. En raison de cette réversibilité, les unités carbonyles d'électrophiles acyles peuvent échanger entre eux, ce qui fournit une stratégie efficace pour l'incorporation d'isotopes de carbone dans les produits pharmaceutiques. Cela permet ultimement l'échange direct d'isotopes de carbone sur des dérivés pharmaceutiques de type acide carboxylique avec des sources de carbone isotopique disponibles commercialement (c.-à-d. chlorure de benzoyle), évitant ainsi de refaire la synthèse complète de produits pharmaceutiques avec les agents marquants. Le palladium a été initialement exploré et prouvé hautement efficace dans l'échange de carbone sp2 de chlorure d'acide, toutefois moins efficace pour les carbones sp3 de chlorure d'acide en raison de l'élimination d'hydrure en position beta. Le nickel a été utilisé comme solution, et a donné de hauts niveaux d'échanges avec une variété de chlorures d'acide de type aromatique et aliphatique.

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Contributions of Co-Authors

This thesis consists of five chapters. Chapter 1 is an introduction to the work described in this thesis. Chapters 2 and 3 are published manuscripts. Chapter 4 is a manuscript in preparation and is a collaborative project between our lab and Merck. Dr. Donald Gauthier at Merck initiated the project, helped guide the project, and will be a co-author on the manuscript. The work presented in this thesis was carried out as part of my doctoral dissertation in chemistry under the supervision of Dr. Bruce A. Arndtsen. Thus, he is the corresponding author on all the manuscripts and assisted in editing this thesis. I performed all the experiments reported in these manuscripts, except where noted below:

Chapter 2: "A General Approach to Intermolecular Carbonylation of Arene C–H Bonds to Ketones Through Catalytic Aroyl Triflate Formation" *Nat. Chem.* (**2018**, *10*, 193). Dr. Gerardo M. Torres performed the stoichiometric experiments with *p*-tolylCOPd(P^tBu_3)OTf. Dr. Gerardo M. Torres, Dr. Jevgenijs Tjutrins, Nina Liu, and Omkar Kulkarni helped make several of the compounds in Table 2.1

Chapter 4: "Palladium- and Nickel- Catalyzed Carbonyl Metathesis Between Acid Chlorides for the Preparation of Carbon Isotope Labeled Products" Pierre-Louis Lagueux-Tremblay, a PhD student in our group, solved the X-ray structure of **[Ni]1.**

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List of Abbreviations

AcOEt	Ethyl Acetate
AcOH	Acetic Acid
Ad	Adamantyl
Atm	Atmosphere
APCI	Atmospheric pressure chemical ionization
Ar	Aryl
nBu	n-butyl
^{t}Bu	tert-butyl
Bpy/Bipy	2,2,-bipyridine
cat.	Catalyst
Cy	Cyclohexyl
COD	Cyclooctadiene
Dba	Dibenzylideneacetone
DCM	Dichloromethane
DCE	1,2-Dichloroethane
Dcpp	1,3-bis(diphenylphosphino)propane
Dcype	1 ,2-bis(dicycloheyxlphosphino)-ethane
DIPEA	N,N-Diisopropylethylamine
DMA	Dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
Dcpp	1,3-Bis(dicyclohexylphosphino)propane
EDG	Electron donation group
Equiv	Equivalent
ESI	Electrospray ionization
Et	Ethyl
FG	Functional group

H	hour
HFIP	Hexafluoro-2propanol
HOTf	Triflic acid
Hertz	J
iPr	Isopropyl
L	Ligand
L_n	Unspecified number of ligands
Ms	methanesulfonyl
MeCN	acetonitrile
M	multiplet
mg	Milligram
mmol	millimole
mL	Milliliter
µL	Microliter
NTf	bis(trifluoromethanesulfonyl)amid
NMR	Nuclear magnetic resonance
N. R	No reaction
NuH	Nucleophile
OAc	Acetate
OTf	Triflate (trifluoromethanesulfonate)
Ppm	parts per million
Ph	Phenyl
PhH	Benzene
PhMe	Toluene
PMB	p-methoxybenzyl
PMP	p-methoxyphenyl
p-Tol	*para*-Tolyl
q	quartet
r.t.	Room temperature
s	singlet

t	triplet
*t*Bu	*tert*-butyl
TMS	trimethylsilyl
TFA	Trufluoroacetate
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine
Ts	p-toluenesulfonyl
WCA	weakly coordinating anion
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

Chapter 1. Introduction: Friedel-Crafts Acylation and Carbonylative Routes to Acyl Electrophiles

1.1. Perspective

The efficient synthesis of products from available chemical feedstocks and with minimal waste represents a central research goal in organic chemistry. One important focus of these efforts is the functionalization of aromatic hydrocarbons. Arenes are broadly available from petroleum resources, and their derivatization leads to substituted aromatic products, which are common motifs in products ranging from pharmaceuticals, fine chemicals, polymers, or advanced materials.[1] One of the oldest known methods to functionalize arenes is the Friedel-Crafts reaction. Friedel-Crafts chemistry was discovered nearly 150 years ago,[2] and became perhaps the most heavily used approach to construct carbon-carbon bonds with arenes. An important subclass of Friedel-Crafts chemistry are Friedel-Crafts acylations, which offer a route to assemble valuable ketones from (hetero)arenes.

Despite its significant use, Friedel-Crafts acylations are limited by the need to create potent acyl electrophiles that can react with weakly nucleophilic arenes. Acyl electrophiles are commonly generated from acyl halides in concert with a stoichiometric Lewis acid. Both the synthesis of the acyl halide and the Friedel-Crafts acylation reaction require caustic, high energy reagents, and often creates corrosive metal-containing waste. In addition, the use of such reactive components can lead to challenges in substrate generality and functional group compatibility in ketone synthesis.

An alternative approach to accessing carbonyl-containing aromatic products is via transition-metal-catalyzed carbonylation reactions. Carbonylations represent one of the most efficient platforms available for assembling carbonyl derivatives such as carboxylic acids, esters, amides or aldehydes, and are exploited in an array of high-volume industrial processes.[3-6] For example, the hydroformylation of alkenes to generate aldehydes is performed on a ca. 10 million metric tons per year scale.[7] Likewise, the Monsanto/Cativa processes produces around 6.2 million metric tons per year of acetic acid via methanol carbonylation. The latter represents 80% of the global demand of acetic acid.[8] However, the ability to adapt carbonylation reactions to ketone synthesis directly from unfunctionalized arenes has been much less successful. This can be

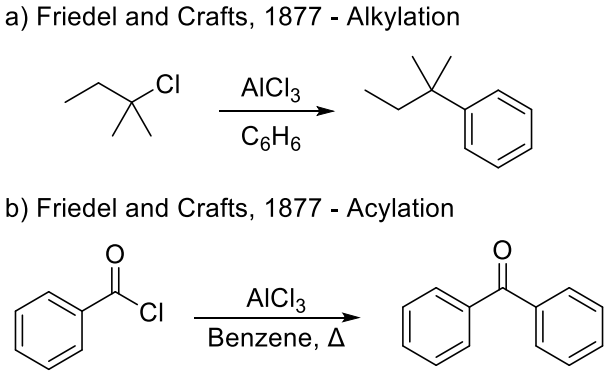
attributed in part to the limited ability of these systems to access intermediates of sufficient electrophilicity to react with arenes.

This introductory chapter will provide an overview of these two general approaches to aromatic ketone synthesis. The first section will offer a general overview of Friedel-Crafts acylation chemistry, and then quickly move to discuss how carbon monoxide has been utilized in the synthesis of these electrophiles both with and without transition metals.

1.2. Friedel-Crafts Acylation

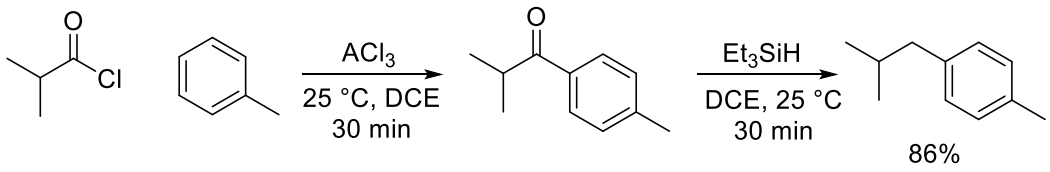
1.2.1. Development and Scope

In 1877, James Mason Crafts and Charles Friedel discovered that the reaction of *tert*-amyl chloride in the presence of thin strips of aluminum and benzene resulted in alkylated benzene products.[2] Further experimentation led to the discovery that aluminum chloride was the active catalyst for this reaction (Scheme 1.1a). This was followed by a series of papers on the topic over the next four years,[9-15] including the report that heating a mixture benzoyl chloride in benzene in the presence of aluminum chloride produced benzophenone as a product of the reaction.[14] Although this latter transformation had first been published 5 years prior by others using zinc metal and zinc oxide,[16-19] they were the first to identify the role of metal halides as the actual catalyst for the reaction (Scheme 1.1b).



Scheme 1.1. Initial Reports on Friedel-Crafts Chemistry (no yields reported)

Friedel-Crafts acylation reactions are often more reliable than the analogous alkylations. For example, alkylations often result in rearrangement of the alkyl electrophile to the more stable carbocation, as well as over-alkylation, since the product is more nucleophilic than the starting material. In contrast, acylation reactions benefit from resistance to rearrangement, and selective access to mono-acylated products, since the electron withdrawing carbonyl unit deactivates the product relative to the starting arene. The Lewis basic ketone product can also sequester the Lewis acid and favor the formation of monosubstituted products (vide infra). Indeed, one approach to alkylated arenes is through initial acylation of the arene, followed by reduction of the ketone (Scheme 1.2).[20]

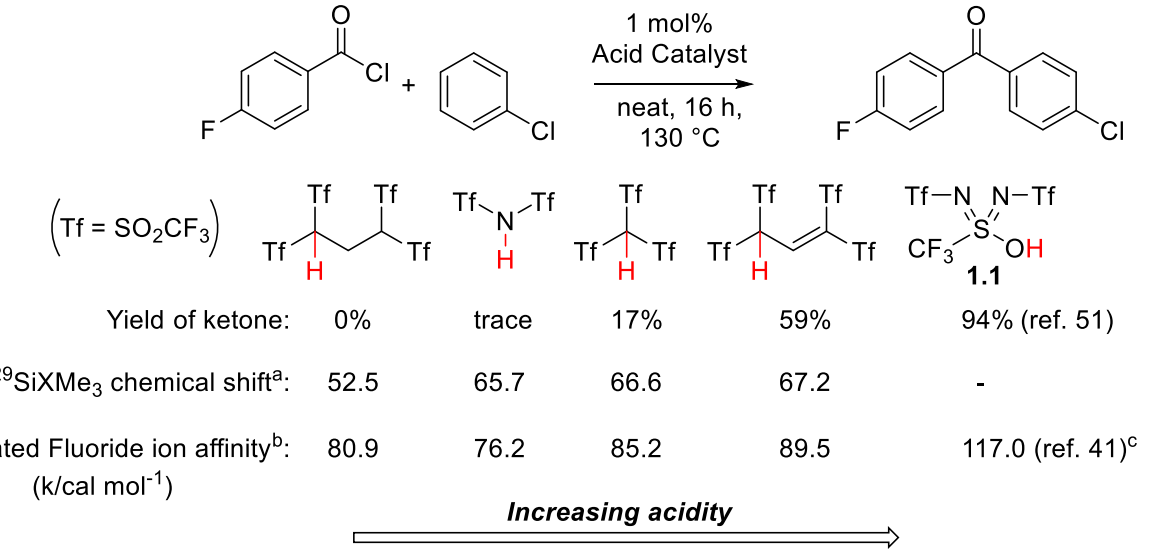


Scheme 1.2. Access to Alkylated Arenes via Acylation/Reduction Sequence

While the initial studies of Friedel-Crafts acylations used $AlCl_3$, it was quickly realized that many other Lewis acids and also Bronsted acids, could facilitate this transformation, and sometime were not necessary at all. The Friedel-Craft acylation reaction is thus generally defined as the coupling of an electrophilic acyl unit, most commonly acyl halides and anhydrides, with an aromatic substrate.[21] In addition, one or more equivalent of the Lewis acid catalyst is typically required for the reaction to proceed in high yields to overcome the sequestration of the catalyst by the ketone product.

Friedel-Crafts acylations are a textbook example of how to convert arenes to ketones, and have been the subject of many books and reviews.[21-35] The efficiency of this reaction depends on several factors. The nature of the acid catalyst has a large influence on the electrophilicity of the *in situ* generated acylating agent. While a number of studies have provided qualitative and quantitative data on this effect,[36-49] a recent illustration of this influence has been reported by List.[50] This compares a range of non-traditional triflyl-containing carbon-based acids with related amine and sulfonic acids in Friedel-Crafts acylation reactions (Scheme 1.3).[51] The relative acidity

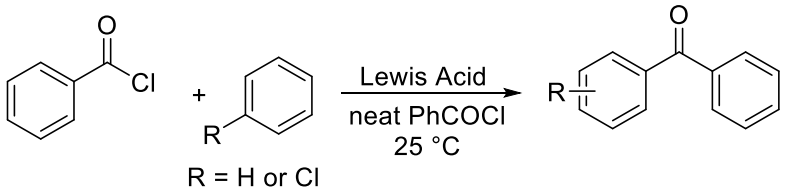
was determined from both their calculated fluoride affinity and by converting the acids to the corresponding silyl anion salts and observing the ^{29}Si NMR chemical shift.[41] A downfield shift represents a more stabilized anion, and thus a stronger protic acid. This shows that increasing acidity leads to a faster Friedel-Crafts acylation reaction, which is attributed to more favored access to the ionized acid chloride.



Scheme 1.3. Bronsted Acidity Influence on Friedel-Crafts Acylation

[a] Each acid was converted to the Me_3SiX, where X is the conjugate base of the acid, and the ^{29}Si chemical shift was recorded. [b]These are calculated values of fluoride affinity for Me_3SiX. Fluoride affinity refers to the change in enthalpy associated with the binding of fluoride to the Lewis acid. [c]This is the value for SbF_6^- which has a very similar pK_a.

Nevertheless, Lewis acid strength does not always correlate with reaction rates. An example of this comes from a seminal study by Jensen in 1958, where the kinetics of acylation of toluene and chlorobenzene in neat benzoyl chloride was investigated.[52] These show that weaker Lewis acids sometimes lead to faster acylation reactions (Scheme 1.4). Although the origin of this observation is not completely understood, the results of kinetics experiments with Lewis acids of varying acidity produce complex rate laws. These suggest that varying amounts of Lewis acid are involved in the reaction, depending upon the Lewis acid employed (*vide infra*), and its aggregation.



Chlorobenzene:	$SbCl_5$	$GaCl_3$	$AlCl_3$
Relative Rates:	1300	500	1.0
Relative Lewis acidity:	0.85	0.74	0.82
Rate Law:	$k\frac{[SbCl_5]^2[ArH]}{[SbCl_5]_0}$	$k\frac{[GaCl_3]^2[ArH]}{[GaCl_3]_0}$	$k[PhCOCl\cdot ACl_3][ArH]$

Toluene:	$AlCl_3$	$SnCl_4$	BCl_3
Relative Rates:	1.0	2.9×10^{-3}	6.3×10^{-4}
Relative Lewis acidity:	0.82	0.52	1.00
Rate Law:	$k[PhCOCl\cdot ACl_3][ArH]$	$k[SnCl_4][ArH]$	$k[BCl_3][ArH]$

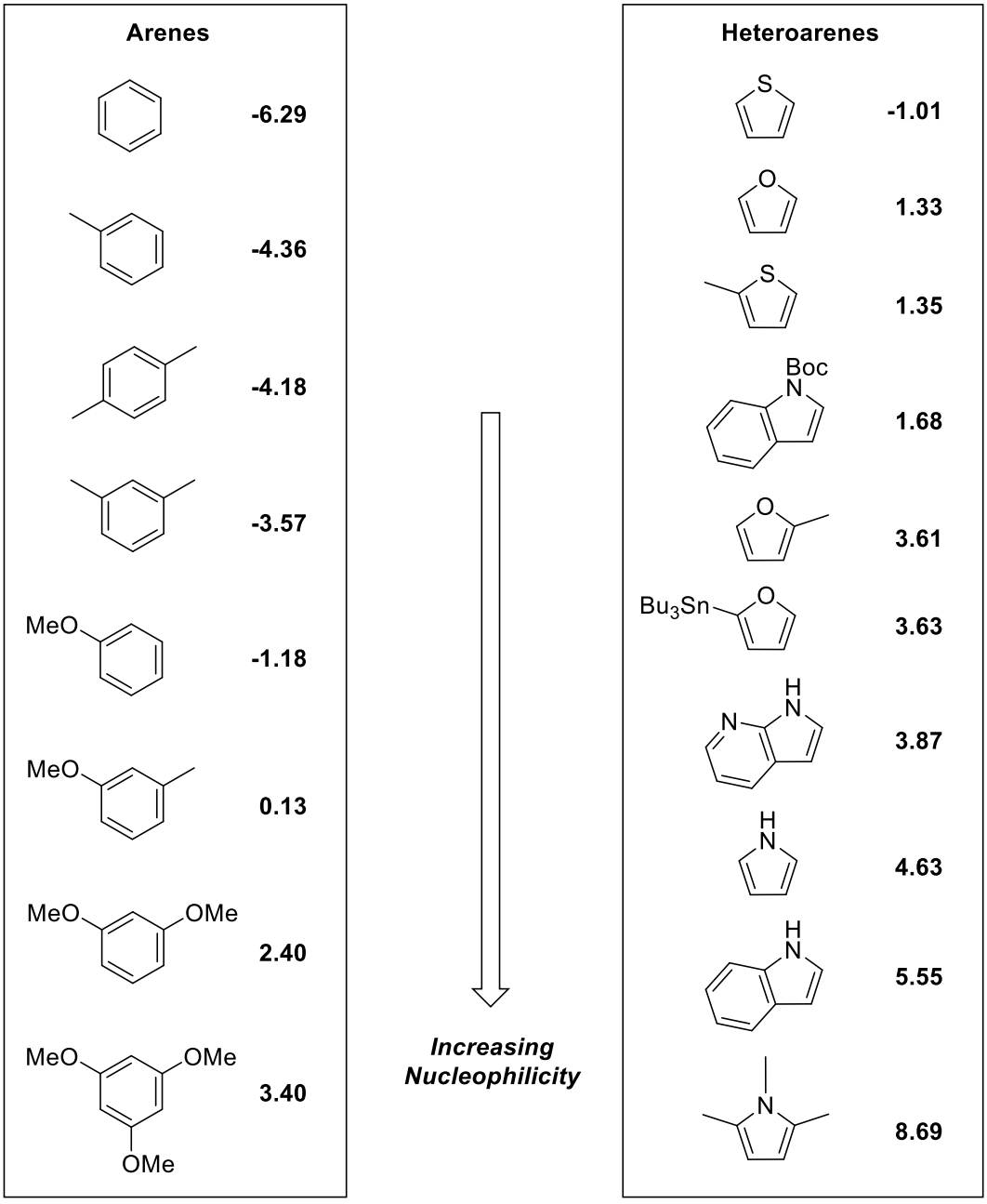
Scheme 1.4. Relative Rates of Acylation with Common Lewis Acids

The nucleophilicity of the (hetero)arene also has a major influence on Friedel-Crafts acylations. The relative nucleophilicity of various common organic nucleophiles has been extensively studied by Mayr and others.[53-70] Due to the vast differences in nucleophilicity of substituted arenes and heteroarenes, it is practically impossible to measure reaction rates with the same electrophile. Therefore, Mayr developed a method for compiling such data onto one global nucleophilicity scale using *para* substituted diarylmethane carbenium ions that span 16 orders of magnitude in electrophilicity.[71-74] By exploring various substrate combinations the following free energy relationship was developed to quantitate the rate of reaction for combinations of nucleophiles and electrophiles.[57]

$$\text{Log } k = S_N(E+N)$$

The values of N and E assess the relative nucleophilicity or electrophilicity of a given compound. N and E are on a log scale where the more positive the value, the more nucleophilic or electrophilic the compound. The current range for the nucleophilic and electrophilic parameters

is $-8.80 \leq N \leq 30.82$ and $-24.69 \leq E \leq 8.02$. S_N is the nucleophile specific parameter, which describes the sensitivity of reaction rate of the nucleophile with electrophiles of various strength. This can be ignored when only looking for approximate rates. In general, a reaction will give 50% conversion in less than 3 hours at 1.0 M concentration if $E + N > -5$ (ignoring steric effects).[56] A database has been constructed of the nucleophilic (N) and electrophilic parameters (E), for 1209 nucleophiles and 316 electrophiles using data from the literature from the past 36 years.[53] A selection of arene nucleophilicities is shown below (Scheme 1.5).

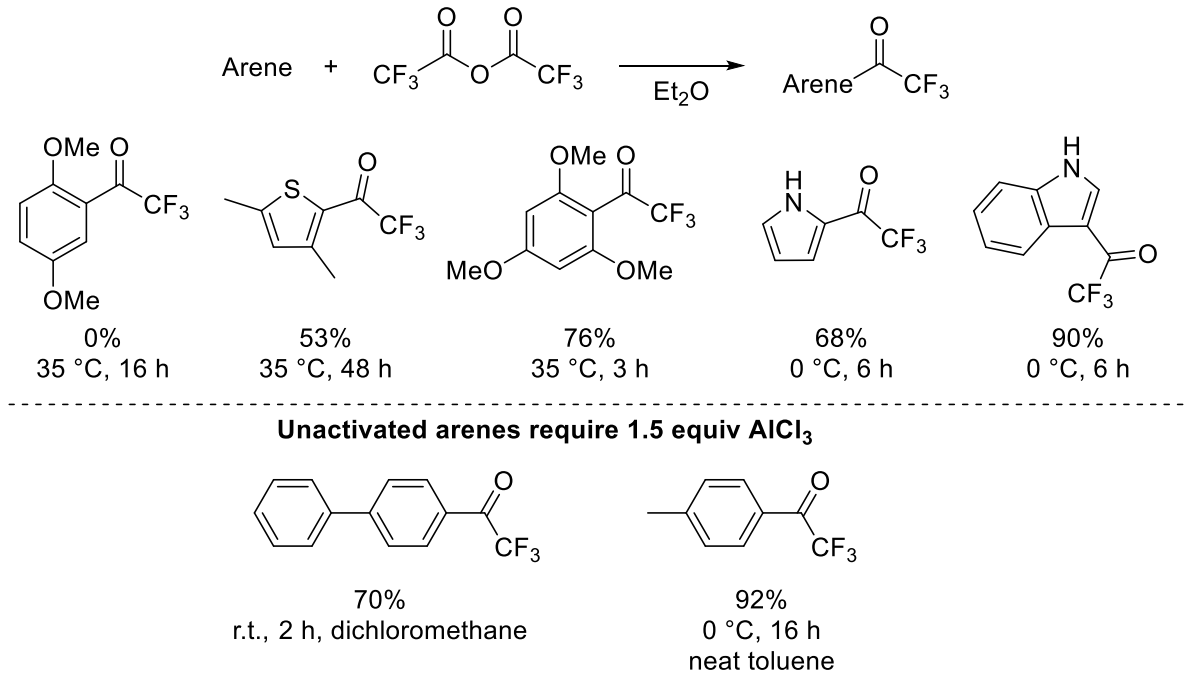


Scheme 1.5. Mayr's Scale of Nucleophilicity for Arenes

In general, five membered-ring heterocycles such as thiophene, furan, pyrrole, and indole are more reactive than benzene. The reactivity differences with the heterocycles can be explained by the balance of the electronegativity of the heteroatom (lower electronegativity leads to higher reactivity) and the degree of overlap between the heteroatom lone pair and the π-bonds (less

overlap leads to lower reactivity).[75] The combination of these opposing effects determines the overall reactivity towards electrophiles.[76] The highest energy nitrogen lone pair makes indole and pyrrole the most nucleophilic, with indole > pyrrole because aromaticity of the fused ring can remain intact upon electrophilic attack. Thiophene is less reactive than pyrrole or furan, despite the low electronegativity of sulfur, since the sulfur 3p orbital overlaps less well with the π-system, and thus cannot stabilize as well the initial product of electrophilic attack. These influences are seen as well in the overall aromatic stabilization of the heterocycles, where the aromaticity increases from pyrrole < furan < thiophene. Benzene is typically less reactive than these heterocycles due to extreme aromatic stabilization resulting from delocalization of identical π orbitals. Within a series of heteroarenes or arenes, the introduction of donor groups increases the nucleophilicity.

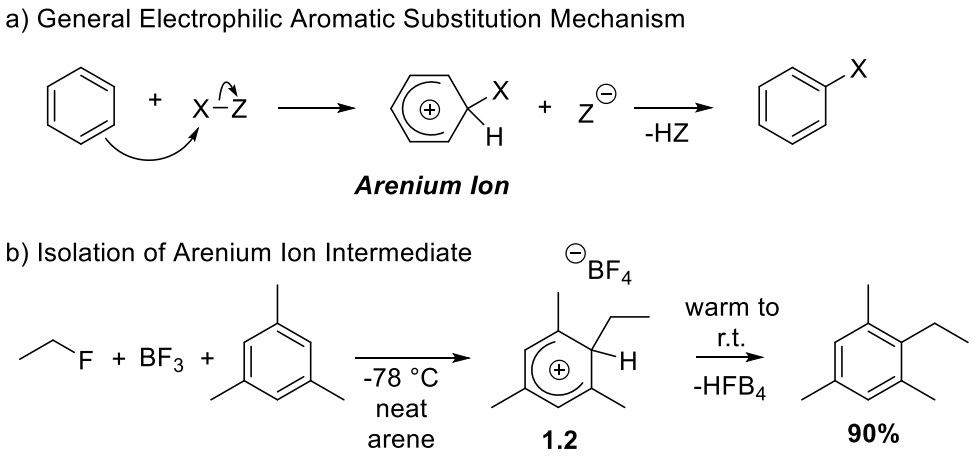
A representative illustration of the influence of arene nucleophilicity can be seen in their reaction with trifluoroacetic anhydride.[77-79] As shown in Scheme 1.6, indole and pyrrole are efficiently acylated at 0 °C, while the less reactive thiophene and trimethoxybenzene require elevated temperature, and no reaction is observed with the less nucleophilic 1,4-dimethoxybenzene under these conditions. The addition of $AlCl_3$ as a Lewis acid increases the strength of the acylating agent to permit functionalization of even less reactive benzene derivatives.



Scheme 1.6. Relative Reactivity of Arenes and Heteroarenes in Trifluoroacetylation

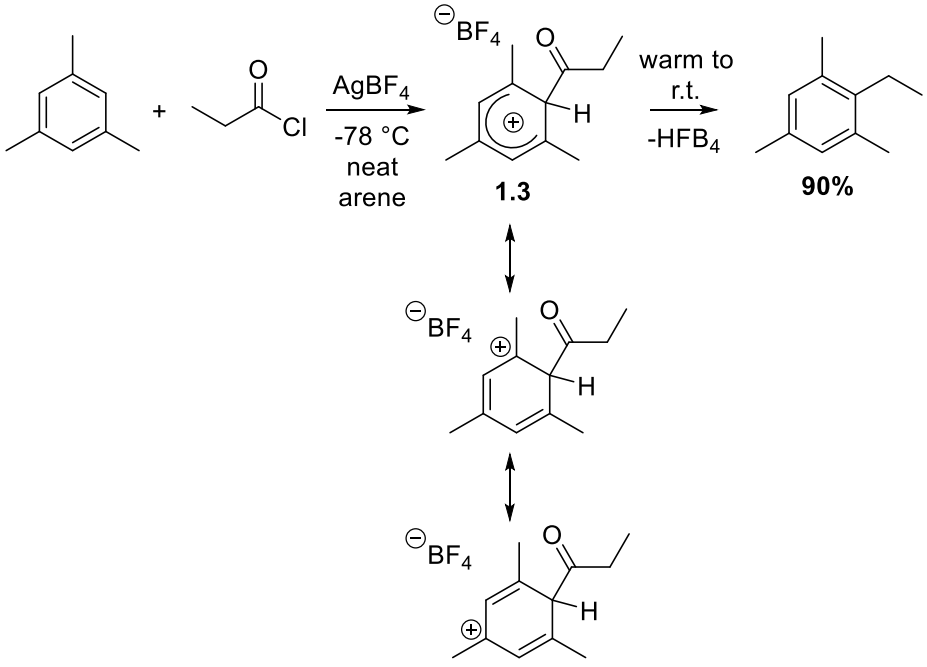
1.2.2. Mechanism and Selectivity of Friedel-Crafts Acylations

Friedel-Crafts acylations fit into the larger category of electrophilic aromatic substitution reactions, for which the mechanism has been studied in great detail.[80-101] These transformations generally proceed via what is called the arenium ion mechanism (Scheme 1.7). In this, the π-electrons from the arene can be considered to attack the electrophile to generate an arenium ion intermediate. The latter is also known as a Wheland intermediate or σ-complex, and was first seriously considered as a potential intermediate by George Wheland in 1942.[102] In 1958, George Olah presented strong evidence for this mechanism from the isolation and characterization of arenium salt **1.2** at low temperature from the reaction of fluoroethane and mesitylene in the presence of BF_3.[103] Warming to room temperature leads to subsequent proton loss (Scheme 1.7).



Scheme 1.7. Generally Accepted Mechanism for Friedel-Crafts Reactions

Friedel-Crafts acylations have been the subject of numerous mechanistic investigations, and are believed to follow the arenium ion mechanism.[80, 86, 104-129] Evidence was also noted by Olah in 1958, where he was able to isolate and characterize the acyl arenium ion **1.3** (Scheme 1.8).[103]

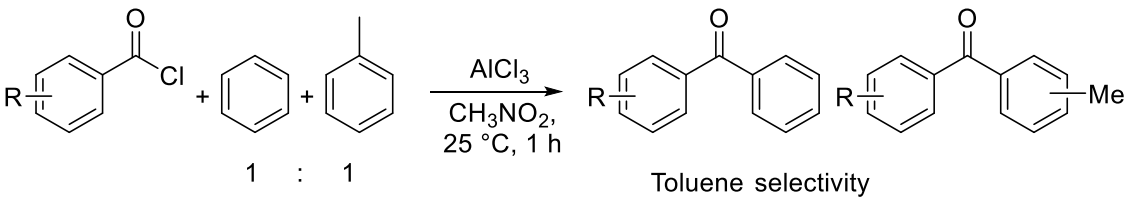


Scheme 1.8. Observation of Acyl σ-complex

The reactivity and product selectivity observed in Friedel-Crafts acylations can be understood via the ability to access and stabilize the arenium intermediate, and how close this intermediate is to the transition state for the reaction. For example, mono-substituted arenes with donor substituents (or "activating" groups) react faster than benzene and favor *ortho/para* substituted products, as this places the formal positive charge in the intermediate by the substituent. In contrast electron withdrawing ("deactivating") substituents destabilize the arenium ion (slowing the reaction) and favor *meta* substituted products. However, the nature of the electrophile can strongly influence this selectivity as well. As one illustration, Olah performed competition experiments between benzene and toluene with aroyl electrophiles of varying electrophilicity (Scheme 1.9a).[115] The electrophile used had a major impact on product selectivity, wherein more electron deficient aroyl chlorides led to a decrease in both selectivity for toluene functionalization, and for the *para* isomer. The favored functionalization of toluene is the result of the ability of the methyl substituent to increase the nucleophilicity of the arene. However, the difference in selectivity when varying the electrophilic reagent is better explained by the nature of the transition state, and how close this is to the arenium ion structure (Scheme 1.9b and c). With electron deficient acylating agents, formation of the arenium ion is more favored and thus these are expected to have an earlier transition state. In this, the arene can be considered to "coordinate" to the electrophile with little deformation from the starting material (π-complex formation) (Scheme 1.9b). Subsequent formation of the σ-complex determines the positional selectivity and is also relatively early along the reaction coordinate. As a result, there is less selectivity observed with, for example, the highly electron deficient $C_6F_5COCl/AlCl_3$ derived acyl electrophile.

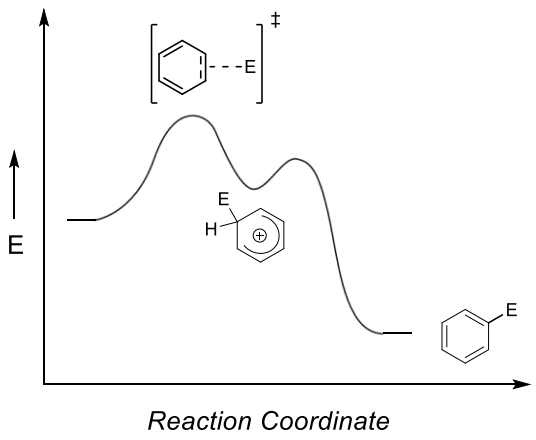
However, as the acylating reagent becomes less electron deficient, higher substrate selectivity and higher *para* selectivity are observed. Since these reactions are less exothermic, they would be expected to have a later transition state and now more closely resemble the arenium ion (Scheme 1.9c). Thus, both the substrate selectivity and positional selectivity will better reflect the relative stability of the σ-complex intermediates. Donor substituents in the *para* position have a positive effect on electronic stabilization, without steric destabilization (as with *ortho* products). Therefore, less electron poor aroylating agents favor a reaction with toluene and at the *para* position.

a) Substrate and ortho/para selectivity in benzene and toluene benzoylation

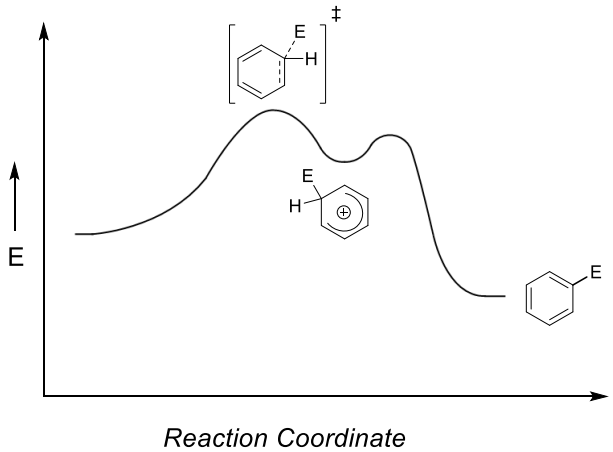


R	$k_{Toluene} : k_{Benzene}$	Toluene selectivity			
		% *ortho*	%*meta*	%*para*	*ortho*:*para*
Ar = C_6F_5	16.1	35.4	7.8	56.8	0.62
2,4-$(NO_2)_2$	29.0	42.4	3.0	54.6	0.78
3,5,-$(NO_2)_2$	38.9	9.4	6.8	83.8	0.11
p-NO_2	52.0	9.5	1.2	89.3	0.14
H	153.5	8.1	1.2	90.7	0.09
p-Me	164.4	7.8	1.1	91.1	0.02

b) Early π-complex transition state

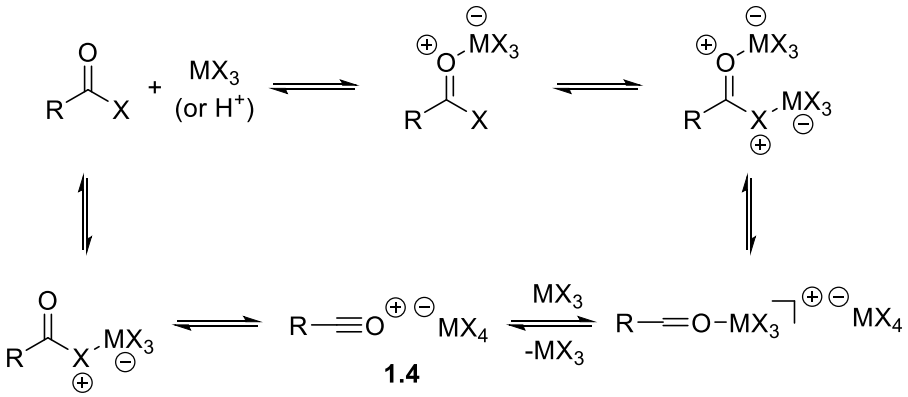


c) Late σ-complex transition state



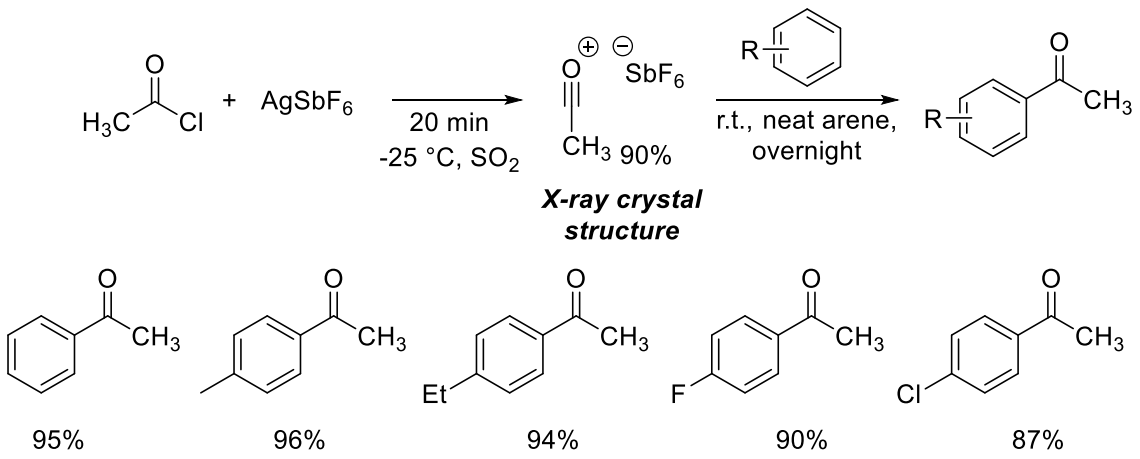
Scheme 1.9. Selectivity and Transition States in Friedel-Crafts Acylation

Significant mechanistic work on Friedel-Crafts acylations has also focused on determining the nature of the electrophilic entity involved in Friedel-Crafts acylations. With a very strong Lewis acid or Bronsted acid present, there are a variety of intermediates that can be generated, any of which could also serve as active acylating agents. Examples of these are shown in Scheme 1.10.



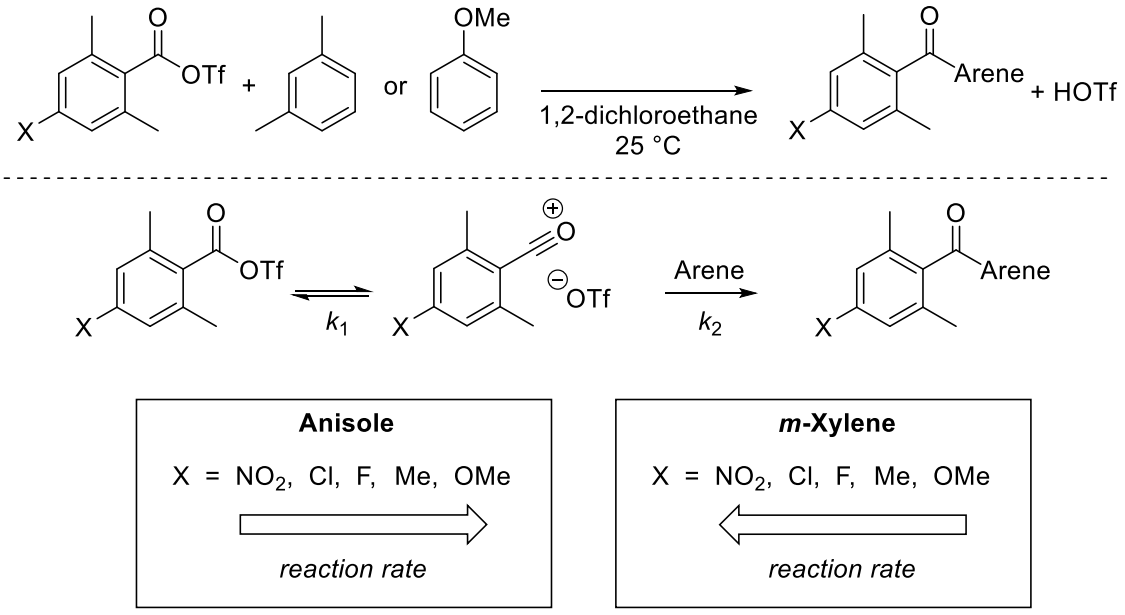
Scheme 1.10. Acylating Agents in Friedel-Crafts Acylation with Lewis or Bronsted Acids

Friedel-Crafts reactions are typically postulated to involve the generation of a highly electrophilic acylium cation. The structure and reactivity of these cations (*e.g.* **1.4)** have been probed through synthesis and subsequent acylation reactions. For example, Olah in 1962 generated a series of acylium cations by reacting acid chlorides with silver salts of weakly coordinating anions (Scheme 1.11), or acyl fluorides with strong Lewis acids.[130] Unequivocal evidence for the structure of the acylium cation was obtained by X-ray crystallography.[131] These salts were viable acylating agents as demonstrated by their acylation of electron poor and electron rich arenes in high yields (Scheme 1.11).



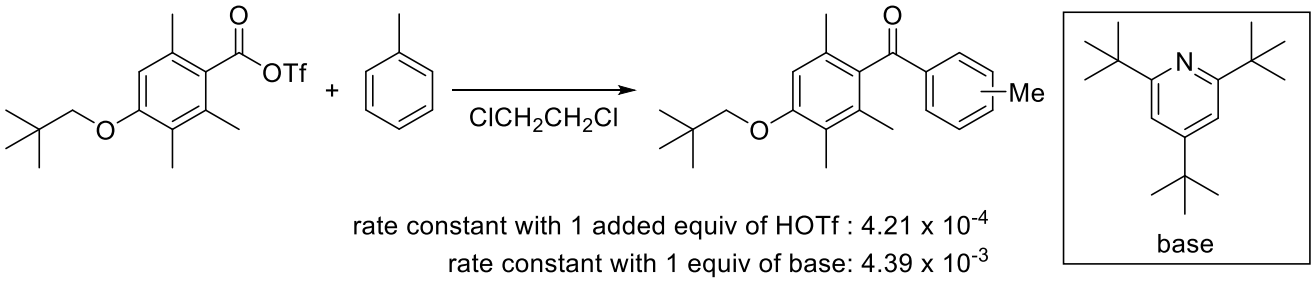
Scheme 1.11. Isolation and Subsequent Reactivity of Acylium Salts

While this reaction established that acylium salts are viable intermediates, it is not representative of typical Friedel-Crafts acylation conditions, which usually use super-stoichiometric quantities of less potent Lewis or Bronsted acids. In addition, it does not take into account the effect of acid produced as a byproduct. Numerous kinetic investigations of Friedel-Crafts acylation reactions with Lewis acids have been performed.[52, 72, 91, 105, 109, 116, 120, 132-145] These often lead to varying rate laws depending on the reaction conditions and Lewis acid employed. One particularly insightful study that examined the reaction of less potent acylating agents comes from the Effenberger group. These probed the reactivity of well-defined aroyl triflate electrophiles,[106, 146] which were discovered by the same research group 25 years prior.[147] Aroyl triflates do not require any catalyst for acylation, and can even react under basic conditions using bulky bases, such as 2,4,6-tri-tert-butylpyridine. Interestingly, Hammet analysis of the reaction with anisole provides strong evidence for the intermediacy of acylium cations in the reactions (Scheme 1.12). Thus, electron donating substituents on the aroyl triflate favor ionization (k_1), and resulted in faster overall acylation reactions with nucleophilic arenes (*e.g.* anisole, $k_1 < k_2$). This trend is reversed with using less nucleophilic arenes such as *m*-xylene. The latter was postulated to arise from a rate determining acylation step with xylene ($k_1 > k_2$), which is accelerated with the more electrophilic acylium cation.



Scheme 1.12. Hammet Plot Analysis with Aroyl Triflate Electrophiles

While the above does strongly support the acylium cation as the reacting electrophile, it does not exclude the possibility of a protonated acylium cation (*i.e* dicationic species) produced from acid generated in the reaction as the active acylating agent. The latter has been previously suggested as a potential intermediate in acylations.[148] In order to probe this possibility, reaction rates were compared under acid and basic conditions (Scheme 1.13). These results reveal that the reaction is around ten times faster under basic conditions, which does rule out the possibility of a dicationic acylium salt as the active acylating agent. Reactions are slower with acid because σ-complex formation can become reversible due its slower deprotonation. The authors ruled out toluene protonation as an explanation for increased rates under basic conditions due to the very low pKa of protonated toluene.

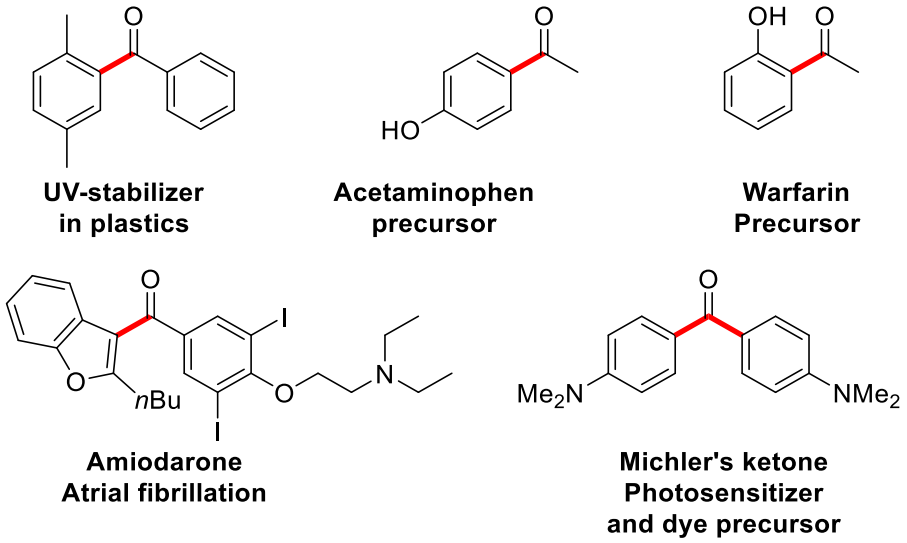


Scheme 1.13. Acylation with Aroyl Triflates Under Basic and Acidic Conditions

1.2.3. Applications and Recent Advances

Friedel-Crafts acylations have become a staple in the organic chemist's toolbox as a reliable C-C bond forming reaction, and have seen applications in all facets of chemical synthesis. Aromatic ketones are valuable motifs in the pharmaceutical, flavor, fragrance, dyes, and agrochemical industries.[149-153] As examples, the acylation of xylenes is of particular interest as the dimethylbenzophenone products are used as UV stabilizers in plastics (Scheme 1.14).[154] Likewise, Michler's ketone is a highly utilized photosensitizer and precursor to triarylmethane dyes. Acetyl phenols are precursors to valuable pharmaceuticals, such as acetaminophen and hydroxycoumarins, which are an important class of anticoagulants used to treat thrombotic

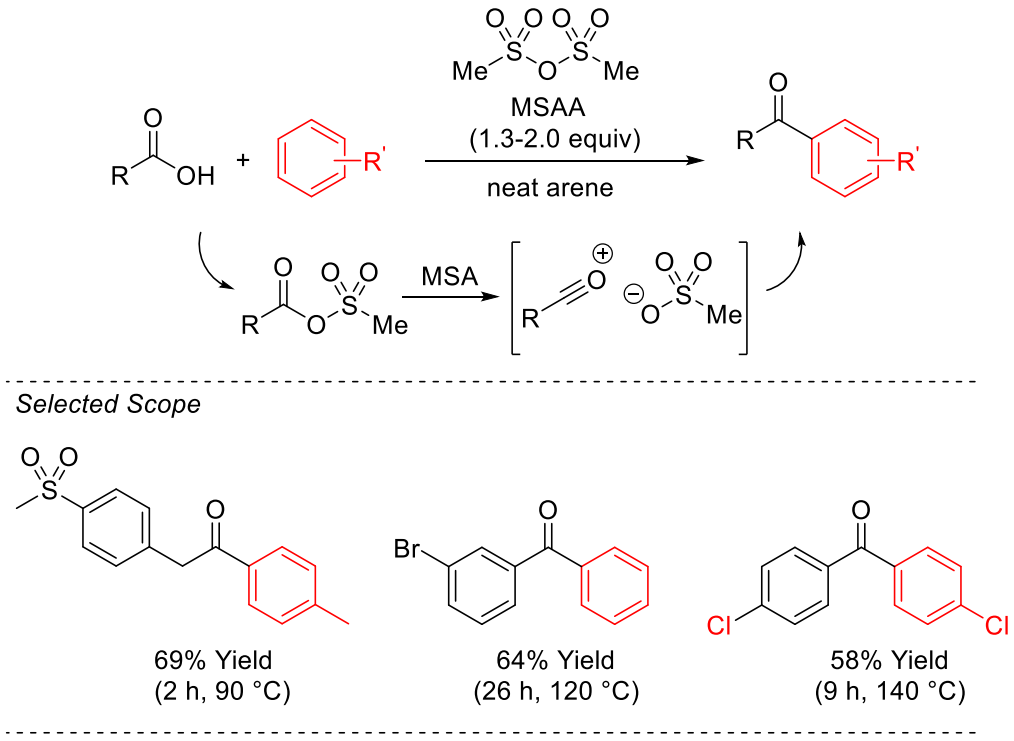
disease.[155] Amiodarone is the most widely utilized drug to treat atrial fibrillation, the most serious of cardiac rhythm disturbances.[156] The importance of Friedel-Crafts acylation reactions has also been exemplified in the ACS round table for Green chemistry, in which more efficient acylation protocols, especially for non-activated aromatics, was identified as one of the major needs of the pharmaceutical industry.[157]



Scheme 1.14. Impact of Friedel-Crafts Acylation as Evidenced by Industrial Importance of Aromatic ketones

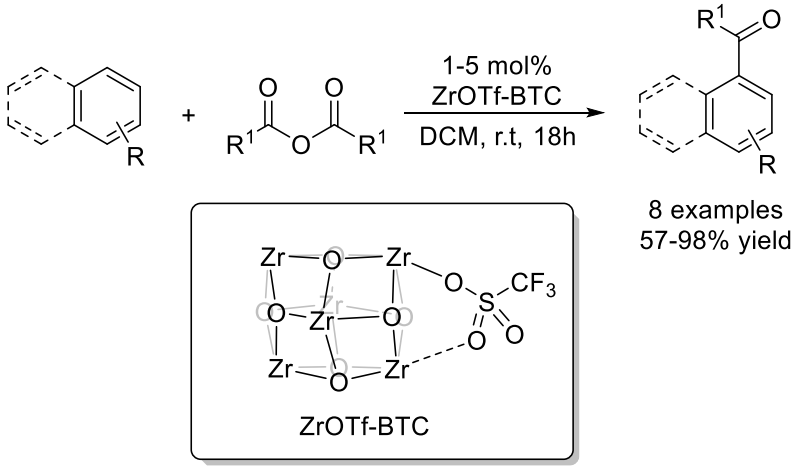
A significant recent thrust of Friedel-Crafts reactions has been to more efficiently access the electrophiles needed to functionalize arenes. Friedel-Crafts acylations have traditionally relied on the use of stoichiometric (or super-stoichiometric) Lewis acids, and thus create significant acidic waste. This can be especially problematic when performing reactions on scale in industry. As one example of a an effort to mitigate these shortcomings, researchers at GlaskoSmithKline have developed a methodology using methanesulfonic anhydride (MSAA) as a Greener alternative to Friedel-Crafts acylations. (Scheme 1.15).[158] Using MSAA, carboxylic acids can be directly employed in acylations with even deactivated aromatics such as chlorobenzene. The reaction of the carboxylic acid with MSAA produces a mixed methanesulfonic anhydride and one equivalent of methanesulfonic acid, which then catalyzes acylation of the arene with the mixed anhydride. Unlike the results of Effenberger, which showed the addition of triflic acid retards the rate of

acylation by slowing deprotonation (*vide supra*), methanesulfonic acid is of the appropriate acidity to ionize the acylium cation but not retard deprotonation. As such, arenes can be effectively acylated without an added Lewis acid, although high temperatures are required.



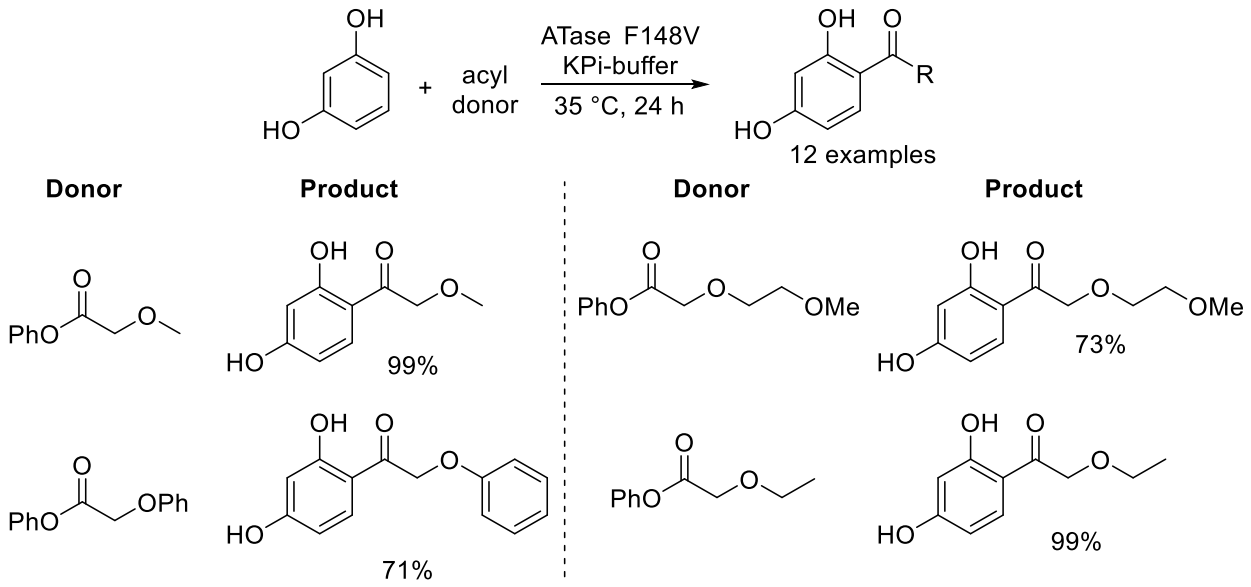
Scheme 1.15. Friedel Crafts Acylation with Methanesulfonic Acid Anhydride

In addition to the development of alternative acylating reagents, there has also been significant work devoted to creating more effective catalysts for this reaction. For example, there has been increasing interest in the development of heterogenous catalysts for Friedel-Crafts acylation,[24] as these can be reused, simplify purification, and may not complex as readily to the ketone product, thus offering the possibility for sub-stoichiometric catalysts. The Lin group has developed one such system using a zeolite catalyst (Scheme 1.16).[159] The ketone product does not sequester on zirconium in this system, permitting catalyst and reuse. The latter was demonstrated by suspending the catalyst on silica and performing reactions in flow. A maximum of 15 runs could be conducted before any loss of the catalytic activity, which could be restored by flushing the column with solvent.



Scheme 1.16. Highly Active Zirconium-based Metal-Organic Frameworks for Acylation

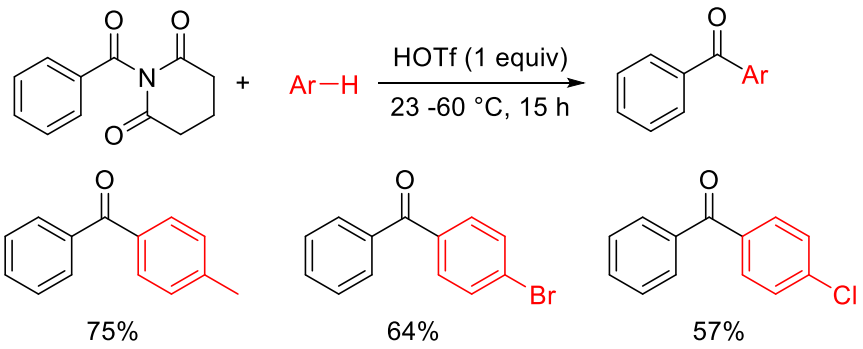
Friedel-Crafts chemistry has also been explored in the context of biocatalysis, which has allowed exquisitely selective reactions to be performed under mild conditions.[160-169] As an example, the Kroutil group has demonstrated that acyltransferases can catalyze the acylation of resorcinol with phenol derived acyl donors (Scheme 1.17).[161] The F148, L300, L383, Y386, and Y298 residues were identified as important in controlling substrate selectivity. Upon varying the identity of these residues, it was found that a single modification of residue F148 (a phenylalanine in the native enzyme) to valine accommodated a range of acyl donors, thus expanding the scope of this transformation relative to the wild-type enzyme.[163]



Scheme 1.17. Enzyme catalyzed Friedel-Crafts Acylation of Resorcinol[a]

[a]ATase F148V: phenylalanine at the 148[th] residue of the acyl transferase enzyme has been replaced with valine. KPi-buffer: potassium phosphate buffer.

There have also been efforts to move beyond the use of electrophilic acyl halides or anhydrides as reagents in Friedel-Crafts chemistry.[170-176] This can potentially allow for improved functional group compatibility, as well as expand the pool of reagents that can be employed in the reaction. For example, the Szostak group has developed "twisted" amides for a variety of applications. In these, C-N π-bonding is disrupted by installing large groups on the amide nitrogen, that favor a non-planar conformation. This significantly reduces the C-N bond strength and allows for more facile amide derivatization. They have applied this concept to Friedel-Crafts acylations in concert with triflic acid as a stoichiometric activator (Scheme 1.18).[177] Interestingly, only a single *para* regioisomer is observed in these reactions, in contrast to classical acylium ion reactivity.[115, 146] Although in depth mechanistic studies were not conducted to elucidate the origin behind this enhanced selectivity, it is likely that a protonated amide is the active acylating agent, and may direct the reaction towards *para* isomers through steric influences.



Single para regioisomer observed

Scheme 1.18. "Twisted" Amides As Acylating Agents

1.3. Carbonylative Routes to Acyl Electrophiles

1.3.1. Activation of Carbon Monoxide

While Friedel-Crafts acylation chemistry has proven itself to be one of the most important methods for the construction of ketones and related products from (hetero)arenes, an intrinsic limitation of this chemistry is the need to generate the reactive acylating reagent. This is most commonly accomplished through the activation of carboxylic acids with high energy reagents (e.g. thionyl or oxalyl chloride for acid chlorides, carbodiimides for anhydrides, etc), which are themselves often the product of a multistep synthesis, generate significant waste, and are not highly functional group compatible.[178, 179]

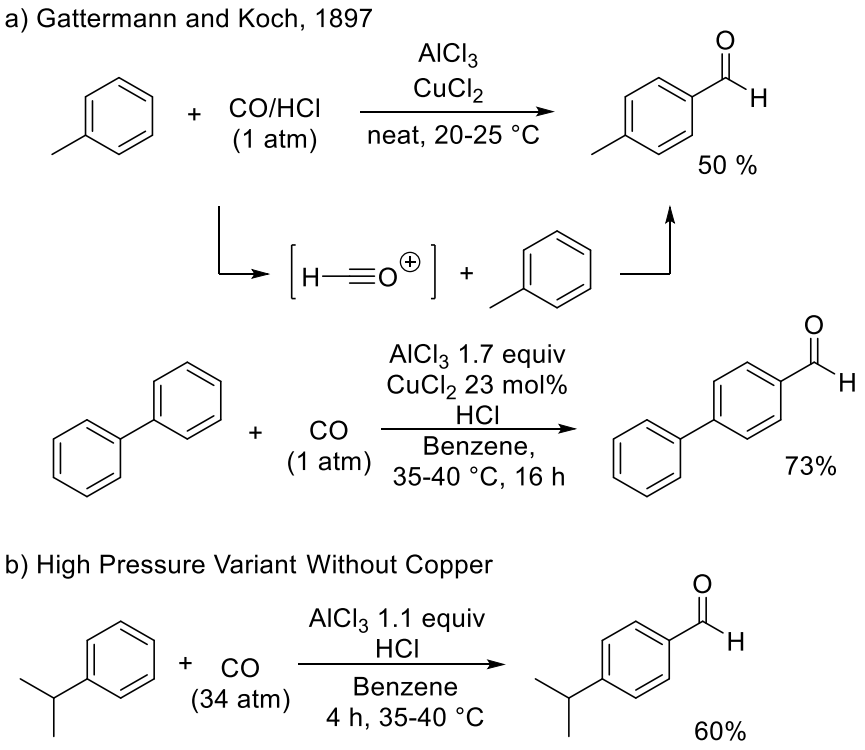
An alternative approach to synthesizing carbonyl-compounds that has seen significant use is carbonylation reactions.[3, 4, 180, 181] Carbon monoxide is a broadly available and stable C1 building block. The C-O bond in carbon monoxide is the strongest naturally occurring bond known (BDE = 256 k/cal).[182] For comparison, the N-N bond in N_2, a prototypical inert diatomic, is only 225 kcal/mol.[182] In addition, carbon monoxide is neither highly Lewis acidic nor basic. Despite these features, the conversion of carbon monoxide into a carboxylic acid derivative is often exergonic, since the π-bond in CO is relatively weak (ca. 75 kcal/mol).[183]

CO can be activated toward reaction with either high energy electrophilic reagents or, more commonly, via metal catalysis. These activation strategies are represented by two discoveries at the end of the 19th century that gave birth to the field of carbonylation. In 1890, Ludwig Mond,

discovered nickel tetracarbonyl, the first metal carbonyl complex, and noted how the unique properties of this volatile complex could be utilized for the purification of nickel ores in what is now known as the Mond process.[184] In 1897, Gattermann and Koch discovered that CO can be activated in strong acids to affect (transition-metal-free) arene carbonylation.[185] The use of these two different approaches to CO activation in synthesis, and in particular the generation of electrophilic acylating agents will be overviewed below.

1.3.2. Non-Transition-Metal-Mediated Carbonylative Routes to Acyl Electrophiles

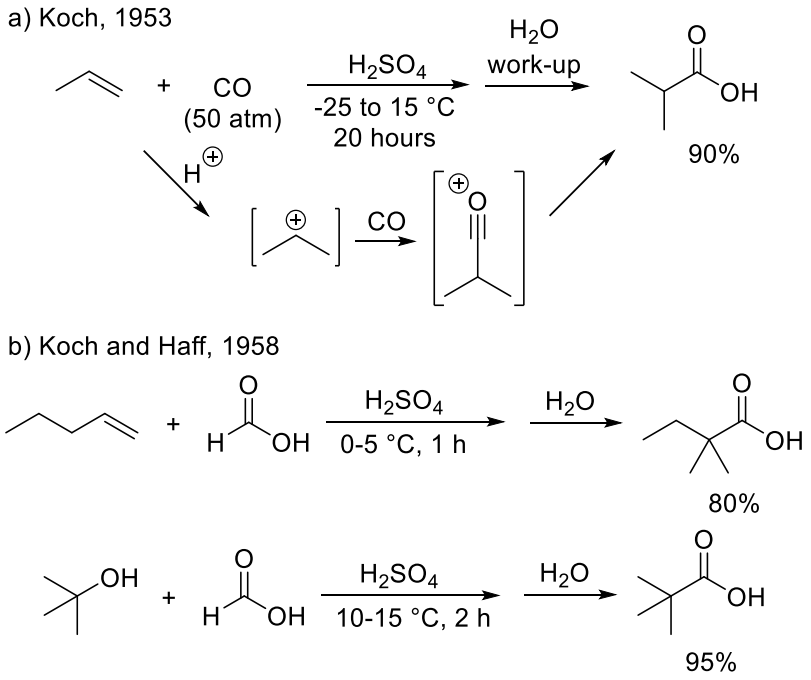
The carbon of carbon monoxide has a lone pair, and could in principle serve as a base. However, CO is not sufficiently basic to react with most electrophilic species, except under pressing conditions. The latter was first demonstrated in 1897 by Ludwig Gattermann and Julius Koch with the discovery that carbon monoxide could be activated by strong acids (HCl) to allow the overall conversion of benzene derivatives into aldehydes (Scheme 1.19a).[185] As with Friedel-Crafts acylations, the reaction requires a Lewis acid catalyst (*e.g.* $AlBr_3$ or $AlCl_3$), and catalytic $CuCl_2$. It is believed that the reaction proceeds via the *in situ* protonation of carbon monoxide to generate a formyl cation, which subsequently reacts with the arene to form aldehyde. Several years later it was discovered that under higher pressures of CO, the copper catalyst is not needed (Scheme 1.19b).[186] Although this strategy has seen less use relative to transition metal catalyzed carbonylations (*vida infra)*, it has seen use in both industrial and academic settings.



Scheme 1.19. Gattermann-Koch Reaction

While the ability of strong acids to activate CO towards addition to arenes was known over a century ago, efforts to expand cationic-type carbonylations towards other substrates laid dormant until the 1950s, when it was found that carbon monoxide could react with carbocations as well, in what are collectively referred to as Koch carbonylations (or Koch-Haaf carbonylation).[187] Herbert Koch in 1953 reported the carbonylation of propene under 50 atm of carbon monoxide in the presence excess of strong acid to produce the branched carboxylic acid (Scheme 1.20a).[188] This reaction is believed to proceed via protonation of the alkene to form the more stable secondary carbocation. This cation is trapped with carbon monoxide to generate an acylium ion, which reacts further with water to form the carboxylic acid. In 1958, Herbert Koch and Wolfgang Haaf reported an important modification of this reaction under ambient pressure using a CO surrogate, formic acid (scheme 1.20b).[189, 190] The sulfuric acid thus serves not only to generate the carbocation, but also to generate CO from formic acid. In the same report, they also demonstrated this chemistry could be extended to alcohols where in this case the alcohol is dehydrated in the presence of strong acids to generate carbocations. High selectivity for tertiary acids is obtained, which is consistent

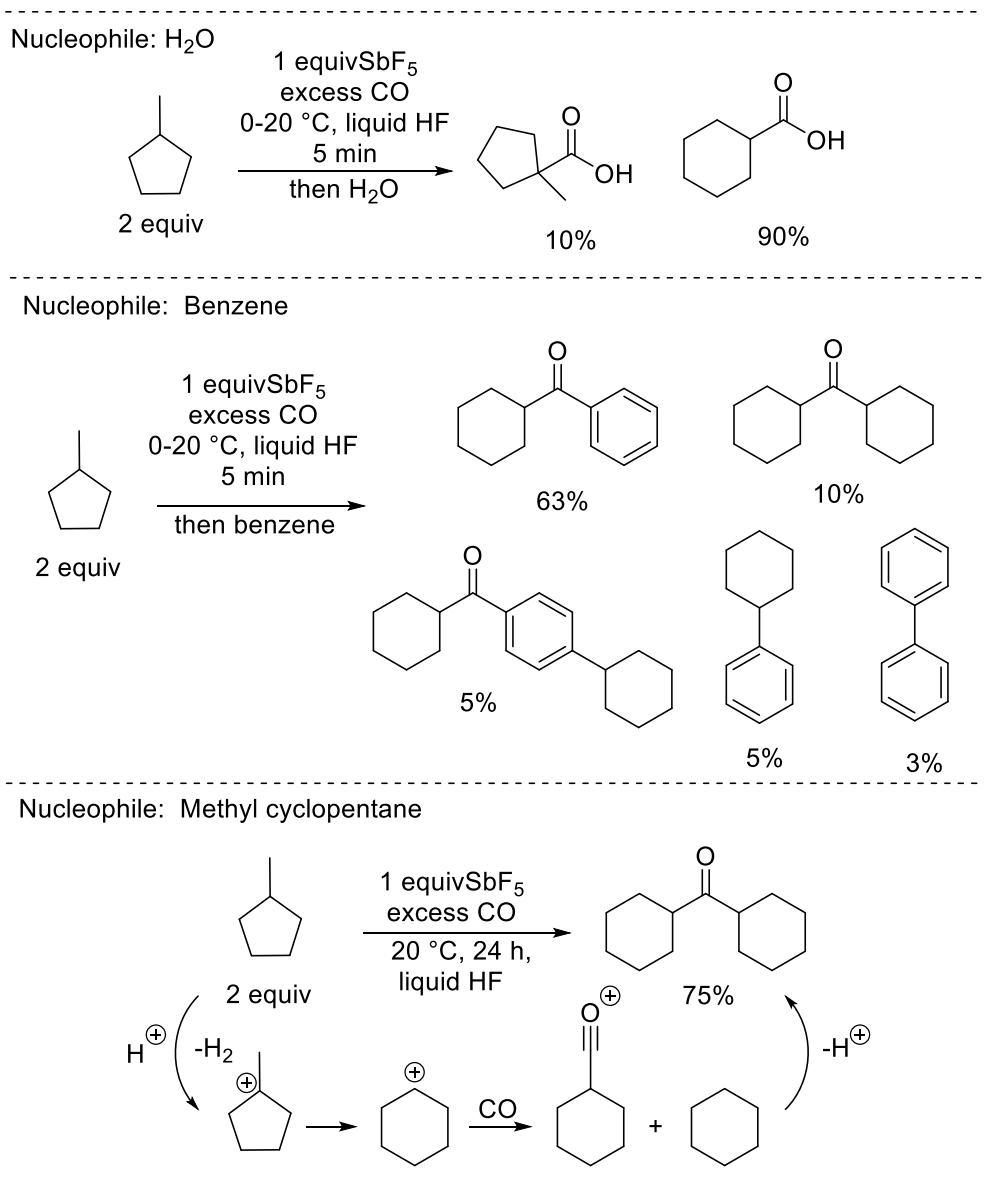
with the stability of carbocations. Shell, Exxon, and Kuhlmann have created industrial processes based on this technology which produce ca. 150,000 metric tons a year of Koch acids.[187]



Scheme 1.20. Koch Carbonylations of Alkenes and Alcohols

By the early 1960s, it had been well established by Olah and others that alkanes could be ionized to carbocations in super acidic media, such as HF/SbF_5.[191-194] In 1967, Paatz intercepted this reactivity with carbon monoxide to generate acyl electrophiles (acylium cations) from alkanes (Scheme 1.21).[195] The combination of very potent Lewis acids such as SbF_5 in the presence of HF creates one of the strongest acids known, "Magic Acid," due to the stabilization of the SbF_6 anion. The resulting acid can react with methyl cyclopentane via hydride abstraction from the tertiary position generating a carbocation. This carbocation isomerizes to the cyclohexyl cation before being trapped by carbon monoxide to form the acylium ion. In this report, it was demonstrated these acylium ions can be trapped with either water, benzene, or even another alkane. The work demonstrated, for the first time, that useful yields of carbonylated alkane products can be obtained via acyl electrophiles. However, given the corrosive, high energy nature of the

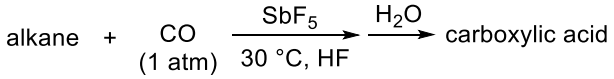
reagents involved, the reaction is restricted to simple alkane substrates with no functional groups present.



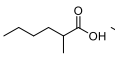
Scheme 1.21. Generation of Acylium Cations Under Superacidic Conditions

Functionalizing alkanes with carbon monoxide comes with the obvious advantage of building up molecular complexity directly from simple (and often inert) starting materials in one synthetic step. However, challenges in product selectivity have severely retarded the more widespread application of this technology. For example, variations in the site of the initial hydride

abstraction, and the ability of the resultant carbocations to rearrange, often leads to a complex mixture of products. Isomer distributions resulting from carbocation rearrangement was investigated extensively by Suzuki (Scheme 1.22).[196] Starting from different hexane isomers, it was noticed that roughly the same distribution of products is observed, indicating a thermodynamic equilibrium of the carbocations is reached prior to trapping.



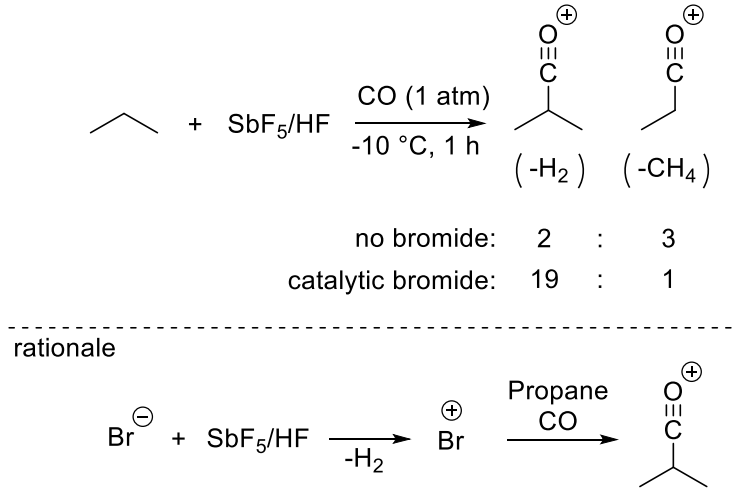
Products

Substrates									
Hexane	12%	9%	12%	12%	11%	4%	7%	25%	5%
2-methylpentane	10%	9%	10%	16%	12%	5%	7%	26%	5%
3-methylpentane	10%	9%	11%	16%	13%	5%	7%	24%	5%
2,3-dimethylbutane	10%	9%	11%	16%	12%	5%	7%	26%	5%
2,3-dimethylbutane	11%	9%	12%	16%	12%	4%	7%	25%	4%
3-methylpentane	15%	20%	20%	10%	7%	3%	3%	19%	3%
3-methylpentane	13%	16%	15%	14%	10%	3%	5%	22%	3%
3-methylpentane	10%	9%	11%	16%	13%	5%	7%	24%	5%
3-methylpentane	7%	8%	8%	17%	13%	5%	8%	28%	7%
3-methylpentane	6%	8%	8%	18%	12%	6%	9%	28%	7%

Scheme 1.22. Isomer Distributions in the Carbonylation of hexanes.

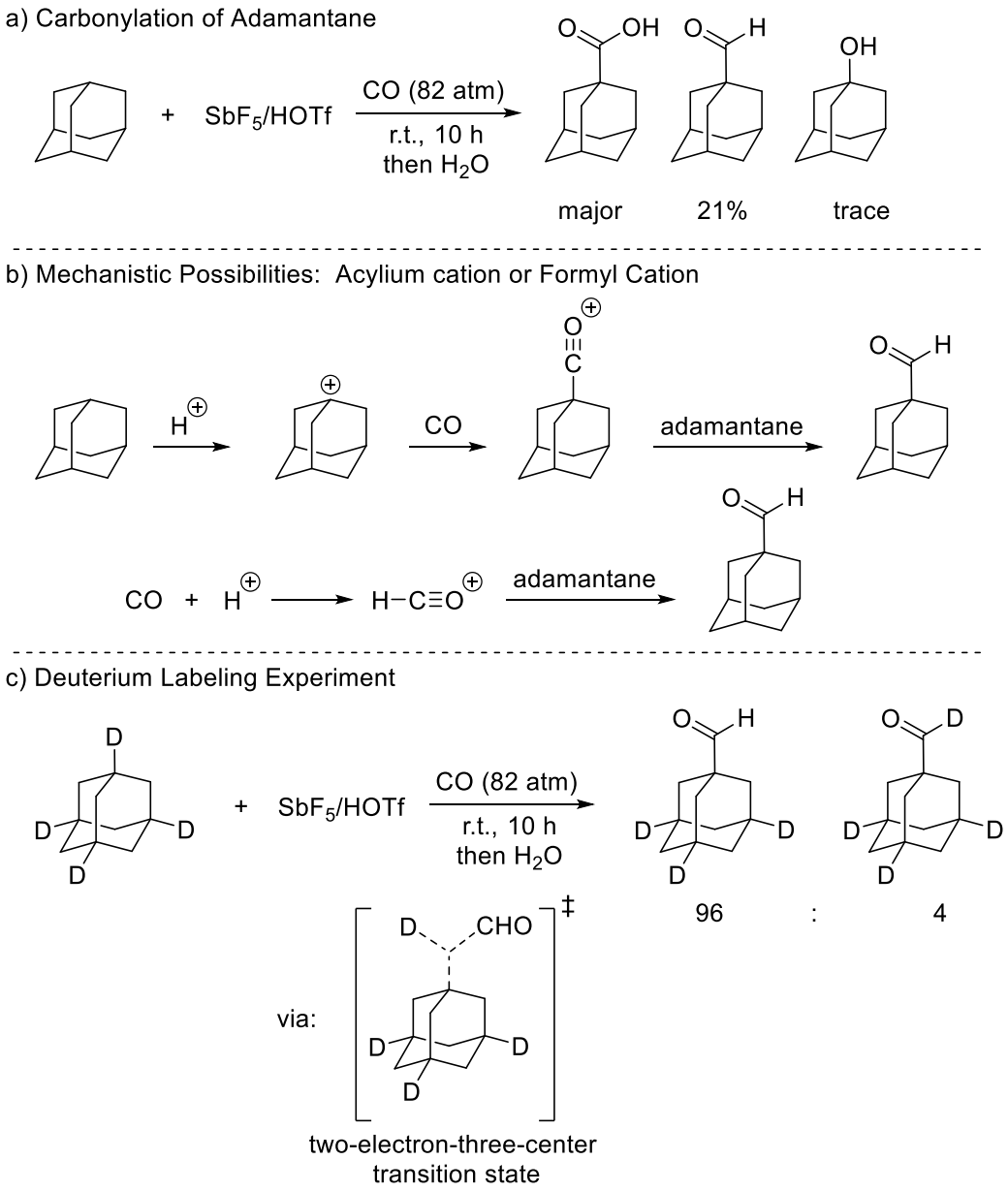
Methods to control this selectivity, at least with lower molecular weight alkanes, were investigated by the Sommer group in the late 1980s by examining selectivity in propane carbonylation (Scheme 1.23).[197] Under standard super acidic conditions, a 3:2 mixture of ethyloxocarbenium ion and isopropyloxocarbenium ion were observed by NMR at low temperature. In a novel strategy to control this selectivity, it was found that addition of catalytic bromide led to greatly improved selectivity for the isopropyloxycarbenium cation. The selectivity enhancement is believed to arise from the generation of a bromonium cation via oxidation of bromide under the superacidic conditions. This bromonium cation is postulated to ionize alkanes

more rapidly than a proton, and, due to the large size of the bromonium ion, favor hydride over methyl abstraction.



Scheme 1.23. Selective Carbonylation of Propane

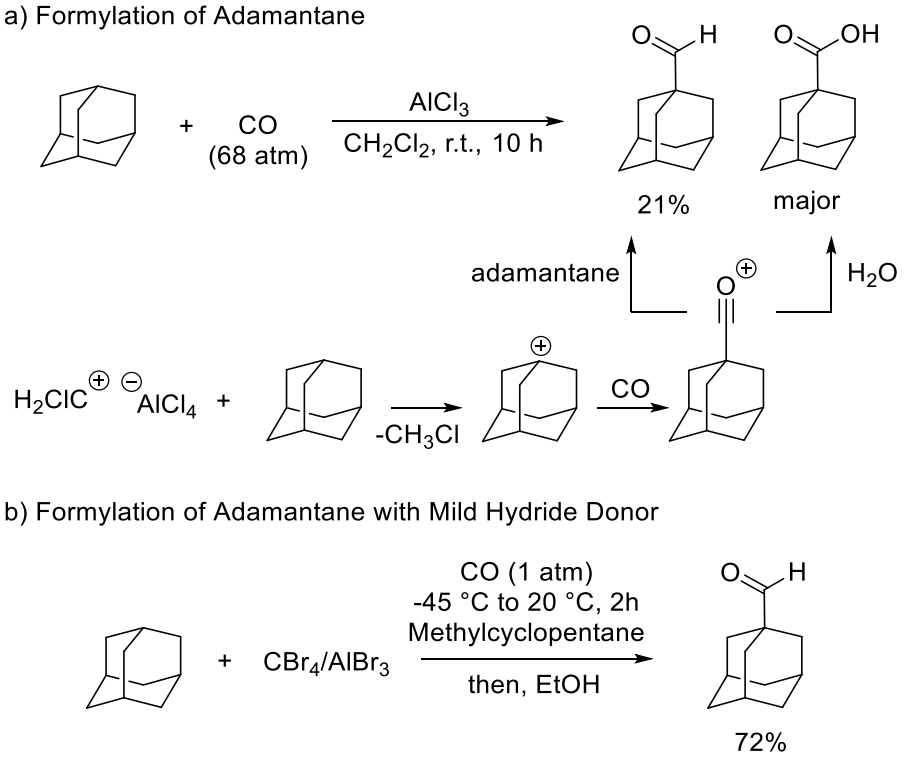
In 1988, George Olah, was able to extend this concept to the first formylation of saturated hydrocarbons under superacidic conditions with carbon monoxide (Scheme 1.24a).[198] There are two viable pathways for this reaction (Scheme 1.24b): a) the formation of an adamantyl cation, which is trapped with CO, followed by hydride abstraction from another equivalent of adamantane, or b) reaction of adamantane with a formyl cation, the postulated intermediate in the Gattermann-Koch formylation. Deuterium labeling experiments were conducted to differentiate these pathways (Scheme 1.24c). These showed that subjecting adamantane, labeled with deuterium at the bridgehead positions to the reaction conditions, resulted in almost complete formation of the hydrogen-incorporated aldehyde, and almost no deuterium aldehyde was observed. These results rule out abstraction of hydride (or deuteride) from another equivalent of adamantane by an acylium cation, and suggest direct reaction of adamantane with a formyl cation via a three-center-two-electron transitions state. The fact that the carboxylic acid is the major product in the reaction indicates that these mechanistic pathways are competing, but once the adamantane acylium cation is formed, abstraction of hydride is very slow. Hydrolysis at the end of the reaction leads to the carboxylic acid product.



Scheme 1.24. First Formylation of Saturated Hydrocarbons Under Superacidic Media with CO

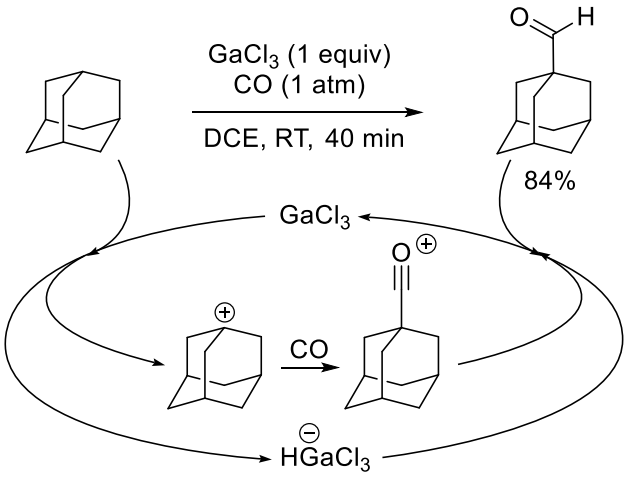
Olah subsequently showed that aprotic superacids generated from halomethanes and group III Lewis acids, which cannot generate a formyl cation, can also facilitate this chemistry (Scheme 1.25).[199] This suggests that without protic superacids, the previously ruled out, hydride abstraction can be operative. Although this result is identical to the result in Scheme 1.24a, the observation

of aldehyde under these conditions is indicative of a change in mechanism. It was later found by Akrem that providing a mild hydride donor (*e.g.* methylcylopentane) could greatly improve the yield of adamantanyl aldehyde using a similar aprotic superacid system (Scheme 1.25b).[200]



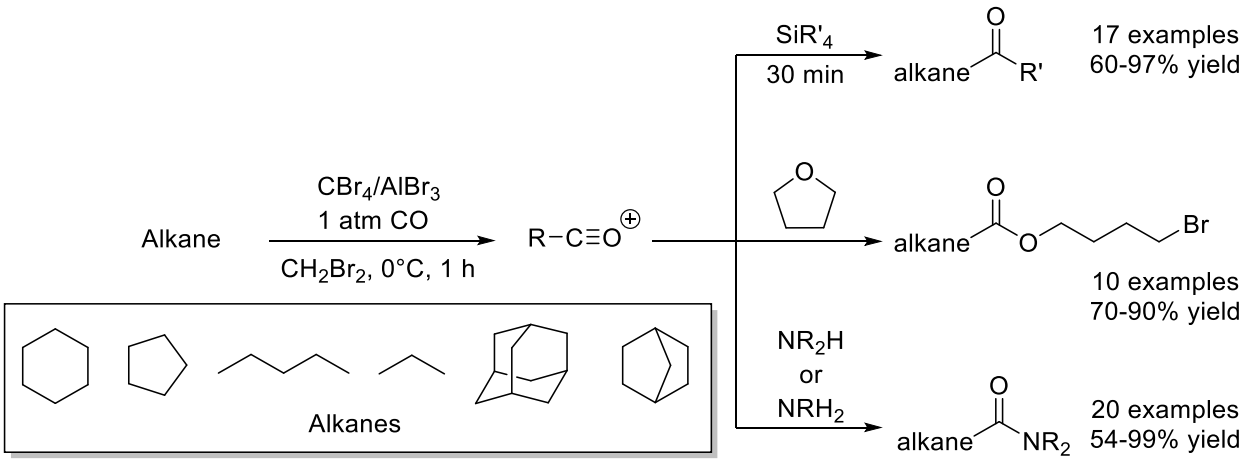
Scheme 1.25. Formylation with Aprotic Acids

In principle, an additional hydride donor is not necessary if hydride abstraction by the Lewis acid is reversible. This idea was realized a number of years later by Chatani by using a relatively simple hydride acceptor, $GaCl_3$ (Scheme 1.26).[201] In this, hydride abstraction is postulated to create the adamantyl cation that is trapped with CO to form the acylium cation. The gallium hydride generated from the initial abstraction adds to the acylium cation to form the product. The reaction mechanism indicates that, in principle, sub-stoichiometric quantities of $GaCl_3$ could be used, although no catalytic reactions were reported.



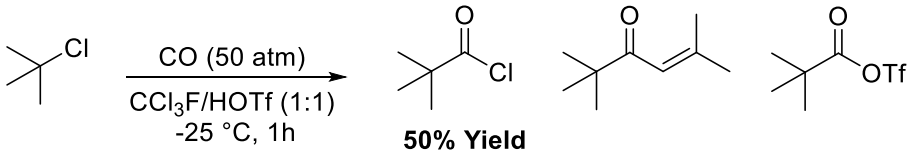
Scheme 1.26. Formylation of Adamantane with $GaCl_3$

The use of superacids based on halomethanes and Lewis acids can allow the generation of acylium cations under less extreme laboratory conditions, and avoid the use of specialized equipment and extremely corrosive acid solvents. In addition, previous observations and mechanistic studies indicate acylium cation formation occurs much more quickly than their subsequent trapping with alkanes (*vide supra*). This suggests that other nucleophiles could also be employed to allow the formation of various carbonyl containing products from simply alkanes and carbon monoxide. Despite the potential of this chemistry, it has not been heavily explored as a route to convert alkanes to carbonyl-containing derivatives. Exceptions to this have been provided by Akhrem, where it was demonstrated acylium cations generated from alkanes could be used to access a range of ketones, amides, and esters (Scheme 1.27).[202-204]



Scheme 1.27. Expansion of Scope of Alkane Functionalization

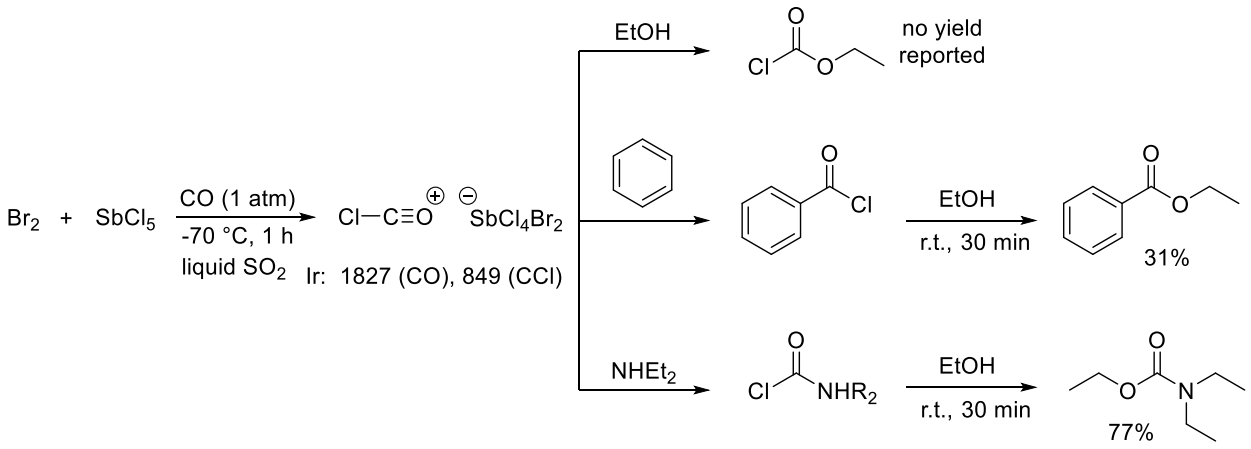
As an alternative to hydride abstraction from alkanes, tertiary alkyl-chlorides and -bromides can also be carbonylated under super acidic conditions. For example, Brunet has shown that chloride abstraction from ^{t}BuCl with strong acids produces a tertiary carbocation that is trapped with CO and then chloride to generate the corresponding acid chloride (Scheme 1.28).[205] A common byproduct observed in the reaction is an α,β-unsaturated ketone, which presumably results from acyl cation reaction with isobutene. The latter is produced from elimination of the tertiary cation. Although these conditions are still quite harsh, they are more user friendly than the superacidic conditions needed for alkane carbonylation.



Scheme 1.28. Carbonylation of tert-butyl chloride

While the coupling of alkyl cations with CO has been the most thoroughly investigated other variants of this chemistry are known. These can create opportunities for increased product

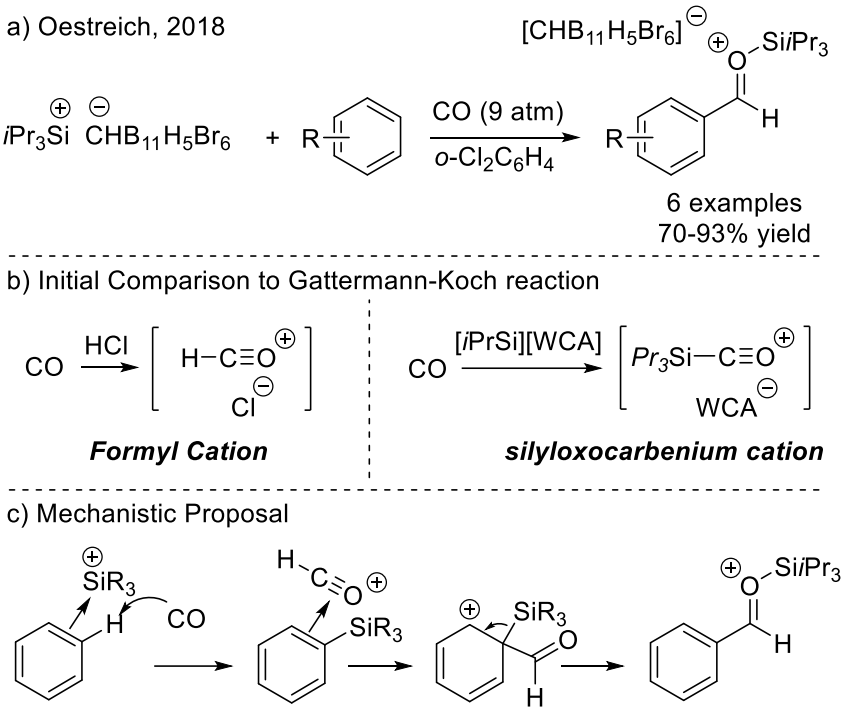
diversity. For example, Tokura showed in 1973 that potent Lewis acids such as $SbCl_5$ in the presence of bromine generates a bromonium cation capable of reacting with CO to create, after halogen exchange with $SbCl_5Br^-$, a chloro-oxocarbonium cation. The latter is analogous to the formyl cation generated under superacidic conditions (Scheme 1.29). This cation shows analogous reactivity to phosgene, as two nucleophiles can add to the electrophilic carbon. When performed in a stepwise sequence, this offers the ability to place the desired functional groups on either side of a carbonyl unit.



Scheme 1.29. Formation of Chloro-oxocarbonium Cation for Enhanced Synthetic Versatility

Transition-metal free electrophilic activation of carbon monoxide continues to receive research interest. For example, the use of weakly coordinating anions (WCA) based on carborane anions can allow the formation of highly electrophilic silyl cations.[206] These can induce a Gattermann-Koch type formylation of arenes with CO, as recently demonstrated by Oestreich.[207] Under moderate CO pressure and temperature (9 atm, 50 °C), benzene and simple derivatives can be formylated in high yield (Scheme 1.30a). The silyl cation/aldehyde adduct is the immediate product of the reaction, and was characterized by X-ray crystallography. The author's initial postulate for this reaction was that it proceeded via a silyloxocarbenium ion, $[Si(CO)]^+$, in analogy to the Gattermann-Koch formylation (Scheme 1.30b). However, all efforts to observe such an intermediate failed. DFT calculations revealed a lower energy pathway involving initial complexation of the silyl cation with benzene. This complex was calculated to deliver a proton to

CO to generate a silyl arene bound formyl cation with an energy barrier of 37 kcal/mol, which is 6 kcal/mol less than the calculated barrier for $[Si(CO)]^+$ formation. Nucleophilic attack from the *ipso* position of the silyl arene, followed by observed silyl cation migration to the oxygen delivers the product (Scheme 1.30c).

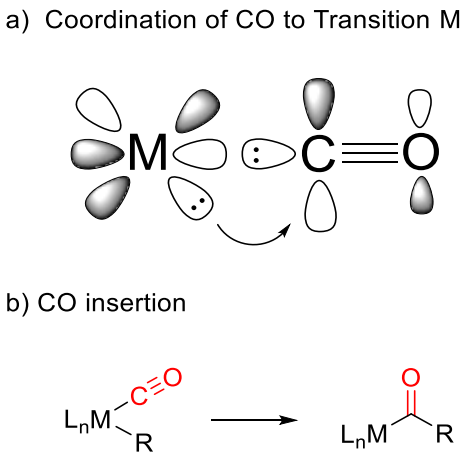


Scheme 1.30. Silyl Cation Activation of CO

1.3.3. Transition-Metal-Catalyzed Routes to Acyl Electrophiles with Carbon Monoxide

While the generation of acyl electrophiles directly from carbon monoxide under superacidic conditions allows for the direct carbonylation of arenes and alkanes to form highly reactive acylium cations, the required conditions are not amenable to most functional groups. There are also challenges in selectivity, as there are many C-H bonds that might be carbonylated, and carbocations generated from alkanes are unstable towards cracking and rearrangement, adding to the complex mixture of products that can result. Transition metal catalysis can offer solutions to a number of these challenges. Metal-catalyzed carbonylation reactions have seen significant use in the efficient assembly of carbonyl-derivatives from carbon monoxide, including carboxylic

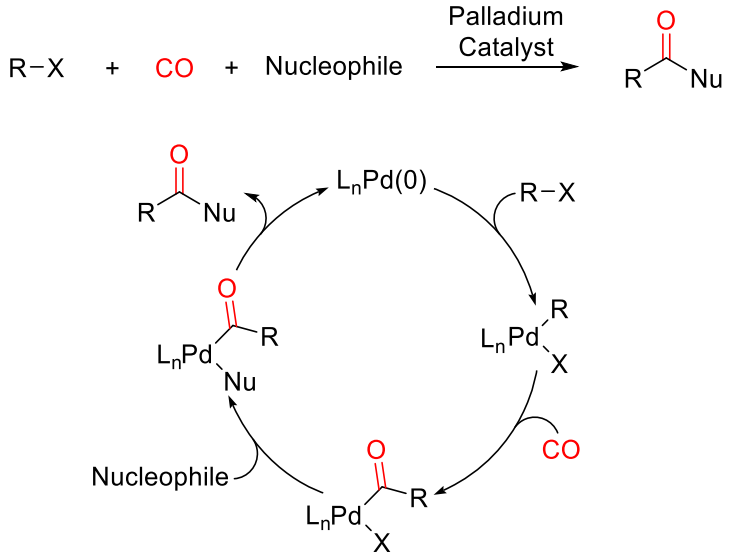
acids, esters, amides or ketones.[5, 208-211] Carbon monoxide readily coordinates to transition metals as a result of having molecular orbitals of appropriate symmetry and energy to engage multiple bonding interactions. With the highest occupied molecular orbital of σ-symmetry located primarily on the carbon, CO can donate electron density to a metal center through σ-donation, while simultaneously accepting electron density from filled d-orbitals on the metal via back donation to relatively low-lying π^* orbitals (Scheme 1.31). The migration of metal coordinated nucleophiles onto carbon monoxide, formally a CO insertion, is the primary mechanism for CO incorporation into organic molecules. The proximity of the empty CO π* orbitals to the migrating nucleophile dramatically lowers the barrier to this reaction, as does the ability of the metal to stabilize the resultant formal acyl anion. This ease of activation has resulted in a plethora of transition-metal-catalyzed carbonylation processes that have been developed in the past century.



Scheme 1.31. CO Activation Mediated by Transition Metals

Palladium catalyzed carbonylations have proven to be a particularly powerful platform for the preparation of many carbonyl containing products.[212-217] These reactions often proceed under mild conditions, and exhibit exceptional functional group compatibility. Carbonylation reactions catalyzed by palladium typically involve the coupling of a formal electrophile, such as an organo(pseudo)halide, with either an organic or organometallic nucleophile and CO (Scheme 1.32). The reaction usually proceeds via oxidative addition of the organic electrophile to Pd(0),

followed by insertion of carbon monoxide into the newly formed palladium carbon-bond. The nucleophile typically reacts with the acyl intermediate by coordination to the palladium center, and then reductive elimination of the acyl-nucleophile fragments to form the new carbonyl derivative.



Scheme 1.32. Palladium Catalyzed Carbonylative Coupling

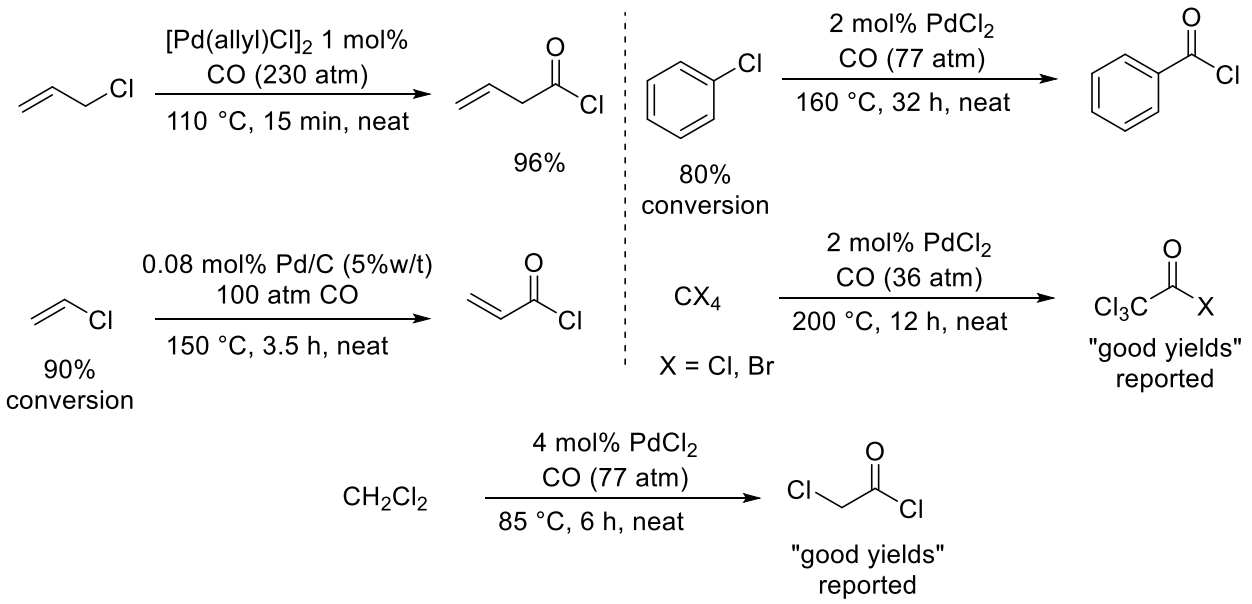
Palladium-catalyzed carbonylations have many similar features to non-carbonylative cross coupling reactions. The obvious difference is the presence of carbon monoxide in the reaction. The latter can have a significant influence on the reactivity of the catalyst. Carbon monoxide is weakly Lewis basic at carbon and its primary bonding interaction occurs through π-backbonding (*vida supra*). The consequence of this bonding mode is a less electron rich palladium center. This means oxidative addition is often more difficult in carbonylations relative to cross-coupling reactions. For example, it is well-established that aryl chlorides can undergo palladium-catalyzed cross coupling with a variety of nucleophiles under mild conditions with the correctly ligated catalyst.[218-226] In contrast, carbonylative cross coupling with aryl chlorides requires elevated temperatures (>100 °C) even with optimized catalysts due to the increased difficulty of oxidative addition.[227-230]

Although significant attention has been given to accelerating the oxidative addition step of carbonylative cross coupling reactions, pushing the limits of reductive eliminations can also create

opportunities to form challenging bonds. The requirement for the nucleophile to first coordinate to the palladium center for reductive elimination limits the scope of coupling partners to relatively strongly coordinating and small nucleophiles. An approach to exit this reaction paradigm is to instead create an organic acyl electrophile as the product of catalysis. As the field of palladium catalyzed carbonylation of organohalides developed, creating acyl electrophiles using these platforms was recognized as a convenient way to expand the breadth of nucleophilic coupling partners. Important discoveries in this area are described below.

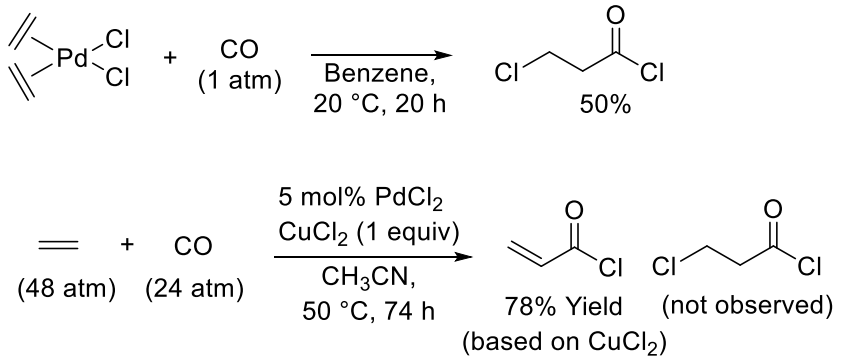
1.3.3.1. Early Examples of Palladium-Catalyzed Carbonylative Routes to Acyl Chlorides

Even before the modern advent of palladium catalyzed carbonylative cross coupling reactions, it was known that palladium is capable of reductively eliminating acyl electrophiles derived from carbon monoxide. For example, Whitfield demonstrated in the early 1960s that allyl chloride could be carbonylated with either palladium allyl chloride or palladium chloride as a catalyst (Scheme 1.33).[231] The reaction was conducted under very pressing conditions (230 atm CO, 110 °C), but afforded the corresponding allylic acid chlorides in high yield and selectivity for the linear products, even when starting from branched allyl chlorides. In the late 1960s, John Sheben and Irving Mador at the U.S industrial Chemical Co. extended this chemistry to the carbonylation of other types of chloride containing substrates such as, vinyl chlorides,[232] aryl chlorides,[233] polyhalomethanes,[234] and more elaborate allylic compounds.[235] The reported yields in these patents appear to be based on substrate conversion, and high temperature and pressure were required, which severely limits synthetic applicability .



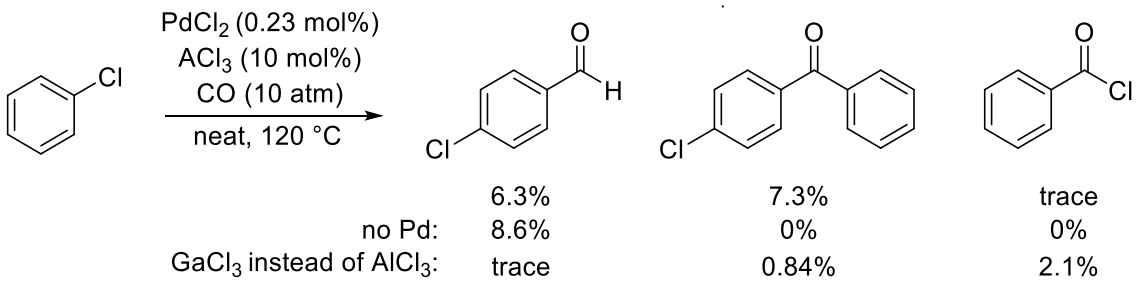
Scheme 1.33. Carbonylation of Organochlorides Forming Acyl Chlorides

It was discovered around the same time by Tsuji that olefins were viable substrates for chlorocarbonylation with stoichiometric palladium chloride (Scheme 1.34).[236] The reaction of the $PdCl_2(ethylene)_2$ complex under an atmosphere of CO at room temperature afforded β-propionyl chloride as the product in moderate yield. It was postulated in this report that the olefin underwent nucleophilic attack from carbon monoxide. However, sequential insertion of carbon monoxide and ethylene into the palladium chloride bond, followed by reductive elimination, may be more likely. Several years later, Blackham discovered that the reaction could be made catalytic in palladium by adding a stoichiometric $CuCl_2$ oxidant, although this resulted in the formation of acrylyl chloride instead of the expected β-chloro acrylyl chloride. It was suggested that copper may be sequestering HCl, in addition to turning over the palladium cycle.



Scheme 1.34. Acid Chloride Formation via Chlorocarbonylation of Alkenes

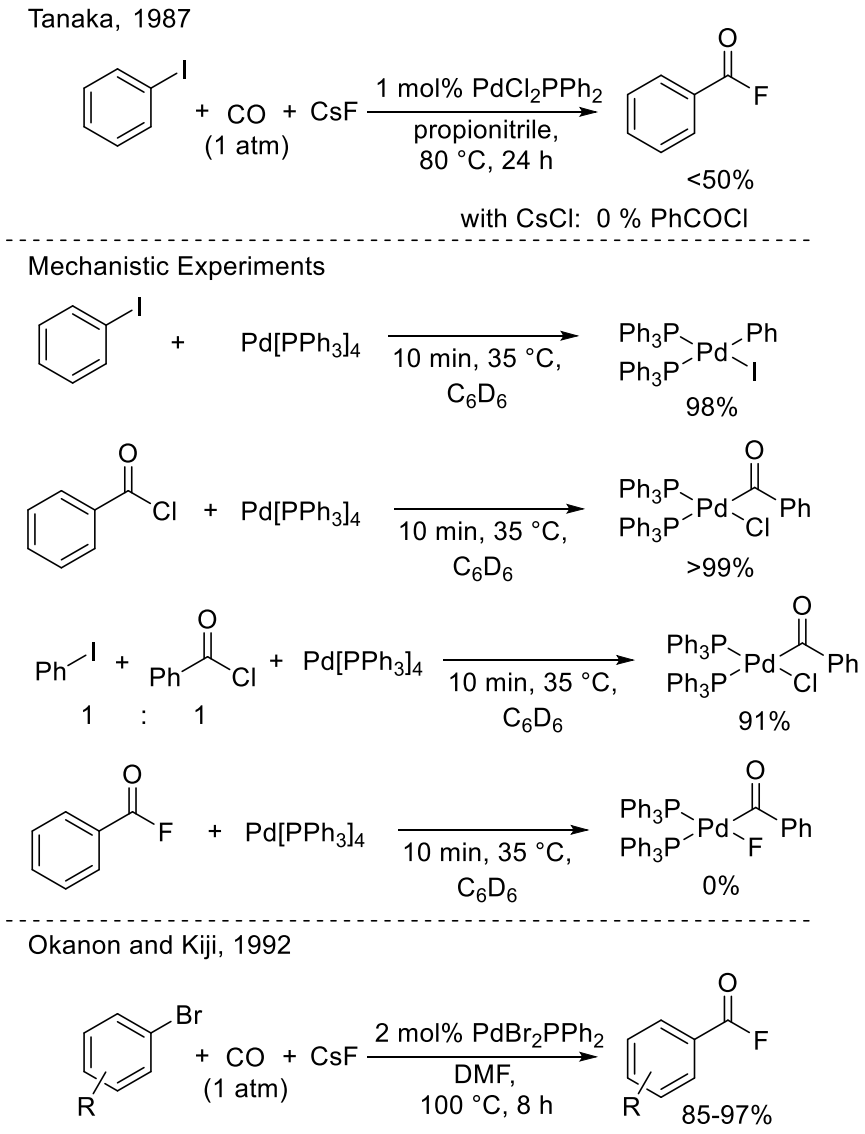
In 1998, Noskov discovered that addition of Lewis acids such as $AlCl_3$ to the carbonylation of chlorobenzene could allow the palladium catalyzed formation of acid chloride and Friedel-Crafts acylations (Scheme 1.35).[237] This reaction also required neat chlorobenzene as solvent, and resulted in low yields of the corresponding ketone. Of note, *p*-chlorobenzaldehyde and benzoyl chloride are also observed under these conditions. The former presumably arises from a Gattermann-Koch reaction under the reaction conditions with strong Lewis acids, which was corroborated by observation of the aldehyde even in the absence of palladium. When a milder Lewis acid was used ($GaCl_3$), the selectivity shifted towards benzoyl chloride as the major product in the reaction. Although the yields from these reactions are not synthetically useful, and chlorobenzene was the only substrate used, this demonstrated the potential synthetic utility of creating reactive electrophiles under palladium catalyzed carbonylative conditions.



Scheme 1.35. Carbonylation of Aryl Chlorides

1.3.3.2. Approaches to Moderate Electrophiles with Carbon Monoxide

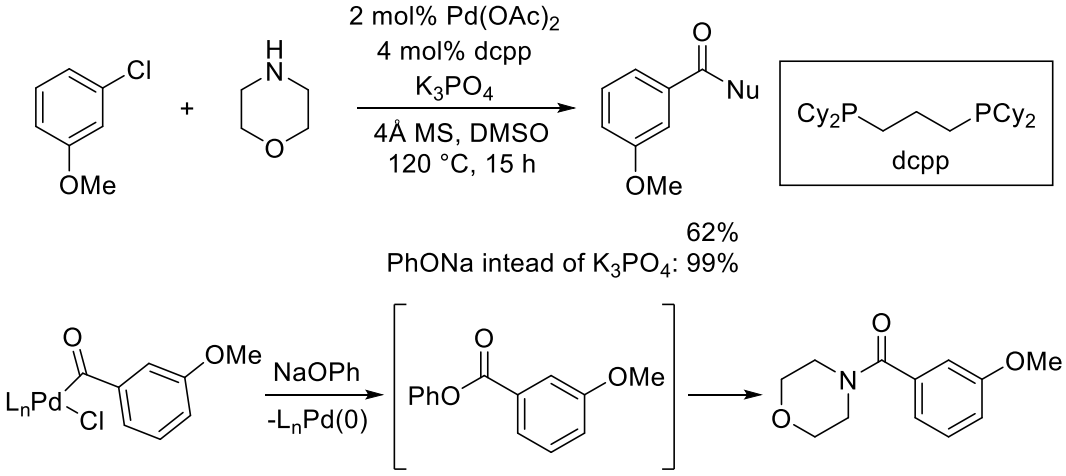
Most early reports noted above on carbonylations of organohalides to produce acyl electrophiles, such as acid chlorides, used "ligandless" palladium systems under very pressing conditions (high temperature and high CO pressure) and often in neat substrate. More recent research has focused on the design of more active palladium/phosphine based catalyst systems to produce less potent acyl electrophiles and under mild and synthetically useful conditions.[238-246] Among other features, these have greatly expanded the scope of nucleophiles that can be used in carbonylative coupling, and the compatibility of the reaction towards functional groups, as now the nucleophile is reacted with the catalytically produced electrophile in a second step. For example, reports from Tanaka, and the groups of Okano and Kiji, demonstrated the first fluorocarbonylations of aryl iodides and bromides, respectively (Scheme 1.36). Acid fluorides are versatile electrophiles that can react with a range of nucleophiles.[247, 248] Both systems utilized triphenylphosphine as a ligand, and a simple change in solvent from isopropyl nitrile to DMF permitted aryl bromides as a coupling partners. Interestingly, efforts were also made to produce acid chlorides, but without success. Competition experiments between aryl iodide and acid chloride revealed that acid chlorides are too reactive towards $Pd(PPh_3)_4$ to be produced in appreciable yield, while acid fluorides are unreactive towards palladium(0) complexes under the same conditions, presumably due to their diminished electrophilicity and the stronger C-F bond.



Scheme 1.36. The First Examples of Fluorocarbonylation

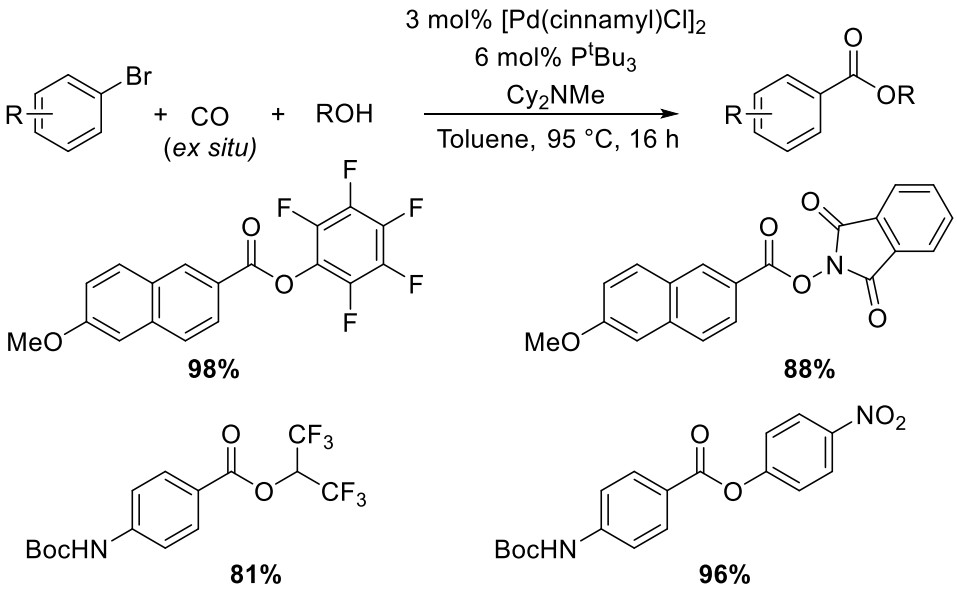
This concept can be extended beyond aroyl fluoride formation to the generation of activated esters. In 2007, the Buchwald group discovered during the development of an aminocarbonylation reaction of aryl chlorides that replacement of traditional bases with sodium phenoxide accelerated the reaction (Scheme 1.37).[230] Following the reaction by IR spectroscopy revealed the formation of the phenoxy ester as an intermediate, which then converted to the final amide product. The rate enhancement is attributed to the increased electrophilicity of the phenoxy ester relative to the palladium-acyl intermediate. In a later report, it was demonstrated that

phenoxy esters could be isolated as the product, and then further reacted with amines in a second step.[229] Alper[242] and Skrydstrup[239] have also reported similar reactions with thiophenols giving thioesters as activated acylating agents via palladium catalysis.



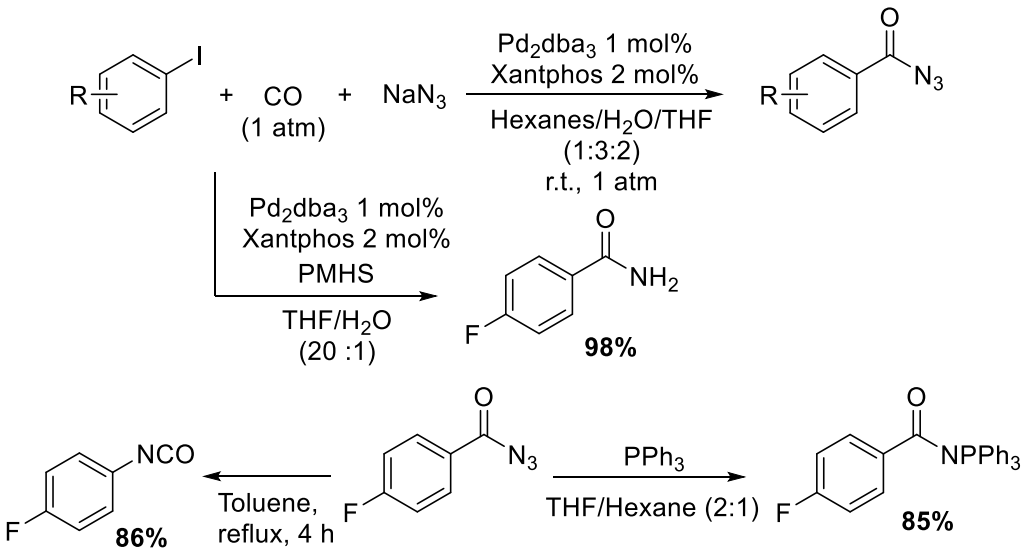
Scheme 1.37. Aminocarbonylation via *in situ* Generation of Phenoxy Esters

In 2015, Skrydstrup developed a palladium catalyzed platform for a synthesis of various activated esters using *ex stiu* generated carbon monoxide (Scheme 1.38).[238] With a single palladium catalyst system, a variety of aryl bromides could be coupled with carbon monoxide and electron deficient alcohols to create activated esters. These esters proved to be active acyl transfer agents to synthesize a range of carbonyl derivatives.



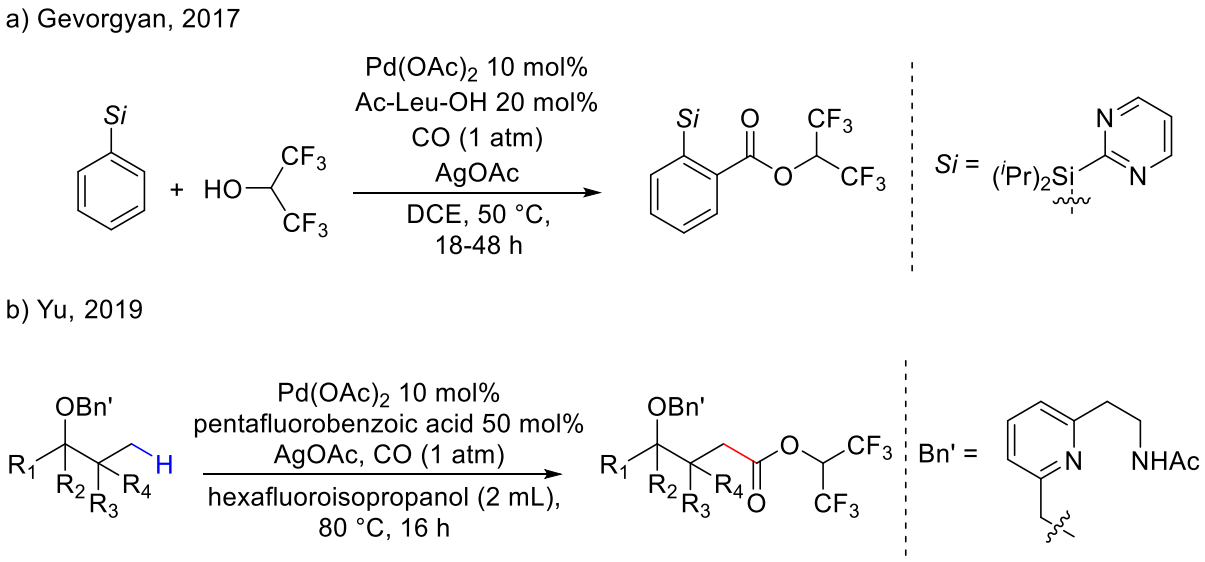
Scheme 1.38. Generation of Aactivated Esters with Carbon Monoxide

Grushin reported the first example of an azidocarbonylation using palladium catalysis (Scheme 1.39).[241] The use of a chelating yet large bite angle Xantphos ligand was found to be important to catalysis, and presumably creates a sterically encumbered Pd(II) intermediate to favor reductive elimination and build-up of these thermally sensitive products. The acyl azides generated here are unique products, and their breadth of reactivity extends beyond that of previously described activated esters. For example, the acyl azide can be directly reduced to the primary amide by simply adding a silane reductant to the reaction mixture. Likewise, Curtius rearrangement and the Staudinger reduction can be used to form isocyanates and iminophosphoranes, respectively.



Scheme 1.39. Azidocarbonylation of Aryl Iodides

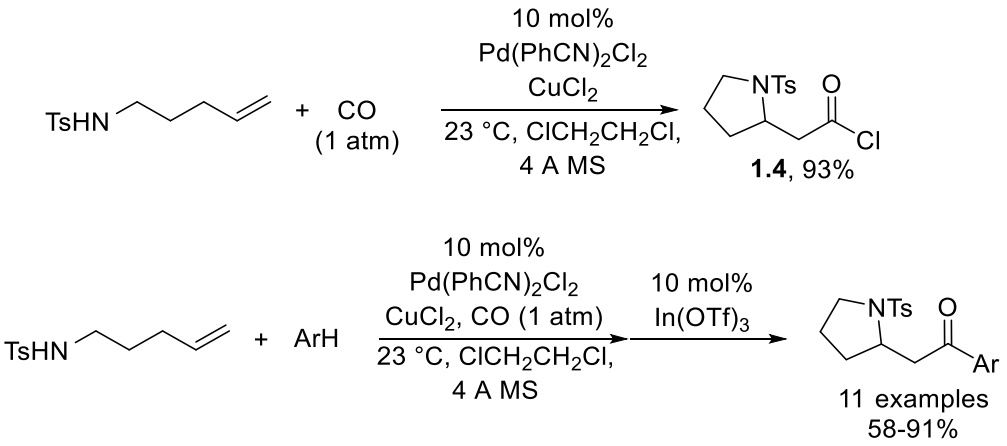
There have also been advances in the metal catalyzed carbonylation of C-H bonds to form acyl electrophiles. The field of transition metal catalyzed C-H functionalization has seen significant advances in the last 20 years,[249-269] but incorporation of carbon monoxide into these platforms was much slower to emerge.[215, 270-280] In palladium catalysis, this can be attributed to the acetate base needed to cleave the C-H bond (via concerted-metallation-deprotonation),[281] which often also reacts with the palladium-acyl intermediates to form anhydrides. However, the groups of Gevorgyan and Yu recently reported the synthesis of activated hexafluoroisopropanol (HFIP) acyl electrophiles from C(sp^2)-H bonds,[282] and C(sp^3)-H bonds,[283] respectively (Scheme 1.40). In the work by Gevorgyan, the hexafluoroisopropanol (HFIP) serves not only as the source of the activated ester, but also as a promoter for the C-H activation event. Experimental data suggests that HFIP hydrogen bonds to the directing group, which activates the substrate while simultaneously situating the alkoxide fragment close to the acyl unit for rapid formation of the activated ester. In the work of Yu, HFIP is used as the solvent to favor formation of the activated ester. This chemistry is reminiscent of the early work in creating electrophiles using carbonylation chemistry from C-H bonds (section 1.3.2). Although less reactive electrophiles are created in these systems, the conditions under which they are created are much milder.



Scheme 1.40 Carbonylative C-H Functionalization Routes to Acyl Electrophiles

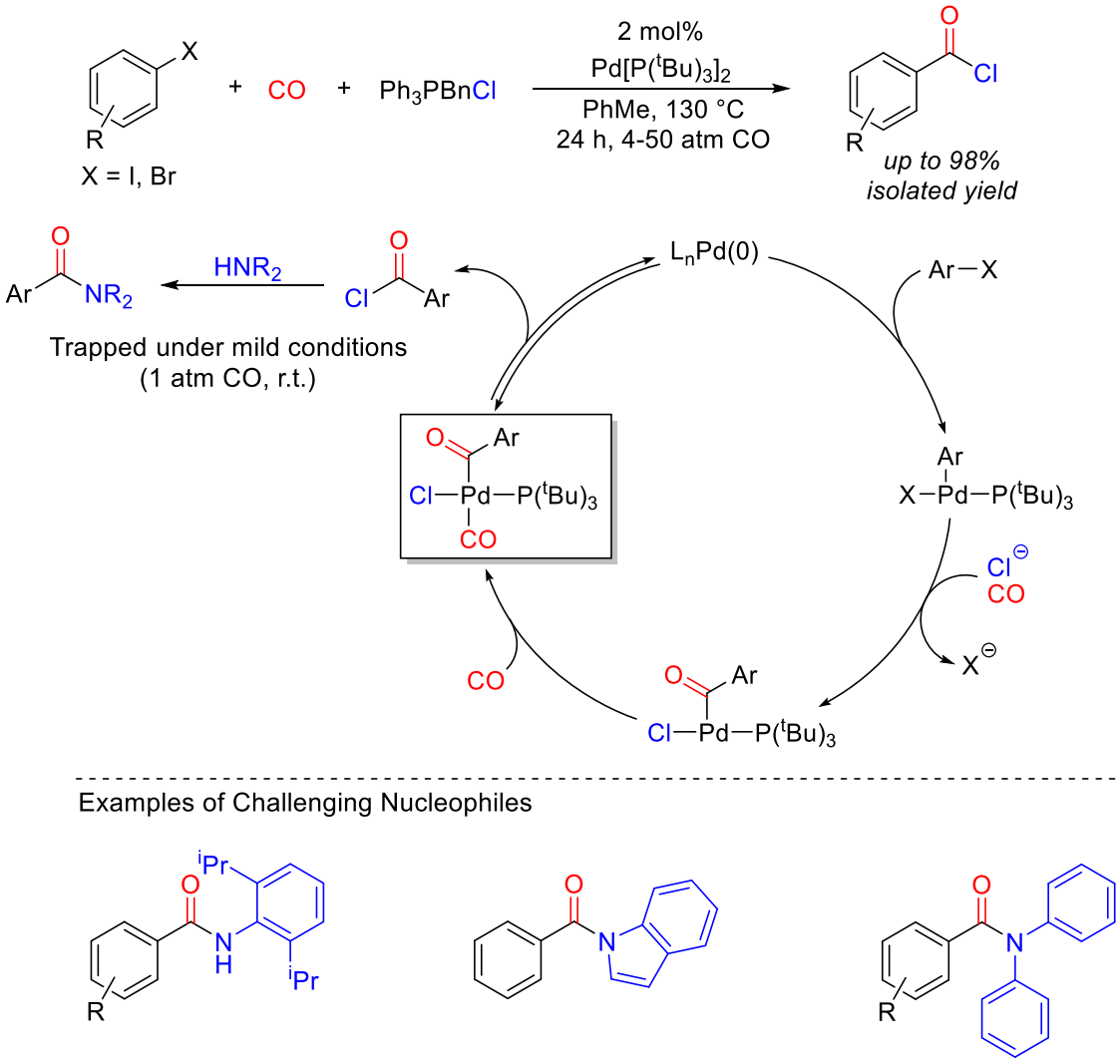
1.3.3.3. Modern Approaches to Acyl Electrophiles via Palladium Catalyzed Carbonylation

There have also been recent efforts to catalytically generate acid chlorides under useful conditions. In 2009, the Lambert group published a further iteration of alkene chlorocarbonylation (Section 1.3.3.1) where the use of an amine-tethered-alkene led to the high yield formation of acid chloride **1.4** (Scheme 1.41).[284] The reaction is postulated to proceed through intramolecular attack of the amine on the palladium coordinated olefin, followed by insertion of CO into the resulting palladium-carbon bond. Reductive elimination produces the acid chloride and palladium(0) which can be reoxidized by the copper(II) chloride to regenerate the catalyst. Coupling this reaction with subsequent Friedel-Crafts Acylation was used to form a range of α-pyrrolidinyl ketones.



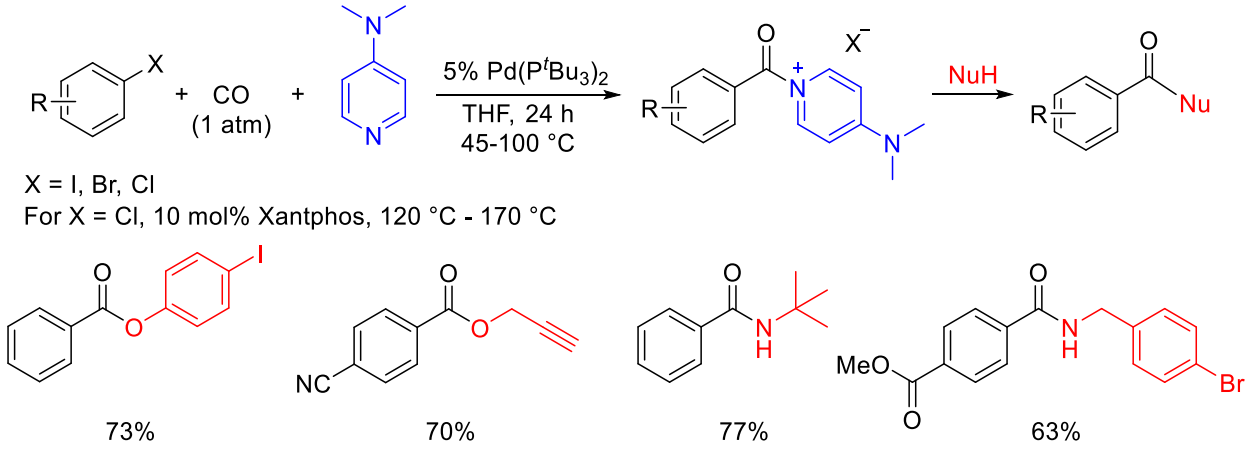
Scheme 1.41. Aminochlorocarbonylation of Alkenes Forming Acyl Chloride

Our laboratory has also made contributions to the area, beginning with the discovery of the synthetically useful palladium-catalyzed chlorocarbonylation of aryl halides to acid chlorides (Scheme 1.42).[160, 285, 286] As previously noted, the acid chloride product is much more reactive towards the Pd(0) catalyst than the aryl halide. To drive this reaction forward, a bulky P^tBu_3 ligand is required. Subsequent DFT analysis showed that this ligand, together with CO coordination, dramatically lowers the barrier to reductive elimination via a combination of steric strain and electronic stabilization of Pd(0). Together this can allow the build-up of acid chlorides at just room temperature from aryl iodides if an acid chloride trap is present. Without a trap, more pressing conditions are required to overcome the rapid re-addition of the acid chloride to Pd(0). Importantly, since nucleophiles no longer needed to coordinate to the catalyst, challenging nucleophiles that do not typically participate in aminocarbonylations are now readily coupled.



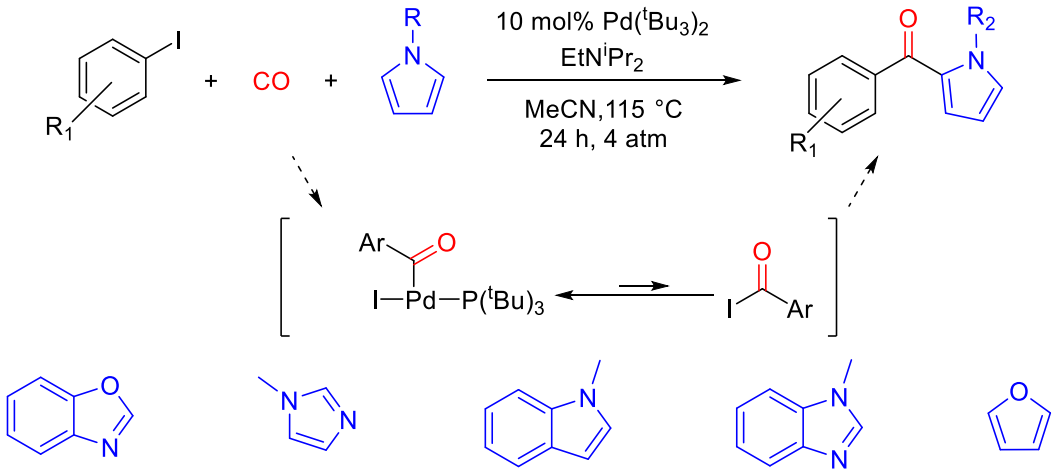
Scheme 1.42. Acid Chloride Formation via Carbonylation of Aryl Halides from the Arndtsen Group

More recent studies have shown that the above mentioned challenge of rapid re-addition of the acid chloride to Pd(0), which slows catalysis, can be overcome by generating another class of electrophile, acyl-DMAP (dimethylaminopyridine) salts (Scheme 1.43).[227, 287] These salts precipitate from non-polar solvents as they form, and allow the formation of reactive acyl electrophiles under much milder conditions. In a subsequent step, nucleophiles that contain functional groups not compatible with palladium can be added.



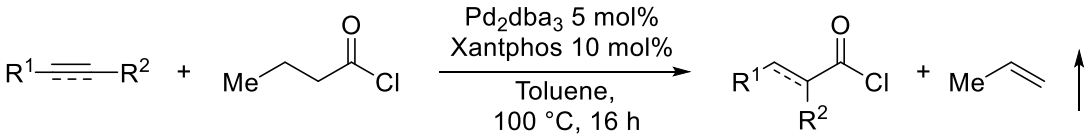
Scheme 1.43. Carbonylative Synthesis of Aroyl DMAP Salts

Our group was able to extend this concept to the *in siu* generation of even more electrophilic acylating agents.[288] In 2015, we reported the carbonylation of aroyl iodides with the same Pd(P^{t}Bu)$_3$ catalyst, but without a chloride additive, allowed the overall C-H functionalization of electron rich heterocycles, to form ketones (Scheme 1.44). Subsequent mechanistic studies suggested this reaction proceeds via the *in situ* formation of aroyl iodide electrophiles. Aroyl iodides are more electrophilic than aroyl chlorides, due in part to their weaker carbon-iodine bond, and therefore more readily react with Pd(0), and thus do not build up as the product of catalysis. However, their *in situ* trapping with heterocycles allowed the synthesis of various substituted ketones.



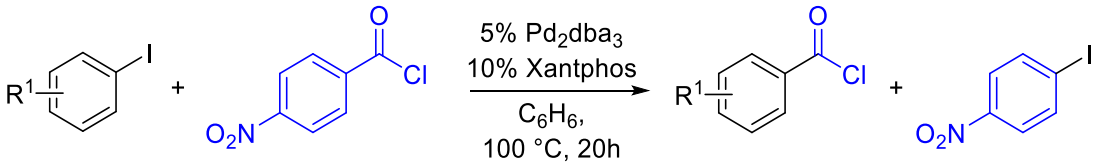
Scheme 1.44. Carbonylative C-H Functionalization of Heterocycles via *in situ* Formation of Aryol Iodides

One potential drawback of creating electrophiles via carbonylation chemistry is the use of gaseous CO, which can pose problems of toxicity and handling, especially when elevated pressures are required. The Morandi group very recently reported the CO-gas-free hydrochlorocarbonylation of olefins and alkynes using an acid chloride as the source of the carbon monoxide. Formally, the acid chloride is produced via the addition of HCl and CO across the alkene or alkyne, but both of these are embedded in the alkyl acid chloride donor (Scheme 1.45),[289] which are transferred through a series of reversible oxidative addition/reductive elimination and insertion steps. The reaction is driven to product by the use of a low-molecular weight donor acid chloride that produces gaseous propene as an easily removed byproduct.



Scheme 1.45. Hydrochlorocarbonylation of Alkenes and Alkynes

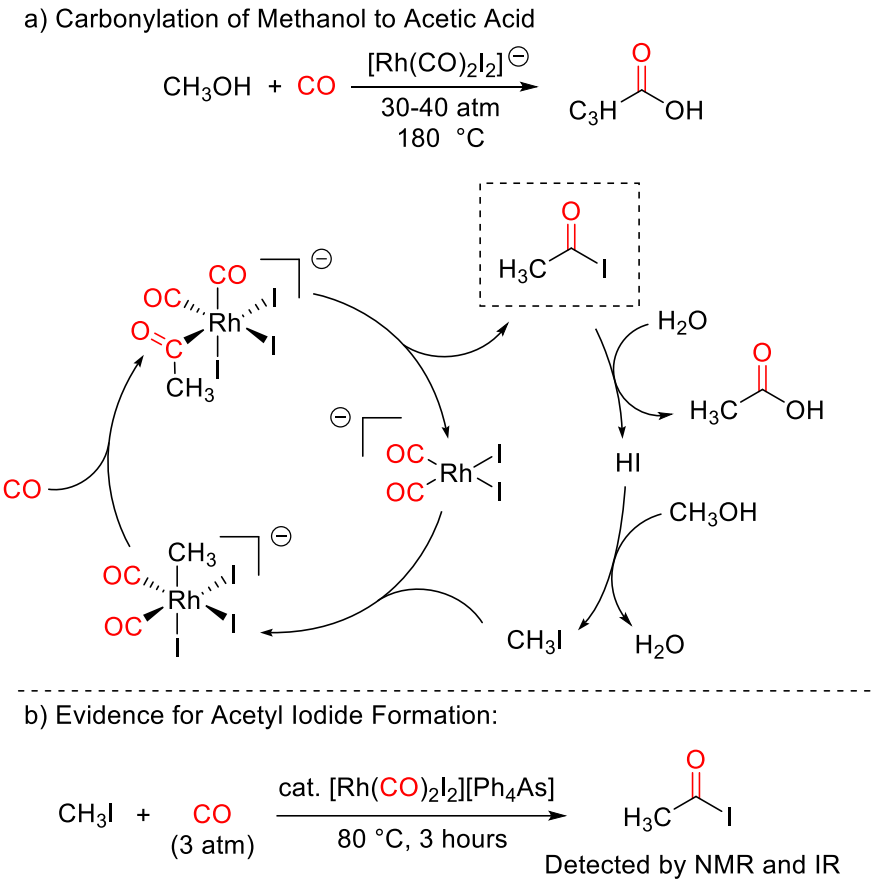
In addition, since both aryl iodide and acid chloride oxidative addition/reductive elimination are reversible,[290-297] palladium can catalyze the overall exchange of Ar-X σ-bonds to build up acid chlorides from aryl iodides (Scheme 1.46). This methodology was simultaneously reported by our group,[298] and the Morandi group,[299] and offers a unique way of generating aroyl electrophiles without gaseous carbon monoxide. While this is an equilibrium, the reaction can be driven toward completion by employing electron poor acid chlorides (*p*-nitrobenzoyl chloride) as donors.



Scheme 1.46. Acid Chloride Generation via σ-Bond Metathesis of Aryl Iodides and Acid Chlorides

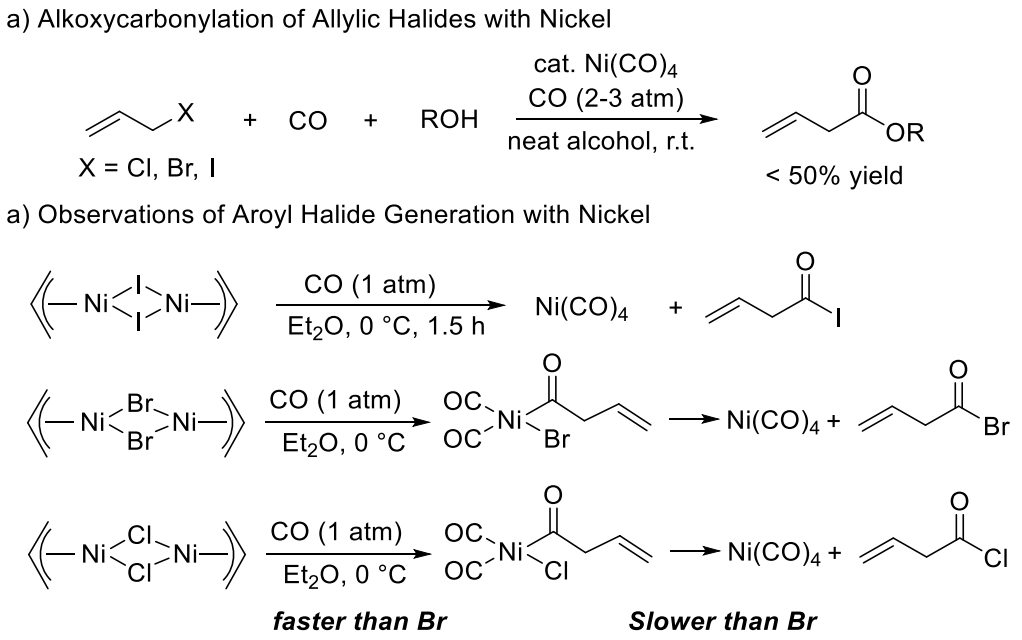
1.3.3.4. Carbonylative Routes to Acyl Electrophiles with Other Metals

While palladium is the most heavily exploited metal for catalytic acyl electrophile synthesis, other metal systems have been reported to catalyze related reactions. Indeed, one of the most successful industrial carbonylation processes, the Cativa/Monsanto carbonylation of methanol to acetic acid, is recognized to proceed through the *in situ* formation of acetyl iodide with rhodium catalyst systems (Scheme 1.47).[300-302] Control experiments show that acetyl iodide can be directly observed as the product of methyl iodide carbonylation under anhydrous conditions with the same anionic rhodium catalyst used for methanol carbonylation (Scheme 1.48b).[300]



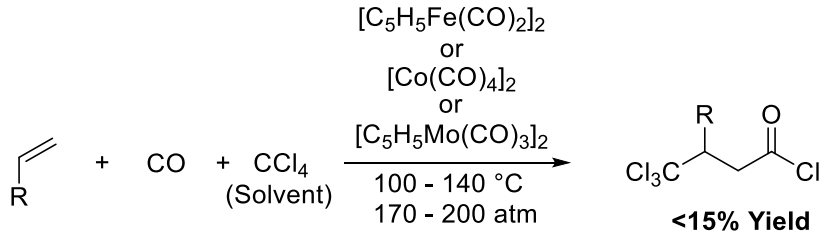
Scheme 1.47. The Monsanto Carbonylation of Methanol via Acetyl Iodide

A number of early studies on the group 10 metals in carbonylations employed nickel catalysts. One example from the 1960s is the carbonylation of allylic systems to from allylic esters (Scheme 1.48a).[303] Heck performed stoichiometric control experiments to aid in the elucidation of the mechanism.[304] When subjecting dimeric nickel allyl halide complexes to excess carbon monoxide, acyl halides (I, Br, Cl) were observed as products (Scheme 1.48b). With the chloride and bromide, an intermediate acyl- nickel complex was observed, but not with the iodide complex. In addition, the nickel acyl intermediate with chloride eliminated acid chloride much slower than with bromide. Together this points to a counterintuitive trend where the formation of the most reactive acid halide is the most favorable (iodide > bromide > chloride). It was postulated that the nickel-acyl iodide is the least stable in this series since it is the most electron poor, which lowers the barrier towards reductive elimination. In all cases, $Ni(CO)_4$ is also produced, which is believed to provide a driving force for the reactions.



Scheme 1.48. Nickel Mediated Generation of Acyl Electrophiles

Metal carbonyl complexes of iron, cobalt, and molybdenum, were also known to catalyze the carbonylative coupling of olefins with carbon tetrachloride solvent to form acid chlorides (Scheme 1.49).[46] Although no mechanistic studies were performed, it was suggested that the first step involves oxidative addition of the carbon-chlorine bond, potentially through a radical mechanism, followed by sequential insertions of olefin and CO and reductive elimination.



Scheme 1.49. Carbonylation of Olefins with First Row Metals

1.4. Overview of Thesis

As discussed in section 1.2, Friedel-Crafts acylations have been heavily explored as the synthetic route to aromatic ketones. Nevertheless, one limit of this reaction is the need for synthetic acylating agents, such as acid chlorides, in concert with high energy Lewis acids, which are needed to create a sufficiently electrophilic reagent capable of reacting with arenes. These limitations in acyl electrophile synthesis can be addressed in part by employing carbon monoxide for their generation. While carbon monoxide can be activated directly with strong acids, or by carbocations generated from alkanes in superacidic media, transition metal catalysis offers a mild approach to use CO for the construction of carbonyl-containing derivatives. As discussed in section 1.3.3, an alternative and somewhat less explored area is the use of transition metal catalysis to create acyl electrophiles from carbon monoxide. However, only moderately electrophilic acylating reagents have been generated, which limits the scope of nucleophilic coupling partners, and thus the breadth of attainable products.

The research described in this thesis demonstrates that potent electrophiles can be generated by the metal catalyzed or mediated reaction of carbon monoxide and stable reagents, capable of reacting with arenes to form ketones. Chapter 2 discusses the generation of aroyl triflates via palladium-catalyzed carbonylation of aryl iodides, in what is the first example of creating such potent acyl electrophiles as the product of catalysis. This led to the first general carbonylative C-H functionalization of arenes to create ketones. Chapter 3 describes how aroyl triflates can also be generated directly from carboxylic acids, in a palladium-free, carbon monoxide promoted decarboxylation. This transformation represents a rare example of a transition-metal free activation of carbon monoxide with bench stable reagents. Mechanistic studies reveal carbon monoxide is ultimately acting as an oxygen atom acceptor and a driving force via the production of carbon dioxide. Chapter 4 shows how the concepts learned during the development of acyl electrophile generation via palladium-catalyzed carbonylation can be applied to the important art of carbon isotope labeling. The reversibility of oxidative addition/reductive elimination and CO insertion/de-insertion were exploited in the design of a carbonyl exchange reaction, which effectively permits scrambling of the carbonyl unit of ^{13}C benzoyl chloride into other acid chlorides. Both palladium and nickel were identified as active catalysts for exchange, while nickel proved to be much more general, tolerating aryl, alkyl, and α-β-unstatured acid chlorides.

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Chapter 2. A General Approach to Intermolecular Carbonylation of Arene C–H Bonds to Ketones Through Catalytic Aroyl Triflate Formation

2.1. Preface

As described in Chapter 1, our lab has previously shown that acid chlorides and acid iodides can be generated from aryl halides via palladium-catalyzed carbonylations. We questioned if this concept could be pushed further to the generation of even more reactive acyl electrophiles that would be capable of reacting with unactivated arenes. This chapter describes the realization of this goal, which entails the catalytic generation of aroyl triflates from aryl iodides. These products are exceptionally potent and capable of engaging in Friedel-Crafts acylation reactions with simple arenes, such as benzene. This led to the first general platform for the carbonylative C-H functionalization of arenes to form ketones. Contrary to previous mechanistic studies on catalytic acyl halide formation conducted in our lab, aroyl triflate reductive elimination is inhibited by phosphine ligands, and instead relies on the generation of an extremely electron poor CO-ligated Pd(II) catalyst. This work has been published in *Nature Chemistry* (**2018**, *10*, 193). Dr. Gerardo M. Torres performed the stoichiometric experiments with *p*-tolylCOPd(P^tBu_3)OTf. Dr. Gerardo M. Torres, Dr. Jevgenijs Tjutrins, Nina Liu, and Omkar Kulkarni helped make several of the compounds in Table 2.1

2.2. Introduction

The generation of reactive electrophiles is one of the cornerstones of traditional synthetic chemistry. A powerful illustration of this is in Friedel–Crafts reactions, wherein the creation of sufficiently high-energy acylating reagents can lead to the functionalization of even the unactivated aromatic C–H bonds (Figure 2.1a).[1-2] The breadth and reliability of Friedel–Crafts acylations has made it a mainstay in the synthetic organic repertoire for the assembly of ketones, and recent advances have expanded the scope of these reactions, as well as offered novel approaches to control product selectivity.[3-6] Nevertheless, an intrinsic limitation of Friedel–Crafts chemistry is the required initial generation of the electrophilic acylating compounds themselves. This usually entails the use of reactive reagents (for example, $SOCl_2$, PCl_3 and strong Lewis acids)

that are synthetic, high energy and create significant chemical waste. The reactivity of acylating reagents also leads to significant challenges in their handling and functional group compatibility.

In this regard, transition-metal-catalyzed C–H bond functionalization has rapidly evolved over the past decade to have tremendous impact.[7-12] Relative to stoichiometric Friedel–Crafts reactions, metal-catalyzed approaches can use benign reagents to functionalize traditionally unreactive C–H bonds, generate minimal waste and often display high functional group compatibility. Although metal-catalyzed C–H functionalization can be advantageous, there remain a number of limitations in this chemistry relative to classical electrophilic substitution reactions. For example, the catalytic functionalization of simple arenes can often require substrate activation, high catalyst or substrate concentrations, or the presence of directing groups in order to proceed with high efficiency.[13-14] In addition, the incorporation of reactive functionalities into catalytic C–H derivatization platforms can be plagued by catalyst inhibition. An important example is in the carbonylative synthesis of ketones (Figure 2.1b). The palladium-catalyzed carbonylative C–H functionalization of arenes to form esters, amides and carboxylic acids was pioneered by Fujiwara and co-workers over two decades ago,[15] and has seen significant recent progress.[16–20] In contrast, the intermolecular carbonylative coupling with simple arenes to generate valuable ketones is not known, and has to date required either intramolecular reactions or the use of acidic/activated substrates, as shown by the groups of Larock, Beller, Skrydstrup, Lei and others.[21–26] This has been attributed, in part, to the common mechanistic pathway for palladium-based C–H functionalization, in which the carboxylate reagents often used in the activation of C–H bonds can react with the palladium–acyl intermediate much more rapidly than with arenes (Figure 2.1c). Instead, the formation of ketones by carbonylations typically requires coupling with pre-synthesized organometallic agents.[27]

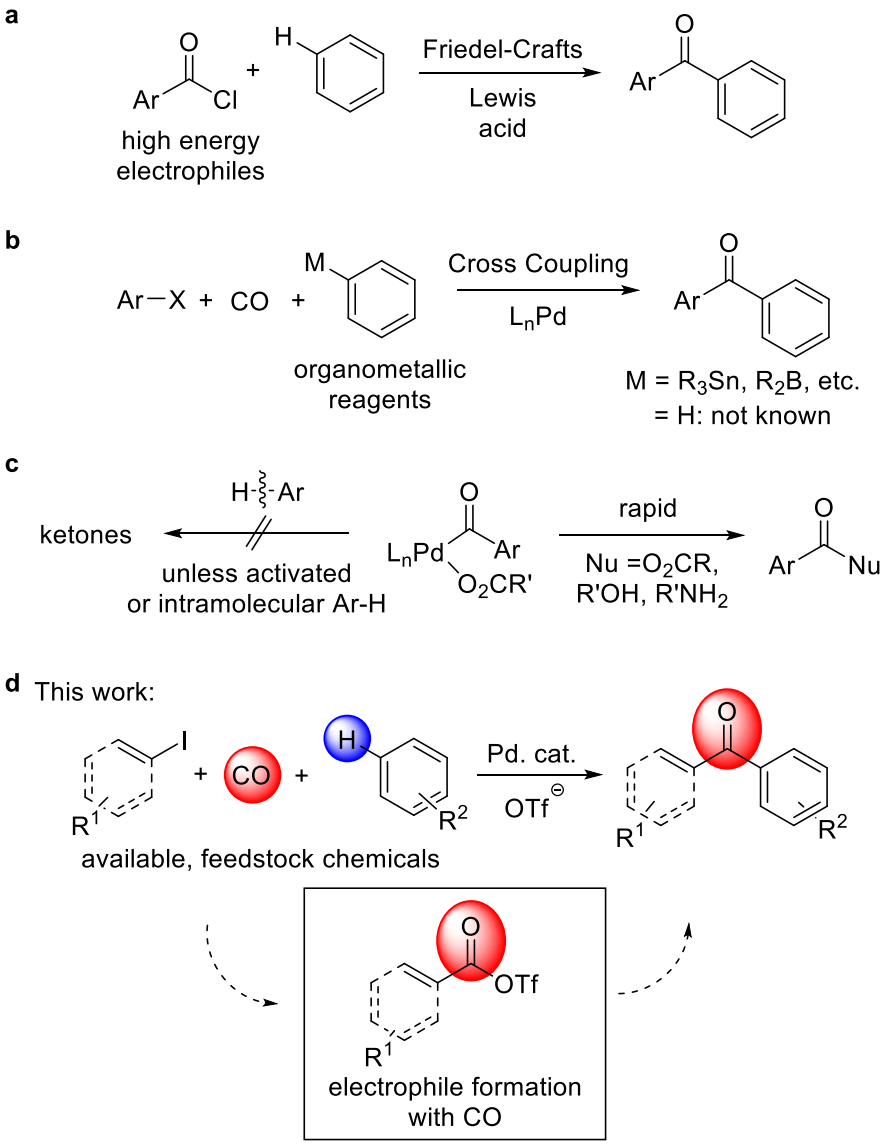


Figure 2.1. Comparison of the Classical Approaches to Ketone Synthesis with the Palladium-Catalyzed Carbonylative C–H Bond Functionalization Reaction

In considering these issues, we questioned if metal catalyzed carbonylations might offer an alternative approach to arene C–H bond functionalization, in which, rather than using transition metals as the active bond-functionalizing agent, carbon monoxide might instead be employed to drive the build-up of potent organic electrophiles capable of reacting with arenes (Fig. 1d). This could provide a method to combine the attractive features of transition-metal catalysis (available reagents, functional group compatibility and atom economy) with that of Friedel–Crafts chemistry

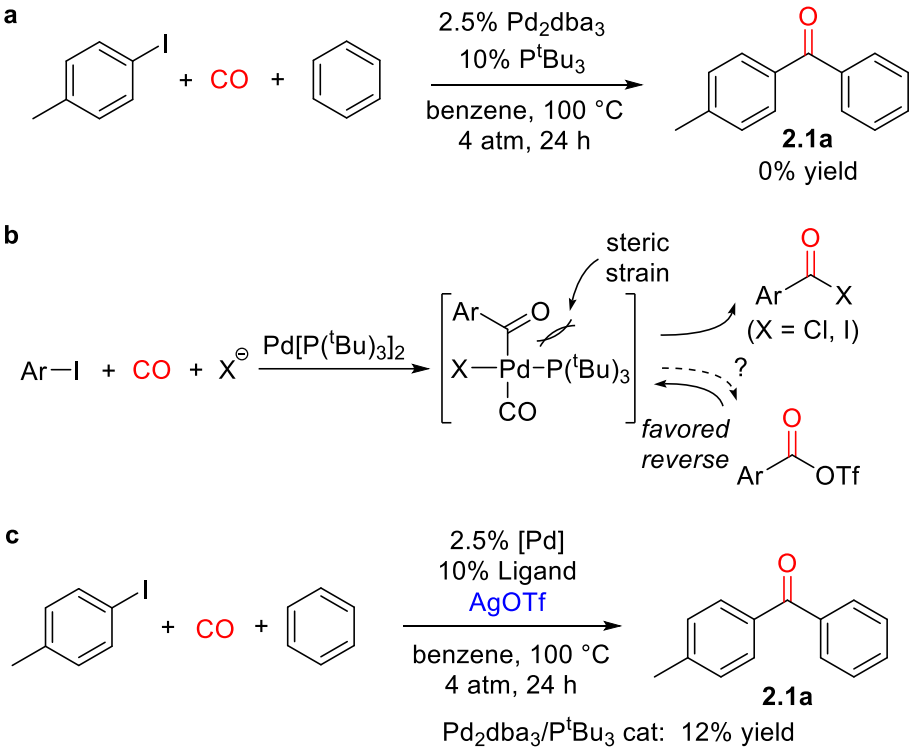
(high reactivity, intermolecular and electrophilic selectivity). The development of this transformation would require a catalyst that can mediate the currently unknown reductive elimination of an electrophile sufficiently reactive to functionalize simple arenes, in contrast with the highly favoured and well-established reverse oxidative addition of acylating electrophiles to palladium.[28,29] We describe below our studies towards this goal. These have led to the discovery of a palladium-catalysed platform to perform the carbonylative C–H functionalization of arenes to form ketones directly from broadly available and stable reagents (aryl halides, arenes and CO). This transformation occurs in common solvents, with low catalyst loadings, uses simple palladium catalysts and illustrates how carbonylation reactions can be employed efficiently to build-up potent electrophilic acylating agents: aroyl triflates.

2.3. Results and Discussion

The catalytic formation of organic electrophiles sufficiently reactive to derivatize aromatic C–H bonds, yet doing so from stable and available substrates, at first glance appears energetically challenging. However, carbonylations may provide a unique entry to such systems. Carbon monoxide is an inexpensive feedstock chemical broadly employed in the assembly of carbonyl-containing products.[30,31] In addition, a less-appreciated feature of carbon monoxide is its energetics, in which the conversion of CO into a carbonyl-containing product is often highly exergonic (by up to 40 kcal/mol).[32] We have recently exploited this feature to generate aromatic acid chlorides and iodides from aryl halides and CO, with the latter having the ability to functionalize electron-rich N-heterocycles.[33–35] Morandi and co-workers have also shown that alkyl and vinyl acid chlorides can be generated by palladium-catalyzed functional group exchange.[36]

Based on these results, we questioned if the energetics of CO might be taken even further, and be employed to drive the generation of electrophilic acylating agents sufficiently reactive to directly derivatize simple arenes. To probe this potential, our initial studies examined the functionalization of benzene with the Pd/P^{t}Bu$_3$ catalyst system found to allow the formation of acid halides (ArCOX, X = Cl, I). However, no evidence for benzene functionalization was observed, and we instead simply recovered the starting materials (Figure 2.2a). This reactivity mirrors that of aroyl iodides, the presumed intermediate generated from the carbonylation of aryl

iodide, which also cannot directly react with benzene (Figure S2.1). In considering approaches to enhance the electrophilicity, one possibility would be to employ anions that are even more ionizable, such as triflate. Aroyl triflates are exceptionally potent electrophiles that are typically generated in situ for aroylation reactions.[37] Unfortunately, their high reactivity would not only make their reductive elimination challenging, but also lead to their much more rapid readdition to Pd(0) than that of the aryl halide reagent (Figure 2.2b). The screening of many triflate salts in this catalytic reaction did not lead to any reaction (Table S2.1). However, we were pleased to find that the addition of silver triflate resulted in the carbonylative functionalization of benzene into ketone **2.1a** in low yield (12%, Figure 2.2c). Interestingly, further studies showed that a number of phosphine ligands can be employed in this catalytic reaction to generate ketone in comparable yields (Figure 2.2c, entries 2–5). This contrasts with the catalytic formation of acid chlorides and iodides, in which the sterically encumbered P^tBu_3 ligand is critical to drive reductive elimination as a mechanism to relieve strain.[38]



Entry	[Pd]	Ligand	Yield 2.1a
1	Pd_2dba_3	PPh_3	31%
2	Pd_2dba_3	$P(o\text{-Tol})_3$	9%
3	Pd_2dba_3	PCy_3	21%
4	Pd_2dba_3	$P(C_6F_6)_3$	29%
5	$[Pd(allyl)Cl]_2$	-	99%
6	5% $PdCl_2$	-	92%
7	0.0075% $[Pd(allyl)Cl]_2$	-	95%

Figure 2.2. Palladium-catalyst Development for the Intermolecular Carbonylative Coupling of Aryl Iodide and Benzene into Ketones.

a) Attempt at benzene carbonylation by in situ aroyl iodide generation leads to no product. b) Mechanism of catalytic acid halide formation, and the challenge of generating even more potent aroyl triflate electrophiles. c) Catalyst design for arene carbonylation into ketones with AgOTf: p-tolyl iodide (55 mg, 0.25 mmol); Pd_2dba_3 (6 mg, 0.0062 mmol); ligand (0.025 mmol); AgOTf (97 mg, 0.375 mmol); benzene (2 ml); and 4 atm CO. ^{1}H NMR yield. Entry 8 performed in DCE solvent. Cy, cyclohexyl; dba, dibenzylideneacetone.

The origin of the lack of ligand influence can be seen by monitoring the catalytic reaction with P^tBu_3 by ^{1}H and ^{31}P NMR analysis, which shows that P^tBu_3 is rapidly consumed by the strong electrophiles generated in catalysis to form protonated phosphine and various degradation products

(Figure S2.2). As a result, simply removing the phosphine ligand from the reaction and employing palladium(II) salts as catalyst leads to the intermolecular derivatization of benzene in near-quantitative yield (Figure 2.2c, entries 6 and 7). The unusual ability of simple palladium salts with no added ligands to catalyze the high-yield intermolecular functionalization of benzene with CO, aryl iodide and a triflate source raises a number of mechanistic questions. The transformation presumably proceeds through the formation of a palladium–aroyl intermediate from oxidative addition followed by CO insertion (Figure 2.3a). One possibility is that this palladium intermediate may undergo reductive elimination of an aroyl triflate electrophile (path A). However, in the absence of any phosphine to favour elimination, we also considered the potential that the non-phosphine coordinated Pd–COAr intermediate **2.2** may be sufficiently electrophilic to palladate benzene (path B), or the silver complex could itself be involved in C–H bond activation (path C), similar to recent results of Hartwig,[39] Larossa,[40] and Sanford[41] and their co-workers.

To gain some insight into which pathway is operative, a series of mechanistic studies were performed. The competition kinetic isotope effect (KIE) for the reaction is 1.24 (Figure S2.3), which is much lower than that previously observed for arene palladation or the formation of a silver–aryl intermediate (KIE = ~4.5 and 2.3, respectively).[39,40,42] However, it is in line with common C–H/D isotope effects in Friedel–Craft acylations with aroyl triflates (KIE = 1.1–1.4).[43] Even greater evidence for the mechanism can be seen by monitoring the catalytic reaction by NMR analysis. As illustrated in Figure 2.3b, removing benzene from the [Pd(allyl)Cl]2-catalysed reaction of aryl iodide, CO and silver triflate leads to the high-yield generation of the potent electrophile aroyl triflate **2.3a** as an isolable product. As far as we are aware, aroyl triflates have not been observed before as products of palladium catalysis or carbonylation chemistry. The identity of this product was confirmed by both in situ multinuclear NMR analysis and, as shown in Figure 2.3b, X-ray crystallography. The subsequent reaction of this aroyl triflate with benzene occurs in the absence of any catalyst, and with the same KIE as noted above (k_H/k_D) = 1.27 (Figure S2.3), which confirms the viability of path A as the mechanism for the catalytic reaction.

The actual build-up and isolation of **2.3a** is surprising, as its potent electrophilicity would normally be thought to result in its more favoured re-oxidative addition to palladium. For example, the addition of **2.3b** to $Pd(P^tBu_3)_2$ leads to the quantitative formation of the oxidative addition product **2.4b** within minutes at ambient temperature (Figure 2.3c). However, such a rapid oxidative

addition is not necessarily the case with the more electron-deficient, non-ligated palladium salt used as catalyst. By itself, the P^tBu_3-coordinated palladium–aroyl triflate complex **2.4b** does not eliminate aroyl triflate, and slowly decomposes into a range of products in the presence of CO. In contrast, the addition of HOTf to protonate the phosphine and generate in situ a presumably CO-bound palladium intermediate **2.2b** leads to the rapid, near-quantitative elimination of aroyl triflate **2.3b** as a product together with protonated P^tBu_3 (Figure 2.3d). As such, we postulate that the catalytic generation of aroyl triflate in this system is facilitated by the electron-deficient Pd(II) catalyst generated in the presence of CO that can undergo a rapid reductive elimination of even a highly electrophilic product such as **2.3**.

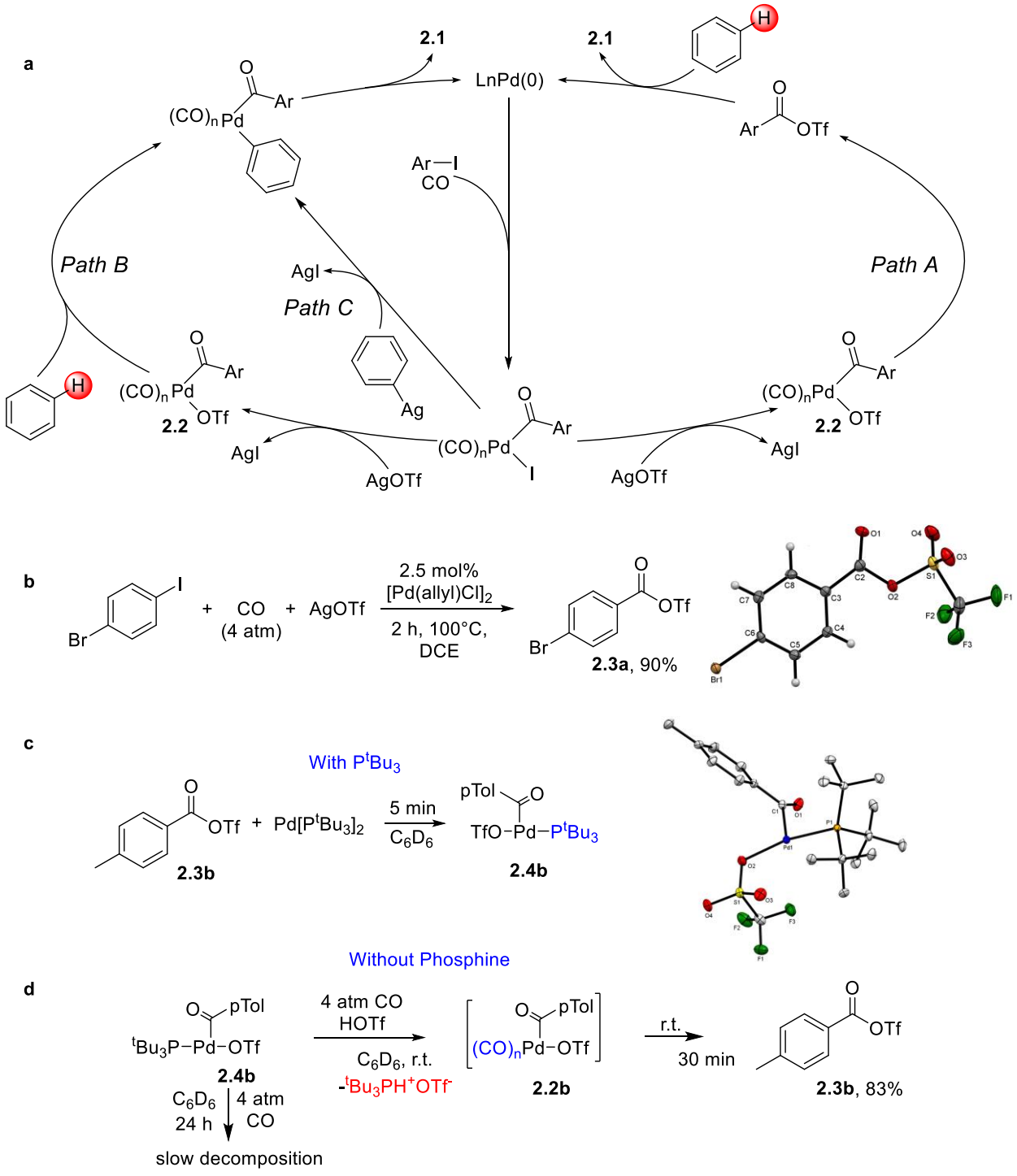


Figure 2.3. Mechanistic Studies Demonstrate this Transformation Proceeds Through the Novel Catalytic Formation of Aroyl Triflate Electrophiles

a) Plausible mechanisms for ketone formation include the in situ formation of aroyl triflate electrophiles (path A), palladium-based arene functionalization (path B) or the formation of a silver–aryl intermediates (path C). Ar, aryl group; L, ligand. b) Removal of benzene from the catalytic reaction leads to the formation of aroyl triflate (ORTEP-style ellipsoids drawn at 50%

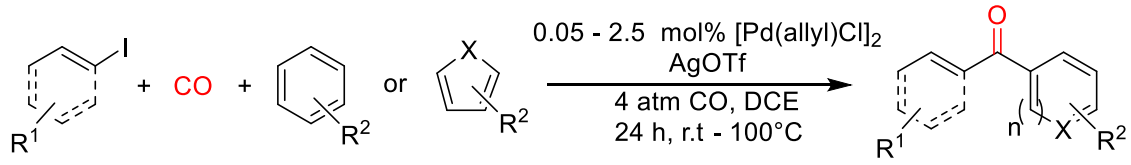
probability). c) Aroyl triflates undergo rapid oxidative addition to Pt Bu3-coordinated palladium. d) The sequestration of P^tBu_3 with HOTf addition leads to the rapid, near-quantitative elimination of aroyl triflate from palladium. r.t., room temperature.

In addition to offering a method to generate high-energy aroyl triflate electrophiles as the products of carbonylation, a notable feature is that the catalytic formation of **2.3** is more rapid than its subsequent reaction with benzene (Figure 2.3b and Figure S2.4). The decoupling of the low-concentration palladium catalyst from the bond-functionalization step leads to a number of useful features. For example, it is straightforward to perform benzene C–H functionalization in common organic solvents (such as 1,2-dichloroethane (DCE) and dichloromethane), rather than in neat arene solvent, because the arene can react with the organic aroyl triflate product built up during catalysis (Table S2.2). The catalyst loadings for arene functionalization can also be significantly lowered, and the reaction proceeds in near-quantitative yields with as little as 0.0075 mol% catalyst (or 150 ppm Pd (Figure 2.2c, entry 8)). As far as we are aware, this represents one of the lowest catalyst loadings known for intermolecular arene C–H functionalization.[44–46]

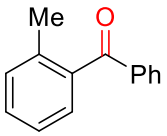
We next examined the generality of this approach to ketone synthesis. Examples are shown in Table 2.1. A wide range of aryl iodides are compatible with this reaction, including those with electron-donating (**2.1a–2.1d**) and electron-withdrawing (**2.1f–2.1m**) substituents. Potentially reactive functionalities can be incorporated, such as esters (**2.1i** and **2.1l**) and nitro substituents (**2.1k**), and the chemoselectivity for aryl iodide oxidative addition makes this chemistry tolerant of other halogen-containing substituents (**2.1g** and **2.1h**). Benzylic C–H bonds, which often exhibit a higher reactivity than arenes in many C–H functionalization systems, are readily tolerated (**2.1a**, **2.1b** and **2.1d**). The reactions can be performed with an equimolar amount of arene with a slightly lower yield (80% **2.1a** (Figure S2.5)). It is also straightforward to tune the arene that is derivatized. Examples include benzene and various electron-rich arenes (**2.1o–2.1z**). With more-elevated temperatures, deactivated arenes can also be employed, such as chlorobenzenes (**2.1aa** and **2.1bb**) and trifluorobenzene (**2.1cc**), with the selectivity mirroring that of Friedel–Crafts chemistry.[1,2] The electrophilicity of the aroyl triflate intermediates in this chemistry can also be applied to functionalize heterocycles, such as pyrroles and indoles, which can react to generate **2.1dd** and **2.1ee**, respectively. Less-activated heterocycles can be similarly functionalized, including furan (**2.1hh**), substituted furans (**2.1ll**), thiophenes (**2.1ii–2.1kk**) or heterocycles with

electron-withdrawing substituents (**2.1ff** and **2.1gg**). Heteroaryl iodides are also viable reagents in this reaction to build-up diheteroaryl ketones (**2.1oo**). Vinyl halides were also explored as substrates. Unlike aryl-substituted acid triflates, vinoyl triflates are often highly labile and difficult to generate by traditional methods.[47] As shown in Table 1, these electrophiles can be formed in situ through palladium-catalysed carbonylations and allow the formation of synthetically useful α,β-unsaturated ketones **2.1pp–2.1ww** with electron-rich arenes. In the case of **2.1uu–2.1ww**, a bulky 2,6-di-*tert*-butylpyridine base is required to remove HOTf.

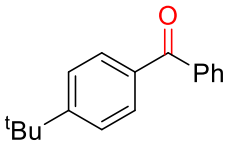
Table 2.1. Scope of the Carbonylative C–H Functionalization of Arenes and Heteroarenes



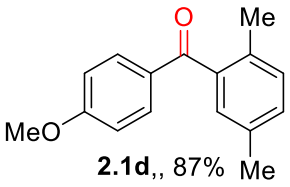
Aryl Iodides



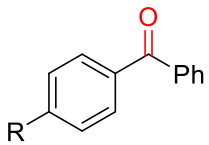
2.1b, 87%



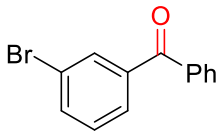
2.1c, 85%



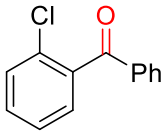
2.1d,, 87%



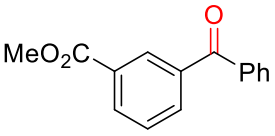
R = H (**2.1e**): 92%
R = SO_3Me (**2.1f**): 71%



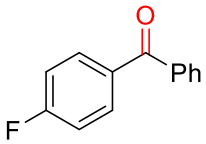
2.1g, 98%



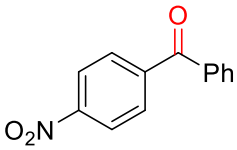
2.1h, 79%



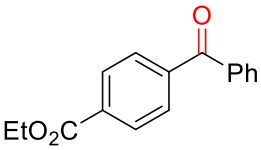
2.1i, 85%



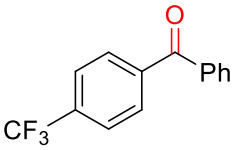
2.1j, 82%



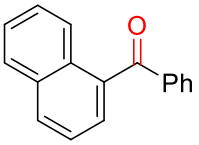
2.1k, 83%



2.1l, 77%

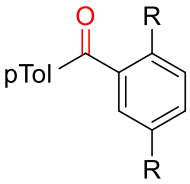


2.1m, 92%

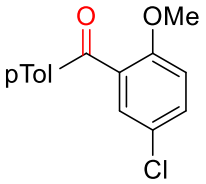


2.1n, 79%

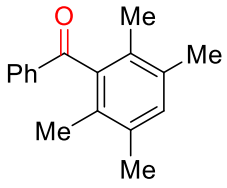
Arenes



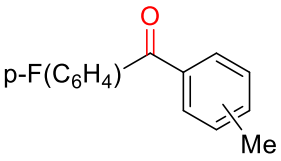
R = Me (**2.1o**): 88%
R = OMe (**2.1p**): 91%



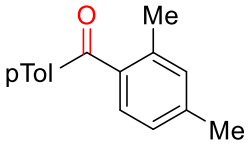
2.1q, 94%



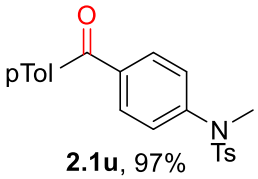
2.1r, 85%



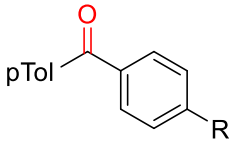
2.1s, 72%
(p:o, 3.7:1)



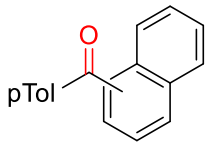
2.1t, 96%



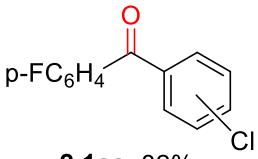
2.1u, 97%
81% recovery of arene



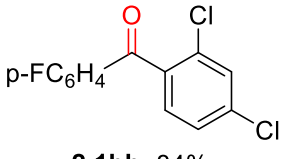
R = SMe (**2.1v**): 85%
R = OMe (**2.1w**): 91%
R = OSO_2Me (**2.1x**): 79%
R = OH (**2.1y**): 47%



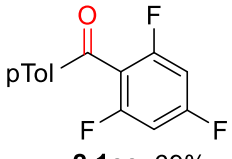
2.1z, 95%
(a:b, 3:1)



2.1aa, 82%
(p:o, 5.5:1)



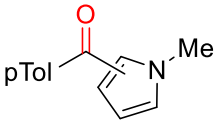
2.1bb, 84%



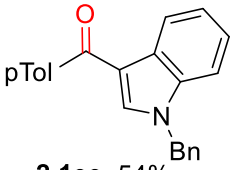
2.1cc, 69%

Table 2.1. Continued

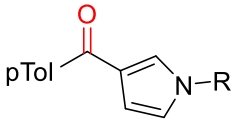
Heterarenes



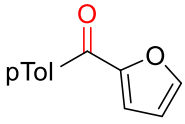
2.1dd, 73%
(2-:3- = 2.3:1)



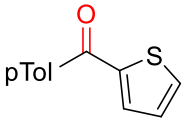
2.1ee, 54%



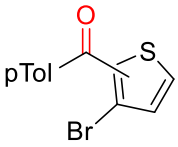
R = Ms (**2.1ff**): 88%
R = Ts (**2.1gg**): 99%



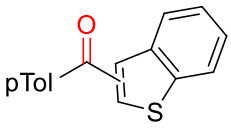
2.1hh, 81%



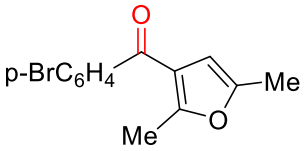
2.1ii, 96%



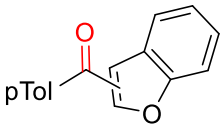
2.1jj, 86%
(5-:2- = 2.6 : 1)



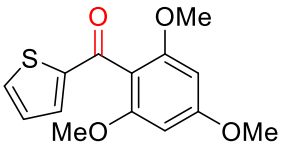
2.1kk, 95%
(a:b, 1:2.7)



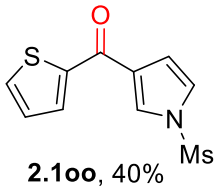
2.1ll, 70%



2.1mm, 58%
(a:b = 3.3:1)

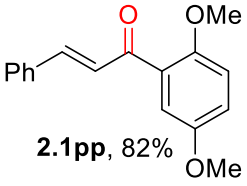


2.1nn, 55%

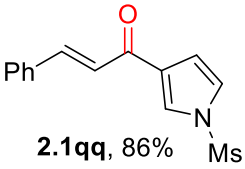


2.1oo, 40%

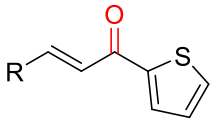
Vinyl Iodides



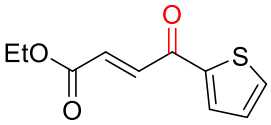
2.1pp, 82%



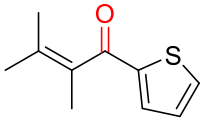
2.1qq, 86%



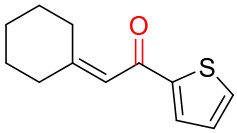
R = Ph (**2.1rr**): 83%
R = fluorenyl (**2.1ss**): 81%



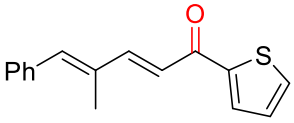
2.1tt, 53%



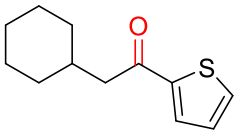
2.1uu, 84%



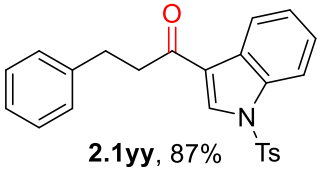
2.1vv, 84%



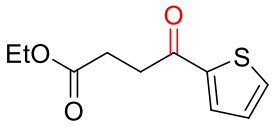
2.1ww, 92%



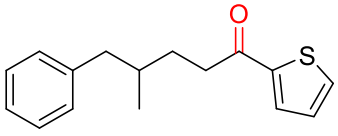
2.1xx, 99%



2.1yy, 87%



2.1zz, 94%



2.1aaa, 98%

Ar–I (1 mmol), arene (2 mmol), [Pd(allyl)Cl]2 (0.2 mg, 5×10^{-4} mmol, from stock solution), AgOTf (385 mg, 1.5 mmol), 4 ml DCE, 4 atm CO, 100 °C, 24 h. **2.1uu–2.1ww** and **2.1u** formed with 2,6-di-*t*-butylpyridine (50 mg, 0.30 mmol). Electron-rich arenes (<80 °C) and vinyl iodides (r.t.) react at lower temperatures; heterocycle added after aroyl triflate formation for **2.1dd**, **2.1ee**, **2.1hh**, **2.1ll** and **2.1mm** (Experimental Section gives full details). Excess arene can be recovered (for example, **2.1u**). **2.1xx–2.1aaa** are generated by hydrogenation of the vinyl ketone (0.15 mmol), Pd/C (38 mg, 5% w/w Pd), 3 atm H_2, 55 °C, 16 h. X = N, O, S; Bn = benzyl; Ts = p-toluenesulfonyl; Ms = methanesulfonyl.

The formation of these products can also be combined with their subsequent reactivity. As an example, coupling the catalytic formation of these α,β-unsaturated ketones with hydrogenation can provide an overall approach to prepare alkyl-substituted ketones (**2.1xx–2.1aaa**). As such, this offers a general method to perform carbonylative arene C–H bond functionalization to generate ketones. Ketones are valuable building blocks in synthetic chemistry, as well as useful products themselves in many areas of application. The ability to generate these compounds from stable and broadly available aryl iodides, CO and arenes can therefore provide an attractive alternative to classical synthetic methods. As an illustration, this transformation can be applied to the targeted formation of pharmaceuticals such as ketoprofen, an effective non-steroidal anti-inflammatory drug,[48] from simply benzene, CO and an aryl iodide in the presence of base to inhibit ester decomposition (Figure 2.4a). Similarly, fenofibrate, a triglyceride and cholesterol regulator,[49] can be generated by the carbonylative coupling of 4-chloroiodobenzene and the appropriate arene. Alternatively, the catalytic formation of ketones can also be coupled with their subsequent reactivity. Performing the carbonylation of arenes with vinyl iodides under mild heating in the absence of base leads to the formal double C–H functionalization of arenes (Figure 2.4b). The latter presumably proceeds through subsequent Friedel–Crafts cyclization from the α,β-unsaturated ketone product under the acidic reaction conditions,[50] and offers a direct method to form indanones from arenes.

Finally, we have probed if this approach can offer a method to build-up electrophiles that are even more reactive. Relative even to triflates, triflimides are exceptional leaving groups. Thus, performing the catalytic carbonylation of aryl iodides in the presence of a triflimide salt can allow the intermolecular carbonylative functionalization of arenes into ketones at ambient temperature (Figure 2.4c). To our knowledge, electrophilic aroyl triflimides have not been reported. Although

these electrophiles are more labile, their formation through carbonylation can even allow the derivatization of deactivated aromatic substrates at temperatures as low as 50 °C and with high regioselectivity. The latter presumably arises from a combination of the lower reaction temperatures and larger triflimide anion that directs this chemistry towards the selective formation of para-derivatized arenes in high yield and under mild conditions.

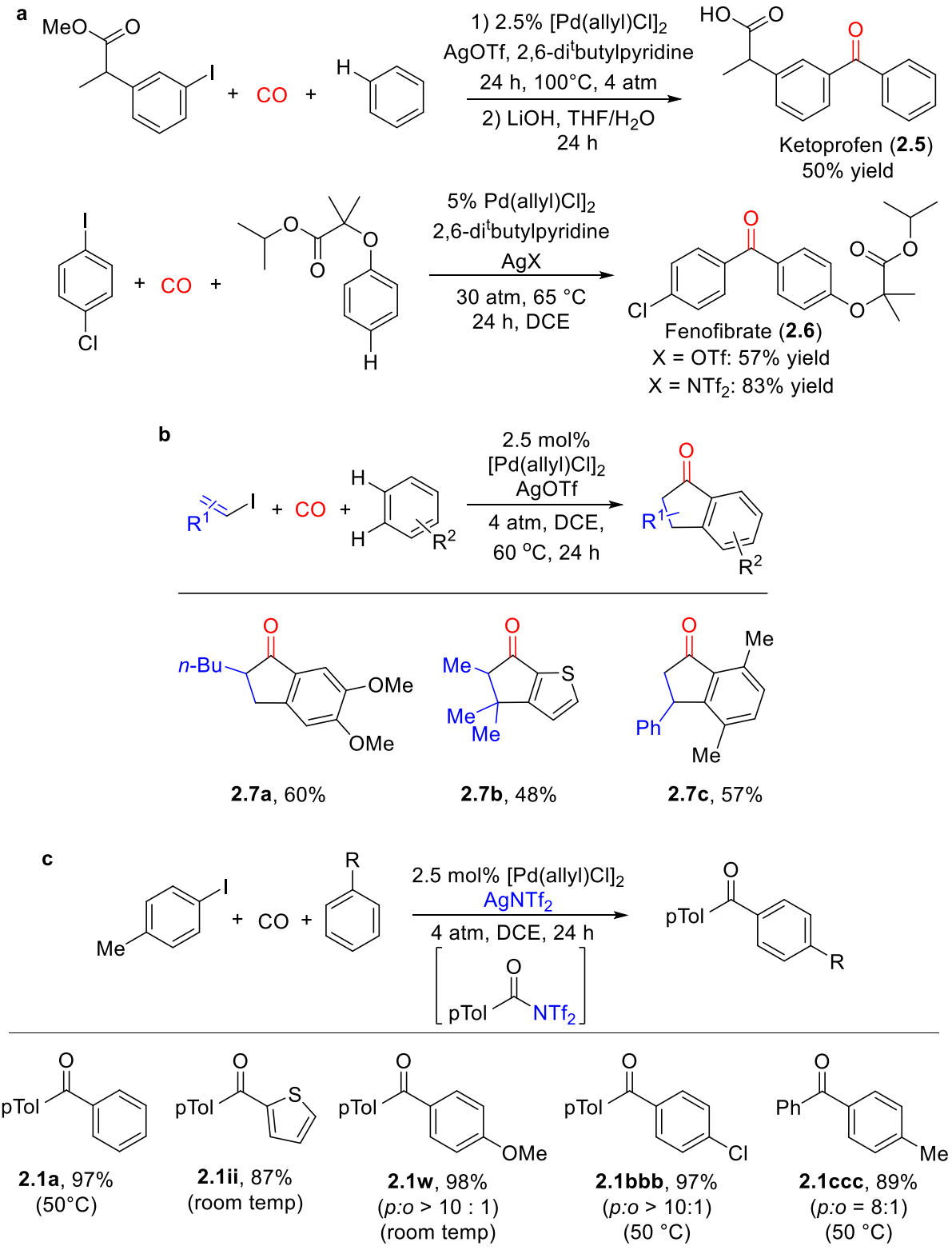


Figure 2.4. Applications of this General Methodology to the Synthesis of Pharmaceutically Relevant Molecules, Double C–H Bond Functionalization and Low-Temperature C–H Bond Functionalization.

a) Synthesis of ketoprofen and fenofibrate by arene carbonylation. b) Palladium-catalysed double C–H functionalization and indanone synthesis with vinyl iodides by in situ acid-mediated cyclization. c) Generation of the even-more electrophilic aroyl triflimides allows the carbonylative C–H functionalization of arenes to proceed at ambient temperature and with high regioselectivity (*p*:*o* selectivity with AgOTf: 2.1bbb, 6:1; 2.1ccc, 5:1)

2.4. Conclusions

In summary, we have developed a conceptually new approach to intermolecular arene C–H functionalization to form ketones. The reaction proceeds through the unprecedented palladium-catalysed formation of aroyl triflates, and demonstrates how carbonylations can be employed to drive the formation of exceptionally reactive electrophiles from available reagents. This opens a method to couple metal-catalysed arene C–H bond functionalization with electrophilic substitution chemistry to generate ketones in high yield with low palladium loadings, and from aryl iodides, CO and arenes. Considering the diverse reactivity of the high-energy acylating agents, we anticipate this approach will find utility as a general platform to functionalize unreactive bonds by carbonylation chemistry.

2.5. Experimental Section

2.5.1. General Considerations

All manipulations were carried in an inert atmosphere glovebox or using standard Schlenk techniques unless stated otherwise. Research grade carbon monoxide (99.99%) was used as received. Solvents were dried over calcium hydride, distilled under argon and stored over activated 4 Å molecular sieves. Pentane was dried using a solvent purifier system and then stored over activated 4 Å molecular sieves in the glovebox. Deuterated solvents were dried over calcium hydride, vacuum transferred and stored over activated 4 Å molecular sieves. Silver triflate was dried by heating under vacuum and then stored in the glovebox. $Pd_2dba_3{\cdot}CHCl_3$ was prepared according to literature procedures and stored at -35 °C in the glovebox to avoid decomposition.[51] N-substituted pyrroles, and N-substituted indoles were prepared according to literature procedures.[52-53] $Pd[(P^tBu)_3]_2$,[54] (E)-(2-iodovinyl)benzene,[55] (E)-2-(2-iodovinyl)-9H-fluorene,[56] 2-iodo-3-methylbut-2-ene,[57] ethyl (Z)-3-iodoacrylate,[58] (iodomethylene)cyclohexane,[56] 2-iodohex-1-ene[59] and silver trifimide[60] were all prepared according to literature procedures. All other

reagents were purchased from commercial suppliers and used as received after thoroughly drying to remove all traces of water. ^{1}H nuclear magnetic resonance (NMR) characterization was performed on 400 and 500 MHz spectrometers (101 and 126 MHz for ^{13}C NMR). High-resolution mass spectra were obtained using a quadrupole-time of flight and an orbitrap detector by direct infusion in positive ESI mode or by atmospheric pressure chemical ionization.

2.5.2. General Synthetic Procedures

Typical Procedure for Catalyst Development (Figure 2.2):

In a glovebox, silver triflate (97 mg, 0.38 mmol) was transferred to a Teflon sealed, thick walled 50 mL glass reaction vessel equipped with a magnetic stir bar. 4-Iodotoluene (55 mg, 0.25 mmol), and $[Pd(allyl)Cl]_2$ (2 mg, 0.006 mmol) were dissolved in benzene (1 mL) and added to the vessel. The vessel was closed, removed from the glovebox, evacuated and backfilled with carbon monoxide three times, and finally pressurized with 4 atm carbon monoxide. The reaction was heated at 100 °C for 24 h with stirring. After the reaction was cooled to room temperature, hexamethylbenzene (7 mg, 0.04 mmol) was added as a standard and the reaction mixture was filter through celite, and the solvent removed *in vacuo*. The yield of ketone **2.1a** (95%) was determined by ^{1}H NMR analysis relative to the external standard.

Procedures for the Synthesis of Ketones in Table 2.1:

All compounds in Table 1 were prepared via one of the three procedures below. See the tabulated NMR data for the specific procedure employed and adjustments regarding time, temperature, and solvent. For compounds **2.1u**, **2.1uu**, **2.1vv**, and **2.1ww** 2,6-di-*tert*-butylpyridine (57 mg, 0.30 mmol) was also added to quench *in situ* generated HOTf and prevent side reactions.

Representative Procedure A: Silver triflate (386 mg, 1.5 mmol) was transferred to a Teflon sealed, thick walled 50 mL glass reaction vessel with a magnetic stir bar. 4-Iodotoluene (218 mg, 1.0 mmol), $[Pd(allyl)Cl]_2$ (0.2 mg, 5×10^{-4} mmol, 575 μL of 0.87 mM stock solution in DCE) and benzene (157 mg, 2.0 mmol) were dissolved in 1,2-dichloroethane to give a final total volume of

4 mL of DCE. The vessel was closed, removed from the glovebox, evacuated and backfilled with carbon monoxide three times, and finally pressurized with 4 atm carbon monoxide. After heating at 100 °C for 24 h with stirring (see tabulated NMR data for the specific conditions for other compounds), the reaction was cooled to room temperature and carbon monoxide was released. The reaction mixture was filtered through celite, eluting with dichloromethane. Saturated $NaHCO_3$ was added and the aqueous layer was extracted with dichloromethane. The combined organic layers were concentrated *in vacuo* and the residue was purified by column chromatography (silica gel, gradient hexane / ethyl acetate 0% to 20%) affording pure diarylketone **2.1a** as a white solid in 82% yield (161 mg).

Representative Procedure B: Silver triflate (386 mg, 1.5 mmol) was transferred to a Teflon sealed, thick walled 50 mL glass reaction vessel equipped with a magnetic stir bar. 4-Iodotoluene (218 mg, 1.0 mmol) and $[Pd(allyl)Cl]_2$ (9 mg, 0.03 mmol) were dissolved in dichloromethane (4 mL) and added. The vessel was closed, removed from the glovebox, evacuated and backfilled with carbon monoxide three times, and finally pressurized with 4 atm carbon monoxide. The reaction was heated at 100 °C for 24 h with stirring. After the reaction was cooled to room temperature, carbon monoxide was released on a Schlenk line under nitrogen and the vessel was brought into the glovebox where N-methyl pyrrole (162 mg, 2.0 mmol) was added and stirred at room temperature for 20 min. The vessel was removed from the glovebox and the reaction mixture was filtered through celite, eluting with dichloromethane. Saturated $NaHCO_3$ was added and the aqueous layer was extracted with dichloromethane. The combined organic layers were concentrated *in vacuo* and the residue was purified by column chromatography (silica gel, gradient hexane / ethyl acetate 0% to 20%) affording pure ketone **2.1dd** as a pale yellow oil in 51% yield (101 mg) and pure ketone **2.1dd'** as a pale yellow oil in 22% yield (45 mg) for a total of 73% isolated yield of both isomers.

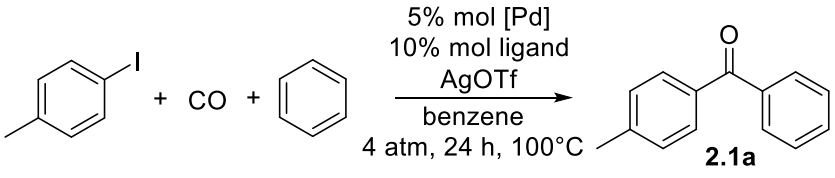
Hydrogenation of Vinyl Ketones: In a glovebox, ketone **2.1ww** (38 mg, 0.15 mmol) was dissolved in 2 mL 1,2-dichloroethane and transferred into a Teflon sealed, thick walled 50 mL glass reaction vessel equipped with a magnetic stir bar. Pd/C (38 mg, 5% w/w Pd) was dry-transferred into the reaction vessel, which was then sealed with a Teflon cap, and taken out of the glovebox. The vessel

was purged with H_2, then charged with 3 atm H_2, and heated at 55 ºC with stirring for 16 h. The vessel was then cooled to room temperature and H_2 was released in a fume hood. The reaction mixture was filtered through silica gel eluting with ethyl acetate, concentrated *in vacuo*, and the resulting oil was triturated with pentane. The solvent was removed under reduced pressure and solvent traces were pumped off in a Schlenk line to afford product **2.1aaa** as a colorless solid in 98% yield (38 mg). No further purification was necessary.

2.5.3 Supplementary Tables and Figures

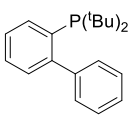
Supplementary Tables* 2.*1*-2.*3*: *Catalyst Development. General Procedure: In a glovebox, the triflate salt (0.38 mmol) was transferred to a Teflon sealed, thick walled 50 mL glass reaction vessel equipped with a magnetic stir bar. Ar-X (0.25 mmol), palladium source (5 mol%) and ligand (if applicable, 0.025 mmol) were dissolved in benzene (1 mL) and added to the vessel. For reactions performed in other solvents (Table S2), benzene (39 mg, 0.50 mmol) was added to 1 mL solvent. The vessel was closed, removed from the glovebox, evacuated and backfilled with carbon monoxide three times, and finally pressurized with carbon monoxide. After heating at 100 °C for 24 hours with stirring, the reaction mixture was cooled to room temperature, hexamethylbenzene (7 mg, 0.04 mmol) was added as a standard, the reaction mixture was filter through celite, and the solvent removed *in vacuo*. The yield of ketone **2.1** was determined by ^{1}H NMR analysis relative to the standard. (Note: for reaction without palladium catalyst, freshly purchased, non-Pd contaminated AgOTf (≥ 99%) must be used, since the reaction can proceed with very low Pd catalyst loading.)

Table S2.1. Influence of Ligands, Palladium Source, and Triflate Salt

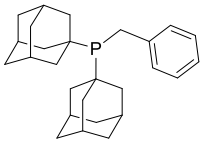


[Pd]	Ligand	MOTf	Yield 2.1a
Pd_2dba_3	P^tBu_3	NaOTf	0%
Pd_2dba_3	P^tBu_3	KOTf	0%

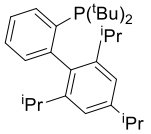
Pd_2dba_3	P^tBu_3	$BaOTf_2$	0%
Pd_2dba_3	P^tBu_3	$Ce(OTf)_4$	0%
Pd_2dba_3	P^tBu_3	TBAOTf	0%
Pd_2dba_3	P^tBu_3	CuOTf	0%
Pd_2dba_3	P^tBu_3	$CuOTf_2$	0%
Pd_2dba_3	P^tBu_3	LiOTf	0%
Pd_2dba_3	P^tBu_3	AgOTf	12%
Pd_2dba_3	-	AgOTf	13%
Pd_2dba_3	PPh_3	AgOTf	31%
Pd_2dba_3	P(*o*-Tol)$_3$	AgOTf	9%
Pd_2dba_3	PCy_3	AgOTf	21%
Pd_2dba_3	$P(C_6F_5)_3$	AgOTf	29%
Pd_2dba_3	P(*p*-$CF_3C_6H_4$)$_3$	AgOTf	32%
Pd_2dba_3	$P(OEt)_3$	AgOTf	4%
Pd_2dba_3	JohnPhos	AgOTf	3%
Pd_2dba_3	Cataxium ABn	AgOTf	15%
Pd_2dba_3	^{t}BuXPhos	AgOTf	10%
Pd_2dba_3	P(O-2,4-di^{t}BuC_6H_3)$_3$	AgOTf	22%
Pd_2dba_3	dppe	AgOTf	0%
Pd_2dba_3	dppf	AgOTf	4%
$[Pd(allyl)Cl]_2$	-	AgOTf	99%
$PdCl_2$	-	AgOTf	92%
$Pd(OAc)_2$	-	AgOTf	92%
-	-	AgOTf	0%



JohnPhos

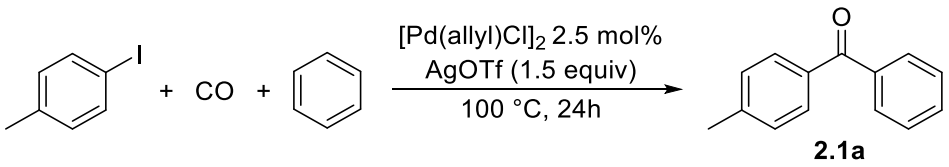


Cataxium ABn



^{t}BuXPhos

Table S2.2. Solvents, CO Pressure, and Catalyst Loading

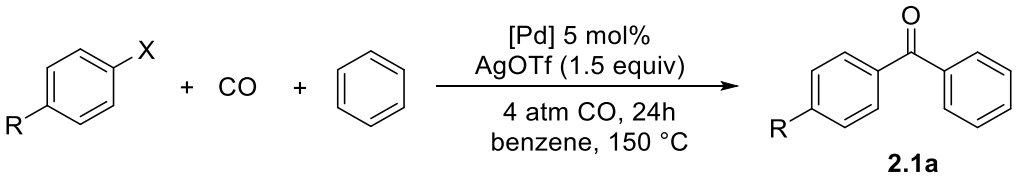


2.1a

Solvent	CO Pressure	Yield 2.1a
CH_3CN	4 atm CO	0%
Pentane	4 atm CO	70%
Dichloromethane	4 atm CO	84%
$PhNO_2$	4 atm CO	75%
CH_3NO_2	4 atm CO	18%
Perfluorohexane	4 atm CO	17%
Sulfolane	4 atm CO	75%
CS_2	4 atm CO	63%
C_6F_6	4 atm CO	96%
1,2-dichloroethane	4 atm CO	99%
1,2-dichloroethane	3 atm CO	90%
1,2-dichloroethane	2 atm CO	90%
1,2-dichloroethane	1 atm CO	77%
1,2-dichloroethane[a]	4 atm CO	99%
1,2-dichloroethane[b]	4 atm CO	96%
1,2-dichloroethane[c]	4 atm CO	95%

[a] 0.1 mol% $[Pd(allyl)Cl]_2$. [b].05 mol% $[Pd(allyl)Cl]_2$. [c].0075 mol% $[Pd(allyl)Cl]_2$.

Table S2.3. Exploration of Aryl Bromide and Aryl Triflate as Substrates



R	X	Pd cat	Yield 2.1a
F	Br	$[Pd(allyl)Cl]_2$	0%
F	Br	(IPr)Pd(allyl)Cl	0%
H	OTf	$[Pd(allyl)Cl]_2$	0%
H	OTf	(IPr)Pd(allyl)Cl	0%
H[a]	OTf	$[Pd(allyl)Cl]_2$	0%
H[a]	OTf	(IPr)Pd(allyl)Cl	0%

[a]Without Silver Triflate

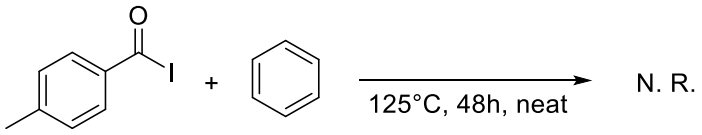


Figure S2.1. Reaction of *p*-$CH_3C_6H_4COI$ and Benzene

In a glovebox, *p*-toluoyl iododde[62] (61 mg, 0.25 mmol) was dissolved in benzene (1 mL) and transferred to a Teflon sealed, thick walled 50 mL glass reaction vessel equipped with a magnetic stir bar. The vessel was closed and removed from the glovebox. After heating at 125 °C for 48 h with stirring, the vessel taken back into the glovebox and hexamethylbenzene (7 mg 0.04 mmol) was added as an external standard. Solvent was removed *in vacuo* and the yield of the remaining aroyl iodide (56%) was determined by ^1H NMR analysis in $CDCl_3$ relative to the external standard. No ketone product was observed.

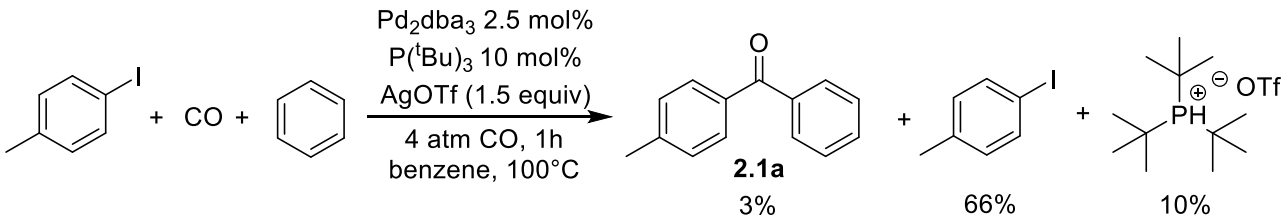


Figure S2.2. Monitoring Catalysis with P^{t}Bu$_3$ by ^{31}P NMR Analysis

In a glovebox, silver triflate (97 mg, 0.38 mmol) was transferred to a Teflon sealed, thick walled 50 mL glass reaction vessel equipped with a magnetic stir bar. 4-Iodotoluene (55 mg, 0.25 mmol), Pd_2dba_3 (7 mg, 0.0063 mmol) and tri-*tert*-butylphosphine (5 mg, 0.025 mmol) were dissolved in benzene (1 mL) and added to the vessel. The vessel was closed, removed from the glovebox, evacuated and backfilled with carbon monoxide three times, and finally pressurized with 4 atm carbon monoxide. After heating at 100 °C for 1 h with stirring, the reaction mixture was cooled to room temperature, carbon monoxide was released on a Schlenk line under nitrogen and the vessel was brought into the glovebox. The reaction mixture was concentrated filtered *in vacuo*. ^{1}H and ^{31}P NMR analysis (C_6D_6) reveals the presence of **2.1a** (3%) and protonated P^{t}Bu$_3$: ^{1}H NMR: δ 5.34 (d, J = 450.8 Hz, 1H), 1.04 (d, J = 15.4 Hz, 27H); ^{31}P NMR: □ 53.5 (10% yield).[61]

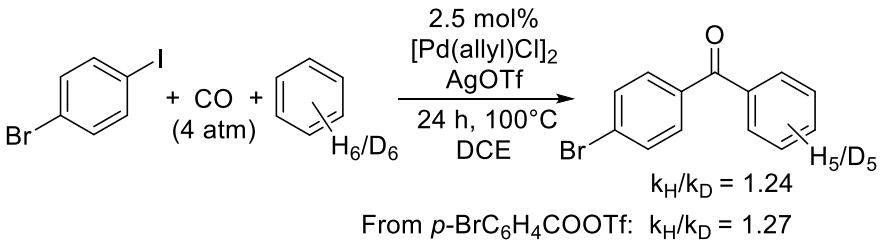


Figure S2.3. Kinetic Isotope Effect Experiments

***Catalytic experiment*:** Silver triflate (386 mg, 1.5 mmol) was transferred to a Teflon sealed, thick

walled 50 mL glass reaction vessel equipped with a magnetic stir bar. 4-Bromoiodobenzene (71 mg, 0.25 mmol) and $[Pd(allyl)Cl]_2$ (2 mg, 0.006 mmol) were dissolved in dichloroethane (1 mL) and added. Benzene (98 mg, 1.3 mmol) and benzene-d_6 (105 mg, 1.23 mmol) were dissolved in dichloroethane (1 mL) and added. The vessel was closed, removed from the glovebox, evacuated and backfilled with carbon monoxide three times, and finally pressurized with 4 atm carbon monoxide. The reaction was heated at 100 °C for 24 h with stirring. After the reaction was cooled to room temperature, carbon monoxide was released. The reaction mixture was passed through celite, eluting with dichloromethane. Saturated $NaHCO_3$ was added and the aqueous layer was extracted with dichloromethane. The combined organic layers were passed through a silica gel and concentrated *in vacuo* to afford a light brown solid. This sample was analyzed by HRMS (average of three runs) to determine the ratio of non-deuterated/deuterated 4-bromobenzophenone. This experiment was repeated in triplicate and the average ratio of non-deuterated/deuterated product was determined to be 1.24.

Stoichiometric Reaction of Acid Triflate with C_6H_6/C_6D_6: *p*-bromobenzoyl triflate **2.3a** (83 mg, 0.25 mmol) was dissolved in dichloroethane (1 mL) and transferred to a Teflon sealed, thick walled 50 mL glass reaction vessel equipped with a magnetic stir bar. Benzene (98 mg, 1.3 mmol) and benzene-d_6 (105 mg, 1.3 mmol) were dissolved in dichloroethane (1 mL) and added. The vessel was closed, removed from the glovebox, and was heated at 100 °C for 24 h with stirring. After the reaction was cooled to room temperature, dichloromethane was added and the reaction mixture was passed through celite. Saturated $NaHCO_3$ was added and the aqueous layer was extracted with dichloromethane. The combined organic layers were passed through a silica gel and concentrated *in vacuo* to afford a light brown solid. This sample was analyzed by HRMS to determine the ratio of non-deuterated/deuterated 4-bromobenzophenone. This experiment was repeated in triplicate and the average ratio of non-deuterated/deuterated product was determined to be 1.27.

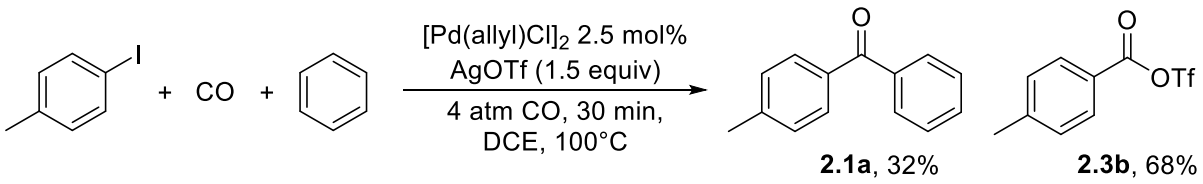


Figure S2.4. Catalytic Build-Up of Aroyl Triflate

Silver triflate (97 mg, 0.38 mmol) was transferred to a Teflon sealed, thick walled 50 mL glass reaction vessel equipped with a magnetic stir bar. 4-iodotoluene (55 mg, 0.25 mmol) and $[Pd(allyl)Cl]_2$ (2 mg, 0.0063 mmol) were dissolved in dichloroethane (1 mL) and added. The vessel was closed, removed from the glovebox, evacuated and backfilled with carbon monoxide three times, and finally pressurized with 4 atm carbon monoxide. After heating at 100 ° for 30 min with stirring, the reaction was cooled to room temperature, the carbon monoxide was released on a Schlenk line under nitrogen, and the vessel was brought into the glovebox. Hexamethylbenzene (6 mg, 0.04 mmol) was added as a standard and the reaction mixture was filter through celite. ^1H NMR analysis showed the build-up of aroyl triflate **2.3b** (68%) at early reaction times together with ketone **2.1a** (32%) .

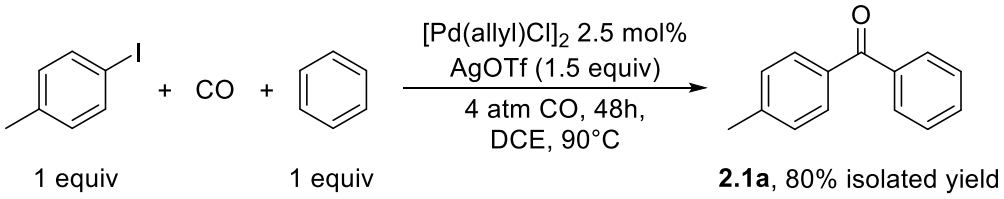


Figure S2.5. Reaction with a 1:1 ratio of Aryl iodide to Arene

(prepared according to procedure A using 0.25 mmol of the aryl iodide and arene at 90ºC)

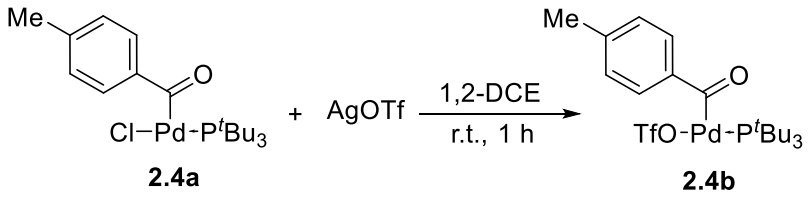
2.5.4. Catalytic Formation of Aroyl Triflate 2.3a

In Situ Formation of 2.3a: Silver triflate (97 mg, 0.38 mmol) was transferred to a Teflon sealed, thick walled 50 mL glass reaction vessel equipped with a magnetic stir bar. 4-bromoiodobenzene (71 mg, 0.25 mmol) and $[Pd(allyl)Cl]_2$ (2 mg, 0.0063 mmol) were dissolved in dichloromethane (1 mL) and added. The vessel was closed, removed from the glovebox, evacuated and backfilled with carbon monoxide three times, and finally pressurized with 4 atm carbon monoxide. After heating at 100 °C for 2 h with stirring, the reaction was cooled to room temperature, the carbon monoxide was released on a Schlenk line under nitrogen, and the vessel was brought into the glovebox. Hexamethylbenzene (6 mg, 0.04 mmol) was added as a standard and the reaction mixture was filter through celite. The yield of aroyl triflate **2.3a** (90%) was determined by ^{1}H NMR analysis relative to the external standard.

*In situ ^{1}H NMR spectra of **2.3a***: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.7 Hz, 2H), 7.75 (d, J = 8.7 Hz, 2H).

Synthesis and Isolation of 2.3a: Silver triflate (386 mg, 1.5 mmol) was transferred to a Teflon sealed, thick walled 50 mL glass reaction vessel equipped with a magnetic stir bar. 4-Bromoiodobenzene (282 mg, 1.0 mmol) and $[Pd(allyl)Cl]_2$ (9 mg, 0.03 mmol) were dissolved in dichloromethane (4 mL) and added. The vessel was closed, removed from the glovebox, evacuated and backfilled with carbon monoxide three times, and finally pressurized with 4 atm carbon monoxide. After heating at 100 °C for 48 h with stirring, the reaction was cooled to room temperature, the carbon monoxide was released on a Schlenk line under nitrogen, and the vessel was brought into the glovebox. All volatiles were removed *in vacuo*, pentane (15 mL) was added, and the solution placed in a glovebox -35 ^{o}C freezer overnight to precipitate the product. The supernatant was decanted and residual pentane was removed in vacuo to afford *p*-bromobenzoyl triflate as a pale yellow solid in 82% yield (273 mg). The solid was redissolved in pentane (5 mL) and placed in the glovebox -35 ^{o}C freezer to grow crystals for X-ray diffraction. After two days, dark yellow crystals were obtained. The X-ray crystal structure is available at the Cambridge Crystallographic Data Centre (CCDC) under the deposition number 1513679.

2.5.5. Synthesis of p-TolylCOPd(P^{t}Bu$_3$)OTf

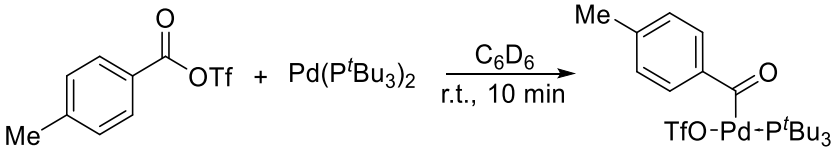


2.4a **2.4b**

In a glovebox, *p*-tolylCOPd(P^{t}Bu$_3$)Cl, synthesized according to literature procedure,[63] (124 mg, 0.27 mmol) was weighed in a vial equipped with a magnetic stir bar. The complex was dissolved in 2 mL 1,2-dichloroethane. To this solution, AgOTf (76 mg, 0.30 mmol) was added and the mixture was stirred for 1 hour at room temperature. The resulting suspension was filtered through celite to afford a yellow solution. The solvent was removed *in vacuo* and the resulting oil was triturated with pentanes (1 mL). Solvent traces were removed under vacuum and product **2.4b** was obtained as a dark yellow solid in 87% yield (134 mg, 0.23 mmol).

Crystals of **2.4b** were grown for X-ray diffraction by vapor diffusion of pentane into a solution of the complex in 1,2-dichloroethane (50 mg in 250 µL) at -33 ºC for 3 days which resulted in dark yellow crystals. The X-ray crystal structure is available at the Cambridge Crystallographic Data Centre (CCDC) under the deposition number 1554343.

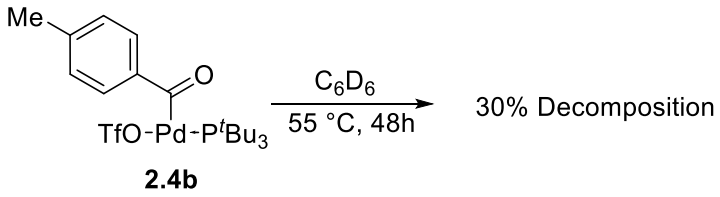
2.5.6. Mechanistic Experiments with p-TolylCOPd(PtBu3)OTf:



2.3b **2.4b**

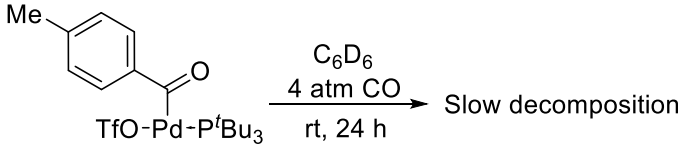
In a glovebox, *p*-tolylCOOTf (12 mg, 0.044 mmol), Pd(P^{t}Bu$_3$)$_2$ (10 mg, 0.020 mmol) and cyclohexane standard (2 mg, 0.02 mmol) were dissolved in C_6D_6 (1 mL). The resulting solution

was transferred into a J-Young NMR tube, which was capped and taken out of the glovebox. ^{1}H, ^{31}P, and ^{19}F NMR analysis shows the formation of *p*-tolylCOPd(P^tBu_3)OTf in quantitative yield within 10 min.



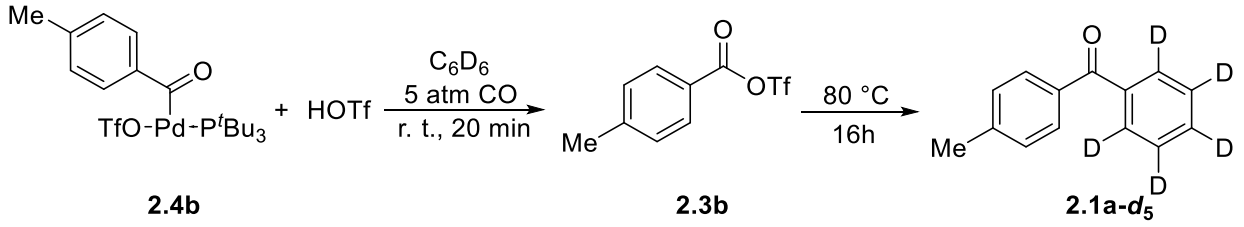
2.4b

In a glovebox, *p*-tolylCOPd(P^tBu_3)OTf (10 mg, 0.017 mmol) and dimethylsulfone standard (1 mg, 0.01 mmol) were dissolved in C_6D_6 (750 µL). The resulting solution was transferred into a J-Young NMR, which was capped and taken out of the glovebox. The tube was heated at 55 ºC in an oil bath for 48 hours and the reaction was monitored by ^{1}H, ^{31}P, and ^{19}F NMR analysis. After 48 hours, the majority of **2.4b** remains in solution (70%) together with a small amount of palladium precipitate. No ArCOOTf (**2.3b**) is observed.



2.4b

In a glovebox, *p*-tolylCOPd(P^tBu_3)OTf (10 mg, 0.017 mmol) and hexamethylbenzene standard (1.4 mg, 0.09 mmol) were dissolved in C_6D_6 (750 µL). The resulting solution was transferred into a J-Young NMR, which was capped and taken out of the glovebox. The NMR tube was connected to a Schlenk line via a glass adapter and placed in liquid nitrogen. The Schlenk line was evacuated and backfilled with CO three times and the headspace in the NMR was evacuated. 4 atm of CO were condensed in the NMR tube. The reaction was monitored by ^{1}H, ^{31}P, and ^{19}F NMR analysis at ambient temperature. After 24 h, NMR analysis shows 56% of **2.4b** remains, together with the growth of various ^{31}P NMR signals (δ 60.7, 55.3, 46.9), with no evidence for ArCOOTf formation.



2.4b **2.3b** **2.1a-d_5**

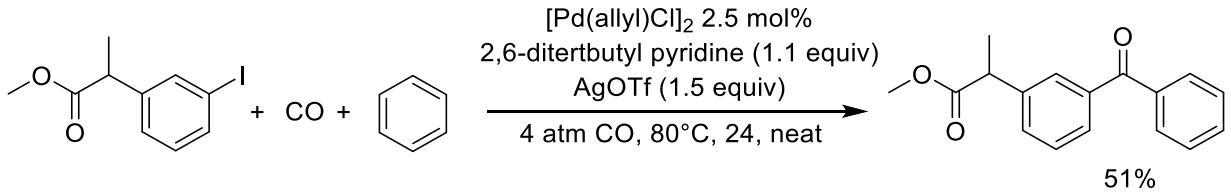
In a glovebox, triflic acid (3 mg, 0.02 mmol) and cyclohexane standard (1 mg, 0.02 mmol) were dissolved in C_6D_6 (750 µL) and the resulting solution was transferred into a J-Young NMR tube. The solution was frozen at -33 ºC inside the glovebox freezer. *p*-TolylCOPd(P^{t}Bu$_3$)OTf (10 mg, 0.017 mmol) was then dry transferred on top of the frozen solution. The NMR tube was quickly taken out of the glovebox and placed in liquid nitrogen. The NMR tube was connected to a Schlenk line via a glass adapter while remaining frozen in liquid nitrogen. The headspace of the NMR tube evacuated and backfilled with CO three times, then 5 atm of CO was condensed into the NMR tube. The contents of the NMR tube was then thawed, and the reaction monitored by ^{1}H, ^{31}P, and ^{19}F NMR analysis. After 20 minutes, *p*-tolylCOOTf was formed in 83% yield, and ^{31}P NMR shows only protonated phosphine (δ 52.6 ppm). The presence of acid triflate was corroborated by comparing the ^{1}H and ^{13}C NMR of the reaction mixture with the spectra of independently synthesized *p*-tolylCOOTf by literature procedure.[64]

Pure acid triflate: ^{1}H NMR (500 MHz, C_6D_6) δ 7.48 (d, *J* = 8.4 Hz, 2H), 6.56 (d, *J* = 7.9 Hz, 2H), 1.79 (s, 3H). ^{13}C NMR (101 MHz, C_6D_6) δ 156.3, 147.9, 131.8, 130.0, 121.7, 119.3 (q, J = 320.2 Hz), 21.5.

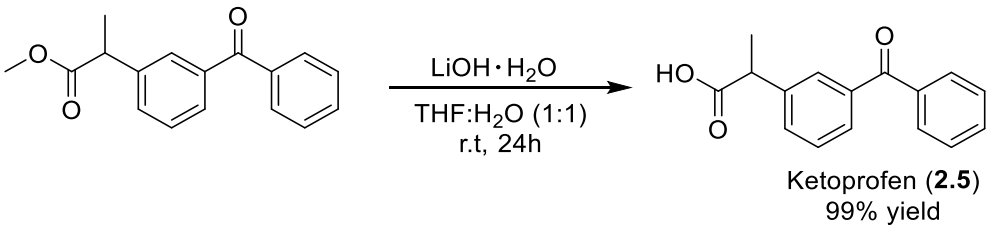
Reaction mixture: ^{1}H NMR (400 MHz, C_6D_6) δ 7.47 (d, *J* = 8.4 Hz, 2H), 6.54 (d, *J* = 8.0 Hz, 2H), 1.77 (s, 3H). ^{13}C NMR (101 MHz, C_6D_6) δ 156.3, 147.8, 131.8, 130.0, 121.8, 21.5. (The CF_3 quartet was not clearly visible)

The NMR tube was then heated at 80 ºC in an oil bath for 16 h. ^{1}H NMR analysis shows the complete consumption of the acid triflate and the formation of ketone **2.1a**-d_5 in 88% ^{1}H NMR yield (also GC-MS: m/z of 201.1).

2.5.7. Synthesis of Ketoprofen

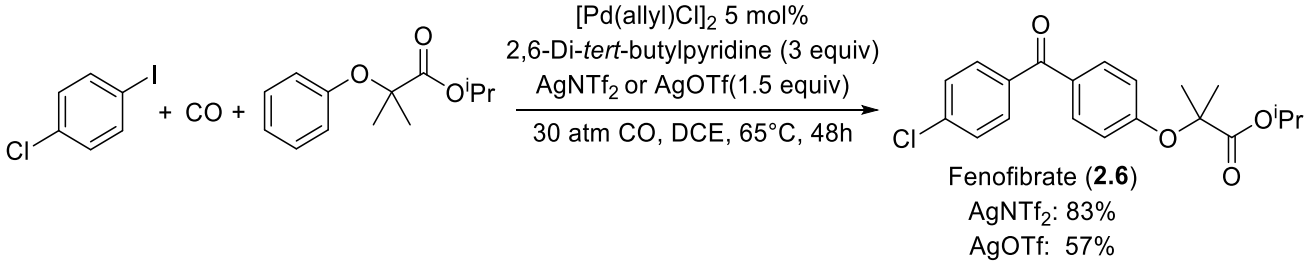


Ketoprofen Methyl Ester: Silver triflate (193 mg, 0.75 mmol) was transferred to a Teflon sealed, thick walled 50 mL glass reaction vessel equipped with a magnetic stir bar. Methyl 2-(3-iodophenyl)propanoate[15] (145 mg, 0.50 mmol), $[Pd(allyl)Cl]_2$ (5 mg, 0.01 mmol) and 2-6-di-*tert*-butylpyridine (115 mg, 0.60 mmol) were dissolved in benzene (2 mL) and added. The vessel was closed, removed from the glovebox, evacuated and backfilled with carbon monoxide three times, and finally pressurized with 4 atm carbon monoxide. After heating at 80 °C for 24 h with stirring, the reaction was cooled to room temperature and carbon monoxide was released. The reaction mixture was diluted with dichloromethane and passed through celite. Saturated $NaHCO_3$ was added and the aqueous layer was extracted with dichloromethane. The combined organic layers were concentrated *in vacuo* and the residue was purified by column chromatography (silica gel, gradient hexane / ethyl acetate 0% to 20%) affording Ketoprofen methyl ester as a white solid in 51% yield (68 mg).



Synthesis of Ketoprofen: Ketoprofen methyl ester (55 mg, 0.20 mmol) was dissolved in a 1:1 mixture of THF/water (2 mL) to which lithium hydroxide hydrate (22 mg, 0.52 mmol) was added. After stirring for 24 hours at room temperature, the THF was evaporated *in vacuo* and 1M HCl was added until the solution was pH 2. The solid precipitate was filtered and washed with cold water to afford Ketoprofen **(2.5)** in 99% yield (50 mg) and 50% yield over two steps.

2.5.8. Synthesis of Fenofibrate:



Silver triflimide or silver triflate (0.30 mmol) was transferred to a Teflon sealed, thick walled 50 mL glass reaction vessel equipped with a magnetic stir bar. 4-Chloroiodotoluene (48 mg, 0.20 mmol), $[Pd(allyl)Cl]_2$ (4 mg, 0.01 mmol), 2-6-di-*tert*-butylpyridine (115 mg, 0.60 mmol) and isopropyl 2-methyl-2-phenoxypropanoate[66] (89 mg, 0.40) were dissolved in 1,2-dichloroethane (1 mL) and added. The pyridine base was added to inhibit decomposition of the ester. The vessel was closed, removed from the glovebox, evacuated and backfilled with carbon monoxide three times, and finally pressurized with 4 atm carbon monoxide. After heating at 65 °C for 48 h with stirring, the reaction was cooled to room temperature and carbon monoxide was released. The reaction mixture was diluted with dichloromethane and passed through celite. Saturated $NaHCO_3$ was added and the aqueous layer was extracted with dichloromethane. The combined organic layers were concentrated *in vacuo* and the residue was purified by column chromatography (silica gel, gradient toluene/DCM 0% to 100%) affording Fenofibrate **(2.6)** as a white solid in 83% yield (60 mg) when using silver triflimide and 57% yield (41 mg) when using silver triflate.

2.5.9. Synthesis of Indanones in Figure 2.4b

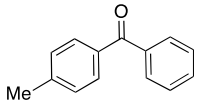
Representative Procedure: Silver triflate (97 mg, 0.38 mmol) was transferred to a Teflon sealed, thick walled 50 mL glass reaction vessel with a magnetic stir bar. 2-iodohex-1-ene (53 mg, 0.25 mmol), $[Pd(allyl)Cl]_2$ (2 mg, 0.0063 mmol)and 1,2-dimethoxy benzene (173 mg, 1.25 mmol) were dissolved in 1,2-dichloroethane (1 mL). The vessel was closed, removed from the glovebox, evacuated and backfilled with carbon monoxide three times, and finally pressurized with 4 atm carbon monoxide. After heating at 50 °C for 24 h with stirring (see tabulated NMR data for the specific conditions for other compounds), the reaction was cooled to room temperature and carbon monoxide was released. The reaction mixture was filtered through celite, eluting with dichloromethane. Saturated $NaHCO_3$ was added and the aqueous layer was extracted with

dichloromethane. The combined organic layers were concentrated *in vacuo* and the residue was purified by column chromatography (silica gel, gradient hexane / ethyl acetate 0% to 20%) affording pure indanone **2.7a** as a slightly yellow solid in 60% yield (37 mg).

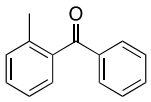
2.5.10. Arene Carbonylation with Silver Triflimide

Representative Procedure: Silver triflimide (291mg, 0.75 mmol) was transferred to a Teflon sealed, thick walled 50 mL glass reaction vessel with a magnetic stir bar. 4-iodotoluene (109 mg, 0.50 mmol), $[Pd(allyl)Cl]_2$ (5 mg, 0.013 mmol) and anisole (108 mg, 1.0 mmol) were dissolved in 1,2-dichloroethane (2 mL). The vessel was closed, removed from the glovebox, evacuated and backfilled with carbon monoxide three times, and finally pressurized with 4 atm carbon monoxide. After letting the reaction stir for 24 h with stirring (see tabulated NMR data for the specific conditions for other compounds), carbon monoxide was released. The reaction mixture was filtered through celite, eluting with dichloromethane. Saturated $NaHCO_3$ was added and the aqueous layer was extracted with dichloromethane. The combined organic layers were concentrated in vacuo and the residue was purified by column chromatography (silica gel, gradient hexane / ethyl acetate 0% to 20%) affording pure ketone **2.1w** as a white solid in 98% yield (111 mg).

2.5.11. Spectroscopic Data for Compounds 2.1-2.7

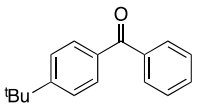


Phenyl(*p*-tolyl)methanone 2.1a.[67] Prepared according to procedure A. White Solid, 82% (161 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.64 – 7.56 (m, 1H), 7.49 (t, *J* = 7.4 Hz, 2H), 7.31 (d, 2H), 2.46 (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 196.5, 143.2, 138.0, 134.9, 132.2, 130.3, 129.9, 129.0, 128.2, 21.7. HRMS. Calculated for $C_{14}H_{12}ONa^+$ ($M+Na^+$): 219.0780, found: 219.0782.

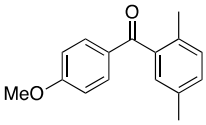


Phenyl(*o*-tolyl)methanone 2.1b.[68] Prepared according to procedure A using 1-iodo-2-methylbenzene (218 mg, 1 mmol). Pale yellow oil, 87% yield (170 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 6.9 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.40 (td, *J* = 7.5, 1.5 Hz, 1H), 7.34 – 7.29 (m, 2H), 7.28 – 7.24 (m, 1H), 2.35 (s, 3H). ^{13}C

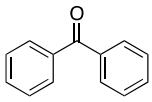
NMR (126 MHz, $CDCl_3$) δ 198.6, 138.6, 137.7, 136.8, 133.1, 131.0, 130.3, 130.1, 128.5, 128.5, 125.2, 20.0.



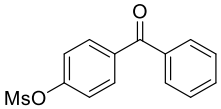
(4-(*tert*-butyl)phenyl)(phenyl)methanone 2.1c.[67] Prepared according to procedure A using 1-(*tert*-butyl)-4-iodobenzene (260 mg, 1 mmol). Pale yellow oil, 85% yield (202 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 – 7.81 (m, 2H), 7.80 – 7.76 (m, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.53 – 7.46 (m, 4H), 1.38 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.4, 156.2, 137.9, 134.8, 132.2, 130.2, 130.0, 128.2, 125.3, 35.1, 31.2. HRMS. Calculated for $C_{17}H_{18}ONa^+$ ($M+Na^+$): 261.1250, found: 261.1250.



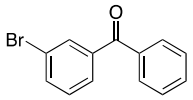
(2,5-dimethylphenyl)(4-methoxyphenyl)methanone 2.1d.[69] Prepared according to procedure A at 60°C with 4-iodoanisole (234 mg, 1 mmol) and $[Pd(allyl)Cl]_2$ (9 mg, 0.025 mmol) in neat *p*-xylene (4 mL). White Solid, 87% yield (209 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.9 Hz, 2H), 7.23 – 7.17 (m, 2H), 7.11 (s, 1H), 6.95 (d, *J* = 8.9 Hz, 2H), 3.90 (s, 3H), 2.35 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.6, 163.7, 139.2, 134.8, 132.9, 132.5, 130.7, 130.6, 130.5, 128.4, 113.7, 55.5, 20.9, 19.3. HRMS. Calculated for $C_{16}H_{17}O_2^+$ ($M+H^+$): 241.1223, found: 241.1228.



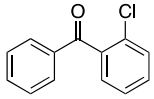
Benzophenone 2.1e.[65] Prepared according to procedure A using iodobenzene (204 mg, 1 mmol). White solid, 92% yield (167 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.9 – 7.8 ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 – 7.80 (m, 4H), 7.60 (t, *J* = 7.4 Hz, 2H), 7.49 (t, *J* = 7.7 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.7, 137.6, 132.5, 130.1, 128.3. HRMS. Calculated for $C_{13}H_{11}O^+$ ($M+H^+$): 183.0804, found: 183.0811.



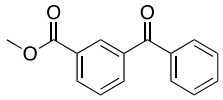
4-benzoylphenyl methanesulfonate 2.1f.[68] Prepared according to procedure A using $[Pd(allyl)Cl]_2$ (0.1 mg , 3 x 10^{-4} mmol), 4-iodophenyl methanesulfonate (149 mg, 0.5 mmol) in DCE (2 mL). White solid 71% (98 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.7 Hz, 2H), 7.82 (d, *J* = 7.1 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.53 (t, *J* = 7.7 Hz, 2H), 7.43 (d, *J* = 8.7 Hz, 2H), 3.25 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.2, 151.9, 137.0, 136.6, 132.8, 132.0, 130.0, 128.5, 121.9, 37.9.



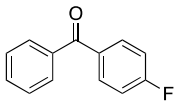
(3-bromophenyl)(phenyl)methanone 2.1g.[67] Prepared according to procedure A using 1-bromo-3-iodobenzene (283 mg, 1 mmol). Pale yellow solid, 98% yield (259 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (t, *J* = 1.8 Hz, 1H), 7.81 – 7.76 (m, 2H), 7.73 – 7.68 (m, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.35 (t, *J* = 7.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.0, 139.5, 136.9, 135.3, 132.9, 132.8, 130.0, 129.9, 128.6, 128.5, 122.6. HRMS. Calculated for $C_{13}H_{10}OBr^+$ ($M+H^+$): 260.9910, found: 260.9922.



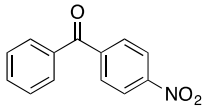
(2-chlorophenyl)(phenyl)methanone 2.1h.[67] Prepared according to procedure A using 1-chloro-2-iodobenzene (239 mg, 1 mmol). White Solid, 79% yield (171mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 6.9 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.51 – 7.40 (m, 4H), 7.42 – 7.34 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.3, 138.6, 136.5, 133.8, 131.3, 131.2, 130.1, 129.1, 128.7, 128.3, 126.7. HRMS. Calculated for $C_{13}H_{10}OCl^+$ ($M+H^+$): 217.0415, found: 217.0422.



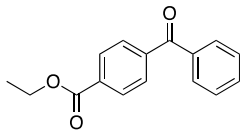
Methyl 3-benzoylbenzoate 2.1i. Prepared according to procedure A using methyl 3-iodobenzoate (262 mg, 1 mmol) and benzene (780 mg, 10 mmol). Pale yellow oil, 85 % yield (205 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (s, 1H), 8.22 (d, *J* = 7.8 Hz, 1H), 7.96 (d, *J* = 7.7 Hz, 1H), 7.77 (d, *J* = 7.3 Hz, 2H), 7.56 (dt, *J* = 15.6, 7.6 Hz, 2H), 7.46 (t, *J* = 7.7 Hz, 2H), 3.89 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.6, 166.2, 137.9, 137.0, 134.0, 133.1, 132.8, 130.9, 130.4, 130.0, 128.6, 128.5, 52.3. HRMS. Calculated for $C_{15}H_{12}NaO_3^+$ ($M+Na^+$): 263.0679, found: 263.0681.



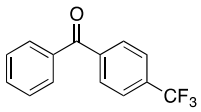
(4-fluorophenyl)(phenyl)methanone 2.1j.[68] Prepared according to procedure A using 1-fluoro-4-iodobenzene (222 mg, 1 mmol). White Solid, 82% yield (164 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.8 Hz, 2H), 7.78 (d, *J* = 6.9 Hz, 2H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.49 (t, *J* = 8.4, Hz, 2H), 7.23 – 7.08 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.2, 165.4 (d, *J* = 254.1 Hz), 137.5, 133.8 (d, *J* = 3.1 Hz), 132.7 (d, *J* = 9.1 Hz), 132.5, 129.9, 128.4, 115.4 (d, *J* = 21.7 Hz). HRMS. Calculated for $C_{13}H_{10}OF^+$ ($M+H^+$): 201.0710 found: 201.0717.



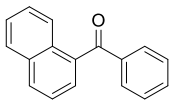
(4-nitrophenyl)(phenyl)methanone 2.1k.[71] Prepared according to procedure A using 1-iodo-4-nitrobenzene (249 mg, 1 mmol) and $[Pd(allyl)Cl]_2$ (9 mg, 0.025 mmol) for 48h. Yellow solid, 83% yield (189 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 – 8.23 (m, 2H), 8.16 – 7.87 (m, 2H), 7.87 – 7.75 (m, 2H), 7.74 – 7.63 (m, 1H), 7.61 – 7.50 (m, 2H).^{13}C NMR (126 MHz, $CDCl_3$) δ 194.8, 149.8, 142.9, 136.3, 133.5, 130.7, 130.1, 128.7, 123.6. HRMS. Calculated for $C_{13}H_9O_3N^+$ (M^+): 227.0584, found: 227.0588.



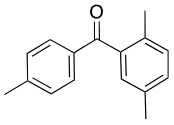
Ethyl 4-benzoylbenzoate 2.1l.[72] Prepared according to procedure A using ethyl 4-iodobenzoate (276 mg, 1 mmol) and benzene (780 mg, 10 mmol). Pale yellow oil, 77% yield (195.6 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.4 Hz, 2H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.82 – 7.78 (m, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 4.42 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.0, 165.8, 141.2, 137.0, 133.6, 132.9, 130.1, 129.7, 129.4, 128.4, 61.4, 14.3. HRMS. Calculated for $C_{16}H_{14}O_3Na^+$ ($M+Na^+$): 277.0835, found: 277.0835.



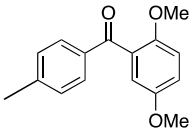
Phenyl(4-(trifluoromethyl)phenyl)methanone 2.1m.[73] Prepared according to procedure A using 1-iodo-4-(trifluoromethyl)benzene (272 mg, 1 mmol) and $[Pd(allyl)Cl]_2$ (9 mg, 0.025 mmol) for 48h. White solid, 92% yield (230 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 – 7.86 (m, 2H), 7.83 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.78 (d, *J* = 8.1 Hz, 2H), 7.70 – 7.61 (m, 1H), 7.53 (dd, *J* = 8.5, 7.1 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.5, 140.7, 136.7, 133.7 (q, *J* = 32.7 Hz), 133.1, 130.1, 130.1, 128.5, 125.3 (q, *J* = 3.8 Hz), 123.7 (q, *J* = 272.7 Hz). HRMS. Calculated for $C_{14}H_{10}OF_3^+$ ($M+H^+$): 251.0678, found: 251.0684.



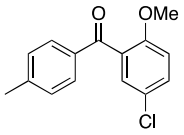
Naphthalen-1-yl(phenyl)methanone 2.1n.[74] Prepared according to procedure A using 1-iodonaphthalene (127 mg, 0.5 mmol) and $[Pd(allyl)Cl]_2$ (5 mg, 0.01 mmol) in DCE (2 mL). White solid, 79% yield (92 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 – 8.11 (m, 1H), 8.01 (d, J = 8.2 Hz, 1H), 7.95 – 7.92 (m, 1H), 7.90 – 7.87 (m, 2H), 7.64 – 7.58 (m, 2H), 7.57 – 7.50 (m, 3H), 7.46 (t, J = 7.7 Hz, 2H). 13C NMR (126 MHz, $CDCl_3$) δ 198.0, 138.4, 136.4, 133.8, 133.3, 131.3, 131.0, 130.4, 128.5, 128.44, 127.8, 127.3, 126.5, 125.7, 124.4.



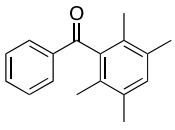
(2,5-dimethylphenyl)(*p*-tolyl)methanone 2.1o.[75] Prepared according to procedure A at 60°C using $[Pd(allyl)Cl]_2$ (9 mg, 0.025 mmol) and *p*-xylene (212 mg, 2 mmol). White Solid, 88% yield (206 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 7.20 (d, *J* = 6.1 Hz, 2H), 7.14 (d, *J* = 1.7 Hz, 1H), 2.45 (s, 3H), 2.36 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.6, 144.0, 139.0, 135.2, 134.8, 133.2, 130.8, 130.8, 130.3, 129.2, 128.7, 21.7, 20.9, 19.4.



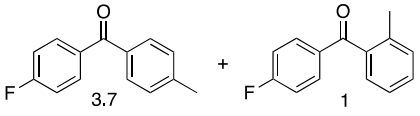
(2,5-dimethoxyphenyl)(*p*-tolyl)methanone 2.1p.[76] Prepared according to procedure A at 60°C using $[Pd(allyl)Cl]_2$ (9 mg, 0.025 mmol) and 1,4-dimethoxybenzene (276 mg, 2 mmol) at 30 atm CO. White solid, 91% yield (234 mg)**.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 7.8 Hz, 2H), 6.98 (dd, *J* = 9.0, 3.1 Hz, 1H), 6.92 (s, 1H), 6.89 (d, *J* = 3.1 Hz, 1H), 3.76 (s, 3H), 3.66 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.8, 153.4, 151.3, 143.9, 135.0, 130.1, 129.8, 129.0, 117.0, 114.4, 113.0, 56.4, 55.8, 21.7.



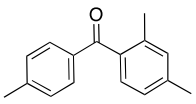
(5-chloro-2-methoxyphenyl)(*p*-tolyl)methanone 2.1q. Prepared according to procedure A at 60°C using $[Pd(allyl)Cl]_2$ (9 mg, 0.025 mmol) and 1-chloro-4-methoxybenzene (285 mg, 2 mmol). White Solid, 94% yield (245 mg). White solid, 241 mg, 94% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.42 (dd, *J* = 8.8, 2.6 Hz, 1H), 7.31 (d, *J* = 2.6 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 6.94 (d, *J* = 8.9 Hz, 1H), 3.73 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.5, 155.7, 144.3, 134.6, 131.2, 130.5, 130.0, 129.1, 129.0, 125.6, 112.8, 56.0, 21.8. HRMS. Calculated for $C_{15}H_{13}O_2ClNa^+$ ($M+Na^+$): 283.0496, found: 283.0497.



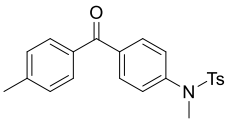
Phenyl(2,3,5,6-tetramethylphenyl)methanone 2.1r. Prepared according to procedure A at 60°C using iodobenzene (204 mg, 1 mmol), $[Pd(allyl)Cl]_2$ (9 mg, 0.025 mmol) and durene (268 mg, 2 mmol). White Solid, 85% yield (203 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 – 7.73 (m, 2H), 7.68 – 7.54 (m, 1H), 7.52 – 7.40 (m, 2H), 7.07 (s, 1H), 2.28 (s, 6H), 2.02 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.6, 140.0, 137.5, 134.2, 133.6, 131.8, 129.7, 129.5, 128.8, 19.5, 16.3. HRMS. Calculated for $C_{17}H_{19}O^+$ ($M+H^+$): 239.1430, found: 239.1440.



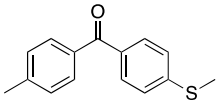
(4-fluorophenyl)(*p*-tolyl)methanone[77] 2.1s and (4-fluorophenyl)(*o*-tolyl)methanone[78] 2.1s'. Prepared according to procedure A using $PdCl_2$ (2 mg, 0.01 mmol), 1-fluoro-4-iodobenzene (222 mg, 1 mmol) and toluene (184 mg, 2 mmol). White Solid, 154 mg, 72% isolated total yield of both isomers (3.7:1 ratio). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 – 7.79 (m, 2H, both isomers), 7.70 (d, *J* = 8.3 Hz, 2H, major isomer), 7.39 (dd, *J* = 7.4, 1.6 Hz, 1H, minor isomer), 7.29 (d, *J* = 8.2 Hz, 2H, both isomers), 7.25 (t, *J* = 7.3 Hz, 1H, minor isomer), 7.15 (t, *J* = 8.6 Hz, 2H, major isomer), 7.12 (t, *J* = 8.7 Hz, 2H, minor isomer), 2.44 (s, 3H, major isomer), 2.33 (s, 3H, minor isomer). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.9, 194.9, 165.8 (d, *J* = 255.1 Hz), 165.2 (d, *J* = 253.6 Hz), 143.3, 138.4, 136.6, 134.8, 134.2, 134.1, 132.7 (d, *J* = 9.4 Hz), 132.5 (d, *J* = 9.1 Hz), 131.1, 130.3, 130.1, 129.0, 128.3, 125.3, 115.6 (d, *J* = 21.9 Hz), 115.3 (d, *J* = 21.9 Hz), 21.6, 19.9. HRMS. Calculated for $C_{14}H_{11}FONa^+$ ($M+Na^+$): 237.0686, found: 237.0687.



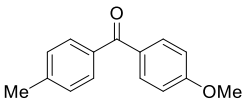
(2,4-dimethylphenyl)(*p*-tolyl)methanone 2.1t.[79] Prepared according to procedure A at 60°C using $[Pd(allyl)Cl]_2$ (9 mg, 0.025 mmol) and *m*-xylene (212 mg, 2 mmol). White solid, 96% yield (215 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.1 Hz, 2H), 7.29 – 7.22 (m, 3H), 7.13 (s, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 2.45 (s, 3H), 2.41 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.3, 143.7, 140.3, 136.9, 136.0, 135.6, 131.8, 130.3, 129.1, 128.9, 125.8, 21.7, 21.4, 20.0. HRMS. Calculated for $C_{16}H_{17}O^+$ ($M+H^+$): 225.1274, found: 225.1278.



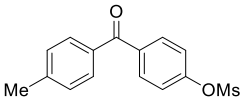
N,4-dimethyl-N-(4-(4-methylbenzoyl)phenyl)benzenesulfonamide 2.1u. Prepared according to procedure A Prepared according to procedure A at 60°C using 4-iodotoluene (109 mg, 0.5 mmol) $[Pd(allyl)Cl]_2$ (5 mg, 0.013 mmol), 2,6-di-*tert*-butylpyridine (105 mg, 0.55 mmol) and *N*,4-dimethyl-*N*-phenylbenzenesulfonamide (108 mg, 1 mmol). White solid, 97% yield (184 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.5 Hz, 2H), 7.70 (d, J = 7.9 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.32 – 7.21 (m, 6H), 3.21 (s, 3H), 2.45 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.4, 145.1, 144.0, 143.6, 136.0, 134.6, 133.3, 130.6, 130.2, 129.6, 129.1, 127.7, 125.5, 37.7, 21.7, 21.6. HRMS. Calculated for $C_{22}H_{21}O_3NSNa$ ($M+Na^+$): 402.1134, found: 402.1137



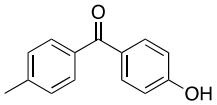
(4-(methylthio)phenyl)(*p*-tolyl)methanone 2.1v.[80] Prepared according to procedure A at 80°C using $[Pd(allyl)Cl]_2$ (9 mg, 0.025 mmol) and thioanisole (248 mg, 2 mmol). Pale yellow oil, 85% yield (206 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.5 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.33 – 7.26 (m, 4H), 2.54 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.5, 144.9, 143.0, 135.1, 134.0, 130.5, 130.1, 129.0, 124.8, 21.6, 14.9.



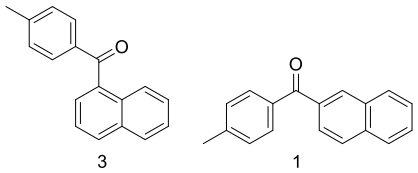
(4-methoxyphenyl)(p-tolyl)methanone 2.1w.[80] Prepared according to procedure A at 60°C using $[Pd(allyl)Cl]_2$ (5 mg, 0.013 mmol) and anisole (108 mg, 1 mmol). White Solid, 91% yield (103 mg). Also prepared using silver triflimide according to the procedure in section XII, giving a white solid in 98% yield (111 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.8 Hz, 2H), 7.70 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 7.9 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 3.89 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (126 MHz, CDCl3) δ 195.3, 163.0, 142.60, 135.5, 132.4, 130.5, 130.0, 128.9, 113.5, 55.5, 21.6.



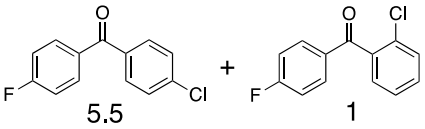
4-(4-methylbenzoyl)phenyl methanesulfonate 2.1x. Prepared according to procedure A using phenyl methanesulfonate (172 mg, 0.5 mmol). White solid, 79% yield (115 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.7 Hz, 2H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 8.8 Hz, 2H), 7.32 (d, *J* = 7.9 Hz, 2H), 3.24 (s, 3H), 2.48 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.9, 151.7, 143.8, 136.9, 134.3, 131.9, 130.3, 129.2, 121.8, 37.9, 21.7. HRMS. Calculated for $C_{15}H_{14}O_4SNa$ ($M+Na^+$): 313.0505, found: 313.0501.



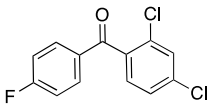
(4-hydroxyphenyl)(*p*-tolyl)methanone 2.1y. Prepared according to procedure A at 60°C using $[Pd(allyl)Cl]_2$ (9 mg, 0.025 mmol) and phenol (188 mg, 2.0 mmol). Pale Yellow solid, 47% yield (100 mg). ^{1}H NMR (500 MHz, DMSO) δ 7.65 (d, *J* = 8.7 Hz, 2H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 7.8 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 194.5, 162.3, 142.5, 135.8, 132.8, 129.9, 129.4, 128.6, 115.6, 21.6. HRMS. Calculated for $C_{14}H_{13}O_2$ ($M+H^+$): 213.0910, found: 213.0908.



Naphthalen-1-yl(*p*-tolyl)methanone 2.1z and Naphthalen-2-yl (*p*-tolyl)methanone 2.1z'.[79, 69] Prepared according to procedure A using naphthalene (256 mg, 2 mmol). White solid, 95% isolated total yield (234 mg) of both isomers (3:1 ratio). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 1.1 Hz, 1H, minor isomer), 8.07 (d, *J* = 8.4 Hz, 1H, major isomer), 8.01 (d, *J* = 8.2 Hz, 1H major isomer), 7.97 – 7.91 (m, 2H for major, 1H for minor isomer), 7.80 (m, 2H, both isomers), 7.62 (dd, *J* = 8.3, 6.8 Hz, 2H, minor isomer), 7.60 – 7.48 (m, 3H, both isomers), 7.34 (m, 2H, minor isomer), 7.27 (d, *J* = 7.8 Hz, 2H, major isomer), 2.49 (s, 3H, minor isomer), 2.45 (s, 3H, major isomer). ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.8, 196.6, 144.3, 143.3, 136.8, 135.7, 135.2, 133.7, 132.3, 131.6, 131.0, 131.0, 130.6, 130.4, 129.4, 129.2, 129.1, 128.4, 128.3, 128.2, 127.8, 127.2, 126.8, 126.4, 125.9, 125.7, 124.4, 21.8. HRMS. Calculated for $C_{18}H_{14}ONa^+$ ($M+Na^+$): 269.0937, found 269.0936.

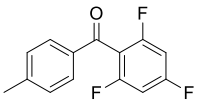


(4-chlorophenyl)(4-fluorophenyl)methanone[81] **2.1aa and (2-chlorophenyl)(4-fluorophenyl)methanone**[82] **2.1aa'.** Prepared according to procedure A at 150°C using $PdCl_2$ (2 mg, 0.01 mmol), 1-fluoro-4-iodobenzene (222 mg, 1 mmol) and chlorobenzene (225 mg, 2 mmol) in C_6F_6 (4 mL). Pale yellow solid, 82% isolated total yield (192 mg) of both isomers (5.5:1 ratio). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 8.8, 5.4 Hz, 2H, both isomers), 7.73 (d, *J* = 8.5 Hz, 2H, major isomer), 7.47 (d, *J* = 8.5 Hz, 2H, both isomers), 7.38 (dd, *J* = 3.2, 1.3 Hz, 2H, minor isomer), 7.17 (t, *J* = 8.6 Hz, 2H, major isomer), 7.14 (t, *J* = 8.6 Hz, 2H, minor isomer). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.9, 193.6, 166.1 (d, *J* = 256.2 Hz), 165.5 (d, *J* = 254.8 Hz), 138.9, 138.3, 135.8, 133.5 (d, *J* = 3.1 Hz), 132.9 (d, *J* = 2.8 Hz), 132.7 (d, *J* = 9.6 Hz), 132.5 (d, *J* = 9.2 Hz), 131.3, 131.3, 130.1,129.0, 128.8, 128.7, 126.8, 115.8 (d, *J* = 22.1 Hz), 115.6 (d, *J* = 21.9 Hz). HRMS. Calculated for $C_{13}H_8ClFONa^+$ ($M+Na^+$): 257.0140, found 257.0135.

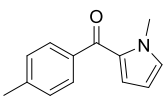


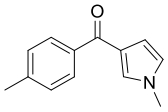
(2,4-dichlorophenyl)(4-fluorophenyl)methanone 2.1bb. Prepared according to procedure A at 150°C using $PdCl_2$ (2 mg, 0.01 mmol), 1-fluoro-4-iodobenzene (222 mg, 1 mmol) and 1,3-dichlorobenzene (294 mg, 2 mmol) in C_6F_6 (4 mL). Pale

yellow oil, 84% yield (226 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.8 (dd, *J* = 8.9, 5.5 Hz, 2H), 7.5 (d, *J* = 1.9 Hz, 1H), 7.4 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.3 (d, *J* = 8.2 Hz, 1H), 7.1 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.6, 166.2 (d, *J* = 256.5 Hz), 136.7 (d, *J* = 13.3 Hz), 132.7, 132.7 (d, *J* = 9.4 Hz), 132.7, 132.3, 130.1, 130.0, 127.3, 116.0 (d, *J* = 22.1 Hz). HRMS. Calculated for $C_{13}H_7Cl_2FONa^+$ (M+Na^+): 290.9750, found 290.9748.

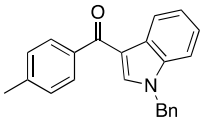


p-tolyl(2,4,6-trifluorophenyl)methanone 2.1cc. Prepared according to procedure A using 4-iodotoluene (55 mg, 0.25 mmol), $[Pd(allyl)Cl]_2$ (2 mg, 0.006 mmol) and trifluorobenzene (825 mg, 6.3 mmol). Colorless solid, 69% yield (43 mg). ^{1}H NMR (500 MHz, CDCl3): δ 7.75 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 6.77 (dd, J = 8.8, 7.1 Hz, 2H), 2.43 (s, 3H). ^{13} C NMR (126 MHz, CDCl3) δ 187.5, 163.7 (dt, J = 253.1, 14.9 Hz), 160.5 (ddd, J = 252.8, 15.0, 10.5 Hz), 145.7, 134.5, 129.9, 129.7, 113.9 (td, J = 22.1, 4.6 Hz), 101.3 – 100.7 (m), 21.9. HRMS. Calculated for $C_{14}H_{10}F_3O$ (M+H+): 251.0678, found: 251.0679.



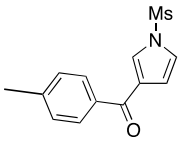


(1-methyl-1*H*-pyrrol-2-yl)(*p*-tolyl)methanone 2.1dd.[83] Prepared according to procedure B. Pale yellow oil, 51% yield (102 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 6.92 (s, 1H), 6.76 (dd, *J* = 4.1, 1.7 Hz, 1H), 6.17 (dd, *J* = 4.0, 2.5 Hz, 1H), 4.05 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.0, 141.9, 137.2, 131.2, 130.6, 129.4, 128.7, 122.5, 108.0, 37.3, 21.6. **(1-methyl-1H-pyrrol-3-yl)(p-tolyl)methanone 2.1dd'.** Pale yellow oil, 22 % (44 mg). ^{1}H NMR (500 MHz, Chloroform-d) δ 7.76 (d, J = 7.9 Hz, 2H), 7.27 (d, J = 7.9 Hz, 2H), 7.20 (t, J = 1.7 Hz, 1H), 6.69 (dd, J = 2.7, 1.7 Hz, 1H), 6.64 (t, J = 2.4 Hz, 1H), 3.71 (s, 3H), 2.44 (s, 3H). 13C NMR (126 MHz, Chloroform-d) δ 190.3, 141.8, 137.3, 129.1, 128.8, 128.8, 124.7, 123.2, 111.1, 36.6, 21.6.

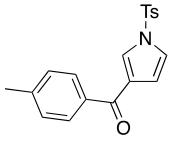


(1-benzyl-1*H*-indol-3-yl)(*p*-tolyl)methanone 2.1ee. Prepared according to procedure B using 1-benzyl-1*H*-indole (415 mg, 2 mmol). Light Brown solid, 54% yield (176 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 7.2 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.66 (s, 1H), 7.39 – 7.27 (m, 8H), 7.17 (d, *J* = 6.2 Hz, 2H), 5.38 (s, 2H),

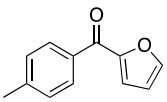
2.47 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.7, 141.7, 138.1, 137.1, 136.9, 135.9, 129.0, 129.0, 129.0, 128.1, 127.5, 126.8, 123.7, 122.8, 122.7, 116.2, 110.2, 50.8, 21.6. HRMS. Calculated for $C_{23}H_{20}NO^+$ ($M+H^+$): 326.1539, found: 326.1544.



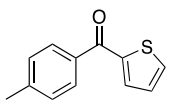
(1-(methylsulfonyl)-1*H*-pyrrol-3-yl)(phenyl)methanone 2.1ff. Prepared according to procedure A at 60°C using $[Pd(allyl)Cl]_2$ (9 mg, 0.025 mmol) and N-mesyl pyrrole (290 mg, 2 mmol). White solid, 88% yield (232 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.2 Hz, 2H), 7.66 – 7.63 (m, 1H), 7.32 (d, *J* = 7.9 Hz, 2H), 7.22 (dd, *J* = 3.3, 2.2 Hz, 1H), 6.91 (dd, *J* = 3.3, 1.6 Hz, 1H), 3.26 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.6, 143.3, 135.7, 129.2, 129.2, 128.2, 125.6, 121.2, 114.2, 43.2, 21.6. HRMS. Calculated for $C_{13}H_{13}NNaO_3S^+$ ($M+Na^+$): 286.0508, found: 286.0512.



***p*-tolyl(1-tosyl-1*H*-pyrrol-3-yl)methanone 2.1gg.** Prepared according to procedure A at 60°C using $[Pd(allyl)Cl]_2$ (9 mg, 0.025 mmol) and N-tosyl pyrrole (443 mg, 2 mmol). White Solid, 99% yield (336 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.75 (d, *J* = 8.1 Hz, 2H), 7.69 – 7.64 (m, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 2H), 7.22 (dd, *J* = 3.3, 2.2 Hz, 1H), 6.81 (dd, *J* = 3.3, 1.6 Hz, 1H), 2.45 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.6, 145.9, 143.1, 135.9, 135.1, 130.3, 129.2, 129.2, 128.0, 127.2, 125.8, 121.4, 114.1, 21.7, 21.6. HRMS. Calculated for $C_{19}H_{18}O_3NS^+$ ($M+H^+$): 340.1002, found: 340.1006.

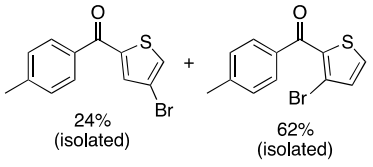


Furan-2-yl(*p*-tolyl)methanon 2.1hh.[79] Prepared according to procedure B using furan (136 mg, 2 mmol). White solid, 81% yield (151 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.1 Hz, 2H), 7.68 (d, *J* = 1.4 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 3.5 Hz, 1H), 6.58 (dd, *J* = 3.5, 1.7 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.3, 152.4, 146.9, 143.4, 134.6, 129.5, 129.1, 120.2, 112.1, 21.7. HRMS. Calculated for $C_{12}H_{10}O_2Na^+$ ($M+Na^+$): 209.0573, found: 209.0573.

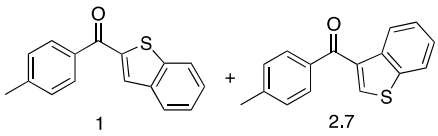


Thiophen-2-yl(*p*-tolyl)methanone 2.1ii.[79] Prepared according to procedure A at 60°C using $[Pd(allyl)Cl]_2$ (9 mg, 0.025 mmol) and thiophene (290 mg, 2 mmol). Pale yellow oil, 96% yield (194 mg). Also prepared using silver triflimide according to the

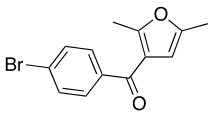
procedure in section XII, giving a white solid in 87% yield (88 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.1 Hz, 2H), 7.72 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.67 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.32 (d, *J* = 7.9 Hz, 2H), 7.18 (dd, *J* = 5.0, 3.8 Hz, 1H), 2.47 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.9, 143.8, 143.0, 135.4, 134.5, 133.8, 129.4, 129.1, 127.9, 21.7.



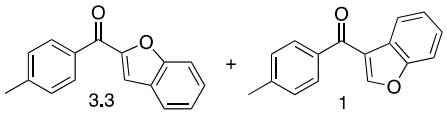
(3-bromothiophen-2-yl)(p-tolyl)methanone 2.1jj. Prepared according to procedure A at 60°C using $[Pd(allyl)Cl]_2$ (9 mg, 0.025 mmol) and 3-bromothiophene (326 mg, 2 mmol). Pale brown oil, 62% yield (174 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.1 Hz, 2H), 7.54 (d, *J* = 5.2 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 2H), 7.13 (d, *J* = 5.2 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.7, 144.1, 135.9, 135.0, 132.6, 130.7, 130.0, 129.1, 114.7, 21.8. HRMS. Calculated for $C_{12}H_9BrOSNa^+$ ($M+Na^+$): 302.9450, found 302.9448. **(4-bromothiophen-2-yl)(*p*-tolyl)methanone 1jj'.** Pale brown oil, 24% yield (68 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.2 Hz, 2H), 7.61 (d, *J* = 1.4 Hz, 1H), 7.55 (d, *J* = 1.4 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 2H), 2.47 (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 186.6, 144.2, 143.7, 136.1, 134.5, 131.0, 129.4, 129.3, 110.5, 21.7. HRMS. Calculated for $C_{12}H_9BrOSNa^+$ ($M+Na^+$): 302.9450, found 302.9451.



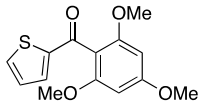
Benzo[*b*]thiophen-2-yl(*p*-tolyl)methanone[84] 2.1kk and benzo[*b*]thiophen-3-yl(*p*-tolyl)methanone[85] 2.1kk'. Prepared according to procedure A at 60°C using $[Pd(allyl)Cl]_2$ (9 mg, 0.025 mmol) and benzothiophene 268 mg, 2 mmol). Pale yellow solid, 95% isolated total yield (240 mg) of both isomers (1 : 2.7 ratio). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (d, *J* = 8.1 Hz, 1H, major isomer), 8.01 (s, 1H, major isomer), 7.93 (m, 1H both isomers), 7.90 (d, *J* = 7.9 Hz, 2H, minor isomer), 7.89 – 7.86 (m, 1H, major isomer), 7.82 (d, *J* = 8.0 Hz, 1H, major isomer), 7.42-7.55 (m, 2H for major isomer, 4H for minor isomer), 7.36 (d, *J* = 7.8 Hz, 2H, minor isomer), 7.33 (d, *J* = 7.8 Hz, 2H, major isomer), 2.50 (s, 3H, minor isomer), 2.48 (s, 3H, major isomer). ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.6, 189.3, 143.3, 143.3, 143.2, 142.6, 140.0, 139.1, 137.5, 137.4, 136.5, 135.2, 135.0, 131.8, 129.8, 129.5, 129.2, 129.1, 127.3, 126.0, 125.6, 125.5, 125.1, 125.0, 122.9, 122.3, 21.7, 21.7. HRMS. Calculated for $C_{16}H_{12}NaOS^+$ ($M+Na^+$): 275.0501, found 275.0497.



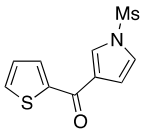
(4-bromophenyl)(2,5-dimethylfuran-3-yl)methanone 2.1ll. Prepared according to procedure B using 1-bromo-4-iodobenzene (283 mg, 1 mmol) and 2,5-dimethylfuran (192 mg, 2 mmol). Brown Solid, 70% yield (195 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.6 Hz, 2H), 7.60 (d, *J* = 8.6 Hz, 2H), 6.14 – 6.12 (m, 1H), 2.49 (s, 3H), 2.29 (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 190.1, 158.2, 150.0, 138.1, 131.5, 130.5, 126.9, 120.8, 107.2, 14.2, 13.2. HRMS. Calculated for $C_{13}H_{12}O_2Br^+$ ($M+H^+$): 279.0015, found: 279.0025.



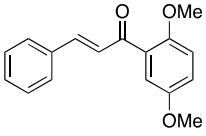
Benzofuran-2-yl(*p*-tolyl)methanone 2.1mm and benzofuran-3-yl(*p*-tolyl)methanone 2.1mm'.[79] Prepared according to procedure B using 2,3-benzofuran (237 mg, 2 mmol). Yellow solid, 58% isolated total yield (137 mg) of both isomers (3.3:1 ratio)**.** ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 – 8.23 (m, 1H, minor isomer), 8.09 (s, 1H, minor isomer), 7.99 (d, *J* = 8.2 Hz, 2H, major isomer), 7.83 (d, *J* = 8.2 Hz, 2H, minor isomer), 7.74 (d, *J* = 7.9 Hz, 1H, major isomer), 7.65 (dd, *J* = 8.4, 0.9 Hz, 1H, major isomer), 7.59 – 7.56 (m, 1H, minor isomer), 7.53 (d, *J* = 1.0 Hz, 1H, major isomer), 7.50 (dt, *J* = 8.4, 1.3 Hz, 1H, major isomer), 7.43 – 7.40 (m, 2H, minor isomer), 7.35 (d, *J* = 8.2 Hz, 3H, major isomer), 7.32 (m, 2H minor isomer), 2.47 (s, 3H, major), 2.46 (s, 3H, minor isomer). ^{13}C NMR (126 MHz, $CDCl_3$) δ 189.8, 184.0, 155.9, 155.5, 152.4, 151.8, 143.8, 143.3, 136.6, 134.6, 129.7, 129.5, 129.5, 129.5, 129.3, 129.3, 129.2, 129.0, 128.9, 128.2, 127.1, 125.7, 125.4, 125.3, 124.4, 123.9, 123.3, 122.9, 121.3, 116.1, 112.5, 111.5, 77.4, 77.1, 76.9, 21.7, 21.7. HRMS. Calculated for $C_{16}H_{12}O_2Na^+$ ($M+Na^+$): 259.0730, found 259.0735.



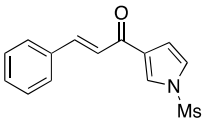
Thiophen-2-yl(2,4,6-trimethoxyphenyl)methanone 2.1nn. Prepared according to procedure A using $[Pd(allyl)Cl]_2$ (5 mg, 0.013 mmol) 2-iodothiophene (105 mg, 0.5 mmol), 1,3,5-trimethoxybenzene (168 mg, 1 mmol), at room temperature and 30 atm CO. Pale yellow oil, 55% yield (77 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 4.9, 1.2 Hz, 1H), 7.47 (dd, *J* = 3.7, 1.2 Hz, 1H), 7.08 (dd, *J* = 4.9, 3.7 Hz, 1H), 6.18 (s, 2H), 3.88 (s, 3H), 3.74 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.9, 162.5, 158.7, 146.0, 134.0, 133.8, 127.9, 111.2, 90.7, 55.9, 55.5. HRMS. Calculated for $C_{14}H_{14}O_4SNa^+$ ($M+Na^+$): 301.0505, found 301.0504



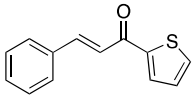
(1-(methylsulfonyl)-1H-pyrrol-3-yl)(thiophen-2-yl)methanone 2.1oo. Prepared according to procedure A using $[Pd(allyl)Cl]_2$ (5 mg, 0.013 mmol) 2-iodothiophene (210 mg, 1 mmol), and N-mesyl pyrrole (290 mg, 2 mmol) at room temperature Pale yellow liquid, 40% yield (102 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.75 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.58 (dd, *J* = 3.1, 1.7 Hz, 1H), 7.20 (dd, *J* = 5.0, 3.8 Hz, 1H), 7.06 (dd, *J* = 3.7, 1.7 Hz, 1H), 6.36 (t, *J* = 3.4 Hz, 1H), 3.85 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.8, 143.4, 134.4, 134.4, 132.2, 129.0, 128.1, 124.3, 110.4, 44.1. HRMS. Calculated for $C_{10}H_9NO_3S_2Na$ ($M+Na^+$): 277.9916, found 277.9914.



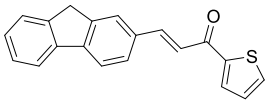
(E)-1-(2,5-dimethoxyphenyl)-3-phenylprop-2-en-1-one 2.1pp. Prepared according to procedure A at room temperature using (*E*)-(2-iodovinyl)benzene (115 mg, 0.5 mmol), $[Pd(allyl)Cl]_2$ (5 mg, 0.013 mmol), and 1,4-dimethoxybenzene (138 mg, 1 mmol) at 30 atm CO. Brown oil, 82% yield (110 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 15.9 Hz, 1H), 7.64 – 7.60 (m, 2H), 7.45 (d, *J* = 15.9 Hz, 1H), 7.42 (dd, *J* = 5.0, 2.0 Hz, 3H), 7.22 (d, *J* = 3.2 Hz, 1H), 7.06 (dd, *J* = 9.0, 3.2 Hz, 1H), 6.97 (d, *J* = 9.0 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.4, 153.6, 152.6, 143.3, 135.2, 130.3, 129.7, 128.9, 128.4, 126.9, 119.2, 114.4, 113.4, 56.5, 55.9. HRMS. Calculated for $C_{17}H_{16}SO_3Na$ ($M+Na^+$): 291.0992, found 291.0992.



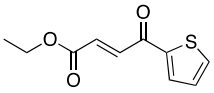
(E)-1-(1-(methylsulfonyl)-1H-pyrrol-3-yl)-3-phenylprop-2-en-1-one 2.1qq. Prepared according to procedure A using (*E*)-(2-iodovinyl)benzene (23 mg, 0.1 mmol), $[Pd(allyl)Cl]_2$ (0.9 mg, 0.003 mmol), and N-mesyl pyrrole (29 mg, 0.2 mmol) in DCE (1 mL) at room temperature. Pale yellow oil, 86% yield (24 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 15.7 Hz, 1H), 7.67 – 7.59 (m, 3H), 7.49 – 7.41 (m, 3H), 7.31 (d, *J* = 15.7 Hz, 1H), 7.23 (dd, *J* = 3.7, 1.6 Hz, 1H), 6.38 (t, *J* = 3.5 Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.5, 144.5, 134.6, 134.2, 130.7, 130.0, 129.0, 128.5, 123.8, 122.8, 110.4, 43.6. HRMS. Calculated for $C_{14}H_{13}NO_3SNa^+$ ($M+Na^+$): 298.0508, found 298.0515.



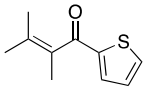
(E)-3-phenyl-1-(thiophen-2-yl)prop-2-en-1-one 2.1rr.[86] Prepared according to procedure A using (*E*)-(2-iodovinyl)benzene (23 mg, 0.1 mmol), $[Pd(allyl)Cl]_2$ (0.9 mg, 0.003 mmol), and thiophene (0.2 mmol, 18 mg) in DCE (1 mL) at room temperature. Brown oil, 83% yield (18 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 – 7.85 (m, 2H), 7.71 (dd, *J* = 4.9, 1.1 Hz, 1H), 7.70 – 7.66 (m, 2H), 7.49 – 7.43 (m, 4H), 7.22 (dd, *J* = 4.9, 3.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.0, 145.5, 144.1, 134.7, 133.9, 131.8, 130.6, 129.0, 128.5, 128.3, 121.6. HRMS. Calculated for $C_{13}H_{10}SONa^+$ ($M+Na^+$): 237.0345, found 237.0347.



(E)-3-(9H-fluoren-2-yl)-1-(thiophen-2-yl)prop-2-en-1-one 2.1ss. Prepared according to procedure A at room temperature using (*Z*)-2-(2-iodovinyl)-9*H*-fluorene (80 mg, 0.25 mmol), $[Pd(allyl)Cl]_2$ (2 mg, 0.0063 mmol), in neat thiophene (1 mL) instead of DCE. Yellow solid, 81% yield (61 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, *J* = 15.5 Hz, 1H), 7.90 (dd, *J* = 3.8, 1.0 Hz, 1H), 7.86 – 7.78 (m, 3H), 7.71 – 7.65 (m, 2H), 7.58 (d, *J* = 7.4 Hz, 1H), 7.48 (d, *J* = 15.5 Hz, 1H), 7.41 (t, *J* = 7.2 Hz, 1H), 7.36 (td, *J* = 7.4, 1.1 Hz, 1H), 7.20 (dd, *J* = 4.9, 3.8 Hz, 1H), 3.96 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.1, 145.9, 144.7, 144.6, 144.1, 144.0, 141.0, 133.8, 133.4, 131.8, 128.3, 128.1, 127.7, 127.2, 125.3, 125.0, 120.8, 120.6, 120.4, 37.0. HRMS. Calculated for $C_{20}H_{14}OSK$ (MK^+): 341.0397, found: 341.0397.

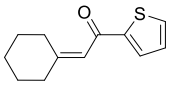


Ethyl (*E*)-4-oxo-4-(thiophen-2-yl)but-2-enoate 2.1tt. Prepared according to procedure A at room temperature using ethyl (*Z*)-3-iodoacrylate (113 mg, 0.5 mmol), $[Pd(allyl)Cl]_2$ (2 mg, 0.0063 mmol), and thiophene (42 mg, 0.5 mmol). Yellow solid, 56% yield (59 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 3.8, 0.9 Hz, 1H), 7.83 – 7.75 (m, 2H), 7.21 (dd, *J* = 4.8, 3.9 Hz, 1H), 6.95 (d, *J* = 15.4 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.1, 165.5, 144.3, 136.0, 135.7, 133.4, 132.1, 128.6, 61.4, 14.2. HRMS. Calculated for $C_{10}H_{10}O_3NaS$ ($M+Na^+$): 233.0243, found: 233.0243.

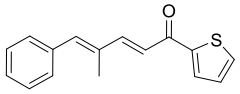


2,3-dimethyl-1-(thiophen-2-yl)but-2-en-1-one 2.1uu. Prepared according to procedure A at room temperature for 48h using 2-iodo-3-methylbut-2-ene (49 mg, 0.25 mmol), $[Pd(allyl)Cl]_2$ (2 mg, 0.0063 mmol), 2,6-di-*tert*-butylpyridine (57 mg, 0.30 mmol) in

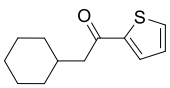
neat thiophene (1 mL) instead of DCE. Yellow oil, 84% yield (38 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 4.9, 1.1 Hz, 1H), 7.60 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.13 (dd, *J* = 4.9, 3.8 Hz, 1H), 1.94 (s, 3H), 1.83 (s, 3H), 1.69 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.0, 144.2, 134.2, 133.7, 133.1, 1230.0, 128.1, 22.6, 20.0, 16.7. HRMS. Calculated for $C_{10}H_{12}ONaS$ ($M+Na^+$): 203.0501, found: 203.0496.



2-cyclohexylidene-1-(thiophen-2-yl)ethan-1-one 2.1vv . Prepared according to procedure A at room temperature using (iodomethylene)cyclohexane (56 mg, 0.25 mmol), $[Pd(allyl)Cl]_2$ (2 mg, 0.0063 mmol), 2,6-di-*tert*-butylpyridine (57 mg, 0.30 mmol) in neat thiophene (1 mL) instead of DCE. White solid, 84% yield (43 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.58 (dd, *J* = 4.9, 1.1 Hz, 1H), 7.10 (dd, *J* = 4.9, 3.8 Hz, 1H), 6.55 (s, 1H), 2.88 (t, *J* = 5.8 Hz, 2H), 2.34 – 2.23 (m, 2H), 1.72 (qd, *J* = 7.8, 7.0, 4.9 Hz, 2H), 1.68 – 1.59 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.1, 164.2, 147.1, 133.1, 131.1, 128.1, 117.9, 38.6, 30.7, 29.0, 28.1, 26.4. HRMS. Calculated for $C_{12}H_{14}OSNa$ ($M+Na^+$): 229.0658, found: 229.0657.

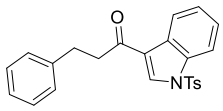


(2E,4E)-4-methyl-5-phenyl-1-(thiophen-2-yl)penta-2,4-dien-1-one 2.1ww. Prepared according to procedure A at room temperature using ((1*E*,3*Z*)-4-iodo-2-methylbuta-1,3-dien-1-yl)benzene (68 mg, 0.25 mmol), $[Pd(allyl)Cl]_2$ (2 mg, 0.0063 mmol), 2,6-di-*tert*-butylpyridine (57 mg, 0.30 mmol) in neat thiophene (1 mL) instead of DCE. Yellow solid, 92% yield (59 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 – 7.81 (m, 1H), 7.72 – 7.63 (m, 2H), 7.43 – 7.36 (m, 4H), 7.31 (ddd, *J* = 8.7, 5.7, 2.8 Hz, 1H), 7.17 (dd, *J* = 4.8, 3.9 Hz, 1H), 7.00 – 6.93 (m, 2H), 2.16 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.4, 149.5, 145.9, 140.8, 136.8, 134.6, 133.6, 131.6, 129.7, 128.5, 128.3, 128.0, 121.1, 14.1. HRMS. Calculated for $C_{16}H_{14}OSNa$ ($M+Na^+$): 277.0658, found: 277.0659.

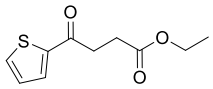


2-cyclohexyl-1-(thiophen-2-yl)ethan-1-one 2.1xx. Prepared according to the vinyl ketone hydrogenation procedure using compound **2.1vv** (35 mg, 0.17 mmol) Colourless oil, 99% yield (35 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.61 (dd, *J* = 4.9, 1.1 Hz, 1H), 7.12 (dd, *J* = 5.0, 3.8 Hz, 1H), 2.74 (d, *J* = 6.9 Hz, 2H), 2.02 – 1.93

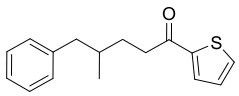
(m, 1H), 1.80 – 1.73 (m, 2H), 1.72 – 1.62 (m, 3H), 1.27 (ddt, *J* = 12.6, 6.3, 2.6 Hz, 2H), 1.20 – 1.11 (m, 1H), 1.07 – 0.97 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.3, 145.3, 133.6, 131.9, 128.2, 47.2, 35.3, 33.5, 26.3, 26.2. HRMS. Calculated for $C_{12}H_{16}OSNa$ ($M+Na^+$): 231.0814, found: 231.0819.



3-phenyl-1-(1-tosyl-1*H*-indol-3-yl)propan-1-one 2.1yy. Prepared according to the vinyl ketone hydrogenation procedure using (E)-3-phenyl-1-(1-tosyl-1H-indol-3-yl)prop-2-en-1-one (32 mg, 0.08 mmol). Colorless solid, 87% yield (28 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 – 8.32 (m, 1H), 8.16 (s, 1H), 7.95 – 7.89 (m, 1H), 7.80 (d, *J* = 8.5 Hz, 2H), 7.36 (dtd, *J* = 12.8, 6.7, 6.1, 1.5 Hz, 2H), 7.31 (d, *J* = 7.3 Hz, 2H), 7.29 – 7.25 (m, 4H), 7.25 – 7.20 (m, 1H), 3.23 (dd, *J* = 8.6, 6.8 Hz, 2H), 3.10 (dd, *J* = 8.5, 6.8 Hz, 2H), 2.37 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.2, 146.0, 141.2, 135.0, 134.6, 131.8, 130.3, 128.7, 128.6, 127.7, 127.3, 126.3, 125.9, 124.9, 123.2, 121.3, 113.2, 41.9, 30.3, 21.8. HRMS. Calculated for $C_{24}H_{21}NO_3SNa$ ($M+Na^+$): 426.1134, found: 426.1127.

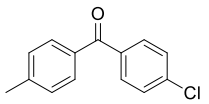


ethyl 4-oxo-4-(thiophen-2-yl)butanoate 2.1zz. Prepared according to the vinyl ketone hydrogenation procedure using compound **1x** (24mg, 0.11 mmol). Colourless oil, 96% yield (23 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.66 (dd, *J* = 4.9, 1.1 Hz, 1H), 7.16 (dd, *J* = 4.9, 3.8 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.28 (t, *J* = 6.8 Hz, 2H), 2.78 (t, *J* = 6.8 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.0, 172.7, 143.7, 133.6, 131.9, 128.1, 60.7, 34.0, 28.3, 14.2. HRMS. Calculated for $C_{10}H_{12}NaO_3S$ ($M+Na^+$): 235.0399, found: 235.0397.

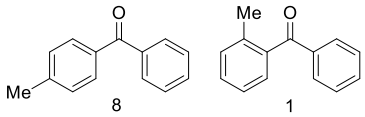


4-methyl-5-phenyl-1-(thiophen-2-yl)pentan-1-one 2.1aaa. Prepared according to to the vinyl ketone hydrogenation procedure using compound **1ww** (37 mg, 0.15 mmol). White solid, 98% yield (38 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.66 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.60 (dd, *J* = 4.9, 1.1 Hz, 1H), 7.29 – 7.23 (m, 2H), 7.20 – 7.12 (m, 3H), 7.10 (dd, *J* = 4.9, 3.8 Hz, 1H), 2.99 – 2.82 (m, 2H), 2.68 (dd, *J* = 13.5, 5.8 Hz, 1H), 2.43 (dd, *J* = 13.5, 7.8 Hz, 1H), 1.84 (tdd, *J* = 10.9, 4.7, 3.4 Hz, 2H), 1.62 (dt, *J* = 9.5, 5.7 Hz, 1H), 0.91 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.5, 144.5, 141.0, 133.5, 131.8, 129.3, 128.3, 128.2,

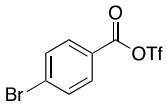
125.9, 43.6, 37.7, 34.9, 31.6, 19.4. HRMS. Calculated for $C_{16}H_{18}OSNa$ ($M+Na^+$): 281.0971, found: 281.0970.



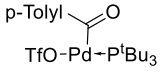
(4-chlorophenyl)(p-tolyl)methanone 2.1bbb[87]. Prepared according to the procedure described in section XII in chlorobenzene (2 mL) and 50°C. White solid, 97% yield (112 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 8.5 Hz, 2H), 7.71 (d, J = 8.1 Hz, 2H), 7.47 (d, J = 8.5 Hz, 0H), 7.31 (d, J = 7.9 Hz, 2H), 2.47 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.2, 143.5, 138.6, 136.2, 134.5, 131.4, 130.2, 129.1, 128.6, 21.7.



Phenyl(*p*-tolyl)methanone 2.1ccc[67] and phenyl(o-tolyl)methanone[68] 2.1ccc'. Prepared according to the procedure described in section XII using iodobenzene (102 mg, 0.5 mmol) and toluene (92 mg, 1 mmol). White solid, 98% isolated total yield (97 mg) of both isomers (8:1 ratio). 1H NMR (400 MHz, $CDCl_3$) δ 7.79 (m, 2H for major isomer, 2H for minor isomer), 7.73 (d, *J* = 8.1 Hz, 2H, major isomer), 7.57 (m, 1H, both isomers), 7.46 (m, 2H, both isomers), 7.39 (td, *J* = 7.5, 1.5 Hz, 1H, minor isomer), 7.34 – 7.22 (m, 2H for major isomer, 3H for minor isomer), 2.44 (s, 3H for major isomer), 2.34 (s, 3H for minor isomer). 13C NMR (126 MHz, CDCl3) δ 198.6, 196.5, 143.2, 138.6, 138.0, 137.7, 136.7, 134.9, 133.1, 132.2, 131.0, 130.3, 130.3, 130.1, 129.9, 129.0, 128.5, 128.5, 128.2, 125.2, 21.7, 20.0.

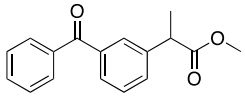


4-bromobenzoic trifluoromethanesulfonic anhydride 2.3a. Light yellow solid**,** 82% yield (273 mg). ^{1}H NMR (500 MHz, CD_3NO_2) δ 8.04 (d, *J* = 8.7 Hz, 1H), 7.85 (d, *J* = 8.7 Hz, 1H). ^{13}C NMR (126 MHz, CD_3NO_2) δ 156.3, 132.9, 132.9, 132.1, 118.4 (q, *J* = 319.9 Hz). ^{19}F NMR (471 MHz, CD_3NO_2) δ -75.8.

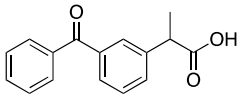


Yellow solid, 87% yield (134 mg). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 2.41 (s, 3H), 1.50 (d, *J* = 13.3 Hz, 27H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 198.2 (d, *J* = 7.8 Hz), 145.3, 131.1, 130.0 (d, *J* = 18.5 Hz), 129.7, 118.6, 40.1 (d, *J* = 11.1 Hz), 32.2 (d, *J* = 3.5 Hz), 22.0. ^{31}P NMR (162 MHz, $CDCl_3$): δ 80.7. Elemental

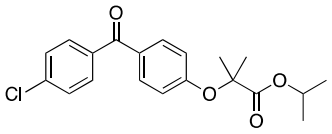
analysis for $C_{21}H_{34}F_3O_4PSPd$: Theory 43.72 %C, 5.94 %H, 5.56 %S, Found 43.62 %C, 6.09 %H, 6.23 %S.



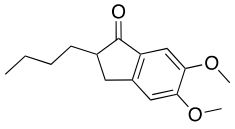
Ketoprofen methyl ester.[88] White solid, 51% yield (68 mg). 1H NMR (500 MHz, CDCl3) δ 7.83 (d, *J* = 7.1 Hz, 2H), 7.77 (s, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.57 (d, *J* = 7.7 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 7.47 (t, *J* = 7.7 Hz, 1H), 3.83 (q, *J* = 7.2 Hz, 1H), 3.70 (s, 3H), 1.56 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.5, 174.5, 140.8, 137.9, 137.5, 132.5, 131.50, 130.1, 129.2, 129.0, 128.6, 128.3, 52.2, 45.3, 18.5.



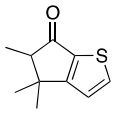
Ketoprofen 2.5.[89] White Solid, 99% yield (50 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.59 (s, 1H), 7.84 – 7.79 (m, 3H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.60 (q, *J* = 7.7 Hz, 2H), 7.48 (dt, *J* = 13.6, 7.7 Hz, 3H), 3.85 (q, *J* = 7.2 Hz, 2H), 1.58 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.5, 180.0, 140.1, 137.9, 137.4, 132.6, 131.7, 130.1, 129.3, 129.3, 128.6, 128.3, 45.2, 18.1.



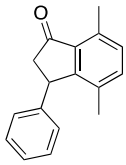
Fenofibrate 2.6.[89] White solid, 83% yield (60 mg) when using silver triflmide and 57% yield (41 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.6 Hz, 2H), 7.72 (d, *J* = 8.2 Hz, 2H), 7.47 (d, *J* = 8.2 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 5.11 (m, *J* = 5.7 Hz, 1H), 1.69 (s, 6H), 1.23 (d, *J* = 6.3 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.3, 173.1, 159.7, 138.4, 136.4, 131.94, 131.2, 130.2, 128.5, 117.3, 79.4, 69.4, 25.4, 21.5.



2-butyl-5,6-dimethoxy-2,3-dihydro-1*H*-inden-1-one 2.7a. Prepared according to procedure A at 50°C using $[Pd(allyl)Cl]_2$ (2 mg, 0.0063 mmol), 2-iodohex-1-ene (53 mg, 0.25 mmol) and 1,2-dimethoxy benzene (173 mg, 1.25 mmol). Slight yellow solid, 60 % yield (37 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (s, 1H), 6.89 (s, 1H), 3.99 (s, 3H), 3.93 (s, 3H), 3.25 (dd, *J* = 16.9, 7.5 Hz, 1H), 2.75 (dd, *J* = 17.0, 3.4 Hz, 1H), 2.71 – 2.63 (m, 1H), 2.01 – 1.92 (m, 1H), 1.48 – 1.31 (m, 5H), 0.94 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.8, 155.4, 149.4, 149.0, 129.6, 107.4, 104.4, 56.2, 56.1, 47.8, 32.6, 31.5, 29.60, 22.8, 14.0. HRMS: Calculated for $C_{15}H_{20}O_3Na$ ($M+Na^+$): 271.1305, found: 271.1316.



4,4,5-trimethyl-4,5-dihydro-6*H*-cyclopenta[*b*]thiophen-6-one 2.7b. Prepared according to procedure A at room temperature using $[Pd(allyl)Cl]_2$ (2 mg, 0.0063 mmol), 2-iodo-3-methylbut-2-ene (49 mg, 0.25 mmol) in neat thiophene (1 mL) instead of DCE. Slight yellow solid, 48 % yield (22 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 4.8 Hz, 1H), 7.06 (d, *J* = 4.8 Hz, 1H), 2.79 (q, *J* = 7.5 Hz, 1H), 1.43 (s, 3H), 1.24 (d, *J* = 7.5 Hz, 3H), 1.22 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.7, 176.6, 140.12, 137.9, 121.6, 59.0, 40.9, 28.1, 25.8, 10.6. HRMS: Calculated for $C_{10}H_{12}OSNa$ ($M+Na^+$): 203.0501, found: 203.0510.



4,7-dimethyl-3-phenyl-2,3-dihydro-1H-inden-1-one 2.7c.[91] Prepared according to procedure A at 60°C using $[Pd(allyl)Cl]_2$ (5 mg, 0.013 mmol), (*E*)-(2-iodovinyl)benzene (115 mg, 0.5 mmol) and *p*-xylene (106 mg, 1 mmol). Bright yellow oil, 57 % yield (67 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.20 (m, 4H), 7.12 (d, *J* = 7.5 Hz, 1H), 7.05 (dd, *J* = 8.2, 1.1 Hz, 2H), 4.54 (dd, *J* = 8.4, 2.4 Hz, 1H), 3.22 (dd, *J* = 19.0, 8.5 Hz, 1H), 2.70 (s, 3H), 2.59 (dd, *J* = 19.0, 2.7 Hz, 1H), 1.99 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.6, 156.2, 144.1, 135.8, 135.8, 134.5, 133.7, 130.2, 128.8, 127.4, 126.5, 48.0, 43.3, 18.1, 18.1. HRMS calculated for $C_{17}H_{16}ONa$ ($M+Na^+$): 259.1093, found 259.1095.

2.5.12. NMR Spectra

See supporting information for publication: *Nat. Chem.* **2018,** *10*, 193.

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Chapter 3. Decarboxylation with Carbon Monoxide: The Direct Conversion of Carboxylic Acids into Potent Acid Triflate Electrophiles

3.1. Preface

Chapter 2 described the palladium-catalyzed generation of reactive acid triflate electrophiles from aryl iodides and CO. Although aryl iodides are commercially available and stable reagents, we questioned if other even more broadly available reagents, such as carboxylic acids might be viable starting materials for the synthesis of acid triflates. This chapter describes the realization of this goal, and proceeds without a palladium catalyst. The reaction involves oxidative carbonylation of carboxylic acids with I_2 in the presence of AgOTf, and is postulated to proceed via acyl hypoiodites that react with CO to form acid triflates. Coupling this chemistry with subsequent trapping with arenes offers a mild, room temperature approach to generate ketones directly from broadly available carboxylic acids. This work has been published in *Angewandte Chemie International Edition* (**2019**, *58*, 5085).

3.2. Introduction

Carboxylic acids are broadly available, low cost, and often accessible from renewable resources, making them attractive building blocks in organic synthesis. A classic use of carboxylic acids is their conversion to other carbonyl-containing derivatives, including amides, esters and ketones.[1] Such acylation reactions have been estimated to account for 22% of all pharmaceutical transformations,[2] and are also heavily employed in large scale polymer syntheses and other applications.[3] As carboxylic acids are themselves stable, they must be transformed into reactive acylating agents, which can lead to limitations.[4] The *in situ* activation of carboxylic acids with coupling reagents is broadly employed in esterification and amidation reactions (e.g. with carbodiimides, hydroxytriazoles, Figure 3.1a), but these reagents are synthetic, can present purification challenges, and generate significant chemical waste. In addition, the modest electrophilicity of the intermediates in this chemistry limits its scope. Alternatively, acyl halides are potent electrophiles capable of rapid reaction with a diverse array of nucleophiles.[5] Their preparation in this case requires the use of high energy and caustic reagents such as thionyl chloride, oxalyl chloride, or PCl_3, none of which are desirable in synthesis, and can lead to

significant difficulty when used on large scale. These features have made more efficient acylation protocols a high priority, especially as we move towards creating more efficient, less waste-intensive syntheses.[6]

An alternative approach for the preparation of carboxylic acid derivatives is the carbonylation of organic halides (Figure 3.1b).[7] These reactions typically exploit transition metal catalysis to incorporate carbon monoxide, a stable and abundant C1 building block, into a variety of carbonyl-containing products. This includes research in our lab and others that has demonstrated that acyl halide and even potent acyl triflate electrophiles can be generated from carbonylations.[8] A limitation here is the required use of aryl- or vinyl-halides as reagents. Although a number of organic halides are commercially available, they are rarely naturally occurring.

In considering methods to more efficiently access acylating agents one attractive possibility would be to do so by combination of these two broadly available reagents: carboxylic acids and carbon monoxide. There has been significant recent effort directed towards the replacement of organic halides with carboxylic acids, giving rise to various transition-metal catalyzed decarboxylative cross-coupling and related transformations.[9] In contrast, metal catalyzed decarboxylative carbonylations are rare, and to date limited to the use of alkynyl carboxylic acids or activated benzylic/allylic carbonate derivatives.[10] An intriguing alternative to metal catalyzed decarboxylations is the Hunsdiecker reaction, wherein halogenation of carboxylic acids can lead to decarboxylation to generate aryl halides (Figure 3.1c).[11] This transformation has been recently shown by the Larossa lab to offer efficient metal free access to aryl halides.[12] In addition to generating aryl halides, the aroyl hypohalite intermediates generated in these systems are themselves reactive, and can associate with Lewis bases such as pyridine to form adducts **A**.[13] In this light, we questioned if this platform might be used in an alternative fashion, where the interception of the hypoiodite intermediate with carbonylation chemistry could offer a route to generate high energy acylating agents (Figure 3.1d). This would both replace aryl halides with carboxylic acids in carbonylations, and at the same time create a new route to perform acylation reactions directly from carboxylic acids. Described below are our efforts to develop this reaction. This has led to a new, carbonylative approach to convert aromatic carboxylic acids directly into electrophilic acid triflates. The transformation combines the useful features of classical acyl electrophile synthesis (carboxylic acid reagents), with those of transition metal catalyzed

carbonylations (exploiting broadly available CO). In addition, the high reactivity of the electrophiles offers a method to use carboxylic acids in Friedel-Crafts acylation reactions under mild conditions, and without the classical use of reactive, caustic reagents.

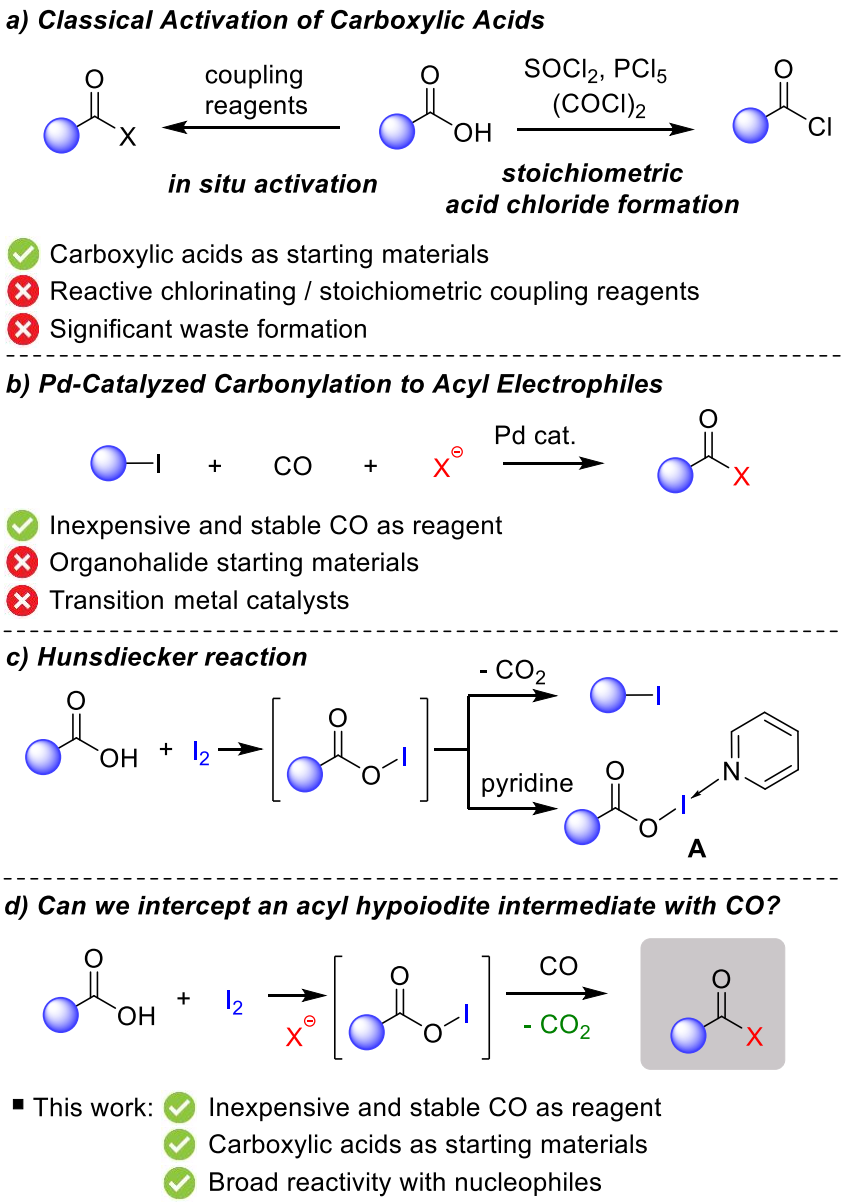
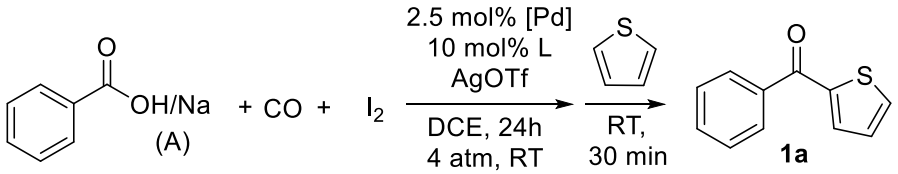


Figure 3.1. Approached to Carboxylic Acid Activation and Derivitization

3.3. Results and Discussion

Our initial studies involved the use of benzoic acid in concert with I_2 as replacement feedstocks for aryl iodides in the previously reported palladium catalyzed carbonylative synthesis of acid triflates.[8d] Thiophene was employed to trap any electrophile generated to form ketone **3.1a**. After examining a number of reaction conditions, it was found that reaction of sodium benzoate and iodine in the presence of CO, silver triflate and the $[Pd(allyl)Cl]_2$ catalyst leads to ketone **3.1a** in 29% yield (Table 3.1, entry 1). Added ligands have only a minimal effect of the reaction (entries 2-4). In an attempt to further improve the yield, a simple control experiment was to remove the palladium catalyst. To our surprise, not only did the reaction still proceed, but did so as effectively as with palladium (entry 6), and in good yield at 60 °C (80%, entry 7). Moreover, and in contrast to previous reports of carboxylic acid iodination, the reaction can proceed at ambient temperature when starting directly from the carboxylic acid, and allows the high yield formation of **3.1a** (entry 10).

Table 3.1. Development of a Decarboxylative Synthesis of Acid Triflates[a]



entry	A	Pd	L	Temp	Yield 1a
1	Na	$[Pd(allyl)Cl]_2$	-	r.t.	29%
2	Na	$[Pd(allyl)Cl]_2$	P^tBu_3	r.t.	36%
3	Na	$[Pd(allyl)Cl]_2$	PPh_3	r.t.	47%
4	Na	$[Pd(allyl)Cl]_2$	Xantphos	r.t.	29%
5[b]	Na	-		r.t.	0%
6	Na	-		r.t.	47%
7	Na	-		60 °C	80%
8	H	-		60 °C	92%
9[c]	H	-		30 °C	79%
10	H	-		r.t.	92% (87%)[d]

[a]benzoic acid derivative (0.25 mmol), AgOTf (161 mg, 0.63 mmol), I_2 (140 mg, 0.55 mmol), 4 atm CO, $[Pd(allyl)Cl]_2$ (2.3 mg, 0.0063 mmol), Ligand (0.025 mmol), 1 mL DCE, 24 h, then thiophene (100 µL, 5 equiv) 30 min. [b]NaOTf instead of AgOTf. [c]1 atm CO. [d]Isolated.

The generation of ketone **3.1a** directly from a carboxylic acid under such mild reaction conditions, and without a palladium catalyst, led us to question what electrophilic intermediate is generated in this system. To probe this, the reaction was monitored by in situ ^{1}H, ^{13}C, and ^{19}F NMR analysis, which showed the rapid initial generation of benzoic anhydride **3.2a** within 90 min at ambient temperature (Figure 3.2a). This is followed by a slower conversion of **3.2a** to a new product **3.3a** that has been characterized to be benzoyl triflate. Of note, ^{13}C NMR analysis of **3.3a** shows a diagnostic carbonyl signal for an aroyl triflate (δ 155.5 ppm), while ^{19}F NMR reveals the presence of the triflate (δ -77.5 ppm). All other data are consistent with previously reported **3.3a**.[14]

Benzoyl triflates are a high energy electrophiles that can undergo uncatalyzed Friedel-Crafts reactions with a range of arenes, yet only rarely exploited, presumably due to their synthesis from also reactive acid chlorides.[15] Control experiments show that carbon monoxide, I_2 and AgOTf are all needed for the formation of **3.3a** (Figure 3.2a). In order to probe the role of carbon monoxide in this transformation, the reaction was performed with ^{13}C-labeled CO (Figure 3.2b). This led to no detectable ^{13}C-label in ketone **3.1a**, and we instead observed the generation of $^{13}CO_2$ by ^{13}C NMR. Alternatively, the use of ^{13}C-labeled benzoic acid results in the exclusive formation of the ^{13}C-labeled ketone **3.1a**. As such, unlike the Hunsdiecker reaction, decarboxylation does not occur directly from the hypoiodite, and instead CO is required to remove the oxygen in this intermediate. Further control experiments show no detectible reaction of CO with I_2 and AgOTf by themselves, implying that iodine reacts with the carboxylic acid rather than CO (Figure S3.5.1).[16] In order to probe the reactivity of CO with the acyl hypoiodite intermediate, the pyridine-stabilized adduct **3.4** was generated via previously reported procedures.[13] As shown in Figure 3.2c, the addition of carbon monoxide to **3.4** does indeed result in its ambient temperature decarboxylation to generate benzoic anhydride **3.2a** arising from the rapid reaction of *in situ* generated benzoyl triflate **3.3a** and **3.4**.

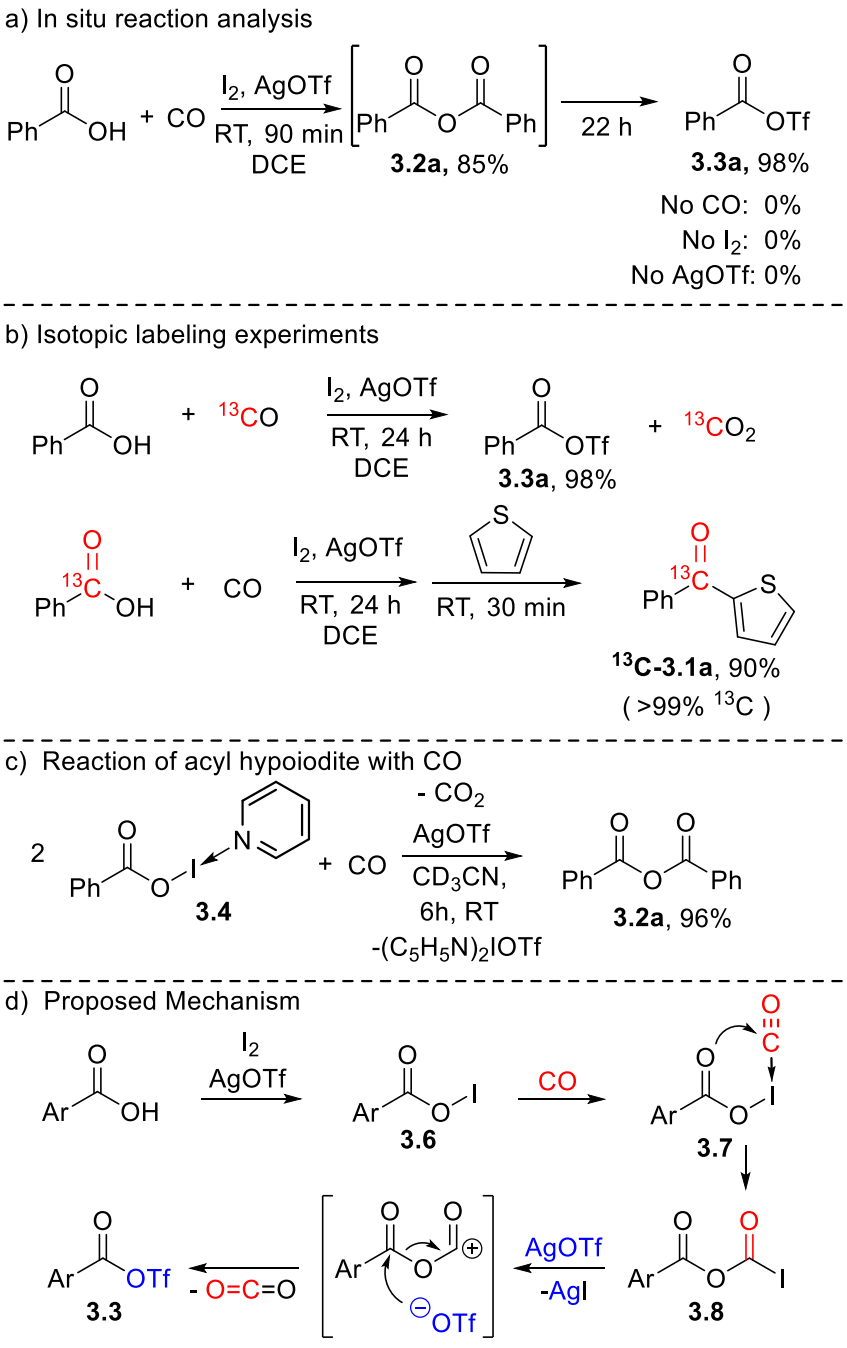


Figure 3.2. Mechanistic and Control Experiments

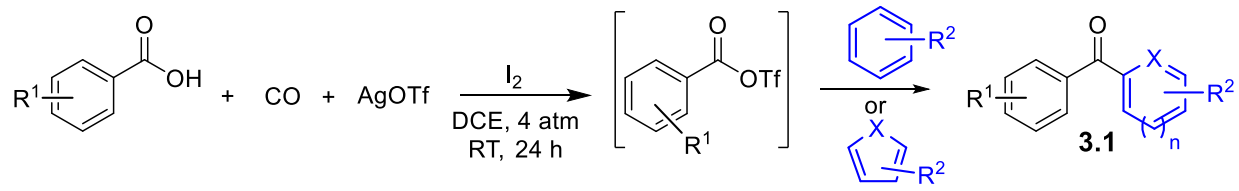
Together, these data are consistent with a mechanism similar to that shown in Figure 3.2d. In this, the AgOTf mediated iodination of benzoic acid allows the formation of hypoiodite intermediate **3.6**. While **3.6** can undergo decarboxylation to form aryl iodide, it is also Lewis acidic at iodine. We therefore postulate that carbon monoxide can intercept this Hunsdiecker

intermediate via an acid-base adduct **3.7**. The reaction of carbon monoxide with organic reagents without transition metal catalysts is rare (e.g. **3.6** with CO), especially at ambient temperature. The ability of **3.6** to do so presumably reflects its high electrophilicity, as well as its potential for subsequent rearrangement to **3.8**, followed by its ultimate decarboxylation to form aroyl triflate. The latter is in equilibrium with the observed anhydride prior to complete formation of the high energy aroyl triflate electrophile.[17,18] Overall, this provides a platform to convert a carboxylic acid under mild conditions into a potent electrophile with reagents (CO, I_2, AgOTf) that are each readily available.

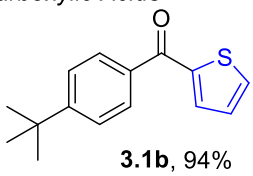
With a method to generate potent acyl triflate electrophiles from carboxylic acids in hand, we directed our attention to the use of this reaction. A wide range of aromatic carboxylic acids can be converted to aroyl triflates and ketones under these conditions (Table 3.2). Electron neutral and electron rich substrates react rapidly to generate the corresponding aroyl triflate at room temperature (**3.1a-3.1f**). Alternatively, electron poor carboxylic acids require mild heating to 40 °C (**3.1g-3.1s**). Due to the lack of the transition metal catalyst that is normally used in decarboxylative coupling reactions, aryl-chloride, -bromide, -iodide or -triflate functionalities are all compatible with the reaction (**3.1d-3.1j**). Substituents at all positions of the aromatic ring are tolerated, including even highly sterically congested 2,6-disubstituted benzoic acid derivatives (**3.1f-3.1g**). Potentially reactive functionalities can also be incorporated into the carboxylic acid unit, such as thioether (**3.1f**), esters (**3.1k**), nitro (**3.1l**), and nitrile (**3.1c**, **3.1m**) groups. In addition to variation of the carboxylic acid, aroyl triflates are exceptional electrophiles that offer the ability to functionalize a wide range electronically diverse arenes. This includes electron rich benzene derivatives, which react at room temperature (**3.1t-3.1u**), and also more deactivated arenes such as 1,3-dichlorobenzene (**3.1cc)** and 1,3,5-trifluorobenzene (**3.1dd**) at elevated temperatures (100 °C). The latter are typically sluggish in Friedel-Crafts acylation chemistry. Heterocycles can also be easily functionalized to heteroaryl ketones using this methodology. Examples include thiophenes (**3.1s**), furans (**3.1ii**), benzothiophene (**3.1jj**) and pyrroles (**3.1hh**). A feature of this transformation is its ability to generate ketones directly from carboxylic acids without multiple synthetic steps, or the use of high energy, caustic and strongly acidic reagents, and instead from compounds that are each relatively benign and bench stable.[19] As a result, it is also possible to perform Friedel-Crafts acylations under basic conditions in the presence of sensitive functionalities, such as with *N*-tosyl aniline. The latter undergoes deprotection under acidic

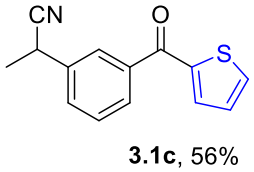
conditions to form various products,[20] but is cleanly acylated with the carbonylative reaction (**3.1z**).

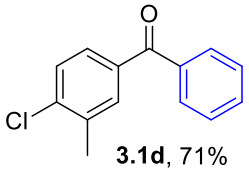
Table 3.2. CO Mediated Synthesis of Ketones from Arenes and Carboxylic Acids[a,b]

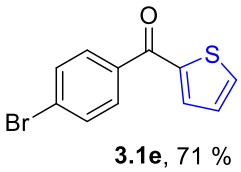


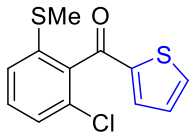
Carboxylic Acids

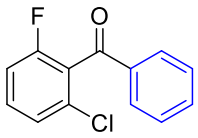

3.1b, 94%

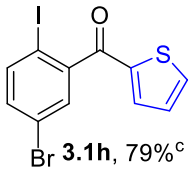

3.1c, 56%

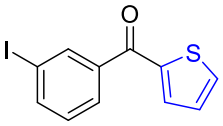

3.1d, 71%

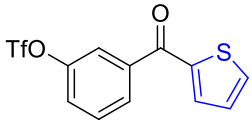

3.1e, 71 %

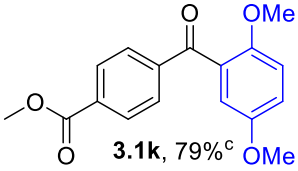

3.1f, 58%

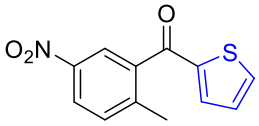

3.1g, 86 %[c]

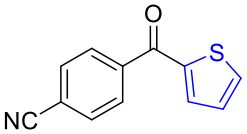

3.1h, 79%[c]

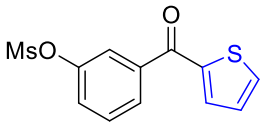

3.1i, 82%[c]

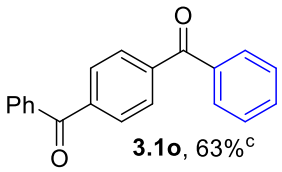

3.1j, 80%[c]

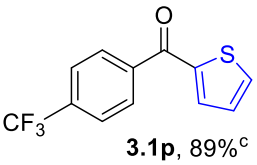

3.1k, 79%[c]

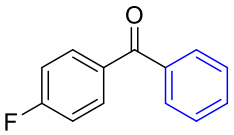

3.1l, 89%[c]

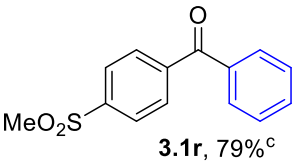

3.1m, 61%[c]


3.1n, 81%[c]


3.1o, 63%[c]


3.1p, 89%[c]


3.1q, 97%[c]


3.1r, 79%[c]

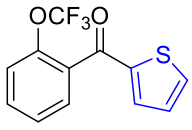
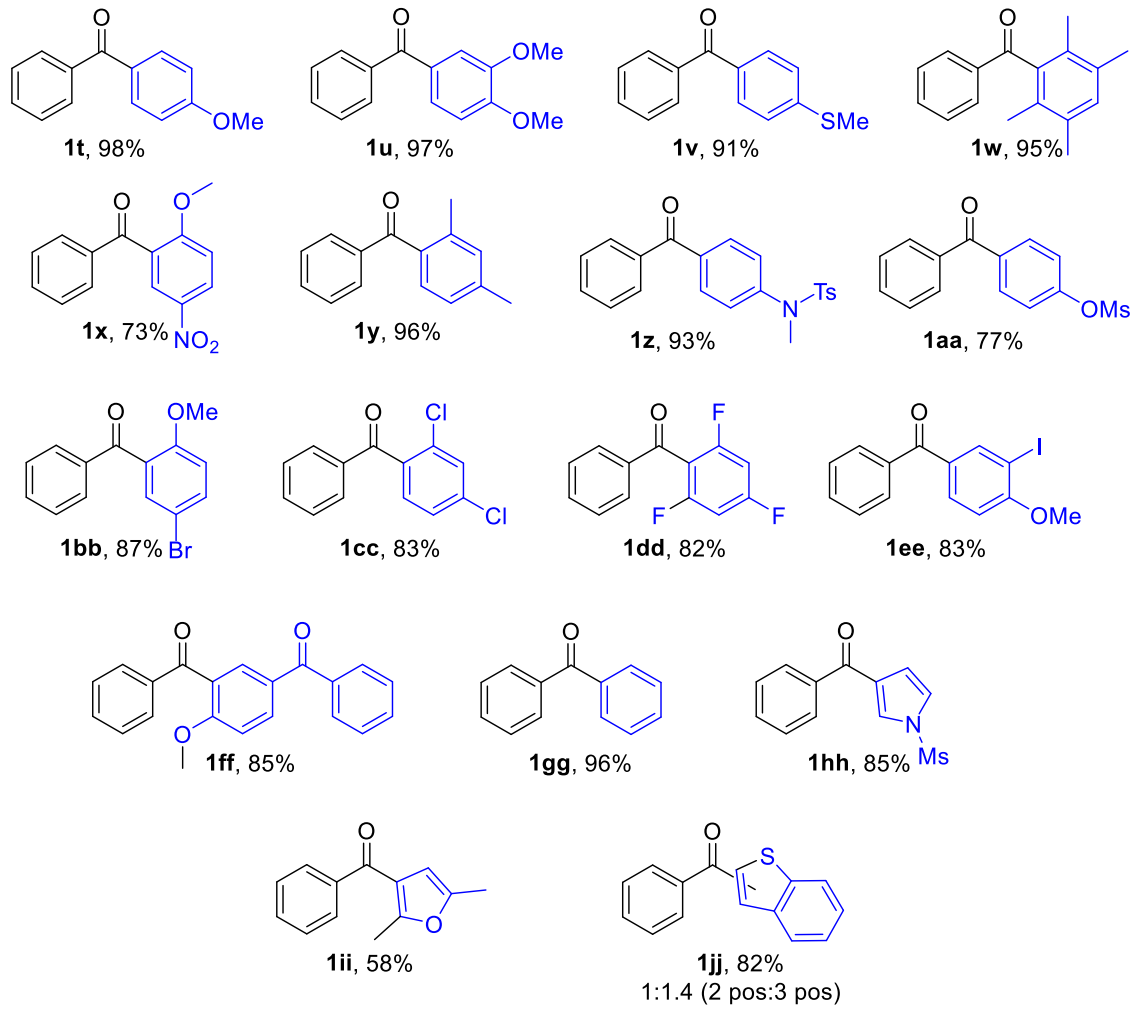

3.1t, 84%[c]

Table 3.2. CO Mediated Synthesis of Ketones from Arenes and Carboxylic Acids (Cont)

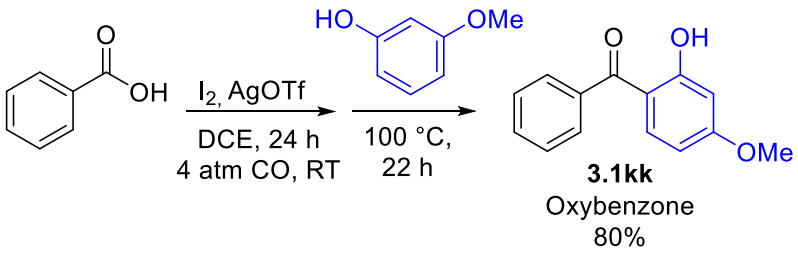
Arenes



[a]ArCOOH (0.5 mmol), silver triflate (321 mg, 1.25 mmol), I_2 (140 mg, 0.55 mmol), DCE (2 mL), 4 atm CO, then addition of arene (1 mmol), DCE (0.5 mL), RT-90 °C, 30 min – 16 h (see supporting information for full details). [b]Isolated Yields. [c]Generation of aroyl triflate at 40 °C.

Finally, we have explored the application of this chemistry to the targeted synthesis of Oxybenzone, a UV active reagent found in a broad array of personal care products, sunscreens, and plastics as a stabilizer (Scheme 3.1).[21] In contrast to its classical synthesis from high energy acid chlorides in the presence of Lewis acid catalysts (e.g. AlCl3), which can lead to

demethylation, **3.1kk** can be formed directly from benzoic acid using this protocol in high overall yield.[22]



Scheme 3.1. Application to the synthesis of Oxybenzone from benzoic acid[a]

[a]Presumably acylation of the phenol occurs initially, followed by a Fries rearrangement to form the ketone.

3.4. Conclusions

In conclusion, we have described a general approach to form aroyl triflate electrophiles directly from carboxylic acids. This proceeds via a carbon monoxide mediated deoxygenation, wherein carbon monoxide is postulated to intercept the iodination intermediate of the Hunsdiecker reaction. Overall, this offers a method to generate a diverse array of aroyl electrophiles from carboxylic acids under mild conditions with reagents that are each available and functional group compatible, and could prove of utility in situations where working with highly Lewis or Bronsted acidic reagents is undesirable. Studies towards exploiting this approach to create alternative classes of carbonyl-containing products are currently underway.

3.5. Experimental Section

3.5.1. General Considerations

All manipulations were carried in an inert atmosphere glovebox or using standard Schlenk techniques unless stated otherwise. Research grade carbon monoxide (99.5%) was used as received. Solvents were dried over calcium hydride, distilled under argon and stored over activated 4 Å molecular sieves. Pentane was dried using a solvent purifier system and then stored over activated 4 Å molecular sieves in the glovebox. Deuterated solvents were dried over calcium hydride, vacuum transferred and stored over activated 4 Å molecular sieves. Silver triflate was

dried by heating under vacuum and then stored in the glovebox. Iodine was dried by grinding with calcium oxide and then sublimed. N-Mesyl pyrrole,[23] and substituted aryl-mesylates,[24] -tosylates,[24] and -triflates[25] were prepared according to literature procedure. All other reagents were purchased from commercial suppliers and used as received after thoroughly drying to remove all traces of water. ^{1}H nuclear magnetic resonance (NMR) characterization was performed on 400 and 500 MHz spectrometers (101 and 126 MHz for ^{13}C NMR). High-resolution mass spectra were obtained using a quadrupole-time of flight and an orbitrap detector by direct infusion in positive ESI mode or by atmospheric pressure chemical ionization.

3.5.2. General Synthetic Procedures

Typical Procedure for Reaction Development: In a glovebox, silver triflate (161 mg, 0.63 mmol), iodine (70 mg, 0.28 mmol), and either benzoic acid (31 mg, 0.25 mmol) or sodium benzoate (36 mg, 0.25 mmol) were dry transferred to a Teflon sealed, thick walled 50 mL glass reaction vessel equipped with a magnetic stir bar. 1,2-dichloroethane (1 mL) was added to the vessel. The vessel was closed, removed from the glovebox, evacuated and backfilled with carbon monoxide three times, and finally pressurized with 4 atm carbon monoxide. After stirring at room temperature for 24 h, carbon monoxide was released on a Schlenk line and the vessel was brought back into the glovebox. Thiophene (100 μL, 1.25 mmol) was added to vessel and stirred for 30 min at room temperature in the glovebox. The vessel was removed from the glovebox, hexamethylbenzene (7 mg, 0.04 mmol) was added as a standard, and the reaction mixture was filtered through a pad of silica and thoroughly rinsed with DCM/EtOAc (1:1). The solvent was removed *in vacuo* and the yield of ketone **1a** (92% from benzoic acid) was determined by ^{1}H NMR analysis relative to the external standard.

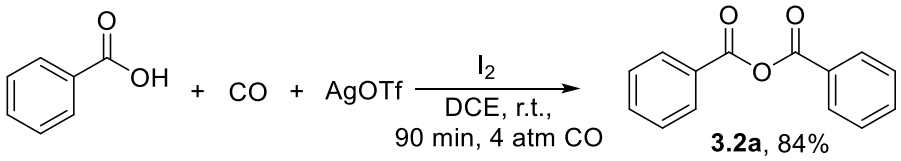
Procedures for the Synthesis of Ketones in Table 1:

All compounds in Table 1 were prepared via the following general procedure. See the tabulated NMR data for the specific adjustments regarding time, temperature, and scale.

Representative Procedure: In a glovebox, silver triflate (321 mg, 1.25 mmol), iodine (140 mg, 0.55 mmol), and benzoic acid (61 mg, 0.50 mmol) were dry transferred to a Teflon sealed, thick walled 50 mL glass reaction vessel equipped with a magnetic stir bar. 1,2-dichloroethane (2 mL)

was added to the vessel. The vessel was closed, removed from the glovebox, evacuated and backfilled with carbon monoxide three times, and finally pressurized with 4 atm carbon monoxide. After stirring for 24 h at room temperature (see tabulated NMR data for the specific conditions for other compounds), carbon monoxide was released on a Schlenk line and the vessel was brought back into the glovebox. Thiophene (100 μL, 1.25 mmol, 2.5 equiv) was added to vessel and stirred for 30 min at room temperature (see tabulated NMR data for the specific reaction conditions employed with other arenes). The vessel was removed from the glovebox and the reaction mixture was filtered through a pad of silica and thoroughly rinsed with DCM/EtOAc (1:1). The solvent was removed *in vacuo* and the residue was purified by column chromatography (silica gel, gradient hexane / ethyl acetate 0% to 5%) affording pure diarylketone **1a** as a pale yellow solid in 87% yield (82 mg).

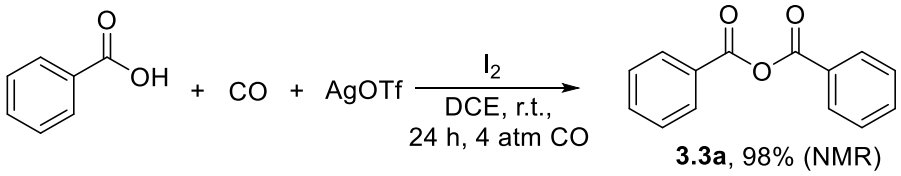
3.5.3. Reaction Progress Analysis



Reaction progress after 90 min: In a glovebox, silver triflate (161 mg, 0.63 mmol), iodine (70 mg, 0.28 mmol), and benzoic acid (31 mg, 0.25 mmol) were dry transferred to a Teflon sealed, thick walled 50 mL glass reaction vessel equipped with a magnetic stir bar. 1,2-dichloroethane (1 mL) was added to the vessel. The vessel was closed, removed from the glovebox, evacuated and backfilled with carbon monoxide three times, and finally pressurized with 4 atm carbon monoxide. After stirring at room temperature for 90 min, carbon monoxide was released on a Schlenk line, and brought back into the glovebox. Cyclooctane (11 mg, 0.09 mmol) was added as a standard and the reaction mixture was filtered through a Kimwipe pipette directly into a J. Young NMR tube. Under the acidic conditions, the ^{1}H NMR signals for benzoic anhydride **2a** and benzoyl triflate **3a** overlap, and their combined yield was determined to be 97% relative to the standard. To resolve these signals, the NMR tube was brought back into the glovebox and 2,6-di-*tert*-butyl-pyridine (67 μL, 0.3 mmol) was added. The ratio of benzoic anhydride to benzoyl triflate was 6.7 to 1 (or 84% yield of **2a**). The identity of benzoic anhydride was confirmed by comparison of ^{1}H NMR data to an authentic sample.

Reaction Mixture: ^{1}H NMR (400 MHz, 1,2-dichloroethane) δ 8.14 (d, *J* = 7.80 Hz, 4H, Bz_2O), 7.72 (t, *J* = 7.4 Hz, 2H, Bz_2O), 7.56 (t, *J* = 7.7 Hz, 4H, Bz_2O)

Commerical benzoic anhydride: ^{1}H NMR (400 MHz, 1,2-dichloroethane) δ 8.15 (d, *J* = 8.1 Hz, 4H), 7.71 (t, *J* = 7.5 Hz, 2H), 7.56 (t, *J* = 7.8 Hz, 4H).



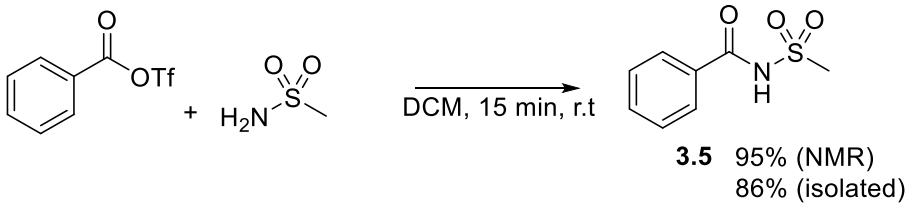
3.3a, 98% (NMR)

Reaction Progress after 24 hours: In a glovebox, silver triflate (161 mg, 0.63 mmol), iodine (70 mg, 0.28 mmol), and benzoic acid (31 mg, 0.25 mmol) were dry transferred to a Teflon sealed, thick walled 50 mL glass reaction vessel equipped with a magnetic stir bar. 1,2-dichloroethane (1 mL) was added to the vessel. The vessel was closed, removed from the glovebox, evacuated and backfilled with carbon monoxide three times, and finally pressurized with 4 atm carbon monoxide. After stirring at room temperature for 24 h, carbon monoxide was released on a Schlenk line, and brought back into the glovebox. Cyclooctane (10.5 mg, 0.09 mmol) was added as a standard and the reaction mixture was filtered through a Kimwipe pipette directly into a J. Young NMR tube. The yield of acid triflate **3a** (98%) was determined by ^{1}H NMR analysis (using the protons in 1,2-dichloroethane to shim) relative to the external standard. The presence of benzoyl triflate was corroborated by comparing the ^{1}H and ^{13}C NMR of the reaction mixture with the spectra of independently synthesized benzoyl triflate by literature procedures[26] and via further derivatization to a sulfonamide (see below).

Reaction Mixture: ^{1}H NMR (400 MHz, 1,2-dichloroethane) δ 8.07 (d, *J* = 7.1 Hz, 2H), 7.81 (t, *J* = 7.3 Hz, 1H), 7.60 (t, *J* = 7.9 Hz, 2H). ^{13}C NMR (126 MHz, 1,2-dichloroethane) δ 155.7, 136.1, 130.9, 128.9, 123.8, 118.2 (q, *J* = 318.7 Hz) ^{19}F NMR (377 MHz, 1,2-dichloroethane) δ -76.6.

Pure Benzoyl Triflate: ^{1}H NMR (400 MHz, 1,2-dichloroethane) δ 8.06 (d, *J* = 7.2 Hz, 2H), 7.81 (t, *J* = 7.5 Hz, 1H), 7.60 (t, *J* = 7.9 Hz, 2H). ^{13}C NMR (101 MHz, 1,2-dichloroethane) δ 155.7, 136.1, 131.0, 128.9, 123.9, 117.8 (q, *J* = 320.5 Hz). ^{19}F NMR (377 MHz, 1,2-dichloroethane) δ -74.4. HRMS. Calculated for $C_8H_5O_4F_3S^{\square+}$ ($M^{\square+}$): 253.9866, found: 253.9869.

Benzoyl Triflate with 1 equiv HOTf: ^{1}H NMR (400 MHz, 1,2-dichloroethane) δ 8.08 (d, *J* = 7.6 Hz, 2H), 7.82 (t, *J* = 7.5 Hz, 1H), 7.60 (t, *J* = 7.9 Hz, 2H). ^{13}C NMR (126 MHz, 1,2-dichloroethane) δ 155.8, 136.3, 131.0, 128.9, 123.6, 117.9 (q, *J* = 318.8 Hz). ^{19}F NMR (377 MHz, 1,2-dichloroethane) δ -76.3.



Derivatization of benzoyl triflate: In a glovebox to a stirring solution of benozyl triflate (248 mg, 0.98 mmol) in 10 mL of DCE was added methanesulfonamide (238 mg, 2.5 mmol). After stirring for 15 minthe reaction was removed from the glovebox, hexamethylbenzene (11.0 mg, 0.07 mmol) was added as a standard, and the reaction mixture was filtered through a pad of silica and thoroughly rinsed with DCM/EtOAc (1:1). The solvent was removed *in vacuo* and the yield of the amide (95%) was determined by ^{1}H NMR analysis relative to the external standard. The amide was isolated via column chromatography (silica gel, gradient DCM(1% TFA) / MeOH (1% TFA) 0% to 10%) affording pure *N*-(methylsulfonyl)benzamide **5** as an off-white solid in 86% yield (171 mg).

N-(methylsulfonyl)benzamide **5.** 1H NMR (400 MHz, CDCl3) δ 8.99 (s, 1H), 7.90 (d, J = 7.6 Hz, 2H), 7.65 (t, J = 7.3 Hz, 1H), 7.53 (t, J = 7.5 Hz, 2H), 3.47 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 133.8, 130.9, 129.1, 127.9, 41.8. HRMS. Calculated for $C_8H_9O_3N\ Na^+$ ($M+Na^+$): 222.0195, found: 222.0194.

3.5.4. Control Experiments

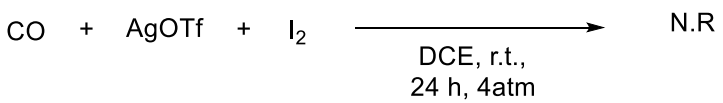
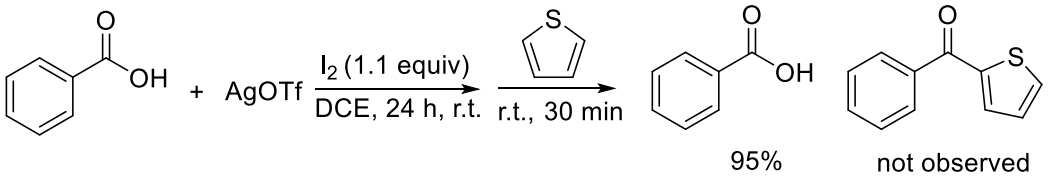
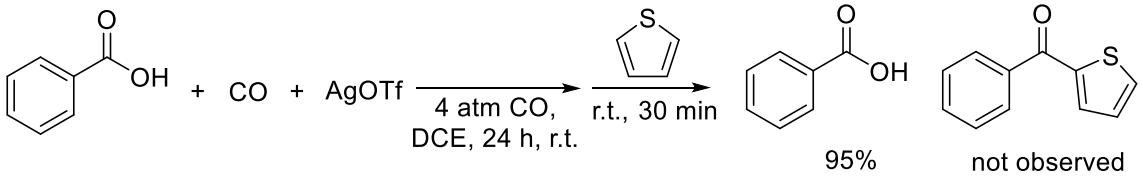


Figure S3.5.1 Carbon Monoxide does not react with silver triflate and iodine.

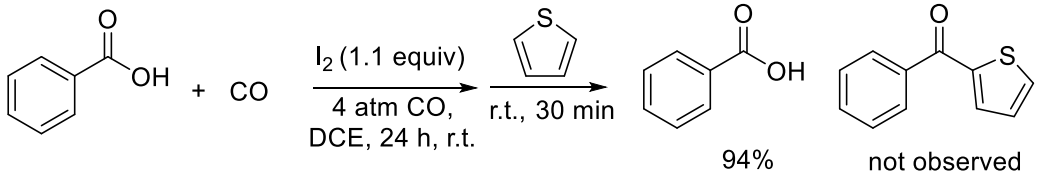
Reaction without PhCOOH: In a glovebox, silver triflate (32 mg, 0.13 mmol) and iodine (15 mg, 0.060 mmol) were dry transferred to a J. Young NMR tube. 1,2-dichloroethane (0.5 mL) was then added. The J. Young NMR tube was capped and taken out of the glovebox. The NMR tube was connected to a Schlenk line via a glass adapter and placed in liquid nitrogen. The Schlenk line and the headspace of the NMR tube was evacuated. 5 atm of CO was condensed in the NMR tube. After 24 hours at ambient temperature, ^{13}C NMR analysis showed only the presence of free carbon monoxide. To test for any electrophile formation, CO was removed on a Schlenk line, and the NMR tube brought back into the glovebox. Thiophene (8 mg, 0.1 mmol) was added. After 30 min, the vessel was removed from the glovebox and the reaction mixture was filtered through a pad of silica and thoroughly rinsed with DCM/EtOAc (1:1). The solvent was removed *in vacuo* and no ketone product was observed by ^{1}H NMR analysis.



Reaction without CO: In a glovebox, silver triflate (161 mg, 0.63 mmol), iodine (70 mg, 0.28 mmol), and benzoic acid (31 mg, 0.25 mmol) were dry transferred to a 20 mL vial equipped with a magnetic stir bar. 1,2-dichloroethane (1 mL) was added to the vial. The vial was closed with a screw cap and stirred at room temperature for 24 h. Thiophene (100 μL, 1.25 mmol) was added to vial and stirred for 30 min at room temperature in the glovebox. The vial was removed from the glovebox, hexamethylbenzene (7 mg, 0.04 mmol) was added as a standard and the reaction mixture was filtered through a pad of silica and thoroughly rinsed with DCM/EtOAc (1:1). The solvent was removed *in vacuo* and the reaction was analyzed by ^{1}H NMR analysis. Only the starting carboxylic acid was observed.



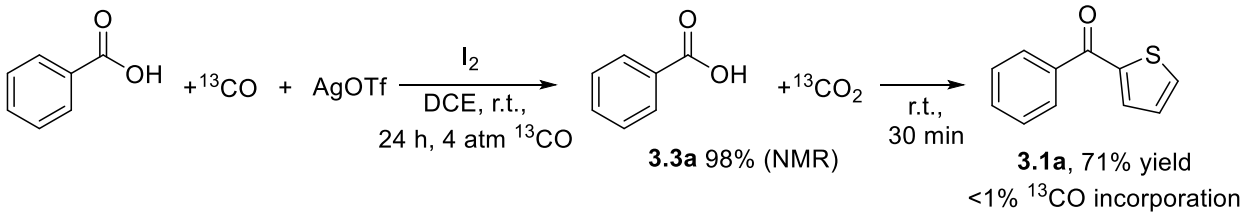
Reaction without Iodine: In a glovebox, silver triflate (161 mg, 0.63 mmol) and benzoic acid (31 mg, 0.25 mmol) were dry transferred to a Teflon sealed, thick walled 50 mL glass reaction vessel equipped with a magnetic stir bar. 1,2-dichloroethane (1 mL) was added to the vessel. The vessel was closed, removed from the glovebox, evacuated and backfilled with carbon monoxide three times, and finally pressurized with 4 atm carbon monoxide. After stirring at room temperature for 24 h, carbon monoxide was released on a Schlenk line and the vessel was brought back into the glovebox. Thiophene (100 μL, 1.25 mmol) was added to vessel and stirred for 30 min at room temperature in the glovebox. The vessel was removed from the glovebox, hexamethylbenzene (7 mg, 0.04 mmol) was added as a standard and the reaction mixture was filtered through a pad of silica and thoroughly rinsed with DCM/EtOAc (1:1). The solvent was removed *in vacuo* and the reaction was analyzed by ^{1}H NMR analysis. Only the starting carboxylic acid was observed.



Reaction without Silver Triflate: In a glovebox, iodine (70 mg, 0.28 mmol) and benzoic acid (31 mg, 0.25 mmol) were dry transferred to a Teflon sealed, thick walled 50 mL glass reaction vessel equipped with a magnetic stir bar. 1,2-dichloroethane (1 mL) was added to the vessel. The vessel was closed, removed from the glovebox, evacuated and backfilled with carbon monoxide three times, and finally pressurized with 4 atm carbon monoxide. After stirring at room temperature for 24 h, carbon monoxide was released on a Schlenk line and the vessel was brought back into the glovebox. Thiophene (100 μL, 1.25 mmol) was added to vessel and stirred for 30 min at room

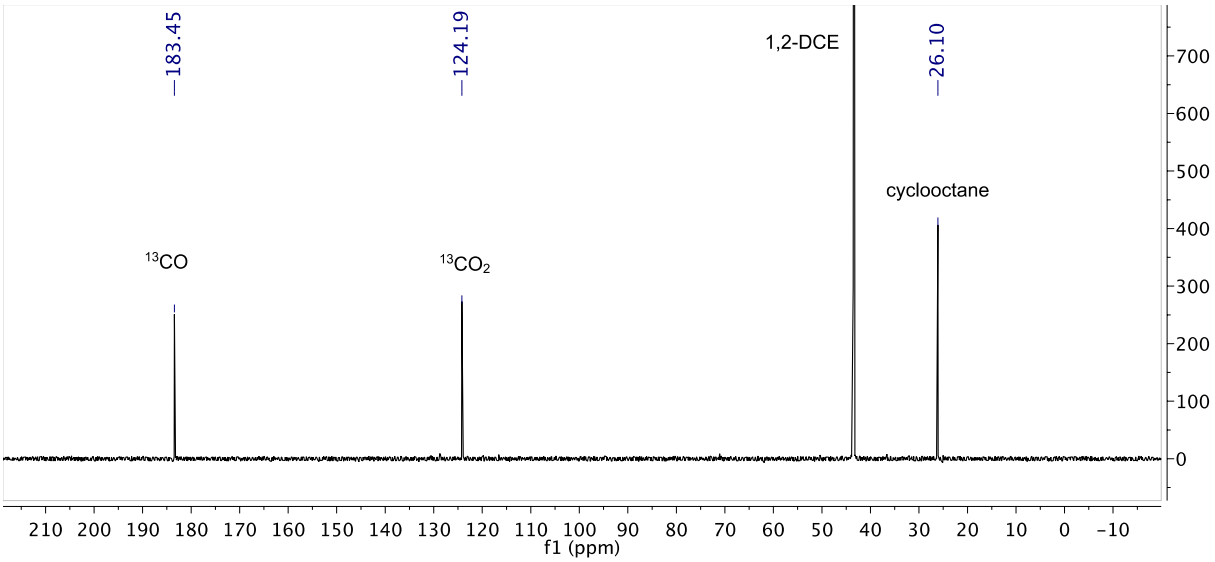
temperature in the glovebox. The vessel was removed from the glovebox, hexamethylbenzene (7 mg, 0.04 mmol) was added as a standard and the reaction mixture was filtered through a pad of silica and thoroughly rinsed with DCM/EtOAc (1:1). The solvent was removed *in vacuo* and the reaction was analyzed by ^{1}H NMR analysis. Only the starting carboxylic acid was observed.

3.5.6. Isotopic Labelling Experiments

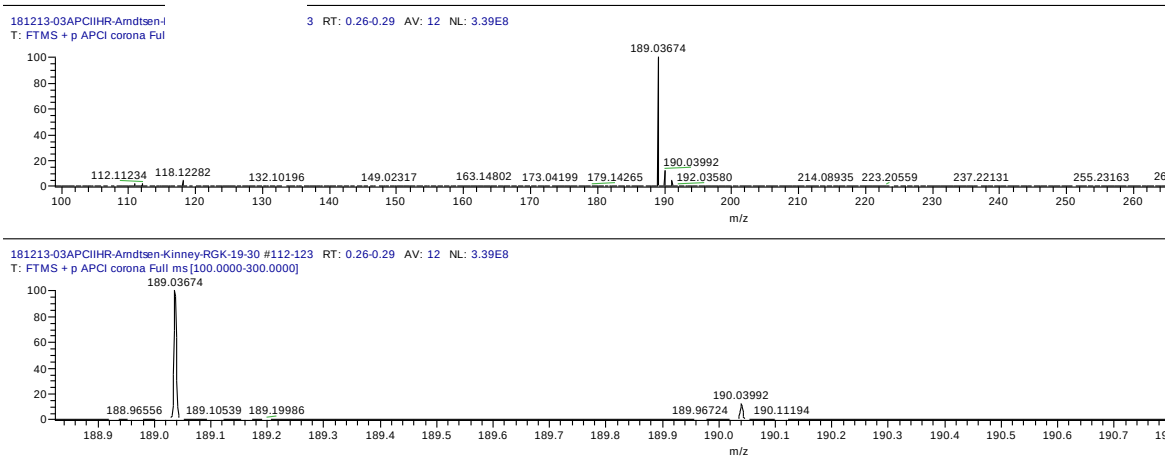


Reaction using ^{13}C labeled carbon monoxide: In a glovebox, silver triflate (32 mg, 0.13 mmol), iodine (15 mg, 0.060 mmol), and benzoic acid (6 mg, 0.05 mmol) were dry transferred to a J. Young NMR tube. Cyclooctane (11 mg, 0.098 mmol) was dissolved in 1,2-dichloroethane (0.5 mL). The resulting solution was transferred to the J. Young NMR tube, which was capped and taken out of the glovebox. The NMR tube was connected to a Schlenk line via a glass adapter and placed in liquid nitrogen. The Schlenk line was evacuated and backfilled with carbon monoxide (not ^{13}CO) three times and the headspace of the NMR tube was evacuated. 5 atm of ^{13}CO was condensed in the NMR tube. The reaction was monitored by ^{1}H and ^{13}C NMR at ambient temperature. After 24 hours, NMR analysis showed 98% yield of acid triflate and the presence of $^{13}CO_2$ in the ^{13}C NMR (see below). The ^{13}CO was removed on a Schlenk line and brought back into the glovebox. Thiophene (8 mg, 0.1 mmol) was added to the NMR tube and allowed to react for 30 min at room temperature. The vessel was removed from the glovebox, hexamethylbenzene (5 mg, 0.03 mmol) was added as a standard and the reaction mixture was filtered through a pad of silica and thoroughly rinsed with DCM/EtOAc (1:1). The solvent was removed *in vacuo* and the yield of ketone **1a** (71%) was determined by ^{1}H NMR analysis relative to hexamethylbenzene. HRMS analysis of this sample shows less than 1% ^{13}C incorporation.

^{13}C NMR of the reaction mixture after 24h

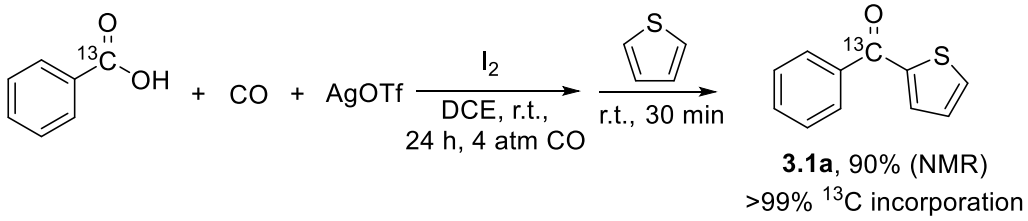


HRMS of ketone **3.1a** formed with ^{13}CO



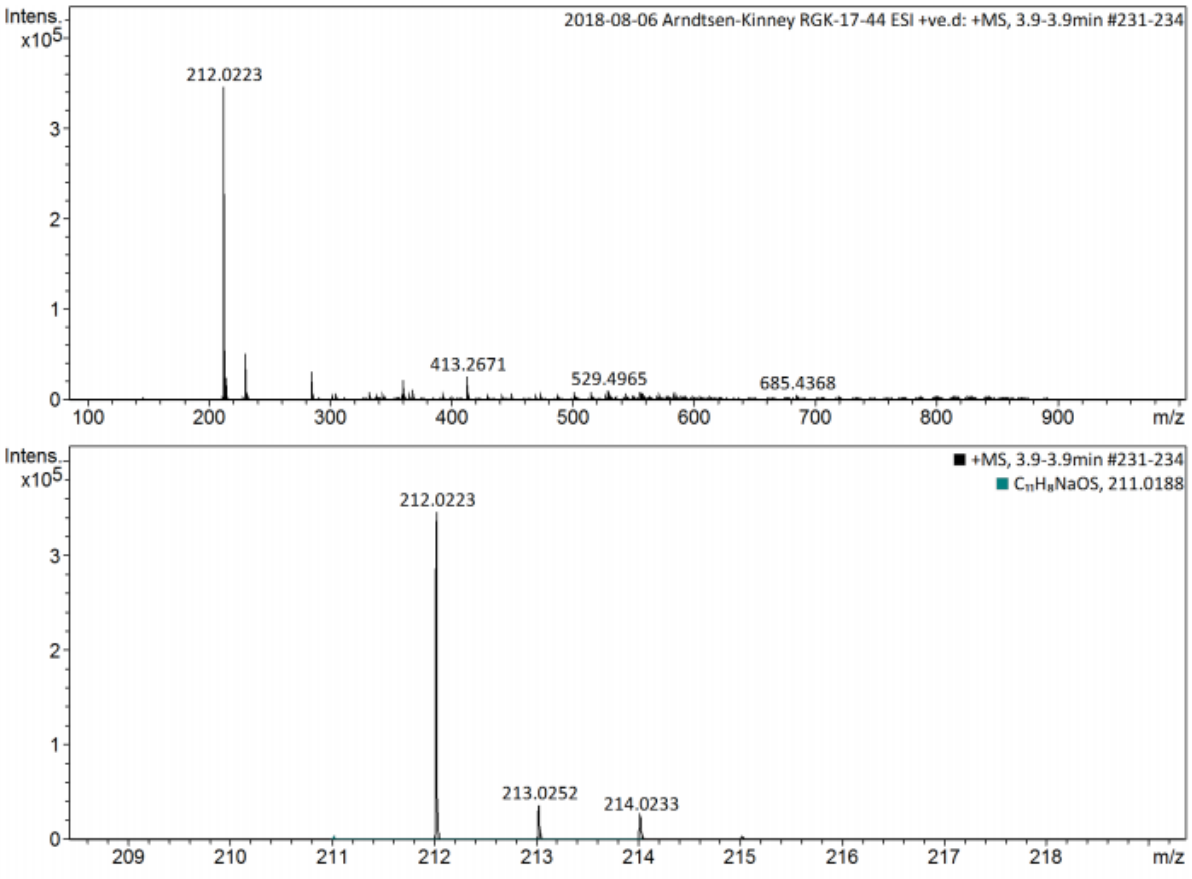
m/z	Intensity	Relative
189.03674	347461472.0	100.0
190.03992	41194136.0	11.86

Expected relative intensity of M+1 peak due to natural abundance of ^{13}C: 11.90



Reaction using ^{13}C benzoic acid: In a glovebox, silver triflate (97 mg, 0.31 mmol), iodine (35 mg, 0.14 mmol), and benzoic acid (15 mg, 0.13 mmol) were dry transferred to a Teflon sealed, thick walled 25 mL glass reaction vessel equipped with a magnetic stir bar. 1,2-dichloroethane (0.5 mL) was added to the vessel. The vessel was closed, removed from the glovebox, evacuated and backfilled with carbon monoxide three times, and finally pressurized with 4 atm carbon monoxide. After stirring at room temperature for 24 h, carbon monoxide was released on a Schlenk line and the vessel was brought back into the glovebox. Thiophene (21 mg, 0.25 mmol) was dissolved in 1,2-dichloroethane (0.5 mL), added to vessel, and stirred for 30 min at room temperature in the glovebox. The vessel was removed from the glovebox, hexamethylbenzene (7 mg, 0.04 mmol) was added as a standard and the reaction mixture was filtered through a pad of silica and thoroughly rinsed with DCM/EtOAc (1:1). The solvent was removed *in vacuo* and the yield of ketone ^{13}C-**3.1a** (90%) was determined by ^{1}H NMR analysis relative to the external standard. HRMS analysis of this sample shows greater than 99% ^{13}C incorporation into the ketone product.

HRMS of ^{13}C-**3.1a**

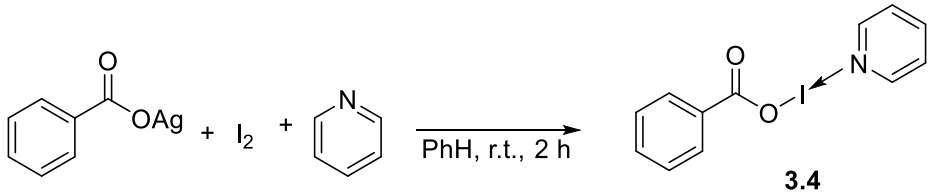


Meas. m/z	#	Ion Formula	m/z	err [ppm]	mSigma	# mSigma	Score	rdb	e¯ Conf	N-Rule
211.0187	1	C11H8NaOS	211.0188	0.5	763.5	1	100.00	7.5	even	ok
212.0223	1	C10H8NaOS^13C	212.0222	-0.9	12.8	1	100.00	7.5	even	-

Intensity of ^{12}C to ^{13}C labeled ketone **3.1a**

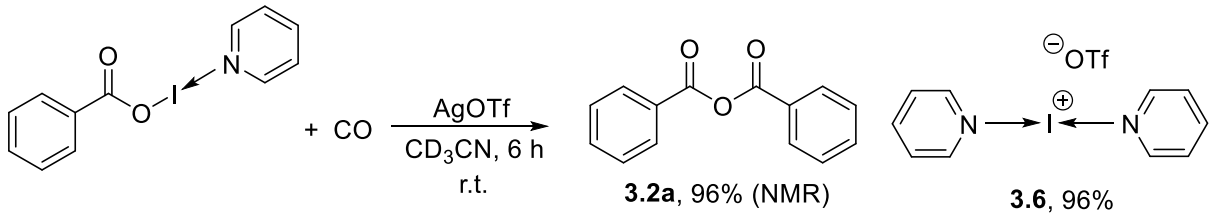
m/z	I	I %
211.0187	2353	0.7
212.0223	345554	100

3.5.7. Mechanistic Experiments with PhCOOI(Py)



3.4
76% Yield

Synthesis of PhCOOI(Py): This complex was prepared using a modified literature procedure.[27] In a glovebox, silver benzoate (114 mg, 0.50 mmol), pyridine (41 mg, 0.53 mmol) and benzene (1 mL) were added to a 4 mL vial equipped with a magnetic stir bar. Iodine (133 mg, 0.53 mmol) was dry transferred to this 4 mL. A yellow precipitate immediately formed upon addition. After stirring at room temperature for 2 hour, the reaction was filtered through a Kimwipe pipette into a 20 mL vial. Pentane (12 mL) was added to precipitate the product. The vial was placed in the freezer in the glovebox for 30 min, and then filtered through a frit and washed with pentane. Solvent traces were removed *in vacuo* and the acyl hypoiodite adduct **4** was obtained as fluffy pale yellow solid in 76% yield (124 mg).



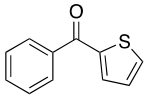
Reactivity of PhCOOI(pyridine) (4) with CO/AgOTf: In a glovebox, silver triflate (8 mg, 0.03 mmol) was added to a J. Young NMR tube. Acyl hypoiodite adduct **3.4** (10 mg, 0.03 mmol) and cyclooctane (2 mg, 0.02 mmol) were dissolved in CD_3CN (0.5 mL) and transferred to the J. Young NMR tube. This sample was subjected to NMR analysis to obtain the initial ratio of standard (cyclooctane) to acyl hypoiodite adduct **3.4**. The NMR tube was connected to a Schlenk line via a glass adapter and place in liquid nitrogen. The Schlenk line was evacuated and backfilled with carbon monoxide three times and the headspace of the NMR tube was evacuated. 5 atm of CO was condensed in the NMR tube. The reaction was monitored by ^1H and ^{13}C NMR at ambient temperature. After 6 hours at room temperature, ^1H NMR analysis showed 96% yield of benzoic anhydride and 96% yield of $I(Py)_2OTf$. The presence of $I(Py)_2OTf$ was corroborated by comparing the ^1H and ^{13}C NMR of the reaction mixture with the spectra of independently synthesized $I(Py)_2OTf$ by literature procedure.[27]

Reaction Mixture: ^1H NMR (400 MHz, CD_3CN) δ 8.81 (d, J = 5.2 Hz, 4H, $I(Py)_2OTf$), 8.28 (t, J = 7.7 Hz, 2H, $I(Py)_2OTf$), 8.19 (d, J = 7.2 Hz, 4H, Bz_2O), 7.79 (t, J = 7.5 Hz, 2H, Bz_2O), 7.70 –

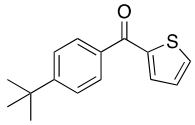
7.57 (m, 8H, $I(Py)_2OTf$ and Bz_2O). ^{13}C NMR (101 MHz, CD_3CN) δ 184.7 (carbon monoxide), 163.2 (Bz_2O), 150.3 ($I(Py)_2OTf$), 142.8 ($I(Py)_2OTf$), 135.4 (Bz_2O), 131.0 (Bz_2O), 129.7 (Bz_2O), 128.4 ($I(Py)_2OTf$).

Pure $I(Py)_2OTf$: ^1H NMR (400 MHz, CD3CN) δ 8.81 (d, *J* = 5.1 Hz, 4H), 8.28 (t, *J* = 7.7 Hz, 2H), 7.69 – 7.63 (m, 4H). ^{13}C NMR (101 MHz, CD_3CN) δ 150.2, 142.8, 128.4. HRMS. Calculated for $C_{10}H_{10}N_2I^+$ (M+): 284.9883, found: 284.9880.

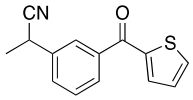
3.5.8. Characterization Data for Compounds.



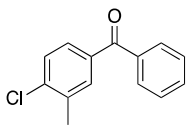
Phenyl(thiophen-2-yl)methanone 3.1a. Prepared according to the general procedure. Pale yellow solid, 87% yield (82 mg, 0.44 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.83 (m, 2H), 7.73 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.66 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.5 Hz, 2H), 7.18 (dd, *J* = 5.0, 3.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.2, 143.6, 138.2, 134.8, 134.2, 132.3, 129.2, 128.4, 128.0. All NMR data matches with the previously reported compound.[28]



(4-(*tert*-butyl)phenyl)(thiophen-2-yl)methanone 3.1b. Prepared according to the general procedure using 4-*tert*-butyl benzoic acid (89 mg, 0.50 mmol). White solid, 85% yield (104 mg, 0.43 mmol). ^{1}H NMR (400 MHz, CDCl3) δ 7.86 (d, *J* = 8.5 Hz, 2H), 7.73 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.70 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.18 (dd, *J* = 5.0, 3.8 Hz, 1H), 1.40 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 187.9, 156.0, 143.9, 135.4, 134.5, 133.8, 129.2, 127.9, 125.4, 35.1, 31.2. All NMR data matches with the previously reported compound.[29]

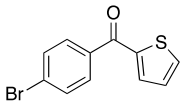


2-(3-(thiophene-2-carbonyl)phenyl)propanenitrile 3.1c. Prepared according to the general procedure using 3-(1-cyanoethyl)benzoic acid (88 mg, 0.50 mmol). Pale yellow liquid, 56% yield (68 mg, 0.28 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (m, 2H), 7.77 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.68 – 7.60 (m, 2H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.20 (dd, *J* = 5.0, 3.7 Hz, 1H), 4.02 (q, *J* = 7.3 Hz, 1H), 1.71 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.4, 143.2, 139.1, 137.7, 135.0, 134.7, 130.5, 129.3, 128.9, 128.2, 127.4, 121.1, 31.2, 21.3. HRMS. Calculated for $C_{14}H_{12}ONSH^{+}$ ($M+H^{+}$): 242.0634, found: 242.0636.

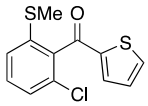


(4-chloro-3-methylphenyl)(phenyl)methanone 3.1d. Prepared according to the general procedure using 4-chloro-3-methylbenzoic acid (85 mg, 0.5 mmol) and benzene (78 mg, 1.0 mmol) at 90 °C for 16h. White solid, 71% yield (82 mg. 0.36 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.77 (m, 3H), 7.65 – 7.58 (m, 2H), 7.51 (t, *J* = 7.5 Hz, 2H), 7.36 (d, *J* = 7.2 Hz, 1H), 2.49 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.1, 141.0,

137.3, 136.8, 134.6, 132.6, 130.8, 130.6, 129.9, 128.4, 128.3, 20.3. HRMS. Calculated for $C_{14}H_{12}OClH^+$ ($M+H^+$): 231.0571, found: 231.0578.

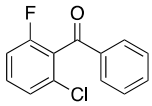


(4-bromophenyl)(thiophen-2-yl)methanone 3.1e. Prepared according to the general procedure using 4-bromobenzoic acid (101 mg, 0.5 mmol). Pale yellow solid, 71% yield (95 mg, 0.36 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.74 (m, 3H), 7.70 – 7.63 (m, 3H), 7.20 (dd, *J* = 5.0, 3.8 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.0, 143.2, 136.9, 134.8, 134.6, 131.7, 130.7, 128.1, 127.3. All NMR data matches with the previously reported compound.[30]



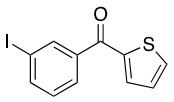
(2-chloro-6-(methylthio)phenyl)(thiophen-2-yl)methanone 3.1f. Prepared according to the general procedure using 2-chloro-6-(methylthio)benzoic acid (101 mg, 0.5 mmol). Pale yellow solid, 58% yield (78 mg, 0.29 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 4.9, 1.2 Hz, 1H), 7.46 (dd, *J* = 3.8, 1.2 Hz, 1H), 7.41 – 7.36 (m, 1H), 7.33 – 7.28 (m, 2H), 7.15 (dd, *J* = 4.9, 3.8 Hz, 1H), 2.50 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.6, 143.5, 138.7, 138.0, 136.1, 135.8, 130.4, 129.0, 128.4, 127.5, 126.1, 15.8. HRMS. Calculated for $C_{12}H_{10}OClS_2H^+$ ($M+H^+$): 268.9856, found: 268.9863.

(2-chloro-6-fluorophenyl)(phenyl)methanone 3.1g. Prepared according to the general procedure using 2-chloro-6-fluorobenzoic acid (87 mg, 0.5 mmol) at 40 °C and benzene (78 mg, 1.0 mmol) at 90 °C for 16h. White solid, 86% yield (101 mg, 0.43 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.3 Hz, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 7.46 – 7.39 (m, 1H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.13 (t, *J* = 8.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.8, 160.7, 158.3, 136.2, 134.30, 132.1 (d, *J* = 5.7 Hz), 131.2 (d, *J* = 8.9 Hz), 129.7, 128.9, 125.6 (d, *J* = 3.4 Hz), 114.4 (d, *J* = 21.5 Hz). All NMR data matches with the previously reported compound.[31]

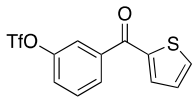


(5-bromo-2-iodophenyl)(thiophen-2-yl)methanone 3.1h. Prepared according to the general procedure using 5-bromo-2-iodobenzoic acid (82 mg, 0.25 mmol) at 40 °C and thiophene (50 μL, 0.63 mmol, 2.5 equiv) at room temperature for 30 min. Pale yellow solid, 79% yield (78 mg, 0.20 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (dd, *J* =

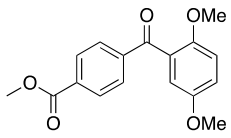
4.9, 1.2 Hz, 1H), 7.74 (d, *J* = 2.1 Hz, 1H), 7.68 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.44 (dd, *J* = 3.8, 1.2 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.17 (dd, *J* = 4.9, 3.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.9, 142.8, 142.3, 140.2, 137.2, 136.3, 136.2, 135.0, 128.5, 119.2, 91.9. HRMS. Calculated for $C_{11}H_7OBrISH^+$ ($M+H^+$): 392.8440, found: 392.8445.



(3-iodophenyl)(thiophen-2-yl)methanone 3.1i. Prepared according to the general procedure using 3-iodobenzoic acid (124 mg, 0.5 mmol) at 40 °C. Pale yellow solid, 82% yield (129 mg, 0.41 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.77 (dd, *J* = 4.9, 1.0 Hz, 1H), 7.65 (dd, *J* = 3.8, 1.0 Hz, 1H), 7.26 (t, *J* = 7.8 Hz, 1H), 7.20 (dd, *J* = 4.9, 3.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.4, 143.0, 141.0, 140.0, 137.8, 135.0, 134.8, 130.1, 128.2, 128.1, 94.1. HRMS. Calculated for $C_{11}H_7OISNa^+$ ($M+Na^+$): 336.9155, found: 336.9142.

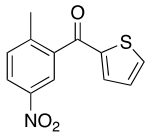


3-(thiophene-2-carbonyl)phenyl trifluoromethanesulfonate 3.1j. Prepared according to the general procedure using 3-(((trifluoromethyl)sulfonyl)oxy)benzoic acid (68 mg, 0.25 mmol) at 40 °C and thiophene (50 μL, 0.63 mmol, 2.5 equiv) at room temperature for 30 min. Pale yellow liquid, 80% yield (67 mg, 0.20 mmol). 1H NMR (400 MHz, CDCl3) δ 7.93 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.84 – 7.78 (m, 2H), 7.67 (dd, *J* = 3.9, 1.2 Hz, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.53 (ddd, *J* = 8.3, 2.5, 1.0 Hz, 1H), 7.23 (dd, *J* = 5.0, 3.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.7, 149.3, 142.6, 140.3, 135.3, 135.2, 130.6, 128.9, 128.3, 124.9, 122.1, 118.7 (q, *J* = 320.9 Hz). ^{19}F NMR (377 MHz, $CDCl_3$) δ -72.70. HRMS. Calculated for $C_{12}H_8O_4F_3S_2H^+$ ($M+H^+$): 336.9811, found: 336.9817.

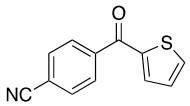


methyl 4-(2,5-dimethoxybenzoyl)benzoate 3.1k. Prepared according to the general procedure using 4-(methoxycarbonyl)benzoic acid (90 mg, 0.5 mmol) at 40 °C and 1,4-dimethoxybenzene (138 mg, 1.0 mmol) at room temperature for 16h. White solid, 79% yield (119 mg, 0.40 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.4 Hz, 2H), 7.85 (d, *J* = 8.4 Hz, 2H), 7.06 (dd, *J* = 8.9, 2.9 Hz, 1H), 6.98 (d, *J* = 3.1 Hz, 1H), 6.94 (d, *J* = 9.0 Hz, c1H), 3.96 (s, 3H), 3.81 (s, 3H), 3.64 (s, 3H). ^{13}C NMR

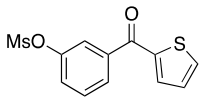
(101 MHz, $CDCl_3$) δ 195.6, 166.4, 153.6, 151.7, 141.4, 133.5, 129.4, 129.4, 128.7, 118.3, 114.6, 113.1, 56.2, 55.9, 52.4. All NMR data matches with the previously reported compound.[32]



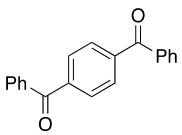
(2-methyl-5-nitrophenyl)(thiophen-2-yl)methanone 3.1l. Prepared according to the general procedure using 2-methyl-5-nitrobenzoic acid (91 mg, 0.5 mmol) at 40 °C. Pale yellow solid, 89% yield (110 mg, 0.44 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 2.3 Hz, 1H), 8.27 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.84 (d, *J* = 4.9 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.45 (d, *J* = 3.8 Hz, 1H), 7.19 (dd, *J* = 4.8, 3.9 Hz, 1H), 2.51 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 187.6, 145.6, 144.4, 143.6, 139.4, 136.2, 135.9, 132.1, 128.6, 124.8, 122.8, 20.0. HRMS. Calculated for $C_{12}H_{10}O_3NSH^+$ ($M+H^+$): 248.0376, found: 248.0381.



4-(thiophene-2-carbonyl)benzonitrile 3.1m. Prepared according to the general procedure at 40° C using 4-cyanobenzoic acid (74 mg, 0.5 mmol). White solid, 61% yield (65 mg, 0.30 mmol). ^{1}H NMR (500 MHz, CDCl3) δ 7.95 (d, *J* = 8.5 Hz, 2H), 7.85 – 7.79 (m, 3H), 7.62 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.21 (dd, *J* = 4.9, 3.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 186.5, 142.6, 141.7, 135.5, 135.4, 132.3, 129.5, 128.4, 118.0, 115.6. HRMS. Calculated for $C_{12}H_7ONSH^+$ ($M+H^+$): 213.0254, found: 213.0247.

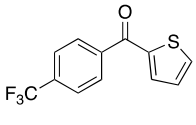


3-(thiophene-2-carbonyl)phenyl methanesulfonate 3.1n. Prepared according to the general procedure using 3-((methylsulfonyl)oxy)benzoic acid (108 mg, 0.5 mmol) at 40 °C. Pale yellow solid, 81% yield (112 mg, 0.40 mmol). ^{1}H NMR (400 MHz, CDCl3) δ 7.90 – 7.82 (m, 1H), 7.83 – 7.75 (m, 2H), 7.69 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 7.55 (ddd, *J* = 8.2, 2.4, 1.3 Hz, 1H), 7.21 (dd, *J* = 4.9, 3.8 Hz, 1H), 3.23 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.3, 148.9, 142.8, 139.9, 135.3, 135.0, 130.3, 128.3, 128.0, 125.8, 122.8, 37.7. HRMS. Calculated for $C_{14}H_{12}O_3$ NSH^+ ($M+H^+$): 213.0254, found: 213.0247.

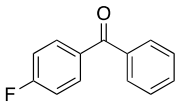


(4-benzoylphenyl)(thiophen-2-yl)methanone 3.1o. Prepared according to the general procedure using 4-benzoylbenzoic acid (113 mg, 0.5 mmol). White solid, 63% yield (92 mg, 0.32 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 4H), 7.87

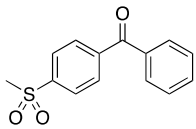
(d, *J* = 7.2 Hz, 4H), 7.64 (d, *J* = 7.4 Hz, 2H), 7.54 (t, *J* = 7.6 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.0, 140.7, 137.0, 133.0, 130.1, 129.7, 128.5. All NMR data matches with the previously reported compound.[33]



Thiophen-2-yl(4-(trifluoromethyl)phenyl)methanone 3.1p. Prepared according to the general procedure using 4-(trifluoromethyl)benzoic acid (95 mg, 0.5 mmol) at 40 °C. White solid, 89% yield (114 mg, 0.44 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.1 Hz, 2H), 7.81 – 7.75 (m, 3H), 7.63 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.20 (dd, *J* = 5.0, 3.8 Hz, 1H). 13C NMR (126 MHz, CDCl3) δ 187.0, 143.0, 141.2, 135.2 (d, *J* = 18.4 Hz), 133.67 (q, *J* = 32.8 Hz), 129.3, 128.3, 125.5 (q, *J* = 3.7 Hz), 123.7 (q, *J* = 272.5 Hz). All NMR data matches with the previously reported compound.[34]



(4-fluorophenyl)(phenyl)methanone 3.1q. Prepared according to the general procedure using 4-fluorobenzoic acid (70 mg, 0.5 mmol) at 40 °C and benzene (78 mg, 1.0 mmol) at 90 °C for 16h. Pale yellow liquid, 97% yield (97 mg, 0.48 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.83 – 7.76 (m, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.18 (t, *J* = 8.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.22, 165.38 (d, *J* = 254.1 Hz), 137.51, 133.81 (d, *J* = 3.1 Hz), 132.66 (d, *J* = 9.1 Hz), 132.46, 129.87, 128.35, 115.45 (d, *J* = 21.9 Hz). All NMR data matches with the previously reported compound.[35]



(4-(methylsulfonyl)phenyl)(phenyl)methanone 3.1r. Prepared according to the general procedure using 4-(methylsulfonyl)benzoic acid (100 mg, 0.5 mmol) at 40 °C and benzene (78 mg, 1.0 mmol) at 90 °C for 16h. White solid, 79% yield (103 mg, 0.40 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.5 Hz, 2H), 7.88 (d, *J* = 8.5 Hz, 2H), 7.73 (d, *J* = 7.0 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 3.04 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.1, 143.5, 142.4, 136.4, 133.4, 130.5, 130.1, 128.7, 127.5, 44.4. All NMR data matches with the previously reported compound.[36]

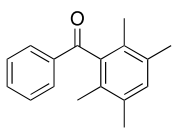
thiophen-2-yl(2-(trifluoromethoxy)phenyl)methanone 3.1s. Prepared according to the general procedure using 2-(trifluoromethoxy)benzoic acid (52 mg, 0.25 mmol) and thiophene (50 μL, 0.63 mmol, 2.5 equiv). Pale yellow solid, 84% yield (57 mg, 0.21 mmol) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.63 – 7.54 (m, 2H), 7.46 (dd, *J* = 3.8, 1.2 Hz, 1H), 7.45 – 7.38 (m, 2H), 7.15 (dd, *J* = 4.9, 3.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.5, 145.9, 143.8, 135.6, 135.4, 132.8, 131.9, 129.7, 128.2, 126.7, 121.4, 120.3 (q, *J* = 258.9 Hz). ^{19}F NMR (377 MHz, $CDCl_3$) δ -57.3. All NMR data matches with the previously reported compound.[37]

(4-methoxyphenyl)(phenyl)methanone 3.1t. Prepared according to the general procedure using benzoic acid (31 mg, 0.25 mmol) and anisole (54 mg, 0.5 mmol) as the arene at room temperature for 16 hours. White solid, 98% yield (53 mg, 0.25 mmol). ^{1}H NMR (500 MHz, CDCl3) δ 7.85 (d, *J* = 8.9 Hz, 2H), 7.78 (d, *J* = 7.0 Hz, 2H), 7.57 (d, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 3.90 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.5, 163.2, 138.3, 132.6, 131.9, 130.2, 129.7, 128.2, 113.6, 55.5. All NMR data matches with the previously reported compound.[38]

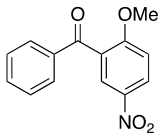
(3,4-dimethoxyphenyl)(phenyl)methanone 3.1u. Prepared according to the general procedure using 1,2-dimethoxy benzene (138 mg, 1mmol) as the arene at room temperature for 16 hours. White solid, 97% yield (118 mg, 0.49 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.0 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.54 – 7.45 (m, 3H), 7.40 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 3.97 (s, 3H), 3.96 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.5, 153.0, 149.0, 138.3, 131.8, 130.2, 129.7, 128.1, 125.5, 112.2, 109.8, 56.1, 56.0. All NMR data matches with the previously reported compound.[39]

phenyl(2,3,5,6-tetramethylphenyl)methanone 3.1v. Prepared according to the general procedure using thioanisole (124 mg, 1mmol) as the arene at 40 °C for 16 hours. Pale yellow solid, 91% yield (104 mg, 0.46 mmol). 1H NMR (500 MHz, CDCl3) δ 7.78 (t, *J* = 8.6 Hz, 4H), 7.59 (d, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 2.56 (s, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 195.80, 145.29, 137.87,

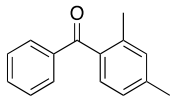
133.65, 132.19, 130.66, 129.83, 128.27, 124.85, 14.87. All NMR data matches with the previously reported compound.[40]



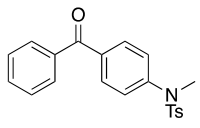
phenyl(2,3,5,6-tetramethylphenyl)methanone 3.1w. Prepared according to the general procedure at 40° C for 16h using 1,2,4,5-tetramethylbenzene (134 mg, 1.0 mmol). White solid, 95% yield (114 mg, 0.48 mmol). ^{1}H NMR (400 MHz, CDCl3) δ 7.84 (d, *J* = 7.1 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.06 (s, 1H), 2.26 (s, 6H), 2.00 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.7, 139.9, 137.4, 134.2, 133.5, 131.8, 129.7, 129.5, 128.8, 19.5, 16.3. HRMS. Calculated for $C_{17}H_{19}NOH^+$ ($M+H^+$): 239.1430, found: 239.1439.



(2-methoxy-5-nitrophenyl)(phenyl)methanone 3.1x. Prepared according to the general procedure using 4-nitroanisole (53 mg, 1mmol) as the arene at 60 °C for 16 hours. Pale yellow solid, 73% yield (94 mg, 0.37 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (dd, *J* = 9.1, 2.8 Hz, 1H), 8.28 (d, *J* = 2.8 Hz, 1H), 7.81 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.70 – 7.57 (m, 1H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.11 (d, *J* = 9.2 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.6, 161.9, 141.1, 136.6, 133.8, 129.8, 129.4, 128.6, 127.6, 125.3, 111.3, 56.5. HRMS. Calculated for $C_{14}H_{12}NO_4H^+$ ($M+H^+$): 258.0761, found: 258.0768.

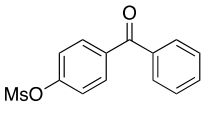


(2,4-dimethylphenyl)(phenyl)methanone 3.1y. Prepared according to the general procedure using 1,3-dimethylbenzene (106 mg, 1mmol) as the arene at 60 °C for 16 hours. White solid, 96% yield (101 mg, 0.48 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.9 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.25 (d, *J* = 7.8 Hz, 1H), 7.13 (s, 1H), 7.06 (d, *J* = 7.8 Hz, 1H), 2.40 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.5, 140.6, 138.2, 137.3, 135.6, 132.8, 131.9, 130.1, 129.2, 128.3, 125.8, 21.4, 20.1. All NMR data matches with the previously reported compound.[41]

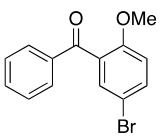


***N*-(4-benzoylphenyl)-*N*,4-dimethylbenzenesulfonamide 3.1z**. Prepared according to the general procedure using *N*,4-dimethyl-*N*-phenylbenzenesulfonamide (261 mg, 1mmol) as the arene and 2,6-di-*tert*-

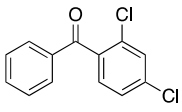
butylpyridine (239 mg, 1.25 mmol, 2.5 equiv) as a base at 40 °C for 16 hours. Off white solid, 93% yield (170 mg, 0.47 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 – 7.76 (m, 4H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 7.0 Hz, 4H), 3.23 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.7, 145.4, 144.0, 137.3, 135.6, 133.3, 132.6, 130.8, 130.0, 129.6, 128.4, 127.7, 125.5, 37.7, 21.6. All NMR data matches with the previously reported compound.[42]



4-benzoylphenyl methanesulfonate 3.1aa. Prepared according to the general procedure using phenyl methanesulfonate (172 mg, 1mmol) as the arene at 100 °C for 24 hours. White solid, 77% yield (106 mg, 0.38 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.7 Hz, 2H), 7.81 (d, *J* = 7.1 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.43 (d, *J* = 8.7 Hz, 2H), 3.24 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.1, 151.9, 137.0, 136.5, 132.8, 132.0, 130.0, 128.5, 121.9, 37.9. All NMR data matches with the previously reported compound.[43]



(5-bromo-2-methoxyphenyl)(phenyl)methanone 3.1bb. Prepared according to the general procedure using 4-bromoanisole (187 mg, 1mmol) as the arene at 60 °C for 16 hours. Pale yellow solid, 87% yield (127 mg, 0.44 mmol).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.1 Hz, 2H), 7.62 – 7.53 (m, 2H), 7.50 – 7.42 (m, 3H), 6.90 (d, *J* = 8.8 Hz, 1H), 3.72 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.7, 156.4, 137.2, 134.3, 133.3, 131.9, 130.7, 129.8, 128.4, 113.3, 112.8, 55.9. HRMS. Calculated for $C_{14}H_{12}O_2BrH^+$ ($M+H^+$): 291.0015, found: 291.0021.



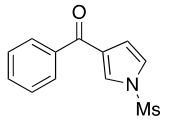
(2,4-dichlorophenyl)(phenyl)methanone 3.1cc. Prepared according to the general procedure using 1,3-dichlorobenzene (571 μL, 5mmol) as the arene at 100 °C for 24 hours. White solid, 83% yield (104 mg, 0.41 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.8 Hz, 2H), 7.63 (t, *J* = 7.3 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 3H), 7.36 (q, *J* = 8.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.3, 137.0, 136.7, 136.3, 133.9, 132.5, 130.2, 130.0, 130.0, 128.7, 127.1. All NMR data matches with the previously reported compound.[44]

phenyl(2,4,6-trifluorophenyl)methanone 3.1dd. Prepared according to the general procedure using 1,3,5-trifluorobenzene (1.293 mL, 12.5 mmol) as the arene at 100 °C for 24 hours. Pale yellow liquid, 82% yield (97 mg, 0.41 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.7 Hz, 2H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 2H), 6.80 (dd, *J* = 8.7, 7.2 Hz, 2H). 13C NMR (126 MHz, CDCl3) δ 187.9, 163.7 (dt, *J* = 253.5, 14.8 Hz), 160.4 (ddd, *J* = 253.2, 15.1, 10.5 Hz), 136.8, 134.3, 129.6, 128.8, 113.6 (td, *J* = 21.9, 4.8 Hz), 101.9 (m). All NMR data matches with the previously reported compound.[45]

(3-iodo-4-methoxyphenyl)(phenyl)methanone 3.1ee. Prepared according to the general procedure using 2-iodoanisole (234 mg, 1mmol) as the arene at 60 °C for 16 hours. Pale yellow solid, 83% yield (140 mg, 0.41 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J* = 2.1 Hz, 1H), 7.85 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.77 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 1H), 3.99 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.1, 161.4, 141.7, 137.7, 132.5, 132.3, 131.9, 129.7, 128.4, 109.9, 85.7, 56.7. All NMR data matches with the previously reported compound.[46]

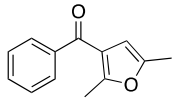
(4-methoxy-1,3-phenylene)bis(phenylmethanone) 3.1ff. Prepared according to the general procedure using 4-methoxybenzophenone (212 mg, 1mmol) as the arene at 80 °C for 16 hours. White solid, 85% yield (134 mg, 0.42 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 – 8.01 (m, 1H), 7.91 – 7.77 (m, 5H), 7.64 – 7.55 (m, 2H), 7.53 – 7.43 (m, 4H), 7.11 (d, *J* = 8.7 Hz, 1H), 3.85 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.3, 194.9, 160.6, 137.7, 137.2, 134.4, 133.4, 132.3, 131.8, 130.0, 129.8, 129.8, 128.7, 128.4, 128.4, 111.0, 56.0. All NMR data matches with the previously reported compound.[47]

Benzophenone 3.1gg. Prepared according to the general procedure using benzoic acid (31 mg, 0.25 mmol) and benzene (39 mg, 0.5 mmol) at 90 °C for 16h using. White solid, 96% yield (43 mg, 0.24 mmol). ^{1}H NMR (400 MHz, CDCl3) δ 7.83 (d, *J* = 7.0 Hz, 4H), 7.61 (t, *J* = 7.4 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 4H). ^{13}C NMR (101 MHz, CDCl3) δ 196.8, 137.6, 132.4, 130.1, 128.3. All NMR data matches with the previously reported compound.[48]

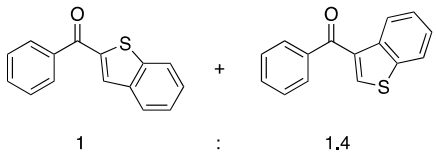


(1-(methylsulfonyl)-1*H*-pyrrol-3-yl)(phenyl)methanone 3.1hh. Prepared according to the general procedure using N-mesyl pyrrole (161 mg, 1.0 mmol) at room temperature for 30 min. White solid, 85% yield (106 mg, 0.43 mmol). ^{1}H NMR (500 MHz, CDCl3) δ 7.92 (d, *J* = 7.0 Hz, 2H), 7.65 – 7.59 (m, 2H), 7.50 (t, *J* = 7.7 Hz, 2H), 6.83 (dd, *J* = 3.7, 1.7 Hz, 1H), 6.36 – 6.31 (m, 1H), 3.88 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 185.0, 137.6, 133.0, 132.9, 129.9, 129.4, 128.4, 126.0, 110.3, 44.0. HRMS. Calculated for $C_{12}H_{12}O_3NS\,H^+$ ($M+H^+$): 250.0532, found: 250.0538.

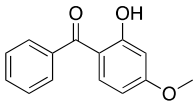
(2,5-dimethylfuran-3-yl)(phenyl)methanone 3.1ii. Prepared according to the general procedure



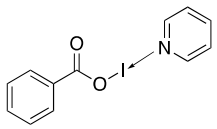
using 2,5-dimethylfuran (96 mg, 1.0 mmol) at room temperature for 30 min. Pale yellow oil, 58% yield (58 mg, 0.29 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.0 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 2H), 6.19 (s, 1H), 2.50 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.4, 157.9, 149.7, 139.4, 131.9, 128.9, 128.2, 121.2, 107.5, 14.1, 13.2. All NMR data matches with the previously reported compound.[49]



Benzo[*b*]thiophen-2-yl(phenyl)methanone 3.1jj and benzo[*b*]thiophen-3-yl(phenyl)methanone 3.1jj'. Prepared according to the general procedure using thianaphthene (134 mg, 1.0 mmol) at room temperature for 16h. Pale yellow solid, 85% yield (98 mg, 0.43 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (d, *J* = 8.1 Hz, 1H, 3-isomer), 8.02 (s, 1H, 3-isomer), 7.98 – 7.86 (m, 5H for 2-isomer, 3H for 3-isomer), 7.69 – 7.59 (m, 1H both isomers), 7.59 – 7.42 (m, 4H for 2-isomer, 4H for 3-isomer). ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.9, 189.7, 143.1, 142.7, 140.1, 139.3, 139.1, 138.3, 137.9, 137.5, 134.8, 132.5, 132.4, 132.3, 129.5, 129.3, 128.5, 128.5, 127.5, 126.1, 125.7, 125.6, 125.2, 125.1, 122.9, 122.4. All NMR data matches with the previously reported compound.[50-51]



Oxybenzone **3.1kk.** Prepared according to the general procedure using 3-methoxyphenol (134 mg, 1.0 mmol) at 100 °C for 22h. Pale yellow solid, 80% yield (46 mg, 0.20 mmol). 1H NMR (400 MHz, CDCl3) δ 12.72 (s, 1H), 7.66 (d, *J* = 6.9 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.55 – 7.47 (m, 3H), 6.55 (d, *J* = 2.5 Hz, 1H), 6.44 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.0, 166.4, 166.2, 138.3, 135.3, 131.5, 128.8, 128.3, 113.1, 107.4, 101.1, 55.6. All NMR data matches with the previously reported compound.[52]



PhCOOI(Py) 3.4. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, *J* = 5.3 Hz, 2H), 8.03 (d, *J* = 7.6 Hz, 2H), 7.97 (t, *J* = 7.7 Hz, 1H), 7.50 – 7.32 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 149.3, 139.8, 131.4, 130.6, 130.1, 127.9, 126.5. HRMS. Calculated for $C_{12}H_{11}O_2NI^+$ ($M+H^+$): 327.9829, found: 327.9816.[53]

3.5.9 NMR Spectra of Products

See supporting information for publication: Kinney, R. G.; Arndtsen, B. A., *Angew. Chem., Int. Ed.* **2019,** *58*, 5085.

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17. We postulate that this equilibrium can be catalyzed by HOTf. Alternatively, benzoic anhydride may be directly iodinated by I_2/AgOTf.
18. The acylation of arenes with **3** presumably proceeds via a similar mechanism to that reported by Effenberger, which has been suggested to involve ionization of **6** to the acylium ion in the presence of triflic acid: see reference 15a.
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Chapter 4: Palladium- and Nickel- Catalyzed Carbonyl Metathesis Between Acid Chlorides for the Preparation of Carbon Isotope Labeled Products

4.1 Preface

In Chapters 2-3, we discussed both transition-metal-catalyzed and transition-metal mediated synthetic routes to potent acyl triflate electrophiles. This chapter shifts focus to the use of metal catalysis to assemble an alternative class of electrophile: acid chlorides. Our laboratory has recently reported that the correctly ligated palladium complex can catalyze the dynamic exchange reaction of the σ-bonded functionalities of aryl-iodides and acid chlorides as a route to generate acid chlorides directly from other acid chlorides. At a similar time, researchers at Merck reported an exchange reaction of isotopically labeled carbon monoxide with acid chlorides as a method to prepare isotopically labeled acid chlorides. While effective, this latter system requires two separate palladium catalyzed reactions, specialized glassware, and an expensive source of isotopically labeled carbon monoxide embedded in a donor acid chloride. To address these challenges, we describe here a joint project between both our lab and Merck towards the design of a new method to generate isotopically labeled acid chlorides. This exploits first palladium and then more effectively nickel catalysts to mediate the dynamic exchange of the carbonyl units between two different acid chlorides. Overall, this has provided a route to generate isotopically labeled acid chlorides (and acid chloride derived products) via exchange reactions with ^{13}C-labeled benzoyl chloride as a donor, thereby avoiding the use of free ^{13}CO, specialized reaction set-ups, elaborate sources of isotopic carbon. All of the experiments in this chapter were performed by me, except for solving the X-ray structure of **[Ni]1**, which was done by Pierre-Louis Lagueux-Tremblay, a PhD student in our group.

4.2 Introduction

The determination of a pharmaceutical compound's pharmacokinetics, including its disposition within the body and metabolism, is vital to the clinical development of a drug candidate.[1-3] Preclinical ADME studies (absorption, distribution, metabolism and excretion) can provide this information by employing radiolabeled pharmaceuticals, which can be detected and

quantified at nanomolar levels of concentration in complex biological settings.[4-10] The radioisotopes of carbon (carbon-14) and hydrogen (tritium) are the most common elements used in these studies.[11] Tritiation is often the first method employed because it can often be directly incorporated into the drug structure via exchange reactions, and therefore requires little manipulation to employ once a candidate is identified.[12, 13] Common approaches include deprotonation/T_2O quench,[14] electrophilic aromatic substitution with strong tritiated acids,[15] or metal-catalyzed C-H functionalization(For examples: Figure 4.1).[16] However, there remain serious drawbacks to tritiation. The sites on the molecule that are easiest to label often coincide with metabolic instability. This can lead to the loss of tritium, and severely limit information on the drug's biodistribution and metabolic fate.[17] In addition, because of the relative mass difference between hydrogen and tritium, significant kinetic isotope effects are possible with tritium, which can result in misleading data on the stability and fate of a drug in biological systems. Due to these features, carbon-14 is ultimately required for all molecules in the clinical development of a drug candidate.[5] Unfortunately, the incorporation of ^{14}C into many sites in a target molecule can be prohibitively difficult and expensive, as these often require *de novo* synthetic routes using ^{14}C reagents. As a result of these synthetic limitations, tritiation is still employed for many early ADME studies.

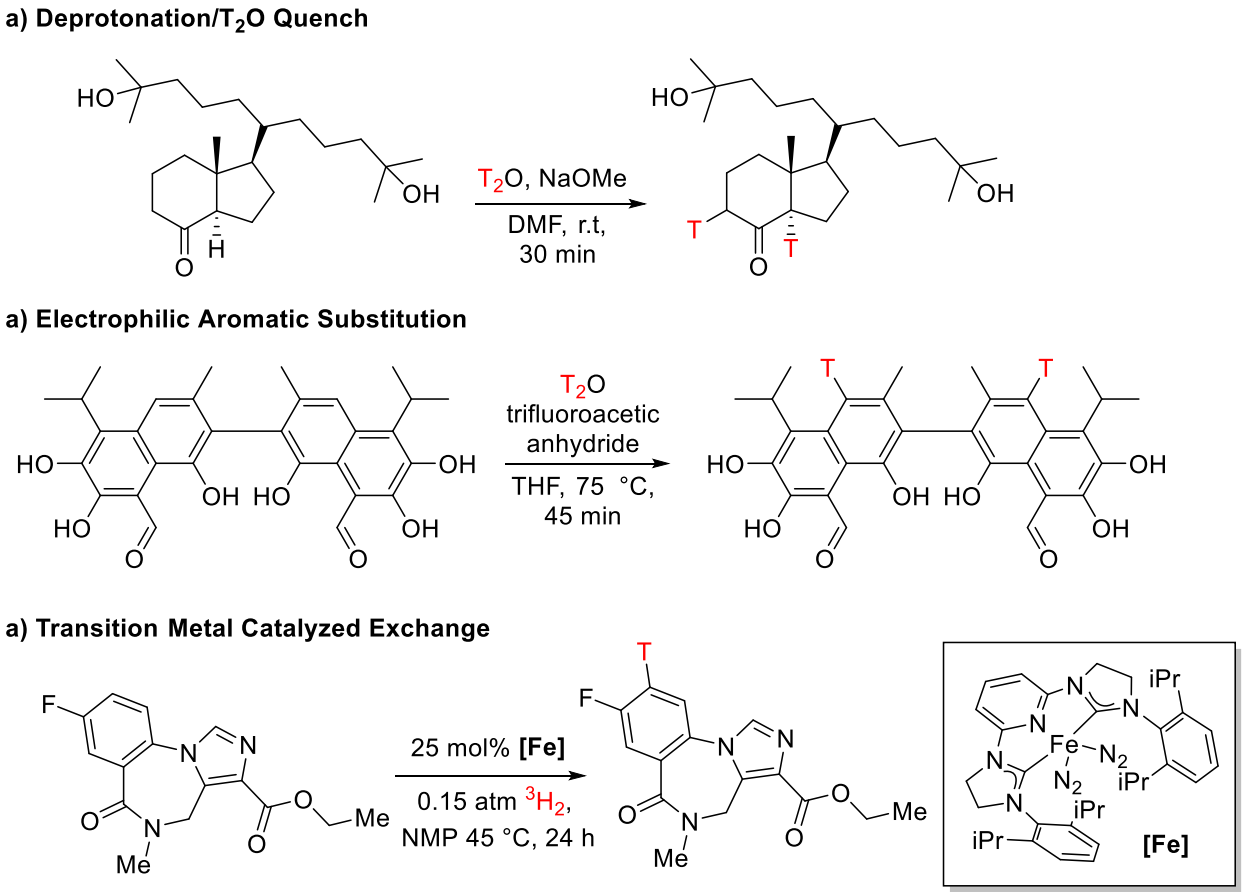


Figure 4.1. Examples of Approaches to Hydrogen Isotope Incorporation

In principle, an attractive scenario for ^{14}C labeling would be to perform this as with tritium: via direct exchange into the pharmaceutical. Such methods would avoid significant synthetic manipulation, and allow a more metabolically stable and innocent carbon radioisotope to be easily incorporated into the drug. Examples of such ^{14}C-exchange reactions have been described using carboxylic acids, which are prevalent units in many drugs.[17] A classic approach to this is via a Hunsdiecker-type degradation of carboxylic acids to an organohalide, which can be followed by either metalation/$^{14}CO_2$ quench,[18] or K^{14}CN/hydrolysis[19] (Figure 4.2a and b). While such methods avoid complete re-synthesis of the molecule, there is substantial synthetic work with radiolabeled material. More recently, Baran[20] and Martin[21] have developed a nickel-catalyzed direct exchange of aliphatic phthalamide esters with $^{13}CO_2$ (Figure 4.2c), which was easily translated to $^{14}CO_2$ labeling. In a complementary methodology, Audisio reported the direct exchange of aromatic

cesium carboxylates using $^{13}CO_2$ under copper catalysis (Figure 4.2d).[22] While effective, these can require stoichiometric nickel or pressing conditions, have limited scope, and all of these methods lead to significant handling issues involving gaseous, radioactive $^{14}CO_2$.

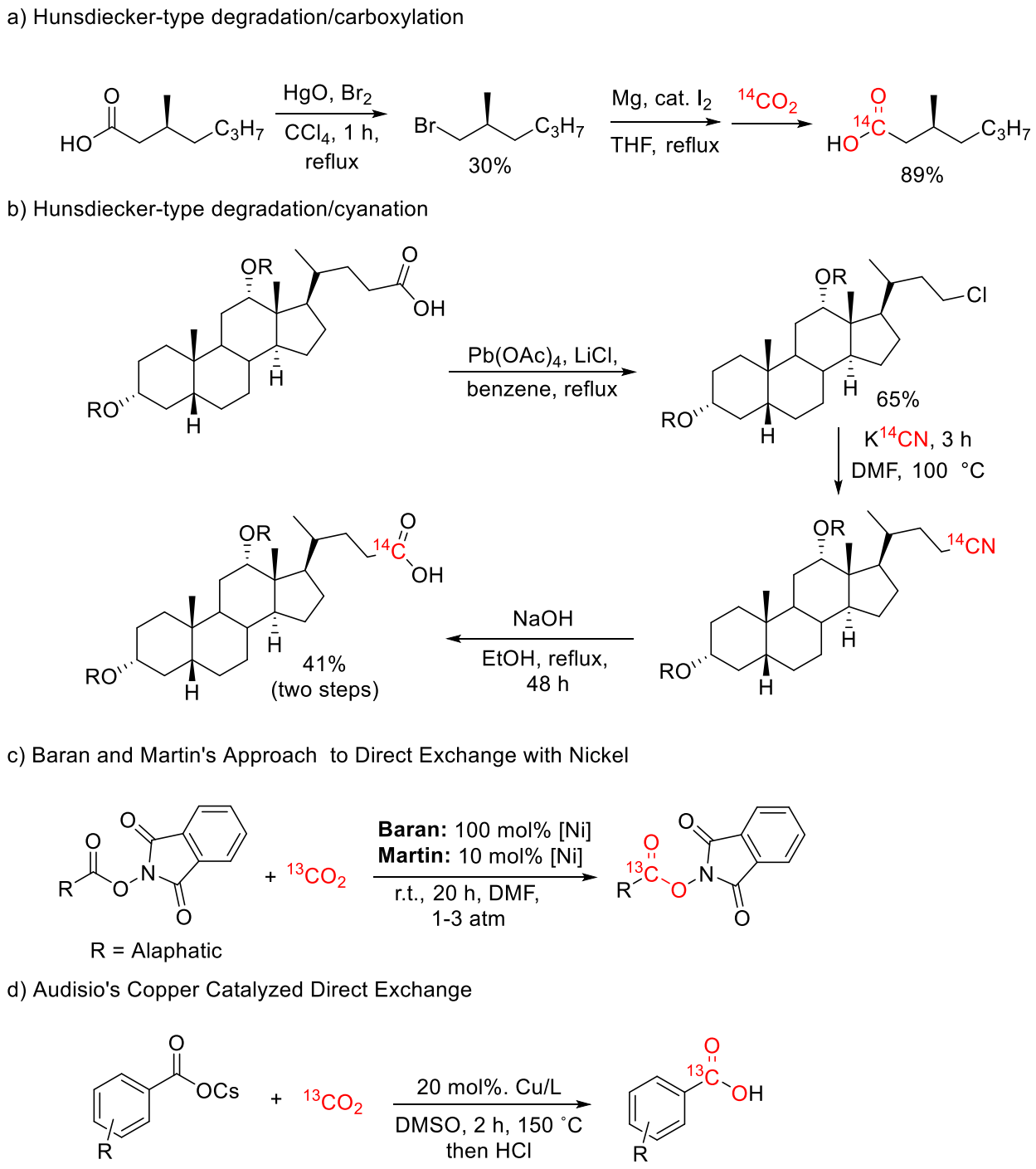


Figure 4.2. Approaches to Carboxylic Acid Isotope Labeling

An alternative way to introduce carbon-14 labels into carboxylic acids is through carbonylation chemistry with ^{14}CO. Traditional approaches to this chemistry involve incorporating a metal-catalyzed carbonylation reaction with ^{14}CO into the overall synthesis of the pharmaceutical.[23-25] Merck researchers have recently reported an interesting new method, wherein carbon isotope exchange of aromatic and aliphatic carboxylic acid drug molecules can be performed by first converting the target carboxylic acid to the corresponding acid chloride. The latter can undergo palladium-catalyzed dynamic exchange with ^{14}CO (Figure 4.3).[26] This reaction proved to be highly effective for a number of complex molecules, including several Merck clinical candidates. However, it requires the use of a special ^{14}CO releasing molecule in a dual chamber system, and entails the generation of gaseous ^{14}CO, which is both chemically and radioactively toxic. Nevertheless, it suggests the viability of creating radiolabeled drugs under mild conditions by simple exchange reactions on pharmaceuticals.

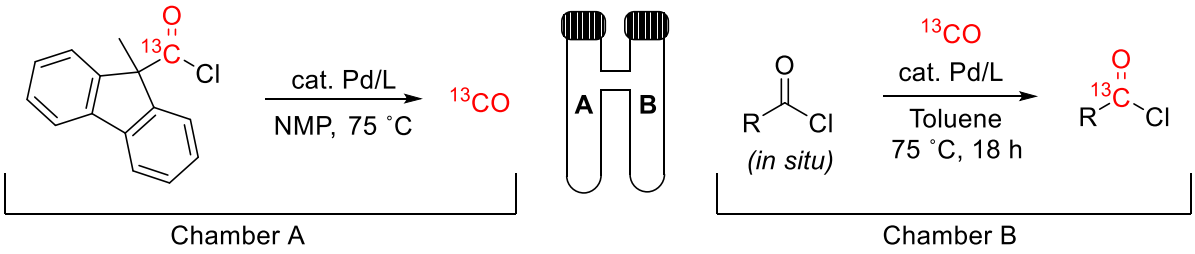


Figure 4.3. Merck's Pd Catalyzed Carbon Isotope Exchange of Acid Chlorides

Our lab and the Morandi lab have recently reported an alternative method to prepare carboxylic acid derivatives: via the palladium-catalyzed metathesis of σ-bonds between two different organic fragments (Figure 4.4a).[27, 28] This was employed to generate aromatic acid chlorides via the dynamic exchange between acid chlorides and aryl iodides. This transformation exploits the ability of Pd(0) systems to mediate the reversible oxidative addition/reductive elimination of both acid chlorides and aryl iodides, in concert with exchange of halides and CO between two catalysts. In considering this chemistry, we questioned if this may offer a unique avenue to access isotopically labeled carboxylic acid derivatives in pharmaceuticals: via the dynamic exchange of CO between two different acid chlorides (Figure 4.4b). Among other

features, this would open a route to generate carbon-labeled carboxylic acid derivatives from a simple acid chloride donor without a specialized reaction setup, and the handling of a radioactive gas.

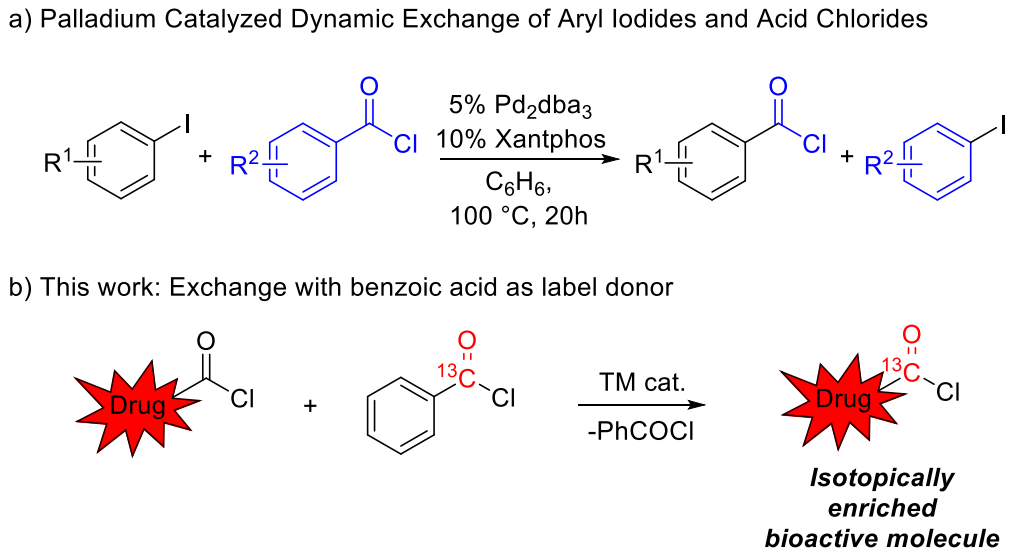
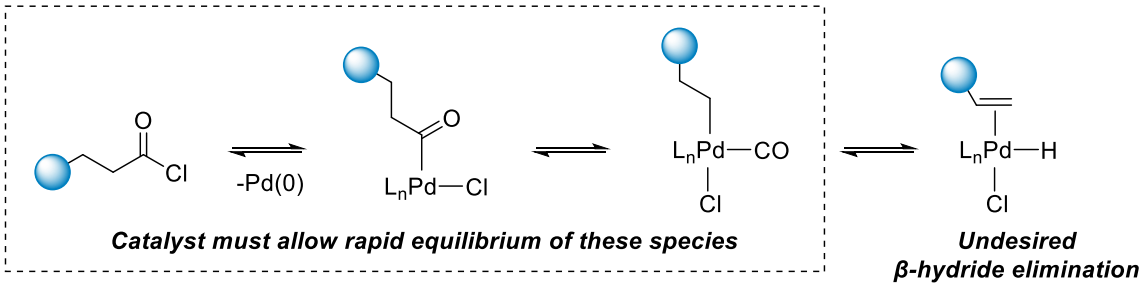


Figure 4.4. Dynamic Exchange of Acid Chlorides

While appearing viable, there are challenges associated with such a transformation (Figure 4.5). Firstly, the reductive elimination of acid chlorides, while possible, has to date required free CO to associate to palladium to both lower the reaction barrier and make the reaction thermodynamically viable.[29-31] Secondly, catalysts that favor CO de-insertion of carbon monoxide would also favor β-hydride elimination, and lead to loss of product when employing alkyl acid chlorides. The presence of free CO in previous systems can suppress β-hydride elimination by retaining the catalyst in the CO-inserted state. Without excess CO, ways in which this step can be controlled are unclear. We describe below our studies towards surmounting these challenges, the realization of this carbonyl exchange reaction, and its application to the carbon isotope labeling of pharmaceuticals.



- Catalyst must favor reductive elimination and CO de-insertion, but disfavor β-hydride elimination
- Lack of excess gaseous CO makes reductive elimination more difficult and favors alkene formation

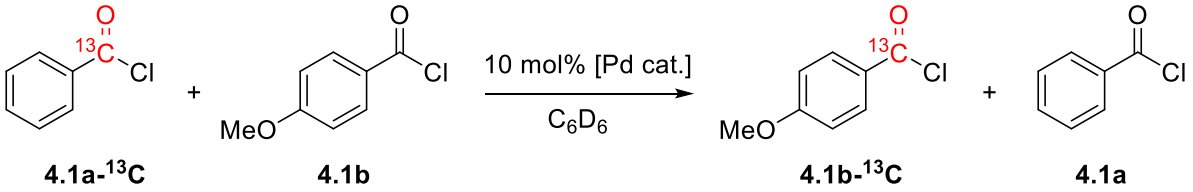
Figure 4.5. Challenges in Palladium-Catalyzed Carbonyl Exchange

4.3. Results and Discussion

4.3.1. Palladium Catalysis for 13C-Labeled Acid Chlorides via Dynamic Exchange

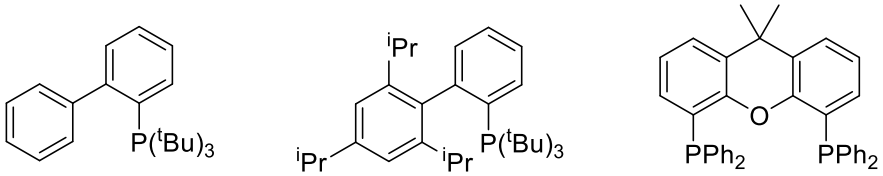
We began our studies by examining the potential palladium-catalyzed exchange of carbonyls between ^{13}C-labeled benzoyl chloride, **4.1a-^{13}C** and *p*-anisoyl chloride, **4.1b**. As shown in Table 4.1, using Pd[P^{t}Bu$_3$]$_2$ as a catalyst, which was found to be effective in carbonylative acid chloride synthesis led to no observable exchange between the acid chlorides at 50 °C (Table 4.1, entry 1), although exchange is noted at high temperatures (entries 2 and 3). The slow exchange noted here presumable results from the absence of added carbon monoxide, which has been found to dramatically accelerate reductive elimination of acid chlorides by coordination to Pd(II).[29, 31] Other sterically encumbered phosphine ligands were also unreactive (entries 4-6). However, we were pleased to find that using the large bidentate ligand Xantphos (**L3**) provided complete exchange to give the fully equilibrated mixture of ^{13}C-products within 16 h at 50 °C (entry 7). (Since the acid chlorides are mixed in equal molar amounts, a statistical mixture of 50% incorporated isotope represents complete exchange.)

Table 4.1. Palladium Catalyzed Dynamic CO Exchange of Aryl Acid Chlorides[a]



4.1a-^{13}C **4.1b** **4.1b-^{13}C** **4.1a**

Entry	[Pd cat.]	Temp,Time	%4.1b-^{13}C (from 4.1b-^{13}C:4.1a-^{13}C)[b]
1	$Pd[P^tBu_3]_2$	50 °C, 24h	0%
2	$Pd[P^tBu_3]_2$	70 °C , 18 h	9%
3	$Pd[P^tBu_3]_2$	110 °C , 5h	47%
4	Pd_2dba_3/P(*o*-tolyl)$_3$	50 °C, 18 h	0%
5[c]	Pd_2dba_3/**L1**	50 °C, 18 h	0%
6[c]	Pd_2dba_3/**L2**	50 °C, 18 h	0%
7	Pd_2dba_3/**L3**	50 °C, 16 h	50%



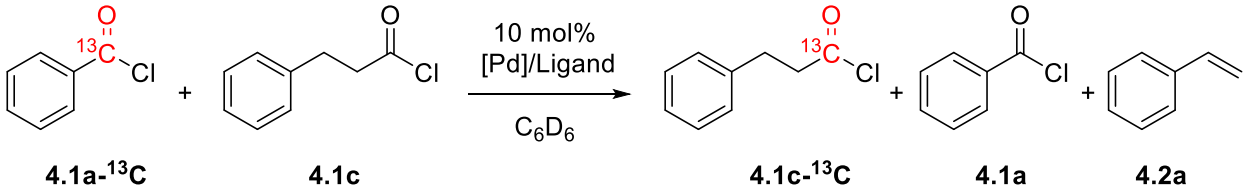
L1 **L2** **L3**

^{13}C-benzoyl chloride (5 mg, 0.038 mmol), *p*-methoxybenzoyl chloride (6 mg, 0.38 mmol), $Pd[P(^tBu)_3]_2$ (2 mg, 0.0038 mmol) or Pd_2dba_3 (0.0019 mmol, 2 mg), Ligand (20 mol% monodentate, 0.0075 mmol or 10 mol% bidentate, 0.0038 mmol), C_6D_6 (0.75 mL). [b]The % **4.1b-^{13}C** is estimated from the relative ^{13}C NMR integrations of **4.1b-^{13}C** and **4.1a-^{13}C**. The maximum yield is 50%. [c]30 mol% catalyst, rection at 0.017 M. ^{13}C-benzoyl chloride (2 mg, 0.013 mmol), *p*-methoxybenzoyl chloride (2 mg, 0.013 mmol), other reagent concentrations remained the same.

While aromatic carboxylic acids are found in pharmaceuticals, expanding to other acids, such as alkyl carboxylic acids, would render this methodology much more broadly applicable. Unfortunately, attempts to use this Pd_2dba_3/Xantphos catalyst with alkyl acid chlorides resulted in no exchange, and instead the formation of styrene as the major product (Table 4.2, entry 1). Styrene formally arises from oxidative addition of the alkyl acid chloride followed by CO de-insertion and β-hydride elimination. The latter is a common challenge in palladium catalysis with

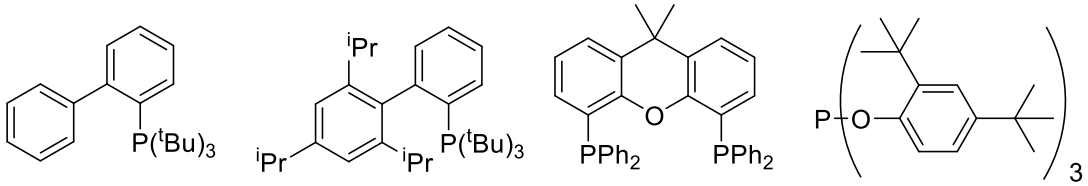
alkyl-substituted reagents, but can be suppressed with sterically encumbered monodentate ligands.[32-34] We do see low to moderate levels of isotopic exchange with P^tBu_3, P(*o*-tolyl)$_3$, or Buchwald-type R_2P(2-biphenyl) ligands (entries 2-8). Unfortunately, even when employing these ligands, significant quantities of styrene are observed.

Table 4.2. Palladium-Catalyzed Dynamic CO Exchange of Alkyl Acid Chlorides[a]



4.1a-^{13}C **4.1c** **4.1c-^{13}C** **4.1a** **4.2a**

Entry	Catalyst System	Temp,Time	% 4.1c-^{13}C[b] (ratio of 4.1c:4.1a in ^{13}C NMR)	% 4.2a[c]
1	Pd_2dba_3/**L3**	70 ˚C, 20h	0%	42%
2	Pd_2dba_3/P(*o*-tolyl)$_3$	70 ˚C , 20h	3%	3%
3	Pd_2dba_3/**L2**	70 ˚C , 20h	3%	3%
4	Pd_2dba_3/**L1**	70 ˚C, 20h	25%	49%
5	Pd_2dba_3/**L1**	50 ˚C, 20h	7%	16%
6	Pd[P^{t}Bu$_3$]$_2$	70 ˚C, 20h	30%	52%
7	Pd[P^{t}Bu$_3$]$_2$	60 ˚C, 15h	29%	35%
8	Pd[P^{t}Bu$_3$]$_2$	50 ˚C, 20h	18%	10%
9	Pd_2dba_3/**L4**	70 ˚C, 20h	7%	13%
10	Pd_2dba_3/P(OPh)$_3$	70 ˚C, 20h	18%	7%
11	Pd_2dba_3/P(OPh)$_3$	50 ˚C, 20h	2%	3%
12	Pd_2dba_3/Bu_4NCl	50 ˚C, 20h	14%	1%
13	Pd_2dba_3/Bu_4NCl	60 ˚C, 24h	35%	6%
14[d]	Pd_2dba_3/Bu_4NCl	80 ˚C, 3h	31%	23%



L1 **L2** **L3** **L4**

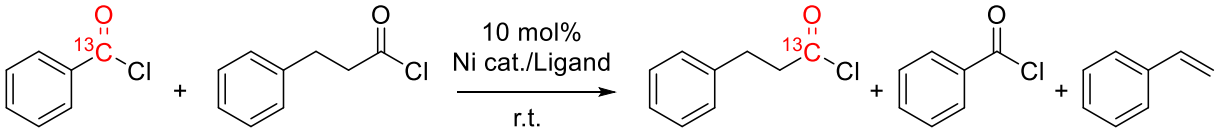
[a]^{13}C-benzoyl chloride (5 mg, 0.038 mmol), hydrocinnamoyl chloride (6 mg, 0.038 mmol), Pd[P(^{t}Bu)$_3$]$_2$ (2 mg, 0.0038 mmol) or Pd_2dba_3 (0.0019 mmol, 2 mg), ligand (20 mol% monodentate, 0.0075 mmol or 10 mol% bidentate, 0.0038 mmol), dimethyl sulfone standard (2 mg, 0.01 mmol), C_6D_6 (0.75 mL). [b]Yield of **4.1c-^{13}C** is estimated from the relative ^{13}C NMR integrations of **4.1a-^{13}C** and **4.1c-^{13}C**; maximum yield is 50%. [c]Yield determined relative to the internal standard by ^{1}H NMR analysis. [d]Entry 13 at 80 °C for 3 additional h.

We next examined the use of phosphites as ligands. These create a more electron- deficient palladium catalyst, which may also inhibit β-hydride elimination. In addition, a more electron-poor catalyst should be better able to facilitate the challenging reductive elimination from the $L_nPd(COR)Cl$ intermediate. The use of less-strongly donating $P(OPh)_3$ does lead to more exchange than β-hydride elimination (entry 10). Productive results were also noted upon removing phosphite ligands and instead using weakly coordinating chloride anion as the ligand (entries 12-13). However, attempts to obtain high levels of ^{13}CO exchange at elevated temperatures led to increased amounts of styrene (entry 14).

4.3.2. Nickel Catalysis

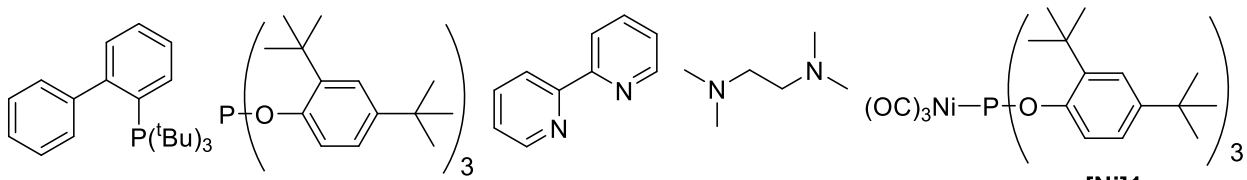
An alternative approach to inhibit β-hydride elimination is to employ nickel catalysis. Nickel complexes are known to be much less susceptible to β-hydride elimination in catalysis,[35-38] and can mediate decarbonylative transformations.[39-41] As was hoped, the use of nickel catalysts with phosphine and phosphite donor ligands completely suppresses styrene formation and leads to low levels of ^{13}CO exchange (Table 4.3 entries 1-4). In an effort to increase the amount of ^{13}C exchange, donor ligands were removed, since this may increase the rate of reductive elimination. While $Ni(COD)_2$ by itself results in no exchange and the formation of nickel black (entry 5), we were pleased to find that the addition of chloride to the stabilize Ni(0) leads to 40% exchange of product **4.1c-^{13}C** without β-hydride elimination (entry 6). Other halogen additives led to lower levels of ^{13}C exchange (entries 7-8). Unfortunately, all efforts to push the exchange to completion with the $Ni(COD)_2/Bu_4NCl$ system were unsuccessful, suggesting that this weakly-ligated catalyst system may decompose before complete exchange. The addition of phosphine- and nitrogen-based ligands in concert with Bu_4NCl had a deleterious effect on exchange (entries 9-12).

Table 4.3. Nickel-Catalyzed Dynamic CO Exchange of Alkyl Acid Chlorides[a]



4.1a-^{13}C **4.1c** **4.1c-^{13}C** **4.1a** **4.2a (none observed)**

Entry	Catalyst	Solvent	Time	% 4.1c-^{13}C (ratio of 4.1c:4.1a in ^{13}C NMR)[b]
1	10% $Ni(COD)_2/P(OEt)_3$	C_6D_6	20 h	0%
2	10% Ni(COD)2/$P(OPh)_3$	CD_3CN	20 h	7%
3	10% $Ni(COD)_2$/**L4**	CD_3CN	20 h	2%
4	10% $Ni(COD)_2/P(o\text{Tol})_3$	CD_3CN	20 h	8%
5	10% $Ni(COD)_2$	CD_3CN	20 h (70 °C)	0%
6	10% $Ni(COD)_2/Bu_4NCl$	CD_3CN	20 h	40%
7	10% $Ni(COD)_2/Bu_4NBr$	CD_3CN	20 h	23%
8	10% $Ni(COD)_2/Bu_4NI$	CD_3CN	20 h	16%
9	10% $Ni(COD)_2/Bu_4NCl/P(^tBu_3)$	CD_3CN	20 h	12%
10	10% $Ni(COD)_2/Bu_4NCl$/**L1**	CD_3CN	20 h	17%
11	10% $Ni(COD)_2/Bu_4NCl$/**L5**	CD_3CN	20 h	27%
12	10% $Ni(COD)_2/Bu_4NCl$/**L6**	CD_3CN	20 h	18%
13	5% $Ni(CO)_3P(^tBu_3)/Bu_4NCl$	C_6H_5CN	4 h	22%
14	5% $Ni(CO)_3PPh_3/Bu_4NCl$	C_6H_5CN	4 h	26%
15	5% $Ni(CO)_3P(OPh)_3/Bu_4NCl$	C_6H_5CN	4 h	3%
16	5% **[Ni]1**/Bu_4NCl	C_6H_5CN	4 h	44%
17	5% **[Ni]1**/Bu_4NCl	C_6H_5CN	22 h	47% (98%[c], 44.0% ^{13}C[d])
18	10% **[Ni]1**	C_6H_5CN	20 h (70 °C)	9%



L1 **L4** **L5** **L6** **[Ni]1**

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[a]^{13}C-benzoyl chloride (9 mg, 0.06 mmol), hydrocinnamoyl chloride (10 mg, 0.06 mmol), nickel catalyst (5 mol%, 0.003 mmol or 10 mol%, 0.006 mmol), ligand (20 mol% monodentate, 0.012 mmol or 10 mol% bidentate, 0.006 mmol), if Bu_4NX is used (1 equiv, 0.06 mmol). Yield of **4.1c-^{13}C** estimated from the relative ^{13}C NMR integrations of **4.1a-^{13}C** and **4.1c-^{13}C**. Since ^{13}CO is potentially incorporated onto the nickel catalyst, the actual %**4.1c-^{13}C** could be up to 7% to 14%

lower than that noted, using 5% or 10% nickel carbonyl catalyst, respectively. [c]^{1}H NMR chemical yield of alkyl acid chloride. [d]^{13}C incorporation from HRMS analysis of the benzylamine derived amide. Maximum 46.5% ^{13}C incorporation.

In order to probe how these nickel catalysts deactivate, the reaction was performed with stoichiometric $Ni(COD)_2$/Bu_4NCl, and the products analyzed by GC-MS. This shows the formation of significant quantities of ketone and diketone products and little acid chloride left in the reaction (Figure 4.6, yields estimated from GC-MS). These ketone products formally arise from the coupling of two $L_nNi(COR)Cl$ and/or $L_nNi(R)Cl$ intermediates, and presumably creates $NiCl_2$ as a byproduct, which would be catalytically inactive.

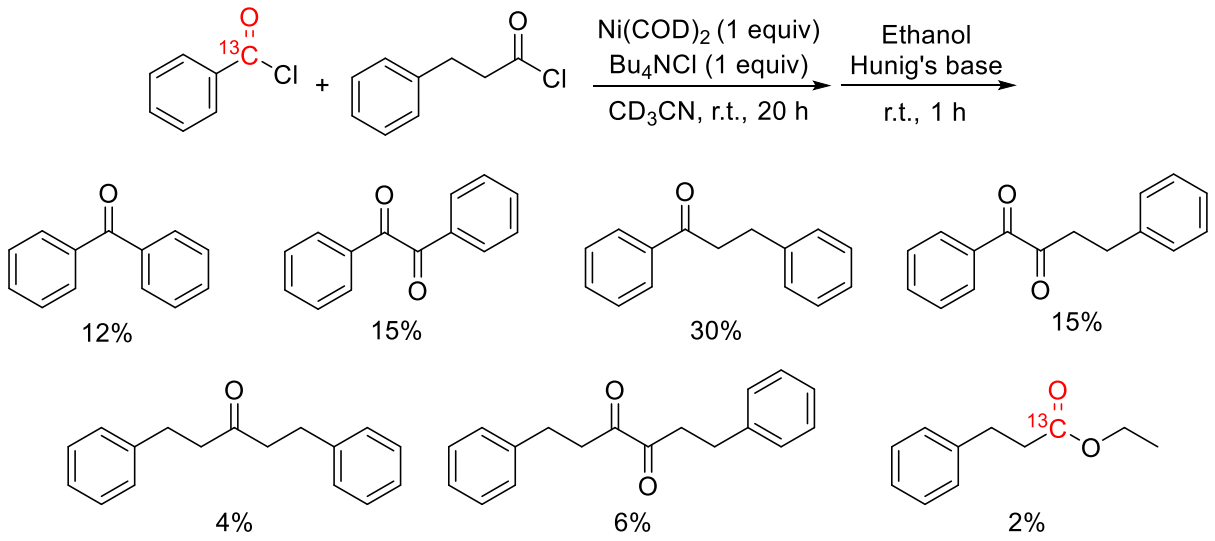


Figure 4.6. Stoichiometric reactivity of $Ni(COD)_2$

In considering approaches to inhibit this catalyst deactivation, one possibility would be to exploit CO itself as a ligand. Nickel carbonyl complexes of the form $Ni(CO)_nL$ are stable, unlike the analogous palladium complexes, and since carbon monoxide is a π-acidic ligand, create a more electron-poor metal. The latter would both favor reductive elimination of the acid chloride, and may slow transmetallation on the saturated nickel catalyst. A range of $Ni(CO)_3L$ catalysts in concert with Bu_4NCl were tested in the reaction and found to mediate much more rapid ^{13}C exchange (13-17). In the case of sterically encumbered electron-poor phosphite catalyst,

$(CO)_3Ni[P(O\text{-}2,4\text{-}^tBuC_6H_3)_3]$ (**[Ni]1**), near complete exchange is observed at room temperature in 4 hours (entry 16). The reaction can be taken to completion at longer reaction times (entry 17). Without chloride present, severely attenuated levels of exchange are observed even under more pressing conditions (entry 18). We do note that since three ^{12}CO are also present in the nickel catalyst, and may get incorporated into both acid chlorides, the actual $\%^{13}C$ in **4.1c** may be up to 7% lower than that estimated from relative ^{13}C signals.

The synergistic influence of both phosphite and chloride in nickel catalysis is unusual. Evidence for the potential role of chloride in catalysis can be seen by monitoring the reaction by *in situ* NMR analysis. ^{31}P NMR data shows the steady loss of ligand from **[Ni]1** to form free phosphite with concomitant increase in ^{13}CO exchange (Figure 4.7a). A potential rationale for the build-up of free phosphite as the reaction progresses, and for the high catalytic activity of the sterically encumbered $P(O\text{-}2,4\text{-}^tBuC_6H_3)_3$ ligand in concert with a chloride source, is that chloride may replace the phosphite ligand to form active catalyst $[Bu_4N][Ni(CO)_3Cl]$ (**[Ni]2**). Anionic nickel carbonyl complexes are known to be the active catalysts in nickel-catalyzed carbonylations.[42-45] $(CO)_3NiCl^-$ has been previously generated in solution, but decomposes to $Ni(CO)_4$, Bu_4NCl, and nickel black upon concentration.[46] To probe this hypothesis, **[Ni]2** was generated *in situ* from $Ni(CO)_4$ and Bu_4NCl, and used as a catalyst. As shown in Figure 4.7b, **[Ni]2** shows nearly identical catalyst activity to **[Ni]1**.

Based on this data, we postulate that the active catalyst in this reaction is an *in situ* generated $(CO)_3NiCl^-$ (**[Ni]2**, Figure 4.7c). The oxidative addition of acid chloride to **[Ni]2** followed by exchange of CO with the acyl ligand can allow CO exchange between two nickel catalysts as a pathway to incorporate ^{13}C label into the new acyl ligand for reductive elimination. Interestingly, performing the reaction even in an open vessel leads to exchange, albeit in lower yield, implying that any free CO formed in the exchange is rapidly sequestered by nickel (Scheme 4.7d). The activity of **[Ni]2** in this reaction is presumably tied to the ability of the electron-poor nickel to more readily undergo acid chloride reductive elimination, both forming the product and limiting the lifetime of the nickel acyl and alkyl intermediates for unproductive side reactions (*e.g.* ketone formation).

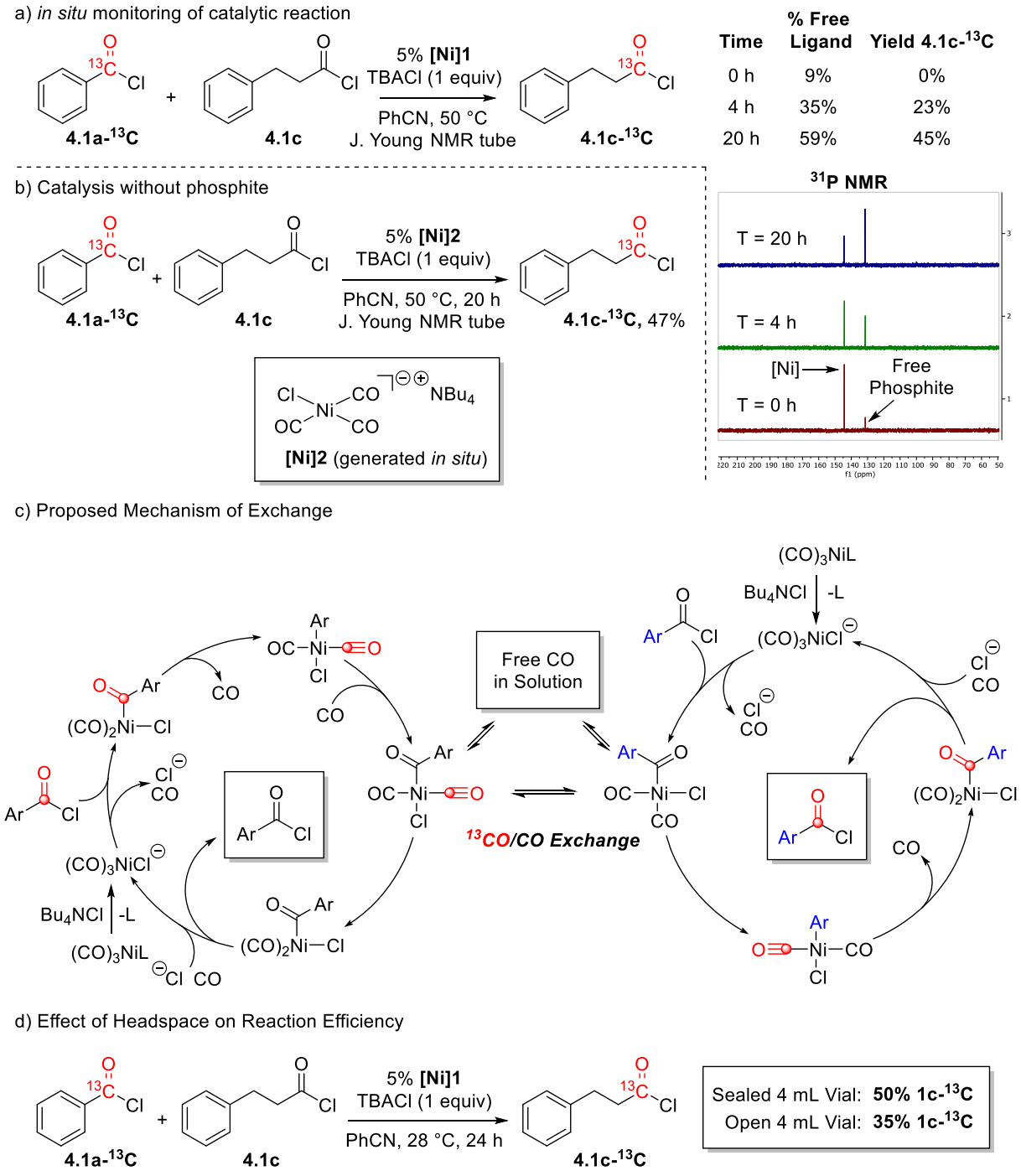
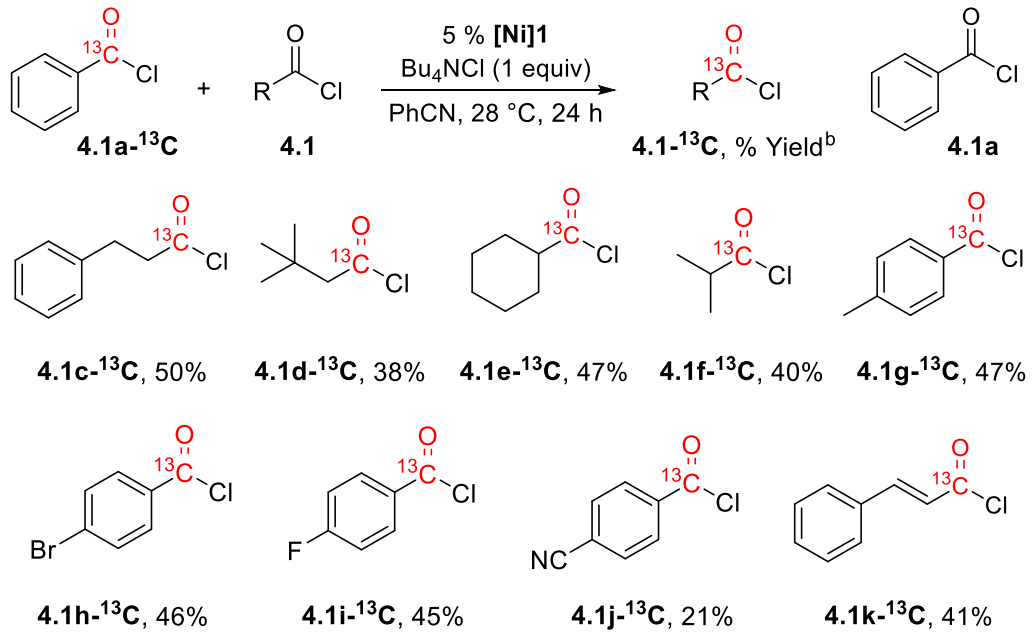


Figure 4.7. Mechanistic Experiments and Preliminary Mechanistic Proposal

As the phosphine complex **[Ni]1** is an isolable, air stable solid (in contrast to $(CO)_3NiCl^-$), it was used to probe the versatility of the reaction. This catalyst is capable of

mediating the room temperature ^{13}CO exchange between $Ph^{13}COCl$ and a variety of $C(sp^2)$- and $C(sp^3)$- acid chlorides (Table 4.4). For example, primary (**4.1c-^{13}C**, **4.1d-^{13}C**), cyclic secondary (**4.1e-^{13}C**), and acyclic secondary alkyl acid chlorides (**4.1f-^{13}C**) give near maximum levels of exchange. Both electron rich (**4.1g-^{13}C**), and electron poor aryl acid chlorides (**4.1h-^{13}C-4.1j-^{13}C**) also undergo CO exchange, as do α, β-unsaturated substrates (**4.1k-^{13}C**). The even more electron poor **4.1j-^{13}C** can also undergo useful levels exchange, although it is incomplete.

Table 4.4. Scope of Acid Chlorides[a]

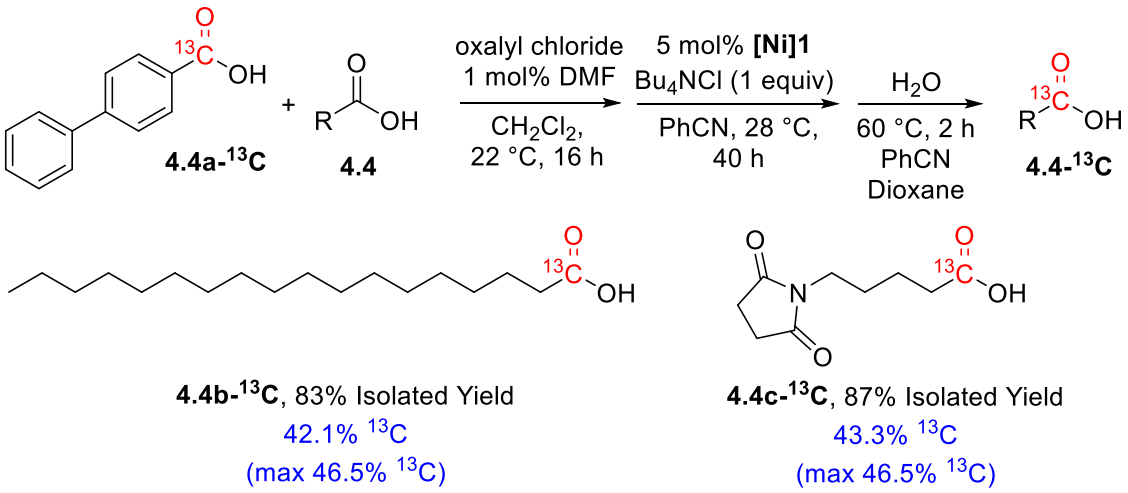


[a]^{13}C-benzoyl chloride (9 mg, 0.06 mmol), acid chloride (0.06 mmol), **[Ni]1** (2mg, 0.003 mmol), Bu_4NCl (17 mg, 0.06 mmol). The % **4.1c-^{13}C** is estimated from the relative ^{13}C NMR integrations of **4.1a-^{13}C** and **4.1c-^{13}C**. Since ^{12}CO is also present in the nickel catalyst, and may get incorporated into both acid chlorides, the actual $\%^{13}C$ in **4.1c** may be up to 7% lower than that estimated from relative ^{13}C NMR signals.

Finally, we have examined the potential of coupling this exchange with the *in situ* formation of acid chlorides, as this would offer an attractive platform for the one pot conversion of carboxylic acids into isotopically labeled products. After probing various conditions we were pleased to find that the *in situ* chlorination of the carboxylic acids with oxalyl chloride, followed

by removal of any remaining oxalyl chloride *in vacuo* and **[Ni]1** exchange, led to efficient incorporation of the ^{13}C label into the product, and with no observable alkene formation.

Table 4.5. Exchange on *in situ* Generated Acid Chlorides.[a]

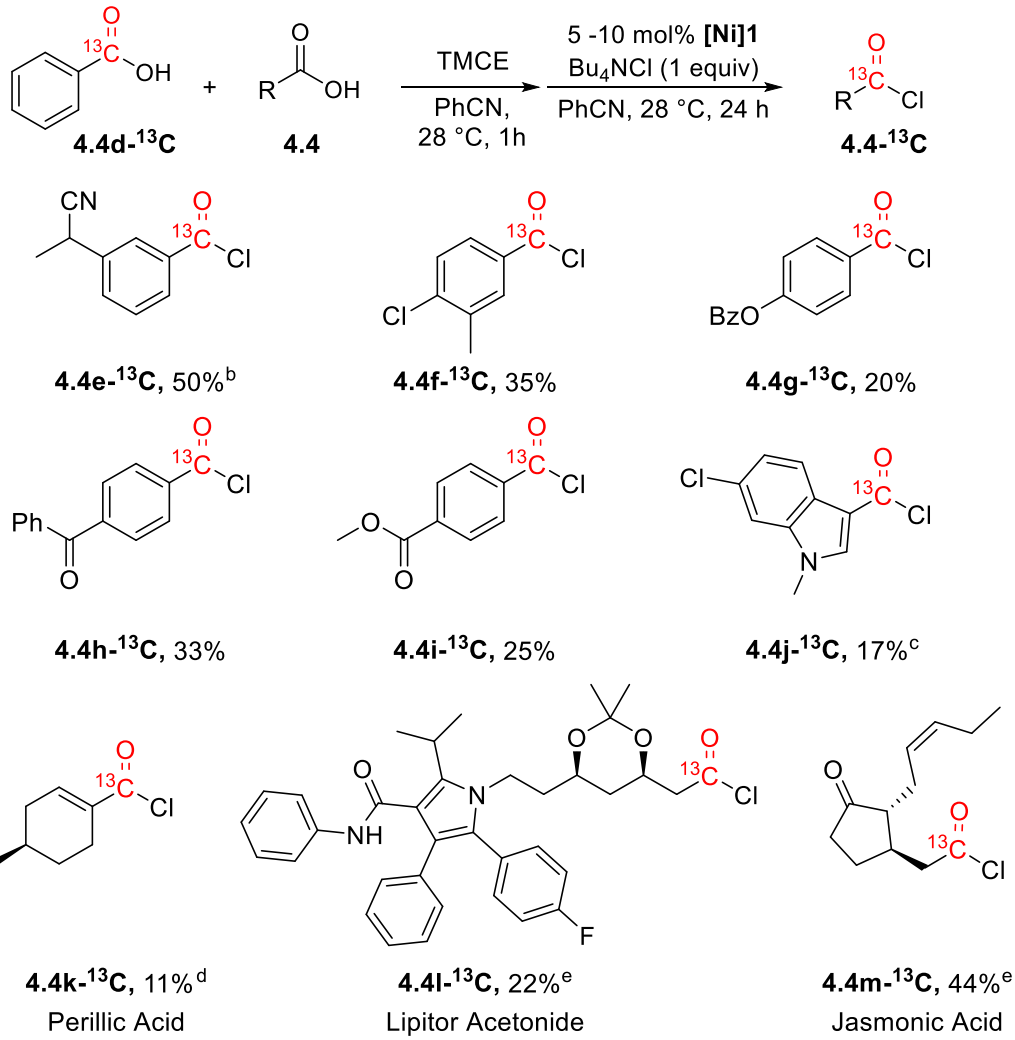


[a]Conditions: Acid chloride formation: ^{13}C-4-phenyl benzoic acid (152 mg, 0.5 mmol), alkyl carboxylic acid (0.5 mmol), oxalyl chloride (127 µL, 1.5 mmol), DMF stock solution (9 mL of a stock solution containing 3 mg dimethylformamide in 40 mL of CH_2Cl_2). CO exchange: **[Ni]1** (20 mg, 0.025 mmol), BuN_4Cl (139 mg, 0.5 mmol), PhCN (5 mL, DCM removed). Hydrolysis: H_2O (2 mL) and dioxane (3 mL) added directly reaction mixture.

Preliminary analysis shows this platform can be applied to a range of carboxylic acids. In these cases 1-chloro-N,N,2-trimethyl-1-propenylamine (TMCE) was used as the chlorinating reagent. By using a slight excess of TMCE, carboxylic acids can be rapidly converted to the acid chloride without the build-up of HCl, or the need for solvent removal before exchange. This allows for a more streamline procedure and the use of acid-sensitive substrates. We do observe less efficient exchange reactions compared to commercial acid chlorides, which is most likely due to small amounts of residual chlorinating reagent and/or trace amounts of anhydride that form during chlorination. However, these levels of exchange are suitable for ADME studies. Electron rich (**4.4e-^{13}C - 4.4g-^{13}C**) and electron poor (**4.4h-^{13}C - 4.4i-^{13}C**) acids give useful levels of exchange, as do heteroaromatic substrates (**4.4j-^{13}C**). This strategy was also applicable to naturally occurring

carboxylic acids, such as perillic acid **4.4k-^{13}C,** and jasmonic acid **4.4m,^{13}C**, as well as pharmaceutical derivatives, such as acetonide protected Lipitor **4.4l-^{13}C**.

Table 4.6. Preliminary Results on *in situ* exchange[a]



[a]Conditions: Acid chloride formation: ^{13}C-benzoic acid (7 mg, 0.06 mmol), carboxylic acid (0.06 mmol), TMCE (tetramethyl chloroenamine (17 mg, 0.13 mmol), PhCN(550 µL). CO exchange: **[Ni]1** (2 mg, 0.003 mmol), Bu_4NCl (17 mg, 0.06 mmol), and PhCN (50 µL) added directly to reaction mixture. [b]10% **[Ni]1 (**4mg, 0.006 mmol) [c]Indole carboxylic acid chlorinated with oxalyl chloride (10.2 µL, 0.12 mmol) in CH_2Cl_2 (1 mL) for 16 h at r.t. Exchange 50 mol% **[Ni]1** (24 mg, 0.03 mmol), ^{13}C benzoyl chloride (9 mg, 0.06 mmol), r.t., 48 h. [d]10% **[Ni]1 (**4mg, 0.006 mmol). [e]48 h.

4.4. Conclusion

In conclusion we have demonstrated how the nickel-catalyzed dynamic exchange of carbonyl groups of acid chlorides can be used to effectively incorporate a ^{13}C label into carboxylic acids. This permits use of a readily available, easy to handle source of carbon isotope instead of handling radioactive gases or requiring specialized equipment. The nickel carbonyl catalyst, $(CO)_3Ni[P(O\text{-}2,4\text{-}^tBuC_6H_3)_3]$, can mediate the complete exchange of $Ph^{13}COCl$ at ambient temperature and with a range of alkyl, aryl, and α-β-unsaturated acid chlorides. Studies to fully explore the scope of this exchange reaction in the contexts of pharmaceutical drugs are in progress.

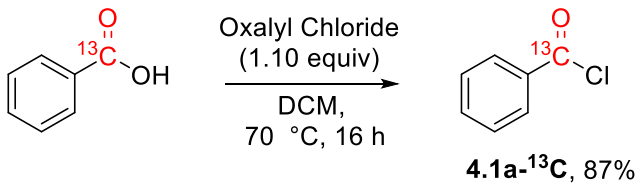
4.5. Experimental Section

4.5.1. General Considerations

All manipulations were conducted in a glovebox under a nitrogen atmosphere, unless specifically stated. Unless otherwise noted, all reagents were purchased from commercial sources and used without purification. ^{13}C-benzoic acid, ^{13}C-4-phenylbenzoic acid, perillic acid, Lipitor acetonide, and jasmonic acid were supplied by Merck. Solvents were dried by using a solvent purifier system, and were stored over activated 4Å molecular sieves inside the glovebox. Benzonitrile was passed through a plug of basic alumina, de-gassed, and stored over 4Å molecular sieves in the glovebox. Deuterated acetonitrile and benzene were stirred over calcium hydride, vacuum transferred, degassed, and stored over 4Å molecular sieves. Tetrabutylammonium chloride was dried in the glovebox by dissolving in dichloromethane, allowing to stand overnight over 4Å activated molecular sieves, filtered and the solvent removed *in vacuo*. $Pd(P^tBu_3)_2$ and $Pd_2dba_3{\cdot}CHCl_3$ were prepared according to literature procedure and stored at -35 °C in the glovebox to avoid decomposition.[30, 47] Nuclear magnetic resonance (NMR) characterization was performed on 400 MHz or 500 MHz spectrometers for proton, 126 MHz for carbon, and 162 MHz for phosphorus. ^1H and ^{13}C NMR chemical shifts were referenced to residual solvent. For NMR spectra of the products, see Appendix 2. Mass spectra were recorded on a high-resolution electrospray ionization quadrupole mass spectrometer.

4.5.2 Synthesis of Starting Materials and Nickel Catalysts

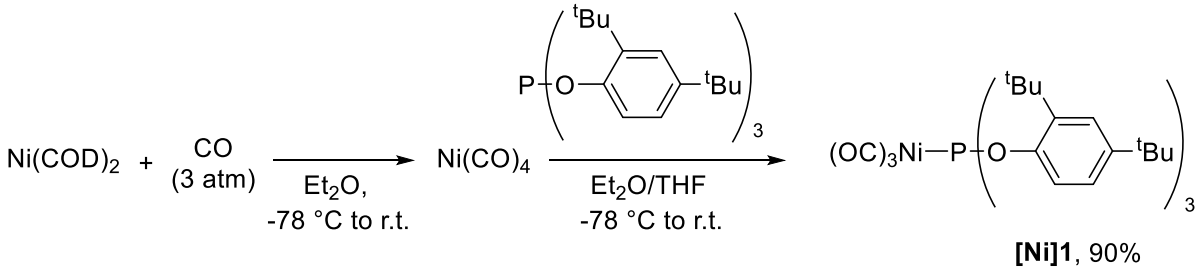
Synthesis of ^{13}C-benzoyl chloride **4.1a-^{13}C**



4.1a-^{13}C, 87%

To an oven dried nitrogen purged 50 mL Schlenk flask was added ^{13}C-benzoic acid (2.01 g, 16.5 mmol), followed by CH_2Cl_2 (8 mL) and oxalyl chloride (1.53 mL, 18.1 mmol). The Schlenk flask was capped with a Teflon screw cap and heated to 70 °C for 16 hours. After cooling to room temperature, the Schlenk flask was slowly opened, and then filtered through a plug of potassium carbonate into a nitrogen purged vial, rinsing the plug with additional dichloromethane. After evaporating the solvent with a stream of nitrogen, **4.1a-^{13}C** was obtained as a slightly yellow oil in 87% yield (2.33 g). Note: No difference in catalytic activity was observed when using distilled ^{13}C-benzoyl chloride.

Representative Procedure for Synthesis of $Ni(CO)_3L$ complexes



[Ni]1, 90%

In a glovebox, tris(2,4-di-tert-butylphenyl) phosphite (1.29 g, 2.0 mmol) and THF (8 mL) were added to 10 mL microwave vial, capped with a cap with septa, and shaken until dissolved. $Ni(COD)_2$ (605 mg, 2.2 mmol) and ether (125 mL) were added to a 250 mL Teflon cap sealable, thick-walled Schlenk flask that can be pressurized to 3 atm. The Schlenk flask and microwave vial were removed from the glovebox and the Schlenk flask was immediately placed in a bath at -78 °C, connected to a Schlenk line, evacuated and back filled with CO 3 times, and then pressurized

to 3 atm while still at -78 °C. With the atmosphere of the Schlenk flask still exposed to the 3 atm from the tank, the flask was slowly warmed to room temperature while swirling vigorously. The yellow color of $Ni(COD)_2$ slowly faded and left a completely colorless solution. [*Note: This solution of $Ni(CO)_4$ is stable at room temperature under CO or argon. $Ni(CO)_4$ IS EXTREMELY TOXIC AND FLAMMABLE]*. The Teflon cap was closed (flask still under 3 atm of CO) and connected to a Schlenk line with argon and cooled again to -78 °C. While at -78 °C, the Teflon cap was slowly opened to release CO out through the bubbler on a Schlenk line, and then allowed to purge for about 5 minutes. The Teflon cap was removed and under a positive pressure of argon the solution of phosphite in THF was added via syringe all at once. The flask was capped with the Teflon cap, allowed to warm to room temperature and stand for one hour. The solvent and excess $Ni(CO)_4$ were pumped into a Schlenk line trap containing triphenylphosphine to quench any $Ni(CO)_4$. [*Note: The Schlenk line trap was warmed to room temperature and methanol and water were added*.] The remaining dark viscous oil was brought into the glovebox, washed with acetonitrile (to remove excess cyclooctadiene), dissolved in ether and filtered (to remove the black precipitate). Ether was removed *in vacuo* to afford **[Ni]1** as a white powdery solid in 90% yield (1.43 g).

4.5.3. Synthetic Procedures for Exchange Reactions

Representative Procedure for optimization of palladium catalysis (Tables 4.1 and 4.2)

In a glovebox, ^{13}C-benzoyl chloride (5 mg, 0.038 mmol), hydrocinnamoyl choride (0.038 mmol), Pd_2dba_3 (2 mg, 0.0019 mmol), P(o-tolyl)$_3$ (2 mg, 0.0075 mmol), and dimethyl sulfone as an internal standard (2 mg, 0.01 mmol) were dissolved in C_6D_6 (0.75 mL) and transferred to a J. Young NMR tube. A ^{1}H NMR was taken to obtain the initial ratios of the reagents to the internal standard. The NMR tube was heated at 70 °C for 20 hours. An estimation of the yield of **4.1c-^{13}C** was determined by a one scan ^{13}C NMR experiment by dividing the integration of **1c-^{13}C** by the integration of (**1a-^{13}C** + **1c-^{13}C)** and determined to be 3%. Although there is error with this yield calculation, we have concluded that this method is reliable for preliminarily assessing the efficiencies of various reactions. The yield of styrene **2a** (in table 4.2) was determined by ^{1}H NMR analysis relative the internal standard and found to be 3%.

Representative Procedure for optimization of nickel catalysis (Tables 4.3 entries 1-12 and 18)

In a glovebox, ^{13}C-benzoyl chloride (9 mg, 0.06 mmol), hydrocinnamoylchoride (10 mg, 0.06 mmol), Ni(COD)$_2$ (2 mg, 0.006 mmol), P^{t}Bu$_3$ (2 mg, 0.012 mmol), and Bu$_4$NCl (17mg, 0.06 mmol) were dissolved in CD_3CN (0.60 mL) and transferred to a J. Young NMR tube and monitored over time by ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR. For entry 17 of Table 4.1, the NMR tube was placed in an oil bath at 70 °C for 20 hours. An estimation of the yield of **4.1c-^{13}C** was determined by a one scan ^{13}C NMR experiment by dividing the integration of **1c-^{13}C** by the integration of (**1a-^{13}C** + **1c-^{13}C)** and determined to 12%. Although there is error with this yield calculation, we have concluded that this method is reliable for preliminarily assessing the efficiencies of various reactions. No styrene was observed in any of reactions with nickel in Table 4.3.

Representative Procedure for optimization of nickel catalysis (Tables 4.3 entries 13-17) and preliminary scope of acid chlorides (Tables 4.4)

In a glovebox, ^{13}C-benzoyl chloride (9 mg, 0.06 mmol), hydrocinnamoyl choride (10 mg, 0.06 mmol), **[Ni]1** (2 mg, 0.003 mmol), Bu$_4$NCl (17mg, 0.06 mmol) and PhCN (0.6 mL) were added to a 4 mL vial equipped with a stir bar. The vial was capped with push cap and allowed to stir in the glovebox (28 °C) for 4 hours. The solutions were then transferred to a normal NMR tube, capped, parafilmed, and analyzed by ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR. An estimation of the yield of **4.1c-^{13}C** was determined by a one scan ^{13}C NMR experiment by dividing the integration of **4.1c-^{13}C** by the integration of (**4.1a-^{13}C** + **4.1-^{13}C)** and determined to 44% (Table 4.3 entry 16). Although there is error with this yield calculation, we have concluded that this method is reliable for preliminarily assessing the efficiencies of various reactions. No styrene was observed in any of reactions with nickel in Table 4.3 or 4.4. For entry 17 of Table 4.3, benzyl amine (50 μL, 0.45 mmol, 3.8 equiv) was added to the final mixture and stirred for 1 hour at room temperature in the glovebox. The vial was removed from the glovebox and the mixture was filtered through a plug of silica rinsed with ethyl acetate, and concentrated *in vacuo*. The crude residue was subjected to HRMS analysis. The ^{13}C isotopic incorporation was determined using the IsoPat excel worksheet using the data from the HRMS and found to be 44.0% ^{13}C. The theoretical maximum incorporation is 46.5% = (1 equiv ^{13}CO)/(2.15 equiv CO total). If the ^{1}H NMR is very well-resolved, the %^{13}C incorporation can determined by comparing the ratio of the integrations of α-carbonyl protons of **4.1c-^{13}C** and **4.1c**.

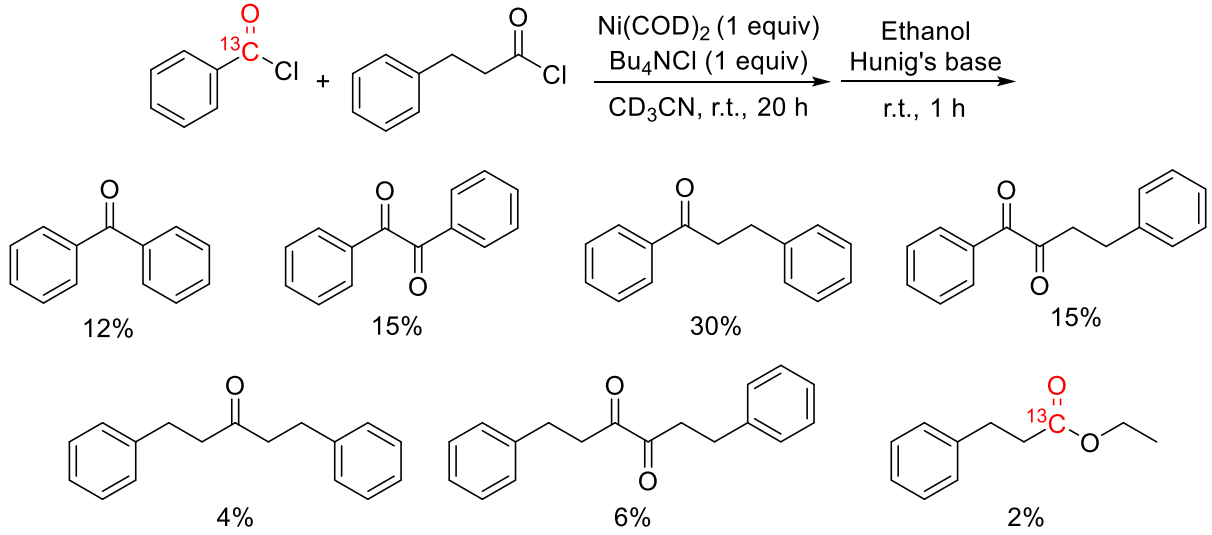
Representative Procedure for Exchange on *in situ* generated acid chlorides (Table 4.5)

On the bench, stearic acid (152 mg, 0.5 mmol) and ^{13}C 4-phenylbenzoic acid (100 mg, 0.5 mmol) were added to a nitrogen purged 20 mL screw cap vial, followed by a DMF/CH_2Cl_2 stock solution (9 mL of a stock solution containing 3 mg DMF in 40 mL of CH_2Cl_2). Oxalyl chloride (127 µL, 1.5 mmol) was added to the vial, which was then quickly closed under a flow of nitrogen. After stirring at room temperature for 16 hours, the cap was carefully removed, and the solvent was evaporated under a stream of nitrogen. The vial was brought in the glovebox and PhCN (5 mL) was added along with **[Ni]1** (20 mg, 0.025 mmol) and Bu_4NCl (139 mg, 0.5 mmol). After stirring in the glovebox for 40 hours at 28 °C, the vial was removed from the glovebox and H_20 (2 mL) and 1,4-dioxane (3 mL) were added to the vial, followed by heating at 60 °C for 2 hours. The solvent was then evaporated under a stream of air. The residue was purified by silica gel chromatography (0-100% acetone/hexanes w/ 2% AcOH) and then reverse phase C-18 chromatography (0-100% acetone/water) affording **4.3b-^{13}C** as a white solid in 83% yield (126 mg) with 42.1% ^{13}C incorporation as determined by HRMS.

Representative Procedure for Exchange on *in situ* generated acid chlorides (Table 4.6)

In a glovebox, 4-chloro-3-methyl benzoic acid (10 mg, 0.06 mmol) and ^{13}C-benzoic acid (7 mg, 0.06 mmol) were added to a 4 mL vial equipped with a stir bar and dissolved in PhCN (550 µL). 1-Chloro-N,N,2-trimethyl-1-propenylamine (TMCE) (17.2 µL, 0.013 mmol) was added, the vial was capped, and the reaction stirred for one hour at room temperature. [*Note: Care must be taken to add exactly 1.08 equiv.*] Then, **[Ni]1** (2 mg. 0.003 mmol) and Bu_4NCl (17 mg, 0.06 mmol) was added along with PhCN (50 µL). The vial was capped and stirred in the glovebox (28 °C) for 24 hours. The solution was then transferred to a normal NMR tubed, capped, parafilmed, and analyzed by ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR. An estimation of the yield of **4.1-^{13}C** was determined by a one scan ^{13}C NMR experiment by dividing the integration of **4.1-^{13}C** by the integration of (**4.1a-^{13}C** + **4.1-^{13}C)** and determined to 35%. Although there is error with this yield calculation, we have concluded that this method is reliable for preliminarily assessing the efficiencies of various reactions.

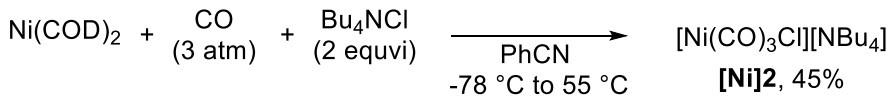
Reaction with Stoichiometric $Ni(COD)_2$



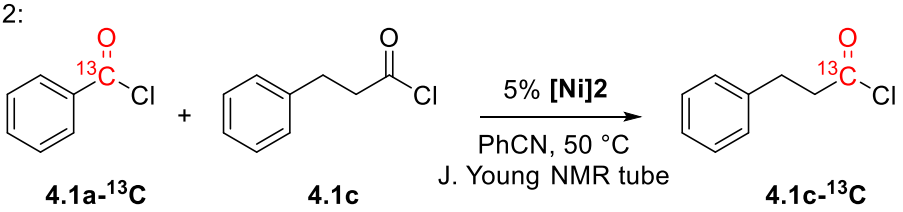
In a glovebox, ^{13}C-benzoyl chloride (9 mg, 0.06 mmol), hydrocinnamoyl choride (10 mg, 0.06 mmol), $Ni(COD)_2$ (2 mg, 0.006 mmol), Bu_4NCl (66 mg, 0.24 mmol) were dissolved in CD_3CN (0.60 mL) and transferred to a J. Young NMR tube and monitored over time by ^{1}H NMR, and ^{13}C NMR, and ^{31}P NMR. After 20 hours at room temperature, trace amounts of acid chloride are seen by ^{13}C NMR. Ethanol (35 µL, 0.6 mmol) and N,N-diisopropylethylamine (62 µL, 0.36 mmol) were added directly to the NMR and shaken for 5 min, then allowed to stand for 1 hour. The reaction was then filtered through a silica plug, rinsing with ethyl acetate. The filtrate was subjected to GC-MS analysis. Although no standard was added, the masses of the ketones shown above were identified and an estimation of the yields were determined by dividing the area of the peak for each ketone by the total area of the chromatogram.

In situ generation of [Ni(CO)$_3$Cl][Bu$_4$N] and use in catalysis

Step 1:



Step 2:

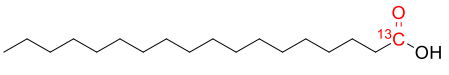


4.1a-^{13}C **4.1c** **4.1c-^{13}C**

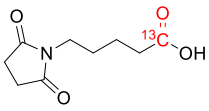
*Step 1: Generation of **[Ni]2:*** In a glovebox, Ni(COD)$_2$ (25 mg, 0.09 mmol) was transferred to a 25 mL Schlenk flask with a Teflon screw cap. The flask was removed from the box and cooled to -78 °C. Under a positive flow of CO, a solution of Bu$_4$NCl (50 mg, 0.18 mmol) in PhCN (1.5 mL) was added via syringe. The flask was then pressurized to 3.5 atm at while at -78 °C and then warmed to room temperature while shaking vigorously and kept at room temperature for 1 hour. The flask was re-cooled to -78 °C and the Teflon cap was slowly opened to release CO out through the bubbler on a Schlenk line, and then allowed to purge for about 5 minutes. The flask was closed, warmed to room temperature, and then placed in a oil bath at 55 °C for 16 hours. The solution was allowed to cool to room temperature and was purged with nitrogen for 15 min before being brought into the glovebox. The concentration of **[Ni]2** in solution was quantified by adding a known excess amount of phosphite ligand to an aliquot of solution and observing the ratio of phosphite complex to free phosphite. The yield of **[Ni]2** was found to be 45%.

*Step 2: use of **[Ni]2** in catalysis:* In a glovebox, ^{13}C-benzoyl chloride (9 mg, 0.06 mmol), hydrocinnamoyl choride (10 mg, 0.06 mmol), and **[Ni]2** (110 µL of solution from step 1, 0.003 mmol), and PhCN (490 µL) were transferred to a J. Young NMR tube and monitored over time by ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR. An estimation of the yield of **4.1c-^{13}C** was determined by a one scan ^{13}C NMR experiment by dividing the integration of **4.1c-^{13}C** by the integration of (**4.1a-^{13}C** + **4.1-^{13}C)** and determined to 47% (Table 4.2 entry 15). Although there is error with this yield calculation, we have concluded that this method is reliable for preliminarily assessing the efficiencies of various reactions.

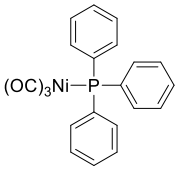
4.5.4 Characterization Data



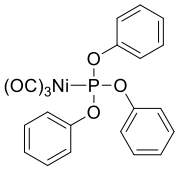
Stearic Acid 4.4b-^{13}C.[26] White solid, 83% yield (127 mg, 0.42 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.11 (s, 1H), 2.42 – 2.33 (m, 2H), 1.71 – 1.61 (m, 2H), 1.40 – 1.23 (m, 28H), 0.90 (t, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.0, 34.3, 34.0, 31.9, 31.4, 30.2, 29.7[1], 29.6[8], 29.6[7], 29.6[5], 29.6, 29.4[4], 29.3[7], 29.3, 29.1, 24.70, 22.7, 14.1. HRMS. Calculated for $C_{18}H_{35}O_2^-$ (M-H$^+$): 283.2643, found: 283.2648 and for $C_{17}{}^{13}CH_{35}O_2^-$ (M-H$^+$): 284.2676, found: 284.2675.



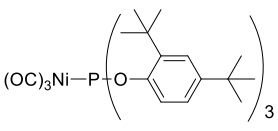
5-(2,5-dioxopyrrolidin-1-yl)pentanoic-1-13C acid **4.4c-^{13}C**. White solid, 87% yield (87 mg, 0.44 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 3.58 – 3.49 (m, 2H), 2.71 (s, 4H), 2.42 – 2.33 (m, 2H), 1.72 – 1.57 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.7, 177.4, 38.3, 30.9, 28.1, 27.0, 27.0, 21.8. HRMS. Calculated for $C_9H_{12}NO_4^-$ (M-H$^+$): 198.0772, found: 198.0767 and for $C_8{}^{13}CH_{12}NO_4^-$ (M-H$^+$): 199.0805, found: 199.0798



White solid, 93% yield (38 mg, 0.094 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.37 (m, 15H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.9, 135.6 (d, J = 34.4 Hz), 133.1 (d, J = 14.1 Hz), 129.8 (d, J = 1.9 Hz), 128.5 (d, J = 9.6 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.28.



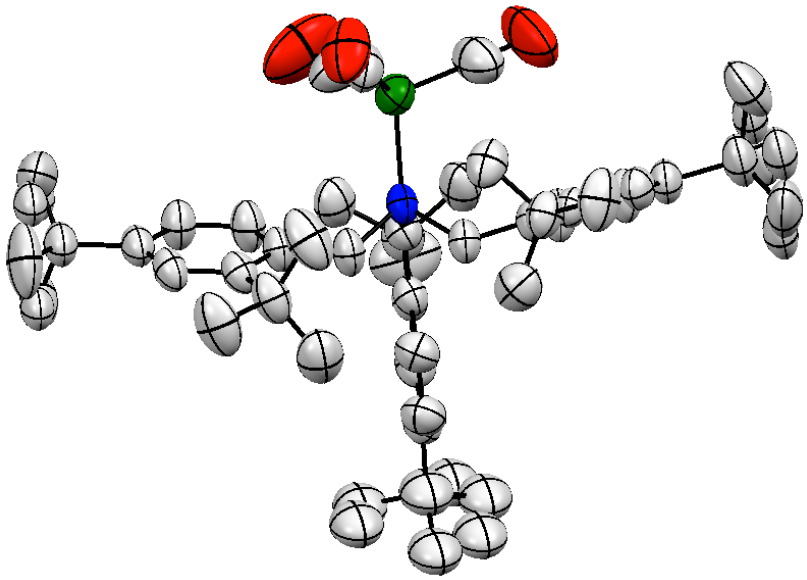
White solid, 87% yield (39 mg, 0.086 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.37 (m, 15H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.5, 129.4, 124.5, 121.7. (the carbonyl peak was not visible due to a large amount of adventitious acetone that reduced signal to noise for the product). ^{31}P NMR (162 MHz, $CDCl_3$) δ 149.01.



[Ni]1, White Solid, 90% Yield (1.43 g, 1.8 mmol) ^{1}H NMR (400 MHz, C_6D_6) δ 7.86 (d, J = 8.6 Hz, 1H), 7.55 (d, J = 2.0 Hz, 1H), 7.12 (dd, J = 8.6, 2.5 Hz, 1H), 1.67 (s, 9H), 1.15 (s, 9H). ^{13}C NMR (126 MHz, C_6D_6) δ 194.01, 148.51 (d, J = 4.2 Hz), 146.7, 138.9 (d, J = 5.3 Hz), 124.7, 123.8, 119.8 (d, J = 8.9 Hz), 35.1, 34.2, 31.1, 30.4. ^{31}P NMR (162 MHz, $CDCl_3$) δ 144.28.

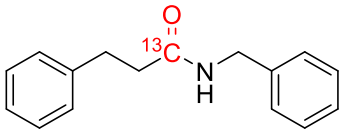
X-ray crystal structure of **[Ni]1:**

X-ray quality crystals of **[Ni]1** were grown by dissolving 10 mg in 1 mL of pentane and allowing the solvent to slowly evaporate at room temperature for two days (ORTEP-style ellipsoids drawn at 50% probability).



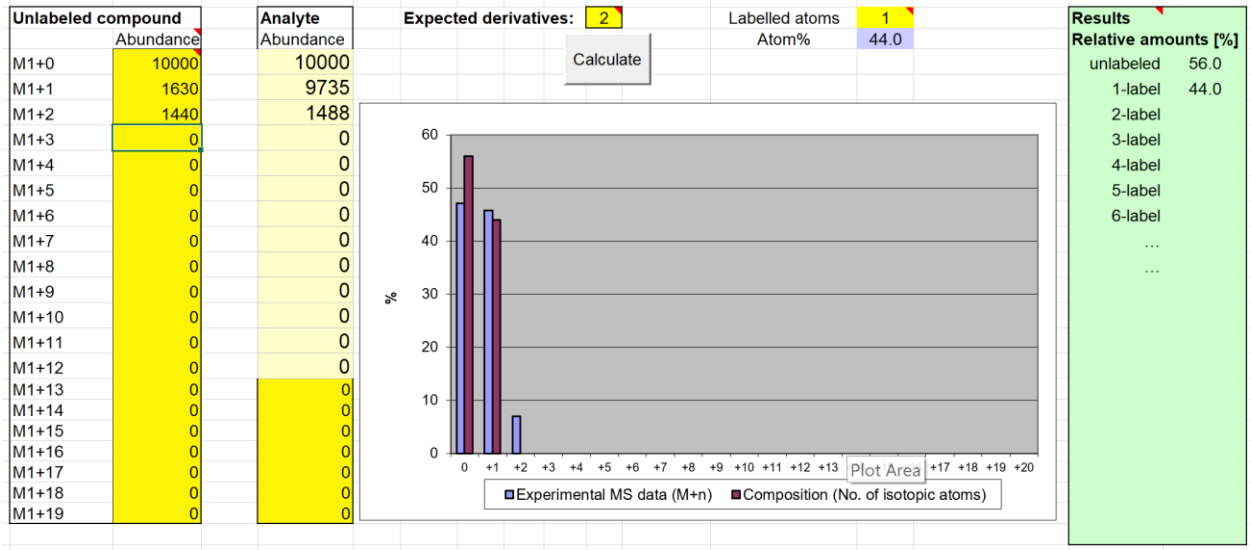
4.5.5. Analysis of HRMS Data for Determination of ^{13}C Incorporation

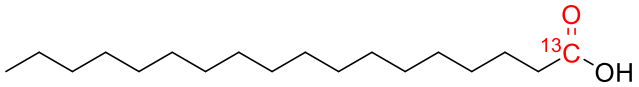
Percent isotope incorporation was determined by comparison of the mass spectral patterns of ^{13}C-labeled products versus authentic starting material using the IsoPat2 spreadsheet2.[48] The mass spectra were tabulated for abundance vs. m/z, and these data were inputted to the Isopat2 spreadsheet, which uses its programmed algorithm to determine the relative percentage of each labeled species differentiated in the number of incorporated isotopes. Sum of these percentages give rise to the overall isotope enrichment.



4.1c-^{13}C, 44.0% ^{13}C

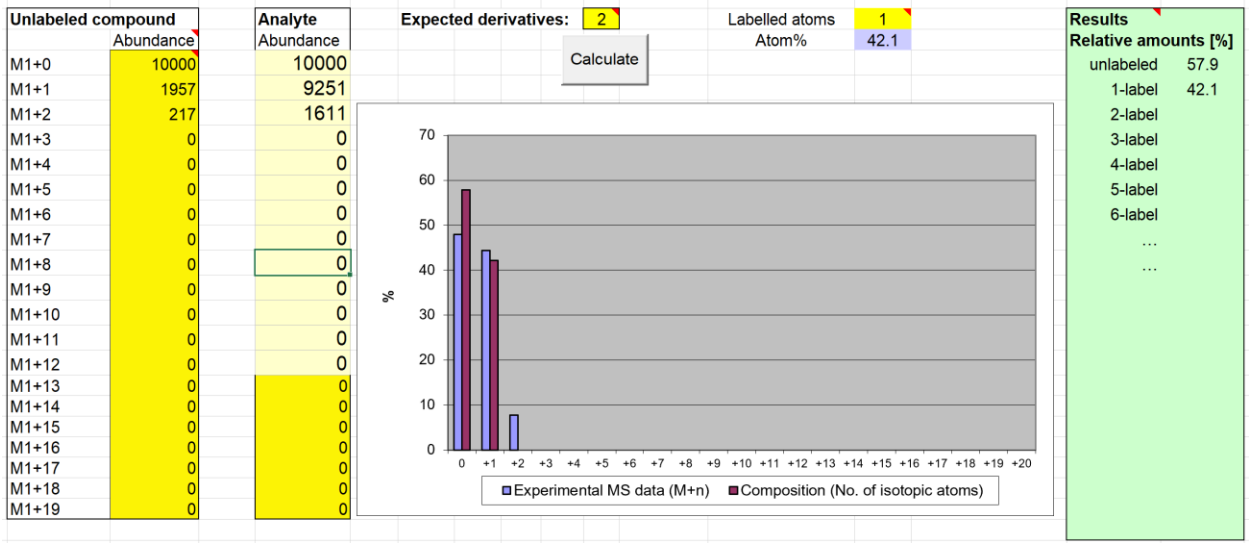
Isopat Calculation:

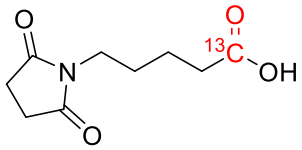




4.4b-^{13}C, 42.1% ^{13}C

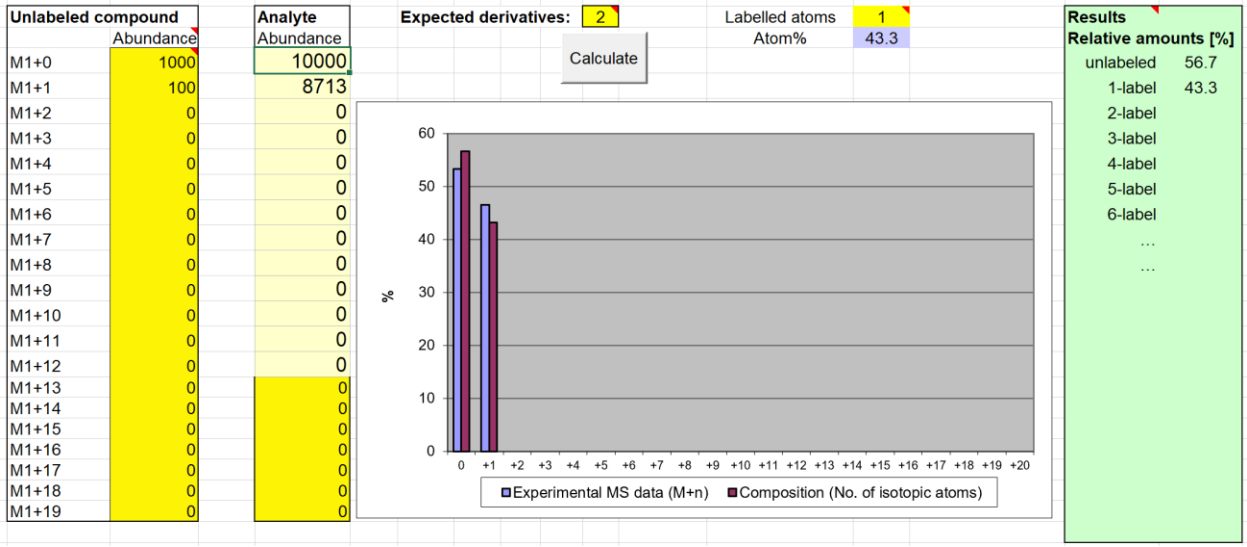
Isopat Calculation:





4.4c-^{13}C, 43.3% ^{13}C

Isopat calculation:



4.6. NMR Spectra

For all NMR spectra of isolated products, please see Appendix 2.

4.7. References

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Chapter 5. Conclusions, Contributions to Knowledge, and Suggestions for Future Work

5.1. Conclusions and Contributions to Knowledge

As described in the introductory chapter, the functionalization of arenes represents a central research goal in organic chemistry. The Friedel-Crafts acylation reaction is one of the most effective strategies identified for the derivatization of aromatic hydrocarbons to ketones. Traditionally, pre-synthesized acylating agents and Lewis acids are required to generate a reactive electrophile capable of reacting with arenes. However, there are limitations in terms of functional group compatibility and corrosive waste. The results in this thesis present alternative routes to generating reactive acylating agents with carbon monoxide. Carbon monoxide is an abundant C1 building block that has been extensively used in industrial and academic settings to prepare a wide range of carbonyl-containing products. We have found that the energetics of CO, in which conversion to a carbonyl containing product is often highly exergonic, can be used to drive the build-up potent acylating agents capable of functionalizing arenes and heteroarenes. In addition, the concepts discovered during the development of acyl electrophile formation via transition metal catalysis have been further exploited, and led to the design of a carbonyl exchange reactions, as a new route to prepare isotopically labeled carboxylic acids, including aryl, alkyl, and α,β-unsaturated derivatives.

In Chapter 2, a palladium catalyzed carbonylative C-H functionalization of arenes was developed. This addressed a long-standing challenge in carbonylative C-H functionalization chemistry, in which ketone synthesis was not generally possible due to their reliance on acetate and carbonate bases for concerted-metallation-deprotonation. An alternative strategy was developed in which arenes are acylated with potent aroyl triflate electrophiles generated from the catalytic carbonylation of aryl iodides. The formation of highly reactive acyl electrophiles as a product of palladium catalysis is unprecedented, but is facilitated by an extremely electron-poor CO-ligated palladium catalyst that greatly lowers the barrier to reductive elimination. Overall, this has led to the first general platform for the carbonylative C-H functionalization of a wide range of arenes with CO and aryl iodides.

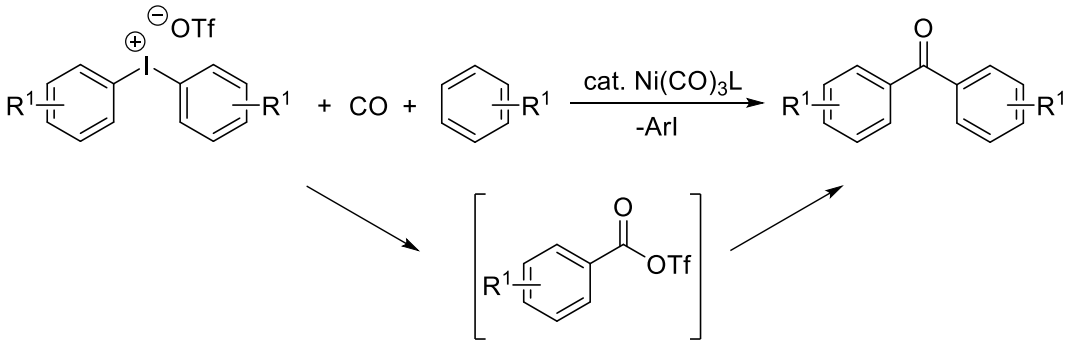
In Chapter 3, we described how CO can be used to the drive the build-up of aroyl triflates from carboxylic acids in the absence of a palladium catalyst. Although mechanistic studies revealed that carbon monoxide is not incorporated into the product, it provides a driving force for the reaction via carbon dioxide formation. This transformation represents a rare example of a transition-metal-free activation of carbon monoxide with bench stable reagents (carboxylic acids, I_2, AgOTf), and allows the direct generation of aroyl triflate electrophiles. Overall this permits acylation of arenes with carboxylic acids under extremely mild conditions, and without the use of high energy reagents such as acid chlorides or Lewis acids.

Chapter 4 described how the reactivity of acyl electrophiles with transition metals can be exploited to design a new catalytic platform for the isotopic enrichment of carboxylic derivatives. Previous studies from our lab had demonstrated that the oxidative addition of acid chlorides to palladium can be reversible. In a collaborative project initiated by Merck, we questioned if this might offer a platform to exchange the carbonyl unit between two acid chlorides as a route to prepare 13C-labeled pharmaceuticals. Palladium catalysts were initially investigated and found to be effective for the exchange of CO/^{13}CO between aromatic acid chlorides. However, the use of these palladium catalysts with alkyl acid chlorides substrates, which represent a large portion of biologically relevant carboxylic acids, resulted in significant quantities of alkene formation due to undesired β-hydride elimination. Nickel carbonyl catalysts were employed to circumvent this problem, and found to be active catalysts for Co exchange with both alkyl or aryl substrates under mild conditions. Overall, this has allowed the design of a new method to directly incorporate carbon isotope labels into carboxylic acid derivatives.

5.2. Suggestions for Future work

The results in chapter 4 detailing the exploitation of nickel carbonyl catalysts for carbonyl exchange reactions demonstrate they are exceptionally suited for the reductive elimination of acyl electrophiles. Relative to palladium catalysts, nickel carbonyl catalysts could therefore be an ideal choice for the generation of even more potent electrophiles such as aroyl triflates. However, a consequence of this reactivity is the now more challenging oxidative addition of organohalides, due to the strong coordination of CO to nickel. This is evidenced by the elevated temperatures required in carbonylative coupling reactions of even activated organohalides, such as aryl iodides.[1]

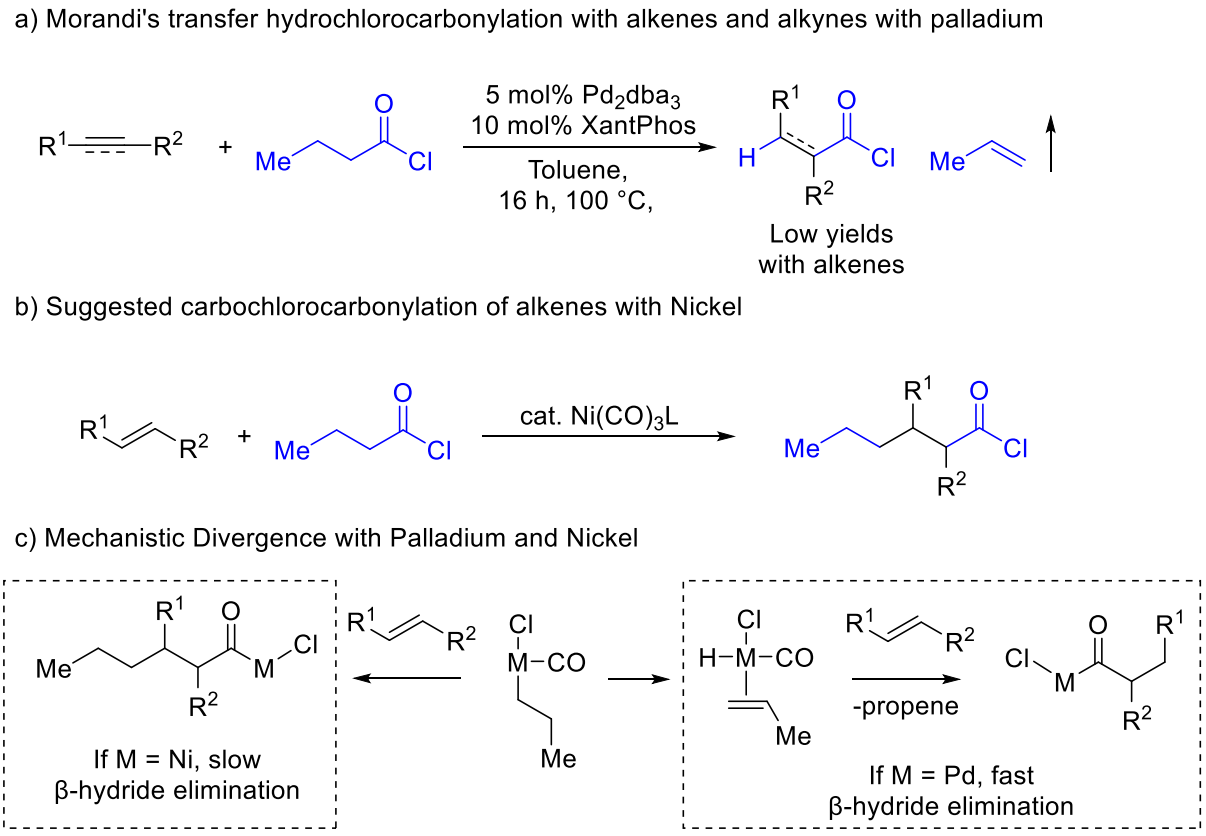
This problem is exacerbated in the context of aroyl triflate formation from aryl iodides, as the nickel carbonyl catalyst must react with the aryl iodide in the presence of the much more reactive aroyl triflate. In this regard, hypervalent iodonium salts are active oxidants, and would presumably result in much faster oxidative addition to a $LNi(CO)_3$ catalyst. Indeed, these reagents have been used in palladium and nickel catalyzed cross coupling chemistry under very mild conditions.[2-8] In addition, the use of an iodonium triflate salt would obviate the need for a stoichiometric amount of silver triflate, which was found to be critical in the palladium catalyzed system discussed in chapter 2. Overall, this transformation would offer a route to the carbonylative C-H functionalization of arenes under nickel catalysis via aroyl triflate formation (Scheme 5.1)



Scheme 5.1. Nickel Catalyzed Carbonylative C-H Functionalization of Arenes via *in situ* Generation of Aroyl Triflates.

Another potential strategy for circumventing sluggish activation of organohalides in the nickel catalyzed generation of acyl electrophiles is the use of alternative organic substrates, such as alkenes. The Morandi group has recently reported a palladium catalyzed transfer hydrochlorocarbonyaltion reaction that effectively transfers CO and HCl embedded in butyryl chloride across unsaturated organic fragments, such as alkenes and alkynes (Scheme 5.2a).[9] Notably, yields with alkene substrates were low, due to the instability of the resulting alkyl acid chloride in the presence of palladium. Critical to this transformation was the ability of the palladium catalyst to facilitate many reversible steps, including oxidative addition/reductive elimination of acid chlorides, CO insertion/de-insertion, and hydride insertion/β-hydride elimination. With the regards to the latter, employing nickel carbonyl catalysts would offer

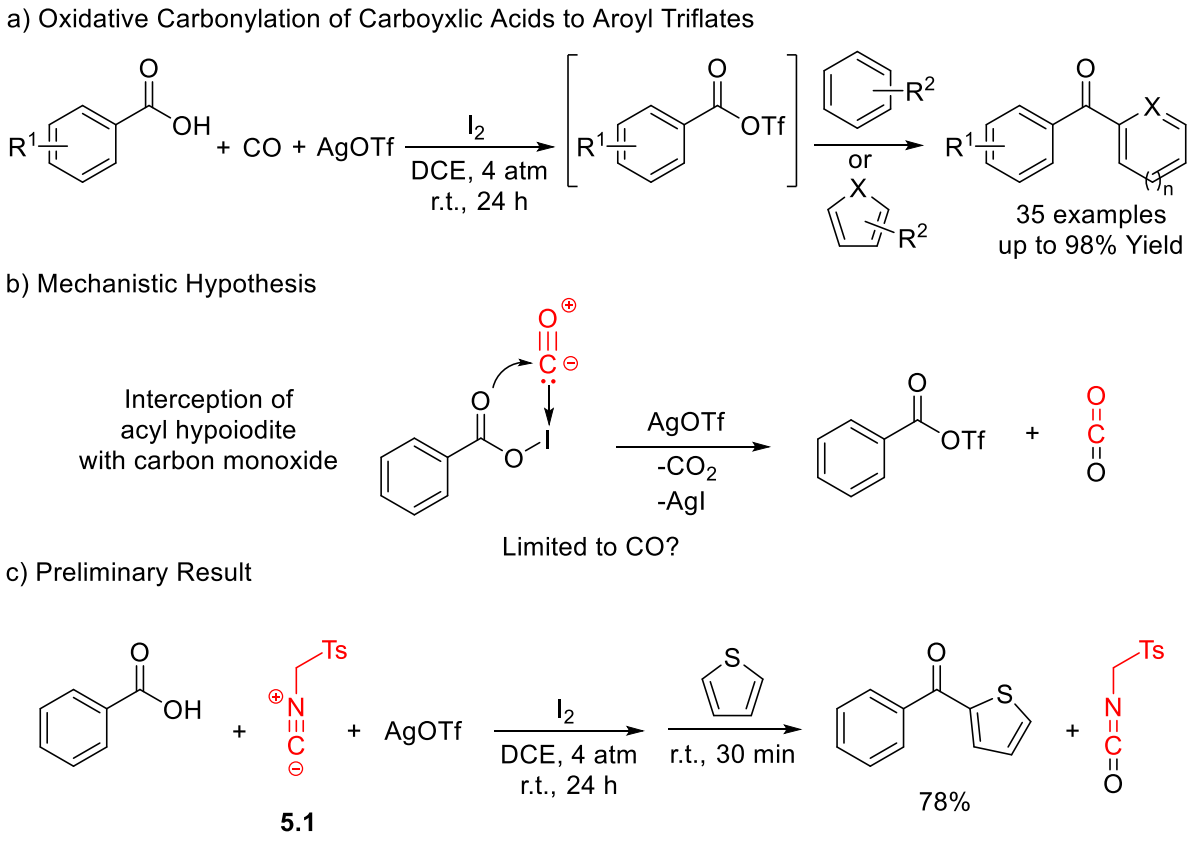
opportunity to instead prepare products formally resulting from carbochlorocarbonylation (Scheme 5.2b). Due to the much slower rate of β-hydride elimination with nickel systems, the alkene could insert into a metal-alkyl bond, instead of a metal-hydride bond (Scheme 5.2c). With R^1 and R^2 = alkyl, the product alkyl acid chloride would presumably be much more stable in the presence of nickel. This could provide a novel route for the preparation of acyl halides from alkenes using nickel catalysis.



Scheme 5.2. Nickel Catalyzed Carbochlorocarbonylation of Alkenes

In chapter 3, the carbon monoxide mediated conversion of carboxylic acids to aroyl triflate electrophiles was described (Scheme 5.3a). Mechanistic studies suggest that carbon monoxide intercepts an *in situ* generated acyl hypoiodite, which promotes decarboxylation and aroyl triflate formation. Labeling studies revealed that carbon monoxide is oxidized to carbon dioxide, and is thus not incorporated into the organic product (Scheme 5.3b). Thus, the role of CO is ultimately

to deoxygenate the carboxylic acid. Therefore, it is plausible that other oxygen atom acceptors could replace gaseous carbon monoxide. In a preliminary result, we have demonstrated that this is indeed possible by replacing carbon monoxide with isocyanide **5.1** (Scheme 5.3c). This offers several advantages over the use of carbon monoxide, including most notable, that it is an easy-to-handle solid. Future work on this project could entail the further exploration of other oxygen atom acceptors, such as phosphines, carbodiimides, and sulfinate salts.



Scheme 5.3. Oxidative Conversion of Carboxylic Acids to Acid Triflates Using CO and Surrogates

5.3 References

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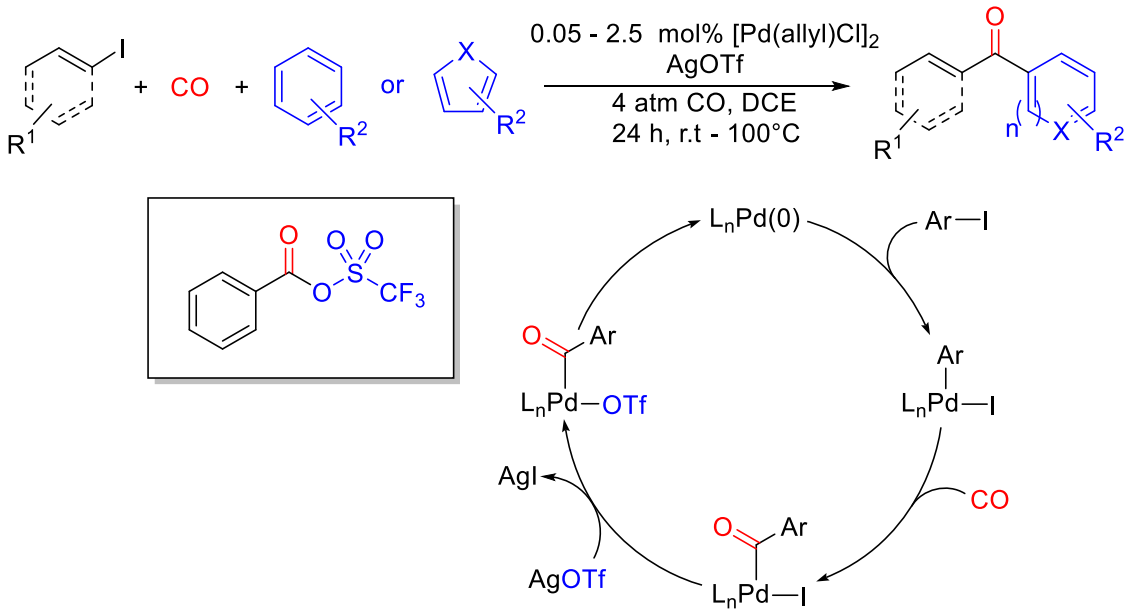
Appendix 1. Palladium-Catalyzed Generation of Acyl Electrophiles with Carbon Dioxide

A1.1. Introduction

In Chapter 2, we described the palladium-catalyzed carbonylative C-H functionalization of arenes to form ketones. The reaction is postulated to proceed via carbonylation of aryl iodides to form aroyl triflates which are sufficiently electrophilic to directly react with react with arenes (Figure A1.1a). In considering this mechanism, and the structure of aroyl triflates, we questioned if these intermediates might instead be generated from CO_2 and a silver sulfinate salt (FigureA1.1b). In contrast to the carbonylation reaction above, these could in principle be formed by oxidative addition of the aryl iodide followed by insertion of CO_2 to form a palladium carboxylate complex **A1.1.** Iodide/sulfinate would form palladium complex **A1.2.** in which reductive elimination of the C-S bond would form the aroyl triflate. Overall, this would replace carbon monoxide with an even more readily available, and inexpensive, non-toxic C1 building block: CO_2. Replacing carbon monoxide with carbon dioxide can also lead to advantages in terms of substrate generality. Since carbon monoxide is a π-acidic ligand, coordination to the palladium catalyst limits the scope of viable electrophilic coupling partners in many carbonylative coupling reactions. Carbon dioxide does not have this same catalyst poisoning effect, and thus could offer access to a more general reaction.

a) Carbonylative C-H Functionalization of Arenes via Catalytic Aroyl Triflate Formation



b) Idea: Aroyl Triflate Synthethesis from CO_2

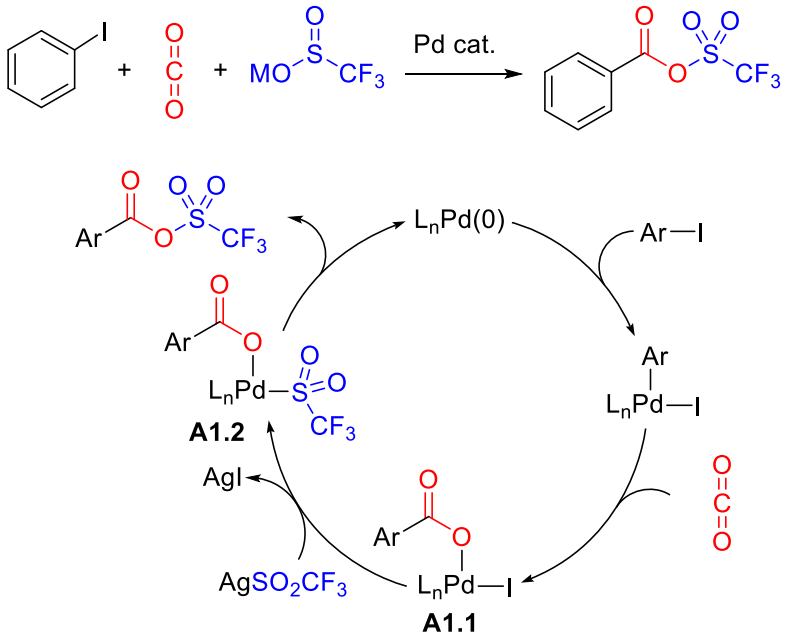


Figure A1.1. Catalytic Aroyl triflate from CO and CO_2

The incorporation of carbon dioxide into organic molecules has been a heavily researched area,[1-5] and includes reactions with organometallic reagents,[6-8] metal-catalyzed cycloaddition with unsaturated substrates,[9, 10] reaction with N- and O- nucleophiles for carbamate and carbonate formation,[11-13] and, more recently, catalytic carboxylation of organohalides for carboxylic acid synthesis (examples shown in Figure A1.2).[14-17] The latter offers many advantages over traditional methods using Grignard reagents which are high energy, and pose major problems with functional group compatibility. Work by Martin, Daugilus, Tsuji, and others has demonstrated many elegant examples of the reductive carboxylation of aryl/alkyl-iodides, -bromides, or -chlorides using nickel, palladium, and copper catalyts.[17-27] While a large array of products have been created via carboxylation of organic substrates, including those in which CO_2 formally acts a CO surrogate in presence of a reductant,[28] there are currently no examples of using carbon dioxide to directly create an acyl electrophile.

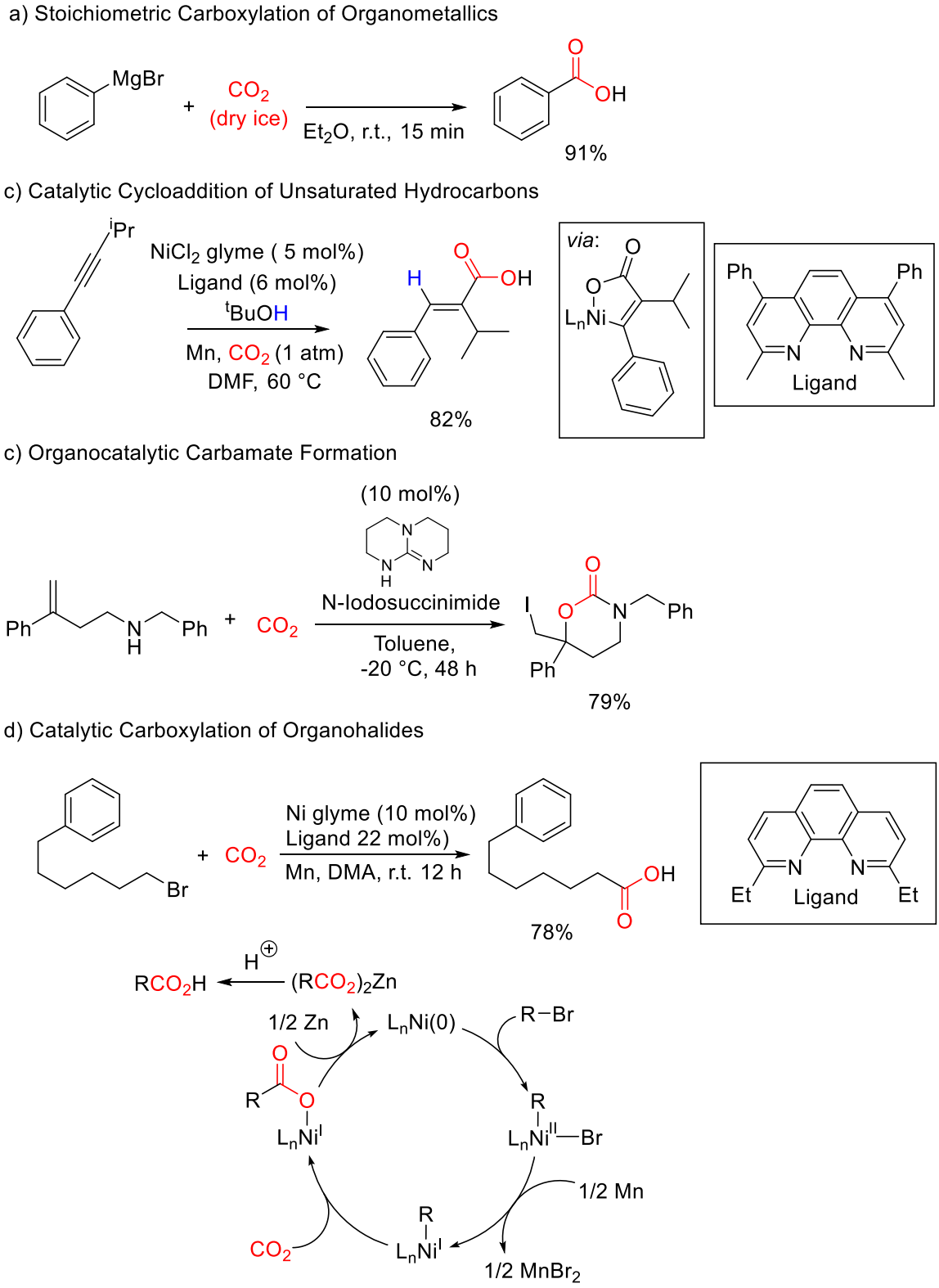


Figure A1.2. Examples of Common Carboxylation Strategies

There are several challenges in using carbon dioxide instead of carbon monoxide. While carbon dioxide can coordinate to palladium, this occurs to a much lesser extent than with CO, and thus makes reductive elimination much less favorable. [29, 30] Secondly, the conversion of CO to a carbonyl derivative provides a thermodynamic driving force for the build-up of a reactive acyl electrophile.[31] Lastly, carbon dioxide insertion into Pd- or Ni-carbon bonds is often slow.[32] Although the reductive carboxylation of aryl halides has been well documented, very specific conditions (*e. g.* ligands, solvents, etc.) are required for these reactions. Mechanistic studies on these systems have suggested CO_2 insertion occurs at Pd(I) or Ni(I) followed by an additional one electron reduction to turn over the cycle (A1.2d).[17, 19, 33-35] Given the challenging reductive elimination of a reactive aroyl triflate electrophile, which to date has required the use of unligated, electron poor palladium catalysts, the addition of designer ligands and additives to carefully tune the properties of the metal for insertion will most likely not be possible. Described below are our preliminary studies toward the design of this route to aroyl triflates with carbon dioxide.

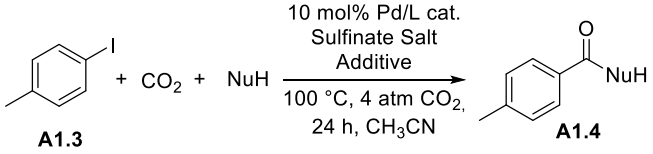
A1.2 Results and Discussion

A1.2.1 Catalytic Studies with Carbon Dioxide

We began our studies by applying similar conditions that were successful for catalytic aroyl triflate formation from aryl iodides (chapter 2), but instead, employing carbon dioxide and silver sulfinate. When using thiophene as solvent, no ketone **A1.4a** was observed (entry 1). The addition of the weak donor ligand $P(C_6F_5)_3$ to stabilize Pd(0) gives similar results (entry 2), as did the use of benzene solvent (entry 3). In the latter, a significant quantity of homocoupled aryl iodide, **A1.5** was obtained along with very small amounts of 4-methylbenzaldehyde **1.6**. The greater than catalytic quantities of biphenyl suggest that $AgSO_2CF_3$ may be facilitating the catalytic reductive coupling of aryl iodide. In order to alleviate potentially unproductive chemistry with $AgSO_2CF_3$, $AgSO_2Me$ was investigated as an alternative, as this would generate a more stable, albeit less electrophilic product. Benzylamine was therefore employed as a nucleophilic trap for any electrophile generated. Generating a weaker electrophile also provides opportunity to use conditions similar to those used for carboxylation of aryl iodides (*e.g.* ^{t}BuXPhos with $[Pd(allyl)Cl]_2$). Although most of the aryl iodide **A1.3** was recovered, a trace amount of the desired amide product **A1.4b** was obtained, along with N-benzylformamide **A1.8** as the major product,

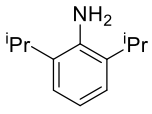
and N-benzylacetimide, **A1.9** (entry 4). In depth mechanistic studies were not performed to elucidate the origin of the byproducts, but formamide **A1.8** could arise from reduction of a palladium-acyl fragment with a hydride generated from Et^iPr_2, while N-benzylacetimide **A1.9** could result ultimately from oxidative fragmentation of $AgSO_2Me$, or transamidation with the dimethylacetamide (DMA) solvent. Other additives (entry 5), palladium sources (entries 6 and 7), ligands (8 and 9) were investigated to improve the efficiency of the reaction, but were not successful.

Table A1.1. Carboxylation of Aryl Iodides to form Ketones and Amides[a]

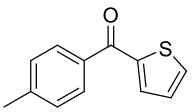


A1.3 **A1.4**

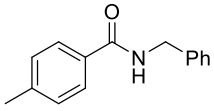
entry	NuH	Sulfinate Salt	Pd cat system	Base/Ligand/Additive	% Yield[b] A1.4	Other Products
1	Benzene	$AgSO_2CF_3$	$[Pd(allyl)Cl]_2/P(C_6F_5)_3$	PPh_3	0%	**A1.5**, 39%, **A1.6** 3%
2	Thiophene	$AgSO_2CF_3$	$[Pd(allyl)Cl]_2$	-	0%	
3	Thiophene	$AgSO_2CF_3$	$[Pd(allyl)Cl]_2/P(C_6F_5)_3$	-	0%	
4[c]	$BnNH_2$	$AgSO_2Me$	$[Pd(allyl)Cl]_2/^t$BuXPhos	NEt^iPr_2	3%	**A1.8**, 17%; **A1.9**, 4%
5[d]	$BnNH_2$	$AgSO_2Me$	$[Pd(allyl)Cl]_2/^t$BuXPhos	$NEt^iPr_2/MgCl_2$	0%	
6[e]	2,6-DIA	$AgSO_2Me$	$(COD)Pd(TMS)_2/^t$BuXPhos	-	0%	
7[f]	2,6-DIA	$NaSO_2Me$	$(COD)Pd(TMS)_2/^t$BuXPhos	-	0%	
8[g]	2,6-DIA	$NaSO_2Me$	$Pd(P^tBu_3)_2$	NEt^iPr_2	0%	**A1.5**, 12%
9[h]	2,6-DIA	$AgSO_2Me$	$Pd_2dba_3/P(^tBu_3)_2$	NEt^iPr_2	0%	



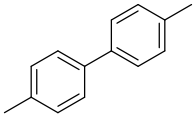
2,6-DIA



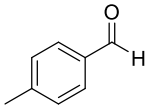
1.4a



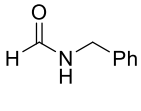
A1.4b



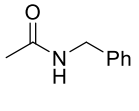
A1.5



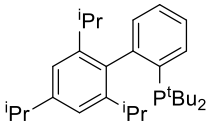
A1.6



A1.8



A1.9



^{t}BuXPhos

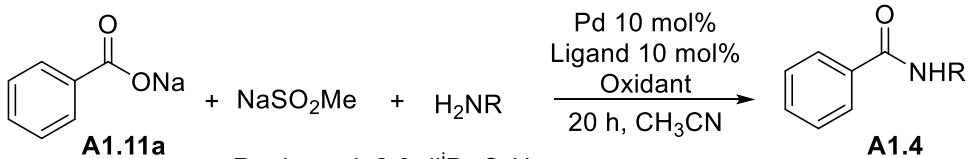
[a]4-iododtoluene (55 mg, 0.25 mmol), $[Pd(allyl)Cl]_2$ (5 mg, 0.0125 mmol), PPh_3 (7 mg, 0.025 mmol), $P(C_6F_5)_3$ (27 mg, 0.05 mmol), $AgSO_2CF_3$ (96 mg, 0.38 mmol), Hexamethyl benzene (5 mg, 0.03 mmol), benzene or thiophene (1 mL). Yields determined relative to external standard by ^{1}H NMR [b]The yield was determined by ^{1}H NMR analysis relative to a standard, hexamethylbenzene (5mg, 0.03 mmol). [c]Benzyl amine (62 mg, 0.5 mmol), ^{t}BuXPhos (13 mg, 0.03 mmol), $AgSO_2Me$ (56 mg, 0.3 mmol), Et^iPr_2N (49 mg, 0.38 mmol), dimethyacetamide (2.5 mL), CH_2Cl_2 (0.5 mL), 80 °C. [d]$MgCl_2$ (24mg, 0.25 mmol). [e]4-iododtoluene (4 mg, 0.02 mmol), 2,6-diisopropyl aniline (11 mg, 0.06 mmol), $(COD)Pd(CH_2TMS)_2$ (1 mg, 0.002 mmol), ^{t}BuXPhos (1

mg, 0.002 mmol), $AgSO_2Me$ (5 mg, 0.02 mmol). [f]Same conditions as footnote d. $NaSO_2Me$ (3mg, 0.02 mmol) instead of $AgSO_2Me$. [g]4-iododtoluene (16 mg, 0.08 mmol), 2,6-diisopropyl aniline (9 mg, 0.05 mmol), $Pd[P(^tBu)_3]_2$ (1 mg, 0.003 mmol), $NaSO_2Me$ (6 mg, 0.06 mmol), Et^iPr_2N (10 mg, 0.08 mmol). [h]4-iododtoluene (109 mg, 0.5 mmol), 2,6-diisopropylaniline (44 mg, 0.25 mmol), Pd_2dba_3 (13mg, 0.0125 mmol), $P(^tBu)_3$ (5mg, 0.03 mmol), $AgSO_2Me$ (49 mg, 0.3 mmol), 1,2-dichloroethane (2.5 mL).

A1.2.2. Generation of Acyl Electrophiles from Carboxylates

In order to study the formation of the desired mixed sulfonic anhydride without added variables such as metal-mediated insertion of carbon dioxide, the oxidative generation of mixed carboxylic sulfonic anhydrides was investigated. The reaction of sodium benzoate **A1.11a**, sodium methane sulfinate, and in the presence of stoichiometric $PdCl_2/P^tBu_3$ resulted in no desired amide **A1.4d** (entry 1). The use of catalytic palladium and added $CuCl_2$ oxidant gave similar results (entry 2). However, amide is observed when employing I_2 (6%) and Na_2SO_8 (21%) as oxidants (entries 3 and 4). Removing the aniline from the reaction and instead adding benzylamine in a second step to trap any electrophile generated resulted in a further increase in yield (entries 5 and 6). Removing $P(^tBu)_3$ severely diminishes the yield (entry 7), as does performing the reaction at room temperature (entry 8). Interestingly, removal of the palladium in the reaction with I_2 led to enhanced yields (entries 9 -12), implying that the strong oxidant I_2 can directly react with the reagents, potentially to form ISO_2R. Given the nucleophilicity of sodium benzoate **A1.11a**, it is very likely that benzoic anhydride could be the product of the first step, meaning the maximum yield for this reaction is 50%. However, it was subsequently found that simple copper salts, such as $CuCl_2$ and $CuOTf_2$ can also mediate the reaction (entries 13 and 14). The success of the copper salts in the reaction is noteworthy, as the overall goal is to create a transition metal catalyzed process from aryl halides and CO_2. Carbon dioxide is known to undergo facile insertion into *in situ* formed Cu-aryl bonds.[36, 37] These results demonstrate the viability of creating reactive electrophiles from carboxylates and sulfinate in the presence of copper.

Table A1.2. Oxidative Amidation of Carboxylates[a]



A1.11a

R = benzyl, 2,6-di^{i}Pr-C_6H_3

A1.4

R = benzyl, **A1.4c**

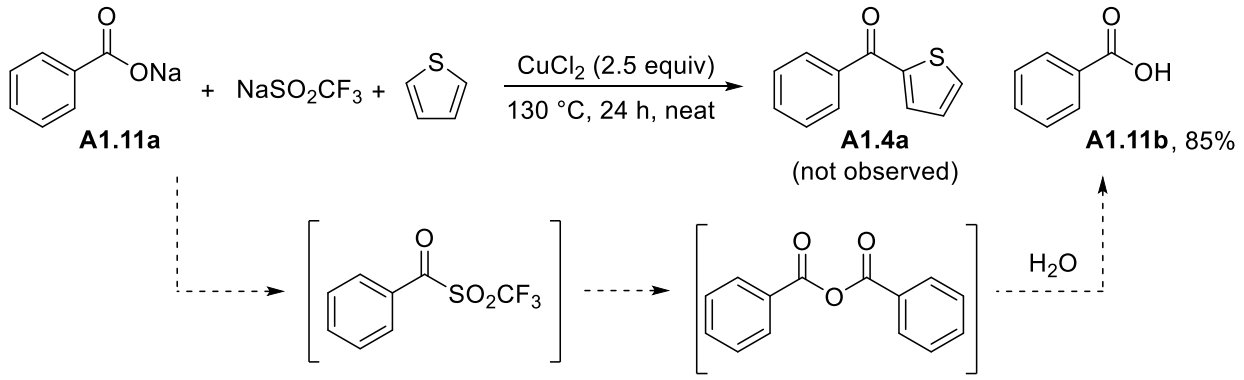
R = 2,6-di^{i}Pr-C_6H_3, **A1.4d**

entry	R	Temp	Sulfinate Salt	Pd/Ligand	Oxidant	% Yield A1.4[b]
1[c]	2,6-di^{i}Pr-C_6H_3	80 °C	$NaSO_2Me$	$PdCl_2/(P^tBu)_3$	-	0%
2	2,6-di^{i}Pr-C_6H_3	80 °C	$NaSO_2Me$	$PdCl_2/(P^tBu)_3$	$CuCl_2$	0%
3	2,6-di^{i}Pr-C_6H_3	90 °C	$NaSO_2CF_3$	$PdCl_2/(P^tBu)_3$	I_2	6%
4	2,6-di^{i}Pr-C_6H_3	90 °C	$NaSO_2CF_3$	$PdCl_2/(P^tBu)_3$	NaS_2O_8	21%
5	$BnNH_2$	90 °C	$NaSO_2CF_3$	$PdCl_2/(P^tBu)_3$	NaS_2O_8	39%
6	$BnNH_2$	90 °C	$NaSO_2CF_3$	$PdCl_2/(P^tBu)_3$	I_2	40%
7	$BnNH_2$	90 °C	$NaSO_2CF_3$	$PdCl_2$	I_2	10%
8	$BnNH_2$	r.t	$NaSO_2CF_3$	$PdCl_2/(P^tBu)_3$	I_2	trace
9	$BnNH_2$	90 °C	$NaSO_2Me$	-	I_2	23%
10	$BnNH_2$	90 °C	$NaSO_2CF_3$	-	I_2	31%
11	$BnNH_2$	r.t.	$AgSO_2Me$	-	I_2	1%
12	$BnNH_2$	r.t., 20 min	$NaSO_2CF_3$	-	I_2/AgOTf	43%
13	$BnNH_2$	r.t.	$NaSO_2Me$	-	$CuCl_2$	22%
14	$BnNH_2$	r.t.	$NaSO_2Me$	-	$CuOTf_2$	5%

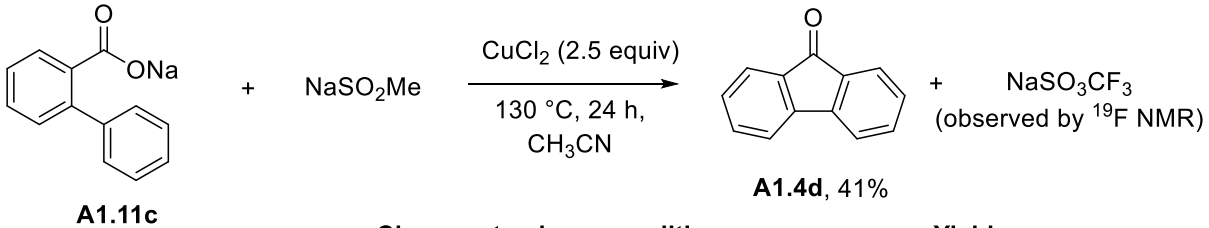
[a]Conditions: Sodium benzoate (36 mg, 0.25 mmol), sulfinate salt (0.25 mmol), amine (0.55 mmol), $PdCl_2$ (4 mg, 0.025 mmol), $P(^tBu)_3$ (5 mg, 0.025 mmol), oxidant (0.25 mmol), for copper oxidants (0.5 mmol), AgOTf (161 mg, 0.63 mmol), MeCN (1 mL). Benzylamine was added in a second step. [b]The yield was determined by ^1H NMR analysis relative to a standard, hexamethylbenzene (5mg, 0.03 mmol). [c] Stoichiometric reaction: sodium benzoate (7 mg, 0.05 mmol), sodium methanesulfinate salt (5 mg, 0.05 mmol), 2-6-diisopropylaniline (21 mg, 0.12 mmol), $PdCl_2$ (9 mg, 0.05 mmol), $P(^tBu)_3$ (10 mg, 0.05 mmol).

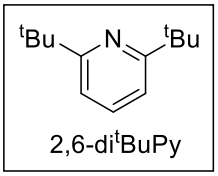
Further stoichiometric experiments were carried out with copper in hope of finding conditions that would be more amenable to eventual translation to a carboxylation platform with carbon dioxide. *In situ* trapping of the electrophile will likely be necessary to obtain catalytic turnover and inhibit its re-addition to the catalyst. While benzylamine reacts rapidly with the electrophile, it is also prone to oxidation and can readily coordinate to copper which could have a negative impact on catalysis. Nucleophilic arenes are ideally suited traps in this regard. We therefore explored thiophene as the nucleophile in the copper mediated reaction. No ketone was found, and instead benzoic acid **A1.11b** was recovered (Figure A1.3a). We postulate that this may arise from the fast reaction of sodium benzoate **A.11a** with any benzoyl triflate to form an anhydride with diminished electrophilicity and incapable of reacting with thiophene. In order to accelerate trapping and prevent anhydride formation, an intramolecular reaction was designed using 2-phenylbenzoic acid **A1.11c**. The latter would both accelerate intramolecular ketone formation and disfavor anhydride formation for steric reasons. We were gratified to find that employing this substrate under the same conditions did lead to the formation of cyclized ketone **A1.4d**, and sodium triflate (Figure A1.4b). Modification of the solvent, addition of base, or the use of other metal halides instead of $CuCl_2$ completely inhibited the reaction. Nonetheless, this provides intriguing preliminary data that suggests the viability of creating ketones from aryl iodides, CO_2 and arenes in the presence of copper catalysts.

a) Attempted Ketone Formation with Thiophene



b) Intramolecular Aroyl Triflate Trapping





Changes to above conditions	Yield
DMA instead of CH_3CN	0%
with $EtPr_2N$	0%
with $PdCl_2$ instead of $CuCl_2$	0%
with $PdCl_2(COD)$ instead of $CuCl_2$	0%
with $PdCl_2$/2,6-diBuPy instead of $CuCl_2$ in DMA	0%
with $NiCl_2$ instead of $CuCl_2$	0%
with $NiCl_2(dme)$ instead of $CuCl_2$	0%
with $NiCl_2$/2,6-diBuPy instead of $CuCl_2$ in DMA	0%

Figure A1.3. Trapping Aroyl Triflates Generated From Aryl Carboxylates

A1.3. Experimental Section

A1.3.1. General Considerations

All manipulations were carried in an inert atmosphere glovebox or using standard Schlenk techniques unless stated otherwise. “Bone dry” carbon dioxide (99.9%) was used as received. Solvents were dried over calcium hydride, distilled under argon and stored over activated 4 Å molecular sieves. N,N-dimethylacetimide was dried over BaO, distilled, and stored over activated

4 Å molecular sieve in the glovebox. Deuterated solvents were dried over calcium hydride, vacuum transferred and stored over activated 4 Å molecular sieves in the glovebox. Silver triflate was dried by heating to 100 °C under vacuum for 24 h, and then stored in the glovebox. Iodine was dried by grinding with calcium oxide for 10 min before allowing to sit overnight; then sublimed and immediately stored under nitrogen at -35 °C. $Pd_2dba_3 \cdot CHCl_3$, $Pd[P(^tBu)_3]_2$, $(COD)Pd(CH_2TMS)_2$ were prepared according to literature procedures and stored at -35 °C in the glovebox to avoid decomposition.[38-40] $AgSO_2CF_3$ and $AgSO_2Me$ were prepared according to literature procedure.[41] All other reagents were purchased from commercial suppliers and used as received. All ^1H and ^{13}C NMR spectra were acquired on 400 and 500 MHz spectrometers.

A1.3.2 General Synthetic Procedures

General Procedure for Screening Table A1.1. (entried 1-5, and 9).

In a glovebox, $AgSO_2Me$ (56 mg, 0.3 mmol), was transferred to a Teflon sealed, thick walled 50 mL glass reaction vessel equipped with a magnetic stir bar. 4-Iodotoluene (55 mg, 0.25 mmol), $[Pd(allyl)Cl]_2$ (2 mg, 0.006 mmol), Et^iPr_2 (49 mg, 0.38 mmol) benzylamine (54 mg, 0.5 mmol), were dissolved in DMA (2.5 mL) and added to the vessel. ^{t}BuXPhos (14 mg, 0.03 mmol) was dissolved in CH_2Cl_2 and added to vessel. The vessel was closed, removed from the glovebox, evacuated and backfilled with carbon dioxide three times, and finally pressurized with 4 atm carbon dioxide. The reaction was heated at 100 °C for 24 h with stirring. After the reaction was cooled to room temperature, hexamethylbenzene (5 mg, 0.03 mmol) was added as a standard and the reaction mixture was filter through celite, and the solvent removed *in vacuo*. The yield of amide **1.4b** (3%) was determined by ^1H NMR analysis relative to the external standard.

General Procedure for the Screening Table A1.2 and all reactions in FigureA1.3.

In a glovebox, $AgSO_2CF_3$ (39 mg, 0.25 mmol) and $Na_2S_2O_8$ (60 mg, 0.25 mmol) were dry transferred to a Teflon sealed, thick walled 50 mL glass reaction vessel equipped with a magnetic stir bar. Sodium benzoate (36 mg, 0.25 mmol), $PdCl_2$ (4 mg, 0.025 mmol), P^tBu_3 (5 mg, 0.025 mmol) were dissolved in CH_3CN (1 mL) and added to the vessel. The reaction was heated at 90 °C for 20 h with stirring. After the reaction was cooled to room temperature, brought back into the

glove box, and benzylamine (137 µL, 1.3 mmol) was added to vessel which then stirred for 30 min in the glovebox. The vessel was removed from the glovebox, hexamethylbenzene (5 mg, 0.03 mmol) was added as a standard, the reaction mixture was filtered through celite, and the solvent removed *in vacuo*. The yield of amide **1.4c** (39%) was determined by ^{1}H NMR analysis relative to the standard.

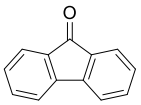
General Procedure for the reactions in FigureA1.3

In a glovebox, 2-phenylbenzoic acid (55mg, 0.25 mmol), $NaSO_2CF_3$ (39 mg, 0.25 mmol), $CuCl_2$ (84 mg, 0.63 mmol) were dry transferred to a Teflon sealed, thick walled 50 mL glass reaction vessel equipped with a magnetic stir bar, along with CH_3CN (1 mL). The reaction was heated at 130 °C for 24 h with stirring. After the reaction was cooled to room temperature, and hexamethylbenzene (5 mg, 0.03 mmol) was added. The yield of amide **1A.4d** (51%) was determined by ^{1}H NMR analysis relative to the standard. Ketone **A1.4d** was isolated by filtering the crude reaction mixture through a plug of silica, rinsing with EtOAc/CH_2Cl_2, and evaporating the solvent *in vacuo*. The residue was purified by column chromatography (silica gel, gradient hexane/ethyl acetate 0% to 20%) affording ketone **A1.4d** as a yellow solid in 41% yield (18 mg).

Procedure for the observation of $NaSO_2CF_3$

In a glovebox, 2-phenylbenzoic acid (55mg, 0.25 mmol), $NaSO_2CF_3$ (39 mg, 0.25 mmol), $CuCl_2$ (84 mg, 0.63 mmol) were dry transferred to a Teflon sealed, thick walled 50 mL glass reaction vessel equipped with a magnetic stir bar, along with CH_3CN (1 mL). The reaction was heated at 130 °C for 24 h with stirring. After the reaction was cooled to room temperature, additional CH_3CN was added to dilute the reaction. ^{19}F NMR analysis showed a signal resonance at δ -79.1 ppm which is consistent with triflate anion.

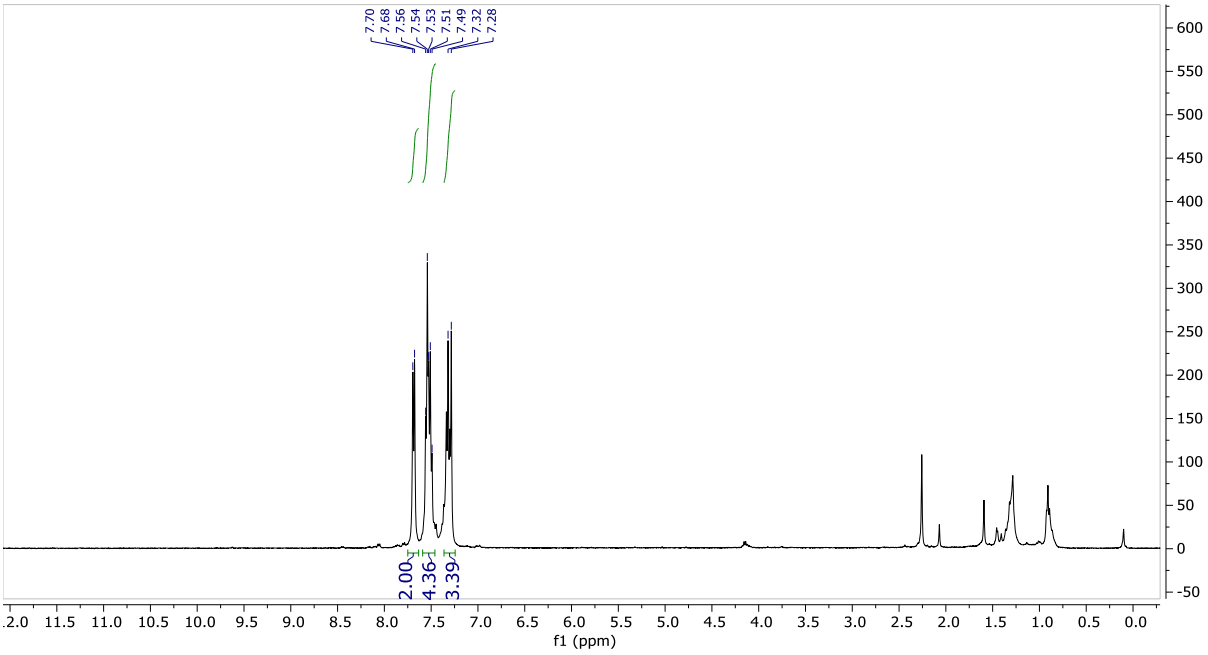
A1.3.2. Characterization Data

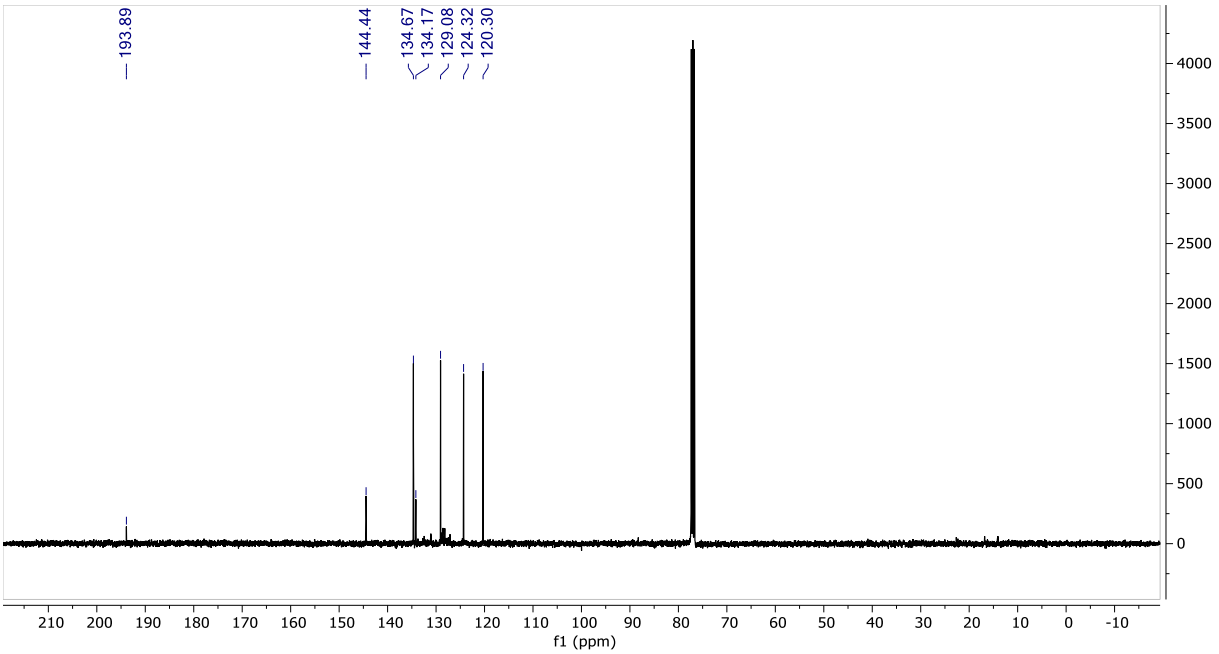


Fluorenone **A1.4d**[42] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.5 Hz, 2H), 7.53 (dt, *J* = 14.7, 7.3 Hz, 4H), 7.30 (d, *J* = 13.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.9, 144.4, 134.7, 134.2, 129.1, 124.3, 120.3.

A1.3.4 NMR Spectra

^{1}H NMR and ^{13}C NMR spectra for compound **A1.4d**





A1.4. References

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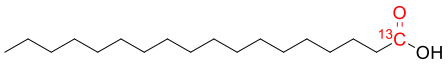
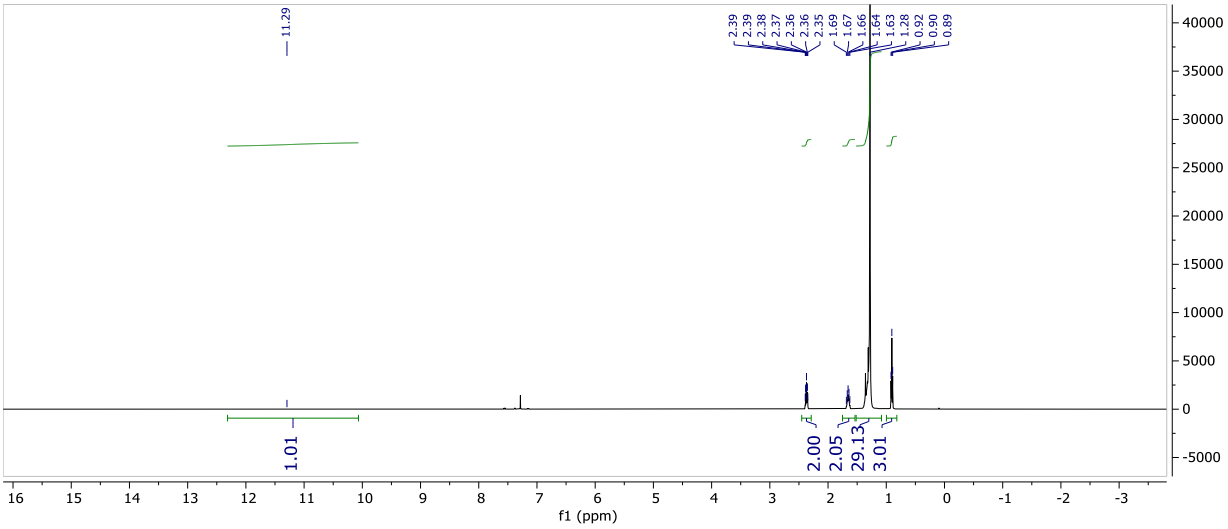
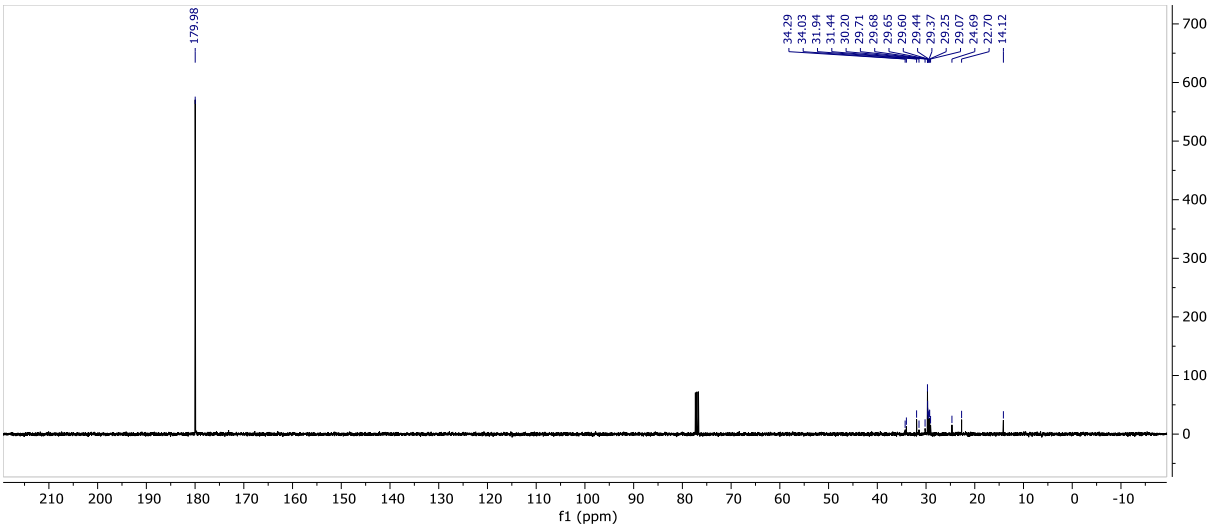
Apendix 2. NMR Spectra for Compounds in Chapter 4

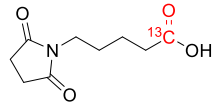
^{1}H NMR and ^{13}C NMR spectra for compound **4.4b-^{13}C**

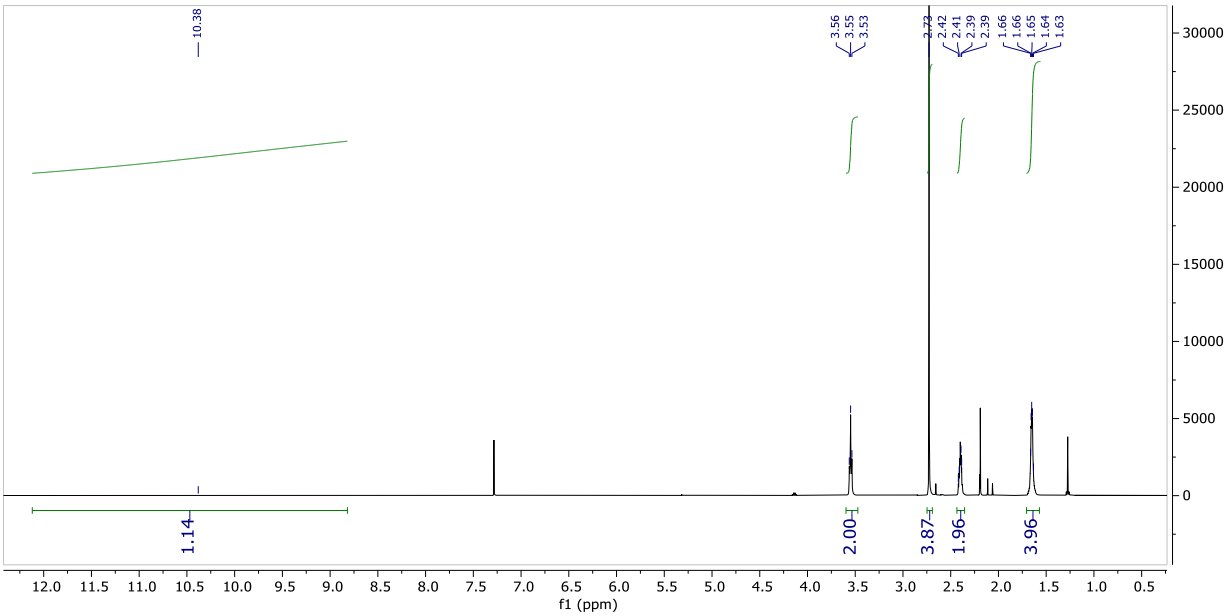


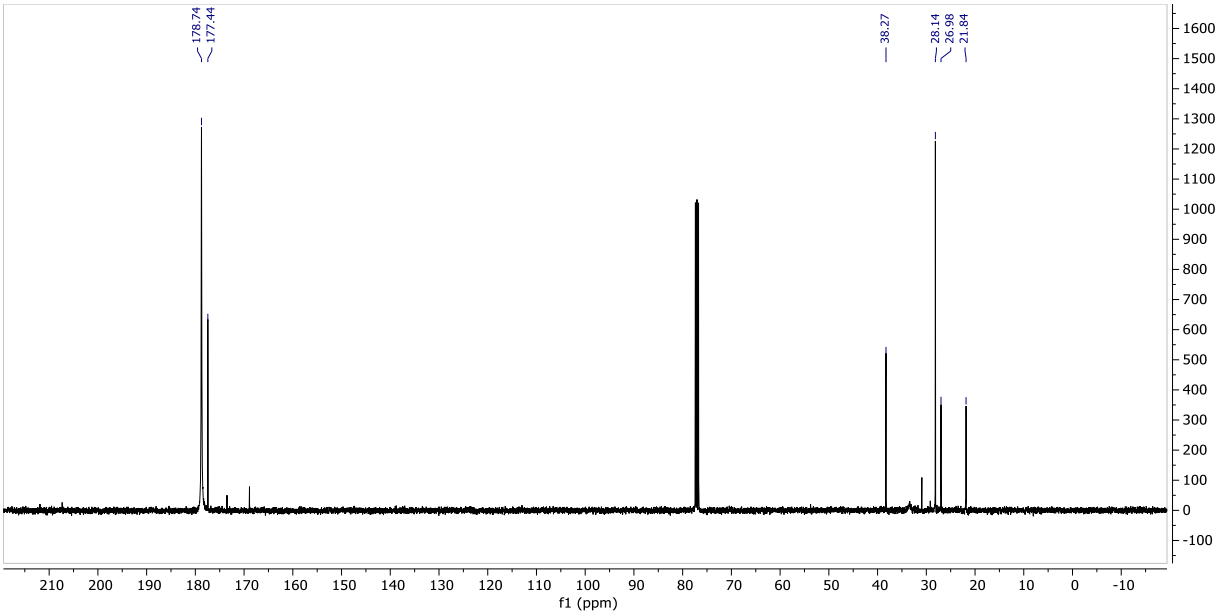




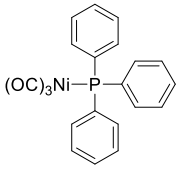
^{1}H NMR and ^{13}C NMR spectra for compound **4.4c-^{13}C**



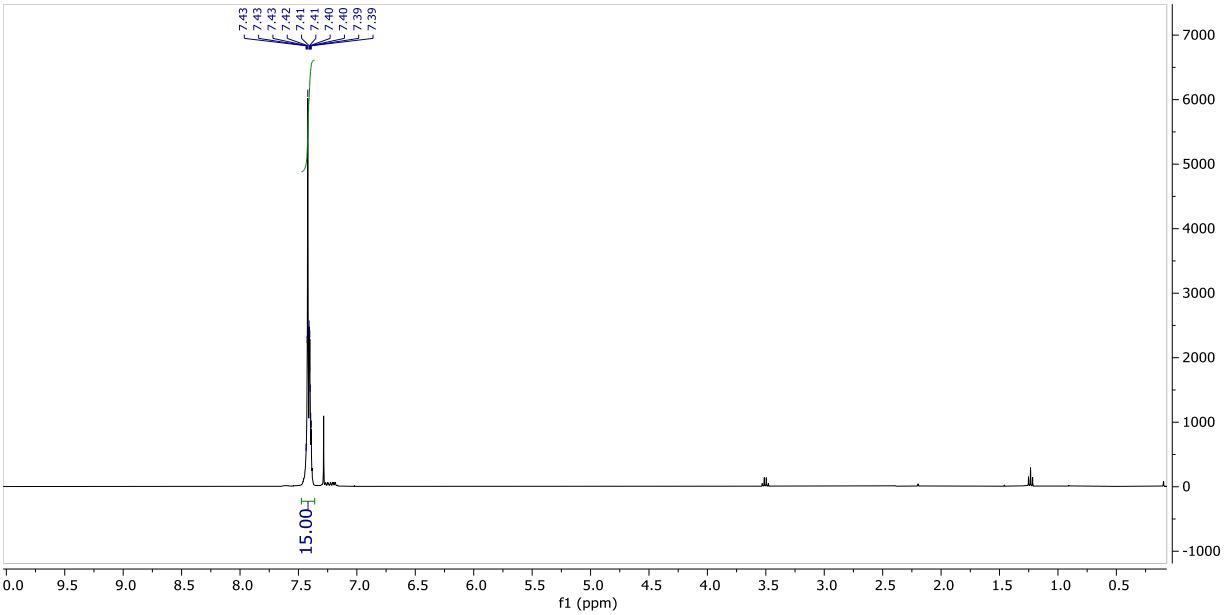




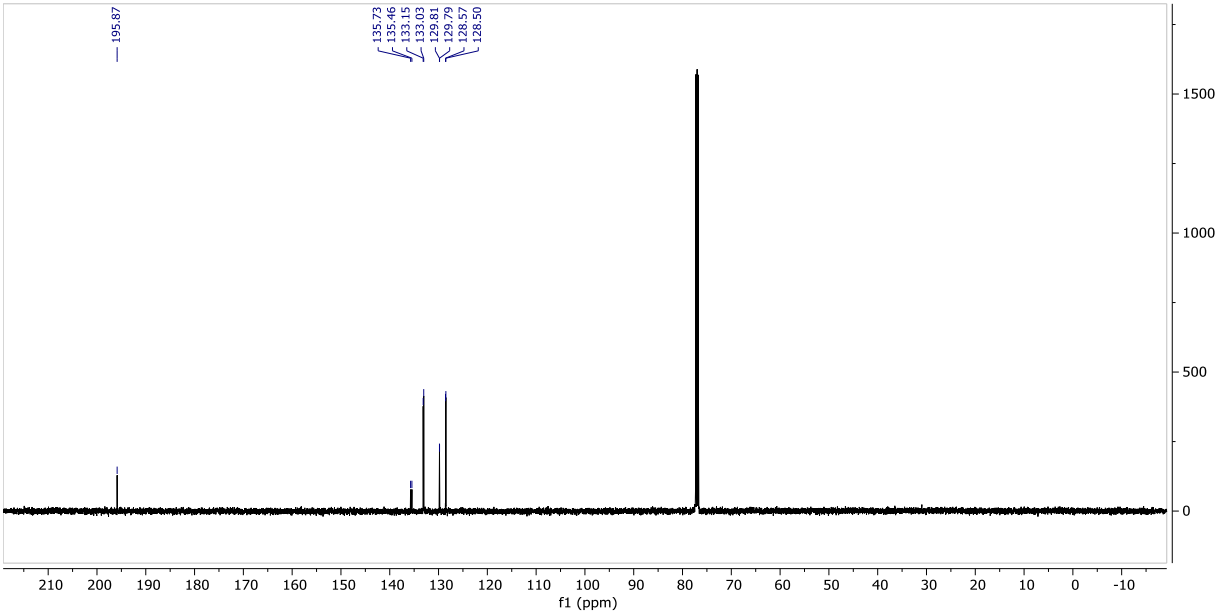
^{1}H NMR, ^{13}C NMR, ^{31}P NMR spectra



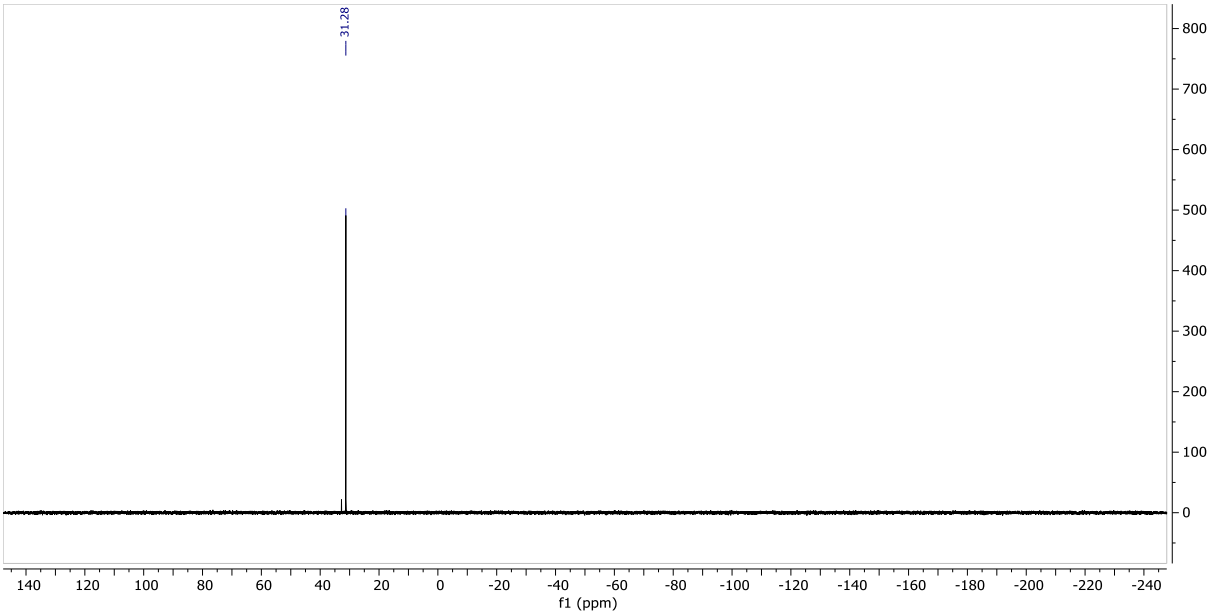
^{1}H NMR



^{13}C NMR



^{31}P NMR


31.28
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-160
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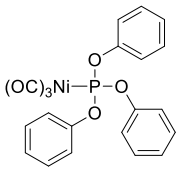
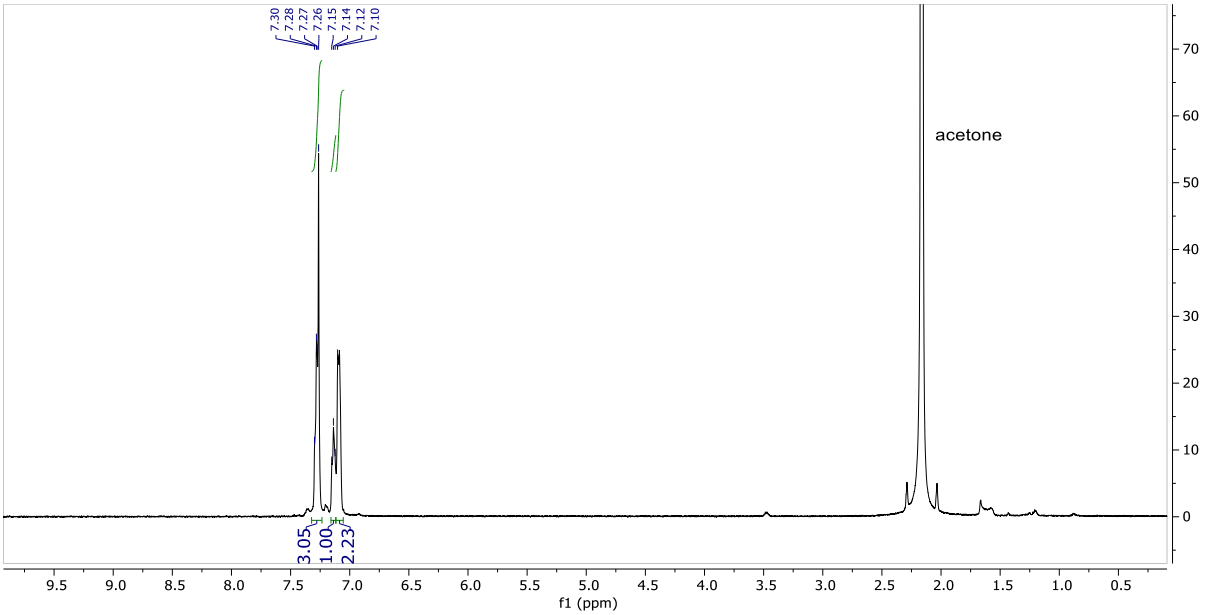
-200
-220
-240
f1 (ppm)

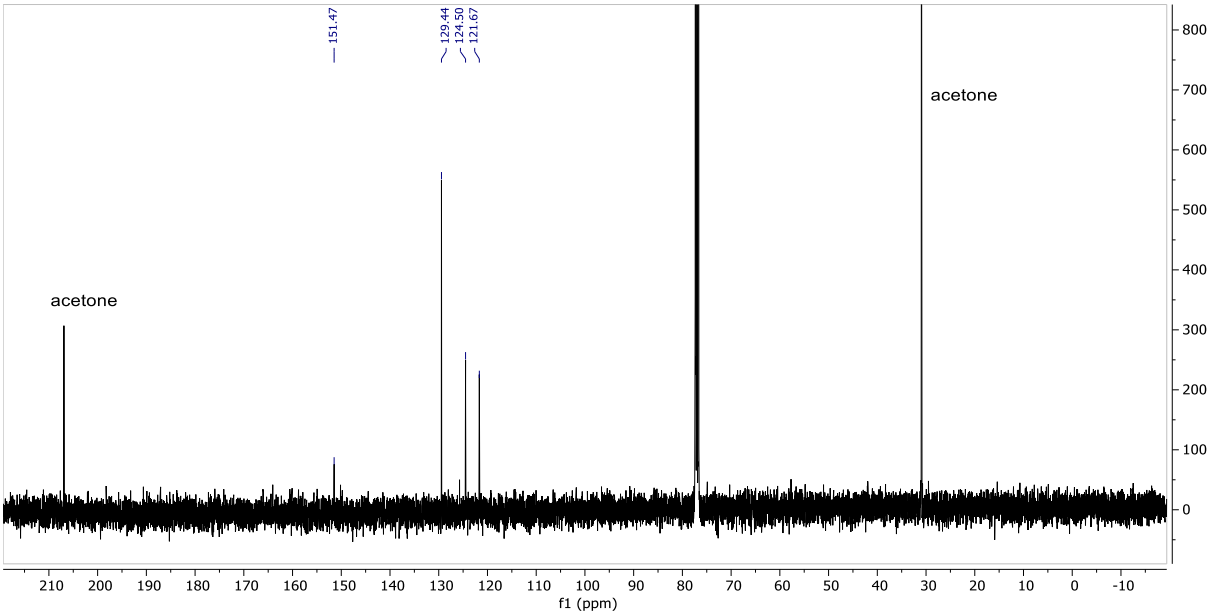
^{1}H NMR, ^{13}C NMR, ^{31}P NMR spectra



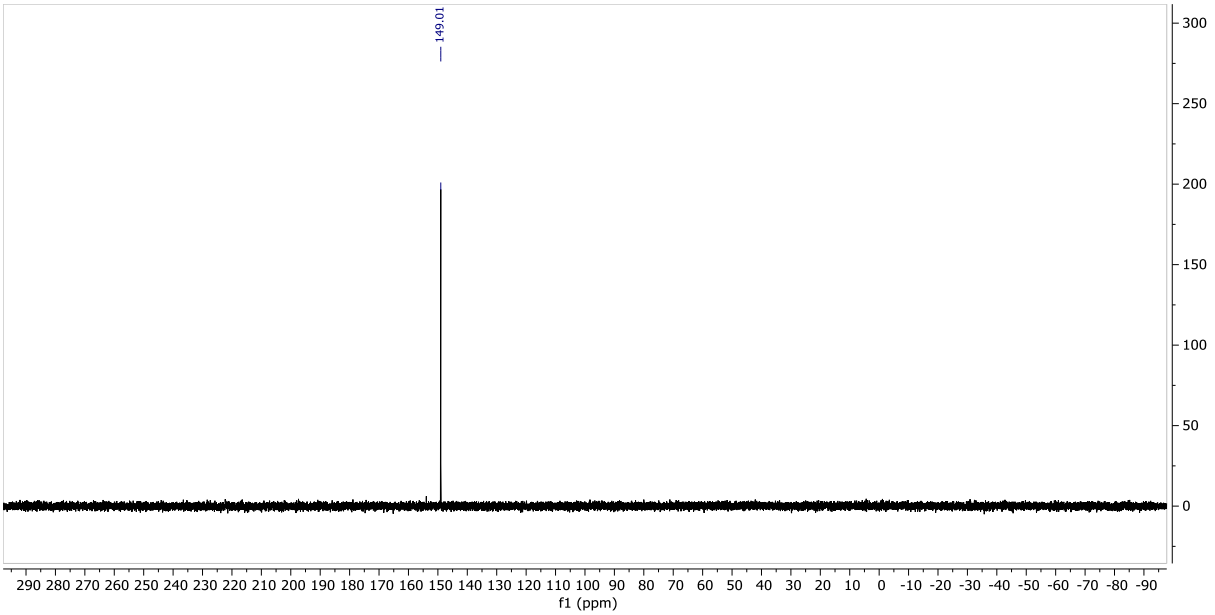
^{1}H NMR



^{13}C NMR (carbonyl is not visible)



^{31}P NMR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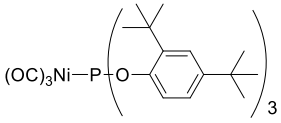
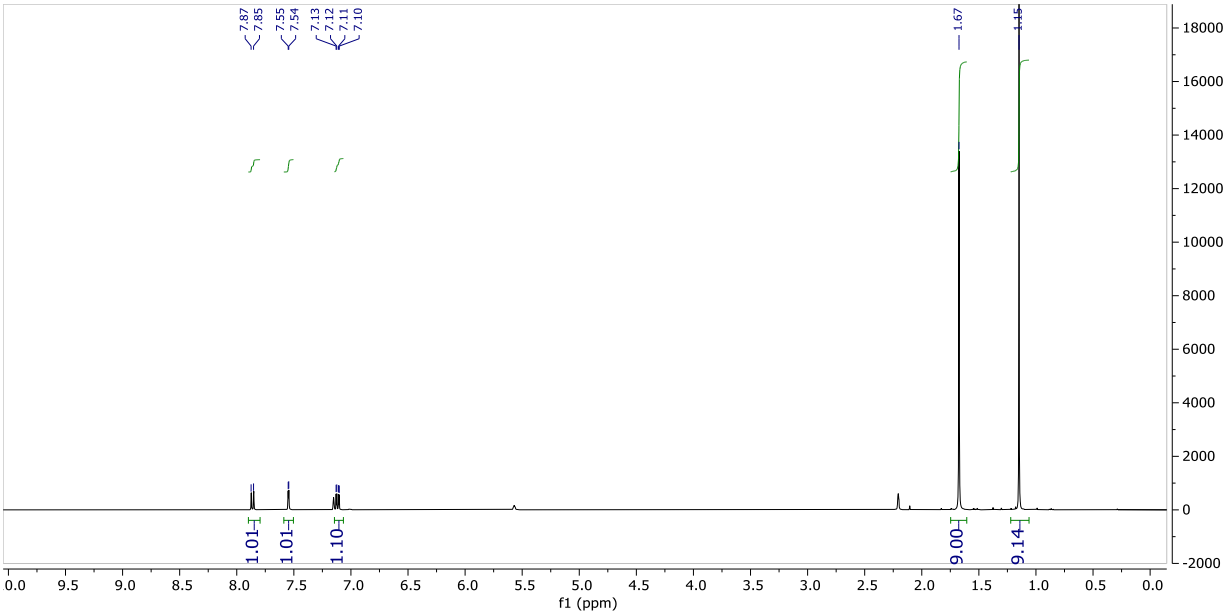
290 280 270 260 250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90
f1 (ppm)

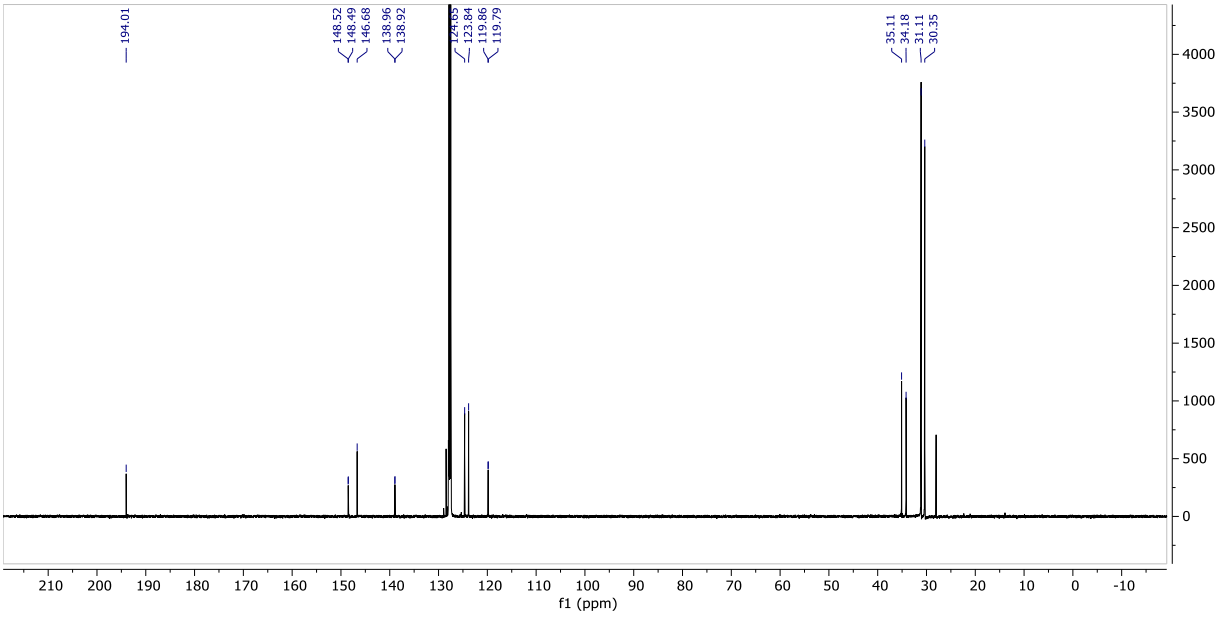
^{1}H NMR, ^{13}C NMR, ^{31}P NMR spectra of **[Ni]1**



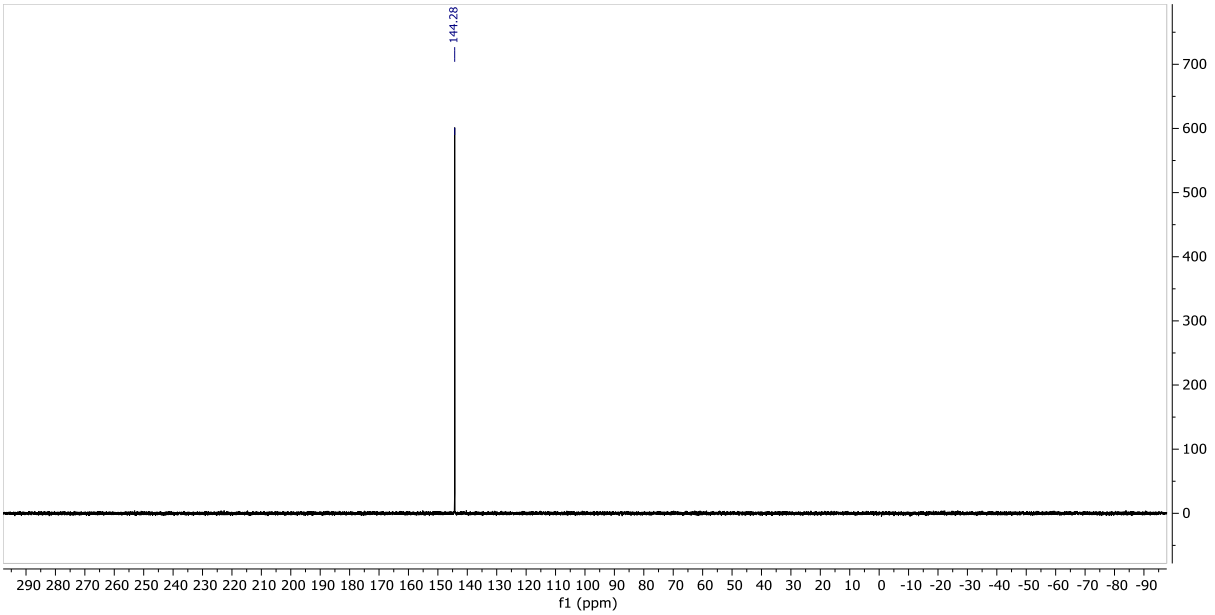
^{1}H NMR



^{13}C NMR



^{31}P NMR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f1 (ppm)