Synthesis of Aryl Ketones via Palladium-Catalyzed Carbonylative C-H Functionalization

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Abstract

Palladium-catalyzed C-H functionalization reactions offer an efficient platform to generate carbon-carbon and carbon-heteroatom bonds directly from hydrocarbon substrates. However, the ability to merge these transformations with carbonylation reactions as a route to generate ketones has presented a more significant challenge. These reactions have, to date, required the use of either one non-C-H bond containing substrate (e.g. an aryl halide) or must be performed in an intramolecular fashion to generate cyclized products. Of note, the generation of aryl ketones directly from their most fundamental building blocks, two arenes and carbon monoxide, has not been previously reported.

To address this limitation, Chapter 2 describes how simple palladium salts can catalyze the oxidative coupling of simple (hetero)arenes and carbon monoxide into biaryl ketones. This transformation employs iodine as the oxidant, which reacts in concert with silver triflate to generate first aryl iodides. Mechanistic studies suggest these aryl iodides undergo *in situ* carbonylation to aroyl triflate electrophiles followed by Friedel-Crafts acylation of a second arene to form ketones. This reaction can be used to generate both symmetrical and unsymmetrical bi(hetero)aryl ketones under relatively mild conditions and directly from simple aromatic compounds and carbon monoxide.

Résumé

Les réactions de fonctionnalisation C-H catalysées au palladium offrent une plateforme efficace pour générer des liaisons carbone-carbone et carbone-hétéroatome directement à partir d'hydrocarbures. Cependant, la capacité de combiner ces transformations avec des réactions de carbonylation comme voie pour générer des cétones a fait face à d'importants défis. Ces transformations requièrent, jusqu'à présent, l'utilisation d'un lien autre qu'un lien C-H (e.g. un iodure d'aryle) ou doivent être effectuées de façon intramoléculaire, générant des produits cycliques. Néanmoins, la capacité de générer des cétones aromatiques directement à partir de précurseurs des plus simples et fondamentaux, deux arènes et le monoxyde de carbone, représente un défi non résolu.

Pour remédier à cette limitation, le chapitre 2 décrit comment de simples sels de palladium peuvent catalyser le couplage oxydatif de simples composés, comme des (hétéro)arènes et du monoxyde de carbone, en diaryle cétones. Cette transformation emploie l'iode comme oxydant, qui réagit en concert avec le triflate d'argent pour générer d'abord des iodures d'aryle. Des études mécanistiques suggèrent que ces derniers sont transformés par carbonylation *in situ* en triflate d'aroyles électrophiles suivis par une acylation de Friedel-Crafts du second composé aromatique pour former la cétone. Cette transformation peut être utilisée pour générer des cétones bi(hétéro)aromatiques symétriques et asymétriques en utilisant des conditions de réaction relativement douces, et directement à partir de simples composés aromatiques et du monoxyde de carbone.

Acknowledgements

I would like first to thank my supervisor Professor Bruce Arndtsen for all the guidance and support that I have received during the completion of my studies. I greatly appreciate the chance to have been a student in his laboratory and have learned much from the fruitful research discussions that we have had in this time.

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I also must thank the support staff at McGill for all the help and technical advice received during this degree. I thank Dr. Robin Stein for the work she did in assisting me with various NMR spectroscopy problems and I thank Dr. Alexander Wahba and Dr. Nadim Saadeh for mass spectrometry assistance. I would also like to extend my thanks to Chantal Marotte, Sandra Aerssen, Nikoo Taghavi, Chelsea Briand-Pitts, Stephanie Trempe, Jean-Philippe Guay, Weihua Wang, Rick Rossi, Linda del Paggio, Ross Commodari, Lina Alvarez, and Jean-Marc Gauthier.

Finally, I must thank all my family and friends for listening and encouraging me throughout every step of this degree. I wouldn't have made it here without you. To Aaron Holmes, thank you for everything.

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List of Abbreviations

Å	Angstrom
Ac_2O	Acetic Anhydride
AcOH	Acetic Acid
Ad	Adamantyl
^{t}AmylOH	*tert*-Amyl Alcohol
Ar	Aryl
atm	Atmosphere
^{n}Bu	*n*-Butyl
^{t}Bu	*tert*-Butyl
bar	Bar
Bn	Benzyl
BQ	Benzoquinone
br	Broad
°C	Degrees Celsius
Cat.	Catalyst
CMD	Concerted-Metalation Deprotonation
Collidine	2,4,6-trimethylpyridine
CSA	Camphorsulfonic acid
Cy	Cyclohexyl
d	Day; Doublet
δ	Delta (ppm)
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane

DCM	Dichloromethane
dd	Doublet of Doublets
DFT	Density Functional Theory
DG	Directing Group
DMA	Dimethylacetamide
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DPPB	1,4-Bis(diphenylphosphino)butane
dppp	1,3-Bis(diphenylphosphino)propane
EDG	Electron Donating Group
Equiv.	Equivalent
ESI	Electrospray Ionization
Et	Ethyl
EWG	Electron Withdrawing Group
F_n	Unspecified Number of Fluorine Atoms
h	Hour
HFIP	Hexafluoro-2-propanol
HOTf	Triflic Acid
HPMV	$H_4PMo_{11}VO_{40}$
HRMS	High-Resolution Mass Spectrometry
Hz	Hertz
J	Coupling Constant
KIE	Kinetic Isotope Effect
L	Ligand
L_n	Unspecified Number of Ligands

m	Multiplet
M	Mass; Unspecified Metal
Me	Methyl
mg	Milligram
MHz	Megahertz
min	Minute
mL	Millilitre
mM	Millimolar
mmol	Millimole
mol	Mole
MS	Molecular Sieves
n	Unspecified Number
NMP	*N*-Methyl-2-pyrrolidone
NMR	Nuclear Magnetic Resonance
NTf	Triflimide
OAc	Acetate
OPiv	Pivalate
OTf	Triflate
o-tol	*o*-Toluene
[Ox]	Oxidant
Ph	Phenyl
PhDavePhos	2’-(Diphenylphosphino)-*N,N’*-dimethyl-(1,1’-biphenyl)-2-amine
Phen	Phenanthroline
PivOH	Pivalic Acid
ppm	Parts per Million

p-tol	*p*-Toluene
py	Pyridine
pym	Pyrimidine
R	Substituent
r.t.	Room Temperature
s	Singlet
S_EAr	Electrophilic Aromatic Substitution
t	Triplet
TBAF	Tetra-*n*-butylammonium Fluoride
TBME	Methyl *tert*-Butyl Ether
td	Triplet of Doublets
TFA	Trifluoroacetic Acid
THF	Tetrahydrofuran
TON	Turnover Number
Ts	Tosyl
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
μL	Microlitre

Contributions of Co-Authors

This thesis consists of three chapters. Chapter 1 is an introduction to the relevant work applicable to the content of this thesis. Chapter 2 is a manuscript currently being submitted and describes the palladium-catalyzed carbonylation of arenes to form ketones. The initial screen of oxidants for this reaction was performed by R. Garrison Kinney, a PhD student in the Arndtsen lab. However, all the work detailed in Chapter 2 was performed by me under the supervision of Dr. Bruce Arndtsen for the completion of the degree of Master of Science in chemistry. As Dr. Arndtsen was my supervisor throughout the duration of this degree, he also assisted in the editing of this thesis. Chapter 3 provides a conclusion to the work described in this thesis.

Chapter 1. Introduction

1.1 Perspective

Transition metal catalysis has revolutionized how chemists approach constructing bonds in organic molecules. Late transition metals in particular have seen significant use in catalyzing these reactions, including many that are relevant to the fine chemical and pharmaceutical industries. A powerful example is the cross-coupling of an aryl halide, or related electrophile, with nucleophilic organometallic reagents. Such cross-coupling reactions usually employ palladium catalysts and can proceed with a variety of nucleophilic coupling partners, including boronic acids (Suzuki-Miyaura couplings), alkenes (Mizoroki-Heck), organozinc reagents (Negishi), organotin reagents (Migita-Kosugi-Stille), alkynes (Sonogashira), and Grignard reagents (Kumada-Tamao-Corriu), among others (Figure 1.1.1).[1-6] In recognition of the impact that this reaction class has had on synthetic chemistry, the 2010 Nobel prize in chemistry was awarded to Negishi, Heck, and Suzuki for their ground-breaking work in the development of cross-coupling chemistry.[1]

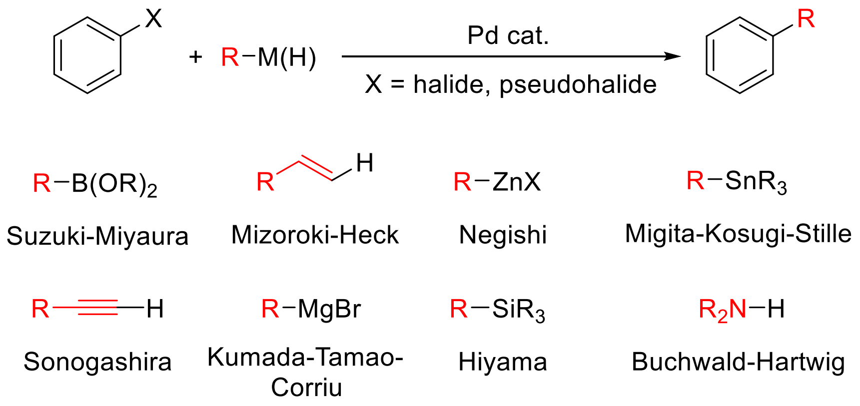


Figure 1.1.1. Palladium-Catalyzed Cross-Coupling Platforms.

Cross-coupling reactions are heavily exploited in the pharmaceutical industry and allow the construction of bonds that would otherwise be difficult to form via classical synthetic methods. However, the required use of organic halides and organometallic reagents, which are both ultimately derived from hydrocarbons, leads to significant chemical waste. This occurs in both the generation of the substrates, as well as the cross-coupling reaction itself, which typically eliminates one equivalent of organometallic by-product. In recent years, the focus on developing greener synthetic methods has led to the desire to replace this need for pre-functionalization of hydrocarbons for use in bond-forming reactions. To do so, many have turned towards the powerful platform of metal-catalyzed C-H bond functionalization. The direct activation and functionalization of C-H bonds can negate much of the waste generated in cross-coupling reactions and also leads to shorter synthetic pathways. One difficulty, however, is that hydrocarbon C-H bonds are notoriously inert due to their high bond strengths and low polarity. Nevertheless, fundamental advances have been made in using metal catalysts to selectively derivatize classically inert C-H bonds. These exploit various mechanistic platforms, including σ-bond metathesis, oxidative addition, electrophilic substitution, radical abstraction, and concerted metalation-deprotonation (CMD).[7-9]

In addition to the issue of stoichiometric waste, these transformations – whether they involve cross-coupling or C-H functionalization reactions – often lead to the generation of carbon-carbon bonds that can be difficult to further modify. An alternative would be one wherein these reactions can generate a functionality that can be further manipulated. An excellent candidate for this is carbon monoxide. Carbon monoxide has well-known insertion chemistry and is a heavily used reagent in many industrially relevant transformations, such as the Monsanto and Cativa acetic acid processes, or hydroformylation reactions (Figure 1.1.2).[10-12] In addition, the incorporation of carbon monoxide into products leads to the formation of carbonyl derivatives such as esters, amides, carboxylic acids, and ketones, which are among the most the valuable and easily manipulated functionalities in synthetic chemistry. This chapter will provide an overview of key discoveries in the development of palladium-catalyzed systems for the direct functionalization of aromatic C-H bonds (Sections 1.2 and 1.3). Section 1.4 will then discuss the methods in which CO has been incorporated into these C-H functionalization systems as a route to prepare ketones.

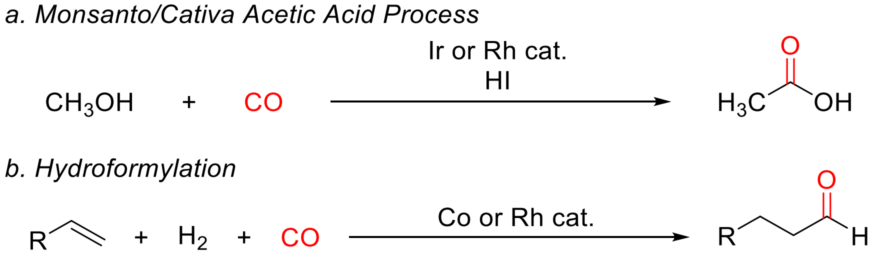
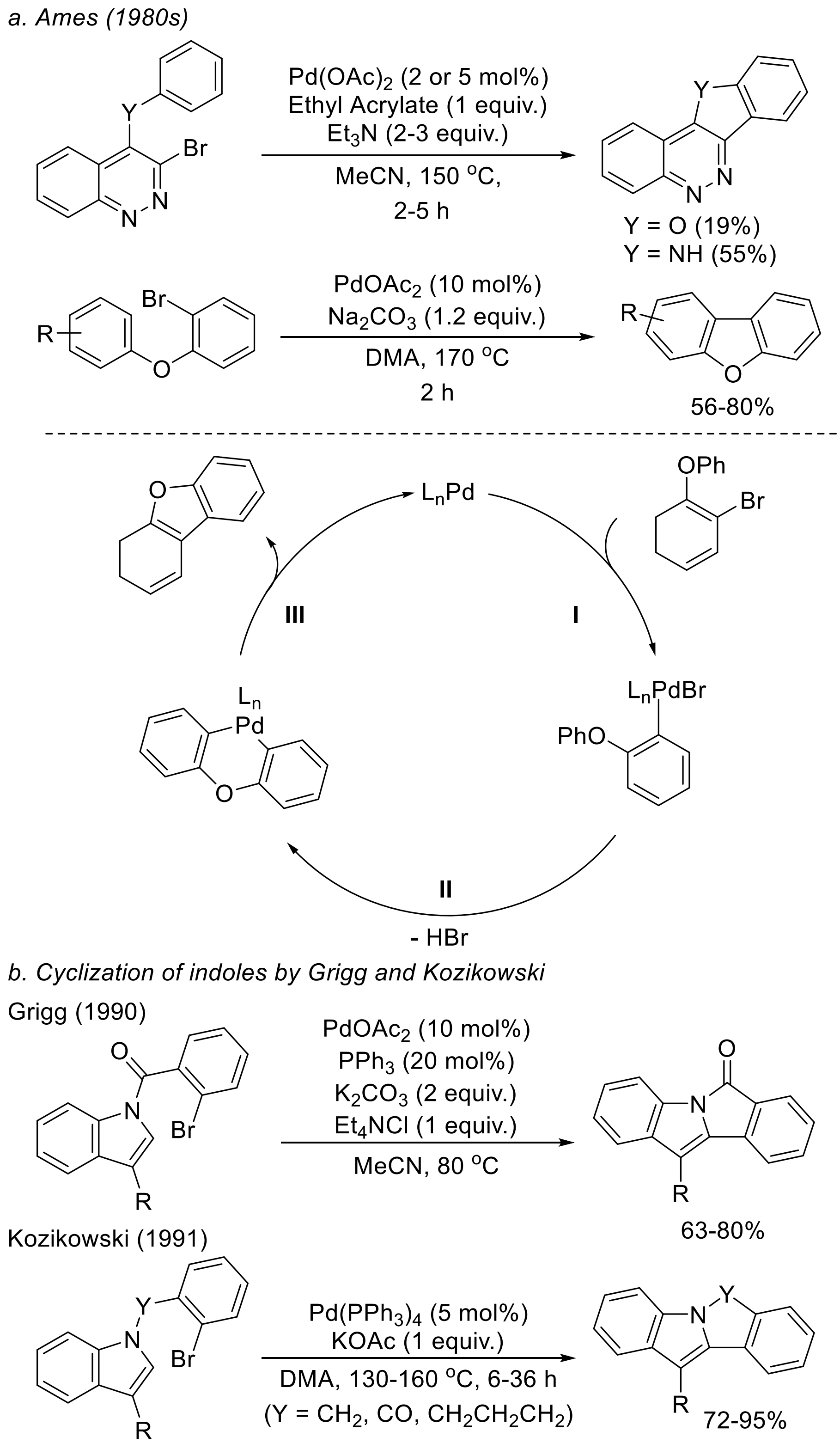


Figure 1.1.2. Important Industrial Examples of Carbonylation Chemistry.

1.2 Palladium-Catalyzed C-H Functionalization of Arenes

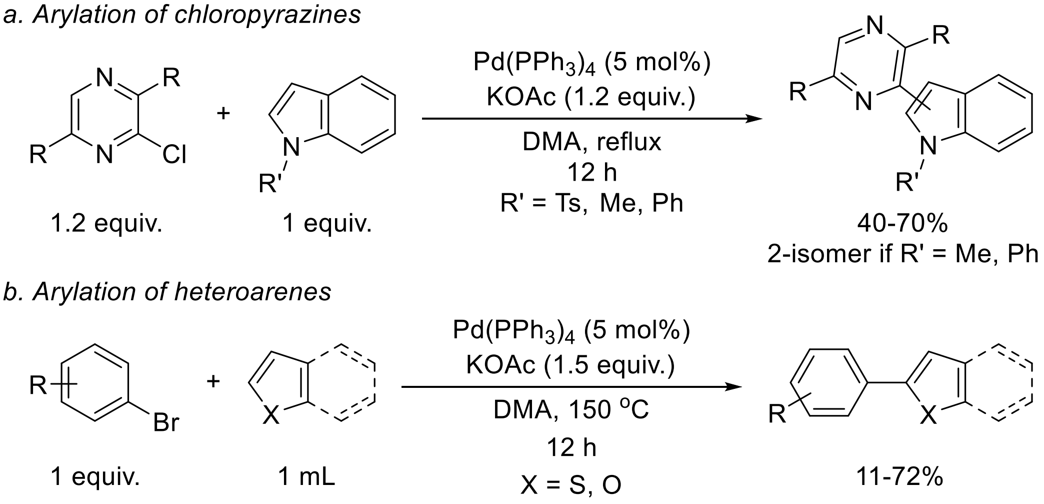
While palladium-catalyzed cross-coupling chemistry has proven to be a powerful platform for C-C and C-heteroatom bond formation, one of the inherent drawbacks is the required use of pre-functionalized arene reagents. Installation of these functional groups typically requires extra steps and reagents, and the cross-coupling reaction itself generates stoichiometric, often metal-containing waste. In contrast, a method wherein cross-coupling chemistry is conducted with the replacement of at least one pre-functionalized substrate by a simple, unfunctionalized arene can lead to a significant improvement in the overall efficiency of these reactions – not to mention the cases where the initial pre-functionalization of the arene leads to unstable or difficult-to-use coupling substrates. Of the two components that make up typical cross-coupling reactions, more success has been found in replacing the pre-functionalized nucleophilic reagent with unfunctionalized arenes, rather than the electrophilic partner. Many palladium-catalyzed direct C-H arylation reactions therefore still employ aryl halides.

Early developmental work in this area involved intramolecular arylation reactions to form cyclized products. In the early 1980s, Ames and co-workers reported catalytic protocols with palladium for the intramolecular cyclization of bromocinnolines and 2-bromophenyl ethers (Scheme 1.2.1a).[13, 14] These systems employed palladium(II) acetate as the pre-catalyst, and were postulated to proceed through initial oxidative addition of the aryl bromide bond to Pd(0) followed by C-H activation of the nearby aryl fragment (Scheme 1.2.1a, steps I and II). Subsequent reductive elimination affords the cyclized product (step III). Nevertheless, the mechanism by which the C-H bond is cleaved was at this stage unclear. Other early intramolecular examples of catalytic direct C-H arylation include those described by Grigg and Kozikowski using N-substituted indoles (Scheme 1.2.1b).[15, 16]

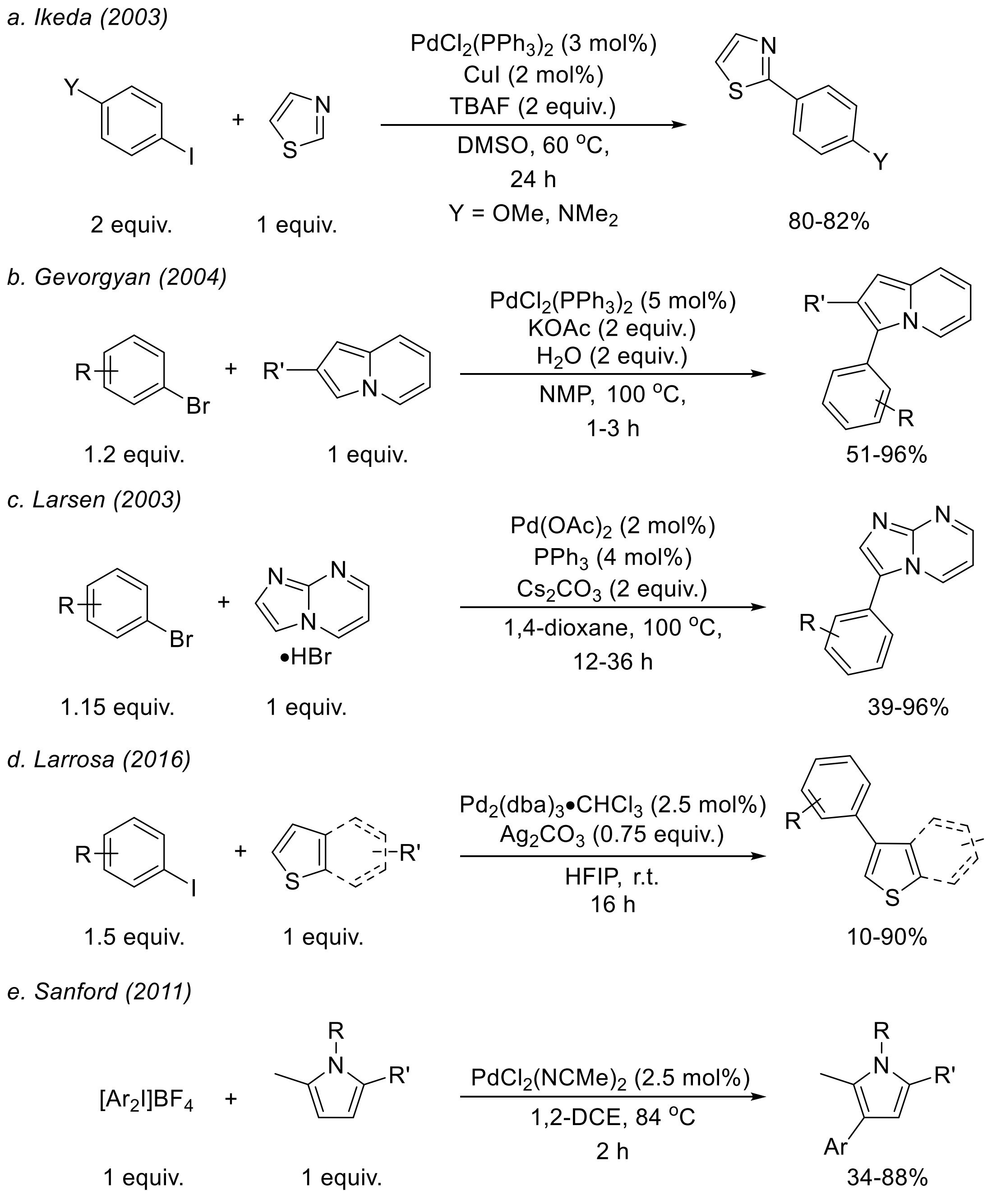


Scheme 1.2.1. Early Examples of Palladium-Catalyzed Intramolecular Direct Arylation.

Early progress in the intermolecular arylation of heteroaromatics came from a series of papers published by Ohta showing that indoles and other heterocycles can be coupled with chloropyrazines using 5 mol% $Pd(PPh_3)_4$ catalyst (Scheme 1.2.2a).[17, 18] Of note, this reaction involved the use of KOAc as base, which was subsequently found to be key to many palladium-catalyzed C-H functionalization reactions (*vide infra*). Ohta also reported the first catalytic coupling of aryl bromides with heteroaromatics such as thiophene, benzothiophene, furan, and benzofuran (Scheme 1.2.2b).[19] While the yields of these reactions were variable, these results demonstrate that electron rich heterocycles are particularly reactive towards direct functionalization with aryl halides. More recent studies by a number of labs have shown that many heteroaromatic substrates can be readily employed in catalytic C-H functionalization, where the nucleophilicity of these compounds can facilitate the C-H activation step. Examples include indoles,[20-24] thiophenes,[25, 26] benzothiophenes,[23-25, 27] furans,[26, 28] benzofurans,[23, 24] pyrroles,[29, 30] and others,[31-37] some of which are highlighted in Scheme 1.2.3.

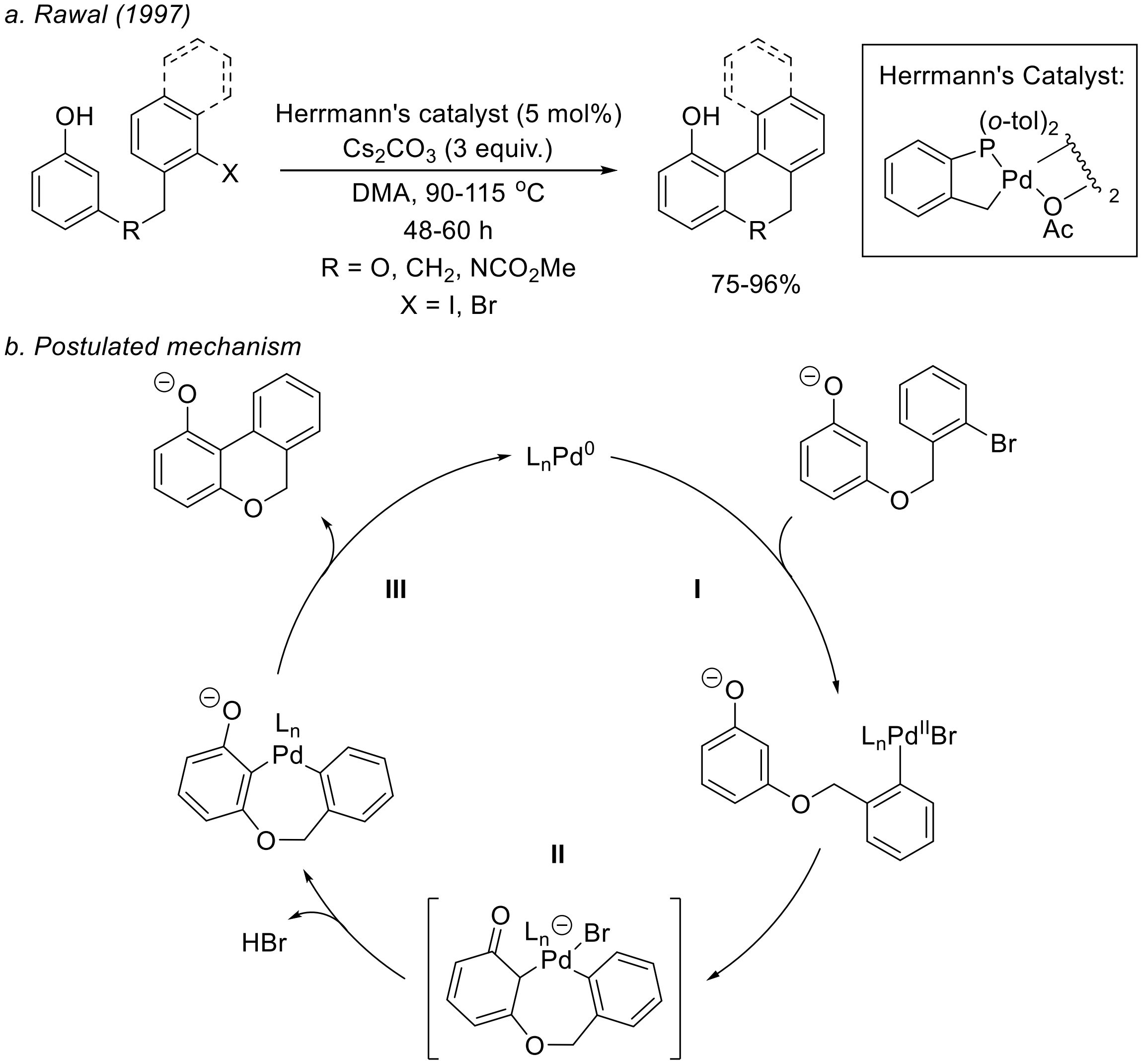


Scheme 1.2.2. Intermolecular Arylation of Heterocycles by Ohta and Co-Workers.



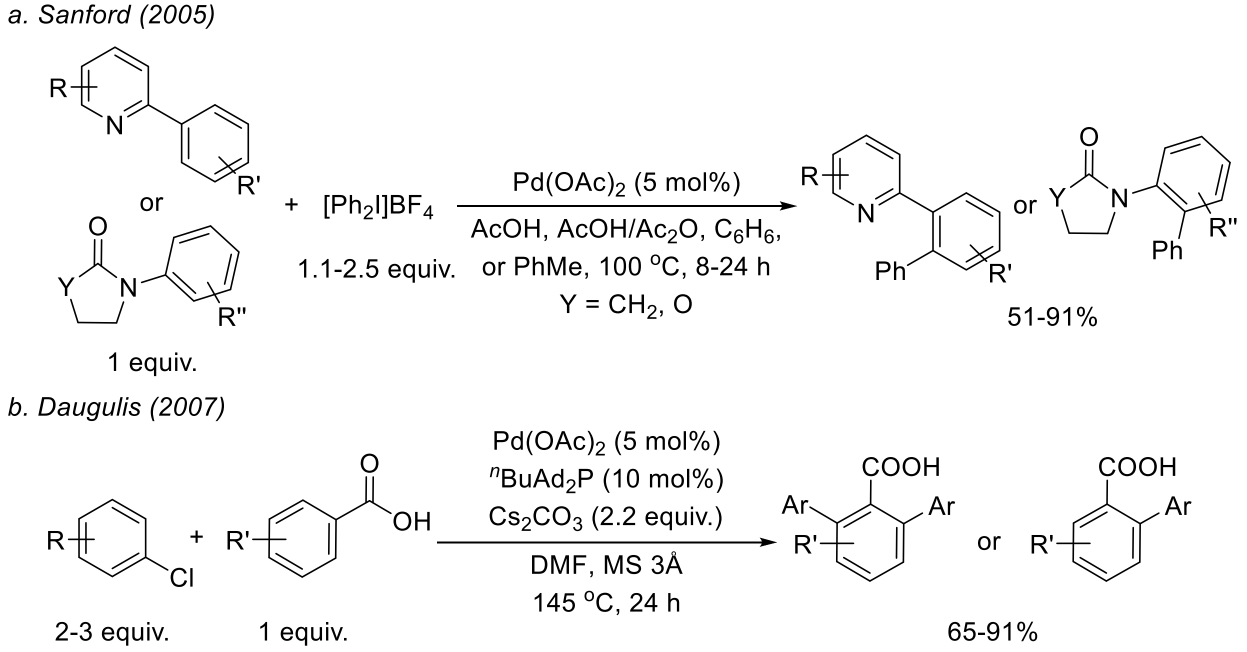
Scheme 1.2.3. Select Examples of Direct C-H Arylation of Heteroarenes.

The direct arylation of simple arenes has proven to be more difficult. One of the early successes in this area was described in 1997 by Rawal when he demonstrated that electron rich, deprotonated phenols could undergo intramolecular coupling with aryl halides (Scheme 1.2.4a).[38] A mechanism was postulated for this reaction involving an initial oxidative addition of the aryl halide (Scheme 1.2.4b, step I) to form a palladium-aryl complex. This palladium(II) complex was believed to react as an electrophile with the electron rich phenolate (step II) to give a diarylated palladium intermediate. Subsequent reductive elimination returns palladium(0) and forms the biaryl product (step III). Following this finding, Miura demonstrated that aryl halides could be also coupled with biphenyls bearing an *ortho*-hydroxy group.[39, 40]



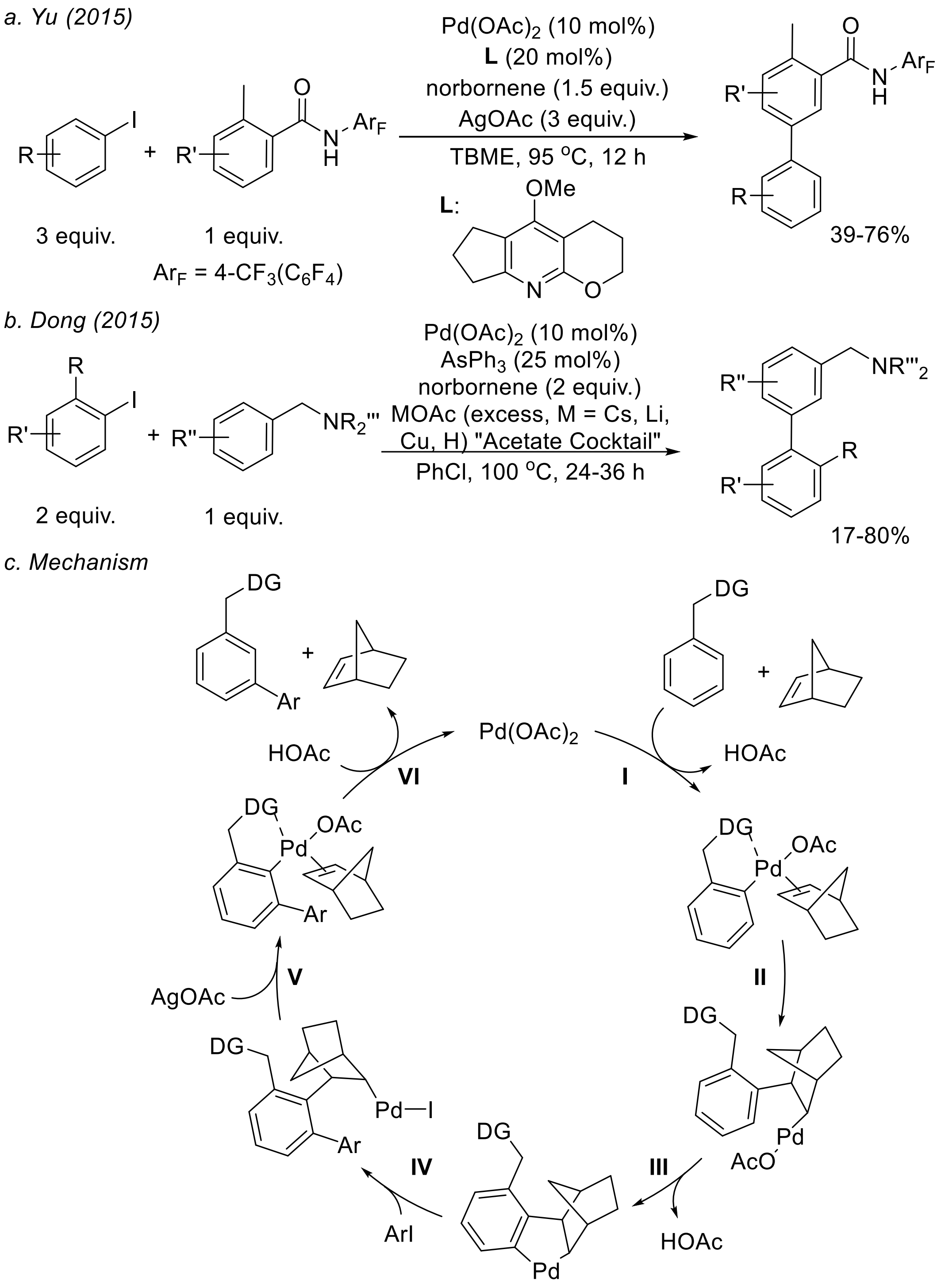
Scheme 1.2.4. Intramolecular Direct Arylation with Phenols.

Metal-coordinating directing groups have also found significant use in the activation of arenes towards C-H functionalization reactions. In this case, coordination of the directing group to the palladium catalyst is postulated to make the C-H bond functionalization step more kinetically viable by generating a 5- or 6-membered palladacycle. Of note is that these transformations can occur in an intermolecular fashion to assemble biaryls. A large variety of directing groups have been found to be compatible in these reactions, with some early examples shown in Scheme 1.2.5. Many of these reactions use nitrogen-based directing groups, such as pyridine scaffolds,[41-44] anilides,[44-47] benzoxazoles,[44, 48] amides,[49-52] and others.[53-56] Additionally, carboxylic acids have also been found to be attractive *ortho*-directing groups in direct arylation reactions due to their abundance and low cost.[57-61] Directing-group assisted direct arylation has since become a very popular method for palladium-catalyzed C-H functionalization reactions, as it both accelerates the C-H bond cleavage and directs it to selectively functionalize the bond adjacent (*ortho*-) to the directing group.



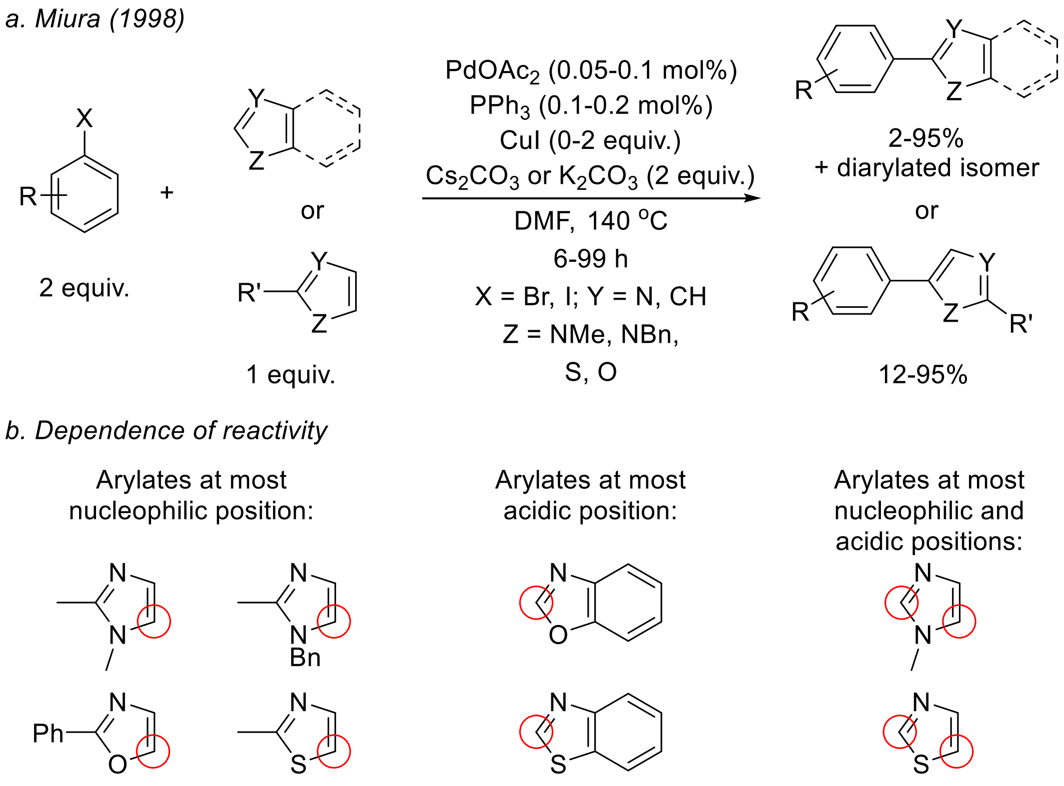
Scheme 1.2.5. Representative Early Examples of Directing-Group Assisted Direct Arylation.

As an alternative to directed *ortho*-functionalization, *meta*-C-H activation platforms have more recently been developed by the Yu and Dong groups involving palladium/norbornene cooperative catalysis (Scheme 1.2.6a, b).[62, 63] Both systems employ directing groups to mediate an initial *ortho*-C-H palladation (Scheme 1.2.6c, step I). However, before the resultant palladium complex can be functionalized with the aryl bromide, norbornene undergoes rapid insertion (step II), which is followed by a second C-H functionalization of the *meta*-C-H bond relative to the directing group (step III). The latter is favored by the generation of a stable 5-membered ring palladacycle. This intermediate can then react with aryl bromide through what is believed to involve a Pd(IV) intermediate (step IV) and eliminate the new C-C bond. At this stage, the sterically encumbered product is postulated to undergo a reverse, norbornene de-insertion (step V), in a similar fashion to Catellani chemistry,[64] to generate a palladium-aryl bond that reacts with acid to liberate the *meta*-substituted product (step VI). As such, the ability of the norbornene co-catalyst to insert and de-insert from the palladium-aryl bond allows for the high *meta*-selectivity (steps II and V). This palladium/norbornene platform for *meta*-C-H arylation has been expanded upon in recent years, resulting in tolerance of a greater variety of aryl iodides,[65-67] expansion of the scope of directing groups,[68-72] and has even been extended to the formation of chiral products.[73]



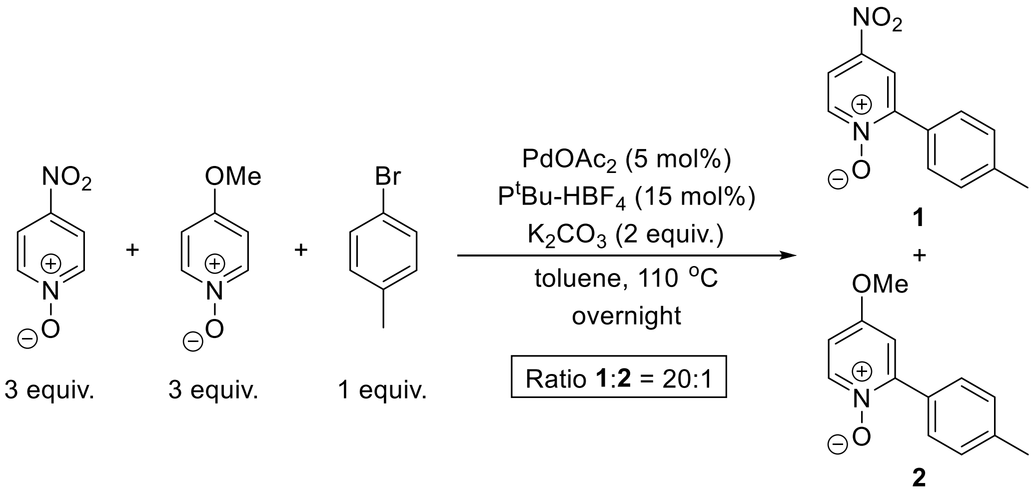
Scheme 1.2.6. Pd/Norbornene-Catalyzed Coupling of Aryl Iodides with Arenes.

Many of these initial reports on C-H arylation reactions invoke a mechanism wherein C-H bond cleavage occurs via an electrophilic aromatic substitution (S_EAr) process. However, early evidence suggested that this may not be the sole mechanism active in these systems. Miura described this in a 1998 paper on the palladium-catalyzed coupling of azoles with aryl halides (Scheme 1.2.7a).[74] After noticing that the products formed from the reaction typically followed the order of the reactive sites of azoles towards electrophilic substitution, the authors postulated that the regioselectivity arises from a mechanism wherein the azole is subject to an electrophilic attack by the (X)Pd(II)-aryl intermediate formed after oxidative addition. However, this paper also noted that certain substrates showed reactivity at positions that were not the most nucleophilic, but rather the positions with the most acidic C-H bond (Scheme 1.2.7b). Additionally, benzofuran and N-methylindole gave low yields of product despite being relatively more activated for electrophilic substitution. The authors suggested that acidity may influence regioselectivity in the arylation of these aromatic compounds, but did not expand further.



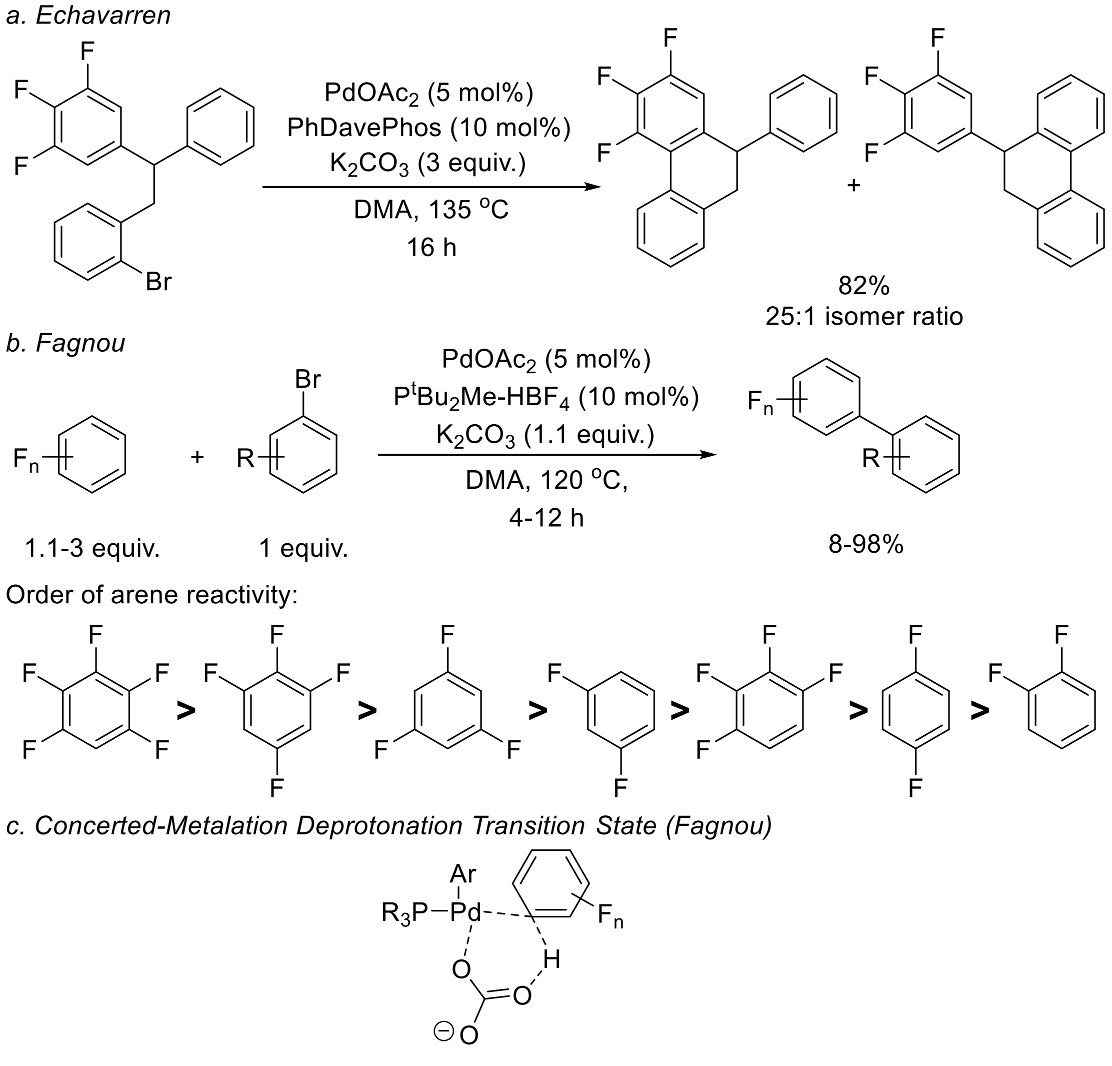
Scheme 1.2.7. Miura's Coupling of Azoles with Aryl Halides.

The seemingly important role of acidity in palladium-catalyzed C-H cleavage processes was also noticed by Fagnou in a 2005 paper on the direct arylation of pyridine N-oxides.[75] To determine whether an electrophilic aromatic substitution process was active in the functionalization of pyridine N-oxides, a competition experiment was conducted wherein both 4-nitropyridine N-oxide and 4-methoxypyridine N-oxide were reacted with 4-bromotoluene (Scheme 1.2.8). Unexpectedly, it was found that the preferred pathway of the reaction was arylation of the electron poor 4-nitropyridine N-oxide, in opposition to the expected outcome from a SEAr reaction.



Scheme 1.2.8. Competition Experiment Showing Opposite Selectivity as Expected for SEAr.

A more thorough study of the mechanism of this reaction came shortly afterward in publications by both the Echavarren and Fagnou groups in 2006. Echavarren showed, through experimental and computational studies on a palladium-catalyzed intramolecular arylation reaction, that product selectivity is inconsistent with a SEAr pathway as the reaction occurred preferentially with electron poor aryl fragments containing more acidic C-H bonds (Scheme 1.2.9a).[76] The authors concluded from their experiments that a proton-abstraction mechanism via a basic ligand most adequately explains the observed data. Fagnou more clearly established the role of acidity in his study on the direct intermolecular arylation of perfluorinated arenes (Scheme 1.2.9b).[77] Through competition experiments with various fluorinated arenes, they were able to clearly show a direct correlation between C-H bond acidity and reactivity. In addition, DFT studies showed that the most favorable pathway was through a concerted-metalation and proton abstraction mechanism – later dubbed concerted-metalation deprotonation – involving a palladium-coordinated carbonate base. The key step in this transformation involves a six-membered transition state with the palladium, the carbonate base, and the arene C-H bond (Scheme 1.2.9c). This seminal work led to greater understanding of the mechanism behind palladium-catalyzed direct arylation reactions and served as a strong rationale for the commonly required use of acetate derivatives or carbonates as bases/ligands in these reactions (*vide supra*), as these can adopt the favored 6-membered ring transition state for C-H bond cleavage.


a. Echavarren

b. Fagnou

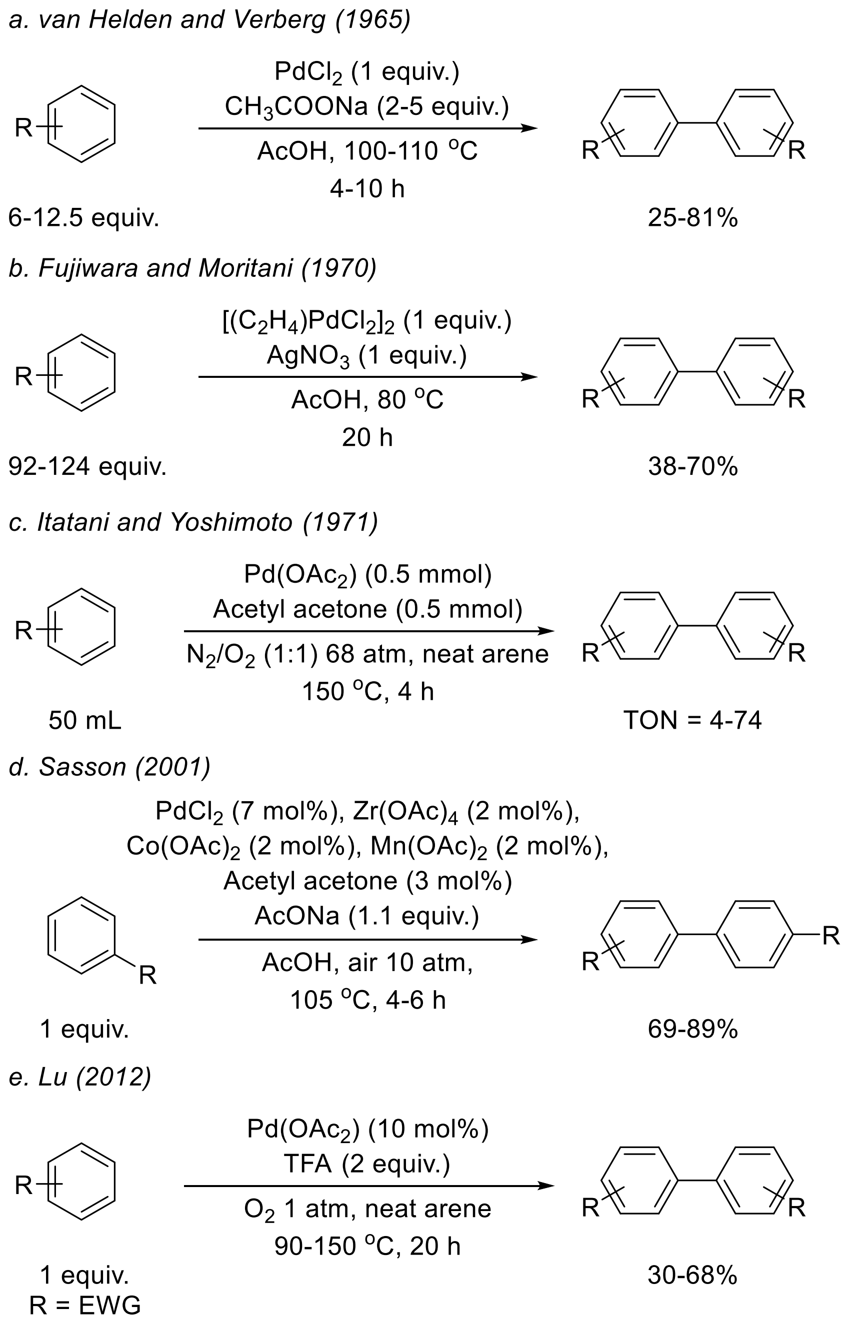
c. Concerted-Metalation Deprotonation Transition State (Fagnou)

Scheme 1.2.9. Initial Work Elucidating the CMD Mechanism in Palladium C-H Cleavage Processes.

1.3 Oxidative Double C-H Functionalization of Arenes

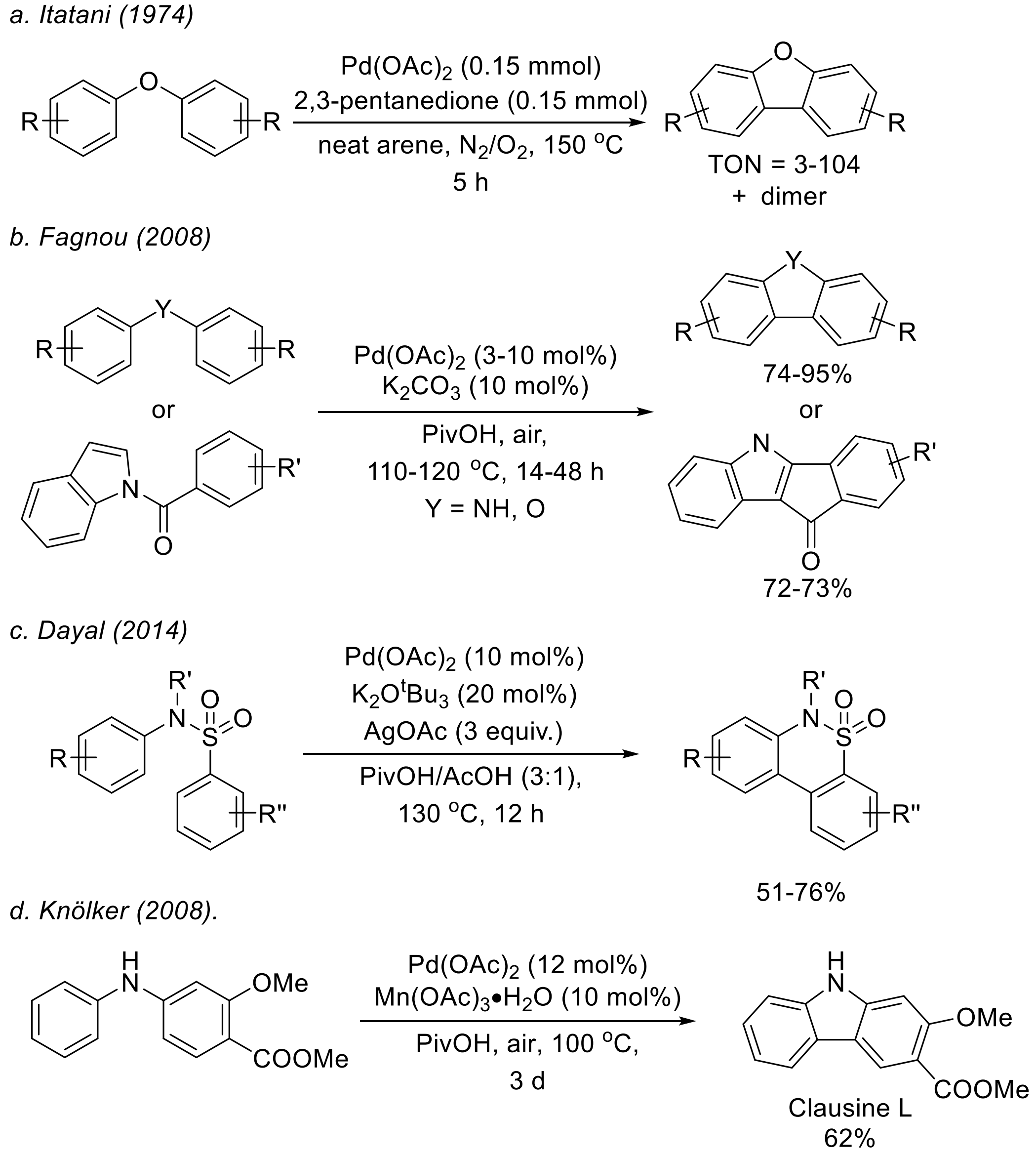
While direct arylation reactions involving the coupling of an unfunctionalized arene with an aryl halide are an area of intense interest, a more ambitious reaction class that has seen growing research efforts is to replace both pre-functionalized reagents in cross-coupling reactions with C-H bonds. Such transformations are commonly referred to as oxidative double C-H functionalization, or more simply oxidative C-H coupling. While appearing to be a straightforward extension of the reactions described in section 1.2, there are significant challenges associated with combining C-H functionalization events. These include how to achieve high reactivity and chemoselectivity with two different C-H bonds. Moreover, these reactions usually require a stoichiometric oxidant to regenerate the Pd(II) catalyst, which must not interfere with the bond functionalization operations.

Much of the early work investigating oxidative C-H coupling is limited to intermolecular homocoupling reactions using a large excess of arene reactants. One of the first examples of oxidative coupling of two aromatic C-H bonds via palladium salts dates back to research conducted by van Helden and Verberg in 1965.[78,79] In this work, the authors describe a protocol for the homocoupling of arenes to form biaryls with stoichiometric $PdCl_2$ at 100 °C (Scheme 1.3.1a). The biaryl products generated show selectivity mirroring that of a S_EAr mechanism. However, as noted above, this catalyst system involves the use of an acetate base, suggesting that a CMD pathway for the cleavage of both C-H bonds (Scheme 1.2.9) may be more likely for this transformation. Shortly thereafter, Fujiwara and Moritani reported a similar reaction involving the homocoupling of arenes mediated by an olefinic palladium chloride complex and silver nitrate (Scheme 1.3.1b).[80] The catalytic version of this reaction was reported by Yoshimoto using molecular oxygen as the oxidant, albeit in neat arene reagent (Scheme 1.3.1c).[81] Other intermolecular homocoupling reactions of simple arenes with palladium catalysts have been more recently reported, where lower pressures of oxygen and greater substrate diversity have been achieved (see Scheme 1.3.1d,e for examples).[82-88]



Scheme 1.3.1. Oxidative Homocoupling Reactions with Palladium.

In addition to intermolecular homocoupling reactions, the intramolecular oxidative coupling of arenes was shown to be viable by Itatani and co-workers in 1974 when they reported that biaryl ethers could be reacted to form dibenzofurans using palladium acetate as catalyst (Scheme 1.3.2a).[89] While this early work was done in neat substrate, subsequent studies have shown that oxidative C-H functionalization does not need an excess of arene reagent, can be applied to the generation of a range of cyclized aromatic compounds (Scheme 1.3.2b, c),[90-95] and has even been used in the synthesis of natural products and related compounds (e.g. Scheme 1.3.2d).[92, 96-101]


a. Itatani (1974)

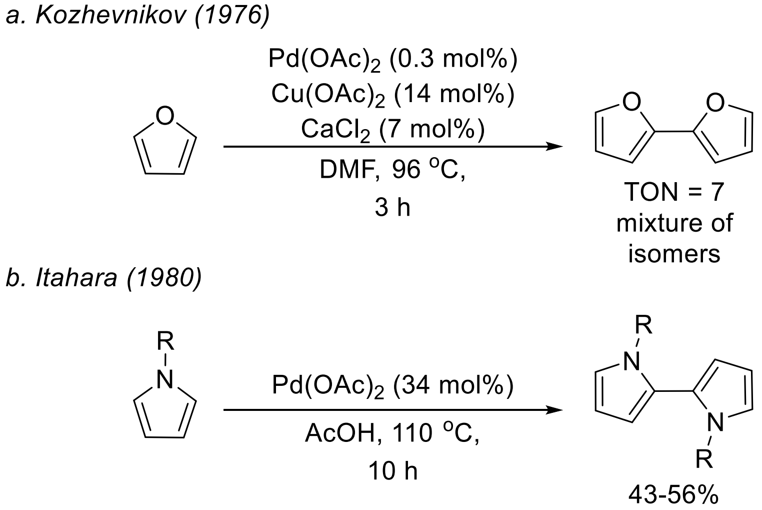
b. Fagnou (2008)

c. Dayal (2014)

d. Knölker (2008).

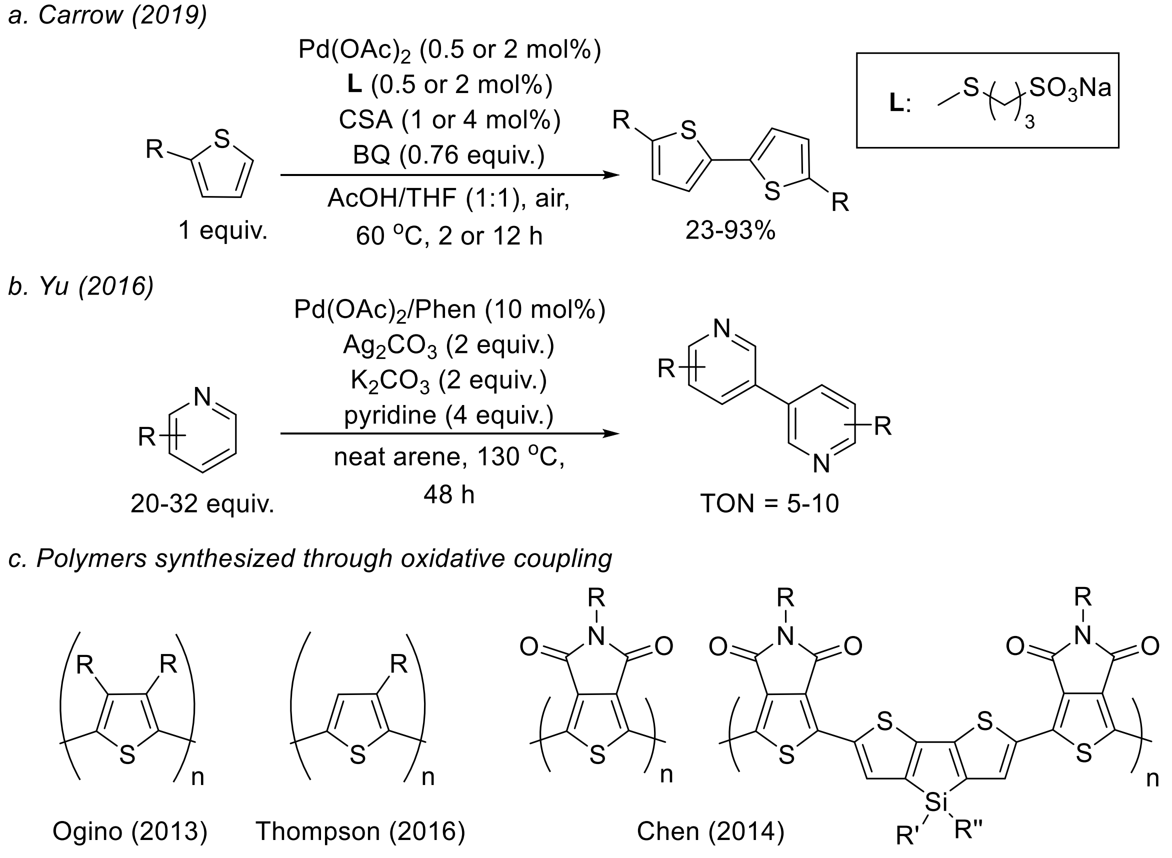
Scheme 1.3.2. Select Intramolecular Cyclizations through Double C-H Activation.

The palladium acetate catalyzed homocoupling of heteroarenes was also reported as early as 1976 by Kozhevnikov (Scheme 1.3.3a).[102] The coupling of furans and thiophene proceeded more readily than with other aromatic substrates, which was attributed to the more electron rich nature of the heterocycles. The homocoupling of pyrroles was reported shortly after in 1980 (Scheme 1.3.3b).[103]



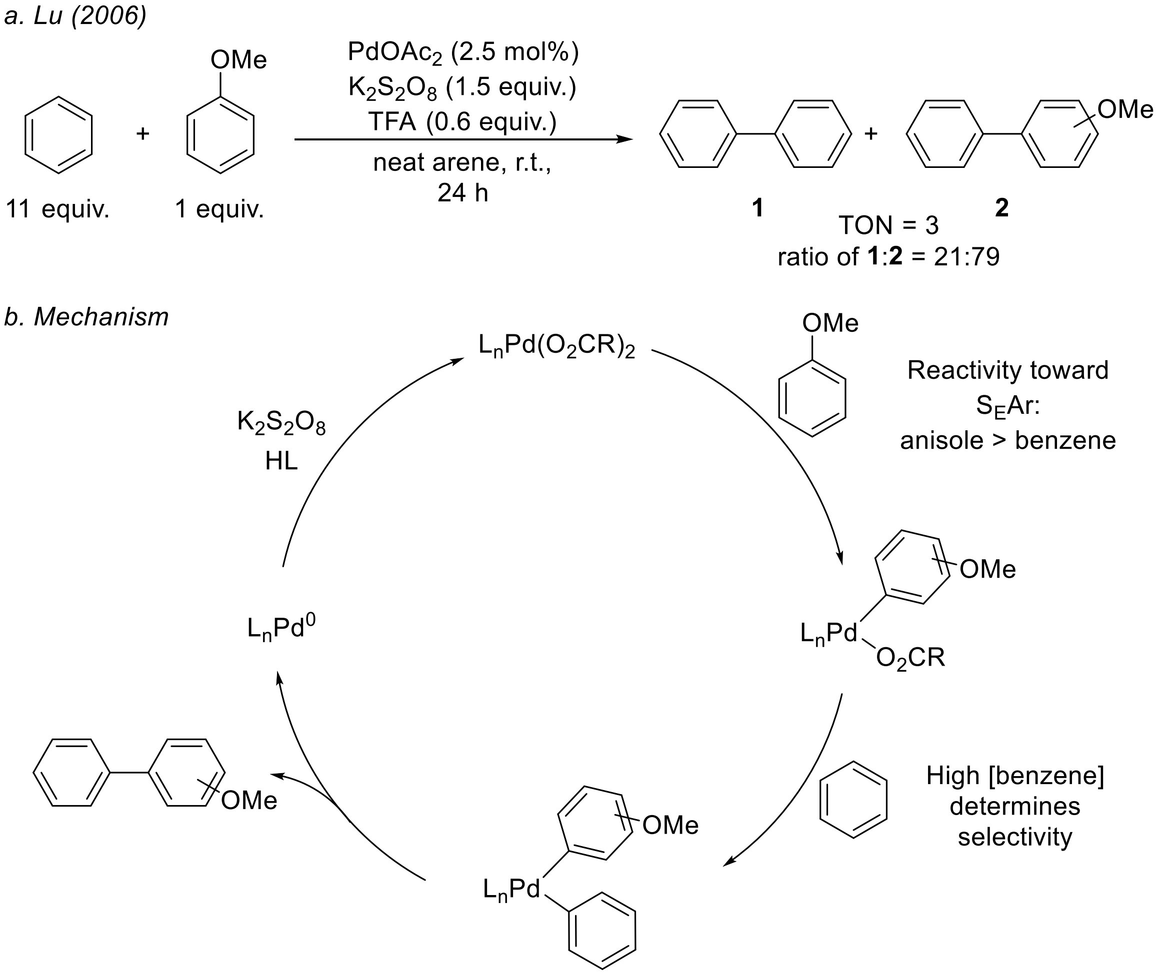
Scheme 1.3.3. First Examples of Catalytic Homocoupling of Heteroarenes.

The design of systems for the homocoupling of heterocycles, such as thiophenes (Scheme 1.3.4a)[104-106] and other N-based heterocycles (Scheme 1.3.4b),[107-110] has continued to be an area of interest. Palladium-catalyzed oxidative coupling has also been employed in the development of heteroarene polymerization reactions (Scheme 1.3.4c).[111-114]



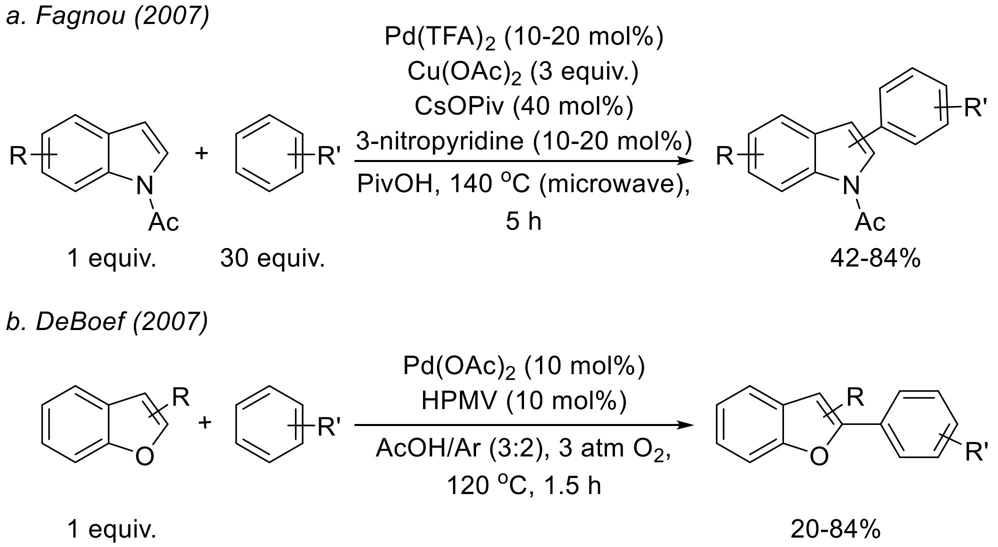
Scheme 1.3.4. Homocoupling of Heteroarenes and its Application to Polymer Synthesis.

Despite early success in the intermolecular homocoupling of (hetero)aromatics via palladium catalysis, the selective cross-coupling version of this reaction remained unknown until recently. In 2006, Lu and co-workers reported the low yield, palladium-catalyzed cross-coupling of two different arenes via careful tuning of arene concentrations (Scheme 1.3.5a).[115] The authors proposed that cross-coupling was achieved through changes in the palladium electronics during the reaction. In particular, the electron deficient $Pd(O_2CCF_3)_2$ catalyst is believed to react selectively with the most electron rich arene (e.g. anisole) to generate a mono-arylated intermediate (Scheme 1.3.5b). However, the resultant palladium intermediate is more electron rich, as it has a strong donor aryl-ligand, and is postulated to now selectively functionalize less electron rich benzene via a CMD pathway where deprotonation plays a more important role. The excess arene reagent accentuates this selectivity change. While the selectivity here is modest (80:20 ratio of products), the use of naphthalene instead of benzene resulted in complete chemoselectivity for the cross-coupled product.



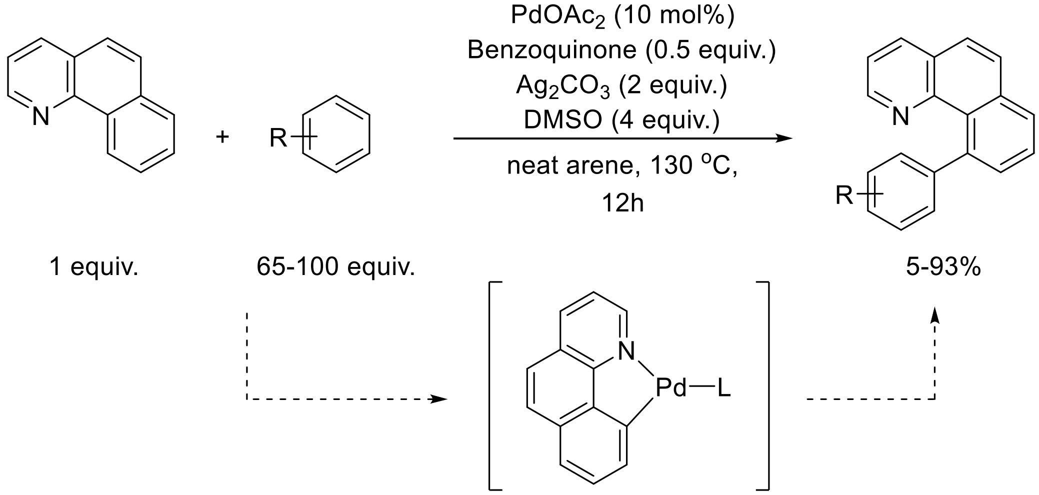
Scheme 1.3.5. Cross-Coupling of Unactivated Arenes by Lu.

An elegant advance in this area followed in 2007 when Fagnou reported the cross-coupling of indoles and arenes using $Pd(O_2CCF_3)_2$ catalyst (Scheme 1.3.6a).[116] This system showed no evidence of homocoupled products and, similar to the aforementioned example by Lu, took advantage of the differing reactivity of the palladium intermediates formed during the catalytic cycle. In particular, the initial electron deficient $Pd(O_2CCF_3)_2$ complex is believed to react with an indole via a S_EAr pathway, while the more electron rich palladium-indoyl intermediate formed can undergo a CMD pathway with a simple arene that is present in excess. Almost concurrently, DeBoef also reported a selective method for the cross-coupling of indoles and benzofurans with arenes (Scheme 1.3.6b).[117] This system used molecular oxygen and HPMV as co-oxidants and resulted in moderate yields of cross-coupled product.



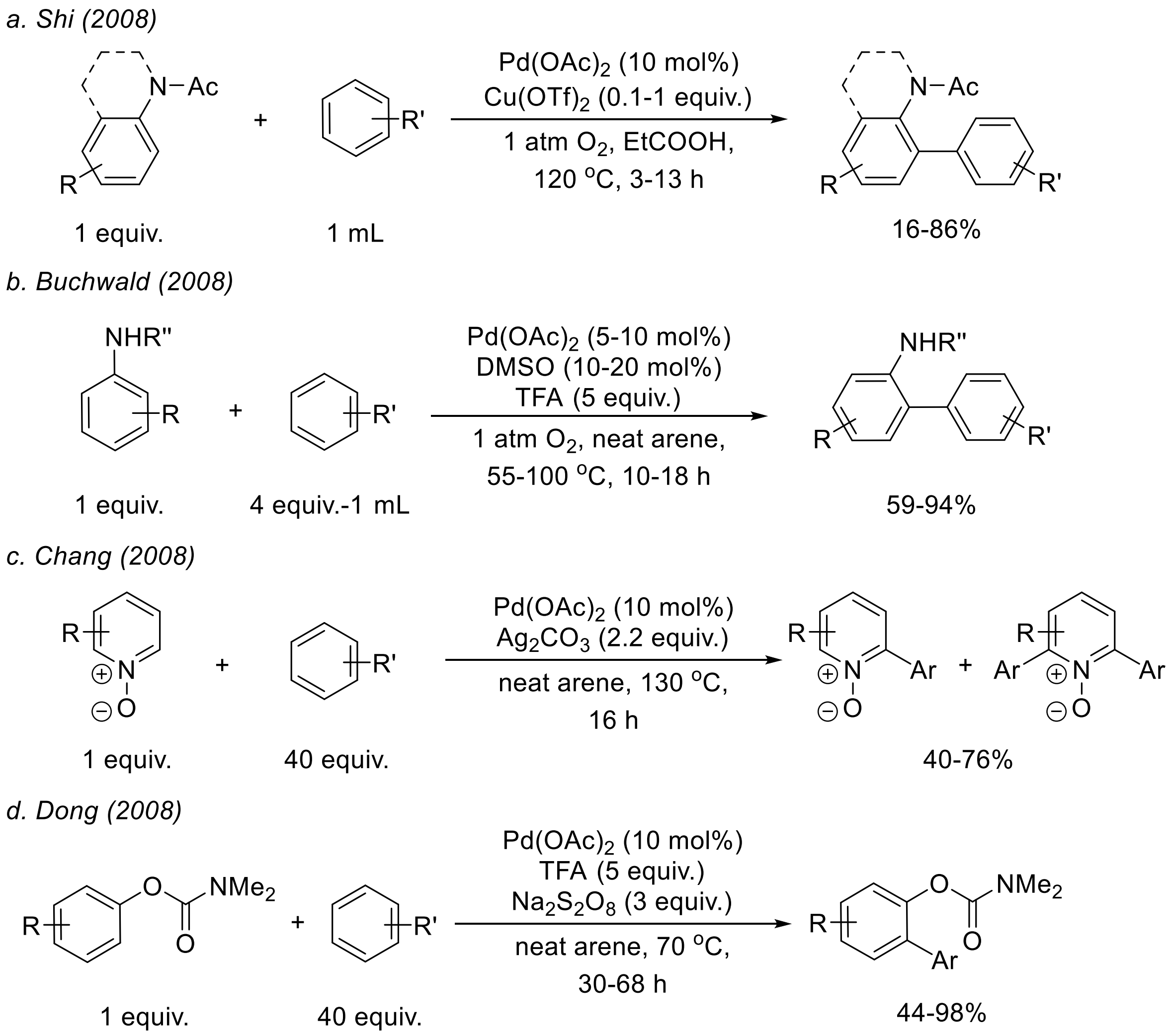
Scheme 1.3.6. Selective Cross-Coupling of Simple Arenes.

An alternative method to control both chemo- and regioselectivity in these palladium-catalyzed systems was reported by Sanford in 2007.[118] This paper described the $Pd(OAc)_2$ catalyzed selective coupling of benzo[*h*]quinoline with simple arenes (Scheme 1.3.7). The success of this coupling came from the realization that directing-group assisted C-H activation by palladium leads to palladacycle complexes that undergo a slower, second directing-group assisted C-H activation event, potentially due to the increased steric crowding on the palladium center. Instead, it is postulated that once the palladacycle forms, a more rapid second C-H activation of an arene occurs to form cross-coupled products. The regioselectivity of the arene functionalization was also found to be distinct from that of both S_EAr and CMD mechanisms, and later studies found that the varying the concentration of benzoquinone in the system allowed for tuning of selectivity in these systems, suggesting that this additive is directly involved in the C-H bond cleavage step.[119] Despite the novelty of the reaction, this system suffered from the requirement of solvent amounts of the simple arene coupling partner to achieve high yield. Nevertheless, this result was an important step forward, and demonstrated the utility of ligand-directed oxidative C-H functionalization for heterocoupling of arenes.



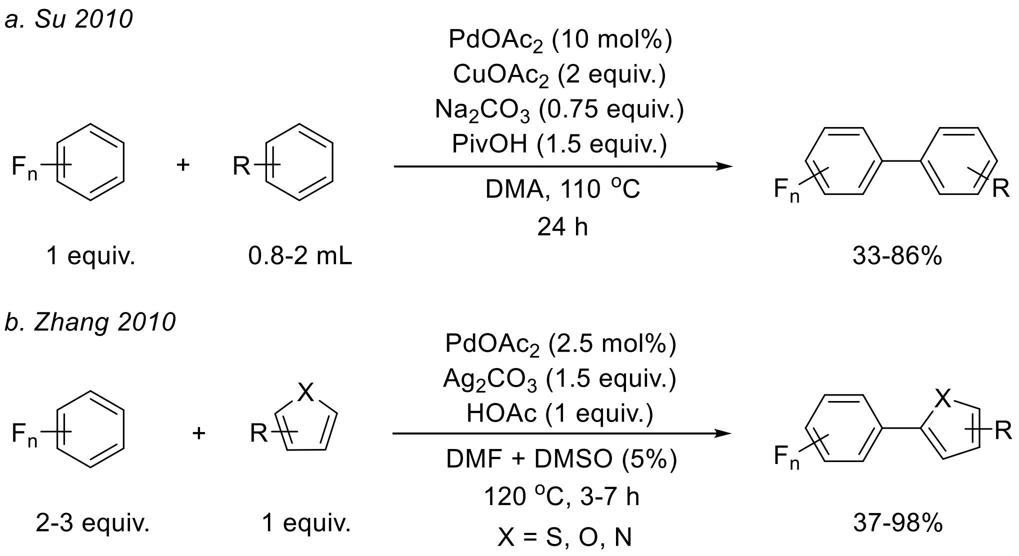
Scheme 1.3.7. Coupling of Benzo[*h*]quinoline with Simple Arenes.

Shi published a related directing-group assisted oxidative C-H coupling reaction shortly after the work of Sanford (Scheme 1.3.8a).[120] This reaction replaced the stoichiometric silver carbonate employed in Sanford's system with molecular oxygen as the terminal oxidant. Concurrently, Buchwald reported a system wherein oxygen could be used as the oxidant and did not require a copper co-catalyst, unlike the system reported by Shi (Scheme 1.3.8b).[121] The latter offers a route to couple anilides with simple arenes using only four equivalents of the arene and at relatively low reaction temperatures. Steric hindrance was found to play an important role in the regioselectivity of the second C-H activation step, a finding that is in agreement with previous work by Sanford.[118] In addition to these reports, pyridine N-oxides were found to be viable substrates for the directing-group assisted coupling of arenes by the Chang group in 2008 (Scheme 1.3.8c),[122] however, the system still required a large excess of the unactivated arene. Dong also contributed to the scope of aryl directing groups by showing that *O*-phenylcarbamates could be cross-coupled with an excess of unactivated arene at 70 °C (Scheme 1.3.8d).[123]



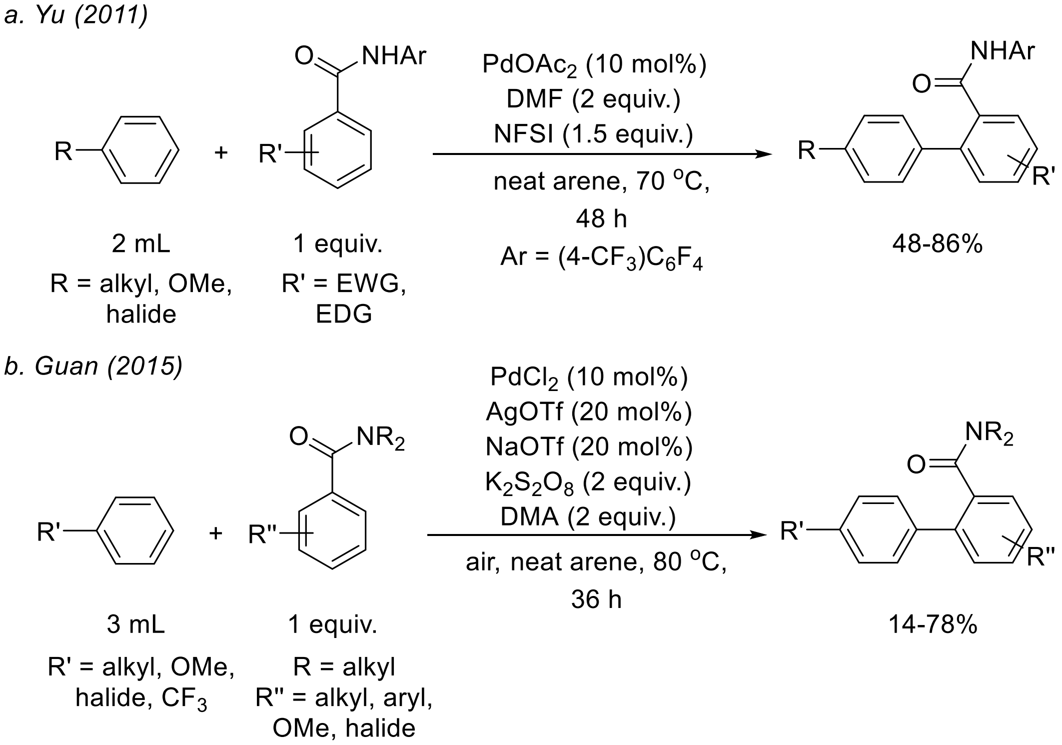
Scheme 1.3.8. Directing-Group Assisted Oxidative Coupling.

A step towards the selective cross-coupling of arenes themselves without utilizing directing groups was achieved in 2010 when Su showed that perfluorinated arenes could be coupled with simple arenes, albeit with a large excess of the second arene reagent (Scheme 1.3.9a).[124] Similar to that noted above (Scheme 1.3.5b), the differences in electronic nature of the two arenes is postulated to be responsible for the high chemoselectivity. That same year, Zhang and co-workers also reported the formation of perfluorinated biaryls through coupling of a polyfluorinated arene and a heteroarene (Scheme 1.3.9b).[125] Other work on the cross-coupling of arenes with perfluorinated arenes has been conducted by both Laali[126] and Lin.[127]



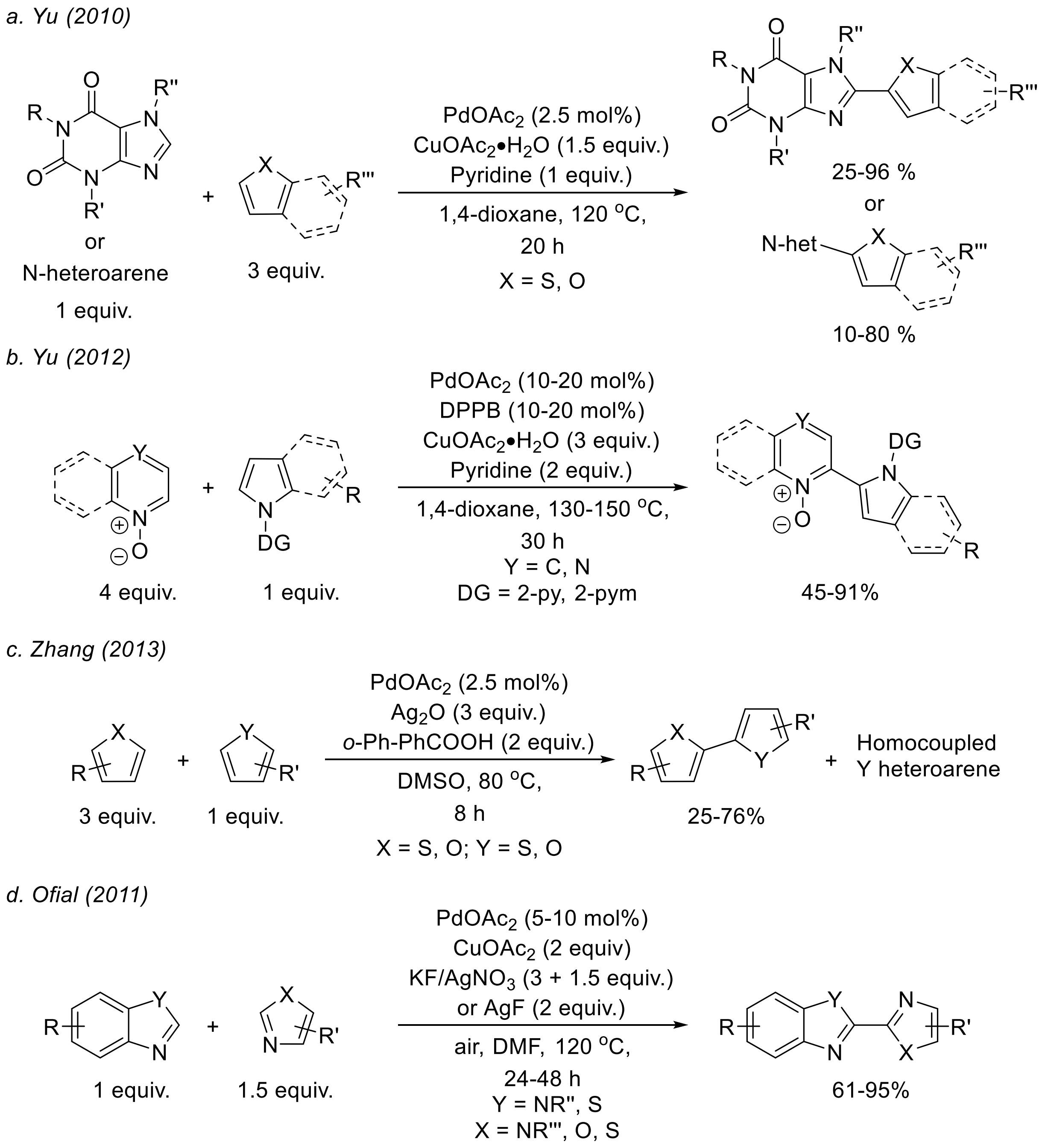
Scheme 1.3.9. Cross-Coupling of Perfluorinated Arenes and Simple Arenes.

One challenge that has plagued these oxidative C-H coupling reactions is that of poor regioselectivity when employing mono-substituted reagents. Yu reported in 2011 that this could be addressed by the addition of N-fluorobenzenesulfonimide (NFSI) as the oxidant, and judicious selection of directing group, which led to high *para*-selectivity (Scheme 1.3.10a).[128] KIE were conducted to probe the nature of the second C-H cleavage event and a k_H/k_D = 1.0 was found suggesting the electrophilic palladation of the arene, rather than C-H cleavage, was more important to this step. The authors postulate that the necessity of the F^+ reagent for selectivity suggests that the reaction proceeds via a [ArPd(IV)F] (Ar = benzamide) intermediate.[129-132] More recently, Guan also reported a system for the highly *para*-selective coupling of arenes that did not require the use of F^+ reagents, but was still postulated to proceed through the formation of a Pd(IV) species (Scheme 1.3.10b).[133] In both systems, the combination of mono-substituted arenes bearing *ortho*/*para*-directing groups with a potentially sterically hindered Pd(IV) species can explain the high *para*-selectivity observed.



Scheme 1.3.10. Coupling of Benzamides with Arenes to give High *para*-Regioselectivity.

The cross-coupling of two heteroarenes has also only recently been achieved. The first efficient and regioselective example of this came in 2010 when You reported the coupling of xanthines and N-heteroarenes with thiophenes and furans (Scheme 1.3.11a).[134] Of note, this system does not require solvent amounts of arene and was chemo- and regioselective. Like Fagnou's earlier report (*vide supra*),[116] the reaction is postulated to rely on an inherent switch in the reactivity of the catalyst from an initial S_EAr type activation of the electron rich heteroarene to a subsequent CMD mechanism for the second C-H activation. Subsequent reports of oxidative coupling of two heterocycles have shown success primarily with cross-coupling of electronically distinct heteroarenes (example: Scheme 1.3.11b).[135-137] However, there have been some reports published in recent years of selective cross-coupling of either two electron-rich (Scheme 1.3.11c)[138] or two electron-poor heteroarenes (Scheme 1.3.11d).[139, 140] These presumably rely upon more subtle electronic/steric differences (and concentration), and achieve selectivity via similar pathways to those noted above.



Scheme 1.3.11. Cross-Coupling of Heteroarenes through Double C-H Functionalization.

1.4 Carbonylative C-H Functionalization using Palladium Catalysis

Oxidative double C-H functionalization is a powerful technique for coupling arenes without requiring prior functionalization. While the biaryl products are useful, it could be advantageous to instead incorporate a reactive functionality such as carbon monoxide into these transformations to assemble ketones. Palladium-catalyzed carbonylative C-H functionalization is a well-known avenue for the formation of carboxylic acids and their derivatives (e.g. esters, anhydrides, amides), as illustrated in an early example of this reaction by Fujiwara (Figure 1.4.1).[141-153] However, much less work has been done on performing double C-H functionalization chemistry with carbon monoxide to assemble ketones. This has been attributed to the rapid reductive elimination of the palladium-acyl intermediate with the acetate bases that are often required for C-H functionalization. As such, these reactions typically lead to the build-up of either anhydrides or anhydride-derived products rather than the functionalization of a second C-H bond to access ketones

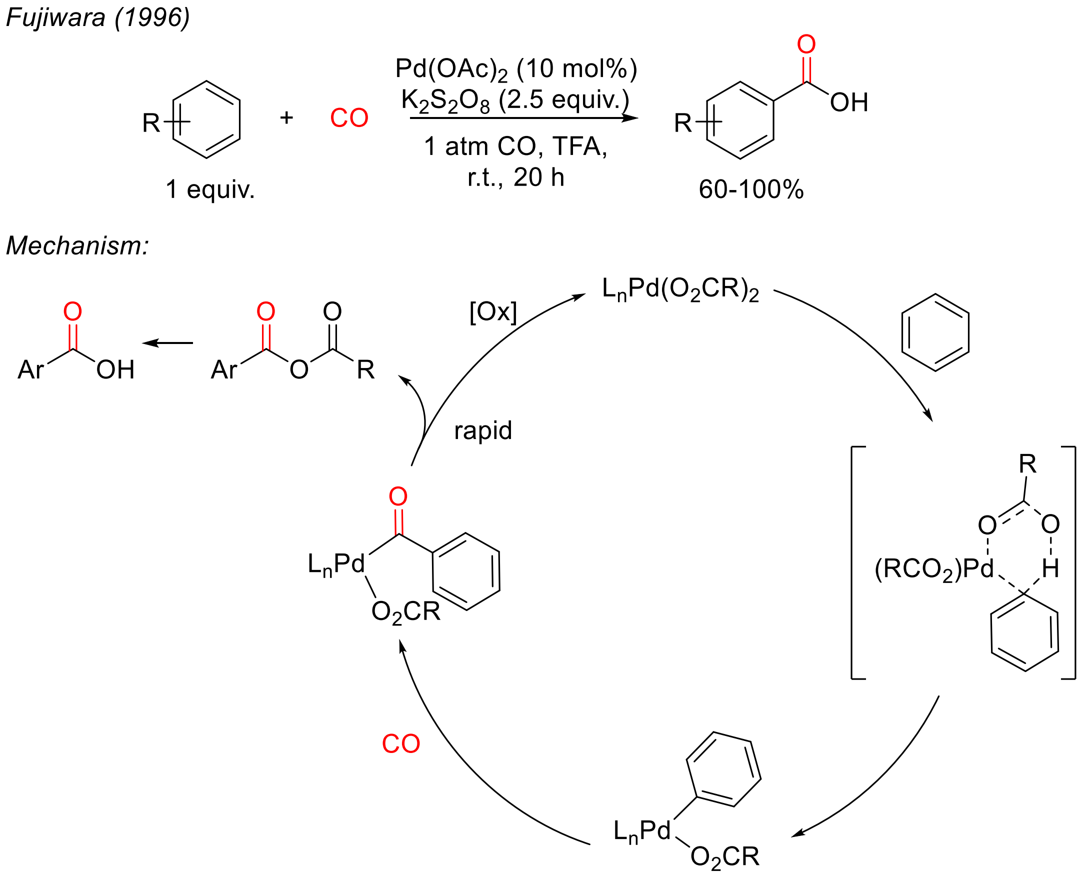
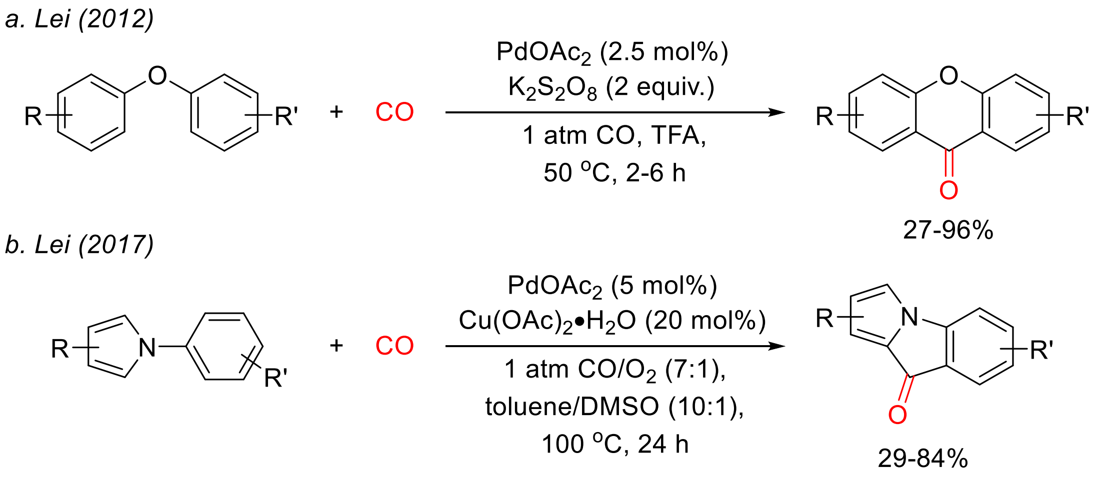


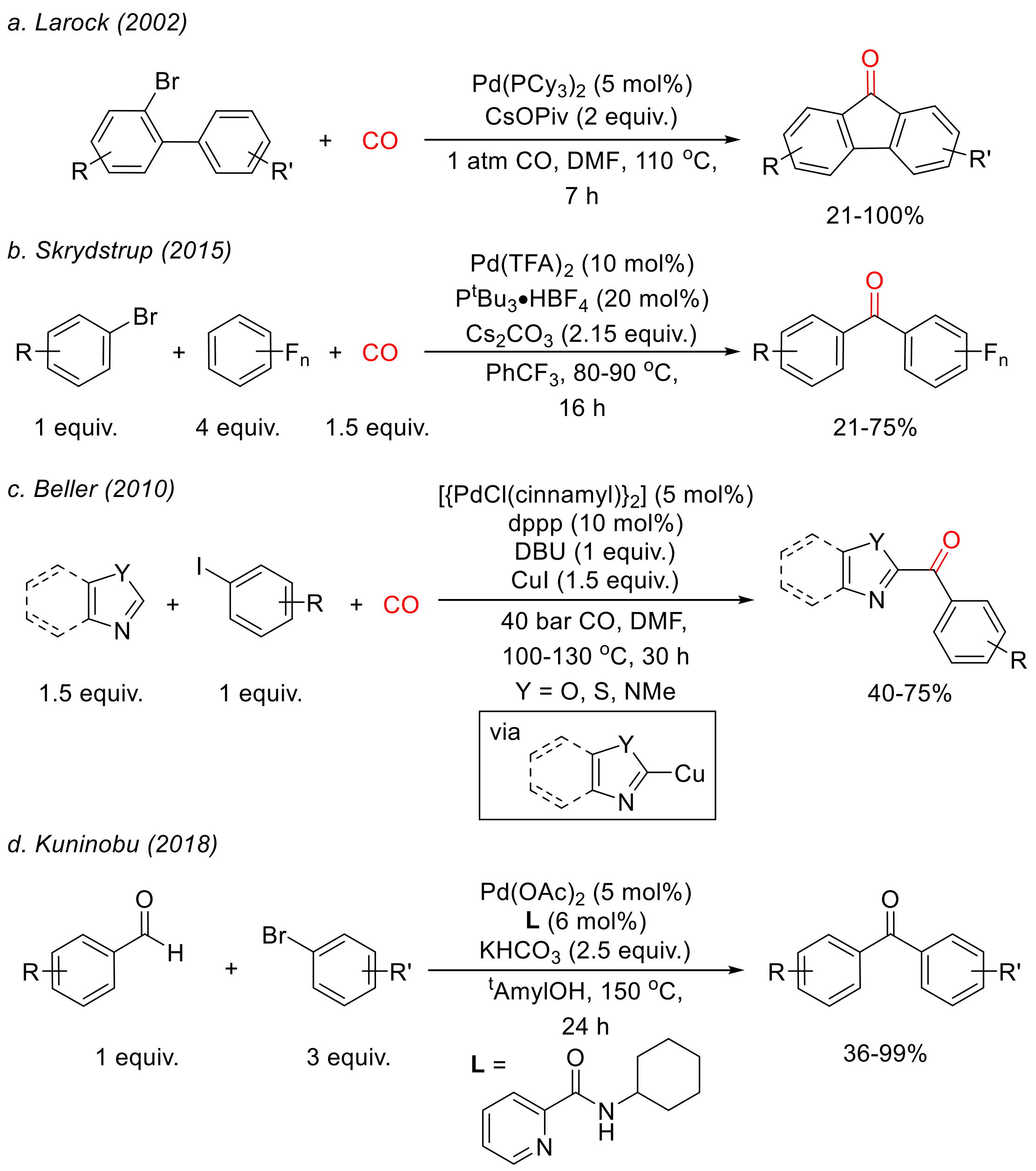
Figure 1.4.1. Preferred Reaction Pathway in Carbonylative C-H Functionalization.

The first example of a combined carbonylation/double C-H functionalization protocol was only reported in 2012 by Lei, and proceeds in an intramolecular fashion (Scheme 1.4.1a).[154] In this, biaryl ethers were carbonylated into xanthones under mild conditions and in up to 96% yield. The same group later followed with a second example of carbonylative double C-H functionalization in 2017 involving N-aryl pyrroles (Scheme 1.4.1b).[155] The success of these platforms presumably arises from the tethered arenes in the substrate. The proximity of the second C-H bond to the coordinated base can accelerate the second C-H activation and allow it to compete with anhydride formation.



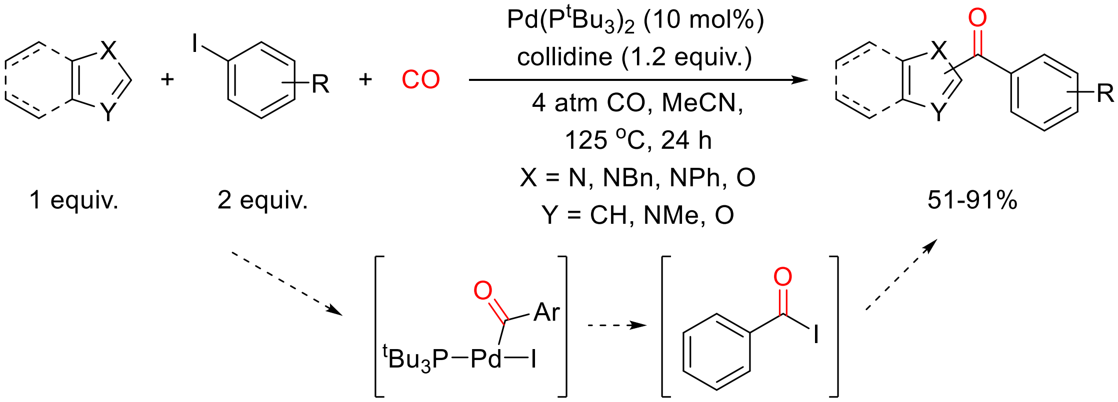
Scheme 1.4.1. Intramolecular Biaryl Coupling through Carbonylation of Two C-H Bonds.

As an alternative to double C-H functionalization, recent progress has been made in the carbonylative coupling of aryl halides with (hetero)arenes to form ketones. For example, Larock reported in 2002 that 2-bromobiaryl can undergo carbonylation to generate ketones (Scheme 1.4.2a).[156] Alternatively, Skrydstrup has shown that pefluoroarenes can undergo carbonylative coupling with aryl iodides (Scheme 1.4.2b),[157] and Beller has described a similar reaction using electron rich benzimidazoles and related heterocycles (Scheme 1.4.2c).[158] However, each of these systems are substrate specific and, in particular, use either intramolecular cyclization (Scheme 1.4.2a), highly acidic C-H bonds (Scheme 1.4.2b), or the use of stoichiometric copper co-catalysts to form a Cu-heteroarene compound (Scheme 1.4.2c) to successfully compete with anhydride formation. An alternative, non-carbonylative C-H functionalization platform for the formation of biaryl ketones that has been developed is the palladium-catalyzed reaction of aldehydes with aryl halides (Scheme 1.4.2d).[159-163]



Scheme 1.4.2. Strategies to form Ketones from CO or Aldehydes via C-H Functionalization.

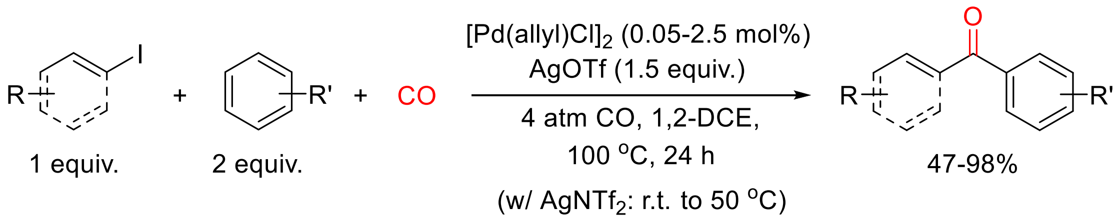
Our laboratory has recently reported a more general approach to carbonylative C-H functionalization for the assembly of ketones. These reactions invoke a different mechanism for C-H functionalization, where instead of relying upon palladium-acetate derivatives (e.g. via a CMD pathway), palladium catalysis is instead used to build-up potent acylating electrophiles that can subsequently react with (hetero)arene C-H bonds. Building upon our previously reported chemistry for the formation of aroyl chlorides,[164, 165] we showed that we could extend this chemistry to form aroyl iodides that can functionalize heterocycle C-H bonds (Scheme 1.4.3).[166] A variety of heterocycles could be acylated – including indoles, benzimidazoles, benzoxazoles, imidazoles, and furan – in good to excellent yield. This system relied on both CO pressure and the presence of the aryl iodide reactant as a palladium(0) trap to drive the reductive elimination of the highly reactive aroyl iodide species.



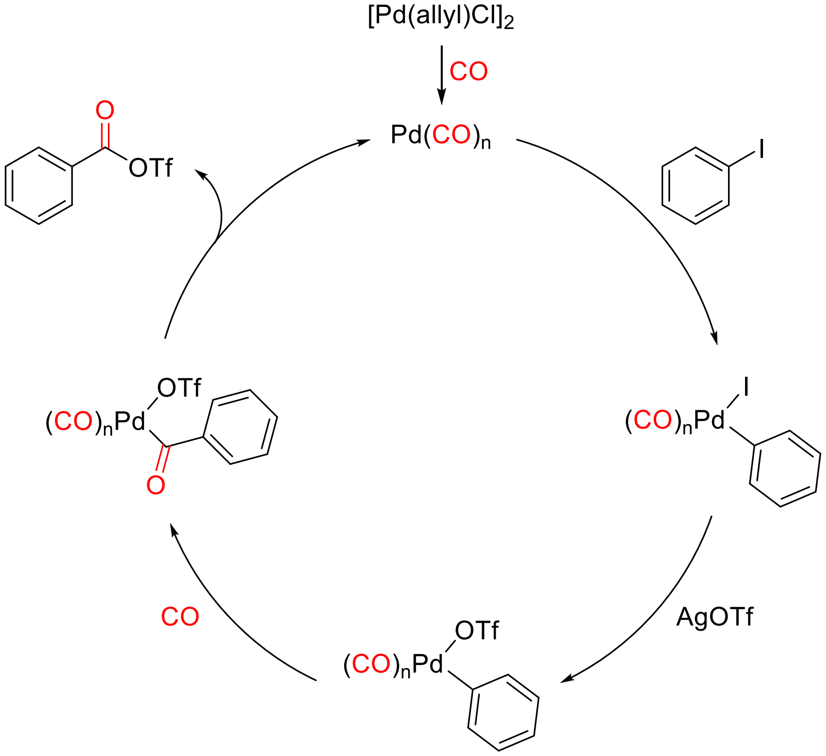
Scheme 1.4.3. C-H Functionalization of Heterocycles through Carbonylation Chemistry.

More recently, our lab has been able to extend this chemistry further by generating even more potent electrophiles – aroyl triflates and triflimides (Scheme 1.4.4a).[167] Key to the success of this reaction was the unligated palladium catalyst that, upon exposure to CO and aryl iodide, forms a highly electron deficient CO-ligated palladium-acyl intermediate that rapidly eliminates aroyl triflate (Scheme 1.4.4b). The electrophilicity of these acylating reagents allowed for simple arenes to be functionalized to form ketones in addition to heteroarenes. Furthermore, vinyl iodides could be used as substrates to form α,β-unsaturated ketones. While this system allows for the C-H functionalization of even simple arenes without need for activation or the presence of a directing group, it still requires the use of synthetic aryl or vinyl iodide reagents. As will be discussed in Chapter 2, this led us to question if we could design a catalytic system wherein neither arene coupling partner is pre-functionalized, resulting in a carbonylative double C-H functionalization platform.

a. Arndtsen (2018)



b. Mechanism



Scheme 1.4.4. Synthesis of Ketones via Acyl Electrophiles.

1.5 Overview of the Thesis

Palladium-catalyzed C-H bond functionalization can offer an efficient alternative to cross-coupling chemistry for the construction of C-C bonds, where these products are instead generated directly from arene(s) and without the need for pre-functionalization of one or both of the substrates. As discussed in sections 1.2 and 1.3, the replacement of one, or even two of these pre-functionalized arene substrates with simple C-H bonds can be achieved with palladium catalysis. While the construction of these robust aryl-aryl bonds is important, a useful extension of this platform would be the inclusion of a reactive functionality that can give products which are easily derivatized. Carbon monoxide represents an attractive reagent for such transformations, since it is both broadly available, and leads to the synthesis of ketones which are among the most heavily exploited substrates in organic chemistry. However, the incorporation of carbon monoxide into palladium-catalyzed, intermolecular double C-H functionalization reactions to form aryl ketones has to date represented an unmet challenge (section 1.4).

Chapter 2 demonstrates how this can be addressed. Namely, that a simple, unligated palladium complex, in combination with an iodine oxidant and silver triflate, is found to catalyze the formation of aryl ketones directly from two arenes and carbon monoxide. This transformation proceeds via the *in situ* generation of both aryl iodide and aroyl triflate intermediates, with the latter undergoing Friedel-Crafts acylation of a second arene, and can be performed in either a single operation or two steps to allow the assembly of cross-coupled ketones. Overall, this research shows how biaryl ketones can be assembled from their most fundamental building blocks, two arenes and CO, and illustrates how two distinct palladium-catalyzed platforms, C-H functionalization and carbonylation, can be combined.

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Chapter 2. A Palladium-Catalyzed C-H Functionalization Route to Ketones via the Oxidative Coupling of Arenes with Carbon Monoxide

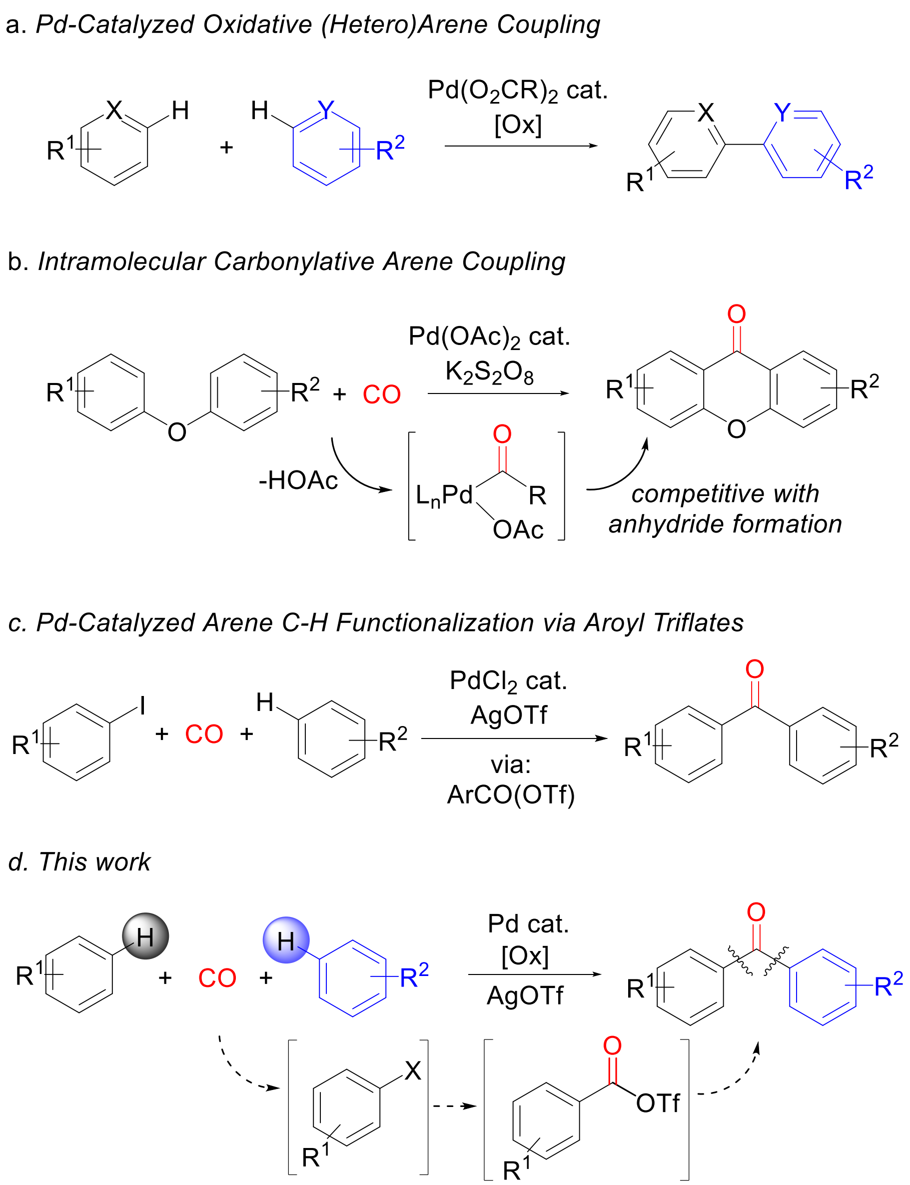
2.1 Preface

As described in Chapter 1, few platforms exist for the carbonylative double C-H functionalization of arenes to form ketones, and those that have been reported are limited to intramolecular cyclization reactions. Previous work in our research group on the *in situ* build-up of potent acylating reagents such as aroyl triflates from aryl iodides led us to question if this chemistry could be extended such that simple, unfunctionalized arenes could be employed. The research described in this chapter details our efforts towards the design of such a transformation. This has led to the discovery that simple palladium sources such as $PdCl_2$ or $[Pd(allyl)Cl]_2$ in concert with an iodine oxidant and silver triflate can catalyze the coupling of arenes or heteroarenes with carbon monoxide to form aryl ketones. This platform demonstrates how double C-H bond functionalization can be coupled with carbonylation by taking advantage of the palladium-catalyzed build-up of aroyl triflate electrophiles. The following chapter is a manuscript that we have prepared detailing this research and is currently in submission. R. Garrison Kinney, a PhD student in the Arndtsen lab, performed an initial screening of oxidants for this reaction. All results detailed in this chapter, however, were performed by me.

2.2 Introduction

Metal-catalyzed arene C-H bond functionalization has emerged as a powerful technique for the efficient and atom-economical build-up of organic products from feedstock chemicals.[1] A particularly powerful variant of these reactions is to form carbon-carbon bonds from the oxidative coupling of two separate C-H bond containing substrates.[2] In contrast to classical synthetic methods employing pre-functionalized substrates (e.g. cross-coupling reactions), this strategy offers a platform to assemble biaryls and related structures directly from arenes with high step efficiency and minimal waste (Figure 2.2.1a).[3] A useful variant would be to perform these in concert with reactive units such as carbon monoxide. Carbon monoxide is a broadly available C1 building block, and its coupling with organic fragments leads to the formation of valuable carbonyl-containing products.[4] Moreover, unlike inert aryl-aryl bonds, carbonyl derivatives such as ketones number among the most synthetically versatile functionalities in organic chemistry. The palladium-catalyzed carbonylative functionalization of aryl or even alkyl C-H bonds is well established, and dates back to early work by Fujiwara and others.[5] However, these reactions commonly lead to carboxylic acids or their derivatives (e.g. esters, amides), and are rarely applicable to the assembly of ketones.[6] This limitation has been attributed in part to the favored reaction of Pd-acyl intermediates with the carboxylate ligands that are often required for the C-H palladation step, therefore leading instead to the formation of anhydrides.[7] As shown by Lei, this can be avoided by performing oxidative C-H functionalization in an intramolecular fashion (Figure 2.2.1b).[8] Nevertheless, the ability to assemble aryl ketones via the simple coupling of its two most fundamental building blocks, arenes and carbon monoxide, has to date presented an unmet challenge.[9,10]

We have recently described an alternative approach to carbonylative C-H functionalization, wherein palladium catalysts can mediate the *in situ* formation of reactive aroyl electrophiles such as acyl iodides and even acyl triflates.[11] The latter have the ability to react with unactivated arenes and allowed the development of a carbonylative method to functionalize arenes to form ketones (Figure 2.2.1c). In considering this chemistry, we questioned if this approach could be taken even further and offer a pathway to perform carbonylative arene/arene coupling with carbon monoxide. In principle, this might be accomplished by devising a method to replace aryl iodides with an oxidative carbonylative platform to convert arenes themselves to high energy acyl triflate electrophiles (Figure 2.2.1d). We describe herein our studies towards such a system. This has led to the discovery of the first metal-catalyzed route to assemble ketones directly from two arenes and carbon monoxide. Mechanistic studies suggest this reaction proceeds via the *in situ* halogenation of arenes followed by aroyl triflate formation. Exploitation of this has opened an additional pathway wherein this chemistry can be performed in a stepwise fashion to create heterocoupled ketones from two separate aromatic fragments.



a. *Pd-Catalyzed Oxidative (Hetero)Arene Coupling*

b. *Intramolecular Carbonylative Arene Coupling*

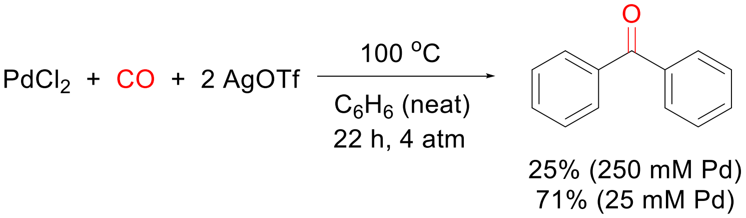
c. *Pd-Catalyzed Arene C-H Functionalization via Aroyl Triflates*

d. *This work*

Figure 2.2.1. Approaches to Intra- and Intermolecular Oxidative C-H Functionalization and Application to Ketone Synthesis.

2.3 Results and Discussion

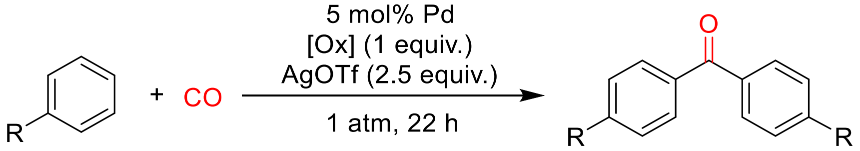
Our research on this topic was initiated by a question of palladium catalyst activation. We have previously reported that the Pd(0)-catalyzed carbonylative formation of aroyl triflate electrophiles from aryl iodides can be performed using $PdCl_2$ and related Pd(II) sources as the catalyst precursor.[11d] While carbon monoxide is established to reduce Pd(II) to Pd(0),[12,13] this often occurs in the presence of nucleophiles (e.g. water) to trap the oxidized carbon monoxide fragment. As the reaction conditions did not include an obvious nucleophile, or even a dative ligand (e.g. phosphines), it is unclear how a catalyst precursor such as $PdCl_2$ is reduced. To probe this, the stoichiometric reaction of $PdCl_2$ with carbon monoxide and AgOTf was examined in benzene. To our surprise, this leads to the formation of an aromatic product, benzophenone, in up to 71% yield at elevated temperatures (100 °C, Scheme 2.3.1).



Scheme 2.3.1. Generation of Benzophenone via Stoichiometric, $PdCl_2$-mediated Arene/CO Coupling.

The ability of metal salts such as $PdCl_2$ to mediate the oxidative carbonylation of arenes to ketones is to our knowledge unknown.[13] While there are several pathways by which this stoichiometric reaction may occur (*vide infra*), the formal by-product of this reaction is Pd(0), suggesting that a suitable oxidant may transform this stoichiometric chemistry into a catalytic route to form aryl ketones. As shown in Table 2.3.1, the addition of various metal salt oxidants that are commonly employed in related oxidative coupling chemistry to the reaction of benzene and CO with 10 mol% $PdCl_2$ catalyst leads to minimal reaction (entries 1-3), and also inhibits the stoichiometric formation of benzophenone. However, we were pleased to find that simple iodine is an effective oxidant and allows the catalytic formation of benzophenone in good yield (79%, entry 4). Further experimentation showed that the reaction does not require the use of arene as solvent and proceeds in high yield with only a small excess of arene in 1,2-dichloroethane (92%, entry 5) and at temperatures as low as 60 °C with 1 atm CO (entries 6, 22-25). Simple $[Pd(allyl)Cl]_2$ is the most effective catalytic precursor under these conditions (entry 25), and the reaction can be performed with as little as 0.1 mol% $[Pd(allyl)Cl]_2$ at elevated temperatures (entry 26).

Table 2.3.1. Development of Conditions for Carbonylative Homocoupling of Arenes.



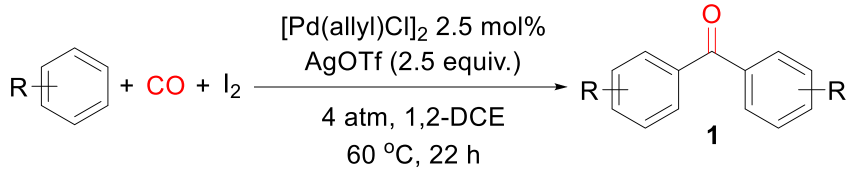
Entry	Pd Cat.	Ligand	Temp.	Solvent	[Ox]	Yield (%)
1[a]	$PdCl_2$	-	100 °C	C_6H_6	$Ce(OTf)_4$	0
2[a]	$PdCl_2$	-	100 °C	C_6H_6	$Na_2S_2O_8$	2
3[a]	$PdCl_2$	-	100 °C	C_6H_6	$CuCl_2$	4
4[a]	$PdCl_2$	-	100 °C	C_6H_6	I_2	79
5[a]	$PdCl_2$	-	100 °C	1,2-DCE	I_2	92
6	$PdCl_2$	-	60 °C	1,2-DCE	I_2	23
7	$PdCl_2$	-	30 °C	1,2-DCE	I_2	3
8	$Pd(OAc)_2$	-	30 °C	1,2-DCE	I_2	9
9	Pd Black	-	30 °C	1,2-DCE	I_2	16
10	$Pd_2(dba)_3$•$CHCl_3$	-	30 °C	1,2-DCE	I_2	33
11	PdI_2	-	30 °C	1,2-DCE	I_2	1
12	$(^tBu_3P)PdCl(C(O)$*p*-tol)	-	30 °C	1,2-DCE	I_2	13
13	$[Pd(allyl)Cl]_2$	-	30 °C	1,2-DCE	I_2	60
14	$[Pd(allyl)Cl]_2$	-	30 °C	NO_2Me	I_2	5
15	$[Pd(allyl)Cl]_2$	-	30 °C	DCM	I_2	49
16	$[Pd(allyl)Cl]_2$	PPh_3[b]	30 °C	1,2-DCE	I_2	28
17	$[Pd(allyl)Cl]_2$	P^tBu_3[b]	30 °C	1,2-DCE	I_2	3
18	$[Pd(allyl)Cl]_2$	Xantphos[b]	30 °C	1,2-DCE	I_2	12
19	$[Pd(allyl)Cl]_2$	$P(C_6F_5)_3$[b]	40 °C	1,2-DCE	I_2	31
20	$[Pd(allyl)Cl]_2$	-	40 °C	1,2-DCE	I_2	70[c]
21	$[Pd(allyl)Cl]_2$	-	40 °C	1,2-DCE	I_2	80
22	$Pd(OAc)_2$	-	60 °C	1,2-DCE	I_2	60
23	$[Pd(allyl)Cl]_2$	PPh_3[b]	60 °C	1,2-DCE	I_2	78

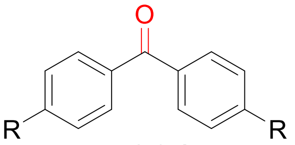
24	[Pd(allyl)Cl]$_2$	P^{t}Bu$_3$[b]	60 °C	1,2-DCE	I$_2$	57
25	[Pd(allyl)Cl]$_2$	-	60 °C	1,2-DCE	I$_2$	87 (93)[d]
26	[Pd(allyl)Cl]$_2$[e]	-	100 °C	1,2-DCE	I$_2$	72

Conditions: Arene (0.53 mmol), silver triflate (176 mg, 0.68 mmol), Ox (0.25 mmol), 5 mol% Pd, 1 atm CO, 22 h, R = ^{t}Bu. [a] 10 mol% Pd, 4 atm CO, R = H. [b] 10 mol%, Xantphos = 5 mol%. [c] 4 atm CO. [d] 3 equiv. arene. [e] 0.1 mol% [Pd(allyl)Cl]$_2$

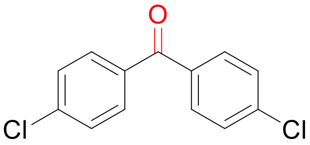
With a palladium-catalyzed method in hand to assemble ketones from arenes and carbon monoxide, we next turned to probing its generality. As shown in Table 2.3.2, various electron neutral and electron rich arenes can be employed in this reaction and form ketones in high yields. These include alkyl-substituted arenes (**2.3.1b**, **2.3.1c**, **2.3.1f**) as well as more electron rich anisole derivatives (**2.3.1i**, **2.3.1j**). In each of the mono-substituted arenes, we observed 4,4'-substituted ketones as the major isolated product, consistent with an electrophilic mechanism for functionalization. Electron deficient substrates, such as mono- and di-halogenated arenes, react under more pressing conditions to form ketones in neat arene (**2.3.1d**, **2.3.1e**, **2.3.1k**). More sterically hindered 1,3- and 1,4-di-substituted arenes can also be converted to ketones (**2.3.1f-h**, **2.3.1k**, **2.3.1l**). In these cases, functionalization proceeds again at the most electron rich site on the arene. This oxidative carbonylation can also be applied to the synthesis of ketones from heteroarenes, with examples including thiophenes (**2.3.1n**, **2.3.1o**), benzothiophene (**2.3.1m**), and N-tosyl pyrrole (**2.3.1p**). The addition of 2,6-^{t}butylpyridine base is required for these latter examples to inhibit substrate decomposition. Overall, this system offers a useful alternative to the use of synthetic aryl iodides in carbonylative ketone synthesis, where instead just arenes themselves can be used as reagents.

Table 2.3.2. Palladium-Catalyzed Oxidative Arene/CO/Arene Coupling to Form Symmetrical Ketones.

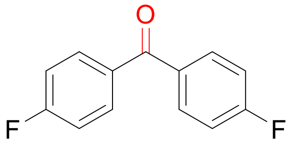




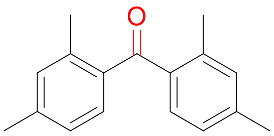
R = H, **2.3.1a** 78%
R = ^{t}Bu, **2.3.1b** 90%
R = Me, **2.3.1c** 91%



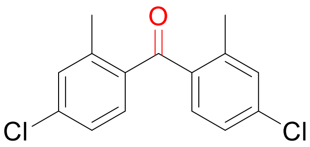
2.3.1d, 88%[a]



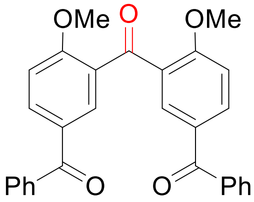
2.3.1e, 82%[a]



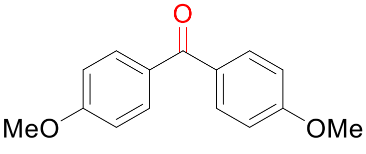
2.3.1f, 65%



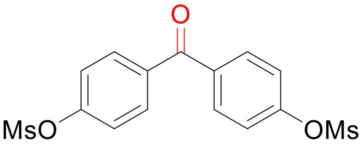
2.3.1g, 91%[b]



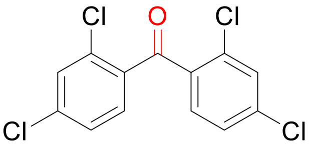
2.3.1h, 55%



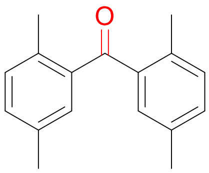
2.3.1i, 73%



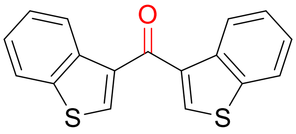
2.3.1j, 62%[b]



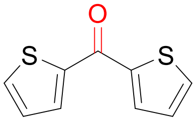
2.3.1k, 81%[a]



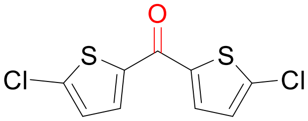
2.3.1l, 85%



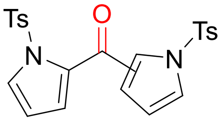
2.3.1m, 65%[c]



2.3.1n, 48%[c]



2.3.1o, 55%[c]

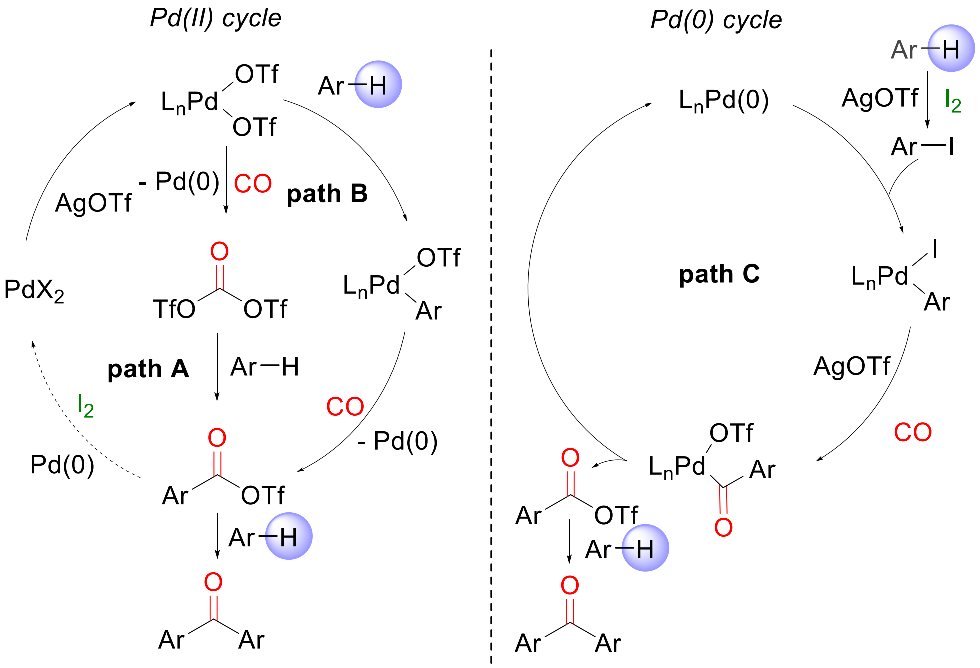


2.3.1p, 32%[c,d]

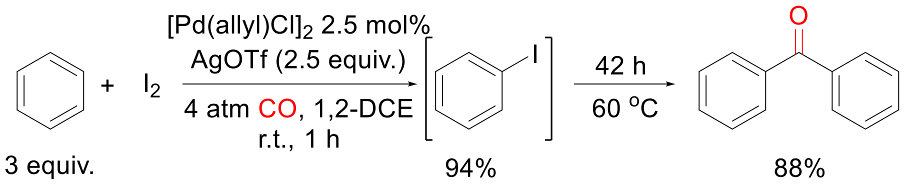
Conditions: Arene (1.50 mmol), silver triflate (350 mg, 1.36 mmol), I_2 (126 mg, 0.50 mmol), $[Pd(allyl)Cl]_2$ (5 mg, 0.013 mmol), 1,2-dichloroethane (2 mL), 4 atm CO, 22 h, 60 °C (see SI for details). Isolated Yield. [a] At 150 °C in arene solvent. [b] At 100 °C. [c] With 2,6-di-tert-butylpyridine (258 mL, 1.15 mmol). [d] 3:2 ratio of 3- to 2-substituted isomers.

The ability of simple palladium sources such as $[Pd(allyl)Cl]_2$ or $PdCl_2$ to catalyze the assembly of ketones directly from arenes and carbon monoxide is unusual, and next led us to probe how precisely this transformation proceeds. There are several viable pathways for this reaction. For example, the stoichiometric reaction of $PdCl_2$ (Scheme 2.3.1) suggests the potential *in situ* formation of phosgene equivalents upon reduction of Pd(II) by CO (Figure 2.3.1a, path A),[13] or the build-up of electrophilic Pd(II) triflate intermediates that may directly palladate arenes (path B).[14] These could each lead to aroyl triflate intermediates for subsequent Friedel-Crafts acylations,[11d] and are consistent with the regioselectivity in the ketone products formed. The re-oxidation of Pd(0) by I_2 would make these viable cycles for catalysis. However, iodine is established to react with arenes in the presence of silver triflate to form aryl iodides.[15] It is therefore possible that the catalytic arene carbonylation occurs via a Pd(0) cycle to form aroyl triflate products (path C). Monitoring the reaction by *in situ* ^{1}H and ^{13}C NMR analysis show that the latter mechanism is likely the case during catalysis, and we observe the rapid, high yield build-up of aryl iodide within 1 h under the catalytic conditions (Figure 2.3.1b, 94% yield). Continued heating converts this aryl iodide to ketone **2.3.1a**. Similarly, control experiments show that the AgOTf mediated iodination of the arene is rapid (30 min at r.t.), relative to catalytic ketone formation (23% after 22 h at r.t.; Figure 2.3.1c). Thus, while the stoichiometric experiments show that the direct reaction of Pd(II) with carbon monoxide and arenes is viable, in the presence of I_2 as oxidant these data suggest that the direct iodination is the more rapid (path C). The ability of this process to compete with oxidation of Pd(0) by I_2 presumably reflects the rapid rate of arene iodination relative to the slower carbonylation and build-up of Pd(0), as well as the ability of any *in situ* generated Pd(II) to re-enter the cycle via a palladium-based C-H functionalization pathway (paths A or B). The lack of potentially oxidizable donor ligands in the reaction further enhances this compatibility.

a. Possible Mechanistic Pathways



b. NMR Monitoring of Catalytic Reaction



c. Rate of Iodination and Carbonylation Reactions at Room Temperature

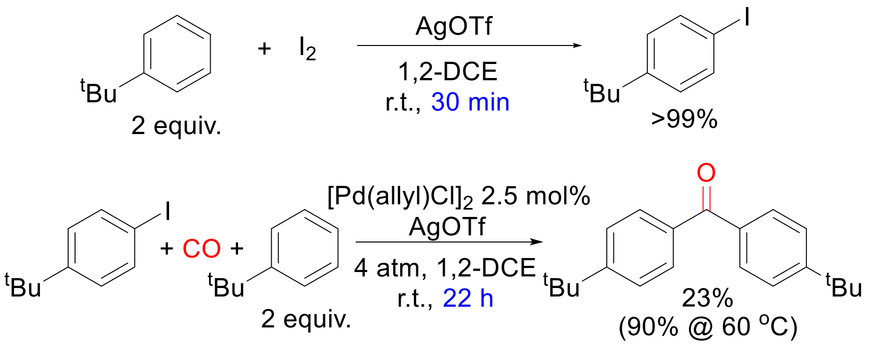
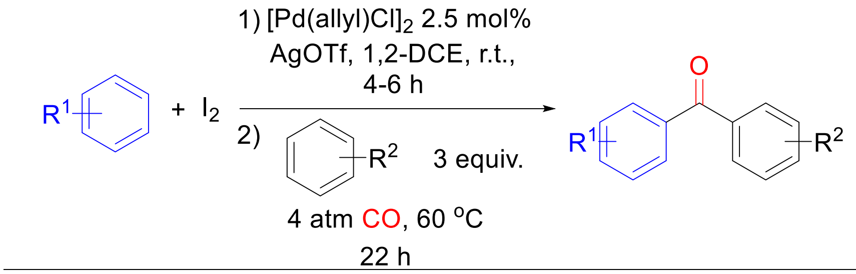
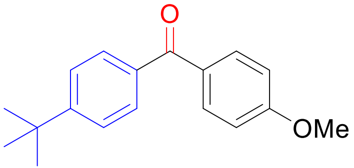


Figure 2.3.1. Mechanism of Catalytic Reaction, and Model Reactions.

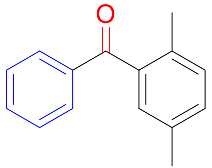
From a synthetic perspective, the generation of halogenated arene intermediates can have useful implications. Since these intermediates are formed more rapidly than carbonylation, the rate difference can be exploited to perform cross arene/arene coupling to build up more structurally diverse ketones. The latter can present a challenge with many oxidative arene/arene coupling reactions, and typically require significant differences in the electronic, steric, or coordinating ability of the two substrates.[2] After examination of various reaction conditions, we were pleased to find that the ambient temperature reaction of arene, $[Pd(allyl)Cl]_2$ catalyst, I_2, and AgOTf, followed by the subsequent addition of a second, more electron rich arene and carbon monoxide leads to the clean overall heterocoupling of arenes to ketones (Table 2.3.3). Both electron neutral and electron rich arenes can be easily cross-coupled to form unsymmetrical ketones in high yield, including sterically encumbered tetra-substituted arenes and an activated benzophenone (**2.3.2f**, **2.3.2h**, **2.3.2l**). Employing more pressing conditions allows for the use of deactivated arenes such as bromo- or dichlorobenzene (**2.3.2e**, **2.3.2g**), and does so without secondary activation of these carbon-halogen bonds. Thiophene, N-substituted pyrrole, and benzothiophene can also be incorporated into this reaction to create mixed (hetero)aryl ketones (**2.3.2k**, **2.3.2m**, **2.3.2n**).

Table 2.3.3. Palladium-Catalyzed Oxidative Arene/CO/Arene Coupling to Form Unsymmetrical Ketones.

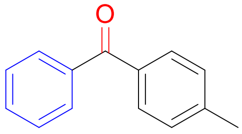




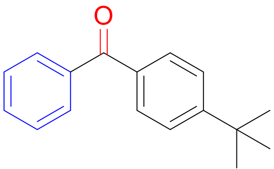
2.3.2a, 72%



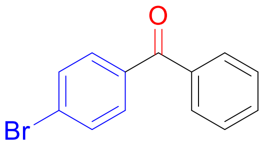
2.3.2b, 99%



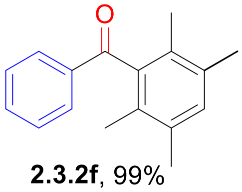
2.3.2c, 68%



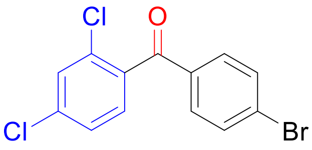
2.3.2d, 92%



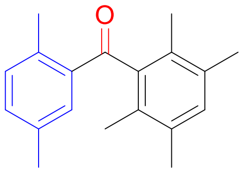
2.3.2e, 54%[a]



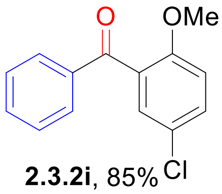
2.3.2f, 99%



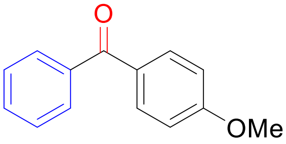
2.3.2g, 36%[b]



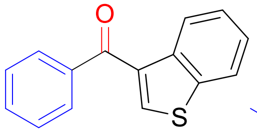
2.3.2h, 95%



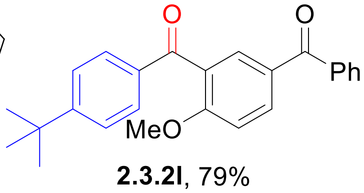
2.3.2i, 85%



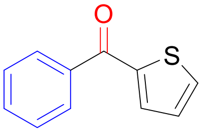
2.3.2j, 90%



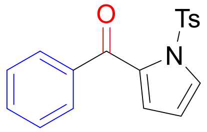
2.3.2k, 59%[c]



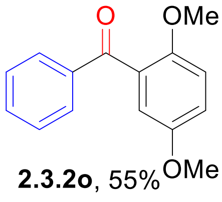
2.3.2l, 79%



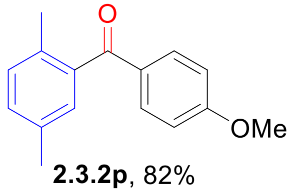
2.3.2m, 51%[c]



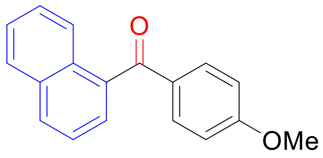
2.3.2n, 39%[c]



2.3.2o, 55%



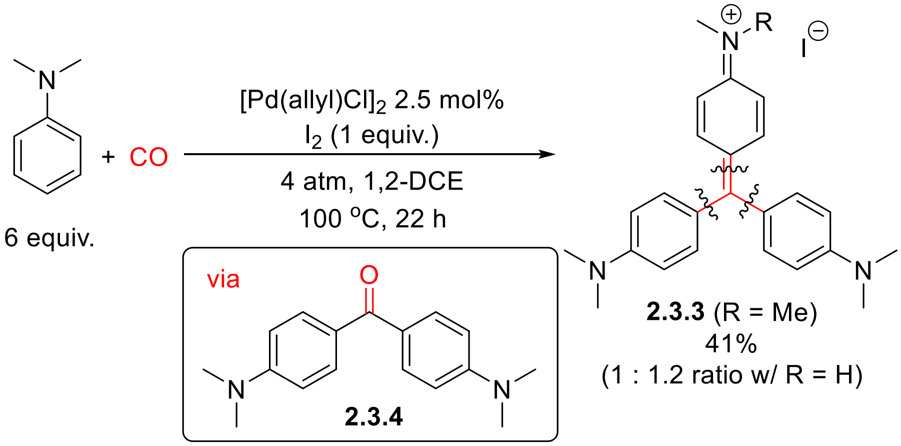
2.3.2p, 82%



2.3.2q, 72%

Conditions: Arene (1.00 mmol), silver triflate (339 mg, 1.32 mmol), I_2 (126 mg, 0.49 mmol), $[Pd(allyl)Cl]_2$ (5 mg, 0.013 mmol), 1,2-dichloroethane (2 mL), 4-6 h, r.t., then addition of second arene (1.50 mmol), 4 atm CO, 22 h, 60 °C (see SI for details). Isolated yields. [a] Both steps at 100 °C. [b] Step 1 at 100 °C, 22 h; step 2 at 150 °C with 10 eq. of bromobenzene (526 µL, 5.00 mmol). [c] With 2,6-di-tert-butylpyridine (258 mL, 1.15 mmol).

Finally, we have examined the use of this system to assemble more structurally elaborate products. For example, Crystal Violet (**2.3.3**, Scheme 2.3.2) is a common dye exploited in textiles and is most commonly generated starting from reactive, synthetic acylating agents (e.g. phosgene), in a sequence that proceeds through the initial build-up of ketone **2.3.4**.[16] As an alternative, the palladium-catalyzed oxidative carbonylation of *N,N*-dimethylaniline can offer a method to generate **2.3.3** together with its de-methylated isomer from the parent arene and carbon monoxide (Scheme 2.3.2). While **2.3.3** is generated in moderate yield (41%), it represents the product of three concurrent arene C-H bond functionalization steps. This reaction presumably proceeds via the initial generation of **2.3.4** that undergoes a spontaneous Friedel-Crafts reaction to liberate H_2O, which can also be trapped by the *in situ* generated aroyl electrophiles. As far as we are aware, this is the first synthesis of such an advanced structure directly from arenes and CO.



Scheme 2.3.2. Synthesis of Crystal Violet from Dimethylaniline and Carbon Monoxide.

2.4 Conclusions

In conclusion, we have described herein the first catalytic route to prepare ketones from arenes and CO. Mechanistic analysis suggests this transformation proceeds via the iodination of arene followed by the palladium-catalyzed, *in situ* generation of potent acylating electrophiles (acyl triflates). By manipulation of the reaction conditions, the transformation can be directed towards either symmetrical or unsymmetrical aryl ketones. Considering the broad utility of acylating electrophiles, we anticipate that the ability to access these intermediates from arenes could prove relevant to the design of various new approaches to carbonylative C-H functionalization.

2.5 Supporting Information

2.5.1. General Considerations

All manipulations were carried out 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 collected under nitrogen from a Solvent Purification System and stored over activated 4 Å molecular sieves. Deuterated solvents were dried over calcium hydride, vacuum transferred, and stored over activated 4 Å molecular sieves. 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 -36 °C. All other reagents were purchased from commercial suppliers and used as received after thoroughly drying to remove all traces of water. This was typically done by either dissolving solids and storing over 4 Å molecular sieves overnight before filtration and removal of solvent to yield solid that is dried under vacuum overnight, or by removing oxygen from liquids via freeze-pump-thaw techniques and subsequent storage over 4 Å molecular sieves. ^1H 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.

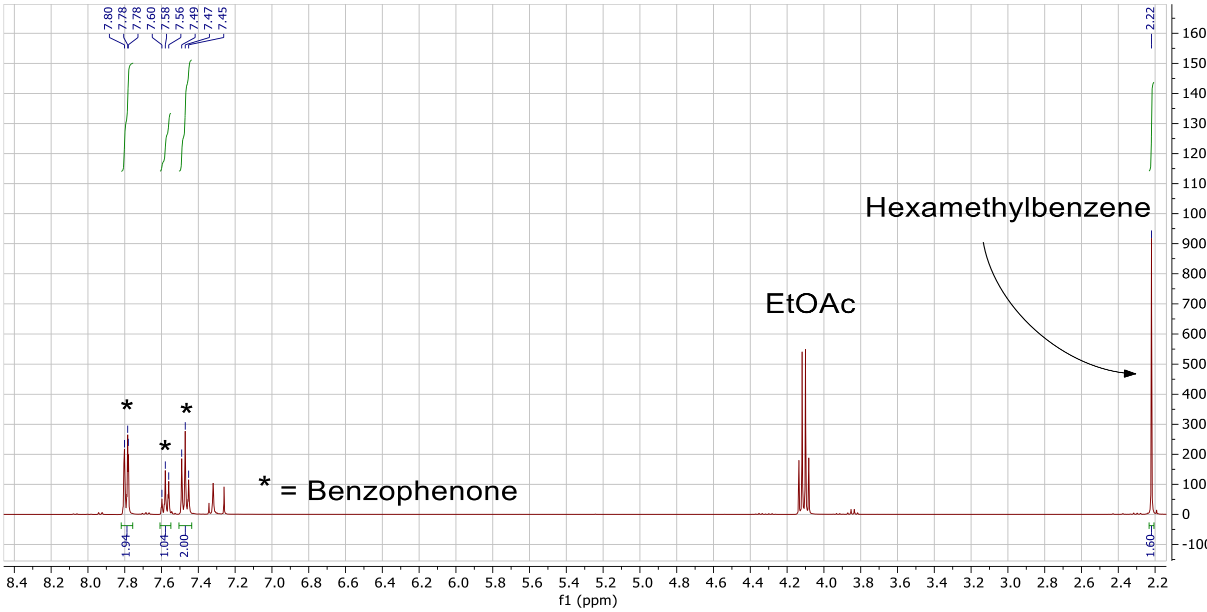
2.5.2. General Synthetic Procedures

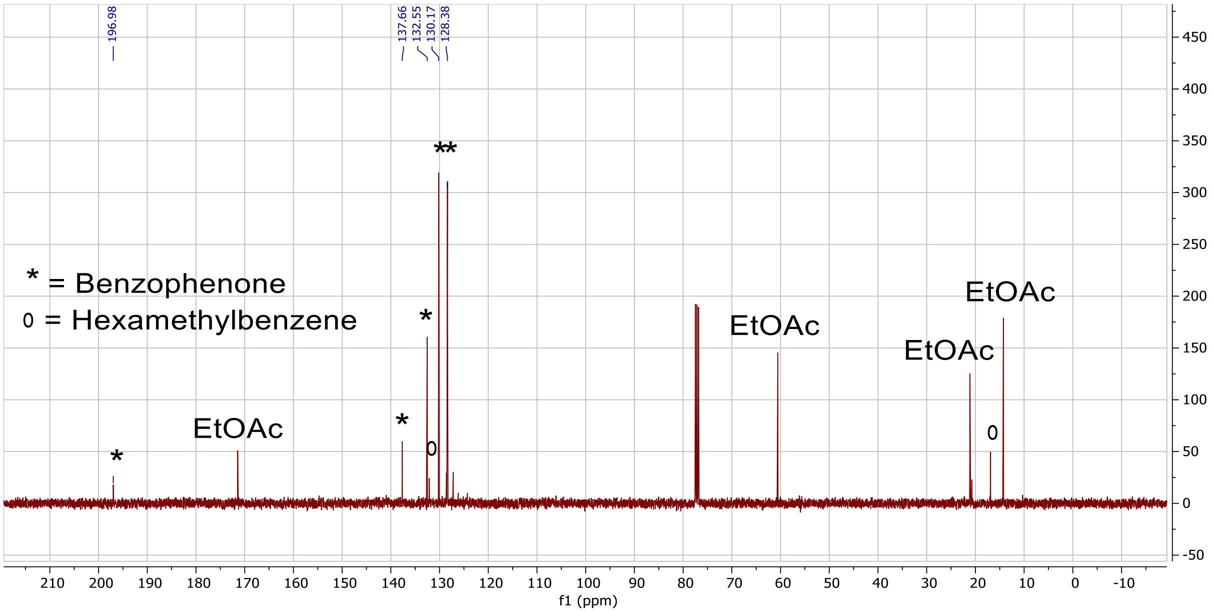
Stoichiometric Reaction of $PdCl_2$ with Carbon Monoxide in Benzene (Scheme 2.3.1):

In a glove box, silver triflate (184 mg, 0.72 mmol) was added to a 50 mL thick-walled, glass reaction vessel sealable with a Teflon stopcock and equipped with a stir bar. $PdCl_2$ (44 mg, 0.25 mmol) was dissolved in 10 mL benzene and added to the reaction vessel. The vessel was sealed, removed from the glove box, evacuated and backfilled three times with carbon monoxide, and finally pressurized with 4 atm carbon monoxide. The contents of the reaction vessel were stirred and heated at 100 °C for 22 h, after which the carbon monoxide was released in a fume hood. Hexamethylbenzene (5 mg, 0.033 mmol) was then added to the reaction vessel as a standard, the mixture was filtered through a pad of silica to remove any solids, and the reaction vessel was thoroughly rinsed with $CHCl_3$ followed by ethyl acetate. The solvents were removed *in vacuo* to yield ketone **2.3.1a** in 71% yield as determined by ^1H NMR spectral analysis relative to the external standard.

In situ Benzophenone ***2.3.1a****:* ^1H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, *J* = 7.0 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 197.0, 137.7, 132.6, 130.2, 128.4. NMR data corresponds with the previously reported compound.[1]

Crude Mixture ^1H and ^{13}C NMR Spectra:





Typical Procedure for Catalyst Development in Neat Benzene (Table 1, Entries 2.3.1-4):

In a glove box, silver triflate (198 mg, 0.77 mmol) and iodine (63 mg, 0.25 mmol) were dry transferred into a 50 mL thick-walled, glass reaction vessel sealable with a Teflon stopcock and equipped with a stir bar. $PdCl_2$ (4 mg, 0.025 mmol) and the residual iodine left after dry transferring were dissolved in 1 mL of benzene and added to the reaction vessel. The vessel was sealed, removed from the glove box, evacuated and backfilled three times with carbon monoxide, and finally pressurized with 4 atm carbon monoxide. The contents of the reaction vessel were stirred and heated at 100 °C for 22 h, after which the carbon monoxide was released in a fume hood. Hexamethylbenzene (6 mg, 0.036 mmol) was then added to the reaction vessel as a standard, the mixture was filtered through a pad of silica to remove any solids, and the reaction vessel was thoroughly rinsed with $CHCl_3$ followed by ethyl acetate. The solvents were removed *in vacuo* to yield ketone **2.3.1a** in 79% yield as determined by ^1H NMR spectral analysis relative to the external standard.

Typical Procedure for Catalyst Development in 1,2-Dichloroethane (Table 2.3.1, Entries 5-26):

In a glove box, silver triflate (182 mg, 0.71 mmol) and iodine (63 mg, 0.25 mmol) were dry transferred into a 50 mL thick-walled, glass reaction vessel sealable with a Teflon stopcock and equipped with a stir bar. $[Pd(allyl)Cl]_2$ (2 mg, 0.0066 mmol) and the residual iodine left after dry transferring was dissolved in 1 mL of 1,2-dichloroethane and added to the reaction vessel followed by *tert*-butylbenzene (81 µL, 0.52 mmol). The vessel was sealed, removed from the glove box, evacuated and backfilled three times with carbon monoxide, and finally pressurized with 1 atm carbon monoxide. The contents of the reaction vessel were stirred and heated at 60 °C for 22 h, after which the carbon monoxide was released in a fume hood. Hexamethylbenzene (8 mg, 0.046 mmol) was then added to the reaction vessel as a standard, the mixture was filtered through a pad of silica to remove any solids, and the reaction vessel was thoroughly rinsed with $CHCl_3$ followed by ethyl acetate. The solvents were removed *in vacuo* to yield ketone **2.3.1b** in 87% yield as determined by ^1H NMR spectral analysis ($CDCl_3$) relative to the external standard.

Procedure for the Synthesis of Ketones in Table 2.3.2:

All compounds in Table 2.3.2 were prepared according to the procedure detailed below. See the tabulated NMR data for any adjustments to the procedure employed or reaction temperature. For compounds **2.3.1m**, **2.3.1n**, **2.3.1o**, and **2.3.1p**, 2,6-di-*tert*-butylpyridine (258 µL, 1.15 mmol) was also added to quench *in situ* generated triflic acid and prevent side reactions.

Representative Procedure: In a glove box, silver triflate (350 mg, 1.36 mmol) and iodine (126 mg, 0.50 mmol) were dry transferred into a 50 mL thick-walled glass reaction vessel sealable with a Teflon stopcock and equipped with a magnetic stir bar. $[Pd(allyl)Cl]_2$ (5 mg, 0.013 mmol) and the residual iodine left after dry transferring were dissolved in 2 mL of 1,2-dichloroethane and added to the reaction vessel. Benzene was added to the reaction vessel via micropipette (134 µL, 1.50 mmol). The vessel was sealed, removed from the glove box, evacuated and backfilled three times with carbon monoxide, and finally pressurized with 4 atm carbon monoxide. The reaction mixture was stirred and heated at 60 °C for 22 h, after which the carbon monoxide was released in a fume hood. The reaction mixture was filtered through a pad of silica, and the reaction vessel was thoroughly rinsed with $CHCl_3$ followed by ethyl acetate. The solvents were removed *in vacuo* and the product was purified via column chromatography (silica gel, gradient hexane / ethyl acetate 0% to 20%) affording pure benzophenone **2.3.1a** as a white solid in 78% yield (70 mg, 0.38 mmol).

<u>Procedures for the Synthesis of Ketones in Table 2.3.3:</u>

All compounds in Table 2.3.3 were prepared according to the procedure detailed below. See the tabulated NMR data for any adjustments to the procedure employed or reaction temperature. For compounds **2.3.2k**, **2.3.2m**, and **2.3.2n**, 2,6-di-*tert*-butylpyridine (258 μL, 1.15 mmol) was also added together with the heterocycle to quench *in situ* generated triflic acid and prevent side reactions.

Representative Procedure: In a glove box, silver triflate (339 mg, 1.32 mmol) and iodine (126 mg, 0.49 mmol) were dry transferred into a 50 mL thick-walled glass reaction vessel sealable with a Teflon stopcock and equipped with a magnetic stir bar. $[Pd(allyl)Cl]_2$ (5 mg, 0.013 mmol) and the residual iodine left after dry transferring were dissolved in 2 mL of 1,2-dichloroethane and added to the reaction vessel. Benzene was added to the reaction vessel via micropipette (89 μL, 1.00 mmol). The vessel was sealed and the reaction mixture was allowed to stir at room temperature for 4.5 h in the glove box, upon which the vessel was opened and *tert*-butylbenzene was added to the reaction mixture via micropipette (232 μL, 1.50 mmol). The vessel was sealed, removed from the glove box, evacuated and backfilled three times with carbon monoxide, and finally pressurized with 4 atm carbon monoxide. The reaction mixture was stirred and heated at 60 °C for 22 h, upon which the pressure was released in a fume hood. The reaction mixture was filtered through a pad of silica and the reaction vessel was thoroughly rinsed with $CHCl_3$ followed by ethyl acetate. The solvents were removed *in vacuo* and the product was purified via column chromatography (silica gel, gradient hexane / ethyl acetate 0% to 20%) affording pure ketone **2.3.2d** as a white solid in 92% yield (109 mg, 0.46 mmol).

Procedure for the Synthesis of Crystal Violet 3 (Scheme 2.3.2):

In a glove box, iodine (61 mg, 0.24 mmol) was dry transferred into a 50 mL thick-walled glass reaction vessel sealable with a Teflon stopcock and equipped with a magnetic stir bar. $[Pd(allyl)Cl]_2$ (2 mg, 0.0066 mmol) and the residual iodine left after dry transferring were dissolved in 1 mL of 1,2-dichloroethane and added to the reaction vessel. *N,N*-dimethylaniline was added to the reaction vessel via micropipette (193 µL, 1.52 mmol). The vessel was sealed, removed from the glove box, evacuated and backfilled three times with carbon monoxide, and finally pressurized with 4 atm carbon monoxide. The reaction mixture was stirred and heated at 100 °C for 22 h, after which the pressure was released in a fume hood. The reaction mixture was filtered with added 300 mL acetonitrile to remove solids. 1,3,5-trimethoxybenzene (13 mg, 0.079 mmol) was added to the reaction solution as an NMR standard, followed by 0.2 mL triethylamine to quench acid generated during the reaction. A 1 mL aliquot of the reaction mixture was taken from the solution and ^1H NMR analysis revealed the formation of **2.3.3** together with its demethylated isomer in 41% yield (ratio of 1:1.2 of R = Me : H).

For isolation of **2.3.3**, the procedure above was repeated on a larger scale [iodine (126 mg, 0.50 mmol), $[Pd(allyl)Cl]_2$ (5 mg, 0.012 mmol), and *N,N*-dimethylaniline (387 µL, 3.05 mmol) in 2 mL 1,2-dichloroethane]. Upon release of CO at the end of the reaction, the reaction mixture was filtered through a pad of basic alumina and the reaction vessel was thoroughly rinsed with acetonitrile. The solvents were removed *in vacuo* and the product was purified via column chromatography (basic alumina, gradient $CHCl_3$ / MeCN 0% to 30%). The products elute close together and care must be taken to very slowly increase the solvent gradient (some overlap in products is unavoidable) to afford pure Crystal Violet **2.3.3** (R = Me) as a green solid in 21% yield (52 mg, 0.10 mmol) and pure Methyl Violet 6B **2.3.3'** (R = H) as a green solid in 7% yield (16 mg, 0.034 mmol). Both of these products are sparingly soluble in many common organic solvents (most notably prior to removal of the acid), and require polar solvents such as acetonitrile or methanol for quantitative dissolution.

2.5.3. Mechanistic Studies

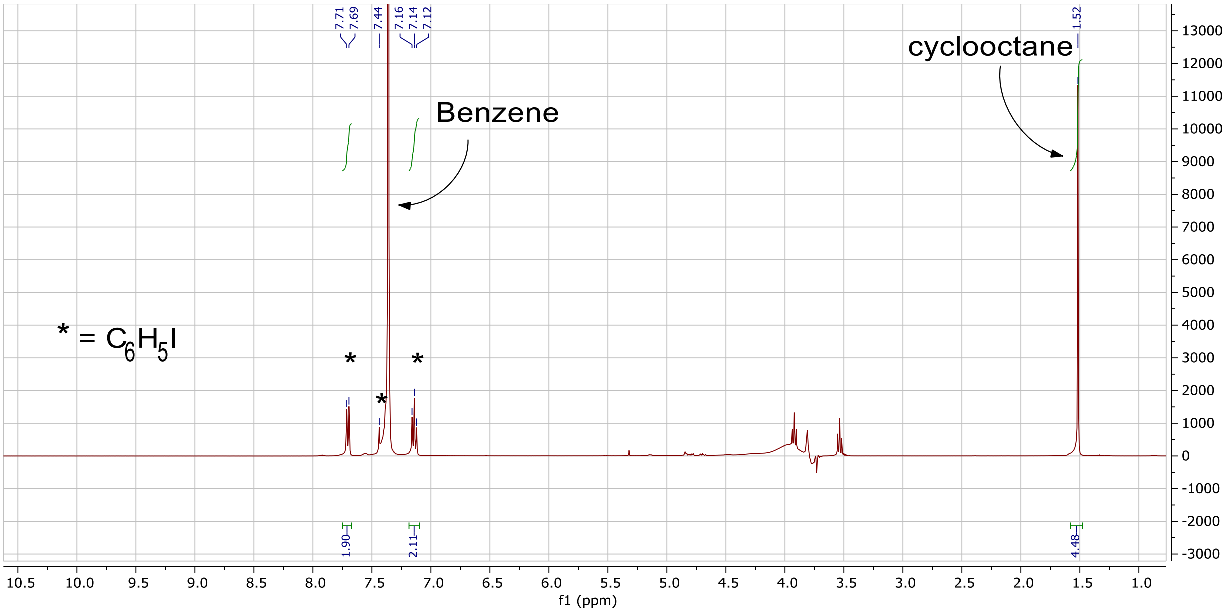
Monitoring Catalysis with ^{1}H NMR in Figure 2.3.1b:

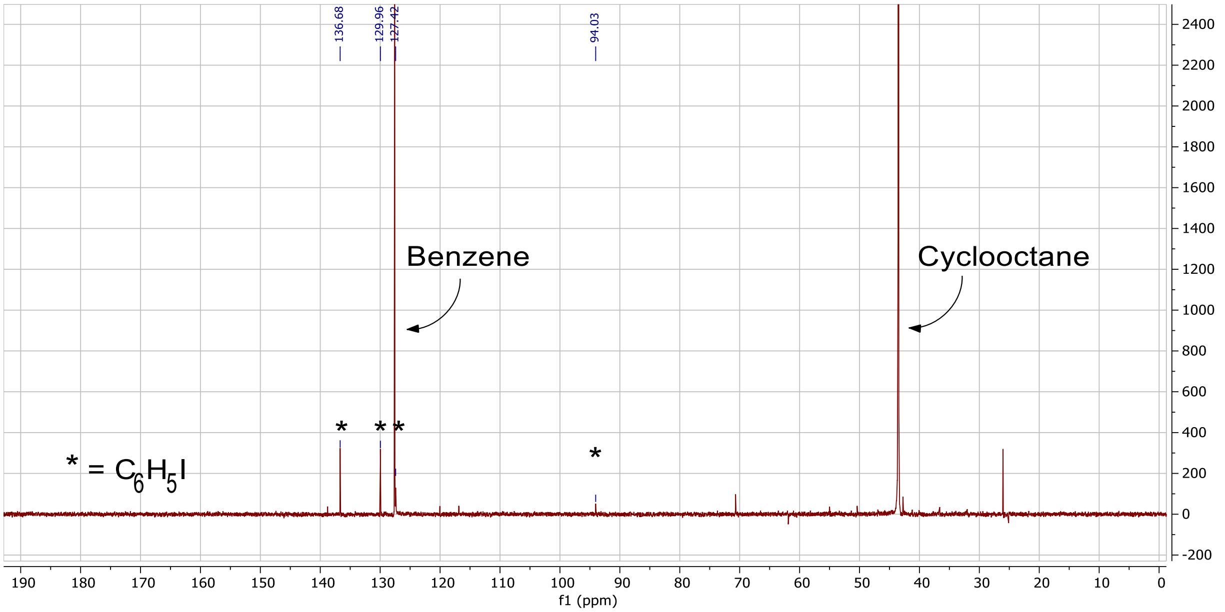
In a glove box, silver triflate (34 mg, 0.13 mmol) and iodine (12 mg, 0.048 mmol) were dry transferred into a J. Young NMR tube. $[Pd(allyl)Cl]_2$ (1 mg, 0.0014 mmol), cyclooctane standard (1 mg, 0.012 mmol), and the residual iodine left after dry transferring were dissolved in 600 μL of DCE and added to the reaction vessel. To this mixture, benzene (13 μL, 0.15 mmol) was added. The J. Young NMR tube was sealed with a Teflon stopcock and removed from the glove box where it was then connected to a Schlenk line via a glass adaptor and placed in liquid nitrogen. The headspace of the NMR tube was evacuated and 5 atm of CO was condensed into the NMR tube. After two hours at room temperature a ^{1}H NMR experiment was taken showing 94% yield of iodobenzene. The J. Young NMR tube was subsequently heated at 60 °C for 42 h and ^{1}H and ^{13}C NMR analysis revealed the formation of benzophenone **2.3.1a** in 88% yield.

In situ iodobenzene: ^{1}H NMR (400 MHz, 1,2-dichloroethane): δ 7.70 (d, *J* = 7.4 Hz, 2H), 7.40 (t, obscured by benzene peak, 1H), 7.14 (t, *J* = 7.8 Hz, 2H). ^{13}C NMR (101 MHz, 1,2-dichloroethane): δ 136.7, 130.0, 127.4, 94.0.

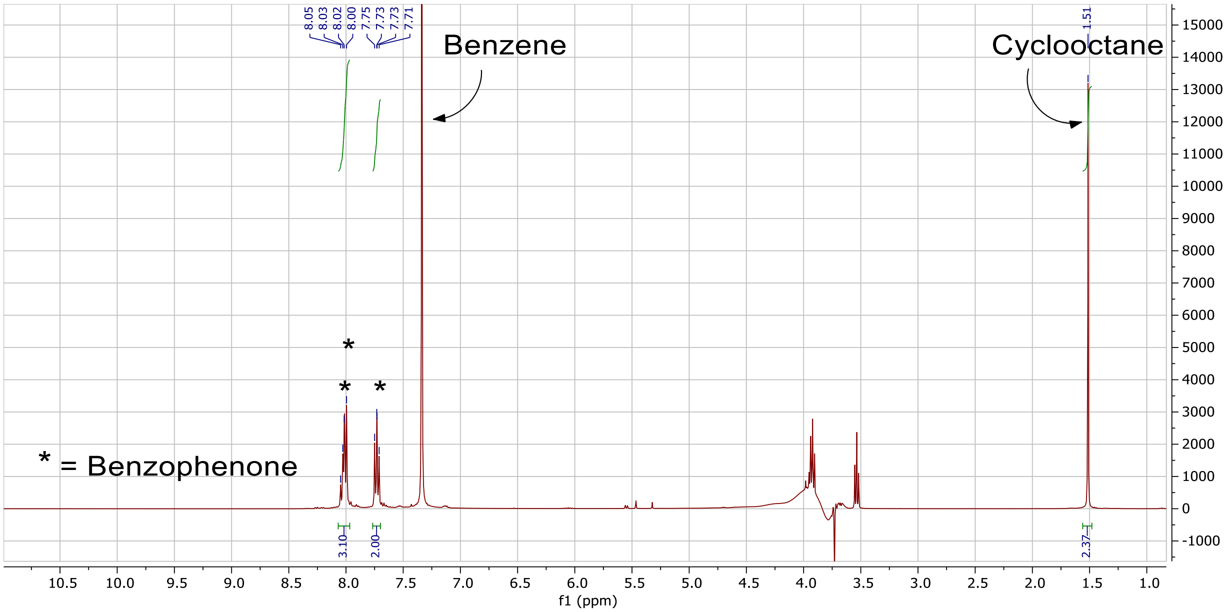
Pure iodobenzene: ^{1}H NMR (400 MHz, 1,2-dichloroethane): δ 7.70 (d, *J* = 7.1 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.10 (t, *J* = 7.8 Hz, 2H). ^{13}C NMR (101 MHz, 1,2-dichloroethane): δ 136.9, 129.8, 127.0, 93.7.

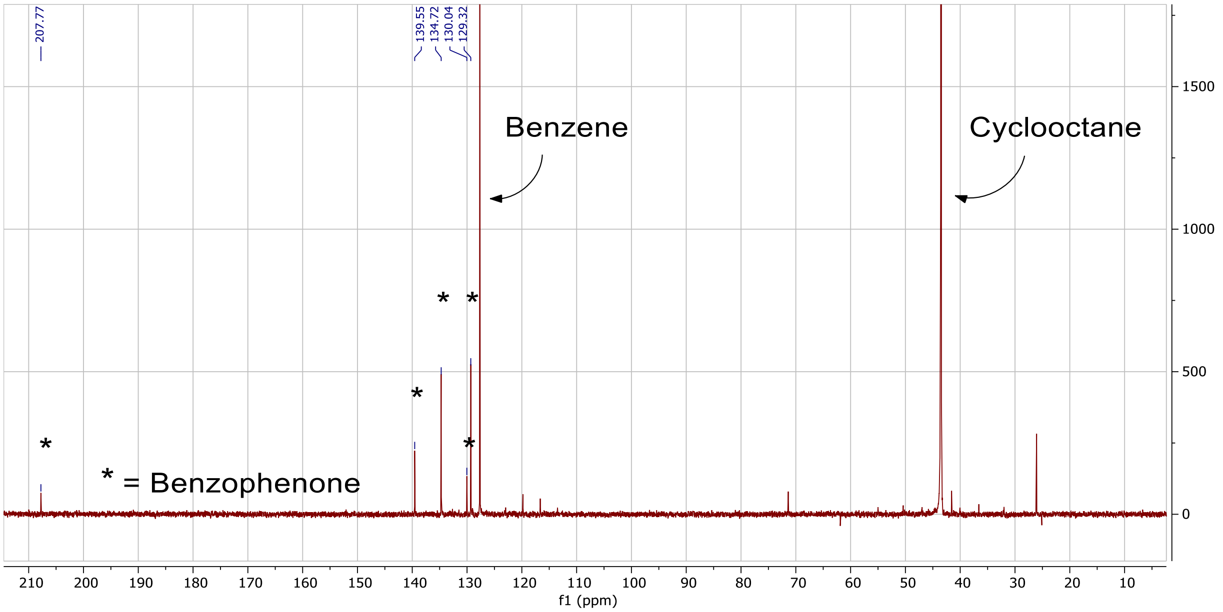
In situ iodobenzene ^{1}H and ^{13}C NMR spectra:





In situ Benzophenone ^{1}H and ^{13}C NMR spectra:





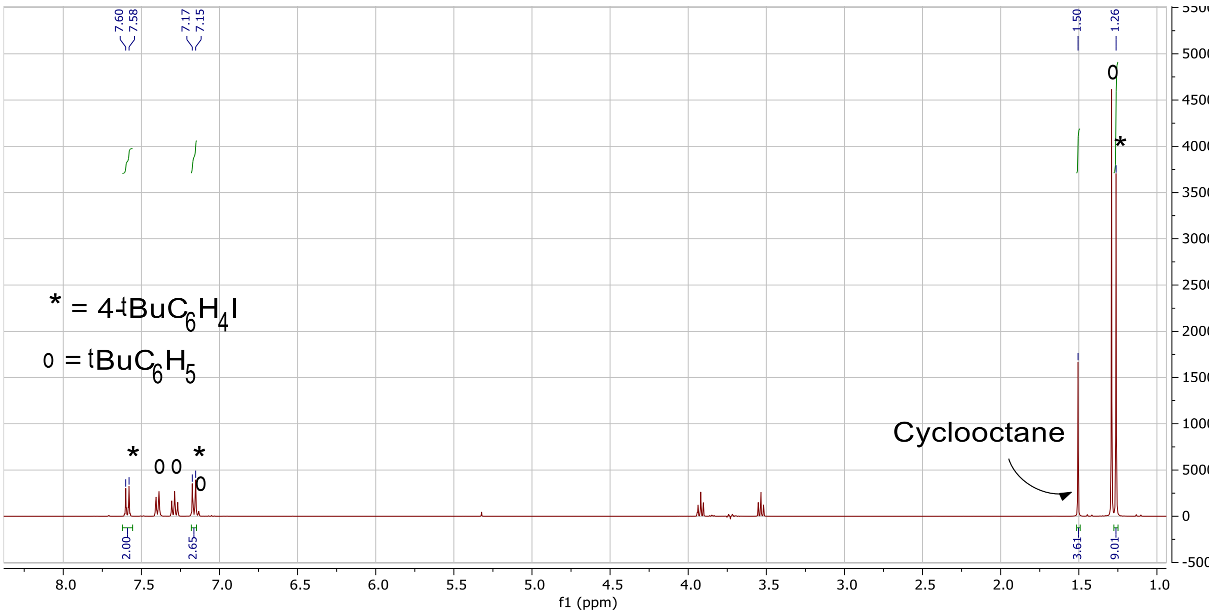
Reaction of *tert*-Butylbenzene, AgOTf, and I$_2$ (Figure 2.3.1c):

In a glove box, iodine (63 mg, 0.25 mmol) and cyclooctane standard (6 mg, 0.057 mmol) were added to a vial containing silver triflate (114 mg, 0.44 mmol) and a stir bar using 1 mL 1,2-dichloroethane. To this mixture, *tert*-butylbenzene (81 µL, 0.52 mmol) was added. The reaction mixture was stirred for 30 min at room temperature, after which the stirring was halted, and the precipitate allowed to settle. 1 ml of this mixture was transferred to an NMR tube, and ^{1}H NMR analysis shows the formation of 4-*tert*-butyliodobenzene in >99% yield.

In situ 4-tert-butyliodobenzene: ^{1}H NMR (400 MHz, 1,2-dichloroethane): δ 7.59 (d, *J* = 8.6 Hz, 2H), 7.16 (d, *J* = 8.7 Hz, 2H), 1.26 (s, 9H).

Pure 4-tert-butyliodobenzene: ^{1}H NMR (400 MHz, 1,2-dichloroethane): 7.59 (d, *J* = 8.6 Hz, 2H), 7.13 (d, *J* = 8.6 Hz, 2H), 1.26 (s, 9H).

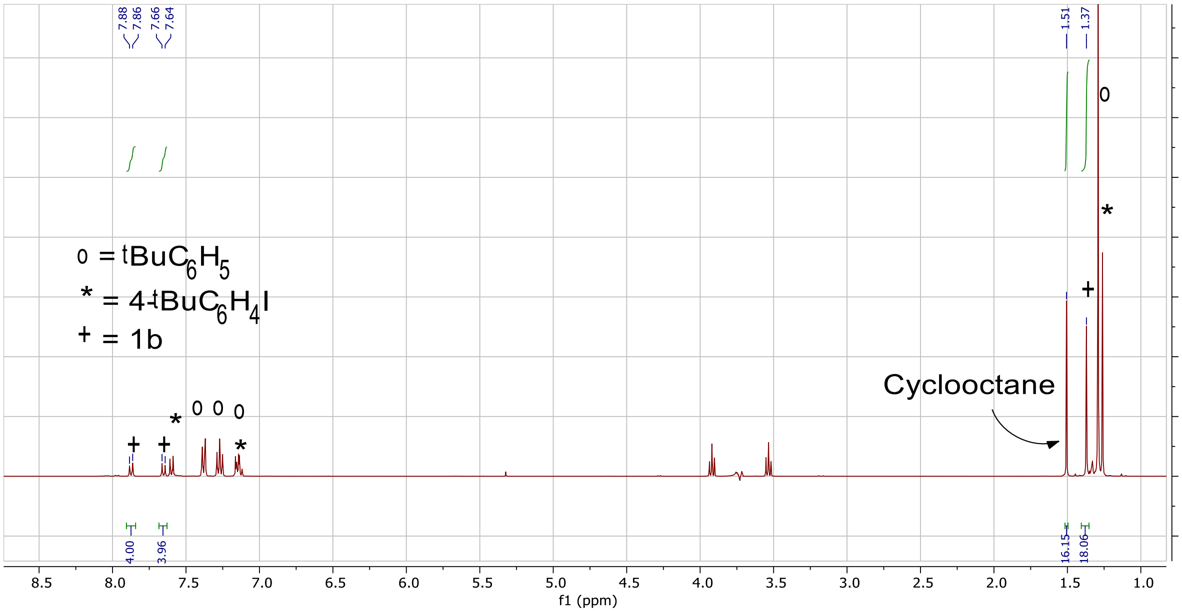
In Situ 4-iodo-*tert*-butylbenzene ^{1}H NMR Spectrum:



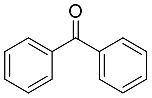
Pd-Catalyzed Carbonylation of 4-Iodo-*tert*-Butylbenzene and *tert*-Butylbenzene at Room Temperature (Figure 2.3.1c):

In a glove box, silver triflate (118 mg, 0.46 mmol) was dry transferred into a 50 mL thick-walled glass reaction vessel sealable with a Teflon stopcock and equipped with a magnetic stir bar. $[Pd(allyl)Cl]_2$ (3 mg, 0.0071 mmol) and 4-*tert*-butyliodobenzene (65 mg, 0.25 mmol) were dissolved in 1 mL of 1,2-dichloroethane and added to the reaction vessel. *tert*-butylbenzene was added to the reaction vessel via micropipette (77 µL, 0.50 mmol). The vessel was sealed, removed from the glove box, evacuated and backfilled three times with carbon monoxide, and finally pressurized with 4 atm carbon monoxide. The reaction mixture was stirred at room temperature for 22 h and afterward the CO was removed on a Schlenk line before the vessel was brought into the glove box. Cyclooctane standard (7 mg, 0.061 mmol) was then added to the reaction vessel. A 1 mL sample of the mixture was added to a J. Young NMR tube and ^{1}H NMR analysis revealed the formation of ketone **2.3.1b** in 23% yield.

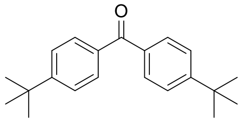
<u>Carbonylation of 4-Iodo-*tert*-butylbenzene at Room Temperature ^{1}H NMR Spectrum:</u>



2.5.4. Spectroscopic Data for Compounds 2.3.1

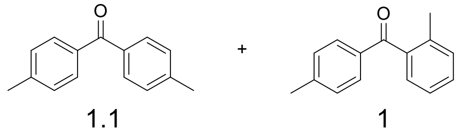


Benzophenone 2.3.1a.[17] Prepared according to the general procedure. White solid, 78% yield (70 mg, 0.38 mmol). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.81 (d, *J* = 7.7 Hz, 4H), 7.58 (t, *J* = 7.4 Hz, 2H), 7.48 (t, *J* = 7.6 Hz, 4H). ^{13}C NMR (126 MHz, CDCl$_3$): δ 196.8, 137.7, 132.5, 130.1, 128.4. NMR data corresponds with the previously reported compound.[17]

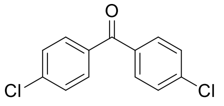


Bis(4-(*tert*-butyl)phenyl)methanone 2.3.1b.[17] Prepared according to the general procedure using *tert*-butylbenzene (232 μL, 1.50 mmol). White solid, 90% yield (132 mg, 0.45 mmol). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.79 (d, *J* =

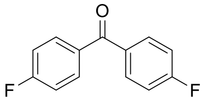
8.5 Hz, 4H), 7.50 (d, *J* = 8.5 Hz, 4H), 1.38 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 196.2, 155.9, 135.2, 130.1, 125.2, 35.1, 31.2. NMR data corresponds with the previously reported compound.[17]



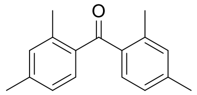
Di-*p*-tolylmethanone 2.3.1c and *o*-toylyl(*p*-tolyl)methanone 2.3.1c'.[17,18] Prepared according to the general procedure using toluene (160 μL, 1.50 mmol). White solid, 91% isolated total yield of both isomers (1.1:1 ratio) (94 mg, 0.45 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (m, 6H, major and minor isomer), 7.37 (td, *J* = 8.1, 1.7 Hz, 1H, minor isomer), 7.32-7.22 (m, 9H, major and minor isomer), 2.42 (s, 6H, major isomer), 2.41 (s, 3H, minor isomer), 2.32 (s, 3H, minor isomer). ^{13}C NMR (126 MHz, $CDCl_3$): δ 198.3, 196.2, 144.1, 142.9, 139.0, 136.5, 135.2, 135.2, 130.9, 130.3, 130.2, 130.0, 129.2, 128.9, 128.3, 125.2, 21.7, 21.6, 19.9. NMR data corresponds with the previously reported compounds.[17,18]



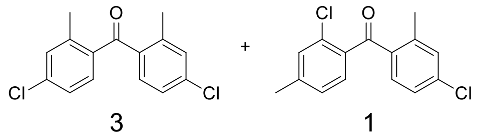
Bis(4-chlorophenyl)methanone 2.3.1d.[17] Prepared according to the general procedure using chlorobenzene (2 mL, 19.6 mmol) and 150 °C. White, crystalline solid, 88% yield (110 mg, 0.44 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.6 Hz, 4H), 7.46 (d, *J* = 8.6 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 194.3, 139.2, 135.6, 131.4, 128.9. HRMS: Calculated for $C_{13}H_8Cl_2ONa$ ($M+Na^+$): 272.9844, found: 272.9844. NMR data corresponds with the previously reported compound.[17]



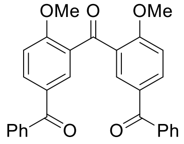
Bis(4-fluorophenyl)methanone 2.3.1e.[19] Prepared according to the general procedure using fluorobenzene as solvent (2 mL, 21.3 mmol) and at 150 °C. Yellow solid, 82% yield (90 mg, 0.41 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (dd, $^{3}J_{HH}$ = 8.8 Hz, $^{4}J_{HF}$ = 5.4 Hz, 4H), 7.16 (dd, $^{3}J_{HH}$ = 8.6 Hz, $^{3}J_{HF}$ = 8.6 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 193.9, 165.5 (d, *J* = 254.2 Hz), 133.8 (d, *J* = 3.1 Hz), 132.6 (d, *J* = 9.1 Hz), 115.7 (d, *J* = 21.8 Hz). NMR data corresponds with the previously reported compound.[19]



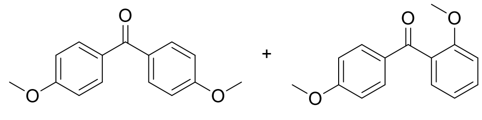
Bis(2,4-dimethylphenyl)methanone 2.3.1f.[19] Prepared according to the general procedure using 1,3-dimethylbenzene (184 µL, 1.50 mmol). Yellow oil, 65% yield (77 mg, 0.32 mmol). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.21 (d, *J* = 7.8 Hz, 2H), 7.09 (s, 2H), 6.99 (d, *J* = 7.7 Hz, 2H), 2.42 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$): δ 200.5, 141.4, 138.3, 136.6, 132.3, 130.7, 126.0, 21.5, 20.7. NMR data corresponds with the previously reported compound.[19]



Bis(2-chloro-4-methylphenyl)methanone 2.3.1g. Prepared according to the general procedure using 1-chloro-3-methylbenzene (177 µL, 1.50 mmol) and at 100 °C. Colourless oil, 91% isolated total yield of both isomers (3:1 ratio) (127 mg, 0.45 mmol). Isomers were separated for characterization purposes using a preparation scale silica TLC plate with 3% ethyl acetate / hexanes. ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.29 (br s, 2H), 7.24-7.17 (m, 4H), 2.41 (s, 6H). ^{13}C NMR (126 MHz, CDCl$_3$): δ 198.5, 140.5, 137.4, 137.0, 131.7, 131.7, 125.9, 20.7. HRMS: Calculated for $C_{15}H_{12}OCl_2Na$ (M+Na$^+$): 301.0157, found: 301.0153. **(4-chloro-2-methylphenyl)(2-chloro-4-methylphenyl)methanone 2.3.1g'.** ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.35-7.31 (m, 1H), 7.29 (br s, 1H), 7.27-7.23 (m, 2H), 7.18-7.13 (m, 2H), 2.51 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$): δ 196.5, 143.0, 141.3, 137.8, 136.3, 136.1, 132.4, 132.1, 131.8, 131.1, 130.4, 127.7, 125.8, 21.4, 21.0. HRMS: Calculated for $C_{15}H_{12}OCl_2Na$ (M+Na$^+$): 301.0157, found: 301.0148.

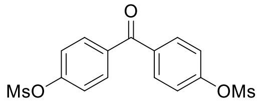


(Carbonylbis(4-methoxy-3,1-phenylene))bis(phenylmethanone) 2.3.1h. Prepared according to the general procedure using (4-methoxyphenyl)(phenyl)methanone (320 mg, 1.51 mmol). Yellow solid, 55% yield (122 mg, 0.27 mmol). ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.04 (s, 2H), 7.98 (d, *J* = 8.3, 2H), 7.74 (d, *J* = 7.3 Hz, 4H), 7.54 (t, *J* = 7.1 Hz, 2H), 7.44 (t, *J* = 7.3 Hz, 4H), 6.99 (d, *J* = 8.6 Hz, 2H), 3.73 (s, 6H). ^{13}C NMR (126 MHz, CDCl$_3$): δ 194.9, 193.1, 161.6, 137.7, 135.4, 133.0, 132.3, 129.9, 129.7, 129.3, 128.4, 111.0, 56.0. HRMS: Calculated for $C_{29}H_{22}O_5Na$ (M+Na$^+$): 473.1359, found: 473.1362.

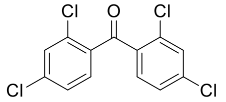


3.5 1

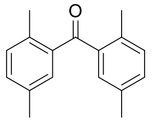
Bis(4-methoxyphenyl)methanone 2.3.1i and (2-methoxyphenyl)(4-methoxyphenyl)methanone 2.3.1i'.[17,20] Prepared according to the general procedure using anisole (163 µL, 1.50 mmol). White solid, 73% isolated total yield of both isomers (3.5:1 ratio) (88 mg, 0.36 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.7 Hz, 6H, both isomers), 7.43 (m, 1H, minor isomer), 7.31 (dd, *J* = 7.5, 1.8 Hz, 1H, minor isomer), 7.02 (t, *J* = 7.5 Hz, 1H, minor isomer), 6.95 (d, *J* = 8.8 Hz, 5H, both isomers), 6.90 (d, *J* = 8.8 Hz, 2H, minor isomer), 3.87 (s, 6H, major isomer), 3.85 (s, 3H, minor isomer), 3.73 (s, 3H, minor isomer). ^{13}C NMR (126 MHz, $CDCl_3$): δ 195.2, 194.5, 163.6, 162.9, 157.1, 132.4, 132.3, 131.5, 130.8, 130.8, 129.4, 129.3, 120.5, 113.6, 113.6, 111.5, 55.7, 55.6. NMR data corresponds with the previously reported compound.[17,20]



Carbonylbis(4,1-phenylene)dimethanesulfonate 2.3.1j. Prepared according to the general procedure using phenyl methanesulfonate (262 mg, 1.52 mmol) and at 100 °C. White solid, 62% yield (115 mg, 0.31 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.5 Hz, 4H), 7.40 (d, *J* = 8.5 Hz, 4H), 3.21 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 193.6, 152.2, 135.9, 132.0, 122.1, 38.0. HRMS: Calculated for $C_{15}H_{15}O_7S_2$ (M+H$^+$): 371.02537, found: 371.02643.

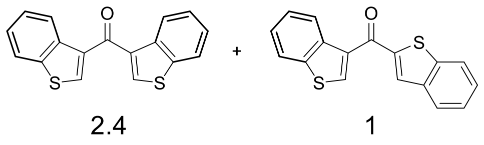


Bis(2,4-dichlorophenyl)methanone 2.3.1k. Prepared according to the general procedure using 1,3-dichlorobenzene as solvent (2 mL, 17.5 mmol) and 150 °C. Orange solid, 81% yield (127 mg, 0.40 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (d, *J* = 8.3, 2H), 7.43 (d, *J* = 1.9 Hz, 2H), 7.33 (dd, *J* = 8.3, 1.9, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 192.3, 138.6, 136.2, 133.7, 131.9, 130.7, 127.6. HRMS: Calculated for $C_{13}H_6Cl_4ONa$ (M+Na$^+$): 340.9065, found: 340.9055.

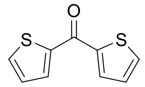


Bis(2,5-dimethylphenyl)methanone 2.3.1l.[17] Prepared according to the general procedure using 1,4-dimethylbenzene (185 µL, 1.50 mmol). White solid, 85% yield (100 mg, 0.42 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (d, *J* = 7.8 Hz, 2H), 7.17

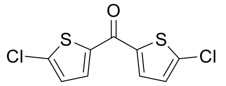
(d, J = 7.8 Hz, 2H), 7.14 (s, 2H), 2.40 (s, 6H), 2.31 (s, 6H). ^{13}C NMR (126 MHz, CDCl$_3$): δ 201.2, 139.1, 135.0, 135.0, 131.8, 131.4, 130.6, 20.9, 20.2. NMR data corresponds with the previously reported compound.[17]



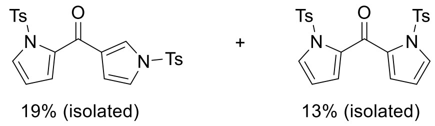
Bis(benzo[*b*]thiophen-3-yl)methanone 2.3.1m and benzo[*b*]thiophen-2-yl(benzo[*b*]thiophen-3-yl)methanone 2.3.1m'.[21,22] Prepared according to the general procedure using benzo[*b*]thiophene (222 mg, 1.65 mmol). Orange solid, 65% isolated total yield of both isomers (2.4:1 ratio) (96 mg, 0.32 mmol). ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.60 (d, J = 8.1 Hz, 2H major isomer), 8.52 (d, J = 8.1 Hz, 2H minor isomer), 8.25 (s, 1H minor isomer), 8.05 (s, 2H major isomer), 7.95 (s, 1H minor isomer), 7.94-7.85 (m, 2H for the major isomer, 3H for the minor isomer), 7.57-7.29 (m, 4H for both isomers). ^{13}C NMR (126 MHz, CDCl$_3$): δ 184.9, 183.3, 144.2, 142.5, 140.2, 140.0, 139.0, 137.3, 137.2, 136.9, 136.4, 134.6, 130.9, 127.4, 126.1, 125.8, 125.7, 125.7, 125.2, 125.0, 124.9, 122.9, 122.5, 122.4. NMR data corresponds with the previously reported compounds.[21,22]



Di(thiophen-2-yl)methanone 2.3.1n.[23] Prepared according to the general procedure using thiophene (120 µL, 150 mmol). Yellow oil, 48% yield (46 mg, 0.24 mmol). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.89 (dd, J = 3.8, 1.2 Hz, 2H), 7.69 (dd, J = 5.0, 1.2 Hz, 2H), 7.18 (dd, J = 5.0, 3.8 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_3$): δ 178.9, 143.0, 133.6, 133.3, 128.1. HRMS: Calculated for $C_9H_6OS_2Na$ (M+Na$^+$): 216.9752, found: 216.9749. NMR data corresponds with the previously reported compound.[23]

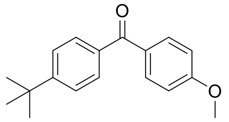


Bis(5-chlorothiophen-2-yl)methanone 2.3.1o. Prepared according to the general procedure using 2-chlorothiophene (138 µL, 1.50 mmol).Yellow solid, 55% yield (72 mg, 0.27 mmol). ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.64 (d, J = 4.1 Hz, 2H), 7.01 (d, J = 4.1 Hz, 2H). ^{13}C NMR (101 MHz, CDCl$_3$): δ 176.5, 140.7, 139.7, 132.6, 127.6. HRMS: Calculated for $C_9H_4OS_2Cl_2Na$ (M+Na$^+$): 284.8973, found: 284.8964.

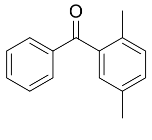


(1-tosyl-1*H*-pyrrol-2-yl)(1-tosyl-1*H*-pyrrol-3-yl)methanone 2.3.1p. Prepared according to the general procedure using 1-tosyl-1*H*-pyrrole (334 mg, 1.51 mmol). Orange oil, 19% yield (44 mg, 0.095 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, *J* = 8.5 Hz, 2H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.71 (dd, *J* = 3.2, 1.7 Hz, 1H), 7.65 (t, *J* = 1.9 Hz, 1H), 7.36-7.29 (m, 4H), 7.14 (dd, *J* = 3.3, 2.2 Hz, 1H), 6.85 (dd, *J* = 3.7, 1.7 Hz, 1H), 6.70 (dd, *J* = 3.3, 1.6 Hz, 1H), 6.33 (t, *J* = 3.4 Hz, 1H), 2.41 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 176.1, 146.2, 145.1, 136.4, 135.0, 133.3, 130.5, 129.6, 129.3, 128.4, 128.4, 127.4, 125.8, 123.6, 121.5, 113.6, 110.8, 21.8. HRMS: Calculated for $C_{23}H_{21}O_5N_2S_2$ (M+H$^+$): 469.08864, found: 469.09030. **Bis(1-tosyl-1*H*-pyrrol-2-yl)methanone 2.3.1p'.** Orange solid, 13% yield (30 mg, 0.065 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.4 Hz, 4H), 7.69 (dd, *J* = 3.2, 1.7 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 4H), 6.80 (dd, *J* = 3.7, 1.8 Hz, 2H), 6.29 (t, *J* = 3.4 Hz, 2H), 2.47 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.2, 145.0, 136.2, 133.3, 129.4, 129.2, 128.9, 124.6, 110.7, 21.9. HRMS: Calculated for $C_{23}H_{21}O_5N_2S_2$ (M+H$^+$): 469.08864, found: 469.09031.

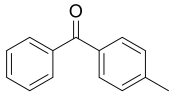
2.5.5. Spectroscopic Data for Compounds 2.3.2



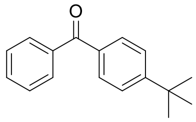
(4-(*tert*-butyl)phenyl)(4-methoxyphenyl)methanone 2.3.2a.[24] Prepared according to the general procedure and allowing *tert*-butylbenzene (155 μL, 1.00 mmol) to iodinate for 4.5 h before addition of anisole (163 μL, 1.50 mmol). White solid, 72% yield (95 mg, 0.36 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.9 Hz, 2H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 8.5 Hz, 2H), 6.95 (d, *J* = 8.9 Hz, 2H), 3.86 (s, 3H), 1.36 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 195.3, 163.1, 155.6, 135.5, 132.5, 130.5, 129.8, 125.2, 113.5, 55.5, 35.1, 31.2. NMR data corresponds with the previously reported compound.[24]



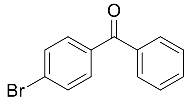
(2,5-dimethylphenyl)(phenyl)methanone 2.3.2b.[25] Prepared according to the general procedure and allowing benzene (89 μL, 1.00 mmol) to iodinate for 4 h before addition of 1,4-dimethylbenzene (185 μL, 1.50 mmol). Orange oil, 99% yield (104 mg, 0.50 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (d, *J* = 7.1 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.46 (t, J = 7.7 Hz, 2H), 7.23-7.15 (m, 2H), 7.13 (s, 1H), 2.34 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$): δ 198.9, 138.7, 137.9, 134.8, 133.5, 133.1, 131.0, 130.9, 130.1, 129.0, 128.5, 20.9, 19.5. NMR data corresponds with the previously reported compound.[25]



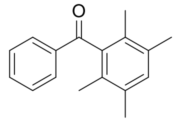
Phenyl(p-tolyl)methanone 2.3.2c.[25] Prepared according to the general procedure and allowing benzene (89 μL, 1.00 mmol) to iodinate for 4 h before addition of toluene (160 μL, 1.50 mmol). Pale-yellow oil, 68% yield (66 mg, 0.33 mmol). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.79 (d, J = 7.0 Hz, 2H), 7.73 (d, J = 8.1 Hz, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.7 Hz, 2H), 7.28 (d, J = 7.9 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$): δ 196.5, 143.3, 138.0, 134.9, 132.2, 130.4, 130.0, 129.0, 128.3, 21.7. NMR data corresponds with the previously reported compound.[25]



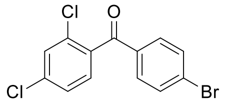
(4-($tert$-butyl)phenyl)(phenyl)methanone 2.3.2d.[25] Prepared according to the general procedure. Yellow oil, 92% yield (109 mg, 0.46 mmol). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.81 (d, J = 7.1 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.50 (d, J = 8.5 Hz, 2H), 7.47 (t, J = 7.7 Hz, 2H), 1.37 (s, 9H). ^{13}C NMR (126 MHz, CDCl$_3$): δ 196.4, 156.2, 138.0, 134.9, 132.2, 130.2, 130.0, 128.2, 125.3, 35.1, 31.2. NMR data corresponds with the previously reported compound.[25]



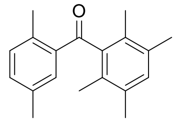
(4-bromophenyl)(phenyl)methanone 2.3.2e.[26] Prepared according to the general procedure and allowing bromobenzene (105 μL, 1.00 mmol) to iodinate at 100 °C for 6 h before addition of benzene (134 μL, 1.50 mmol). The carbonylation step also proceeded at 100 °C. Off-white solid, 54% yield (70 mg, 0.27 mmol). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.77 (d, J = 7.5 Hz, 2H), 7.73-7.56 (m, 5H), 7.48 (t, J = 7.6 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_3$): δ 195.7, 137.2, 136.4, 132.8, 131.7, 131.6, 130.0, 128.5, 127.6. NMR data corresponds with the previously reported compound.[26]



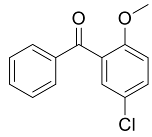
Phenyl(2,3,5,6-tetramethylphenyl)methanone 2.3.2f.[11d] Prepared according to the general procedure and allowing benzene (89 µL, 1.00 mmol) to iodinate for 5.5 h before addition of 1,2,4,5-tetramethylbenzene (222 mg, 1.66). White Solid, 99% yield (118 mg, 0.50 mmol). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.84 (d, *J* = 7.5 Hz, 2H), 7.58 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 7.05 (s, 1H), 2.25 (s, 6H), 2.99 (s, 6H). ^{13}C NMR (126 MHz, CDCl$_3$): δ 201.7, 140.0, 137.5, 134.3, 133.6, 131.9, 129.8, 129.6, 128.9, 19.6, 16.4. NMR data corresponds with the previously reported compound.[11d]



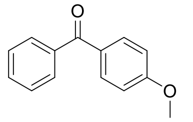
(4-bromophenyl)(2,4-dichlorophenyl)methanone 2.3.2g. Prepared according to the general procedure and allowing 1,3-dichlorobenzene (114 µL, 1.00 mmol) to iodinate at 100 °C for 22 h before addition of bromobenzene (526 µL, 5.00 mmol). The carbonylation step proceeded at 150 °C. Brown oil, 36% yield (60 mg, 0.18 mmol). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.67-7.60 (m, 4H), 7.49 (d, *J* = 1.8 Hz, 1H), 7.38 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.33 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR (126 MHz, CDCl$_3$): δ 193.4, 137.1, 136.5, 135.2, 132.5, 132.2, 131.5, 130.3, 130.2, 129.5, 127.4. HRMS: Calculated for C$_{13}$H$_7$OBrCl$_2$Na (M+Na$^+$): 350.8950, found: 350.8943.



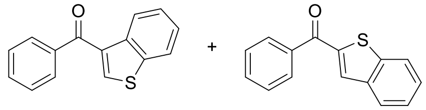
(2,5-dimethylphenyl)(2,3,5,6-tetramethylphenyl)methanone 2.3.2h. Prepared according to the general procedure and allowing 1,4-dimethylbenzene (123 µL, 1.00 mmol) to iodinate for 4 h before addition of 1,2,4,5-tetramethylbenzene (235 mg, 1.75 mmol). Off-white solid, 95% yield (126 mg, 0.47 mmol). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.25-7.11 (m, 3H), 7.02 (s, 1H), 2.68 (s, 3H), 2.25 (s, 9H), 2.00 (s, 6H). ^{13}C NMR (126 MHz, CDCl$_3$): δ 203.8, 141.9, 137.2, 136.7, 135.5, 134.2, 133.2, 132.8, 132.3, 131.7, 129.7, 21.8, 20.9, 19.6, 16.2. HRMS: Calculated for C$_{19}$H$_{22}$ONa (M+Na$^+$): 289.1563, found: 289.1564.



(5-chloro-2-methoxyphenyl)(phenyl)methanone 2.3.2i. Prepared according to the general procedure and allowing benzene (89 µL, 1.00 mmol) to iodinate for 5 h before addition of 4-chloroanisole (184 µL, 1.50 mmol). White solid, 85% yield (104 mg, 0.42 mmol). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.80 (d, *J* = 7.1 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.9 Hz, 2H), 7.41 (dd, *J* = 8.7, 2.7 Hz, 1H), 7.32 (d, *J* = 2.6 Hz, 1H), 6.93 (d, *J* = 8.9 Hz, 1H), 3.70 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 194.9, 156.0, 137.3, 133.4, 131.5, 130.3, 129.9, 129.2, 128.5, 125.8, 113.0, 56.1. HRMS: Calculated for $C_{14}H_{11}O_2ClNa$ (M+Na$^+$): 269.0340, found: 269.0339.

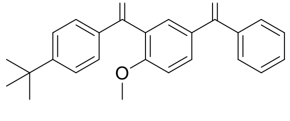


(4-methoxyphenyl)(phenyl)methanone 2.3.2j.[25] Prepared according to the general procedure and allowing benzene (89 μL, 1.00 mmol) to iodinate for 4.5 h before addition of anisole (163 μL, 1.50 mmol). Pale-yellow oil, 90% yield (95 mg, 0.45 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (d, *J* = 8.7 Hz, 2H), 7.74 (d, *J* = 7.3 Hz, 2H), 7.54 (t, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 3.85 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 195.5, 163.2, 138.3, 132.6, 131.9, 130.1, 129.7, 128.2, 113.6, 55.5. NMR data corresponds with the previously reported compound.[25]



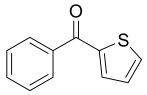
2.3 1

Benzo[*b*]thiophen-3-yl(phenyl)methanone 2.3.2k and Benzo[*b*]thiophen-2-yl(phenyl)methanone 2.3.2k'.[27] Prepared according to the general procedure and allowing benzene (89 μL, 1.00 mmol) to iodinate for 5.5 h before addition of benzo[*b*]thiophene (206 mg, 1.54 mmol). Orange oil, 59% isolated total yield of both isomers (2.3:1 ratio) (71 mg, 0.30 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.60 (d, *J* = 8.2 Hz, 1H, major isomer), 7.99 (s, 1H, major isomer), 7.95-7.81 (m, 5H for minor isomer, 3H for major isomer), 7.64-7.57 (m, 1H for both isomers), 7.57-7.38 (m, 4H for both isomers). ^{13}C NMR (126 MHz, $CDCl_3$): δ 190.9, 189.7, 143.2, 142.7, 140.1, 139.3, 139.1, 138.4, 137.9, 137.5, 134.8, 132.6, 132.4, 132.3, 129.6, 129.3, 128.6, 128.5, 127.5, 126.1, 125.7, 125.6, 125.2, 125.1, 123.0, 122.4. NMR data corresponds with the previously reported compound.[27]

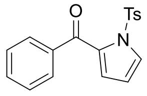


(5-benzoyl-2-methoxyphenyl)(4-(*tert*-butyl)phenyl)methanone 2.3.2l. Prepared according to the general procedure and allowing *tert*-butylbenzene (155 μL, 1.00 mmol) to iodinate for 4.5 h before addition of 4-methoxybenzophenone (322 mg, 1.52 mmol). Orange oil, 79% yield (147 mg, 0.39 mmol).

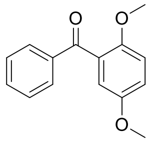
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.82 (d, *J* = 2.3 Hz, 1H), 7.9-7.73 (m, 4H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.49-7.41 (m, 4H), 7.09 (d, *J* = 8.7 Hz, 1H), 3.84 (s, 3H), 1.33 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 195.0, 194.9, 160.6, 157.3, 137.7, 134.5, 134.2, 132.2, 131.6, 130.0, 129.9, 129.8, 129.0, 128.4, 125.5, 111.0, 56.0, 35.2, 31.1. HRMS: Calculated for $C_{25}H_{25}O_3$ (M+H$^+$): 373.17982, found: 373.18112.



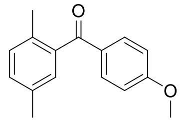
Phenyl(thiophen-2-yl)methanone 2.3.2m.[28] Prepared according to the general procedure and allowing benzene (89 μL, 1.00 mmol) to iodinate for 4.5 h before addition of thiophene (120 μL, 1.50 mmol). Yellow oil, 51% yield (47 mg, 0.25 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (d, *J* = 7.1 Hz, 2H), 7.72 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.65 (dd, *J* = 3.8, 1.2 Hz, 1H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.16 (dd, *J* = 4.8, 3.9 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 188.3, 143.8, 138.3, 135.0, 134.3, 132.4, 129.3, 128.5, 128.1. NMR data corresponds with the previously reported compound.[28]



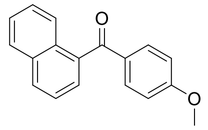
Phenyl(1-tosyl-1H-pyrrol-2-yl)methanone 2.3.2n. Prepared according to the general procedure using 3 mL 1,2-dichloroethane and allowing benzene (89 μL, 1.00 mmol) to iodinate for 5 h before addition of 1-tosyl-1H-pyrrole (332 mg, 1.50 mmol). Yellow solid, 39% yield (64 mg, 0.20 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.4 Hz, 2H), 7.80 (d, *J* = 6.9 Hz, 2H), 7.78 (dd, *J* = 3.2, 1.7 Hz, 1H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 6.71 (dd, *J* = 3.7 ,1.7 Hz, 1H), 6.34 (t, *J* = 3.4 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ 184.6, 145.1, 138.0, 136.3, 133.1, 132.8, 129.8, 129.6, 128.5, 128.3, 125.3, 110.7, 21.8. HRMS: Calculated for $C_{18}H_{15}NO_3SNa$ (M+Na$^+$): 348.0665, found: 348.0671.



(2,5-dimethoxyphenyl)(phenyl)methanone 2.3.2o.[25] Prepared according to the general procedure and allowing benzene (89 μL, 1.00 mmol) to iodinate for 4 h before addition of 1,4-dimethoxybenzene (225 mg, 1.63 mmol). Orange oil, 55% yield (66 mg, 0.27 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (d, *J* = 7.1 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 2H), 7.00 (dd, *J* = 9.0, 3.1 Hz, 1H), 6.94-6.90 (m, 2H), 3.77 (s, 3H), 3.65 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$): δ 196.2, 153.5, 151.5, 137.7, 133.1, 129.9, 129.5, 128.3, 117.4, 114.5, 113.1, 56.4, 55.9. NMR data corresponds with the previously reported compound.[25]

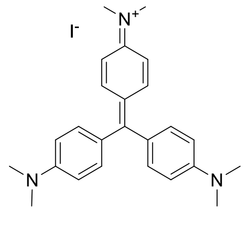


(2,5-dimethylphenyl)(4-methoxyphenyl)methanone 2.3.2p.[11d] Prepared according to the general procedure allowing 1,4-dimethylbenzene (123 µL, 1.00 mmol) to iodinate for 4.5 h before addition of anisole (163 µL, 1.50 mmol). Yellow oil, 82% yield (97 mg, 0.40 mmol). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.79 (d, J = 8.9 Hz, 2H), 7.19-7.12 (m, 2H), 7.09 (s, 1H), 6.92 (d, J = 8.9 Hz, 2H), 3.86 (s, 3H), 2.33 (s, 3H), 2.24 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$): δ 197.7, 163.7, 139.2, 134.8, 132.9, 132.5, 130.8, 130.6, 128.4, 113.8, 55.5, 20.9, 19.4. NMR data corresponds with the previously reported compound.[11d]

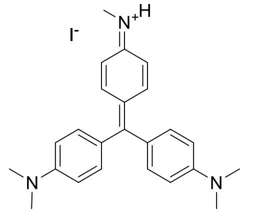


(4-methoxyphenyl)(naphthalen-1-yl)methanone 2.3.2q.[29] Prepared according to the general procedure and allowing naphthalene (129 mg, 1.01 mmol) to iodinate for 5.5 h before addition of anisole (163 µL, 1.50 mmol). Orange oil, 72% yield (95 mg, 0.36 mmol). ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.03 (d, J = 8.3 Hz, 1H), 7.98 (d, J = 8.1 Hz, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.87 (d, J = 8.8 Hz, 2H), 7.60-7.45 (m, 4H), 6.92 (d, J = 8.9 Hz, 2H), 3.85 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$): δ 196.8, 163.9, 137.1, 133.7, 132.8, 131.1, 130.9, 130.7, 128.4, 127.1, 126.9, 126.4, 125.8, 124.5, 113.8, 55.6. NMR data corresponds with the previously reported compound.[29]

2.5.6. Spectroscopic Data for Compounds 2.3.3



Crystal Violet 2.3.3 (R = Me).[30] Prepared according to the general procedure. Green solid in 21% yield (52 mg, 0.10 mmol). ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.29 (d, J = 9.1 Hz, 6H), 6.82 (d, J = 9.2 Hz, 6H), 3.24 (s, 18H). ^{13}C NMR (126 MHz, CDCl$_3$): δ 178.3, 155.6, 139.8, 126.7, 112.5, 40.8. HRMS: Calculated for $C_{25}H_{30}N_3^+$ (M$^+$): 372.2434, found: 372.2437. NMR data corresponds with the previously reported compound.[30]



Methyl Violet 6B 2.3.3’ (R = H). Prepared according to the general procedure. Green solid in 7% yield (16 mg, 0.034 mmol). ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.14 (br s, 1H), 7.28 (d, *J* = 9.1 Hz, 4H), 7.24 (d, *J* = 9.0 Hz, 2H), 7.01 (br s, 2H), 6.79 (d, *J* = 9.1 Hz, 4H), 3.22 (s, 12H), 3.04 (d, *J* = 5.2 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$): δ 177.8, 157.9, 155.1, 140.7, 139.3, 127.0, 126.8, 112.1, 111.8, 40.6, 29.8. HRMS: Calculated for $C_{24}H_{28}N_3^+$ (M$^+$): 358.2278, found: 358.2290.

2.5.7. NMR Spectra

For all ^{1}H and ^{13}C NMR spectra of isolated products, please see Appendix A.

2.6 References

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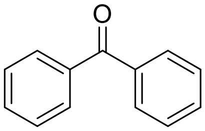
Chapter 3. Conclusions

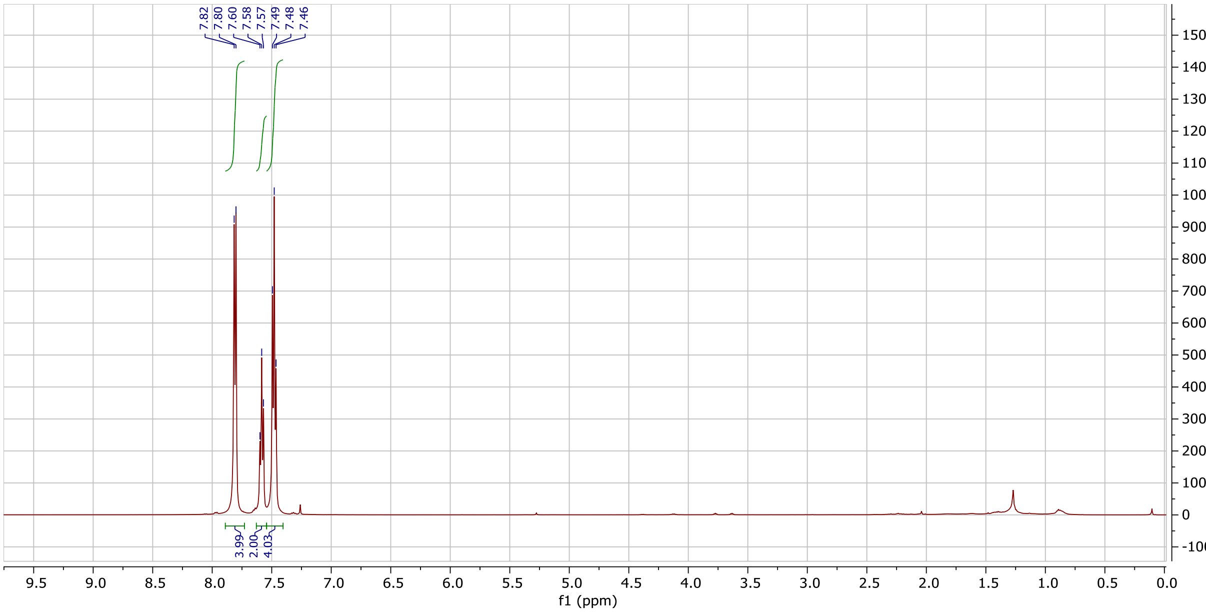
As stated in the introduction to this thesis, palladium-catalyzed cross-coupling reactions have revolutionized modern synthetic chemistry. Although their utility is undeniable, cross-coupling reactions typically result in stoichiometric metal waste due to the requirement for pre-functionalization of the arene substrates employed. As an alternative, the use of arene C-H bonds as substrates in palladium-catalyzed coupling reactions can allow for shorter, less wasteful, and more convenient reaction pathways. However, C-H bond cleavage is non-trivial and leads to issues of chemo- and regioselectivity. Additionally, the C-C bonds often generated in these arene couplings are difficult to further manipulate. As an alternative, the incorporation of a reactive functionality during the bond-forming step could give products that are easier to subsequently modify in synthesis. Carbon monoxide is an excellent candidate for this and can lead to the formation of valuable carbonyl-containing products. This thesis describes research into the combination of palladium-catalyzed carbonylation and C-H bond functionalization as a route to prepare ketones.

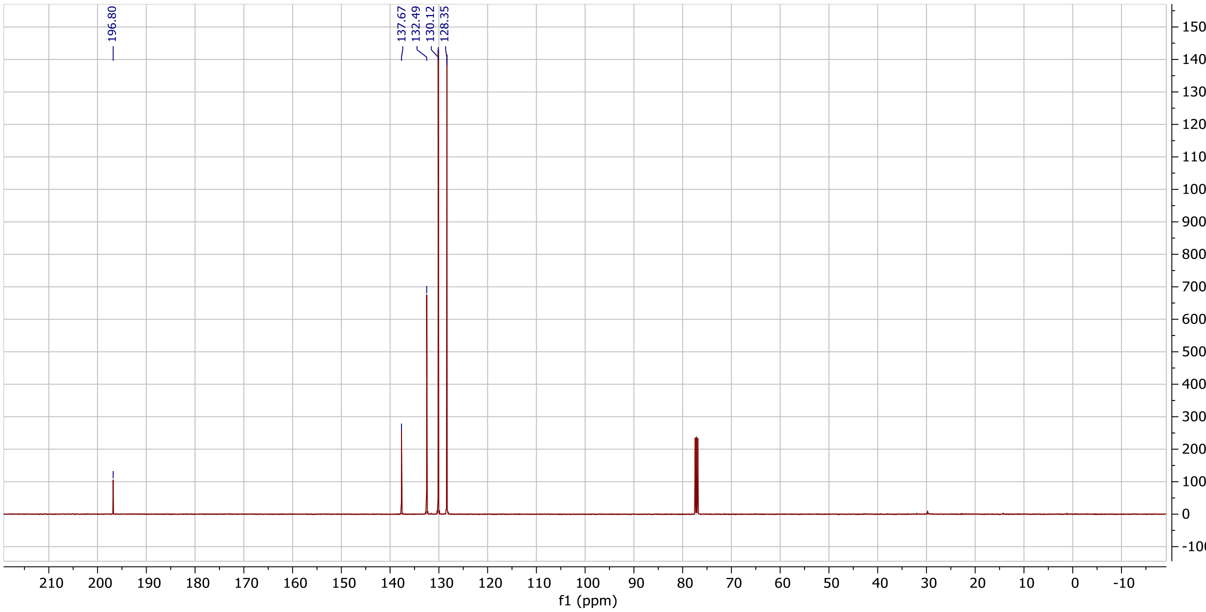
Chapter 2 describes the development of a new palladium-catalyzed platform for the synthesis of biaryl ketones through the carbonylative coupling of two arenes. Mechanistic analysis suggests that this reaction proceeds via the *in situ* formation of aryl iodides followed by potent aroyl triflate electrophiles, with the latter having the ability to functionalize a second arene to form ketones. By performing the reaction in either one or two steps, the selective formation of homocoupled or heterocoupled (hetero)aryl ketones can be achieved. Overall, this system allows for the catalytic formation of biaryl ketones from their most basic building blocks – arenes and carbon monoxide – without any need for pre-functionalization of the arene substrates.

Appendix A: NMR Spectra for Chapter 2.

^{1}H NMR and ^{13}C NMR of 2.3.1a







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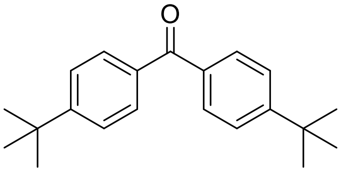

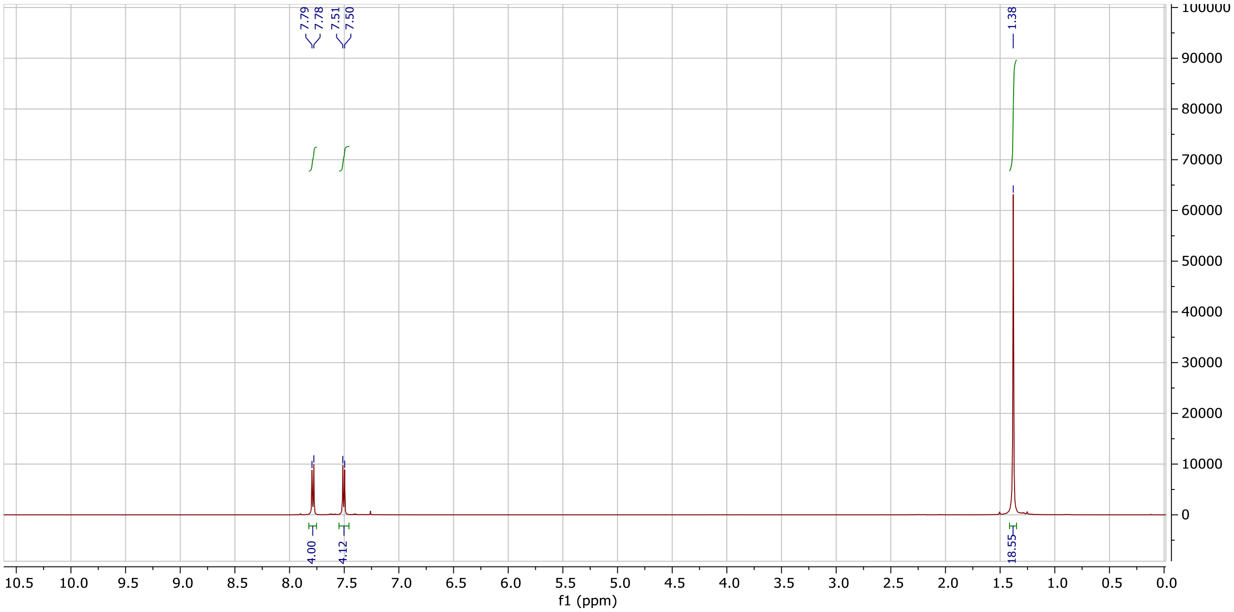

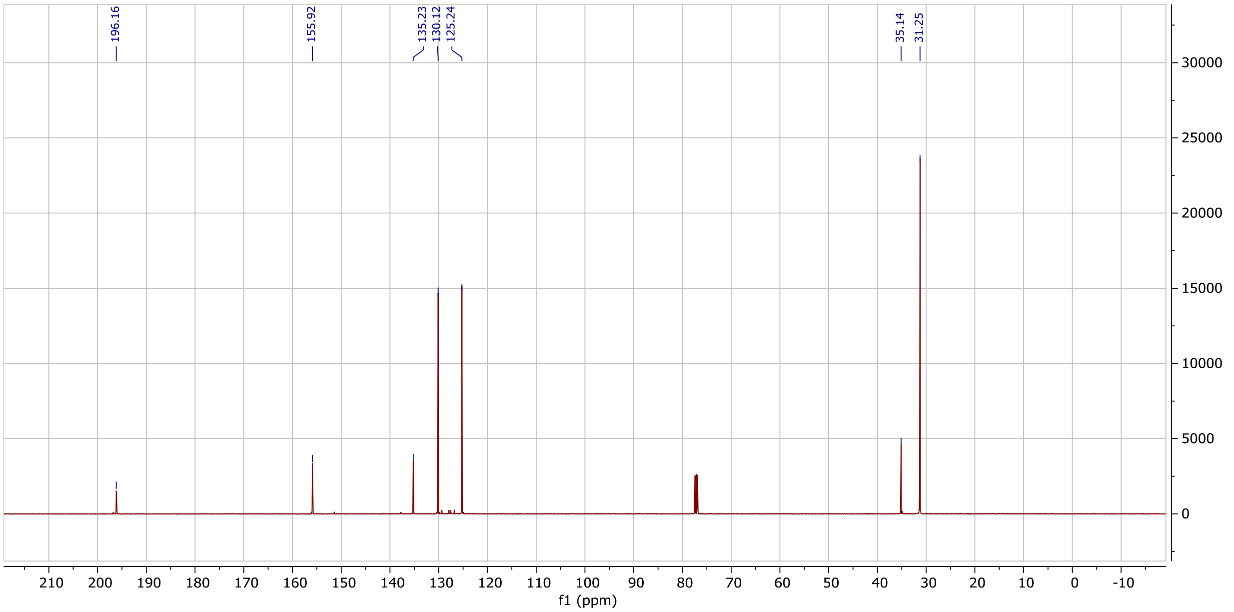

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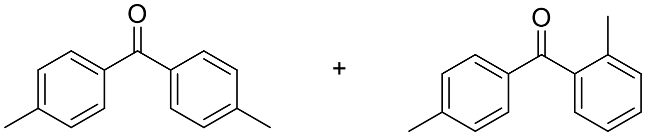
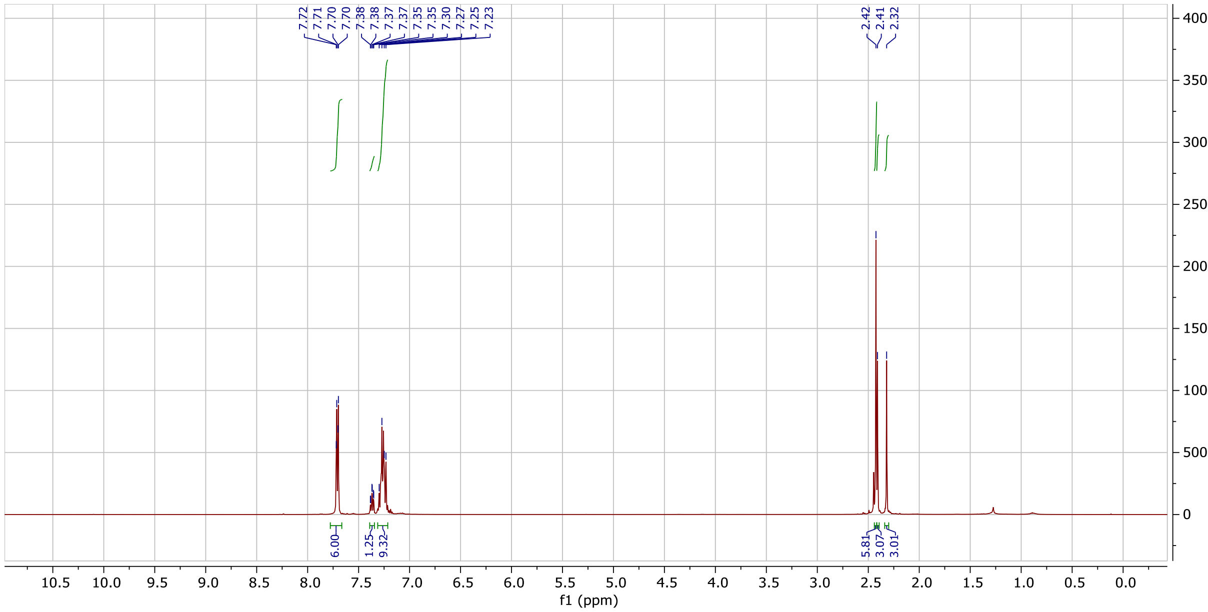
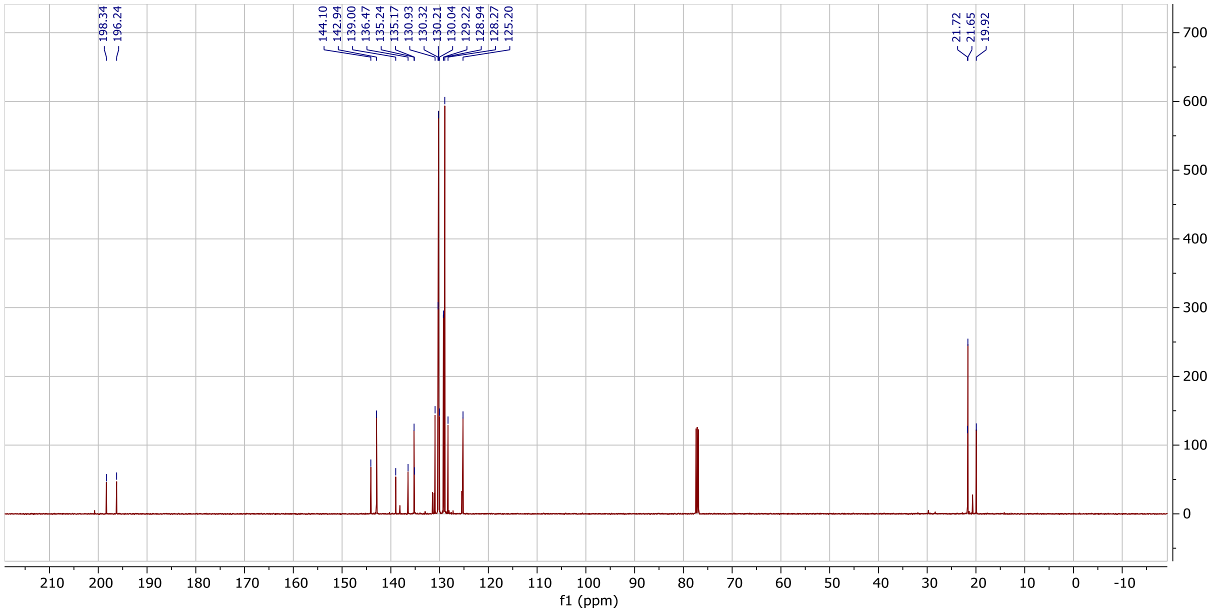
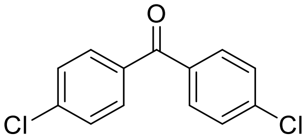
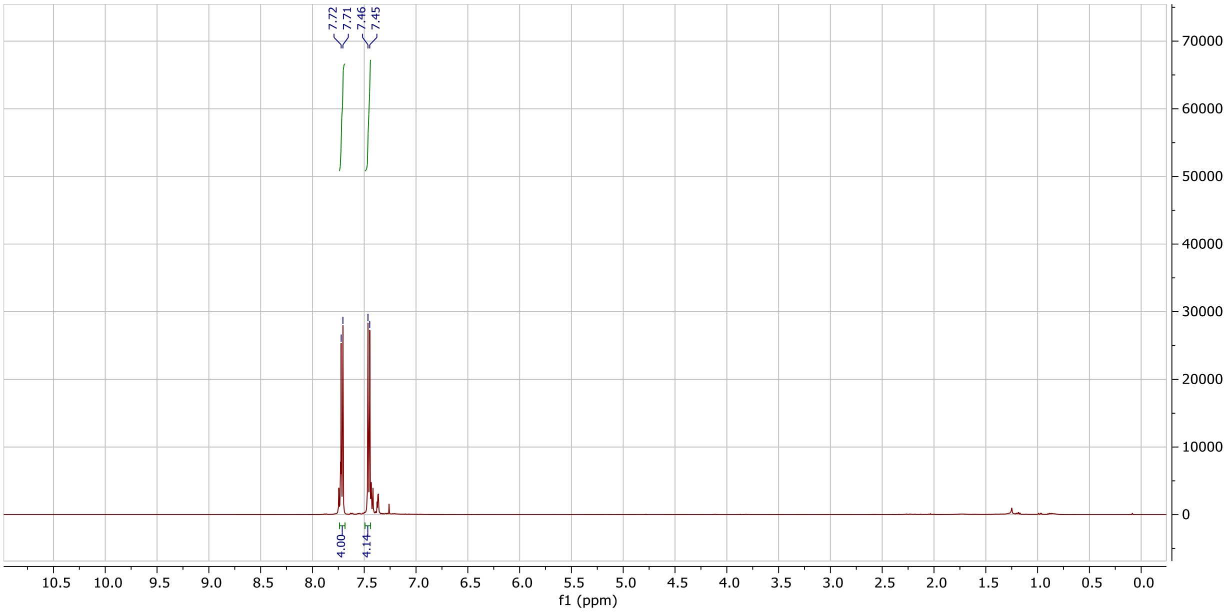


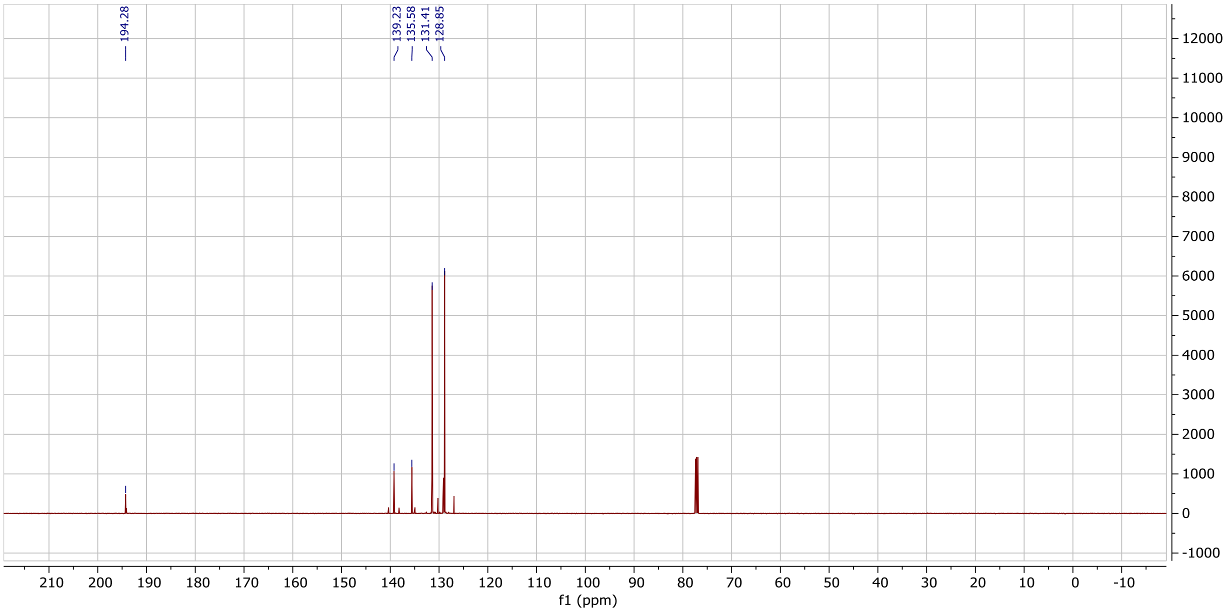




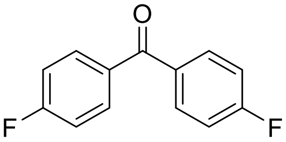
^{1}H NMR and ^{13}C NMR of 2.3.1d

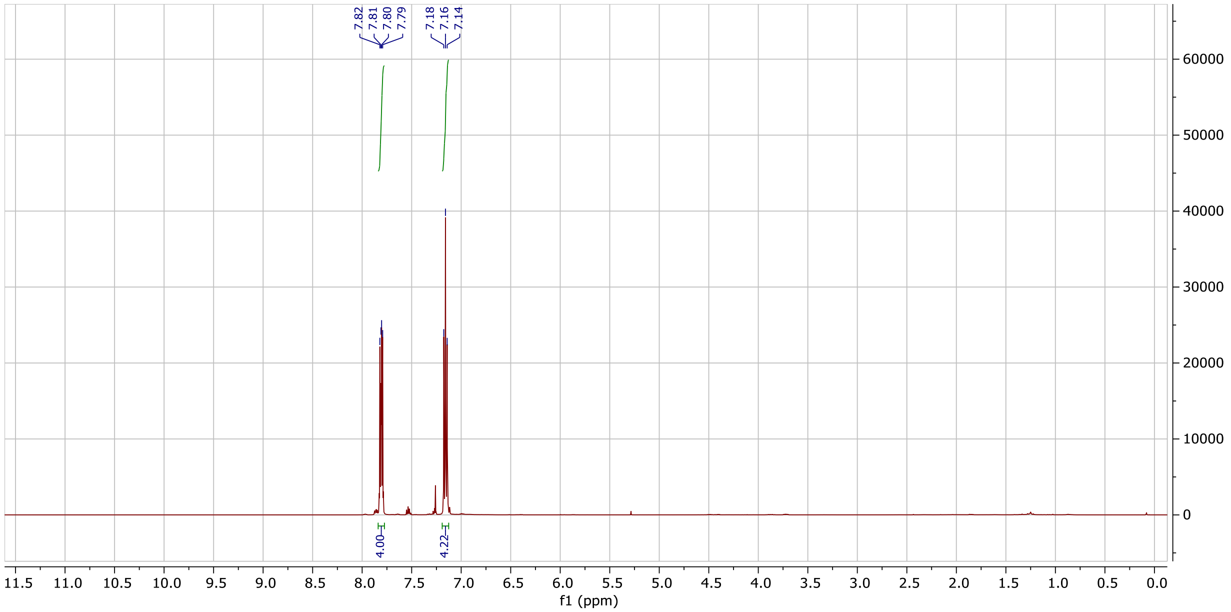


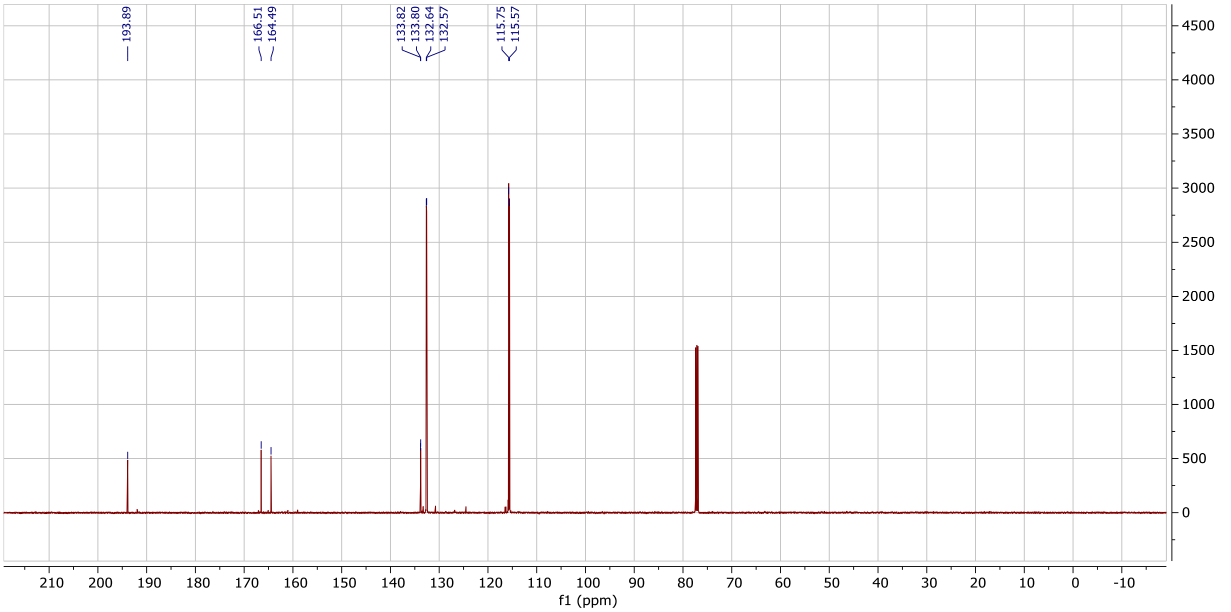




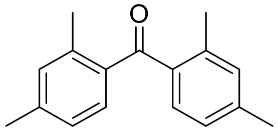
^{1}H NMR and ^{13}C NMR of 2.3.1e

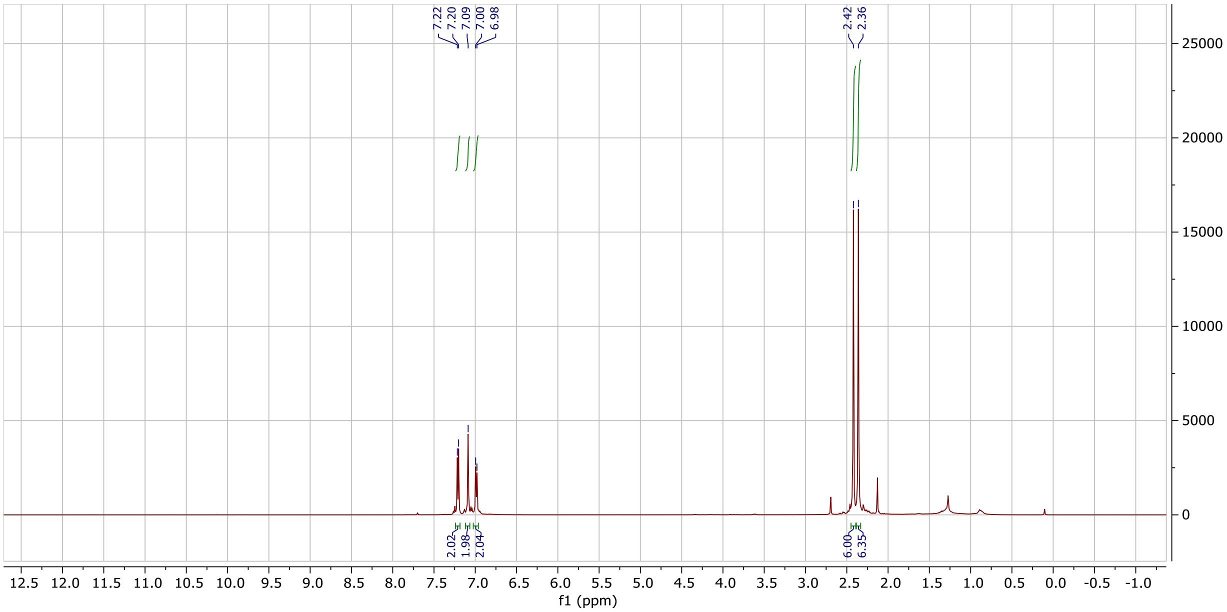


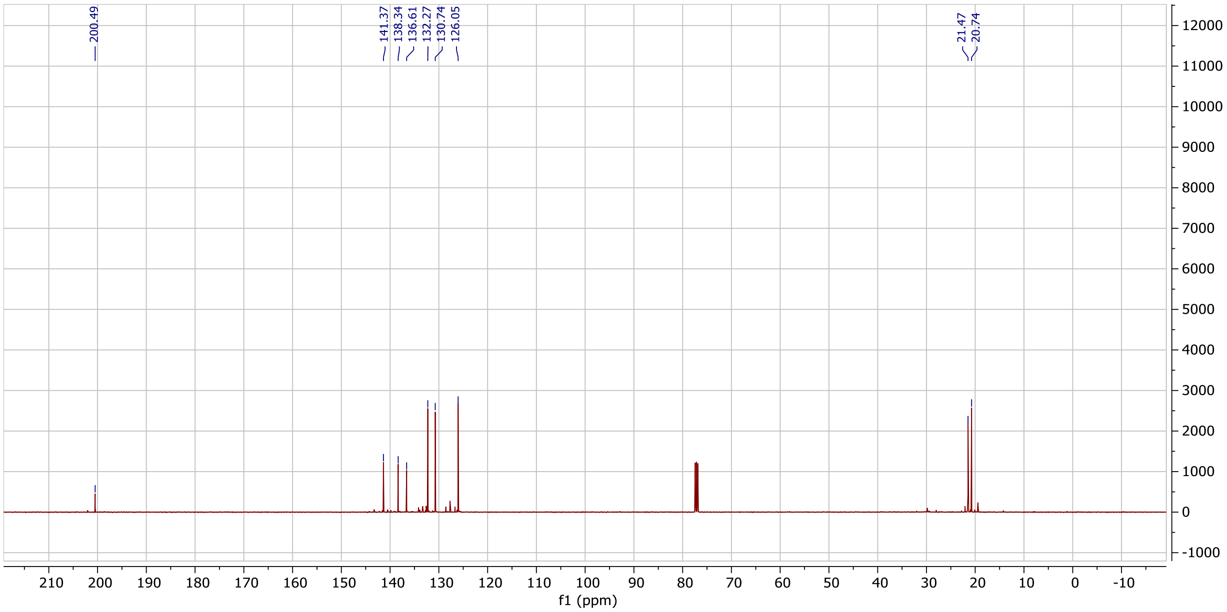




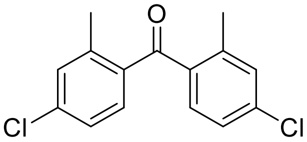
^{1}H NMR and ^{13}C NMR of 2.3.1f

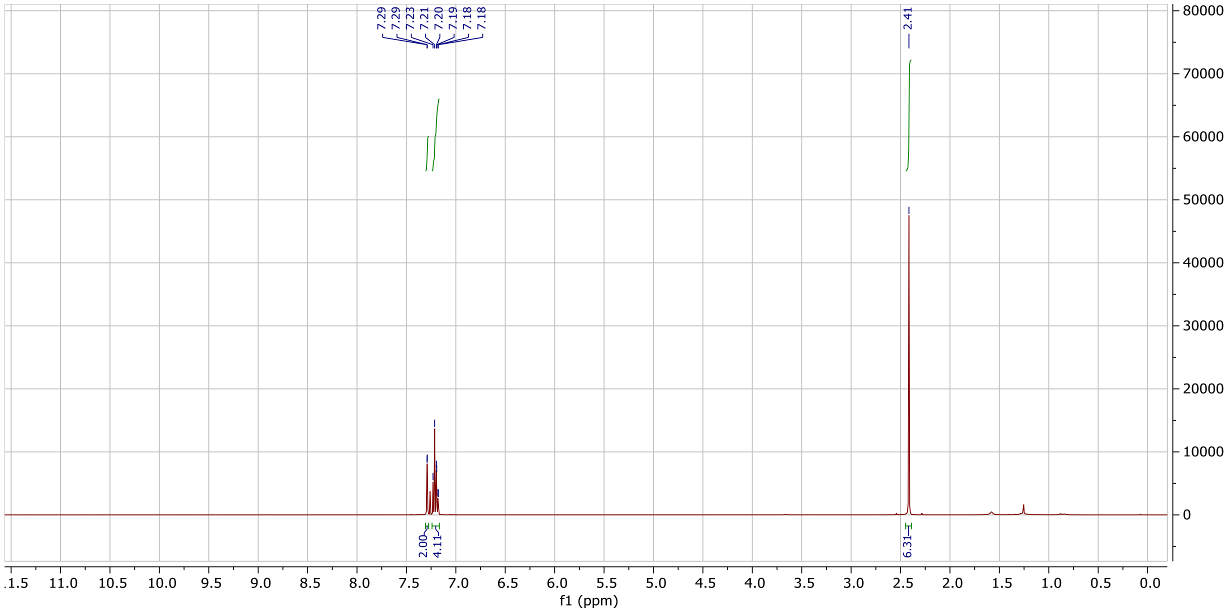


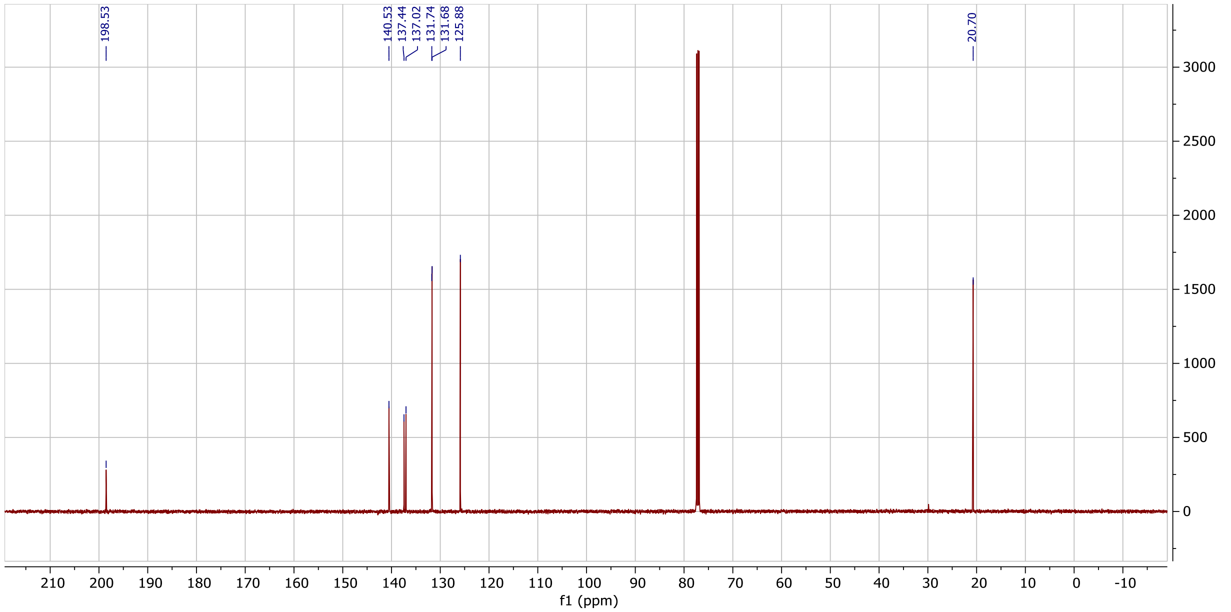




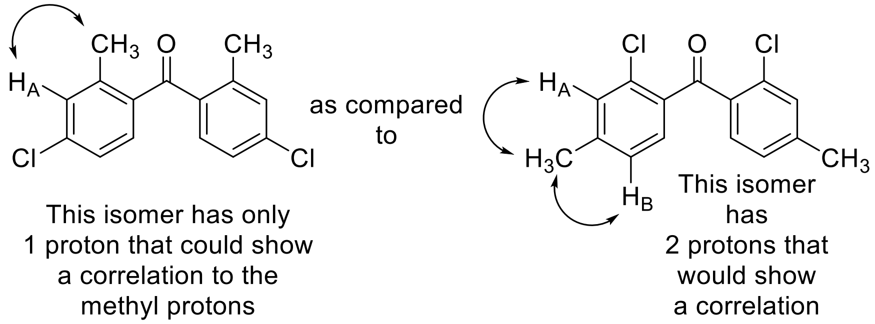
^{1}H NMR and ^{13}C NMR of 2.3.1g







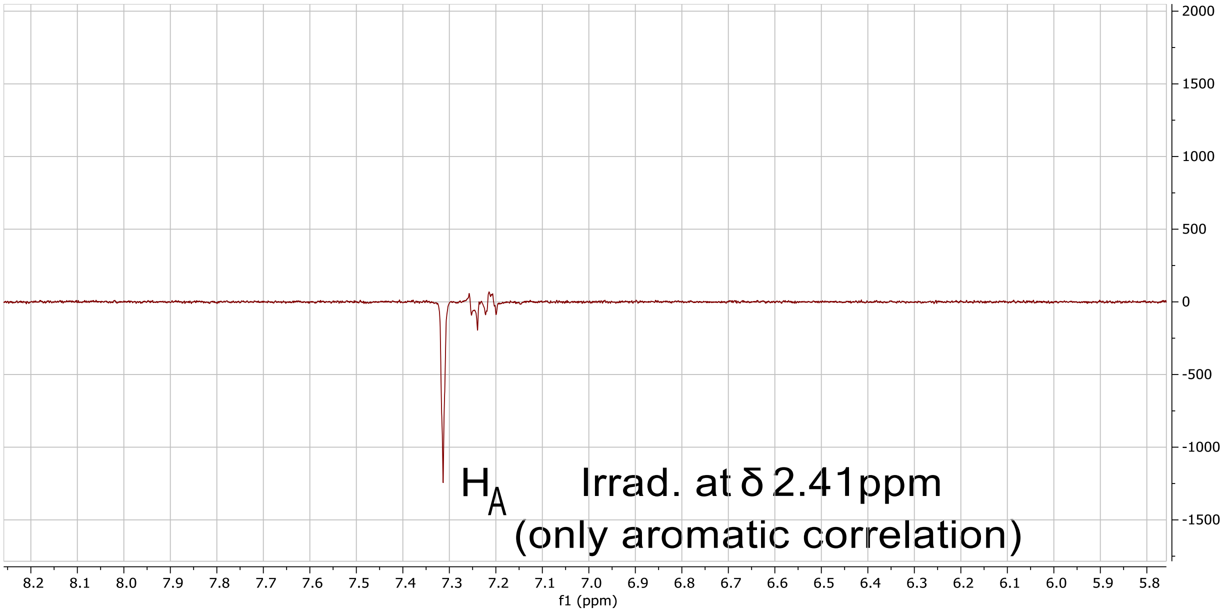
SelNOE NMR Spectrum for 2.3.1g



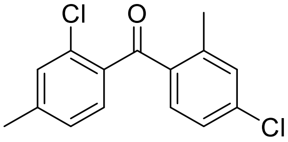
as compared to

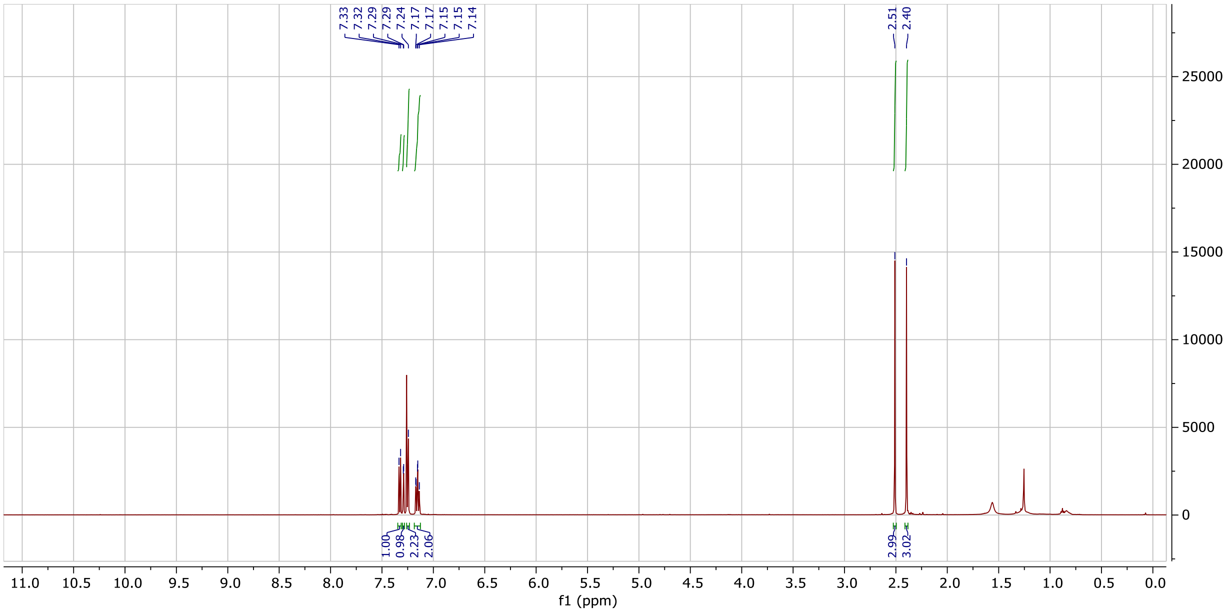
This isomer has only 1 proton that could show a correlation to the methyl protons

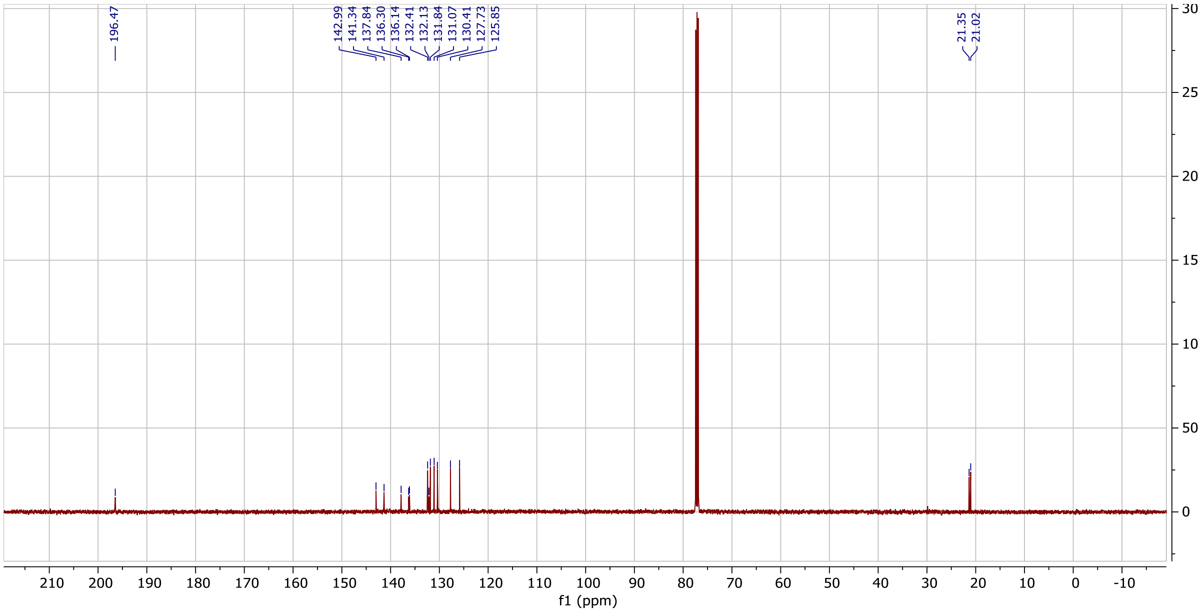
This isomer has 2 protons that would show a correlation



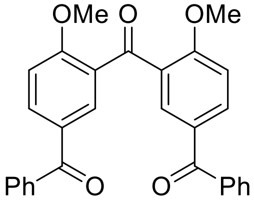
^{1}H NMR and ^{13}C NMR of 2.3.1g’

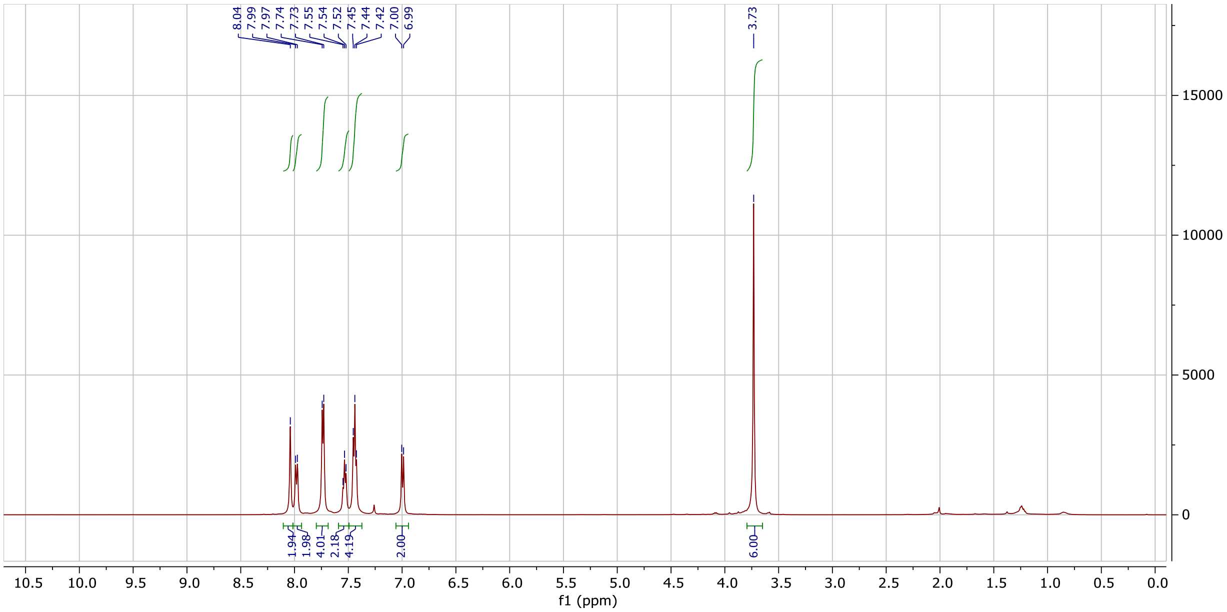


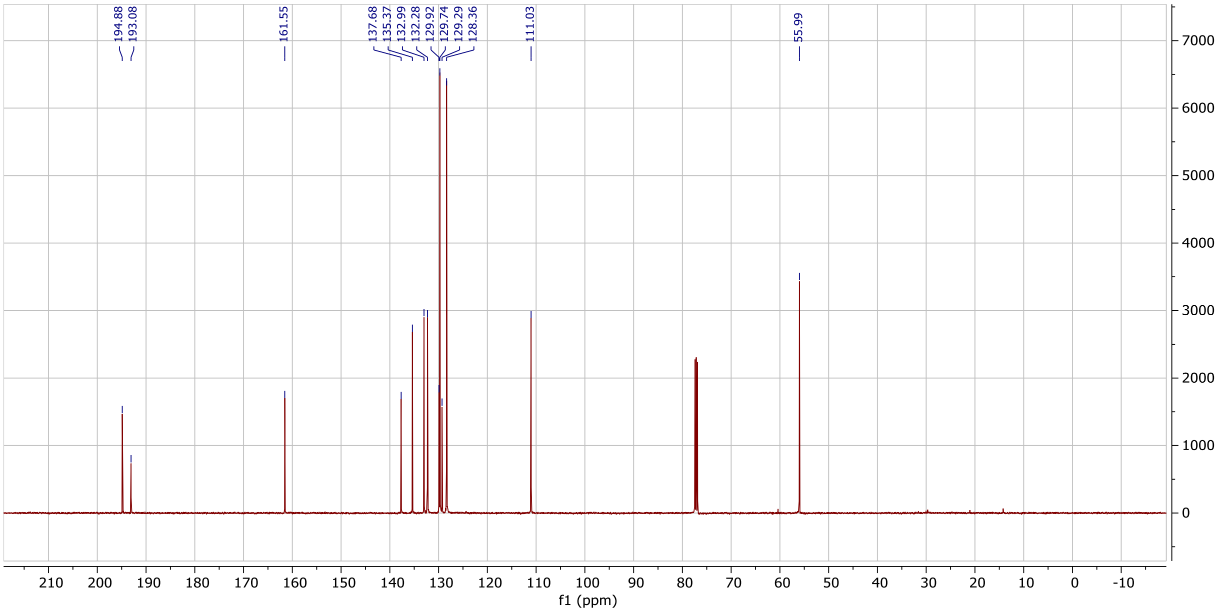




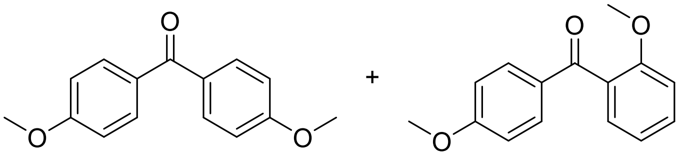
^{1}H NMR and ^{13}C NMR of 2.3.1h

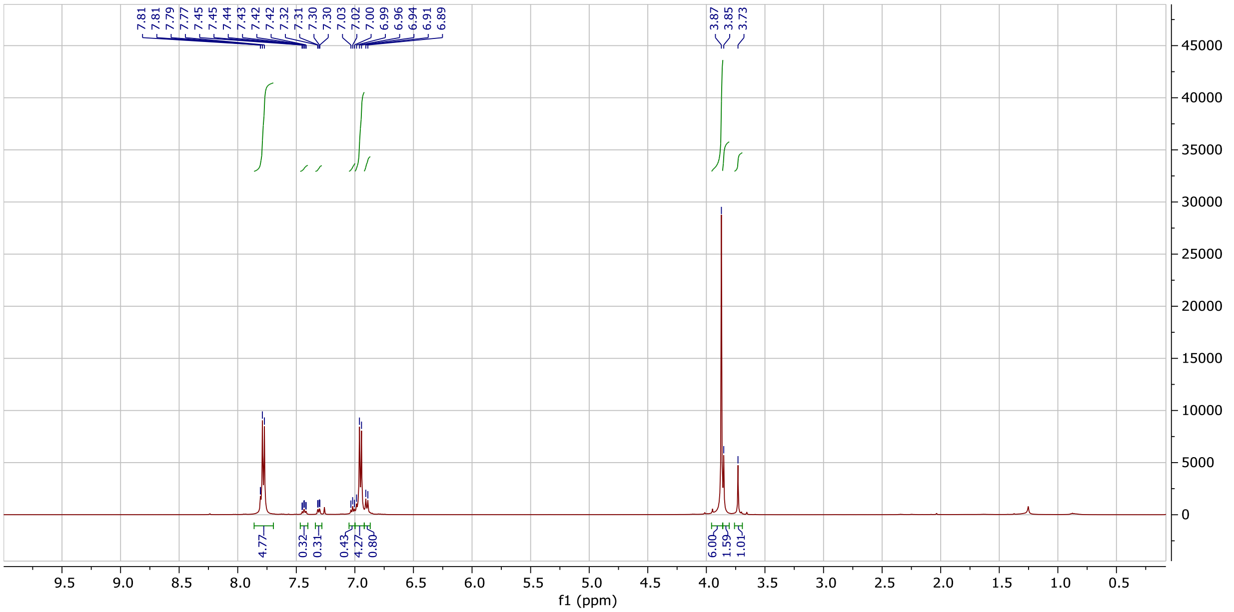


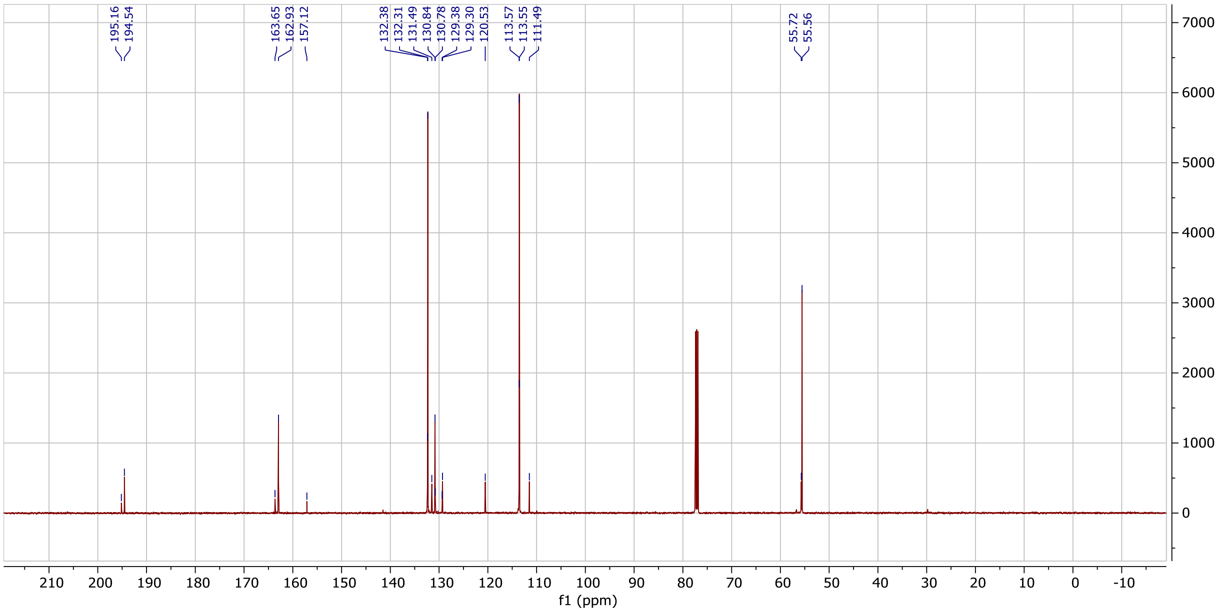




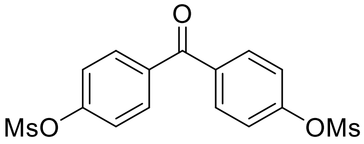
^{1}H NMR and ^{13}C NMR of 2.3.1i and 2.3.1i’

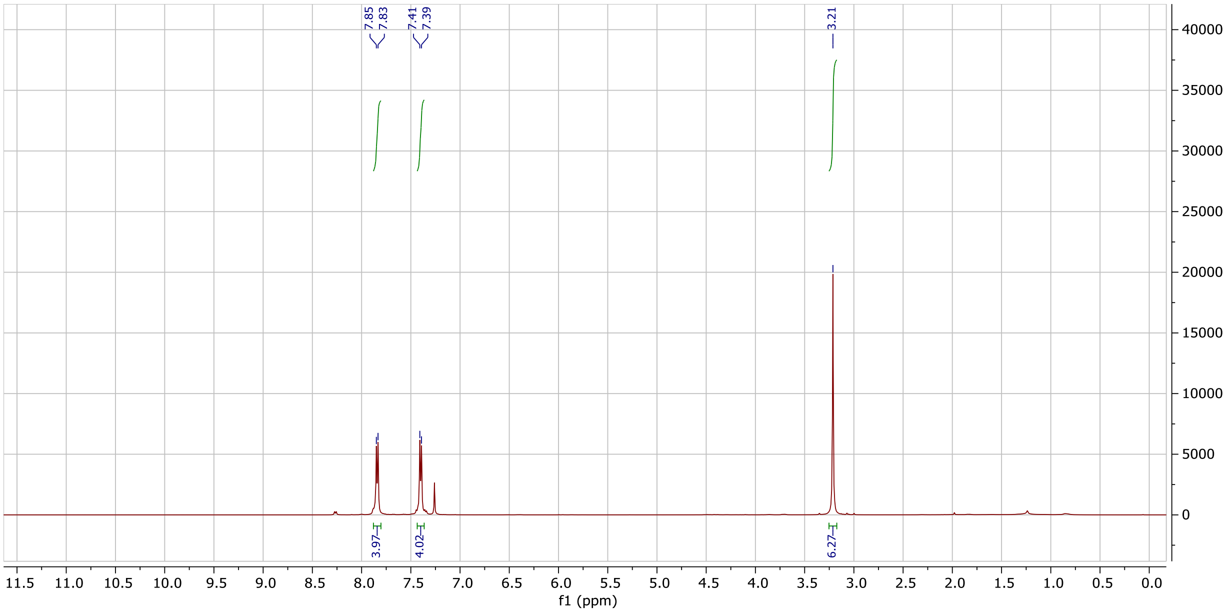


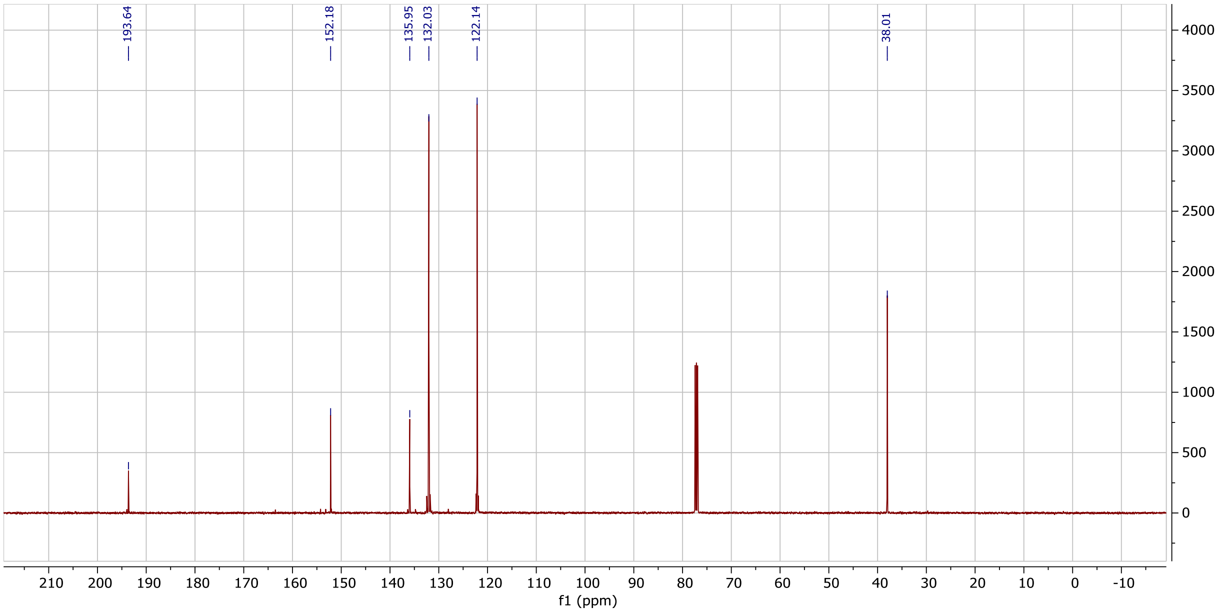




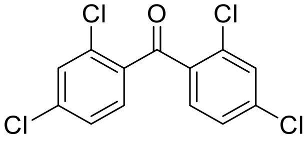
^{1}H NMR and ^{13}C NMR of 2.3.1j

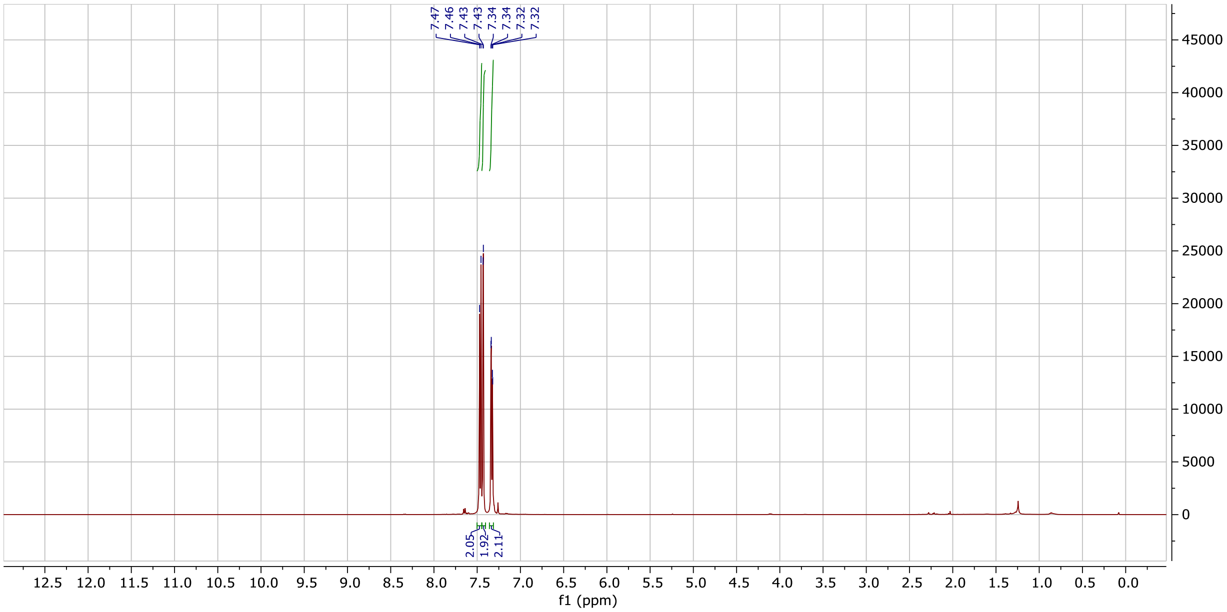


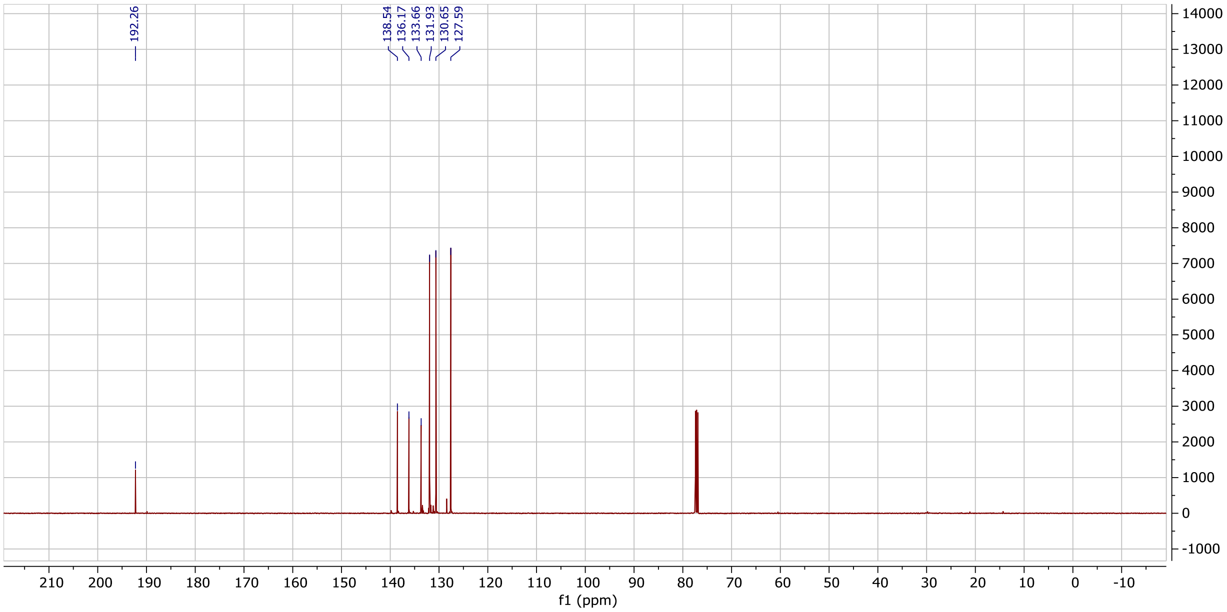




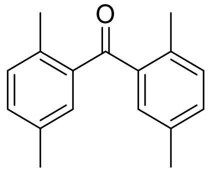
^{1}H NMR and ^{13}C NMR of 2.3.1k

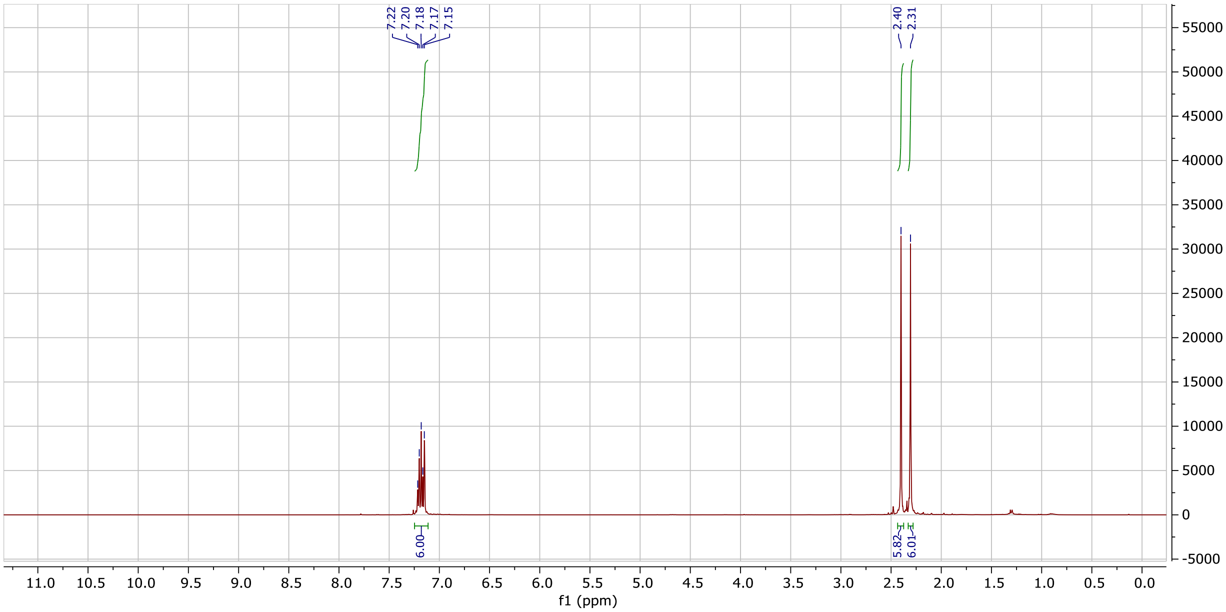


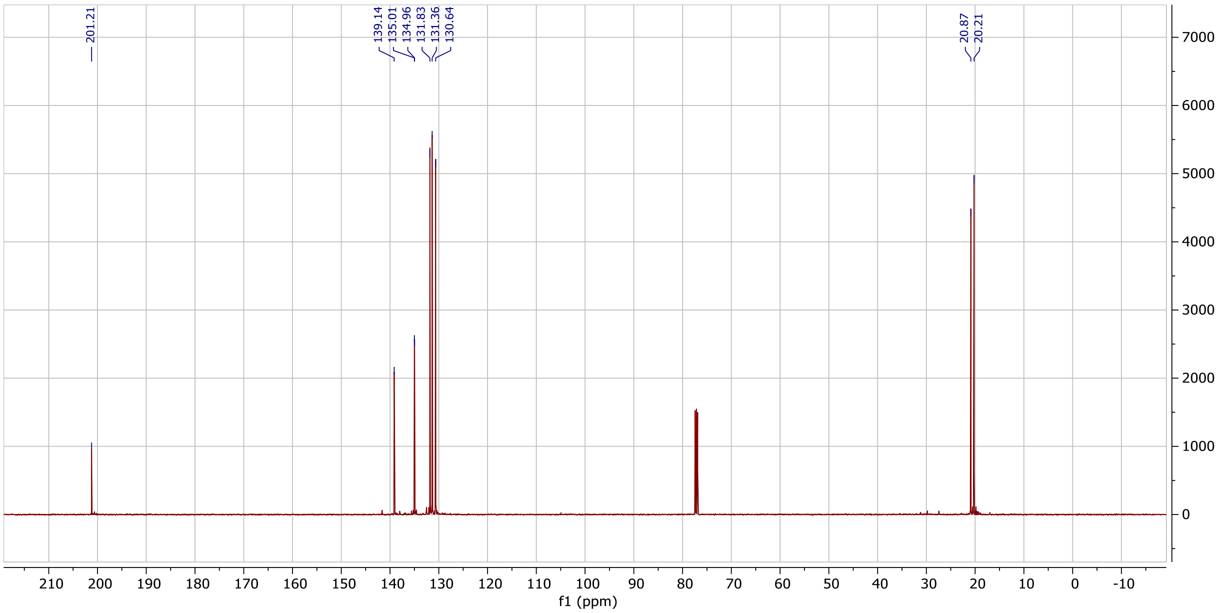




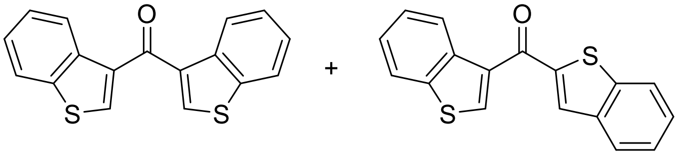
^{1}H NMR and ^{13}C NMR of 2.3.1l

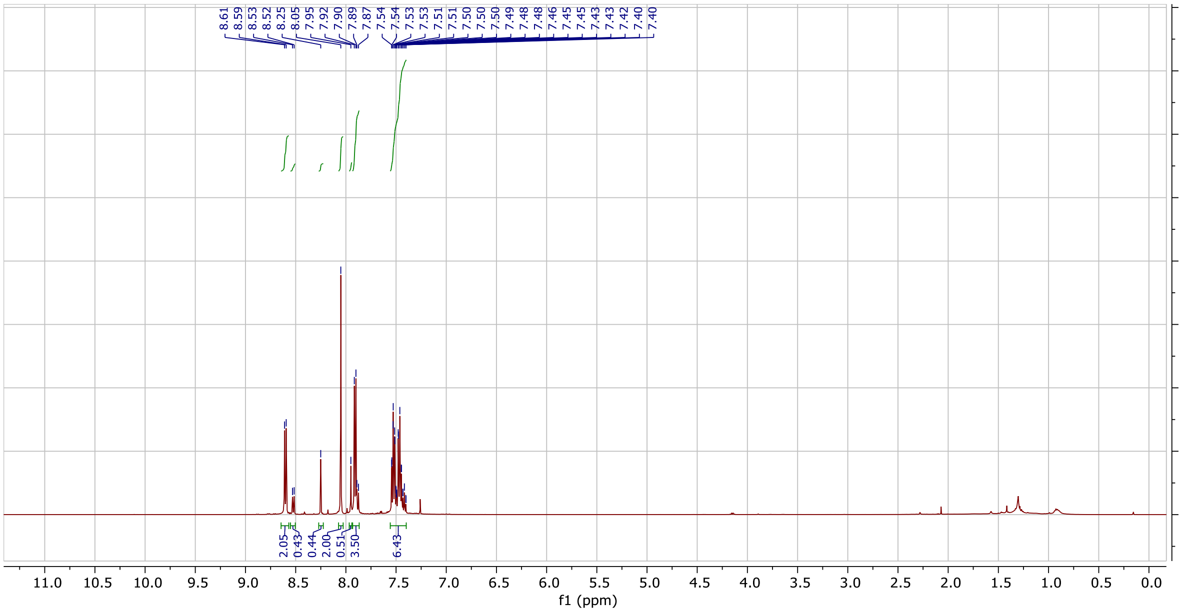


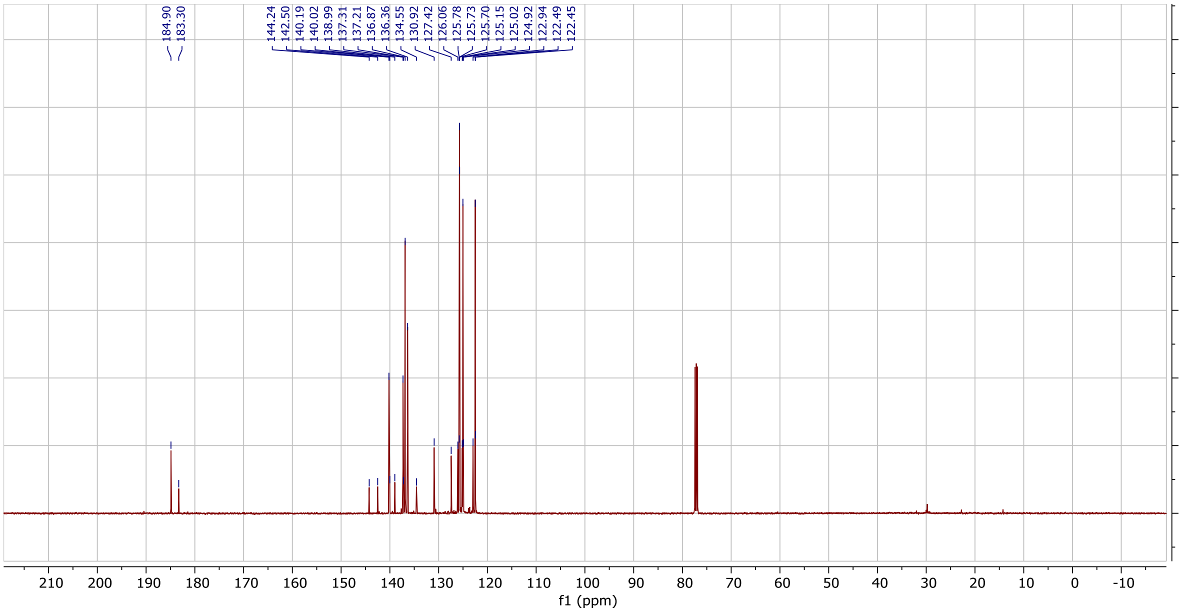




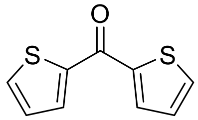
^{1}H NMR and ^{13}C NMR of 2.3.1m and 2.3.1m’

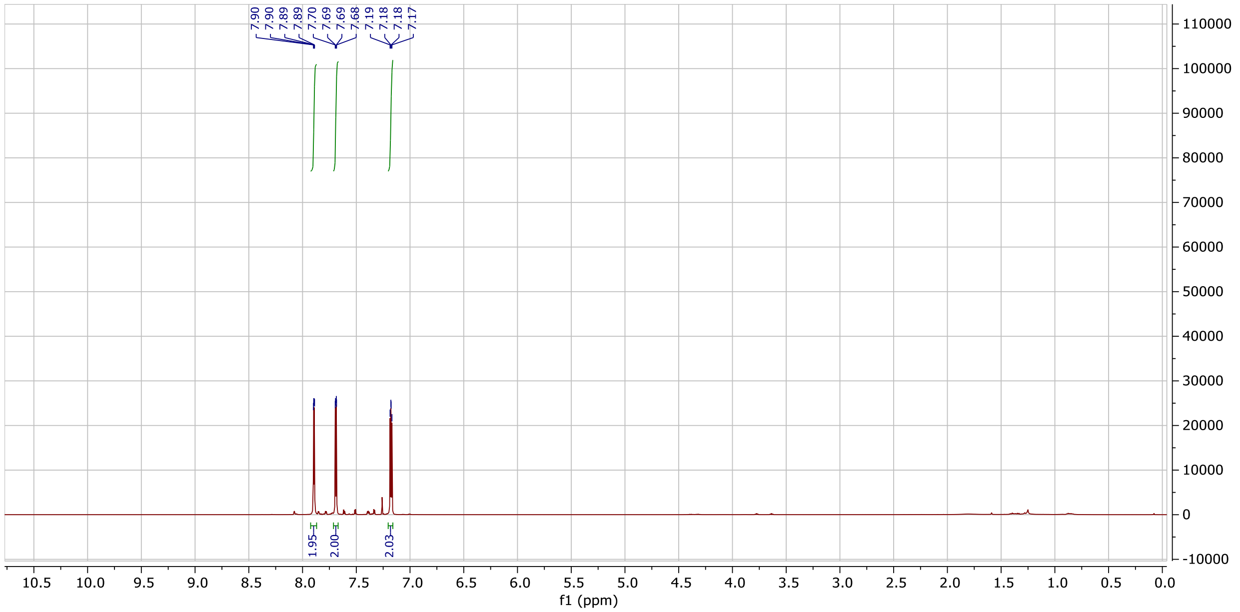


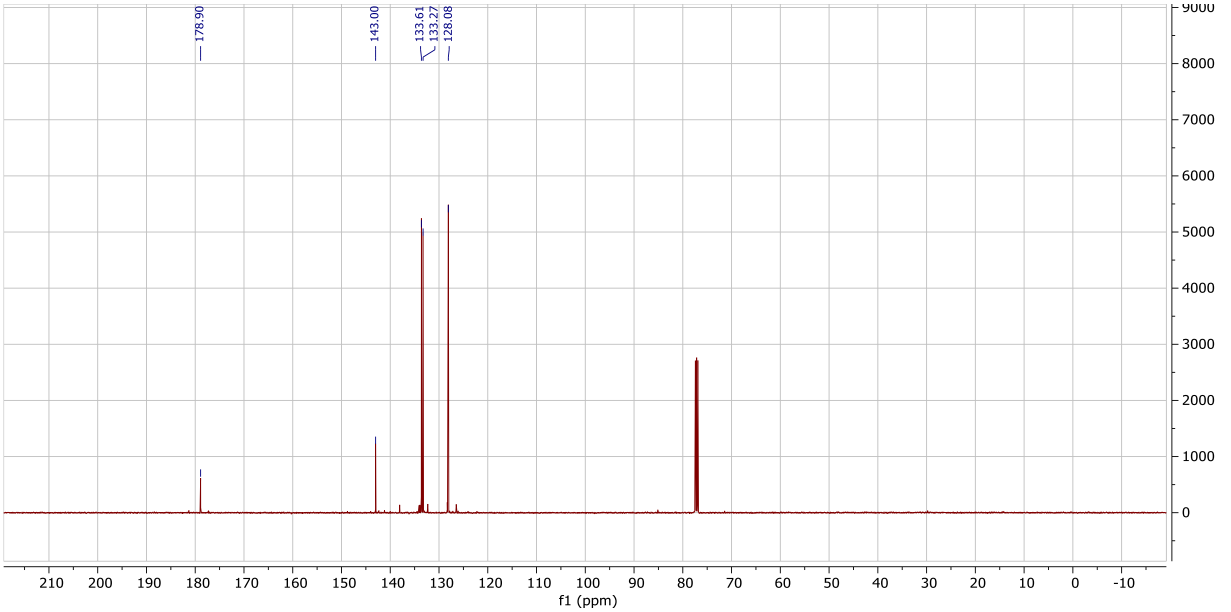




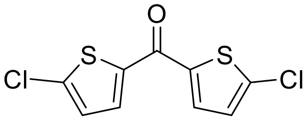
^{1}H NMR and ^{13}C NMR of 2.3.1n

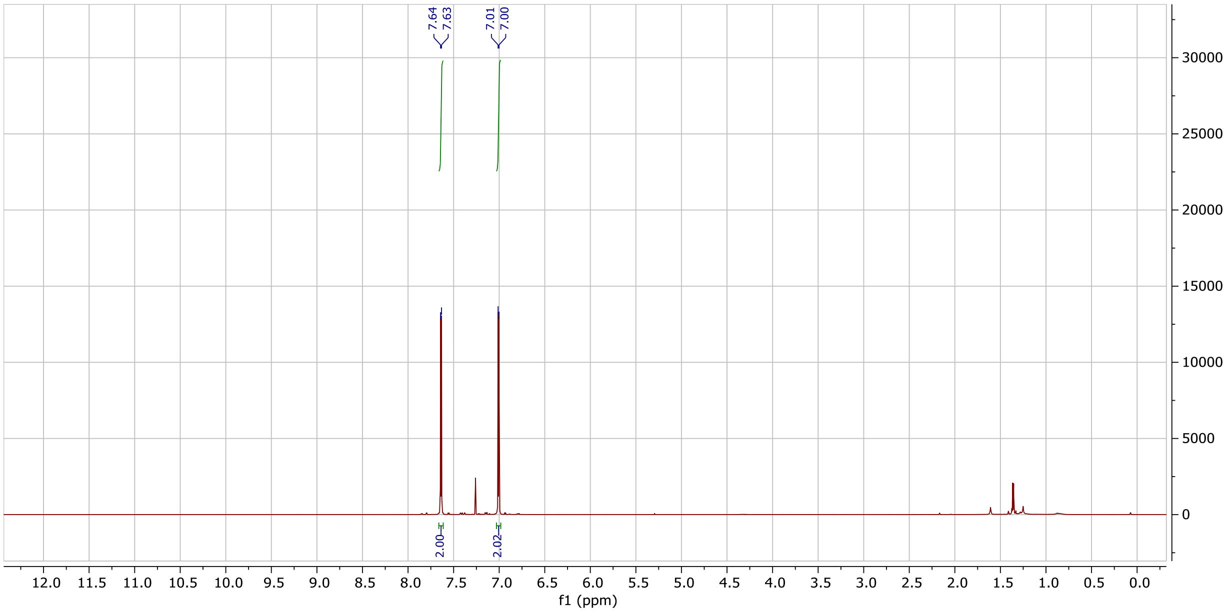


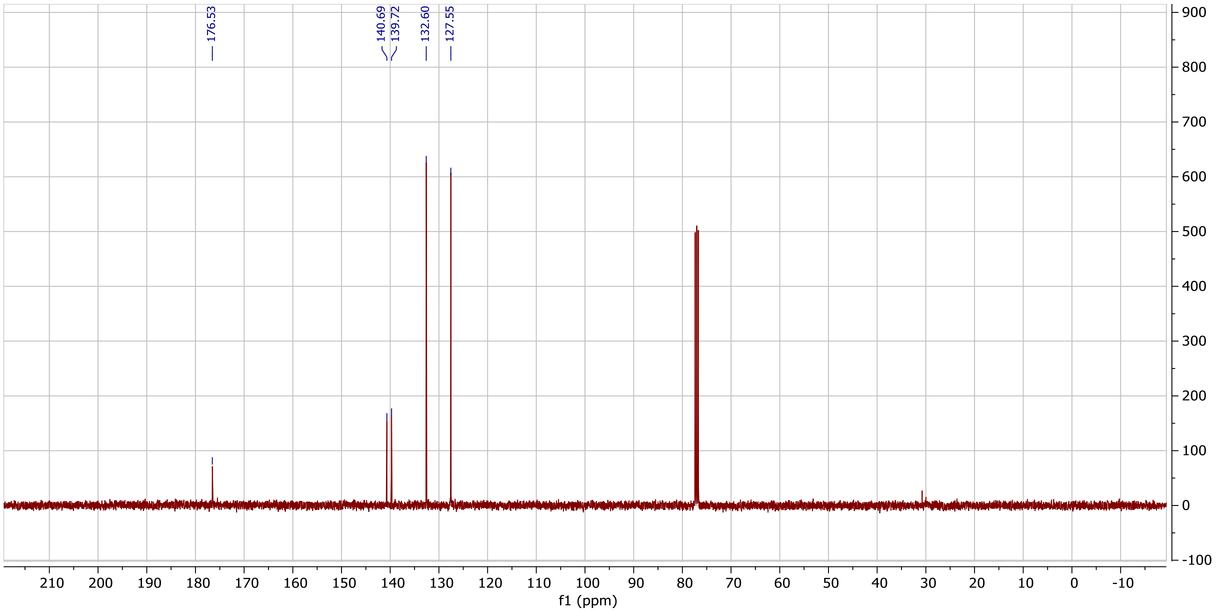




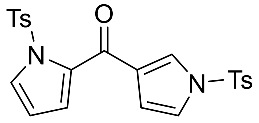
^{1}H NMR and ^{13}C NMR of 2.3.1o

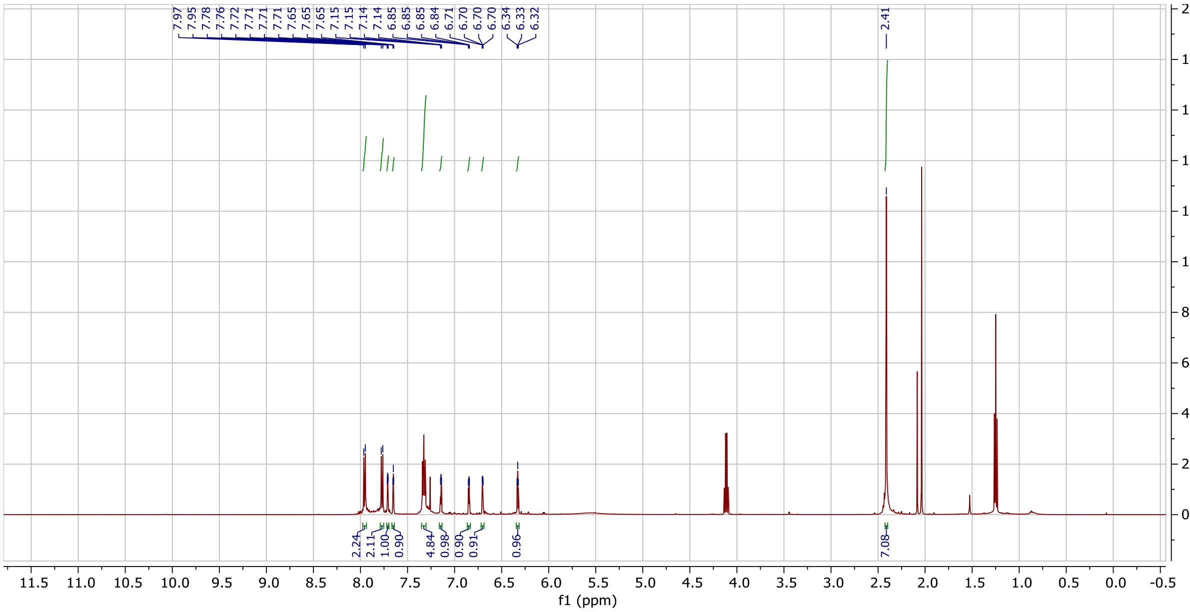


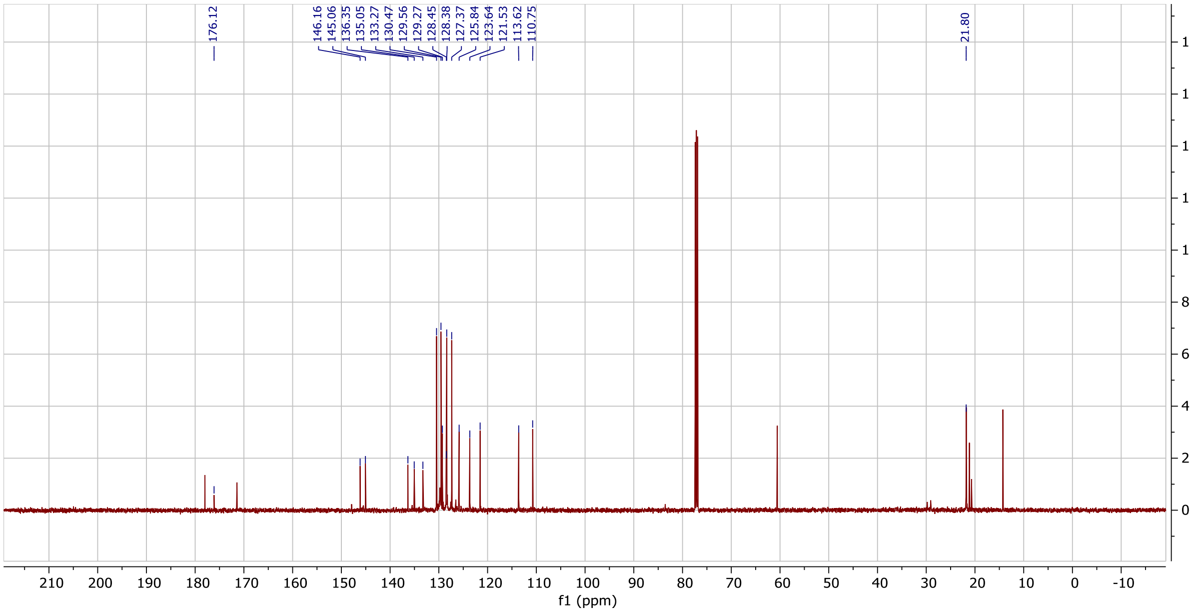




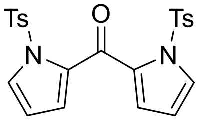
^{1}H NMR and ^{13}C NMR of 2.3.1p

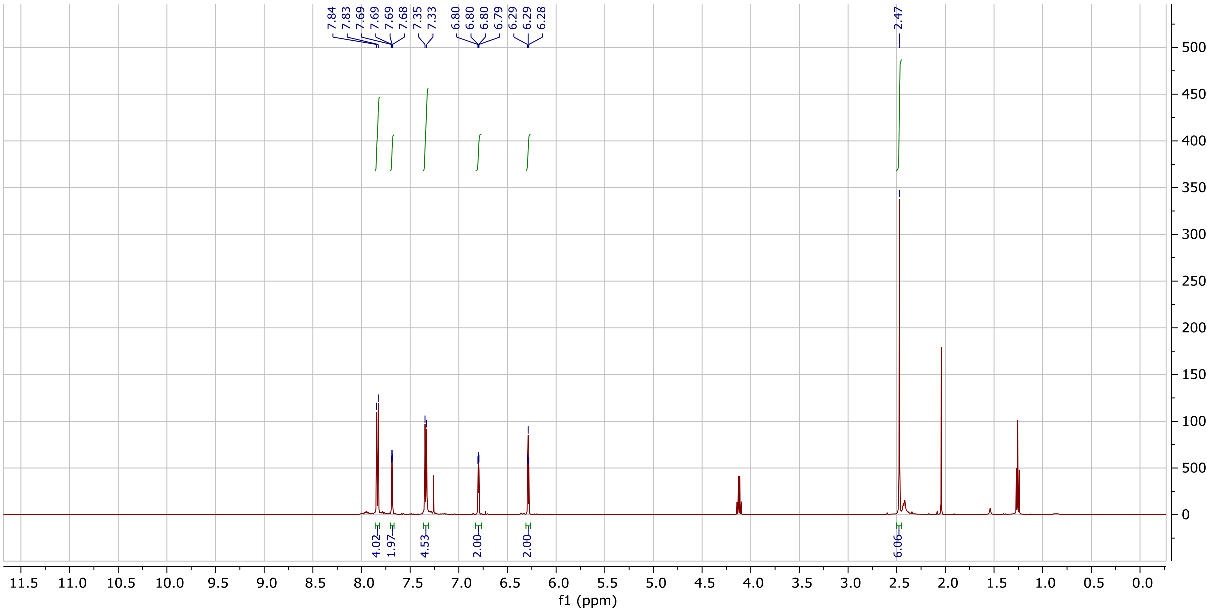


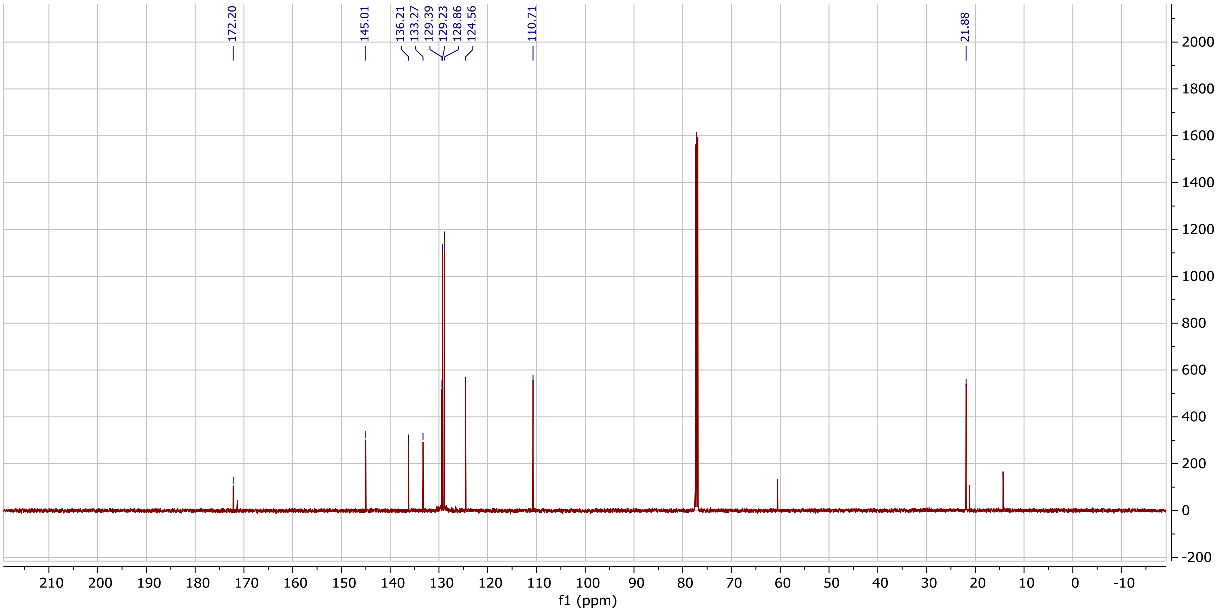




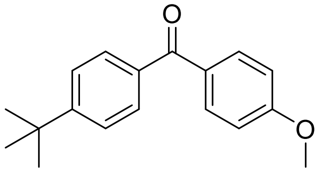
^{1}H NMR and ^{13}C NMR of 2.3.1p'

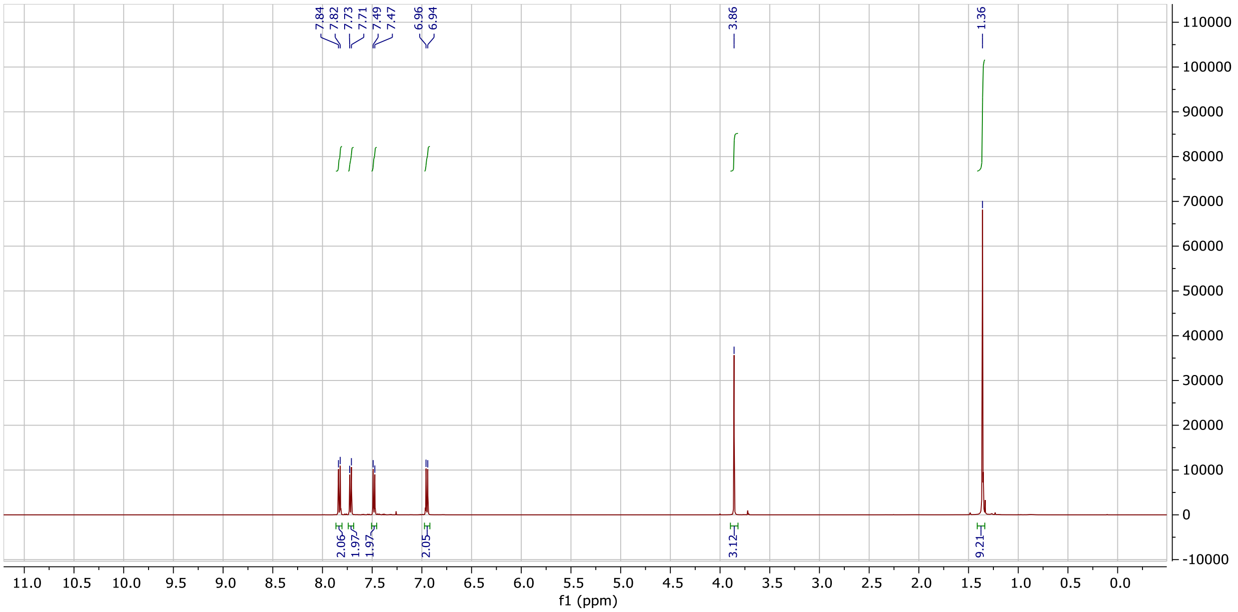


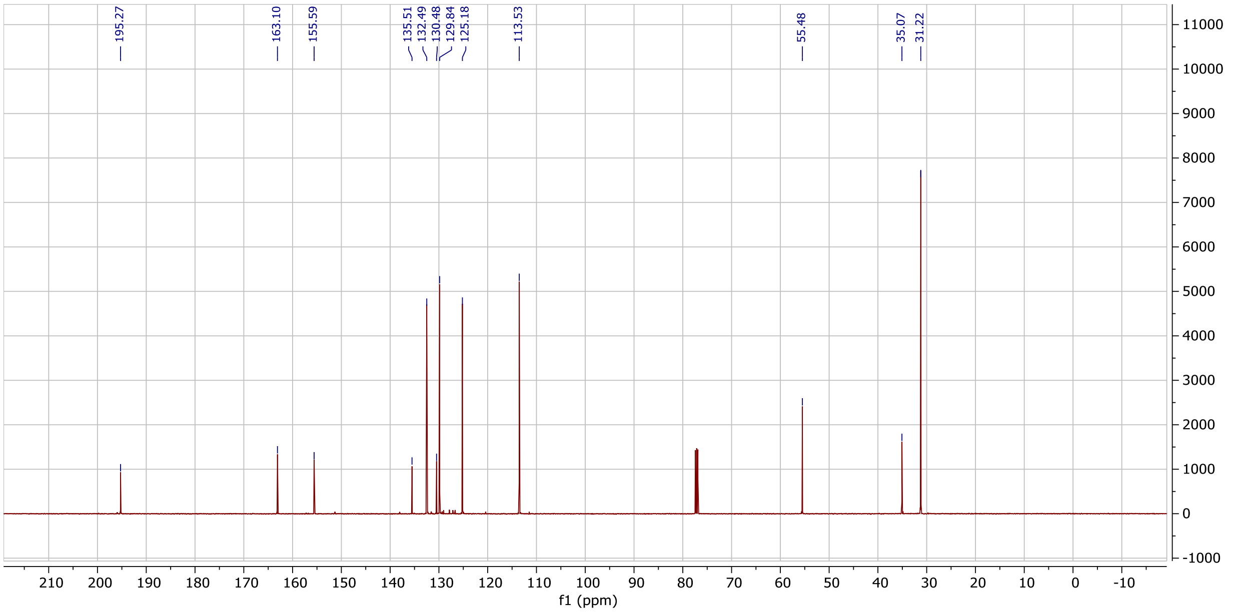




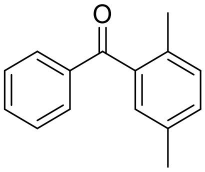
^{1}H NMR and ^{13}C NMR of 2.3.2a

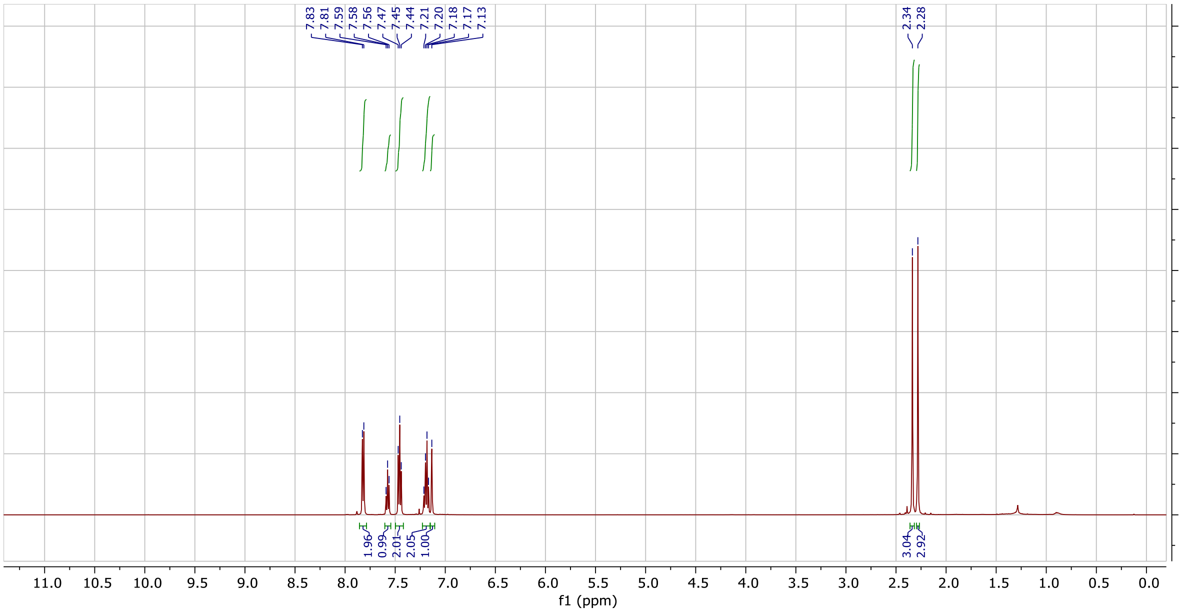


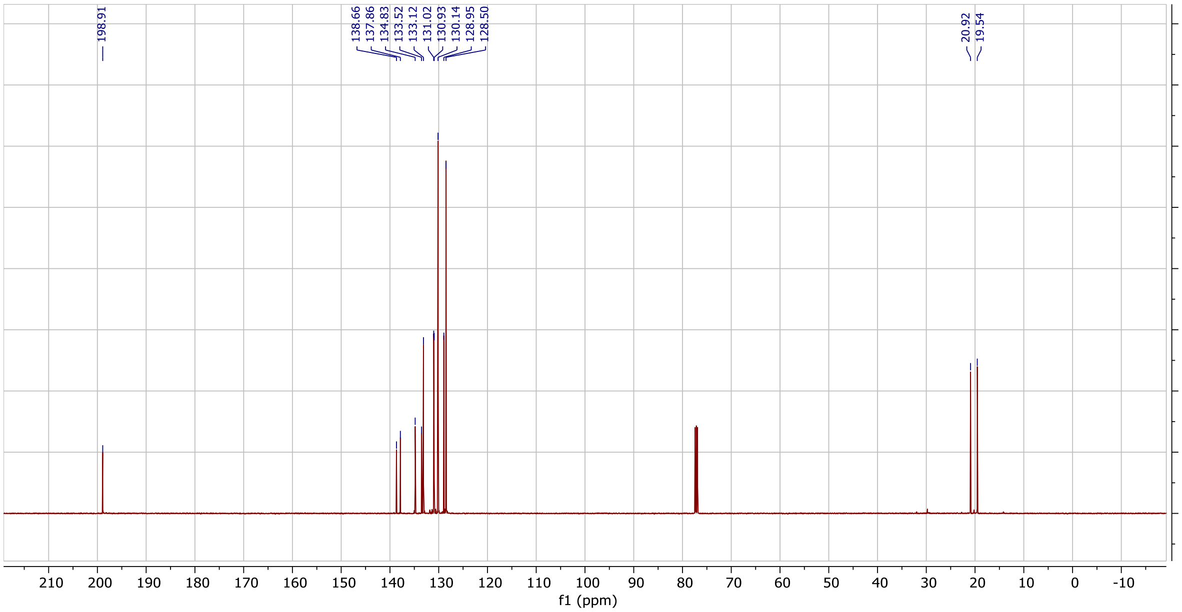




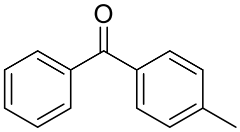
^{1}H NMR and ^{13}C NMR of 2.3.2b

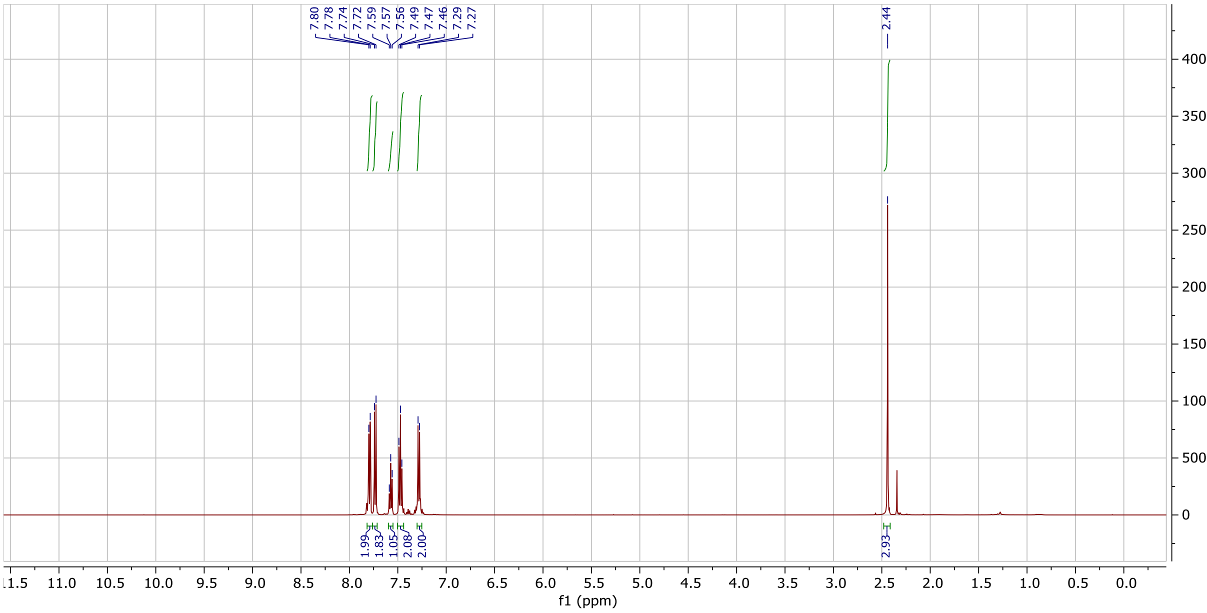


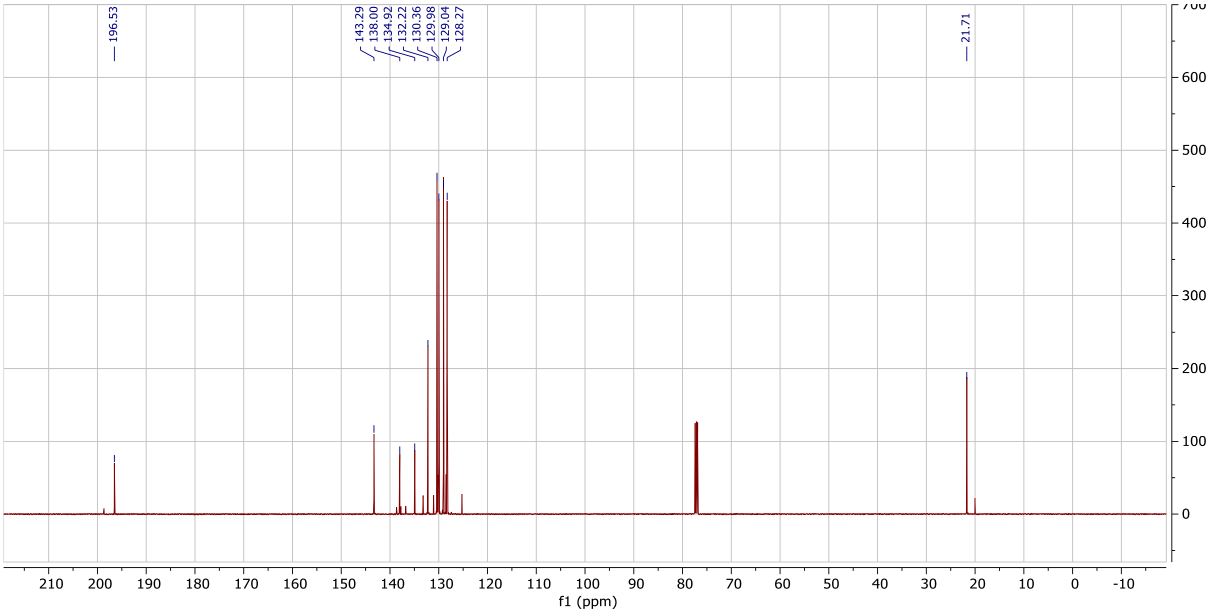




^{1}H NMR and ^{13}C NMR of 2.3.2c







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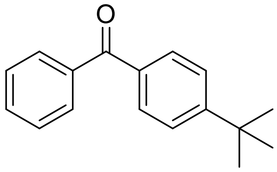

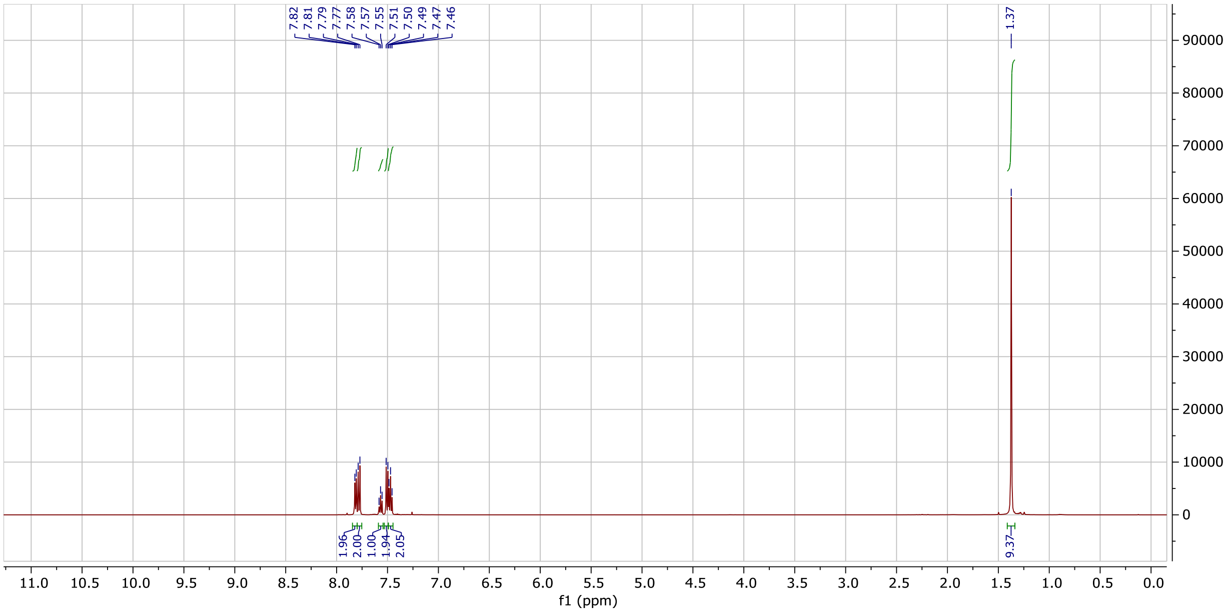

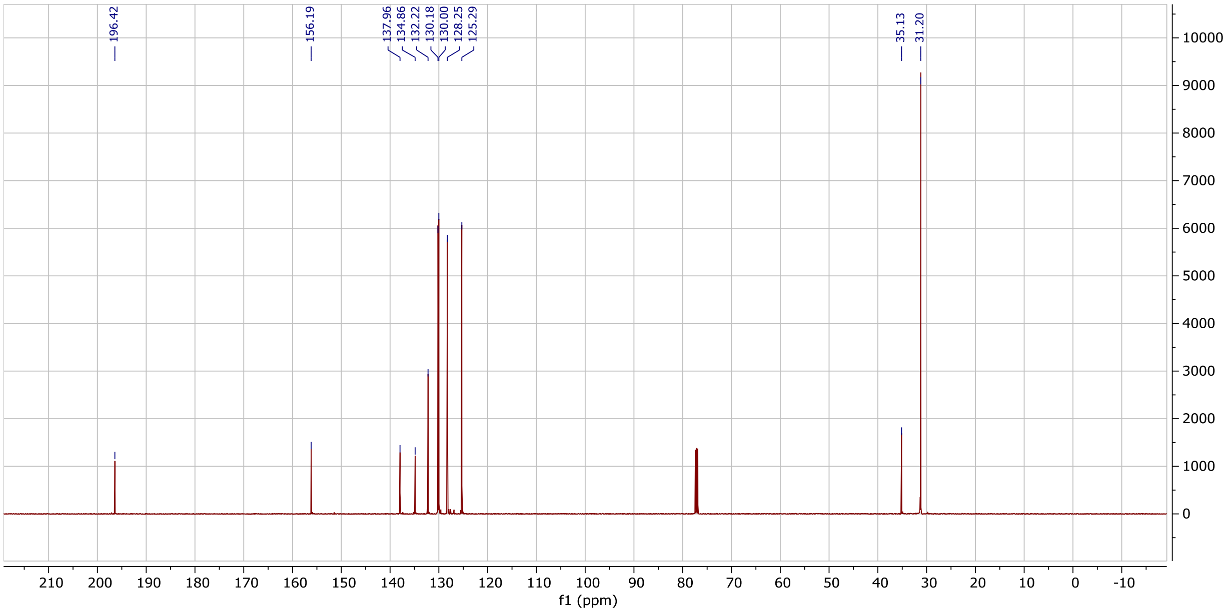

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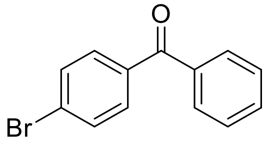

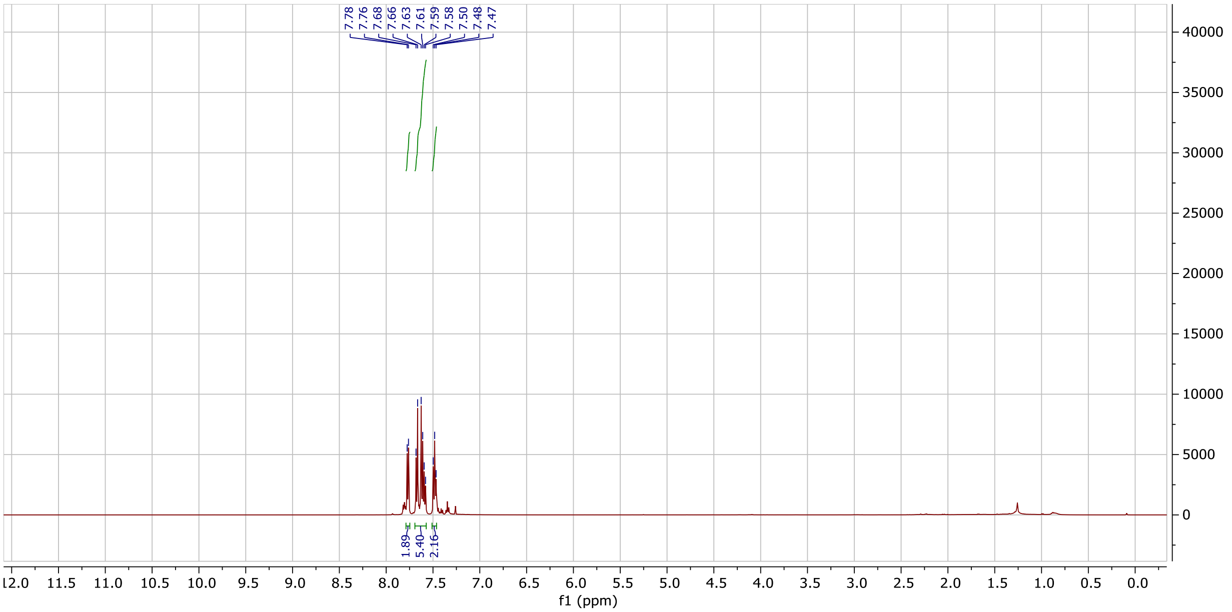

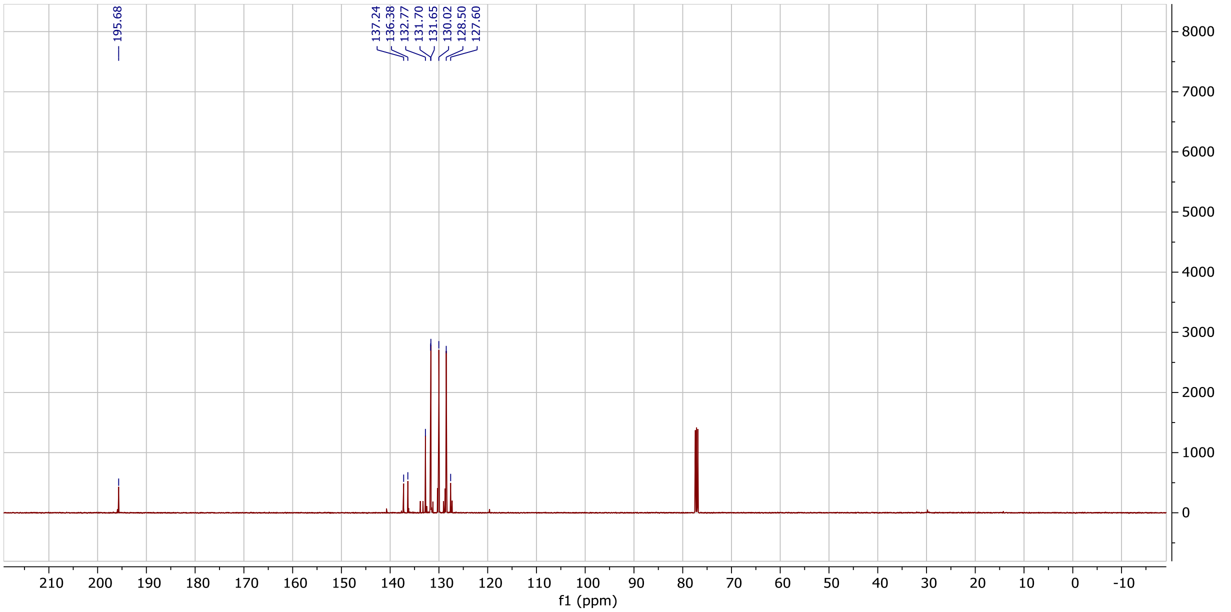

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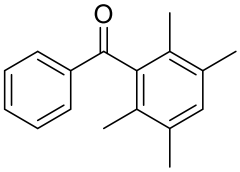

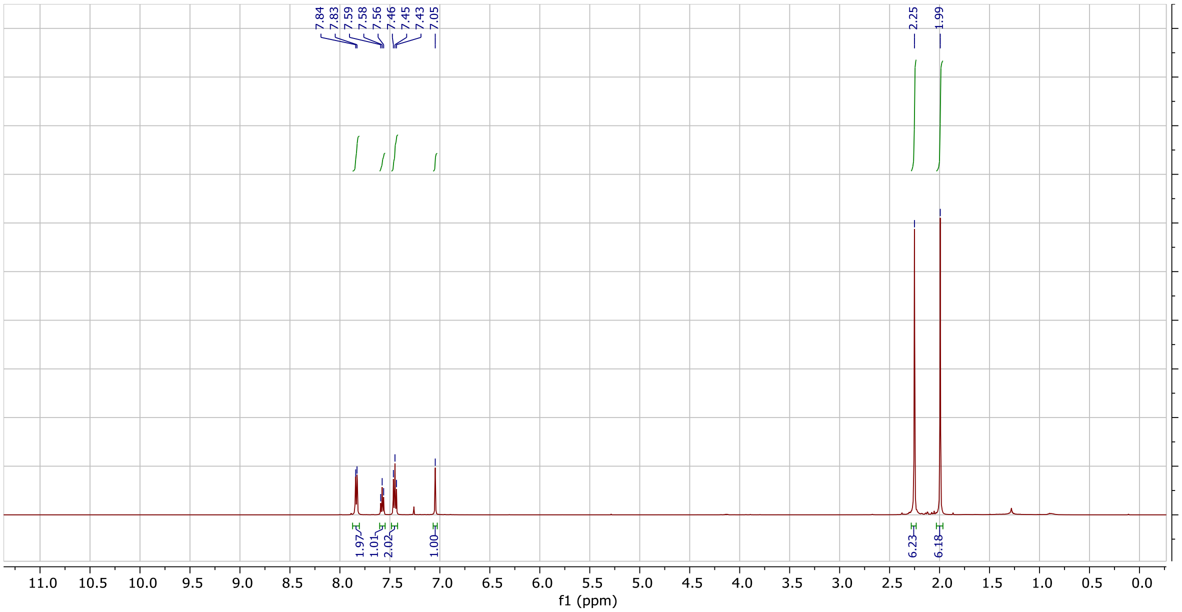

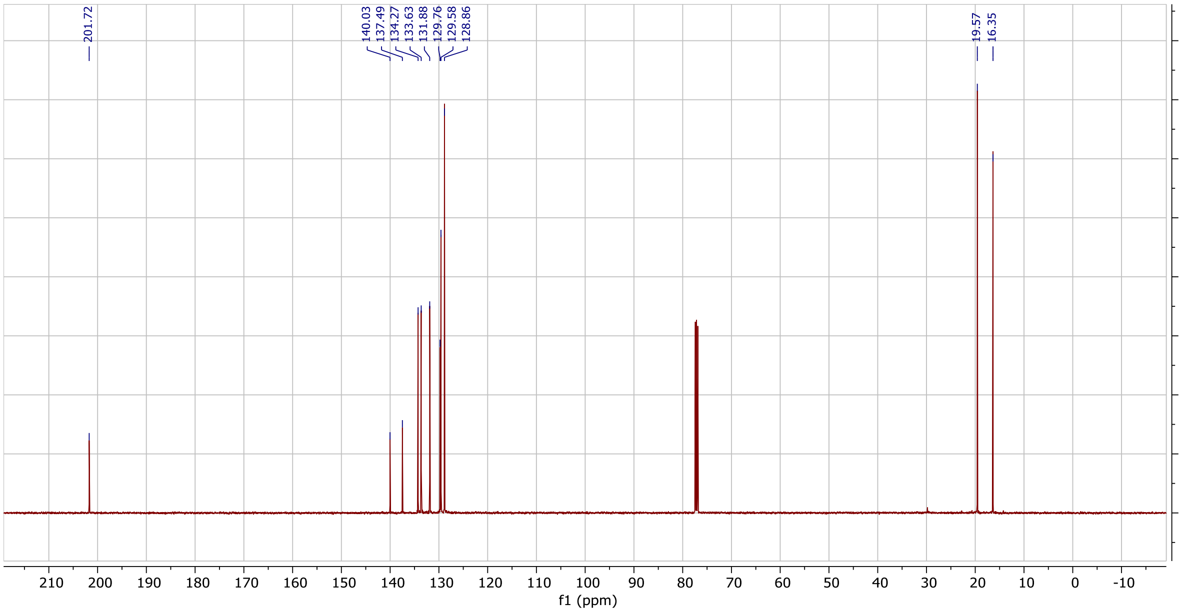

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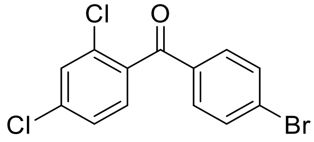

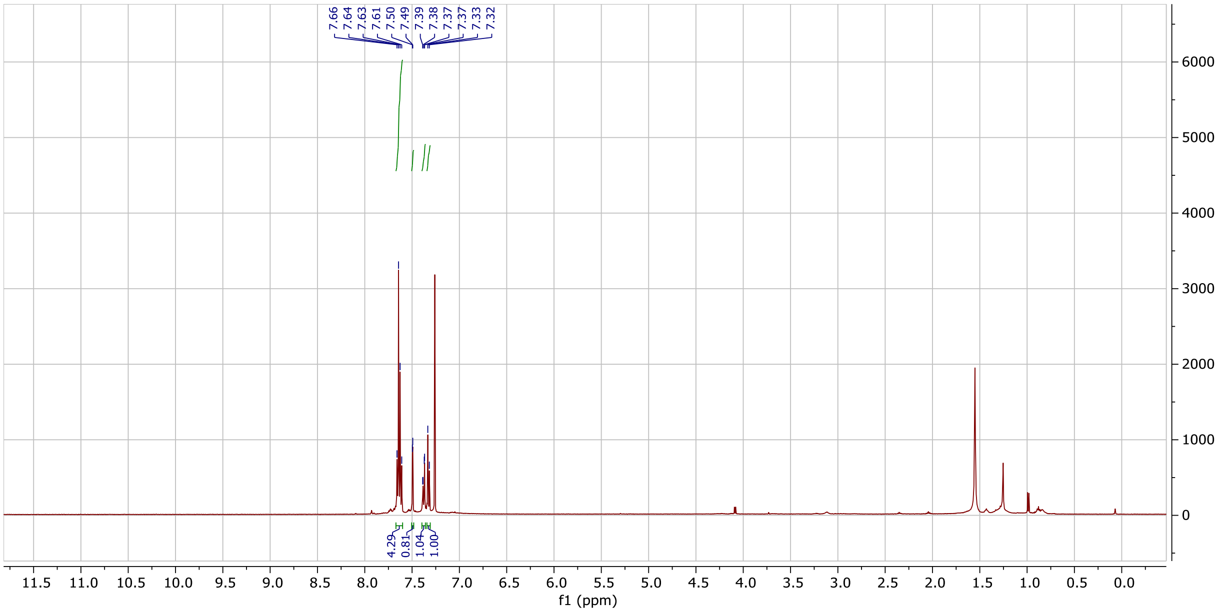

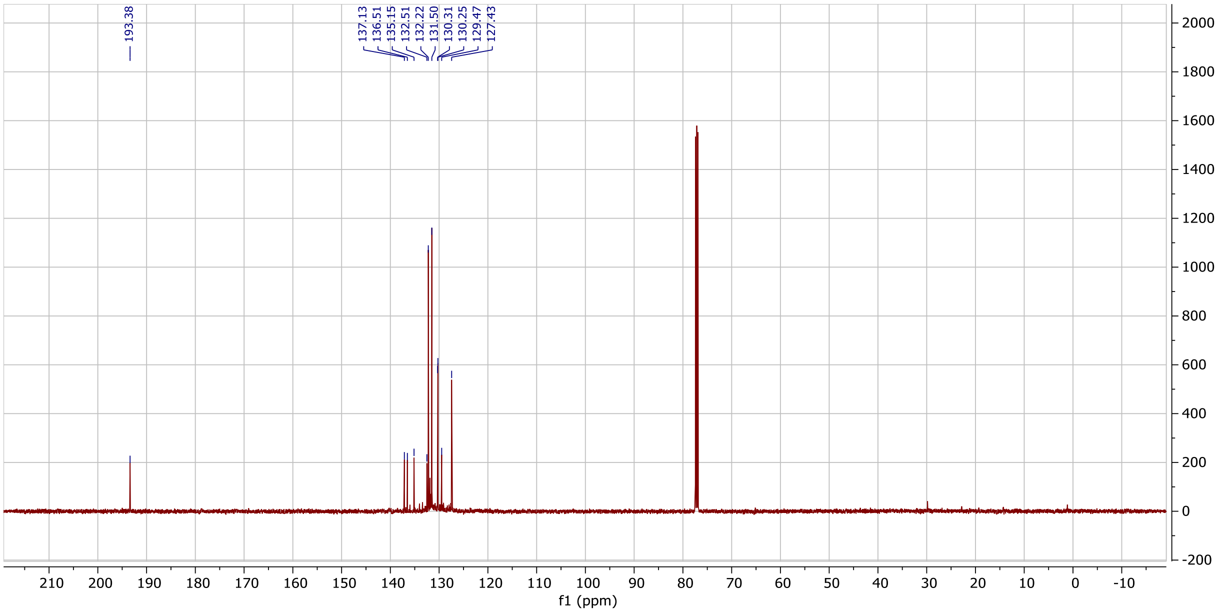

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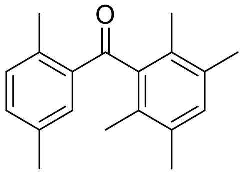
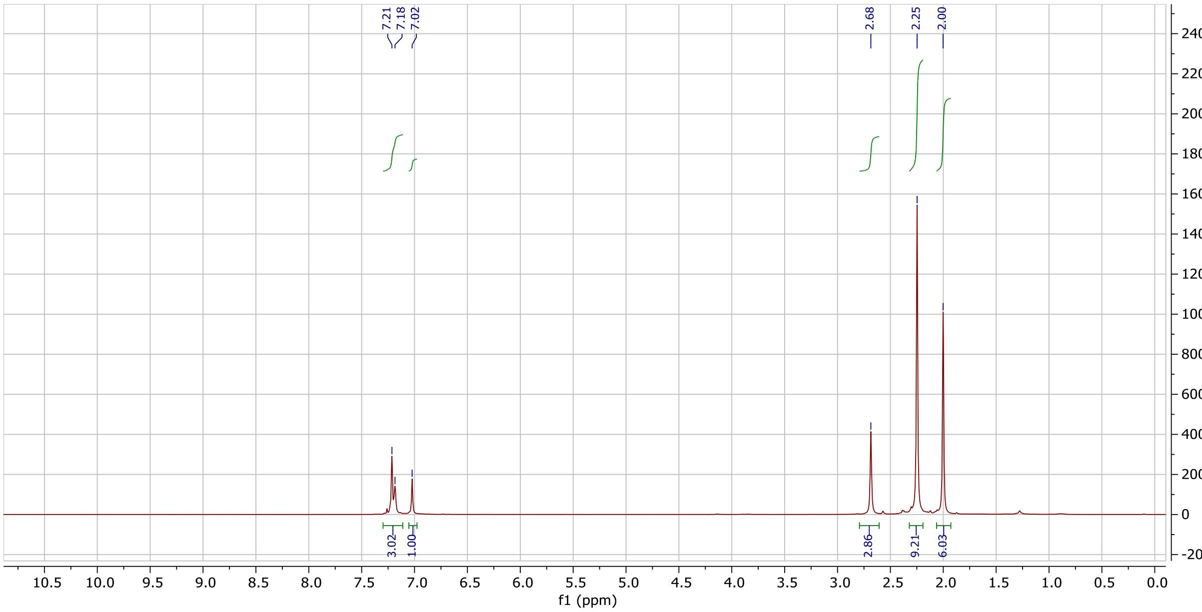
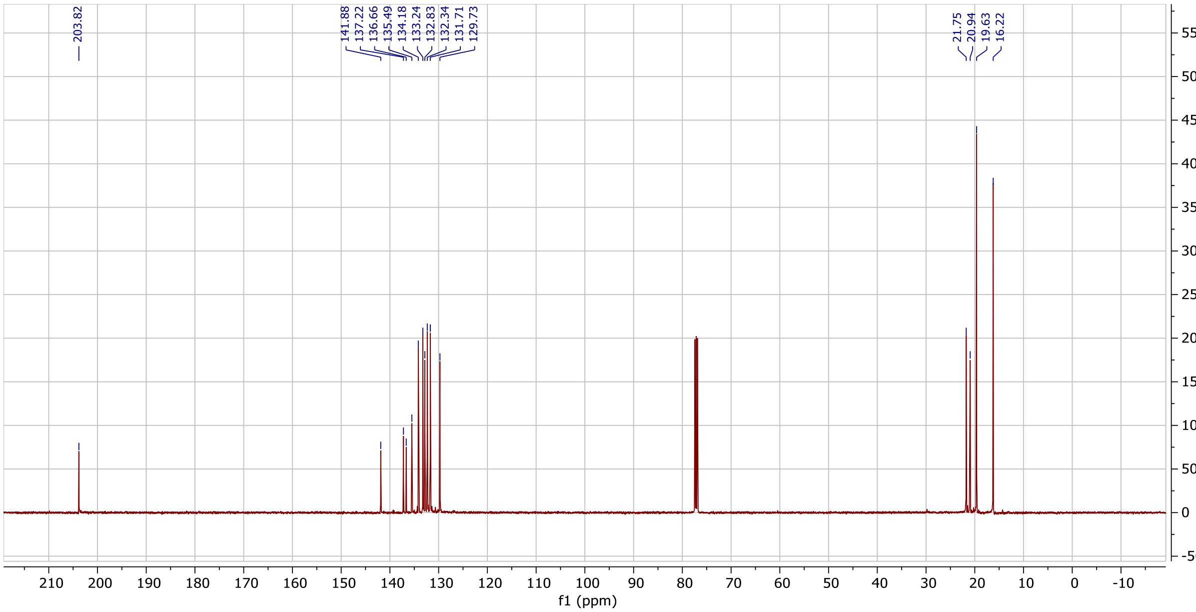
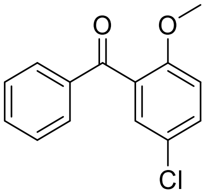
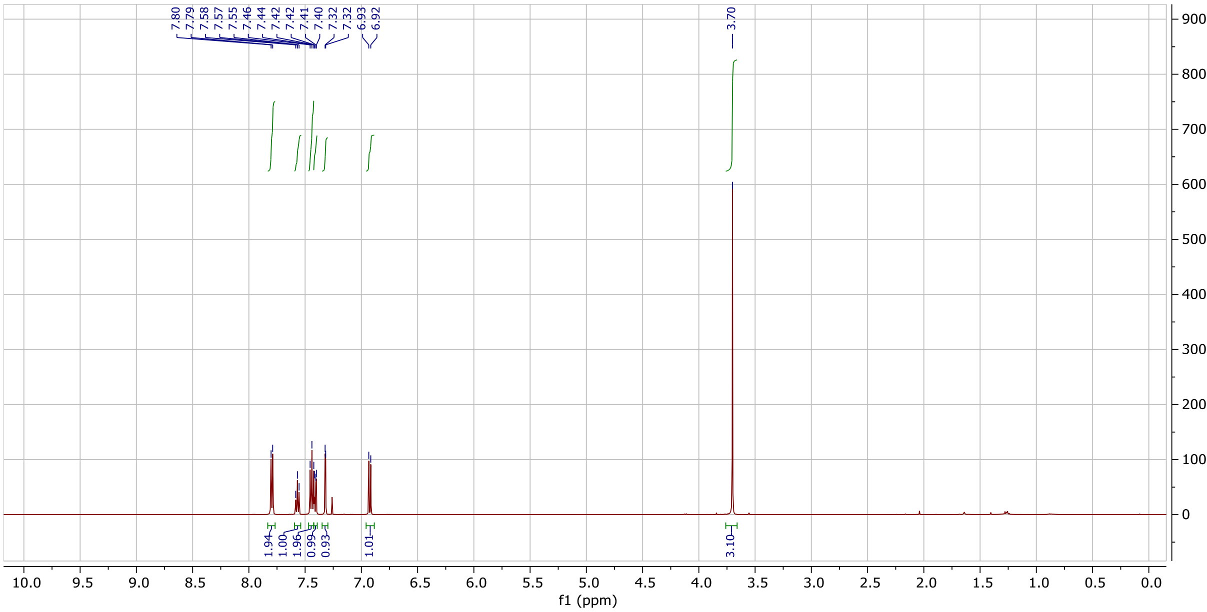


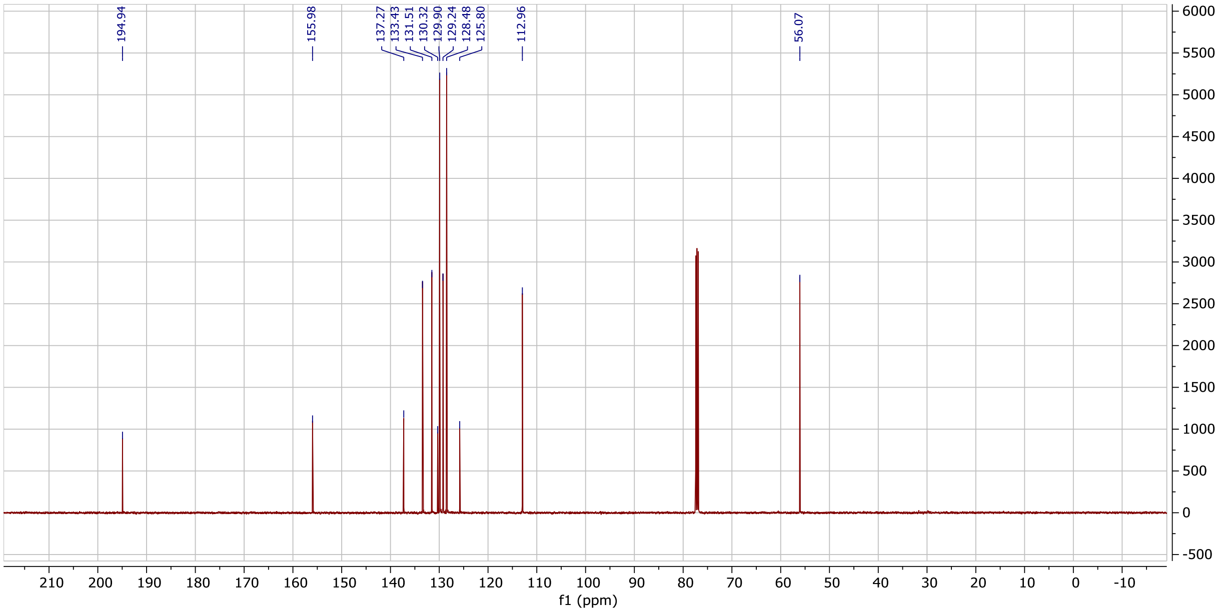




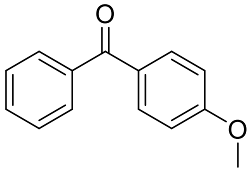
^{1}H NMR and ^{13}C NMR of 2.3.2i

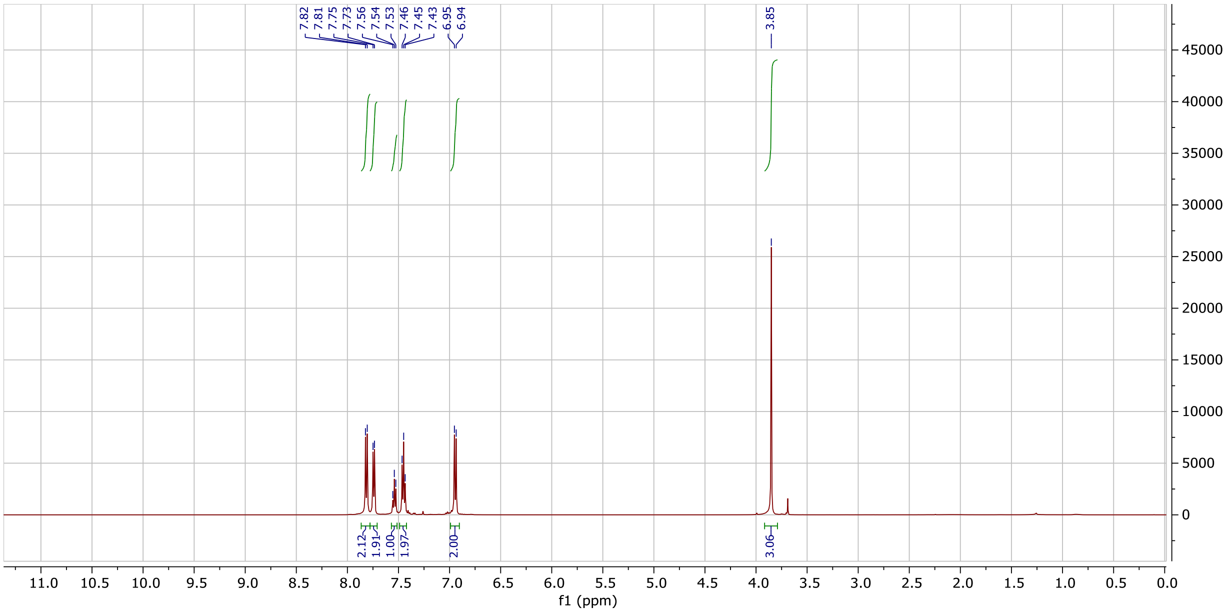


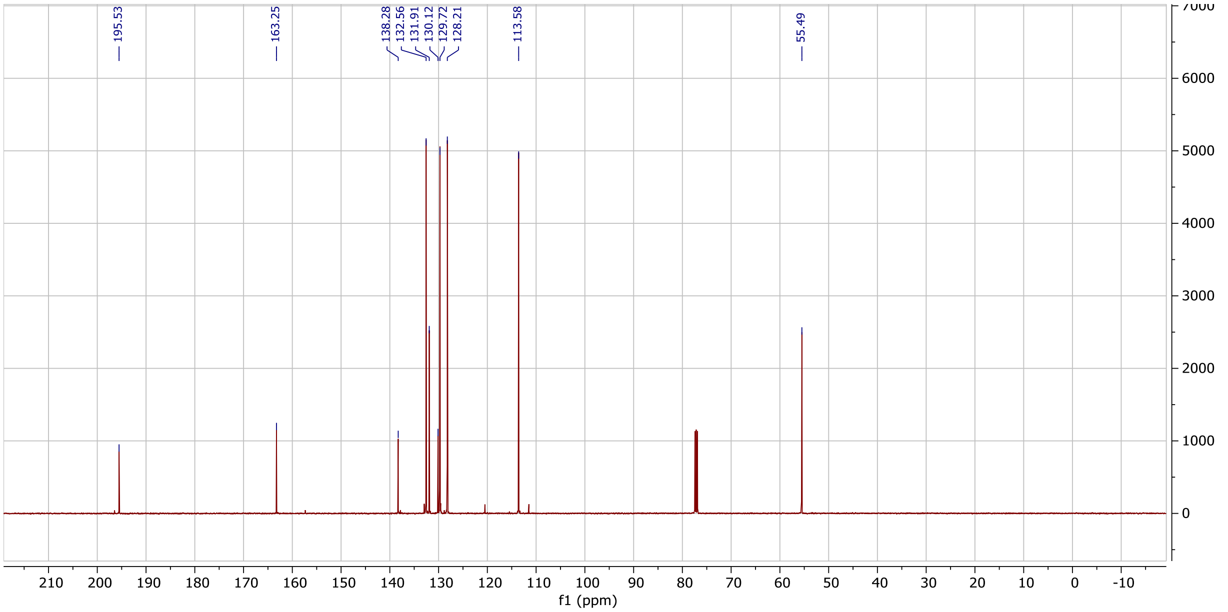




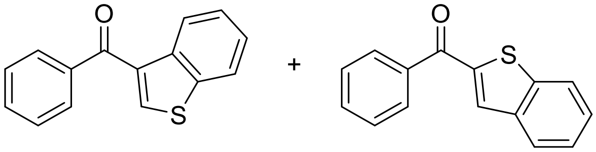
^{1}H NMR and ^{13}C NMR of 2.3.2j

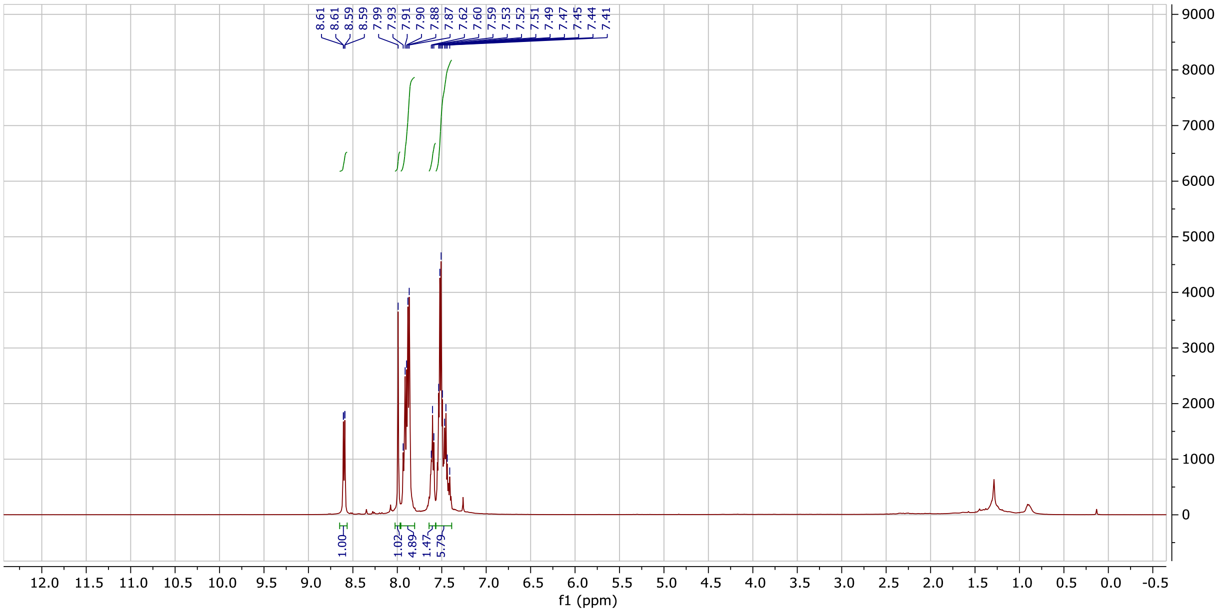


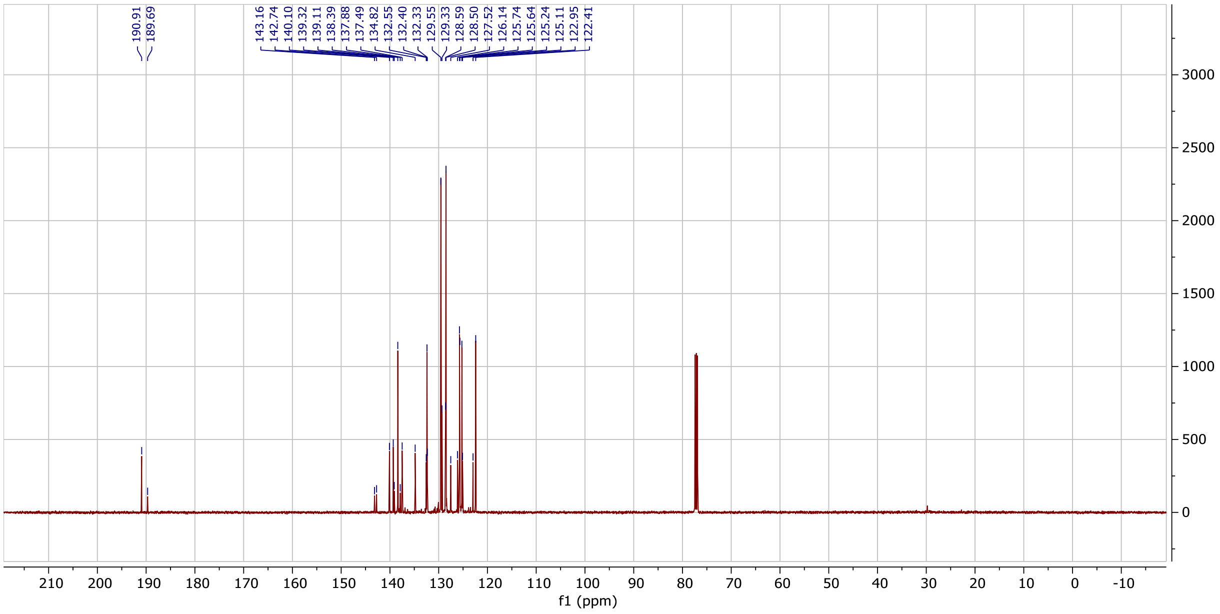




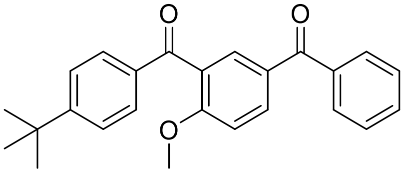
^{1}H NMR and ^{13}C NMR of 2.3.2k and 2.3.2k’

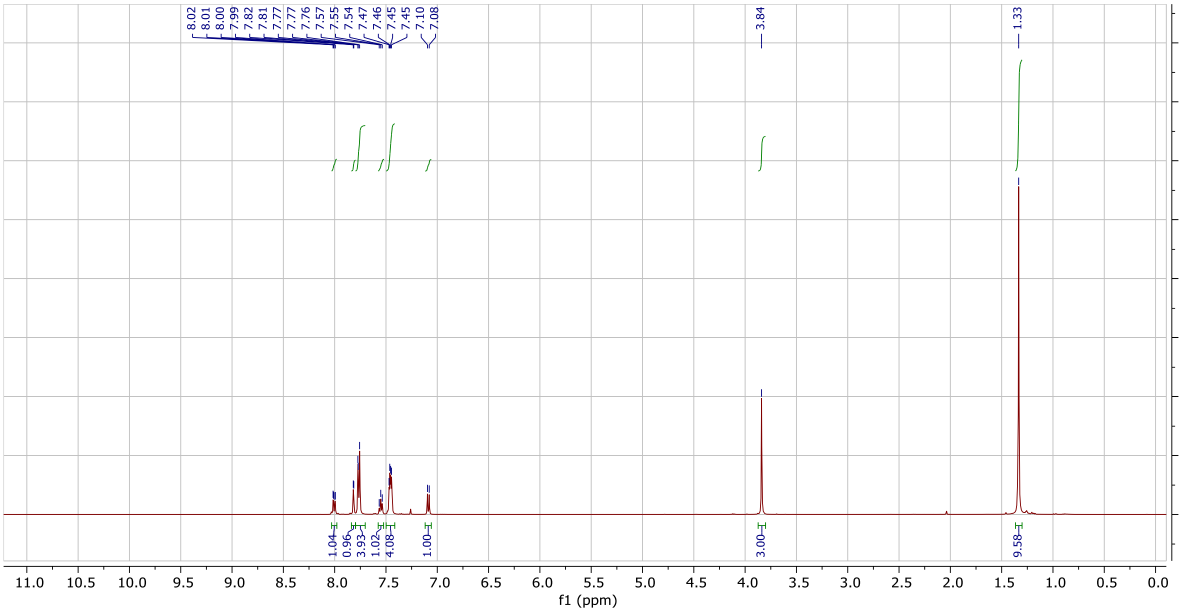


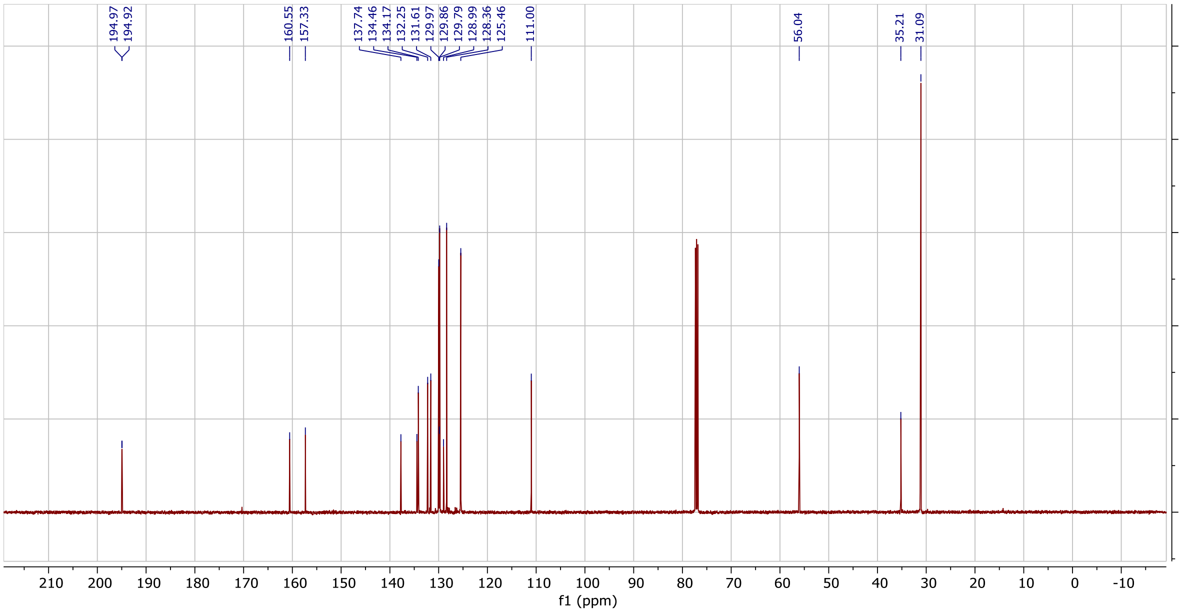




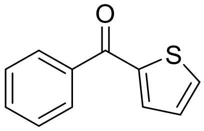
^{1}H NMR and ^{13}C NMR of 2.3.2l

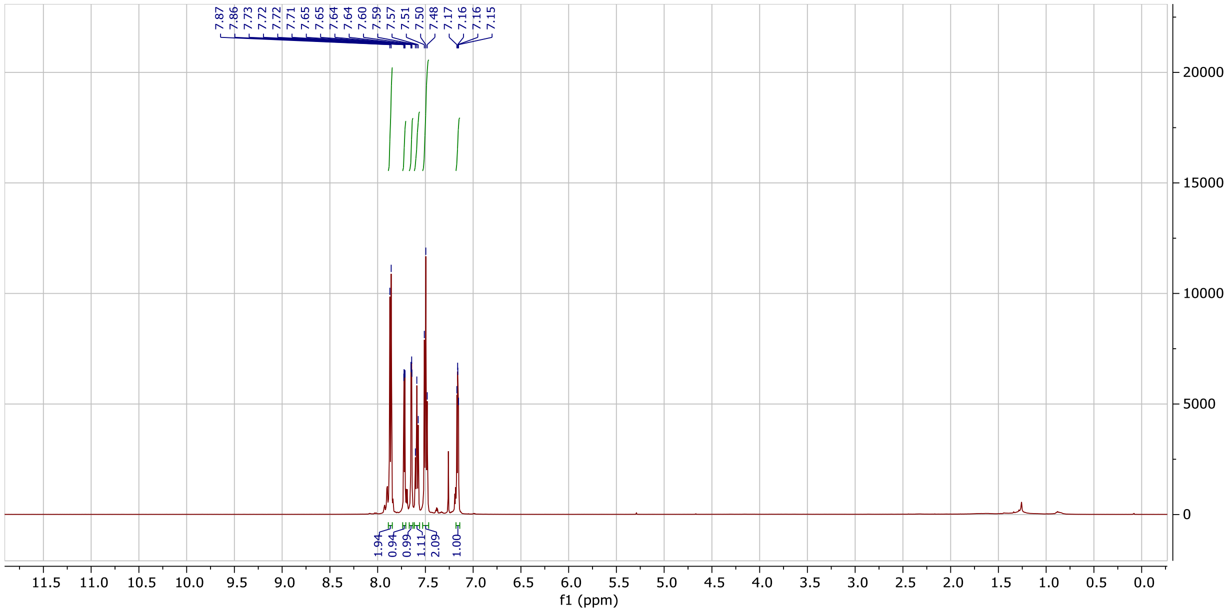


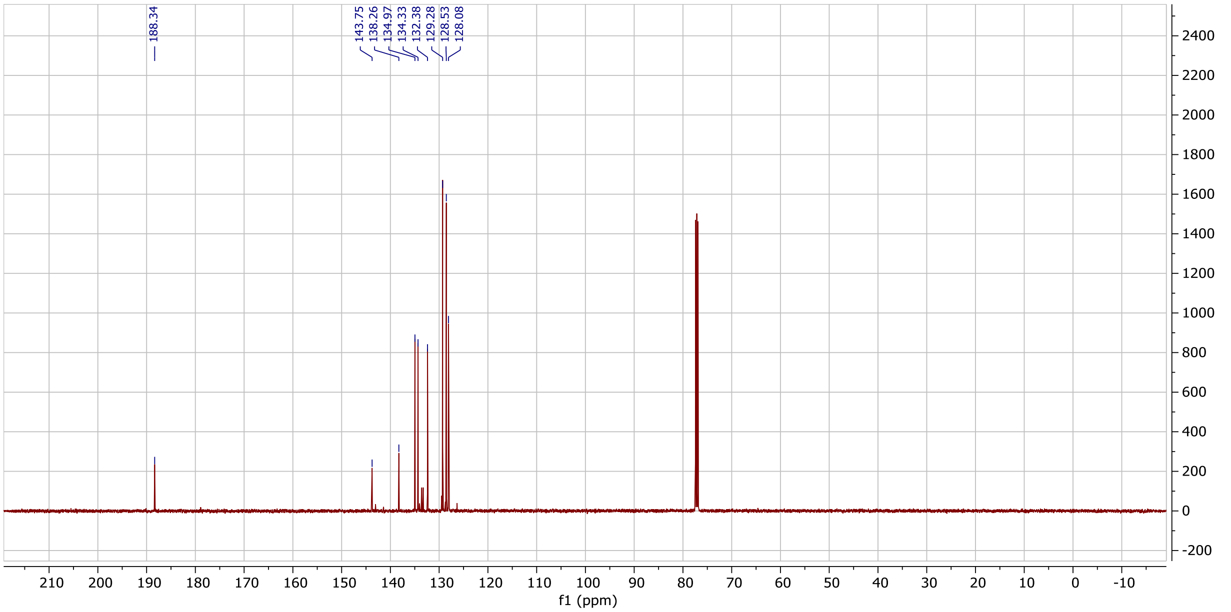




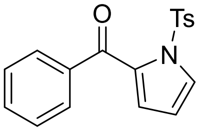
^{1}H NMR and ^{13}C NMR of 2.3.2m

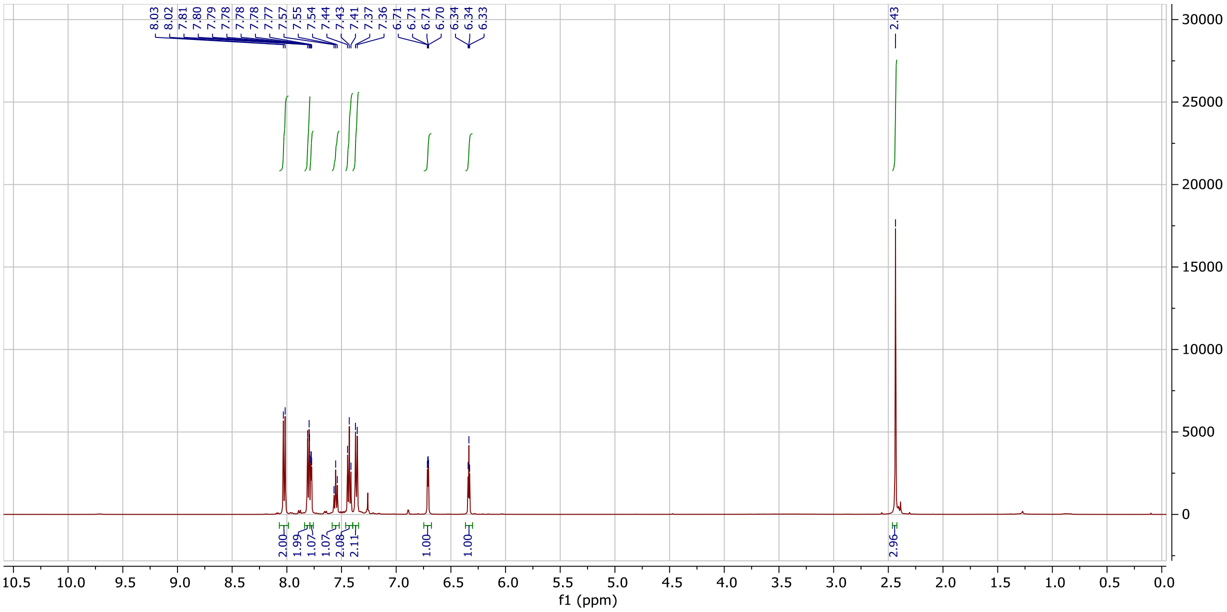


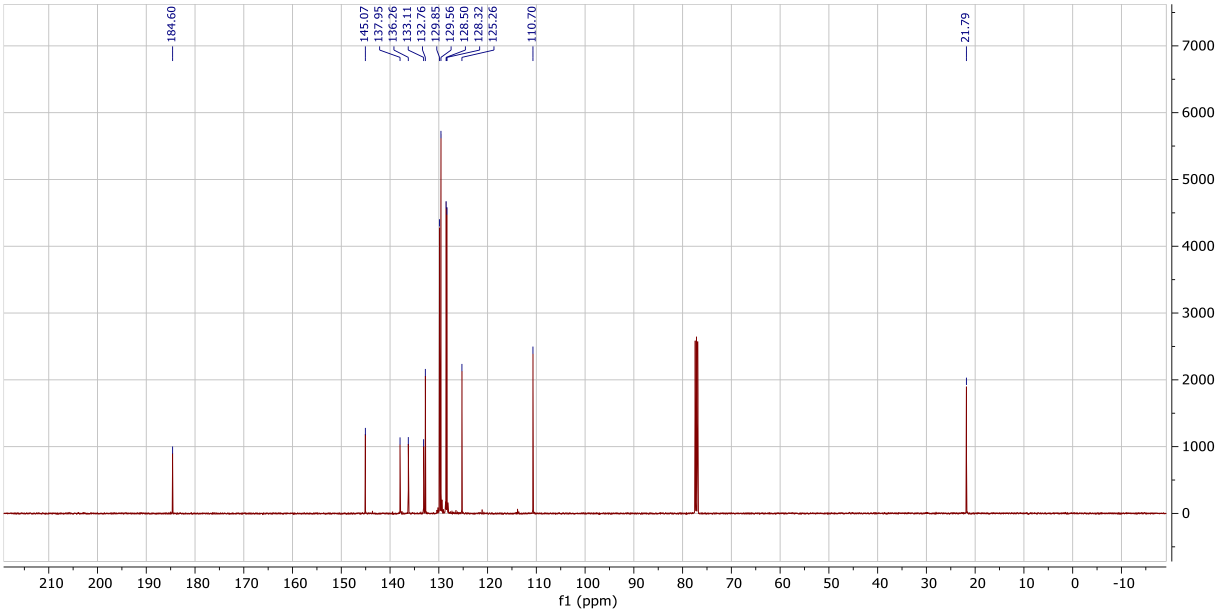




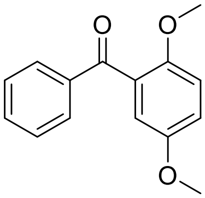
^{1}H NMR and ^{13}C NMR of 2.3.2n

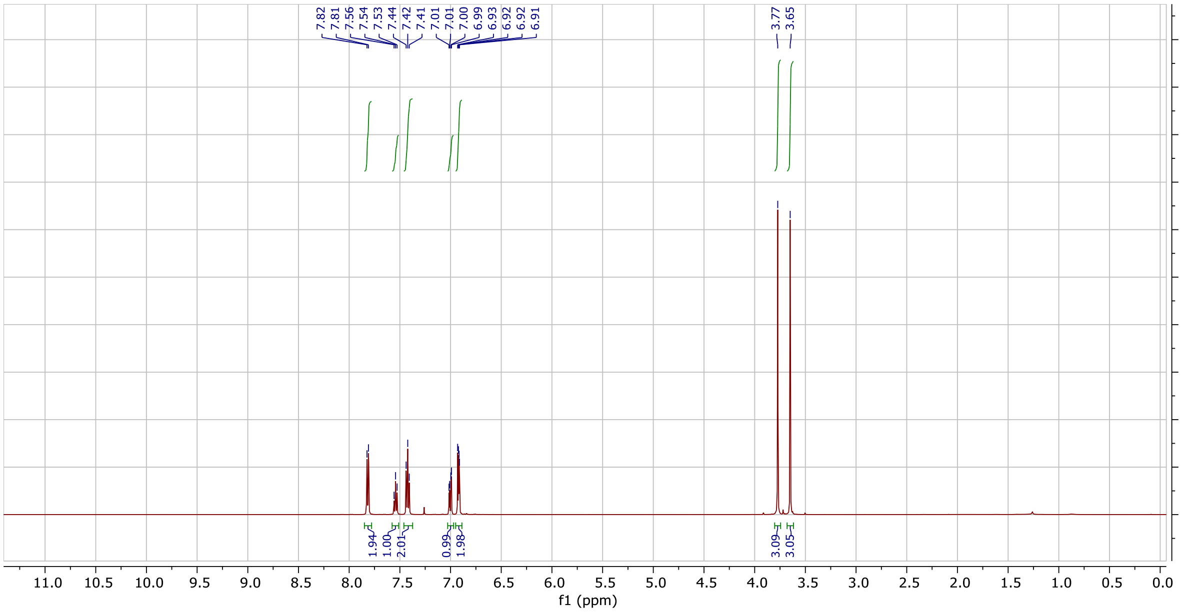


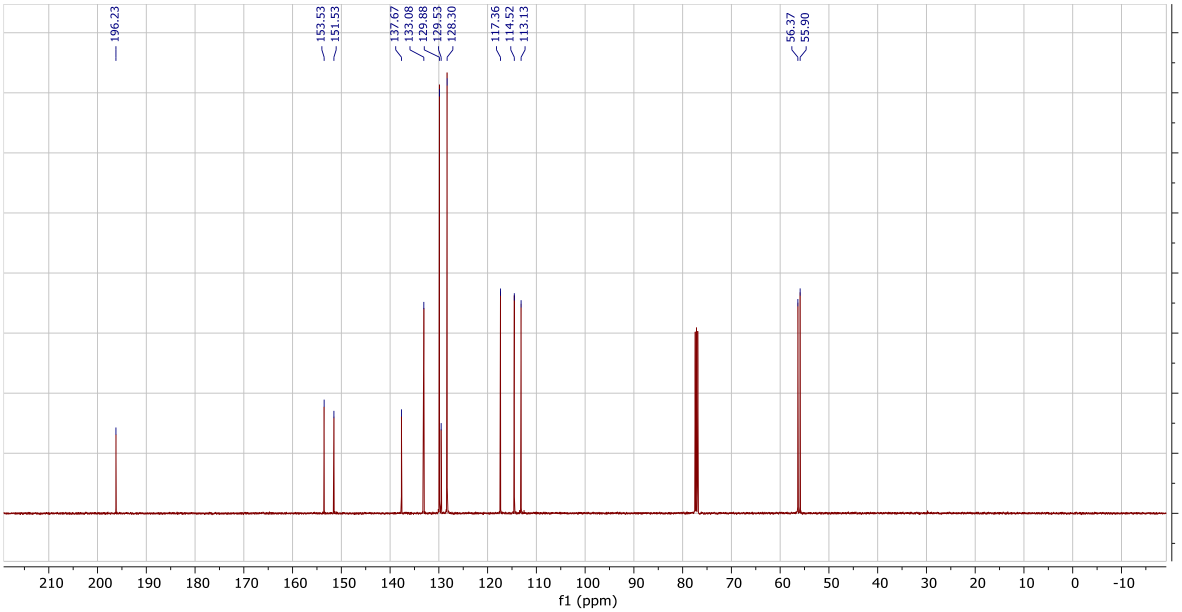




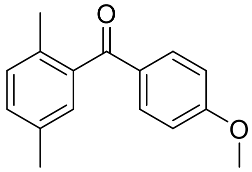
^{1}H NMR and ^{13}C NMR of 2.3.2o

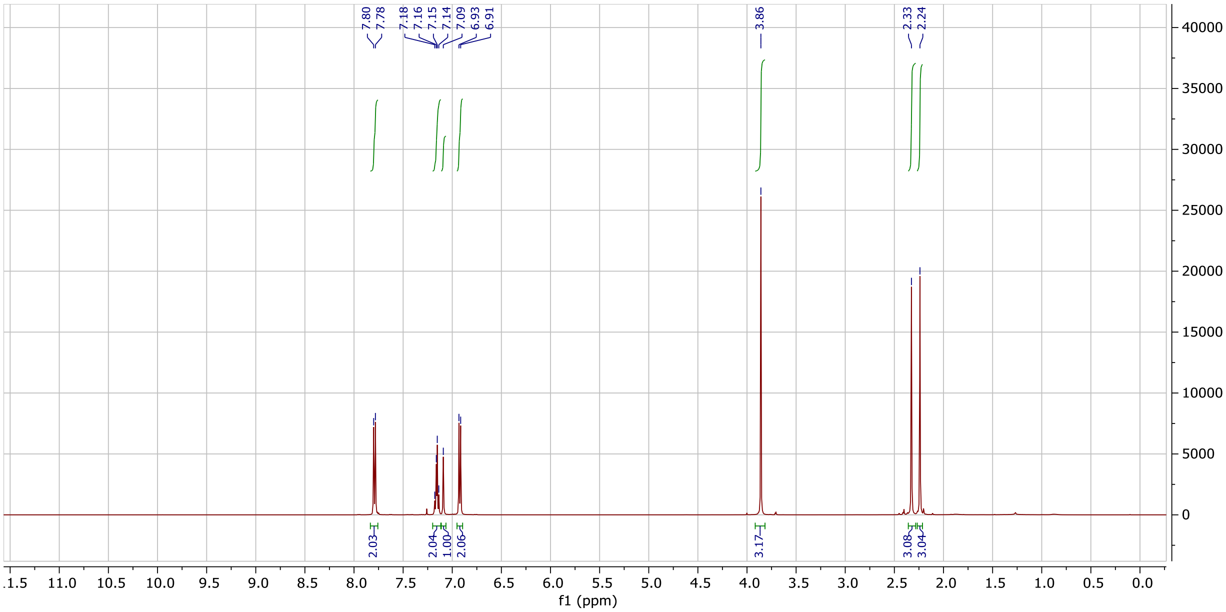


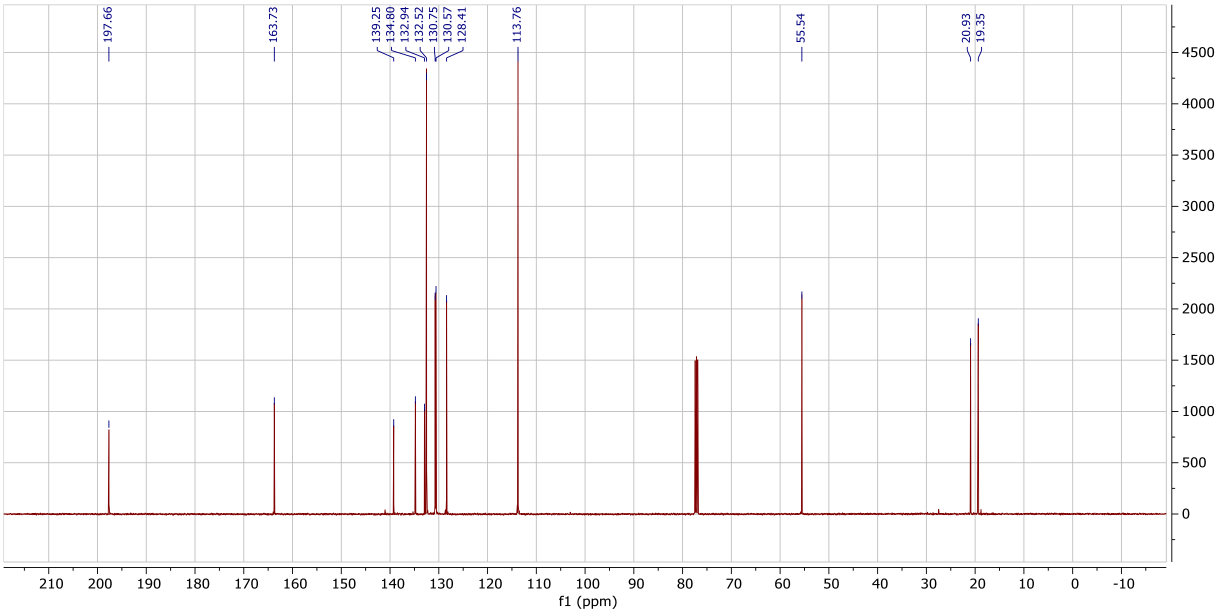




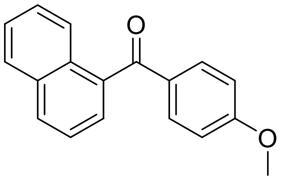
^{1}H NMR and ^{13}C NMR of 2.3.2p

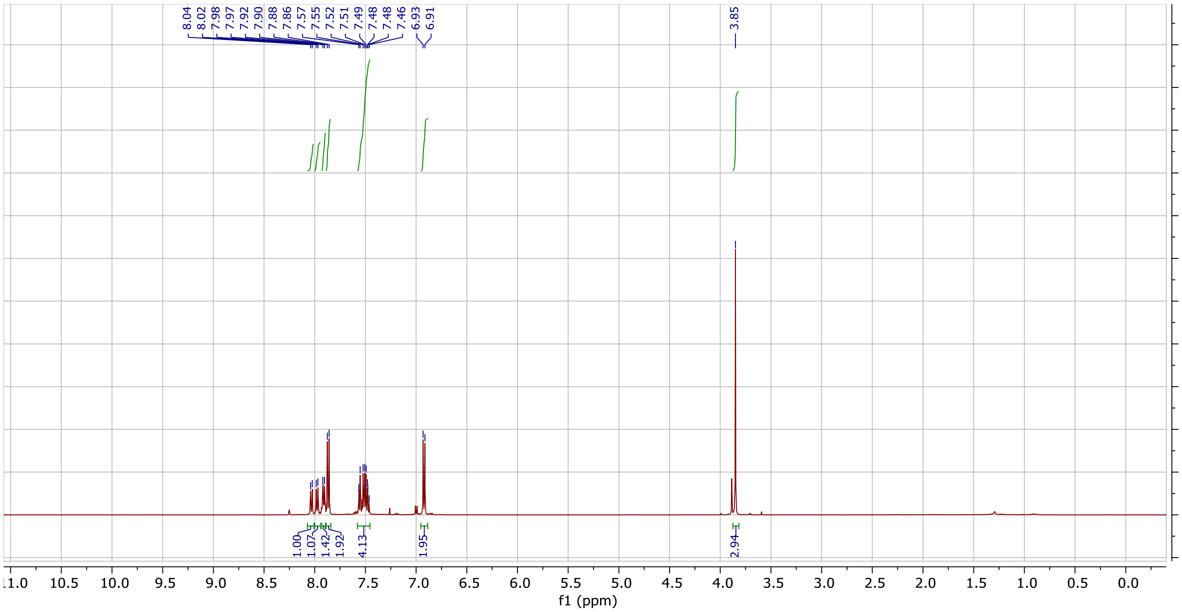


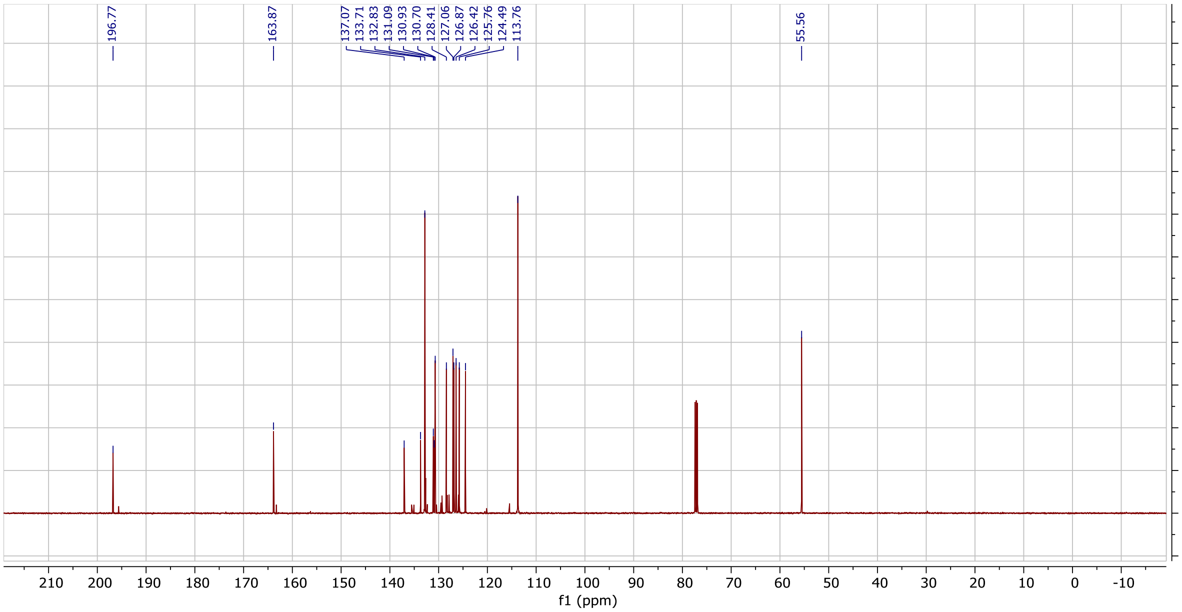




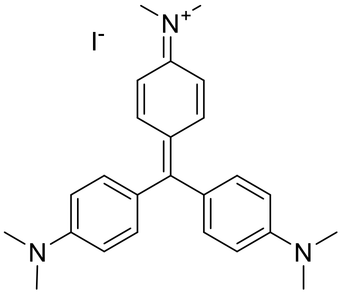
^{1}H NMR and ^{13}C NMR of 2.3.2q

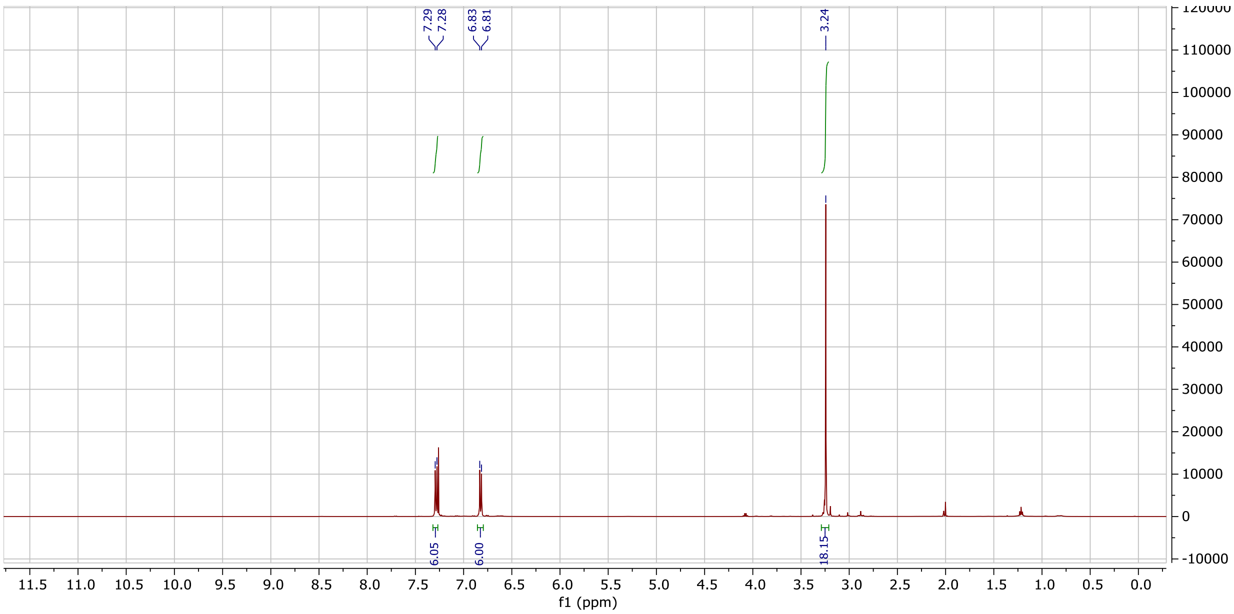


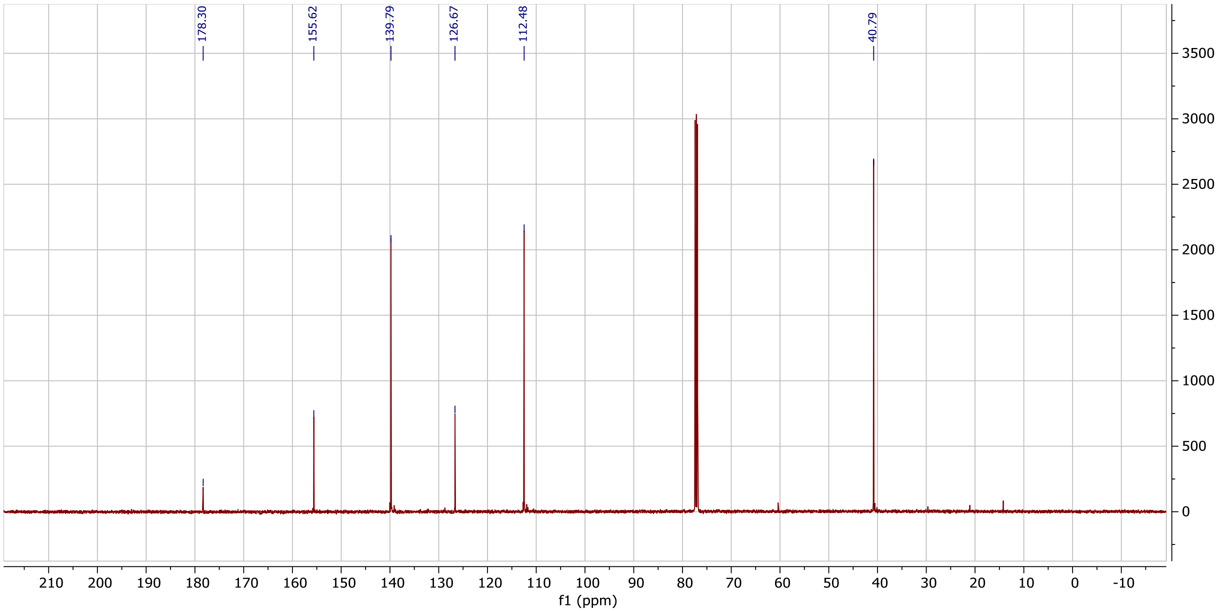




^{1}H NMR and ^{13}C NMR of 2.3.3 (R = Me)







^{1}H NMR and ^{13}C NMR of 2.3.3' (R = H)