The Preparation of Gamma-Arlyated Ketones via Palladium-Catalyzed Cross-Coupling of Cyclopropanol-Derived Homoenolates with Benzyl Chlorides

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Abstract

The first palladium-catalyzed cross-coupling reaction of cyclopropanol-derived ketone homoenolates with benzyl halides, was developed to prepare a variety of γ-arylated ketones. One of the major challenges of this cross-coupling reaction was the competing cleavage of the cyclopropanol starting material to the ring-opened ketone under the reaction conditions. Through systematic optimization studies involving screens of base, ligands, solvents, temperature, Pd sources, conditions for the high yielding cross coupling of 1-phenethylcyclopropanol with 4-methyl benzyl chloride were found. With optimized conditions excellent yields were obtained for the cross-coupling of various electron rich and neutral benzyl chlorides. Moreover, these conditions were also used to successfully cross couple a variety of cyclopropanols to 4-methyl benzyl chloride. This reaction is also shown to work with a low catalyst loading of 1 mol % and in gram-scale without any reduction in yie

Dedication

I would like to dedicate this thesis to my loving *amma* and *appa*.

Acknowledgments

This dissertation would not have been possible without the support and guidance of my supervisor Dr. Arturo Orellana. I would like to thank him for giving me the opportunity to work in his research group. I appreciate all the opportunities I was given to develop my career during my Masters study. I am grateful to Dr. Orellana for allowing me to contribute to publications from the group, and also for encouraging me to present a poster of my work at the 2013 CIC conference. Furthermore I would like to thank him for the meticulous work he does in reviewing my work and providing helpful feedback. His guidance has helped me improve my communication and presentation skills, which will serve me well in my future career as a teacher.

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Table of Contents

List of Tables

List of Figures

List of Schemes

List of Abbreviations

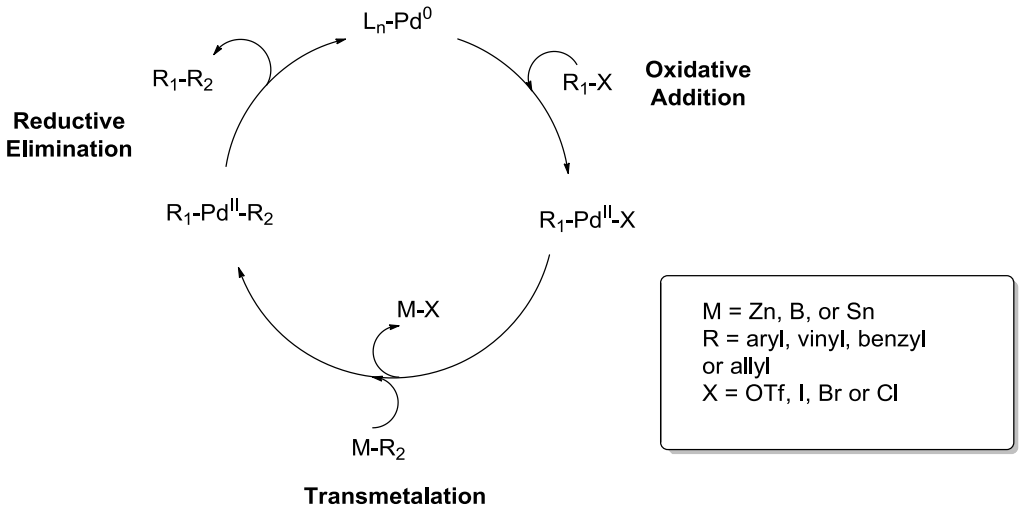
Ar	Aryl
dba	dibenzylideneacetone
DMA	Dimethylacetamide
DME	Dimethoxyethane
DMF	Dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone
dppb	1,4-Bis(diphenylphosphino)butane
dppe	1,2-Bis(diphenylphosphino)ethane
dppp	1,3-Bis(diphenylphosphino)propane
Equiv.	Equivalents
hv	Light energy
IR	Infrared
NHC	N-heterocyclic carbene
NMR	Nuclear magnetic resonance
OiPr	Iso-propoxide
OTf	Triflate
PPh_3	Triphenylphosphine
r.t.	Room temperature
THF	Tetrahydrofuran
TLC	Thin layer chromatography

Chapter 1: Introduction

1.1 Palladium Catalyzed Cross-Coupling Reactions

The formation of carbon-carbon bonds is of critical importance to synthetic organic chemistry. In fact, carbon-carbon bond forming reactions are so powerful and their development has been so monumental that several Nobel prizes in Chemistry were awarded to this feat. This includes the Grignard Reaction in 1912, the Diels-Alder reaction in 1950, the Wittig reaction in 1979 and olefin metathesis in 2005. More recently in 2010 the Nobel prize was given jointly to Heck, Negishi and Suzuki for their work in Palladium-catalyzed cross-coupling reactions, which has revolutionized synthetic chemistry and has led to tremendous advances in the construction of organic molecules.[1]

Palladium has the remarkable ability to catalyze the formation of carbon-carbon, carbon-nitrogen and carbon-oxygen bonds. The synthetic utility of palladium arises from its tolerance of a wide variety of functional groups. Furthermore, many established palladium catalyzed reactions also benefit from stereo- and regioselective control of products in excellent yields. Much of the efficacy of palladium is due to its ability to shuttle between states, Pd(0), Pd(II), and in some rare cases Pd(IV). [2] In a typical Pd-catalyzed reaction the metal undergoes certain elementary steps which make up the general catalytic cycle of a coupling reaction, as shown in Scheme 1.[3]



Scheme 1. General catalytic cycle for palladium-catalyzed cross-coupling reactions.

In most cross-coupling reactions, the catalytic cycle begins with an organohalide or pseudohalide oxidatevely adding across a Pd(0) species and converting it to Pd(II). In cases where the starting material is an organometallic compound, the second step of the cycle involves the transfer of the organic group from the organometallic compound to the Pd(II) complex, releasing metal halide in a process known as transmetalation. In reductive elimination, the final step of the cycle, the two organic groups are coupled together to give a new carbon-carbon single bond and consequently reducing Pd(II) back to Pd(0).There are several well-established cross-coupling reactions based on Pd that have gained widespread use in industry and research. These *name reactions* (what they are commonly referred to), shown in Figure 1, vary by the metal and/or activating group found on the coupling partners.[4]

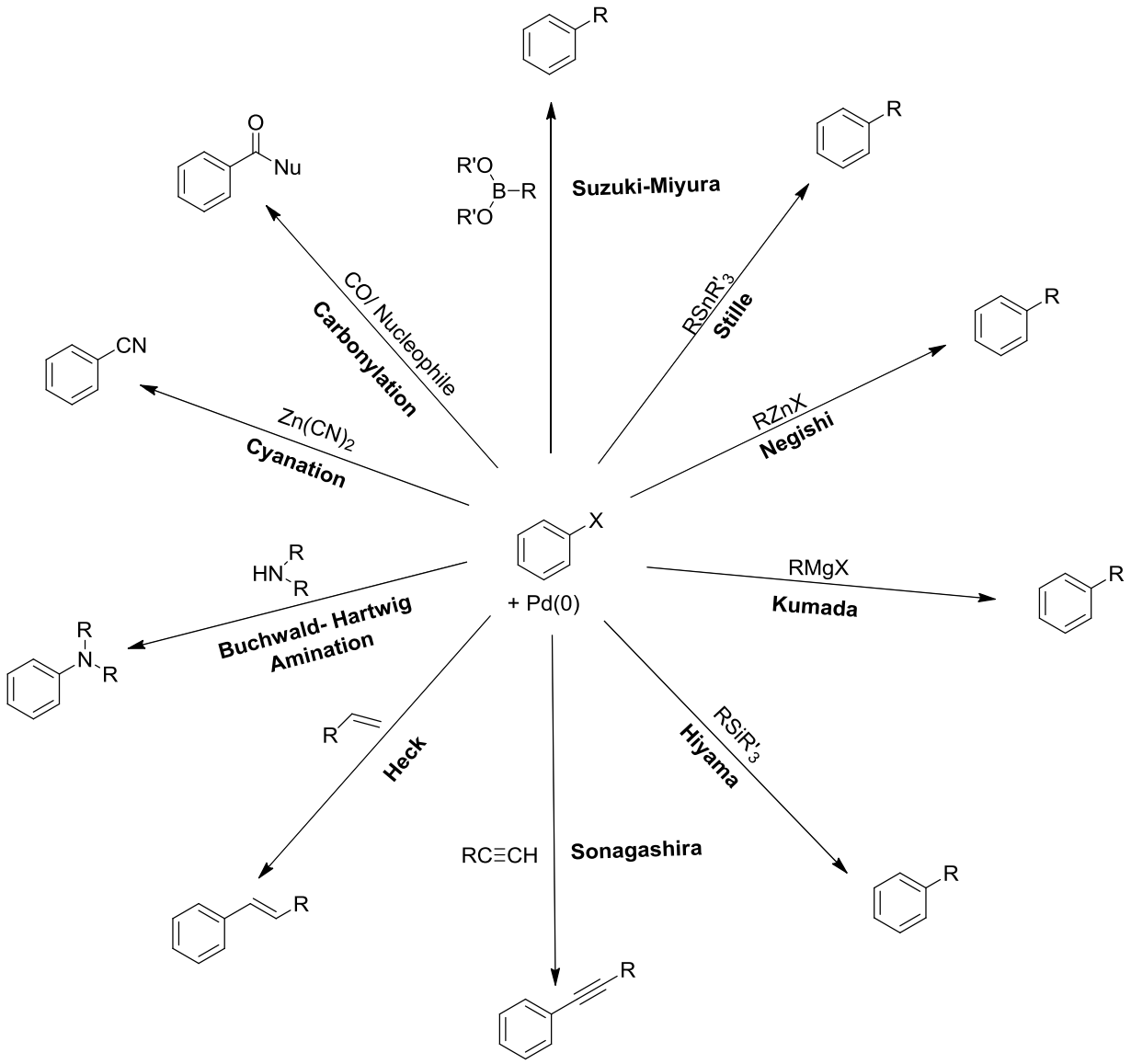


Figure 1. Well-known palladium catalyzed cross-coupling reactions.

There have been significant advances and extensions to these pioneering reactions recently reported literature. However, the use of unusual functional groups in the development of new palladium-catalyzed reactions has received considerably less attention.

1.2. Homoenolates in organic synthesis

Conventional strategies for organic synthesis exploit complementary reactivities based on charge affinity patterns. Consider for example the case of a typical aldol condensation reaction whereby the nucleophilic α-carbon (δ^-) of a ketone reacts favorably with the electrophilic carbonyl carbon (δ^+) of an aldehyde to yield a β-hydroxy ketone as shown in Figure 2. The charge affinity pattern in both reactants is dictated by the carbonyl moiety which imposes an alternating distribution of partial charge in the carbon frame work.[5]

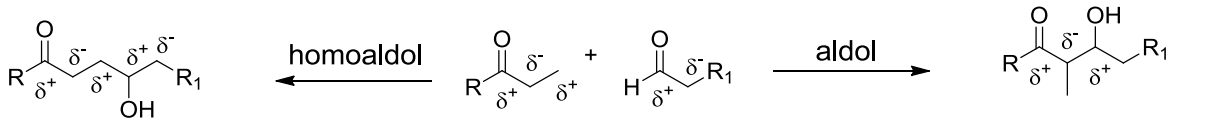


Figure 2. Complementary charge affinity patterns of reactants in aldol and homoaldol reactions.

The analysis of charge affinity patterns is often used in retrosynthetic planning to identify potential disconnections and also to evade functional group incompatibilities. For instance, the β-carbon of a ketone is often viewed as electrophilic based on the charge affinity pattern imposed by the carbonyl group. Hence achieving a 1,3-relationship between functional groups is straight forward, whereas a 1,4-relationship, as in the homoaldol case, is more challenging due to the dissonant (non-matching) relationship between the synthons. For this reason, reactions in which the normal charge affinity patterns are reversed are of great interest in organic synthesis.

Homoenolates are a special class of *umpolung*[6] synthons that display a charge affinity pattern opposite to that of an α,β-unsaturated ketone (Fig. 3). These synthetic tools exhibit reversed polarity owing to a metal (electropositive) bound to the β-carbon. The β-carbon becomes nucleophilic and can then serve as unique means to access useful 1,4-homoaldol disconnections.

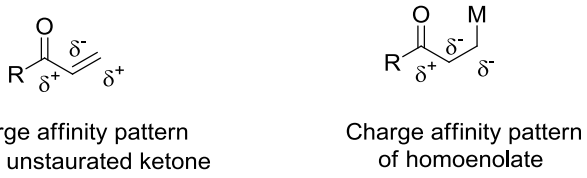
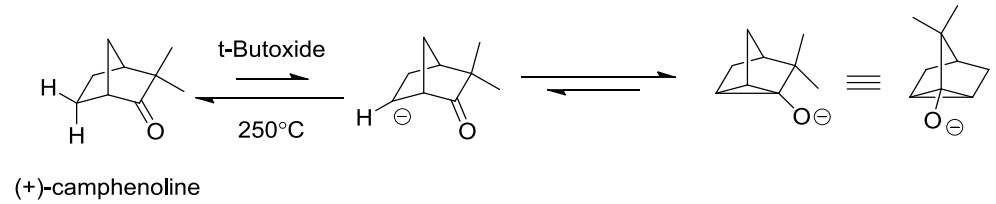


Figure 3. Comparison of charge affinity patterns in α,β- unsaturated ketone and homoenolate.

1.3 Homoenolization *via* direct deprotonation

Homoenolates, unlike enolates, are generally difficult to prepare via direct deprotonation at the β-carbon. Enolates benefit from resonance stabilization whereby delocalization of a negative charge into the neighbouring carbonyl group, lowers the pKa and drives the formation of an α-anion. The pKa of the β-carbon on the other hand is significantly higher since the distance from the carbonyl center prevents delocalization of the negative charge and thus β-anions would not be resonance stabilized.

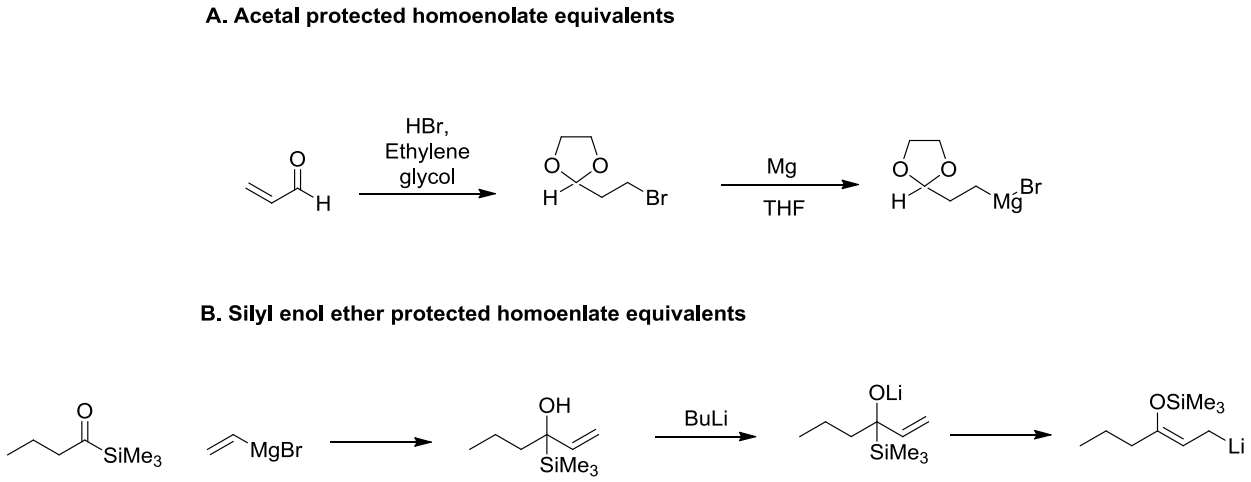
Deprotonation at the β-position is possible[7] but is limited to sterochemicaly constrained systems like (+)-camphenoline as reported by Nickon in 1962. [8] As shown in Scheme 2, deprotonation of (+)-camphenoline occurs selectively at the β-position leading to a homoenolate that is stabilized by the formation of a meso-cyclopropoxide. α-Enolization is not favorable in these bicyclic systems because the α-C-H molecular orbital is not parallel to the π-orbital of the carbonyl group, and so the α-anion cannot be resonance stabilized. This method of generating homoenolate is quite impractical as it requires really high temperatures and is limited to substrates with unique stereochemical requirements that lower the acidity of the α-carbon meanwhile favoring enolization at the β-position.



Scheme 2. Homoenolate generation through direct deprotonation at the β-carbon.

1.4 Protecting-group strategies for homoenolate preparations

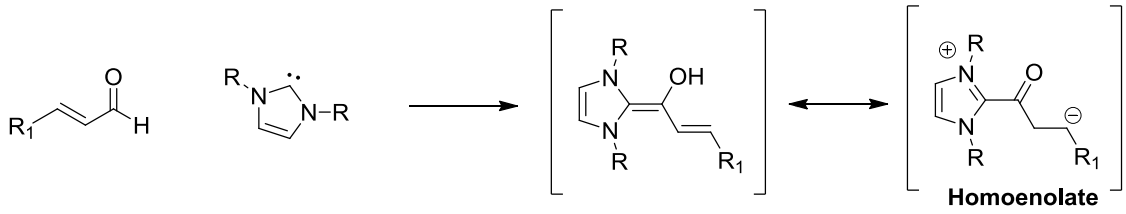
Another major challenge in preparing homoenolate synthons is that the carbonyl carbon, being electrophilic in nature, remains a potential site for attack complicating the use of the homoenolate. To overcome this issue, carbonyl protecting-group strategies have been employed in metalation reactions used to generate homoenolates. Büchi and Wüset showed that acetal protecting groups can be used in the preparation Grignard reagents that serve as homoenolate synthons (Scheme 3A).[9] Other protecting methods involve generating silyl enol ethers of ketones as homoenolate equivalents (Scheme 3B).[10] This approach is disfavored as the use of protecting groups leads to longer synthetic protocols and potential complications.



Scheme 3. Protecting group strategies for generating homoenolate synthons.

1.5 Preparation of homoenolates from NHC

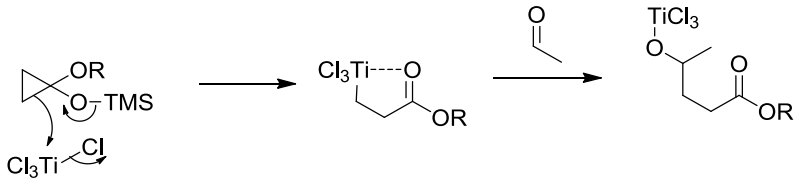
One novel way of circumventing the use of protecting groups is through the use of NHCs to generate homoenolates from α,β- unsaturated aldehydes. In 1958, Breslow reported that the addition of NHC to an activated carbonyl moiety leads to a polarity reversal of the carbonyl species.[11] Based on this postulate, Bode and Glorius independently reported the addition of NHC to α,β-unsaturated aldehyde to catalytically generate aldehyde homoenolates (Scheme 4).[12, 13] One major complication associated with this approach is the competing homodimerization reaction of the enal. Moreover, the scope of NHC- generated homoenolates are predominately limited to those generated from addition of NHC to α,β-unsaturated aldehydes or as in some cases, dienones.[14]



Scheme 4. NHC-mediated formation of homoenolate.

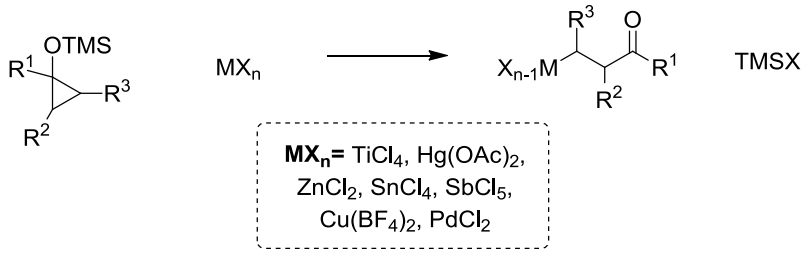
1.6 Homoenolates from ring opening of siloxycyclopropanes

The first reliable method of homoenolate preparation was established by Kuwajima's seminal work in 1977 wherein they reported a $TiCl_4$-mediated reaction of 1-alkoxy-1-siloxy-cyclopropane with aldehydes. This reaction was postulated to go through a titanium homoenolate intermediate followed by a homoaldol condensation (Scheme 5).[15]



Scheme 5. Generation of homoenolate from titanium mediated ring opening of siloxycyclopropane.

These titanium homoenolates were the first stable metal homoenolates that could be isolated. They exhibit significant nucleophilic reactivity towards external electrophiles including carbonyl compounds to give 4-hydroxy esters in good yield.[16] Since the evolution of titanium homoenolates, a host of other metal homoenolates have been prepared via ring opening of siloxycylcopropanes with certain metal salts including zinc, mercury, tin, cooper, antimony and palladium (Scheme 6).[17]



Scheme 6. Preparation of metal homoenolates from siloxycyclopropanes.

1.7 Transmetalation of pre-formed homoenolates to palladium.

Given the advent of palladium chemistry in carbon-carbon bond formation through cross-coupling reactions, the generation of palladium homoenolates has gained interest as a more practical method of incorporating homoenolates into organic synthesis. The most direct route to palladium homoenolates is through transmetalation of pre-formed metal homoenolates. Zinc ester homoenolates, which are prepared from Zn/Cu treatment of β-iodoesters, can be transmetalated to palladium and subsequently cross-coupled to aryl and alkenyl iodides (Fig.

4a).[18] Potassium trifluoroborato homoenolates can be generated from copper-catalyzed conjugate addition of bis(pinacolato)diboron followed by treatment with KHF_2.[19] These boron homoenolates can be cross-coupled to aryl bromides via palladium catalytic cycle (Fig. 4b).[20] Indium ketone homoenolates which are prepared by treatment of α,β-unsaturated ketones with $In/InCl_3$, are remarkably stable due to lone pair interactions between two ketone units and the indium atome. These can be cross-coupled with a variety of acid chlorides, with both homoenolate units participating in the reaction (Fig. 4c).[21]

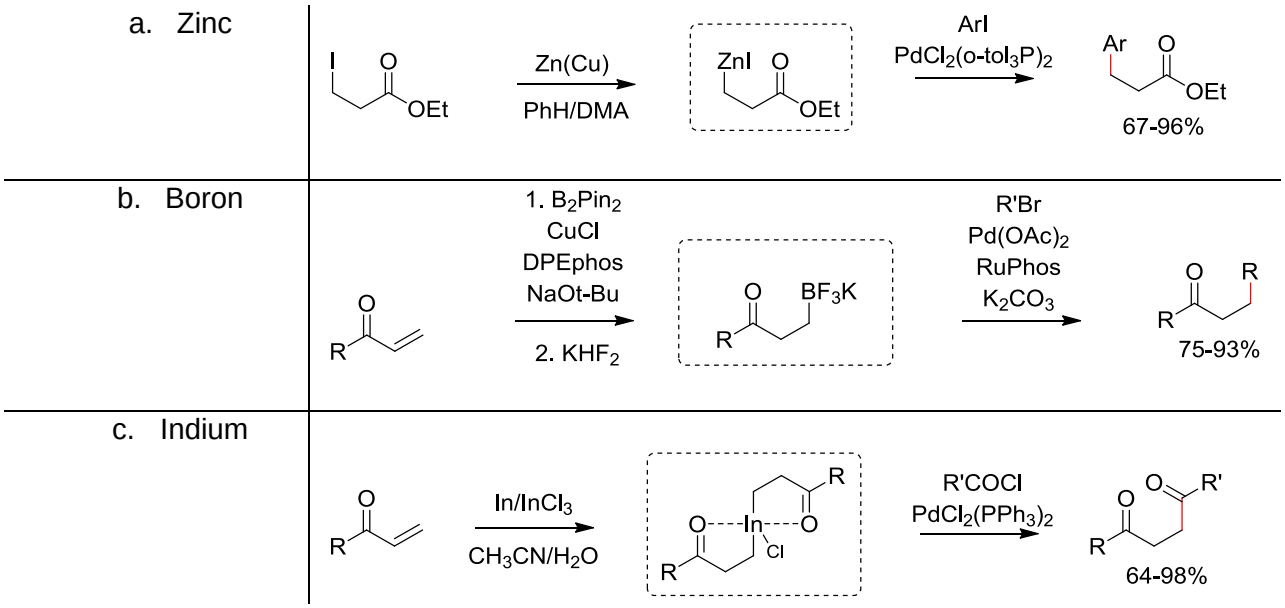


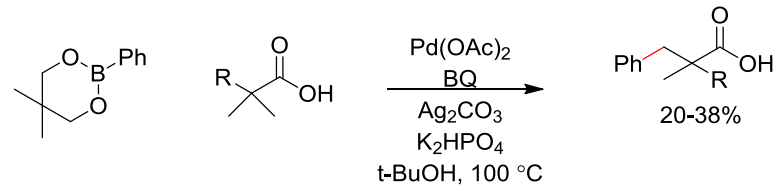
Figure 4. Generation of palladium homoenolates *via* transmetalation with pre-formed metal homoenolates

1.8 Generation of homoenolates via palladium-catalyzed C-H activation

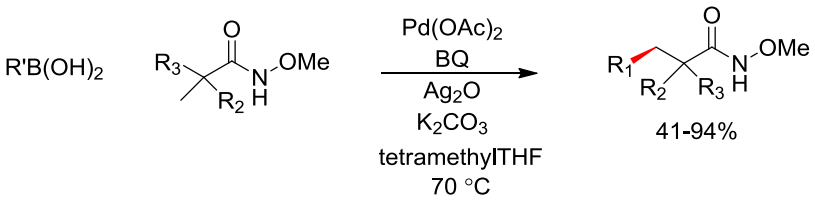
Palladium-catalyzed C-H functionalization at the β-position of a carbonyl group is a strategy used to generate homoenolates that circumvents the need for pre-formed homoenolates. The functionalization of $C(sp^3)$–H often relies on the use of directing groups to guide the metal to a

particular site. In this fashion, the carbonyl group of acids and amides have been shown to direct C–H functionalization leading to homoenolate equivalents. Notable work by Yu and co-workers demonstrate the participation of palladium in directed insertion into β-C(sp^3)-H bonds of carboxylic acids[22] and *O*-methyl hydroxamic acids[23] to generate homoenolates that were subsequently cross-coupled with boronic esters or acids (Scheme 7). This cross-coupling reaction is largely confined to the use of substrates that are incapable of β-hydride elimination, thus bearing an all-carbon quaternary center at the α-position. Another directing group strategy used for selective β-C(sp^3)-H functionalization is the use of auxiliaries like 8-aminoquinoline which can be used for direct arylation at the β-position of aliphatic amides. [24]

Carboxylic acid directed β-C(sp^3)-H functionalization:



O-methyl hydroxamic acid directed β-C(sp^3)-H functionalization:

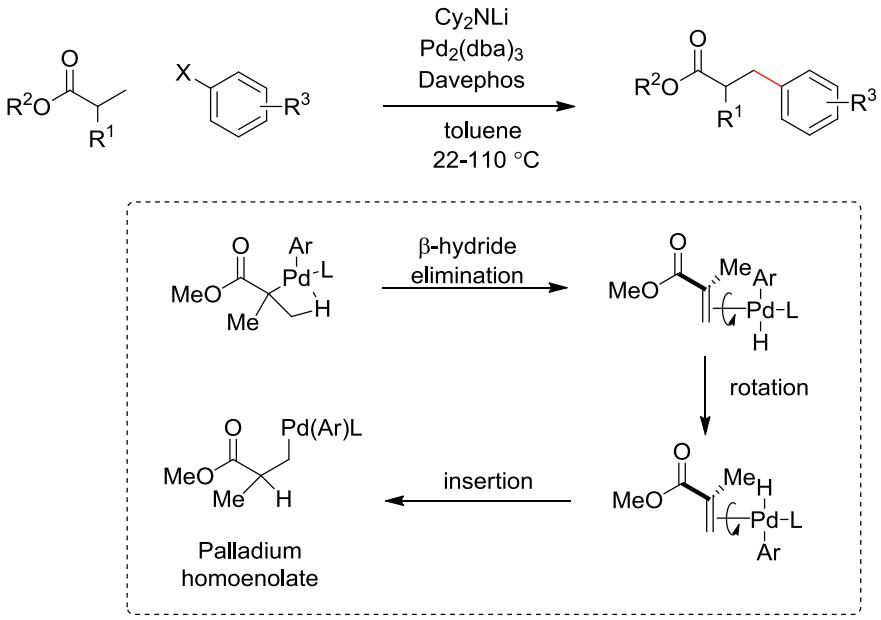


Scheme 7. Generation of homoenolate via palladium catalyzed β- C (sp^3)-H functionalization

1.9 Homoenolate generation by palladium-catalyzed isomerization of enolates

Baudoin, Clot and co-workers showed that under forceful conditions, hindered α-tertiary carboxylic ester-derived palladium enolates can rearrange to form less-hindered palladium

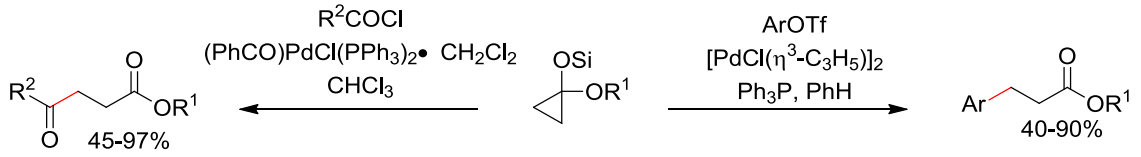
homoenolates, which can be cross-coupled with a range of aryl and heteroaryl bromides and chlorides to yield β-arylated esters (Scheme 8).[25] A strong non-nucleophillic base (Cy_2NLi) is needed to generate a lithium ester enolate, that coordinates to palladium. Mechanistic studies of this reaction suggest that β-hydride elimination occurs upon coordination, followed by rotation of the metal adduct to a less hindered side and then reinsertion of the palladium to the β-carbon, generating the homoenolate.



Scheme 8. Purposed mechanism of palladium homoenolate generation via. enolate-homenolate isomerization

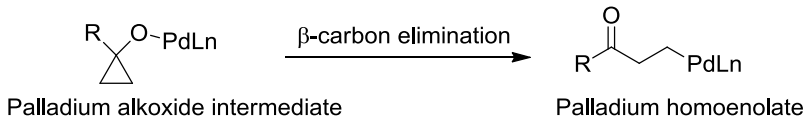
1.10 Palladium homoenolates via ring cleavage of cyclopropanol derivatives

Kuwajima and Nakumara's work in 1988 used the siloxycyclopropane ring cleavage approach to generate palladium homoenolates, which were then shown to cross-couple to aryl and alkenyl triflates[26] and acid chlorides[27] (Scheme 9). This chemistry was later expanded by Nakumara to include carbonylative cross-coupling reactions of cyclopropane acetals.[28]



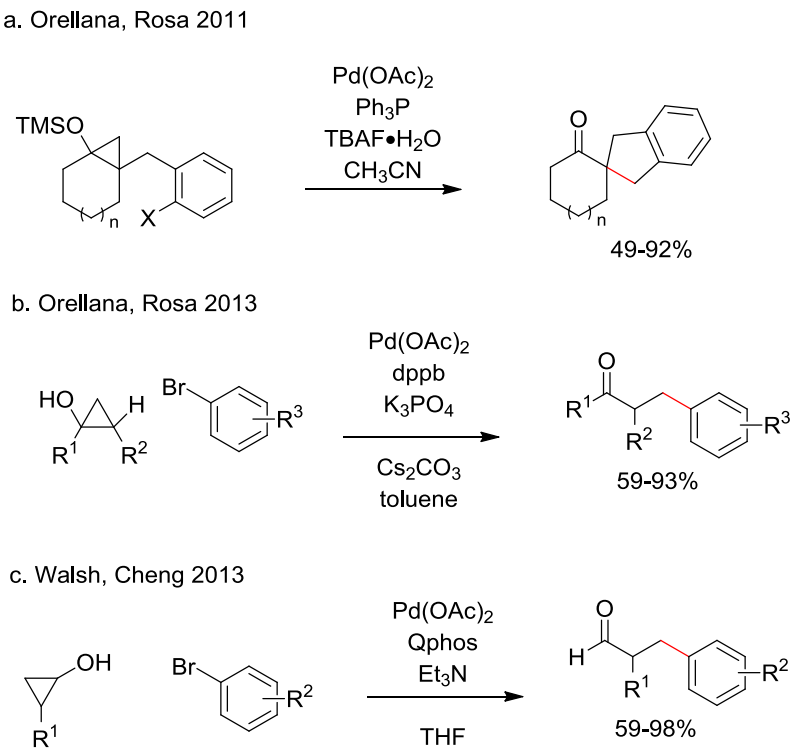
Scheme 9. Catalytic generation of palladium homoenolates from cyclopropane acetals and cross-coupling with aryl triflates and acid chlorides

The first cross-coupling reaction between unprotected cyclopropanol-derived ketone homoenolates (deprotected *in situ*) and aryl halides was reported by the Orellana group in 2011 (Scheme 11a).[29] These reactions employed substrates with quaternary β carbons to avoid the competing β-hydride elimination reaction, which posed a problem. The ring opening of these cyclopropanols is thought to occur via the formation of a palladium alkoxide intermediate followed by a β-carbon elimination step, as suggested by Cha based on studies of palladium-catalyzed oxidative reaarangement of cyclopropanols to α,β-unsaturated ketones (Scheme 10).[30]



Scheme 10. Generation of ketone palladium homoenolates from cyclopropanols

The scope of this reaction was later expanded to include unprotected cyclopropanols bearing β-hydrogens (Scheme 11b).[31] Notably, β-hydride elimination was not observed with the use of bidentate phosphine ligands, such as dppb. Cyclopropanol-derived palladium homoenolates of aldehydes have also been prepared and their cross-coupling reactions with aryl bromides has been reported by Walsh (Scheme 11c).[32]



Scheme 11. Palladium catalyzed cross-coupling of cyclopropanol derived ketone and aldehyde homoenolates with aryl halides

1.11 Ring strain in cyclopropanes

As discussed above, our group has reported on the use of cyclopropanol-derived palladium homoenolates to produce ketones functionalized at the α position (Scheme 10 a & b). These reactions rely on strain release as a driving force to generate the homoenolates. Cyclopropane moieties are used in particular because they exhibit high strain energy of 27.5 kcal/mol when compared to other small ring molecules. This strain energy of cyclopropanes has been attributed to both the angle strain; caused by a huge deviation from the ideal 109.5° of sp^3 hybridized orbitals, and also to torsional strain caused by having all hydrogens eclipsing on both the top and bottom of the ring plane (Fig. 5).[33]

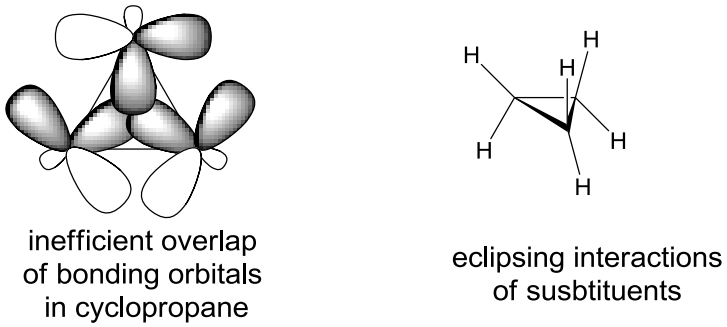
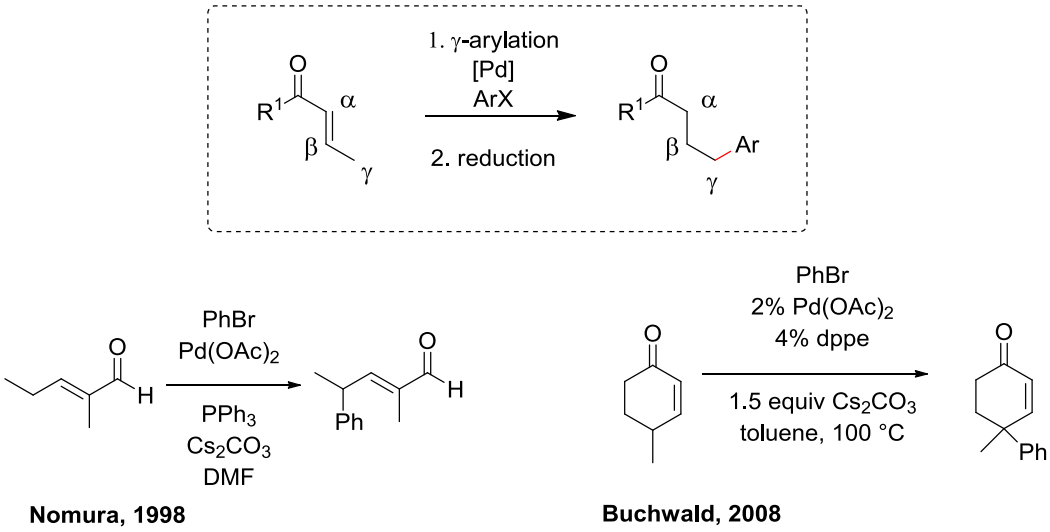


Figure 5. Representation of angle and torsional strain in cyclopropanes

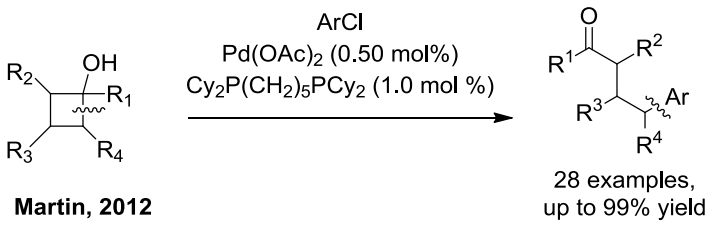
1.12 Palladium-catalyzed preparations of gamma-arylated ketones

A review of literature on the preparation of gamma-arylated ketones gives few examples of palladium catalyzed methods. The first example that employed palladium catalyzed cross-coupling to generate these ketones was reported by Nomura (Scheme 14) wherein they showed regioselective arylation at the gamma position of α,β-unsaturated carbonyl compounds with aryl bromides by palladium catalysis.[34] This reaction was though to occur via a direct catalytic arylative substitution of allylic hydrogens, involving dienolate anions as principle intermediates. Similarly, the Buchwald group reported on the palladium-catalyzed gamma-arylation of cyclic α,β-unsaturated ketones that proceeds through dienolate intermediates.[35] In both Nomura's and Buchwald's methods the enal or enone functionality is retained in the gamma-arylated ketone product.

Pd-catalyzed γ-arylation of α,β–unsaturated carbonyl compounds:



Pd-catalyzed ketone γ-arylation via C–C cleavage of cyclobutanols:

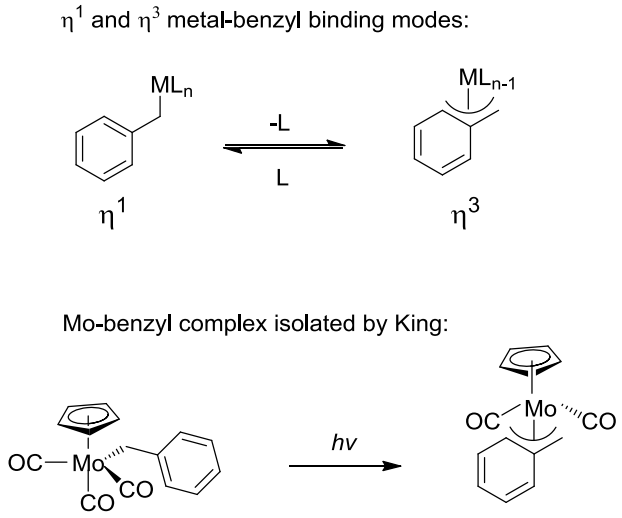


Scheme 14. Palladium-catalyzed routes to γ-arylated ketones

In recent years work by Martin[36] showed a more general approach to γ-arylated ketones through the strain-releasing reactions of cyclobutanols via a palladium-catalyzed arylation that involves β-carbon elimination of deprotonated cyclobutanol and cross-coupling to aryl chlorides. In our study we propose to take an alternate approach using cyclopropanol derived homoenolate ketones with benzyl halides as cross-coupling partners. One of the major practical advantages of this route is that cyclopropanols can be prepared readily by several well-established reactions including those developed by Kulinkovich[37] and Simmons-Smith[38].

1.13 Coordination of benzyl halides to metal centers

The benzyl halides are remarkable cross-coupling partners since they exhibit a fascinating metal binding pattern. Like the bonding in metal-allyl complexes, the metal-benzyl coordination can exist as either a σ-(η^1) complex or a π-(η^3) complex (Scheme 15).[40] The formation of the π (η^3) complex is thought to lead to a loss in aromaticity in the ring. King and Frongzaglia were the first to show evidence for the π-(η^3) binding mode of benzyl systems through NMR studies of an isolated molybdenum-benzyl complex.[41] X-ray studies on the benzyl complex revealed bonding between Mo and all three carbons that make the η^3-coordination. NMR studies also showed a fluxional behavior characteristic of a π-σ-π isomerization of the benzyl ligand. Although not as prevalent as aryl and vinyl halides, benzyl halides have also been successfully exploited in a number of known palladium name reactions such as Heck, Suzuki, Stille, Negishi, Sonagashira and Tsuji-Trost.[42]



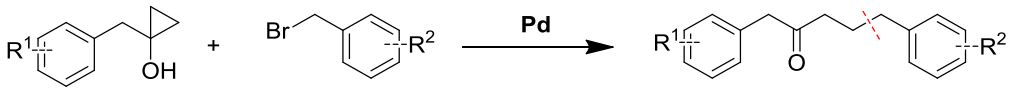
Scheme 15. Metal η^3-benzyl complex

Given the differences in metal-benzyl coordination and benzyl halide reactivities, we anticipated that cross-coupling of cyclopropanol-derived palladium homoenolates with benzyl halides will be

governed by a significantly different mechanism from the previously reported cross-coupling reaction using aryl bromides, and therefore necessitate a new set of conditions.

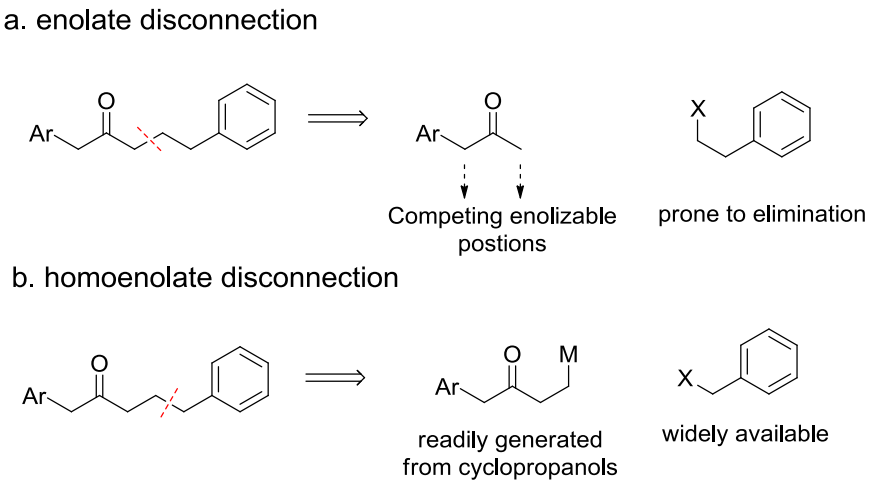
1.14 Plan of study

We are interested in extending the chemistry of cyclopropanol-derived homoenolates as synthons to access unique synthetic disconnections. The goal of this work is to furnish γ-arylated ketones via palladium-catalyzed cross-coupling of cyclopropanol-derived palladium homoenolates to benzyl halides (Scheme 12).



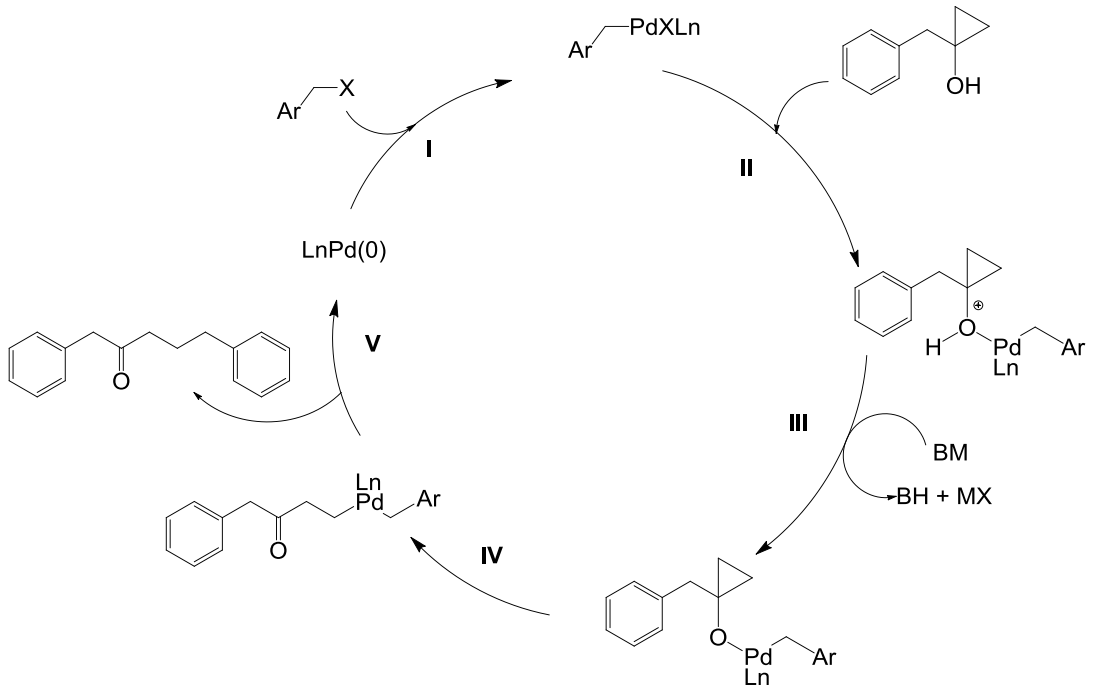
Scheme 12. Proposed cross-coupling of cyclopropanol-derived ketone homoenolates with benzyl bromides

The traditional approach to access gamma-arylated ketones would be through an enolate alkylation approach that involves an electrophillic addition of phenyl ethyl halide to the terminal enolate generated from the ketone shown in Scheme 13a. This approach can suffer from poor enolization regioselectivity due to competing pK_a profiles at the terminal and benzyl position (24.8 and 19.9 in DMSO, respectively), that can lead to the formation of the undesired enolate. Moreover, the phenethyl halide reagent required is prone to E2 elimination reactions in the presence of strong base, making its use difficult. In striking contrast, the use of a homoenolate as the nucleophile avoids these competing enolization and elimination reactions (Scheme 13b).



Scheme 13. Traditional enolate disconnection (top) vs. homoenolate disconnection (bottom) of γ-arylated ketones

A plausible reaction mechanism (Scheme 16) for our proposed transformation would involve oxidative addition to the benzyl halide (Step I) followed by coordination and deprotonation of cyclopropanol onto the Pd(II) complex (Step II and III). β-Carbon elimination to generate the homoenolate (Step IV) followed by reductive elimination would yield the desired ketone (Step V).

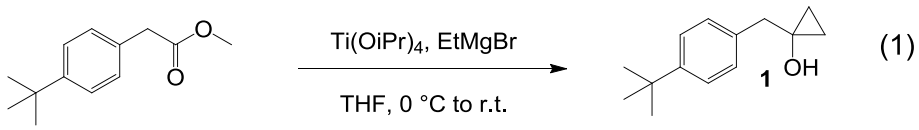


Scheme 16. Plausible catalytic cycle for the cross-coupling of benzyl halides with cyclopropanol derived ketone homoenolates.

Chapter 2: Results and Discussion

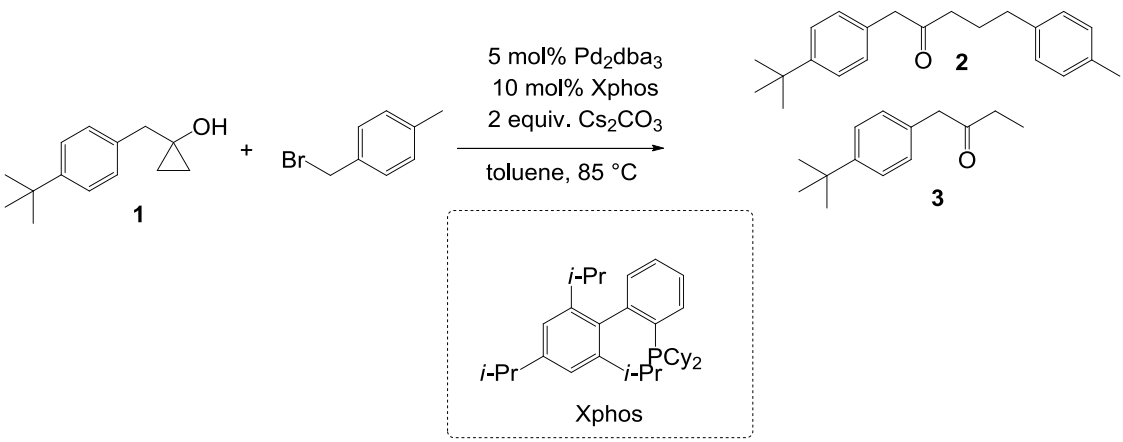
2.1 Initial findings and challenges

We began our study using the model substrate cyclopropanol **1** as was used by Orellana and Rosa in their cross-coupling reactions with aryl bromides.[31] Substrate **1** was prepared according to previously reported procedure using the Kulinkovich reaction (Eq. 1).[37]



(1)

In our initial reaction, benzyl cyclopropanol **1** was coupled with *p*-methyl benzyl bromide (Eq.2) in 27% yield of the coupled product **2** using Pd_2dba_3 as the palladium (0) source and Xphos as the ligand.



(2)

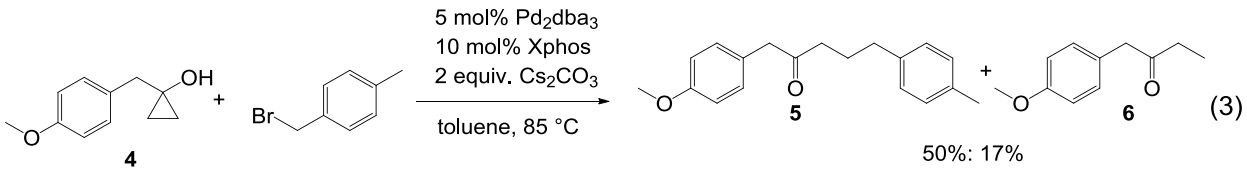
This result however was not reproducible and subsequent trials with the exact same reaction conditions did not yield any coupled product but instead yielded the ketone from the ring opening of cyclopropanol. It was also noted that the ketone **3** and the coupled product **2** had the same R_f by thin layer chromatography, and were not easily separated with various solvent mixtures using traditional silica gel column chromatography.

2.2 Optimization studies

To overcome separation issues we switched to cyclopropanol **4** (Eq. 3). We hypothesized that by replacing the t-butyl group with a more polar substituent on the benzyl cyclopropanol, the coupled product **5** and the ring-opened product **6**, would have a significant difference in polarity and thus could be more readily separated.

Keeping the Pd(0) source consistent, a ligand screen with substrate **4** was carried out using the monodentate ligands; PPh_3, $HP^+(Bu)_3BF_4^-$, Sphos and Davephos and the bidentate ligands dppe and dppp. None of these ligands however yielded the desired coupled product. When the monodentate Buchwald phosphine ligand Xphos was used, the coupled product was observed (eq. 4). Purification of this product by silica gel column chromatography yielded the coupled product **5** plus ketone **6** as a minor impurity that could not be separated. Contrary to our rationale, the difference in polarities between the coupled product the ketone resulting from the

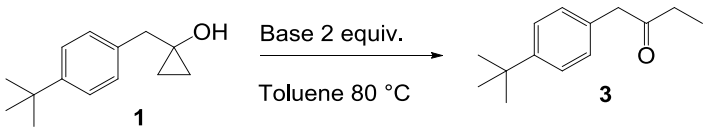
ring opening of the cyclopropanol, did not change significantly with substrate **4** and both products still had the same R_f. We were able to determine the ratio of the coupled product to the ring-opened ketone through NMR analysis. Our initial reaction with Xphos gave a 50%:17% yield ratio of the coupled to the side product.



(3)

In order to avoid the base mediated ring opening of the cyclopropanol to the corresponding ketone, a base screen was carried out to qualitatively asses the stability of the cyclopropanol under different bases (Table 1). Cyclopropanol **1** was subjected to two equivalence of base in toluene at 80°C and the time it took until the first appearance of ring cleavage to form the ketone, was monitored through TLC analysis. Potassium t-butoxide cleaved the cyclopropanol within five minutes. With both phosphate and acetate bases the cyclopropanol remained stable for several hours longer (up to 6 hours) but the ring cleavage starts to occur within 16 hours. The organic base pyridine was also included in the study since, unlike salt bases, it is soluble in organic solvents. The ketone was not observed until 22 hours in the reaction pot with pyridine. Among the carbonate bases silver carbonate mediated the ring opening in 40 minutes, whereas cesium carbonate and potassium carbonate did not cleave the ring even after 25 hours.

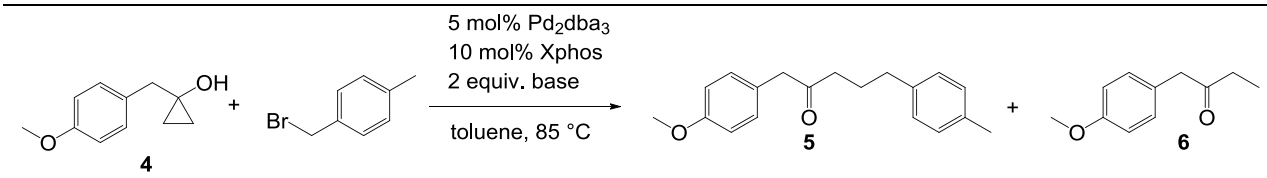
Table 1. Qualitative assessment of cyclopropanol stability under various bases through TLC analysis of the first appearance of the ketone derived from ring opening.



Entry	Base	Time
1	Cs_2CO_3	>25 hours
2	Ag_2CO_3	40 minutes
3	K_2CO_3	>25 hours
4	KOAc	<16 hours
5	CsOAc	<16 hours
6	K_3PO_4	<16 hours
7	KOtBu	5 minutes
8	Pyridine	22 hours

The use K_2CO_3 and Ag_2CO_3 as the base in this coupling reaction (Table 2) was compared to Cs_2CO_3 (eq. 4) and it was found that using Cs_2CO_3 as the base gave the best yield of the coupled product. Yields higher than 50% were not obtained using these reaction conditions with substrate cyclopropanol **4**, so further optimization strategies were needed.

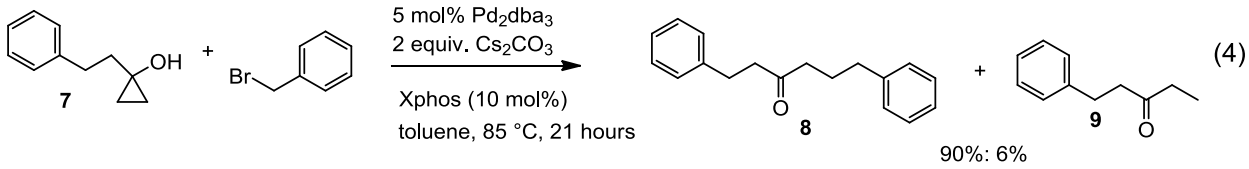
Table 2. Base effects on cross coupling reaction of 4-methoxybenzyl cyclopropanol with 4-methyl benzyl chloride.



Entry	Base	NMR conversion **5** :**6**
1	K_2CO_3	23%: 10%
2	Ag_2CO_3	7%: 16%
3	Cs_2CO_3	50%: 17%

At this point we decided to switch the cyclopropanol substrate from a benzyl cyclopropanol **4**, to a phenylethyl cyclopropanol. It was reasoned that ketones with benzyl groups attached may be prone to enolization under basic conditions via deprotonation at the benzyl position (pKa =19.9 in DMSO). The enolization pathway may in turn be leading to decreased yield of the coupled product. To avoid this possible interference we switched to phenylethyl cyclopropanol **7**, which would have relatively low alpha aciditiy.

This idea was investigated by subjecting cyclopropanol **7** and benzyl bromide to our previous catalyst system. Remarkably, a 90% yield of the desired coupled product was obtained (Eq. 4). Again, we observed ketone **9** as a minor impurity that could not be separated from the coupled product by silica gel coloumn chromatography despite multiple efforts using different solvent systems. NMR analysis of the product yield ratio showed that the yield of **9** was approximately 6%.



(4)

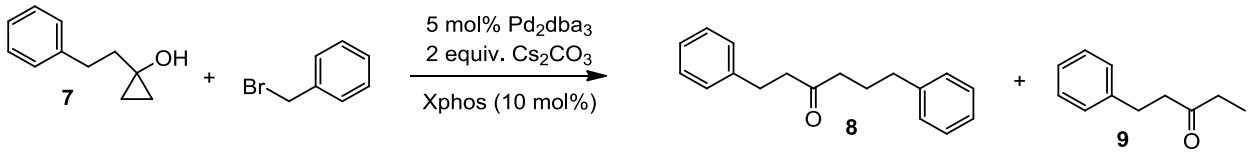
Although a high yield of the coupled product was obtained, we were interested in further suppressing the formation of ketone **9**.

Our next consideration was the role of the solvent in mediating the formation of the ketone from ring opening. Solvents can affect basicity via solubility and coordination. Since cyclopropanols are known to ring open under basic conditions[43], fine tuning the basic environment through solvent selection can have a profound effect on the yields of the desired product.

Thus a solvent screen was carried out using solvents of varying polarities (Table 3). Toluene, which was used in the initial reaction conditions, gave better yield of cross-coupled product (90%) than any of the other solvents screened. Using toluene, the effect of temperature on the yield of coupled product was studied. When the temperature was lowered (Table 3, entry 1) the

ratio of coupled product to **9** decreased. When the temperature was increased all of the cyclopropanol had converted to the ring opened ketone **9** within 2 hours

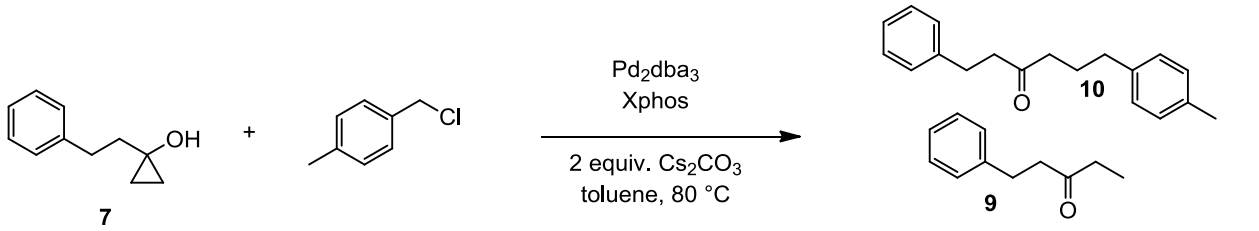
Table 3. Effect of solvent on yield of coupled product.



Entry	Solvent	Temperature[a]	Time	NMR conversions
1	Toluene	65-70°C	17 hours	55%: 11%
2	Toluene	80-85°C	21 hours	90%: 6%
3	Toluene	90-105°C	2 hours	0%: 41%
4	THF	60°C	44 hours	35%: 17%
5	DME	80°C	44 hours	34%: 13%
6	CH_3CN	80°C	16 hours	20%: 6%

[a] Indicates the temperature of the oil bath. Fluctuation in temperature is recorded as a range.

Remarkably, when the benzyl halide used was changed from benzyl bromide to benzyl chloride (Scheme 17, entry 1), keeping the catalyst system consistent, the reaction gave exclusively the coupled product in high yield with no ketone side-product. Furthermore the reaction time dropped significantly from 21 hours to 1 hour.



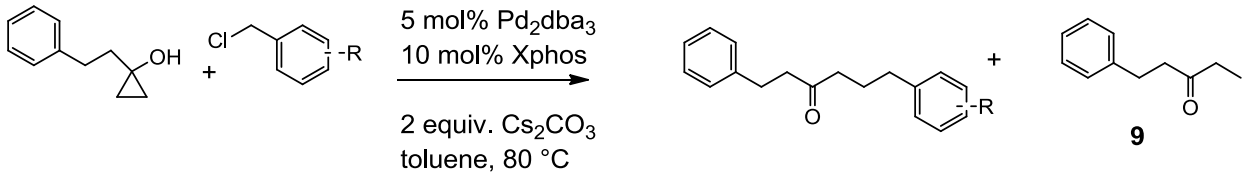
1) 5 mol% Pd_2dba_3 + 10 mol% Xphos: **10** 93%
2) 2.5 mol% Pd_2dba_3 + 5 mol% Xphos: **10** 48% + **9** 21%

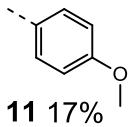
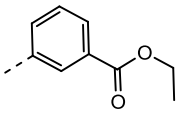
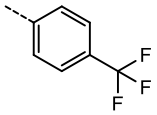
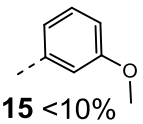
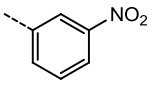
Scheme 17. Cross-coupling of benzyl chlorides to cyclopropanol **7** using different catalyst loading.

Moreover, decreasing the catalyst loading from 10% to 5% Pd (scheme 17, entry 2) increased reaction time (overnight) and led to a low yield of a mixture of the coupled product and the ring opened side product.

Using a 10% catalyst loading, the generality of these reaction conditions was tested using various benzyl chlorides (Table 4) with both electron-donating, electron-withdrawing and electron-neutral substituents on the aryl ring. With our current set of conditions the yields of the coupled products for these reactions were generally low and reduced by the competing base-mediated ring opening of the cyclopropanol. Moreover, there was no trend between electronic nature of the substrates and their relative yields. For example, the substrates benzyl chloride and 4-methyl benzyl chloride have similar electronic properties, however the former coupled with a yield of 93%, while the latter gave 26% of the coupled product. This data suggested that there may be confounding factors at play that are leading to inconsistent results. In light of these findings from our initial substrate scope run, we continued on with optimization and reaction studies to achieve decent yields of product.

Table 4. Cross-coupling reactions using various benzyl chlorides.

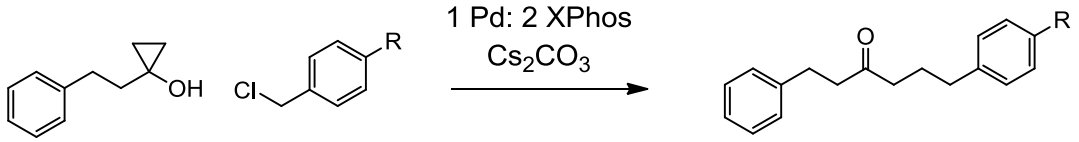


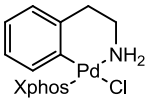
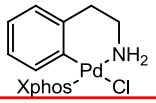
 **11** 17% **9** 40% 4.5 h	 **12** 51% **9 24%** 3 h	 **13** 25% **9** 34% 8.5 h
 **8** 26% **9** 46% 6 h	 **15** <10% **9** 43% 6 h	 **16** 05% **9** 20% 5 h

2.3 Optimization of cross-coupling reactions with electron-rich benzyl chlorides

Having previously explored the effect of bases and ligands and finding optimal activity with Xphos and cesium carbonate, these reagents were kept constant while the effect of solvent, temperature and palladium source was studied (Table 5). The focus here was to find conditions that circumvent the ring opening of the cyclopropanol since this not only reduces the yield of the final product but makes purification difficult. Test reactions were carried out using 4-methyl benzyl chloride and benzyl chloride. Since these two substrates previously gave unpredicted, contradictory results we used them in optimization studies to find a system that produced consistent results.

Table 5. Reaction development through varying catalyst, solvent and temperature



Entry	Benzyl chloride	Pd source	Catalyst load	solvent	Temperature[a]	Yield/ Result
1	R=CH_3	Pd_2dba_3	5 mol%	THF	60 ^{0}C	82%
2	R=H	Pd_2dba_3	5 mol%	THF	60 °C	89%,
3	R=CH_3	$Pd(OAc)_2$	5 mol%	THF	60 °C	82%
4	R=CH_3	$Pd(OAc)_2$	1 mol%	THF	60 °C	80%
5	R=CH_3		1 mol%	THF	60 °C	No reaction after 3 days
6	R=CH_3		1 mol%	THF:toluene, 1:1	80 °C	75%
7	R=CH_3	$Pd(OAc)_2$	1 mol%	THF: toluene 1:1	80 °C	87%
8	R=H	$Pd(OAc)_2$	1 mol%	THF: toluene 1:1	80 °C	94%

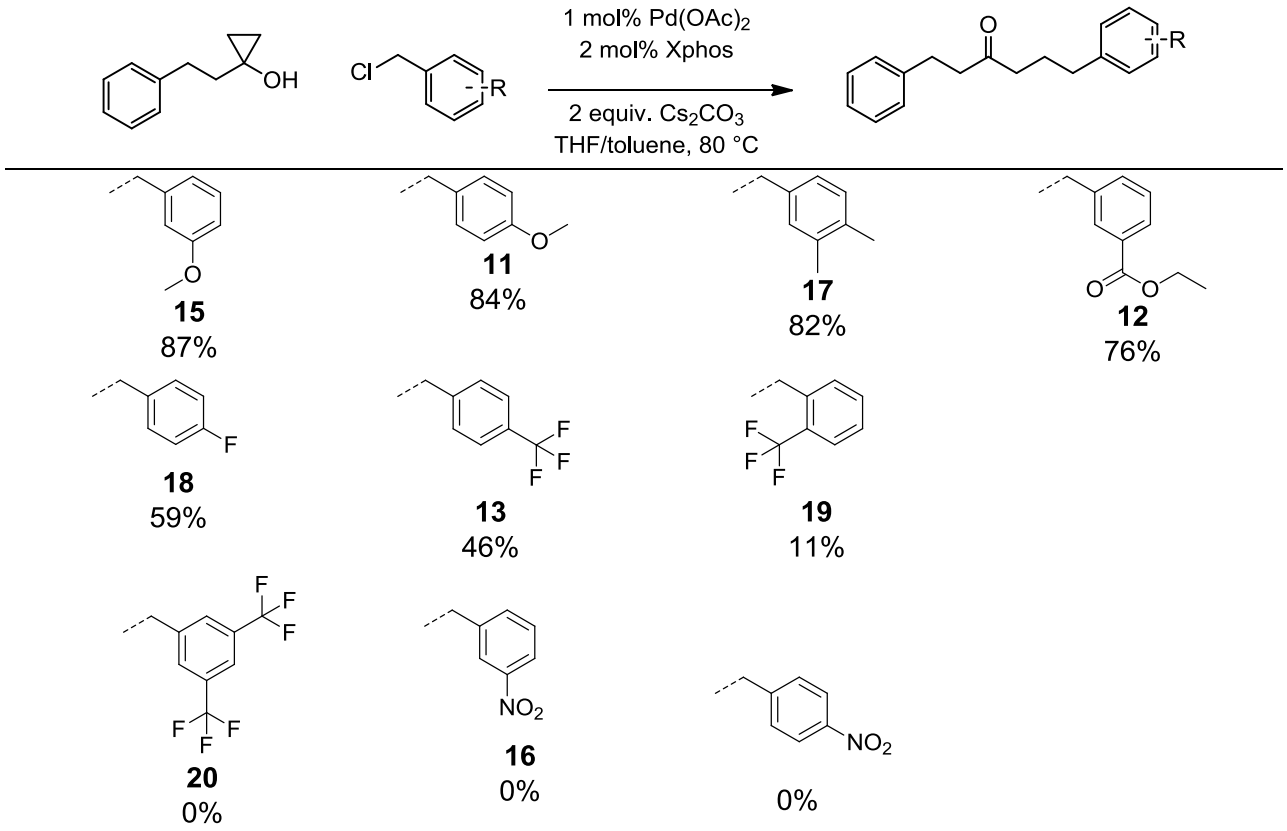
[a]Indicates the temperature of the oil bath.

The first insightful finding was seen when THF was used in place of toluene as the solvent. We chose THF because it is more polar and so it may assist in increased solubility of the base. Using THF at 60°C (entries 1 & 2) we found that the yield of p-methyl benzyl chloride was lower

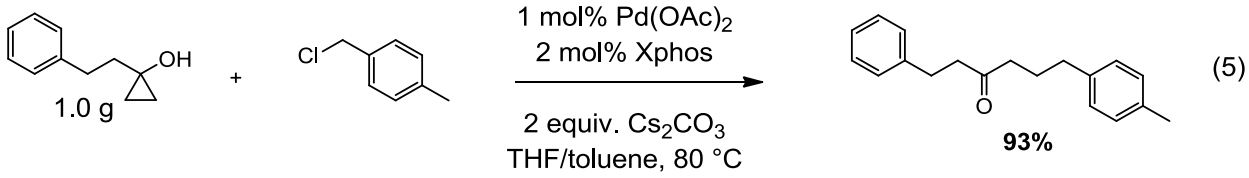
than the previous condition (82% vs. 93%). However, the yield of cross-coupling the benzyl chloride substrate increased (89% vs. 26%). More notably, no side product was observed, suggesting that the coordinating solvent plays a significant role in modulating the rates of cross coupling versus ring opening of the cyclopropanol.

Meanwhile, robust Pd(II) catalysts were also explored as starting points in place of the sensitive Pd_2dba_3 catalyst. We chose to try the first generation Xphos palladacycle pre-catalyst (entry 5) since this Pd(II) source is pre-coordinated to XPhos and can be reduced to Pd (0) under basic conditions through a reductive elimination that releases the adjoining tetrahydroquinoline group. Our results show that this pre-catalyst showed no activity at 60^0C (entry 5). The first generation pre-catalyst are known to require thermal activation in order for the reductive elimination step to occur especially under mild basic conditions. Hence we increased the temperature of the reaction to 80°C. In order to prevent the complete evaporation of THF at 80°C we used a 1:1 mixture of THF and toluene. A yield of 75% was obtained under these conditions (entry 6). Since this is not an excellent yield and because the catalyst is rather expensive, further use of this catalyst was abandoned for our purpose. The most favorable result was obtained using $Pd(OAc)_2$ (entry 7 & 8) whereby using a low catalyst load of 1 mol% under an equimolar THF:toluene solution at 80 °C yielded 94% of coupled product and none of the ring opened cylclopropanol. We chose to use a mixture of THF/ toluene in order to retain the increased polarity and coordinating ability of THF and the high boiling point of toluene, which allows us to carry out the reactions at a high temperature. Thus these conditions were then used to test substrate scope of various benzyl chlorides (Table 6).

Table 6. Scope of benzyl chloride cross-coupling reactions with the improved set of reaction conditions.



To test the robustness of the optimized conditions, the reaction was run using 1.0 gram of phenylethyl cyclopropanol (eq. 5). We were able to obtain an excellent yield of 93% hence demonstrating a large-scale potential for this method.

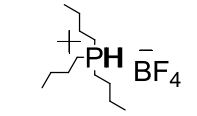


(5)

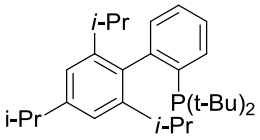
2.4 Optimization of cross-coupling reactions with electron poor benzyl chlorides

Although yields obtained were good to moderate for electron- rich systems, it became apparent that the new set of optimized conditions did not fare well with all types of benzyl

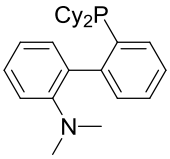
chlorides. The reactivity of the developed catalyst system diminishes as the benzyl chlorides become electron deficient; substrates **13**, **18** and **19** had low yields whereas substrate **20** and the strongly withdrawing nitro group substrates failed to cross-couple at all. It is likely that oxidative addition across these electron-poor benzyl halides is difficult and is the root of the low reactivity. The following electron-rich ligands were screened with $Pd(OAc)_2$ to find a system that would favour oxidative addition of the p-nitro benzyl chloride:



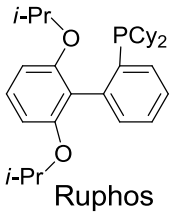
Tributylphosphine tertrafluroborate



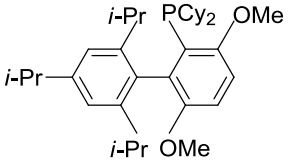
tBuxphos



Davephos



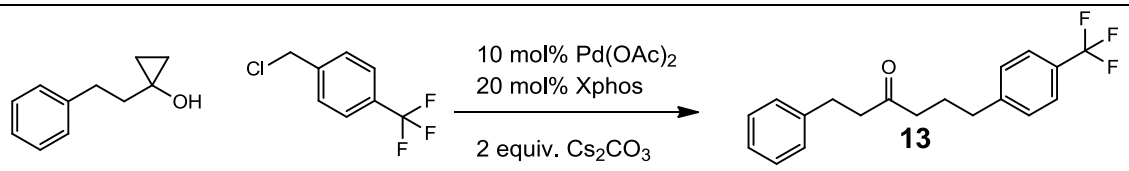
Ruphos



Brettphos

None of these ligands yielded positive results as no cross-coupled product was attained in any of the reactions. Since the 4-trifluoromethyl benzyl chloride showed some potential (46% coupled product; Table 6), as opposed to no coupled product, we chose this as the model substrate to optimize conditions for electron-poor systems. Changes in yields with varying temperatures and solvents were monitored (Table 7).

Table 7. Optimization study on the electron poor substrate 4-triflouromethyl benzyl chloride , with varying temperature and solvent



Entry	Solvent	Temperature[a]	Yield/ Result
1	THF	65°C	12%
2	Toluene	60°C	0%
3	Toluene	80°C	36%
4	Toluene	100°C	31%
5	THF: toluene (1:1)	75°C	9%
6	1,4-dioxane	80°C	54%
7	1,4-dioxane	95°C	0%
8	DMF	80°C	0%
9	DMA	80°C	0%
10	DMI	80°C	0%
11	1.4-dioxane/DMI (1:1)	80°C	22%

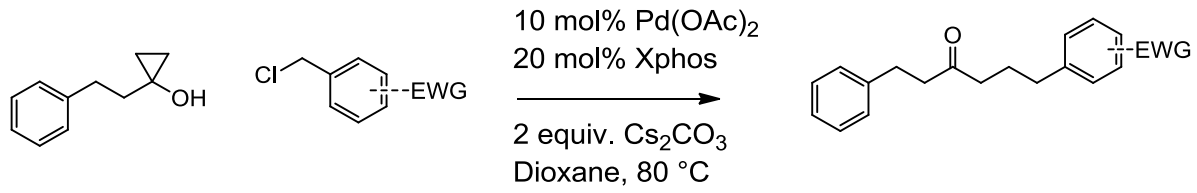
[a] Indicated the temperature of the oil bath.

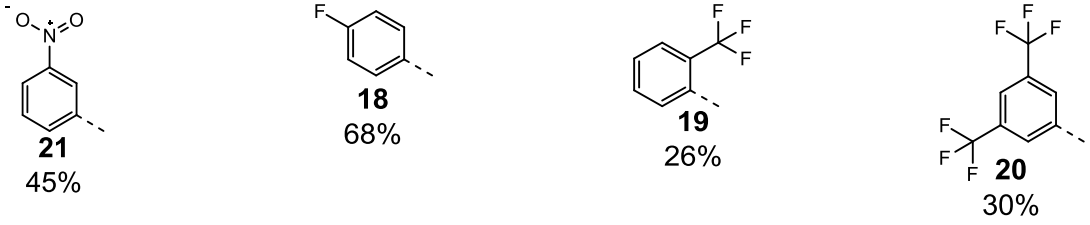
The data from the solvent/temperature study using toluene as the solvent suggested that 80 °C was the ideal temperature range for this reaction. Knowing from previous results that a coordinating solvent like THF helps to minimize the side reaction leading to ring opening of cyclopropanol, the high boiling ether solvent 1,4-Dioxane was tested at 80 °C (entry 6). Although not ideal, dioxane gave the best result thus far with a 54% yield of coupled product. We hypothesized that it may be the polarity of dioxane that may be contributing to increased yields via stabilization of the transition state leading to oxidative addition. We investigated this idea with the use of alternate polar solvents: DMF, DMA, and DMI, however none of these conditions yielded any cross-coupled product. Moreover the starting materials were not consumed within the usual reaction time and Pd black was observed, indicating catalyst decomposition. When a mixture of DMI and dioxane was used as the solvent, a 22% yield of the product is obtained. This suggests that dioxane was solely responsible for increasing the

reactivity, while the other polar solvents interfered with catalyst reactivity. We then proceeded to use dioxane as the solvent in combination with electron-rich phosphine ligands; tri-t-butyl phosphine, dppe, dppp, and dppb to optimize the yield of **13**. These ligands failed completely and in each case the reaction mixture turned black within 5 minutes with the starting materials remaining unreacted over 24 hours.

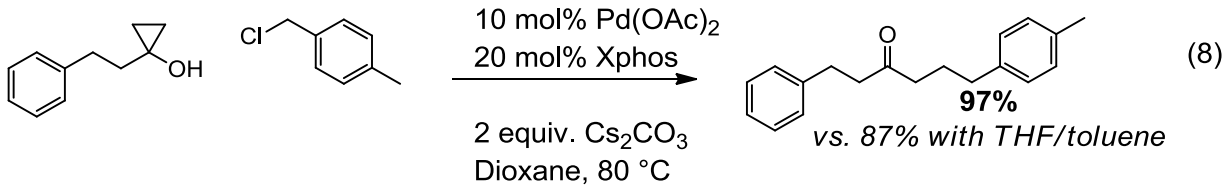
Having explored the effect of solvent, temperature and ligands on the cross-coupling of electron-poor benzyl halide, we proceeded to survey the capacity of cross-coupling the previously unreactive benzyl chlorides using the best conditions found from the optimization study (Table 8).

Table 8: Substrate scope of electron poor benzyl chlorides with re-optimized conditions





Although the yields improved with dioxane, they are still poor. Strongly electron-withdrawing substituents are not suitable substrates for this cross-coupling reaction. This is evident in the reaction with the most deactivated substrate p-nitrobenzyl chloride that did not couple at all under the above set of conditions. On the contrary, for the electron-rich substrate 4-methyl benzyl chloride, the yield exceeded the previously optimized yield when the solvent was switched to dioxane (Eq. 8).

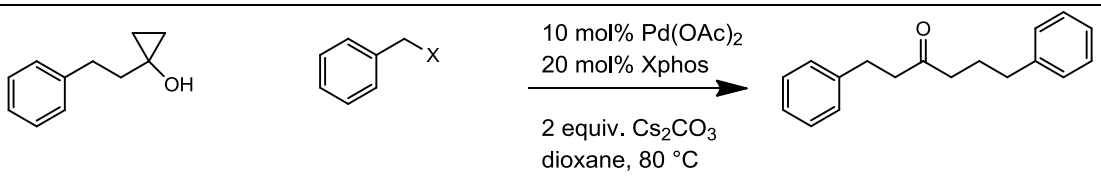


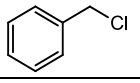
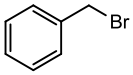
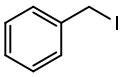
(8)

2.5 Investigation of benzyl halide tolerance in cross-coupling reactions

After investigating tolerance of functionalities on the benzyl halide, we turned our attention to the effect of the halide on the reaction outcome (table 9).

Table 9: Investigation of benzyl halide tolerance



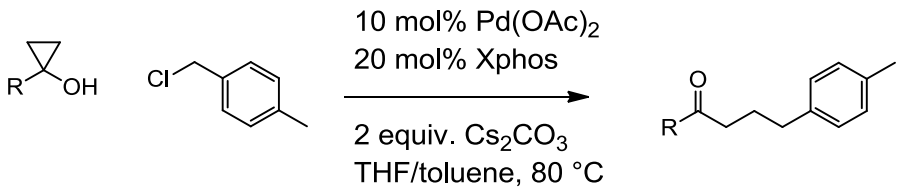
Benzyl Halide	Results
	86%
	67% *note this reaction turned black within 30 min
	72% This reaction also blacks out within 30 min After 24 hours of reaction 18% of cyclopropanol starting material remained.

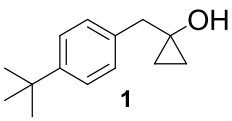
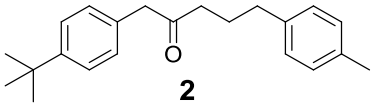
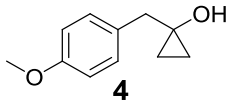
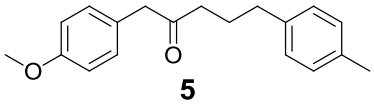
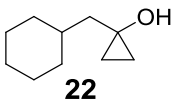
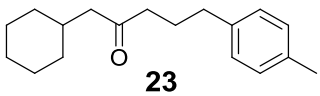
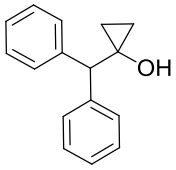
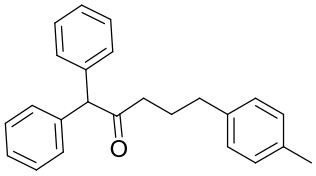
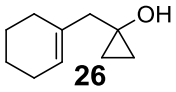
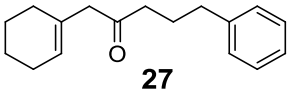
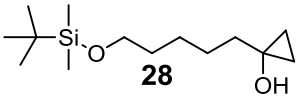
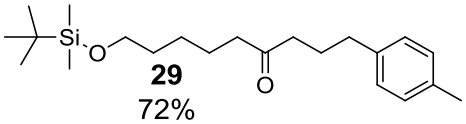
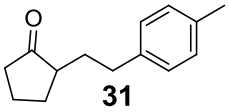
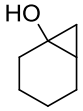
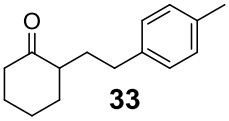
Using the developed conditions benzyl chloride gave the best results, producing 86% of the coupled product within 8 hours. In contrast the reactions using benzyl bromide and benzyl iodide led to catalyst decomposition within 30 minutes and as result, low yields of the coupled product were attained. Although it is not an ideal correlation, it is apparent from the data that as the coordinating ability of the halide decreases the reaction starts to break down. In addition to their reactivity, benzyl chlorides are also widely available and cost effective, which makes them preferable as coupling partners.

2.6 Cyclopropanol substrate scope

After exploring conditions to expand the scope of benzyl chlorides, we then moved on to study the tolerance of the cyclopropanol partner to form catalytically-generated ketone homoenolates and subsequently cross-couple them with the electrophile. Table 10 shows the diverse set of cyclopropanols with various aliphatic or aromatic groups that were successfully cross-coupled to give ɣ-arylated ketones in good-to-excellent yields. Cyclopropanols were prepared either by the Kulinkovich method[37] or by the Simmons-Smith[38] reaction using the corresponding silyl enol ether, as reported in literature.[31]

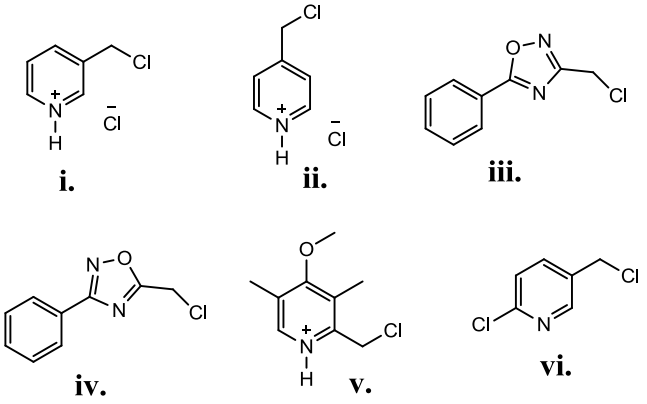
Table 10. Cross-coupling of various cyclopropanols with 4-methyl benzyl chloride



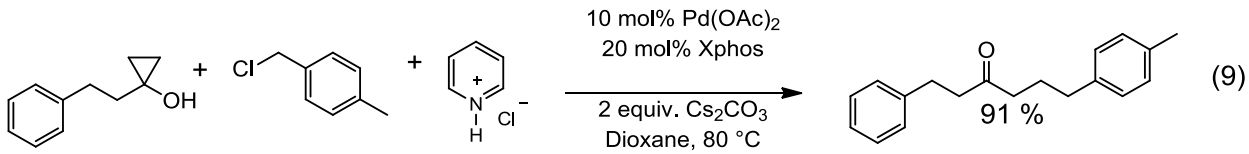
 **1**	 **2** 76%
 **4**	 **5** 84%
 **22**	 **23** 65%
 **24**	 **25** 70%
 **26**	 **27** 74%
 **28**	 **29** 72%
 **30**	 **31** 79%
 **32**	 **33** 66%

2.7. Heterocyclic substrate scope limitation

Heterocycles are important motifs in molecules of biological and medicinal interest and hence attractive substrates for expanding the reaction's scope. Naturally, we attempted to cross-couple several benzylic chlorides with heterocyclic functionalities that were readily available. The following heterocycles were screened using the optimized conditions with phenyl ethyl cyclopropanol.



These heterocyclic partners, however did not yield the corresponding desired coupled products. In all cases, a portion of the cyclopropanol starting material was converted to the corresponding ketone. It was speculated that the heterocycles themselves may be coordinating to the metal and suppressing ideal metal-ligand interactions required for the cross-coupling reaction to take place. To test this hypothesis we carried out a method developed by Collins and Glorius[44] on a robust screen for the rapid assessment of chemical reactions. By this approach we carried out a standard successful cross-coupling reaction and added an equimolar heterocycle additive to the reaction pot to test whether there would be any changes in reactivities caused by the additive (Eq. 9). We used pyridinium chloride as the additive and found that the heterocycle motif did not poison the catalyst as we hypothesized, since there was no significant deviation in the yield compared to the standard reaction. In light of these findings we surmise that the low reactivity of these heterocycles is due to the electron withdrawing nature of the pyridine and oxazole moieties.



(9)

2.8. Conclusion

In conclusion, a new methodology to access γ-arylated ketones using the palladium-catalyzed cross-coupling of cyclopropanol derived homoenolates with benzyl chlorides, has been developed. This methodology works well with electron-rich benzyl chloride rendering excellent product yields. Thorough systematic optimization, we found reaction conditions to supress competing ring opening of cyclopropanol starting materials. Moreover, we have shown that the reactions work well with a low catalyst loading of 1 mol% and can be carried out on a 1 g scale without sacrificing yield. Cross-coupling of electron-poor benzyl chlorides remains a challenge. We have done our best to optimize reaction conditions to render moderate to poor yields of coupled product using the benzyl chlorides with electron-withdrawing substituents.

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Appendices

Appendix A: General experimental

Reactions were conducted in flame- or oven-dried glassware under an atmosphere of argon using freshly distilled solvents unless specified otherwise. Commercial reagents were used as received. Toluene was distilled from CaH_2 prior to use. Tetrahydrofuran (THF) was distilled from sodium/benzophenone. 1,4-dioxane (reagent grade) was used as received.

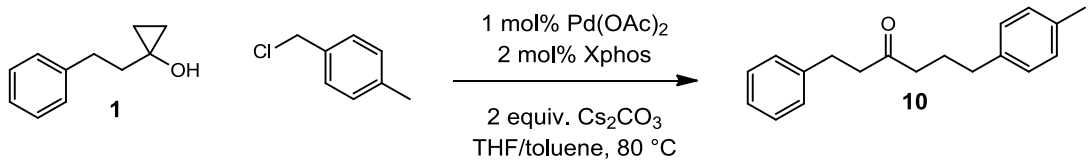
Thin-layer chromatography was performed on Merck silica gel 60 F254 plates. Visualisation was carried out using UV light and/or $KMnO_4$, anisaldehyde or $(NH_4)_2Ce(NO_3)_6$ solutions. Hexanes (ACS grade) and ethyl acetate (ACS grade) were used as received. Flash column chromatography was carried out using Aldrich silica gel (60 Å, 230-400 mesh).

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker 400 AV or Bruker 300 AV spectrometer in chloroform-*d* (99.8% deuterated), or dichloromethane-d_2 (99.9% deutrated). Spectra using chloroform was calibrated to 7.26 ppm ^{1}H and 77.23 ppm ^{13}C. Chemical shifts (δ) are reported in ppm and multiplicities are indicated by s (singlet), d (doublet), q (quartet), t (triplet) m (multiplet), br (broad). Coupling constants are reported in Hertz (Hz). Infrared (IR) spectra were recorded as thin films (neat) using Alpha-Platinum ATR, Bruker, diamond crystal FT-IR instrument. Melting points were recorded using a Fisher Johns melting point apparatus. Mass Spectrometry was conducted at the Mass Spectrometry Facility of Queen's University on either a Waters/Micromass GC-TOF instrument with an EI source or an Applied Biosystems/MDS SCiex QStar XL QqTOF instrument with an ESI source.

Experimental Procedure and Data

General Procedure 1. *Cross-Coupling of Cyclopropanols with Benzyl Chlorides.*

Ketone **10**



An oven dried reaction vial equipped with a stir bar was charged with palladium diacetate (0.004 g, 0.018 mmol, 0.01 equiv.), 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (Xphos) (0.019 g, 0.037 mmol, 0.02 equiv.), cesium carbonate (1.20 g, 3.70 mmol, 2 equiv.) and 4-methylbenzyl chloride (0.261 g, 1.85 mmol, 1 equiv.). The reaction vessel was capped with a rubber septum and flushed with argon for 10 minutes prior to the addition of a 1:1 THF/toluene mixture (15 mL). The resulting reaction mixture was stirred at ambient temperature for 5 min and a solution cyclopropanol **1** (0.309 g, 1.85 mmol, 1 equiv.) in 3 mL of solvent, was added a *via* syringe. The reaction mixture was heated to 80 °C in an oil bath. reaction progress was monitored using TLC. Once complete, the crude reaction mixture was diluted with ethyl acetate, filtered through a plug of Celite and concentrated to dryness. Flash column chromatography[45] of the crude product using a 10% solution of ethyl acetate in hexanes (R_f = 0.33) afforded ketone **10** as a yellow oil (0.42 g, 1.61 mmol) in 87% yield.

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.30-7.26 (m, 2 H), 7.25-7.16 (m, 3 H), 7.11 (d, *J* = 7.9 Hz, 2H), 7.05 (d, *J* = 7.9 Hz, 2H), 2.91(t, *J* = 7.2 Hz, 2 H), 2.72 (t, *J* = 7.2 Hz, 2 H), 2.58 (t, *J* = 7.5 Hz, 2H), 2.41 (t, *J* = 7.5 Hz, 2 H), 2.38 (s, 3 H), 1.90 (tt, *J* = 7.5, 7.5Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 209.9, 141.2, 138.5, 135.4, 129.1, 128.4, 126.1, 44.3, 42.1, 34.6, 29.8, 25.3, 21.1

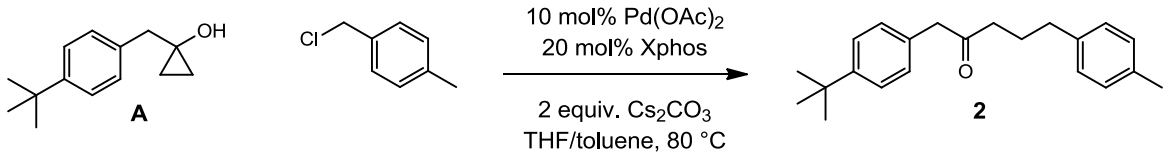
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3029, 2918, 1708, 1512, 1445, 1374, 1258, 1094, 800, 742 cm^{-1}

HRMS TOF EI

Calculated for $[C_{19}H_{22}O]^+$ = 266.1671, found = 266.1665

Ketone **2**



Following *General Procedure 1* cyclopropanol **A** (0.1 g, 0.49 mmol, 1 equiv.) was coupled to 4-methly benzyl chloride (0.07 g, 0.49 mmol, 1 equiv.). Purification by flash column chromatography using 10% solution of EtOAc in hexanes (R_f = 0.33) afforded ketone **2** (0.11 g, 0.37 mmol) as yellow oil in 76% yield.

^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.34 (d, *J* = 8 Hz, 2H), 7.11 (d, 8.0 Hz, 2H), 7.09 (d, 8.0 Hz, 2H), 6.99 (d, 8.0 Hz, 2H), 3.62 (s, 2 H), 2.52 (t, *J* = 7.2 Hz, 2 H), 2.46 (t, *J* = 7.6 Hz, 2 H), 2.33 (s, 3 H), 1.85 (tt, *J* = 7.2 Hz, 7.6 Hz, 2 H), 1.31 (s, 9 H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 208.5, 149.8, 138.4, 135.3, 131.6, 129.0, 129.0, 128.3, 125.6, 49.6, 41.1, 34.5, 31.3, 25.3, 20.99

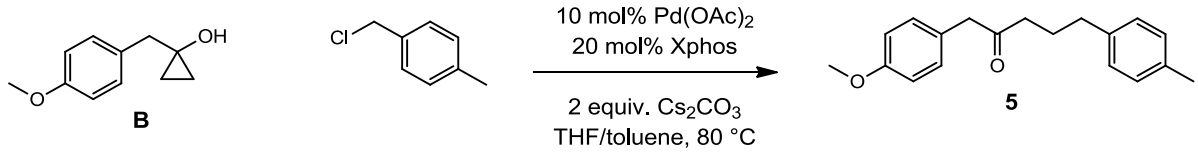
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 2960, 2868, 1698, 1607, 1514, 1412, 1268, 1176, 1108, 805, 702, 546 cm^{-1}

HRMS TOF EI

Calculated for $[C_{22}H_{28}O]^+$ = 308.2140, found = 308.2151

Ketone **5**



Following *General Procedure 1* cyclopropanol **B** (0.10 g, 0.56 mmol, 1 equiv.) was coupled to 4-methyl benzyl chloride (0.08 g, 0.56 mmol, 1 equiv.). Purification by flash column chromatography using 10% solution of EtOAc in hexanes (R_f = 0.34) afforded ketone **5** (0.13 g, 0.47 mmol) as yellow oil in 84% yield.

^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.08 (t, *J* = 8.4 Hz, 2 H), 6.99 (d, *J* = 7.6 Hz, 2 H), 6.88 (d, *J* = 8.4 Hz, 2 H), 3.80 (s, 3 H), 3.59 (s, 2 H), 2.52 (t, *J* = 7.6 Hz, 2 H), 2.44 (t, *J* = 7.2 Hz, 2H), 2.31 (s, 3H), 1.85 (tt, *J* = 7.2 Hz, 7.6 Hz, 2 H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 208.7, 158.6, 138.4, 132.3, 130.4, 129.9, 128.3, 126.3, 114.1, 55.2, 49.2, 40.9, 34.5, 25.3, 20.97

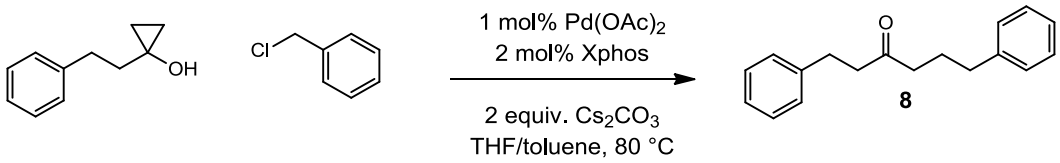
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 29933, 1706, 1600, 1510, 1456, 1245, 1177, 1031, 805, 541 cm^{-1}

HRMS TOF EI

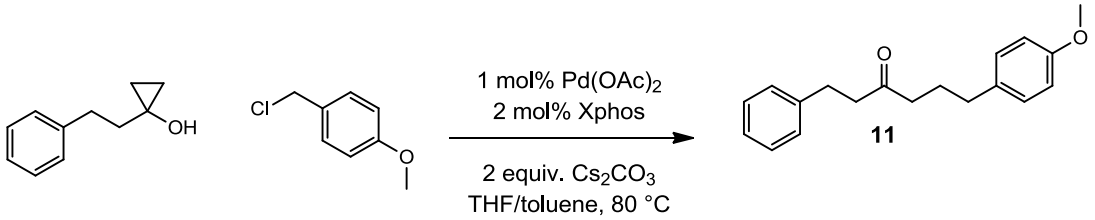
Calculated for $[C_{19}H_{22}O]^+$ = 282.1620, found = 282.1611

Ketone **8**



Following *General Procedure 1* cyclopropanol **1** (0.15g, 0.925 mmol, 1 equiv.) was coupled to benzyl chloride (0.12 g, 0.925 mmol, 1 equiv.). Purification by flash column chromatography using 10% solution of EtOAc in hexanes (Rf = 0.33) afforded ketone **8** (0.22 g, 0.872 mmol) as yellow oil in 94% yield. Spectral data for this compound is consistent with that reported by Too and coworkers[46]

Ketone **11**



Following *General Procedure 1* cyclopropanol **1** (0.15 g, 0.925 mmol, 1 equiv.) was coupled to 4-methoxy benzyl chloride (0.14 g, 0.925 mmol, 1 equiv.). Purification by flash column chromatography using 10% solution of EtOAc in hexanes (R_f = 0.42) afforded ketone **11** (0.22 g, 0.78 mmol) as yellow oil in 84% yield.

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.32- 7.27 (m, 2H), 7.23-7.17 (m, 3H), 7.08 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 3.81 (s, 3 H), 2.90 (t, *J* = 7.2 Hz, 2 H), 2.72 (t, *J* = 7.8 Hz, 2 H), 2.56 (t, *J* = 7.2 Hz, 2H), 2.40 (t, *J* = 7.5 Hz, 2 H),1.88 (tt, *J* = 7.5, 7.5 Hz, 2 H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 209.9, 157.8, 141.1, 129.3, 128.5, 128.3, 126.1, 113.7, 55.2, 44.3, 42.0, 34.1, 29.7, 25.4

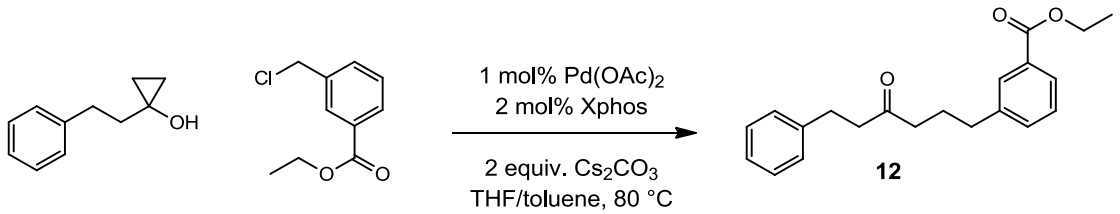
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 2936, 1712, 1605, 1503, 1445, 1294, 1241, 1174, 1085, 1031, 822, 742, 689, 502 cm^{-1}

HRMS TOF EI

Calculated for $[C_{19}H_{22}O_2]^+$ = 282.1620, found = 282.1615

Ketone **12**



Following *General Procedure 1* cyclopropanol **1** (0.15 g, 0.92 mmol, 1 equiv.) was coupled to ethyl 3-(chloromethyl)benzoate (0.18 g, 0.92 mmol, 1 equiv.). Purification by flash column chromatography using 10% solution of EtOAc in hexanes (R_f = 0.40) afforded ketone **12** (0.23 g, 0.70 mmol) as yellow oil in 76% yield.

^{1}H NMR (400 MHz, CD_2Cl_3)

δ 7.87- 7.79 (m, 2H), 7.38-7.32 (m, 2 H), 7.26- 7.22 (m, 2H), 7.18-7.12 (m, 3H), 4.31 (q, *J* = 7.2 Hz, 2H), 2.83 (t, *J* = 7.6 Hz, 2H), 2.68 (t, *J* = 7.6 Hz, 2 H), 2.61 (t, *J* = 7.2 Hz, 2H), 2.38 (t, *J* = 7.2 Hz, 2H),1.91 (tt, *J* = 7.6, 7.6 Hz, 2 H), 1.35 (t, *J* = 7.2 Hz, 3 H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 209.6, 166.7, 141.8, 141.0, 132.96, 130.5, 129.4, 128.45, 128.38, 128.28, 127.2, 126.1, 60.9, 44.3, 41.96, 34.8, 29.7, 24.99, 14.3

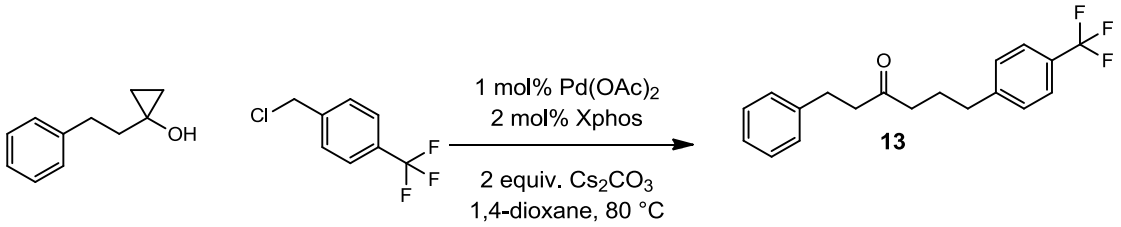
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 2927, 1712, 1597, 1441, 1370, 1276, 1187, 1103, 1018, 747, 684, 506 cm^{-1}

HRMS TOF EI

Calculated for $[C_{21}H_{24}O_3]^+$ = 324.1725, found = 324.1715

Ketone **13**



Following *General Procedure 1* cyclopropanol **1** (0.15 g, 0.92 mmol, 1 equiv.) was coupled to 4-trifluoromethyl benzyl chloride (0.18 g, 0.92 mmol, 1 equiv.) using dioxane as the solvent. Purification by flash column chromatography using 10% solution of EtOAc in hexanes (R_f = 0.36) afforded ketone **13** (0.16 g, 0.50 mmol) as a white solid in 54% yield.

^{1}H NMR (400 MHz, CD_2Cl_2)

δ 7.52 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 7.6 Hz, 2H), 7.20-7.12 (m, 2H), 2.84 (t, *J* =7.6 Hz, 2H), 2.68 (t, *J* = 7.6 Hz, 2H) 2.62 (t, *J* = 7.2 Hz, 2H), 2.38 (t, *J* = 7.2 Hz, 2H), 1.85 (tt, *J* = 7.2, 7.6 Hz, 2H)

^{13}C NMR (100 MHz, $CDCl_3$)

δ 209.4, 145.7, 140.9, 128.67, 128.41, 128.24, 128.14, 126.0, 125.2, 123.98 (q, $^{1}J_{C\text{-}F}$ = 270.1 Hz), 44.4, 41.9, 34.7. 29.7, 24.7

^{19}F NMR (300 MHz, $CDCl_3$)

δ –62.4

IR Alpha-Platinum ATR, Bruker, diamond crystal

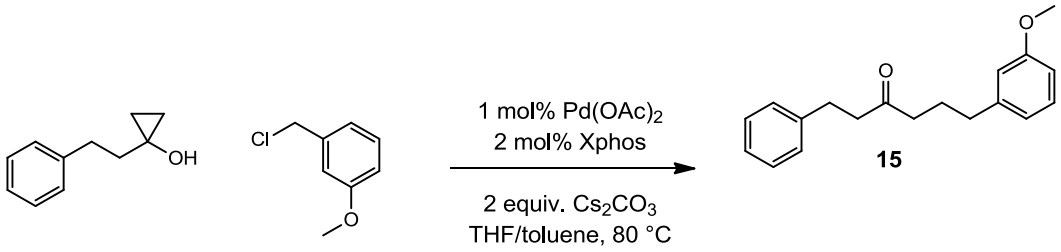
υ = 2927, 1717, 1619, 1321, 1156, 1116, 1063, 1014, 849, 751, 698, 511 cm^{-1}

m.p. 49 °C

HRMS TOF EI

Calculated for $[C_{19}H_{19}OF_3]^+$ = 320.1388, found = 320.1395

Ketone **15**



Following *General Procedure 1* cyclopropanol **1** (0.15 g, 0.92 mmol, 1 equiv.) was coupled to 3-methoxy benzyl chloride (0.14 g, 0.92 mmol, 1 equiv.). Purification by flash column chromatography using 10% solution of EtOAc in hexanes (R_f = 0.42) afforded ketone **15** (0.23 g, 0.80 mmol) as yellow oil in 87% yield.

^{1}H NMR (400 MHz, CD_2Cl_2)

δ 7.26-7.22 (m, 2H), 7.18-7.14 (m, 4H), 6.73-6.68 (m, 3H), 3.75 (s, 3H), 2.85 (t, *J* = 7.2 Hz, 2H), 2.67 (t, *J* = 7.6 Hz, 2 H), 2.53 (t, *J* = 7.2 Hz, 2H), 2.37 (t, *J* = 7.2 Hz, 2H), 1.83 (tt, *J* = 7.2, 7.6 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 209.8, 159.6, 143.2, 141.1, 129.3, 128.5, 128.3, 126.1, 120.85, 114.2, 111.2, 55.1, 44.3, 42.1, 35.1, 29.7, 24.99

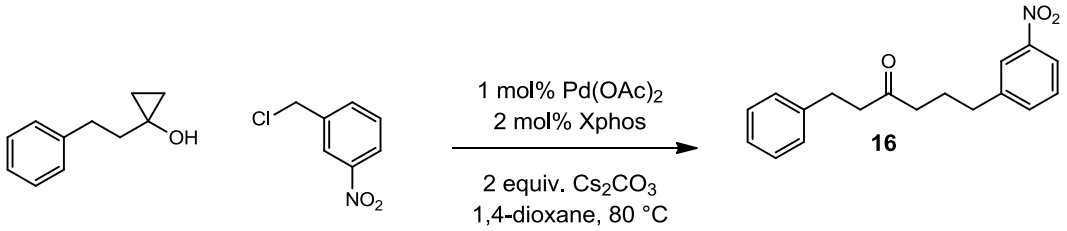
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 2940, 1708, 1605, 1579, 1490, 1450, 1263, 1169, 1045, 773, 742, 689 cm^{-1}

HRMS TOF EI

Calculated for $[C_{19}H_{22}O_2]^+$ = 282.1620, found = 282.1629

Ketone **16**



Following *General Procedure 1* cyclopropanol **1** (0.15 g, 0.92 mmol, 1 equiv.) was coupled to 3-nitro benzyl chloride (0.16 g, 0.92 mmol, 1 equiv.) using dioxane as the solvent. Purification by flash column chromatography using 13% solution of EtOAc in hexanes afforded (R_f = 0.35) ketone **16** (0.12 g, 0.42 mmol) as yellow oil in 45% yield.

^{1}H NMR (400 MHz, $CDCl_3$)

δ 8.05 (d, *J* = 7.6 Hz, 2H), 8.01 (s, 1H), 7.47- 7.41 (m, 2H), 7.28- 7.27 (m, 2H), 7.20- 7.15 (m, 3H), 2.89 (t, *J* = 7.2 Hz, 2H), 2.72 (t, *J* = 7.6 Hz, 2H), 2.68 (t, *J* = 8.0 Hz, 2H), 2.41 (t, *J* = 7.2 Hz, 2H), 1.95 (tt, *J* = 7.2, 8.0 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 209.2, 148.3, 143.6, 140.9, 134.7, 129.2, 128.48, 128.28, 126.1, 123.2, 121.2, 44.3, 41.8, 34.6, 29.7, 24.7

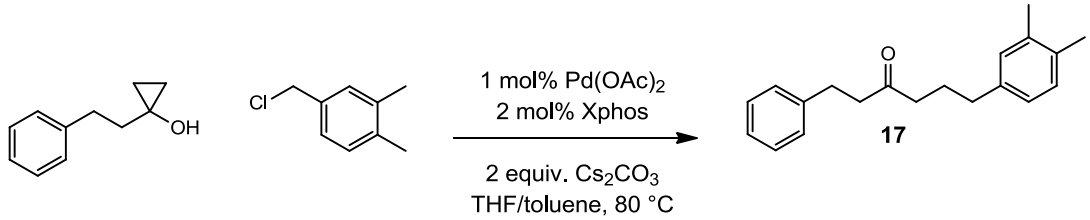
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3023, 2914, 1710, 1590, 1520, 1493, 1450, 1410, 1340, 1362, 1088, 1025, 860, 740, 702 cm^{-1}

HRMS TOF EI

Calculated for $[C_{18}H_{19}O_3N]^+$ = 297.1365, found = 297.1360

Ketone **17**



Following *General Procedure 1* cyclopropanol **1** (0.15 g, 0.925 mmol, 1 equiv.) was coupled to 3,4-dimethyl benzyl chloride (0.14 g, 0.925 mmol, 1 equiv.). Purification by flash column chromatography using 10% solution of EtOAc in hexanes (R_f = 0.30) afforded ketone **17** (0.21 g, 0.76 mmol) as yellow oil in 82% yield.

^{1}H NMR (400 MHz, CD_2Cl_2)

δ 7.26 (t, *J* = 7.6 Hz, 1H), 7.20-7.30 (m, 4H), 7.01 (d, *J* = 7.4 Hz, 1H), 6.92 (s, 1H), 6.85 (d, *J* = 7.4 Hz, 1H), 2.84 (t, *J* = 7.6 Hz, 2H), 2.69 (t, *J* = 7.6 Hz, 2H), 2.49 (t, *J* = 7.2 Hz, 2H), 2.36 (t, *J* = 7.2 Hz, 2H), 2.21 (s, 3H), 2.20 (s, 3H), 1.81 (tt, *J* = 7.2, 7.2 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 209.8, 141.3,139.1, 136.5, 134.1, 130.0,129.8, 128.6, 128.5, 126.2, 126.0, 44.4, 42.2, 34.8, 29.9, 25.5, 19.3, 19.5

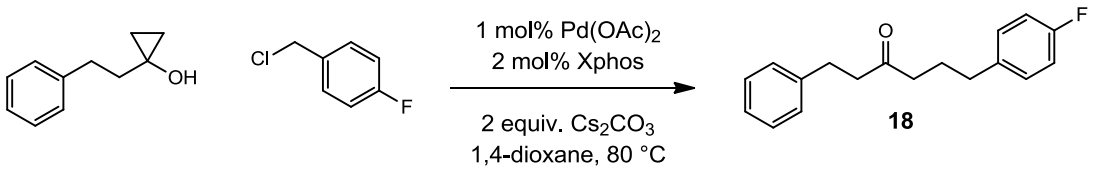
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 2918, 1703, 1490, 1450, 1401, 1356, 1249, 1094, 1009, 809, 742, 689, 560 cm^{-1}

HRMS TOF EI

Calculated for $[C_{20}H_{24}O]^+$ = 280.1827, found = 280.1823

Ketone **18**



Following *General Procedure 1* cyclopropanol **1** (0.15 g, 0.92 mmol, 1 equiv.) was coupled to 4-fluoro benzyl chloride (0.13 g, 0.92 mmol, 1 equiv.) using dioxane as the solvent. Purification by flash column chromatography using 10% solution of EtOAc in hexanes (R_f = 0.37) afforded ketone **18** (0.17 g, 0.63 mmol) as yellow oil in 68% yield.

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.36-7.31 (m, 2H), 7.26-7.22 (m, 3H), 7.14 (dd, $^3J_{H-H}$ = 8.4 Hz, $^4J_{H-F}$ = 5.7 Hz, 2H), 7.01 (dd, $^3J_{H-H}$ = 8.4 Hz, $^3J_{H-F}$ = 9.0 Hz, 2H), 2.95 (t, *J* = 7.2 Hz, 2H), 2.75 (t, *J* = 7.5 Hz, 2 H), 2.61 (t, *J* = 7.5 Hz, 2H), 2.42 (t, *J* = 7.2 Hz, 2H),1.92 (tt, *J* = 7.5, 7.5 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 209.6, 161.3 (d, $^1J_{C-F}$ =242.3 Hz), 141.1, 137.2 (d, $^4J_{C-F}$ = 3.0 Hz), 129.8 (d, $^3J_{C-F}$ =7.5 Hz), 128.3, 126.1, 115.1 (d, $^2J_{C-F}$ =20.3 Hz), 44.3, 41.9, 34.2, 29.8, 25.2

^{19}F NMR (300 MHz, $CDCl_3$)

δ –116.9

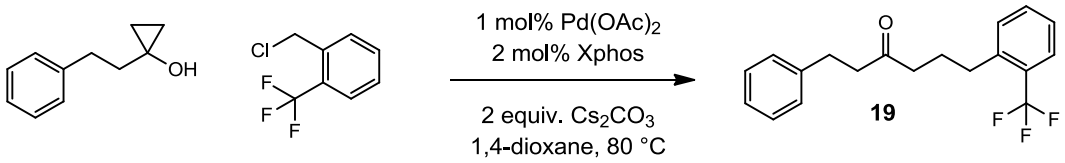
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 2914, 1717, 1597, 1503, 1445, 1401, 1365, 1214, 1152, 1080, 822, 751, 693, 546 cm^{-1}

HRMS TOF EI

Calculated for $[C_{18}H_{19}OF]^+$ = 270.1420, found = 270.1431

Ketone **19**



Following *General Procedure 1* cyclopropanol **1** (0.15g, 0.92 mmol, 1 equiv.) was coupled to 2-trifluoromethyl benzyl chloride (0.18 g, 0.92 mmol, 1 equiv.) using dioxane as the solvent. Purification by flash column chromatography using 10% solution of EtOAc in hexanes (R_f = 0.36) afforded ketone **19** (0.08 g, 0.24 mmol) as yellow oil in 26% yield.

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.52 (d, *J* = 7.8 Hz, 1H), 7.34-7.14 (m, 8H), 2.85 (t, *J* =7.5 Hz, 2H), 2.69 (t, *J* = 7.5 Hz, 2 H), 2.63 (t, *J* = 7.5 Hz, 2H), 2.38 (t, *J* = 7.2 Hz, 2H),1.86 (tt, *J* = 7.5, 7.5 Hz, 2H)

^{13}C NMR (100 MHz, $CDCl_3$)

δ 209.4, 142.5, 140.9, 130.5 (q, $^{2}J_{C\text{-}F}$ = 31.7 Hz), 128.41, 128.24, 127.4 (q, $^{1}J_{C\text{-}F}$ = 305.5 Hz), 125.0, 44.2, 41.8, 34.7, 29.7, 24.8

^{19}F NMR (300 MHz, $CDCl_3$)

δ –62.1

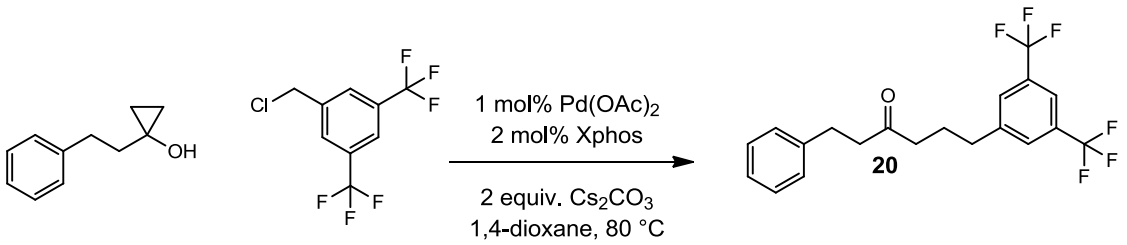
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 2927, 1717, 1619, 1321, 1156, 1116, 1063, 1014, 849, 751, 698, 511 cm^{-1}

HRMS TOF EI

Calculated for $[C_{19}H_{19}OF_3]^+$ = 320.188, found = 320.1395

Ketone **20**



Following *General Procedure 1* cyclopropanol **1** (0.15 g, 0.92 mmol, 1 equiv.) was coupled to 2,4-di-trifluoromethyl benzyl chloride (0.24 g, 0.92 mmol, 1 equiv.) using dioxane as the solvent. Purification by flash column chromatography using 8% solution of EtOAc in hexanes (R_f = 0.35) afforded ketone **20** (0.11 g, 0.28 mmol) as yellow oil in 30% yield.

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.74 (s, 1H), 7.62 (s, 2H), 7.30- 7.28 (m, 1H), 7.23- 7.19 (m, 4H), 2.91 (t, *J* = 7.5 Hz, 2H), 2.76 (t, *J* = 7.5 Hz, 2H), 2.72 (t, *J* = 7.5 Hz, 2H), 2.45 (t, *J* = 7.2 Hz, 2H), 1.94 (tt, *J* = 7.2, 7.5 Hz, 2H)

^{13}C NMR (100 MHz, $CDCl_3$)

δ 209.1, 143.97, 140.8, 131.5 (q, $^{2}J_{C\text{-}F}$ = 32.9Hz), 128.41, 128.20, 126.1, 123.3 (q, $^{1}J_{C\text{-}F}$ = 270.8 Hz), 120.0, 120.0, 44.3, 41.7, 34.6, 29.7, 24.6

^{19}F NMR (300 MHz, $CDCl_3$)

δ –62.8

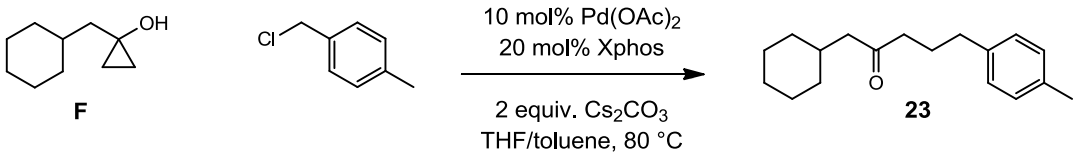
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 2930, 1714, 1379, 1274, 1167, 1123, 924, 843, 748, 699, 681 cm^{-1}

HRMS TOF EI

Calculated for $[C_{20}H_{18}OF_6]^+$ = 388.1262, found = 388.1270

Ketone **23**



F **23**

Following *General Procedure 1* cyclopropanol 2**F** (0.05 g, 0.65 mmol, 1 equiv.) was coupled to benzyl chloride (0.05 g, 0.65 mmol, 1 equiv.). Purification by flash column chromatography using 10% solution of EtOAc in hexanes (R_f = 0.34) afforded Ketone **23** (0.11 g, 0.42 mmol) as a white solid in 65% yield.

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.13 (d, *J* = 8.2 Hz, 2 H), 7.09 (d, *J* = 8.2 Hz, 2 H), 2.61 (t, *J* = 7.2 Hz, 2 H), 2.41 (t, *J* = 7.2 Hz, 2 H), 2.30 (s, 3H), 2.30 (d, *J* = 6.9 Hz, 2 H), 1.91 (tt, *J* = 7.2, 7.2 Hz, 2 H), 1.84 (m, 1H), 1.70 (m, 5H), 1.69 (m, 3H), 1.28 (m, 2H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 210.78, 138.56, 135. 30, 129.02, 128.32, 50.56, 42.57, 34.66, 33.85, 33.22, 26.20, 26.07, 25.28, 20.97

IR Alpha-Platinum ATR, Bruker, diamond crystal

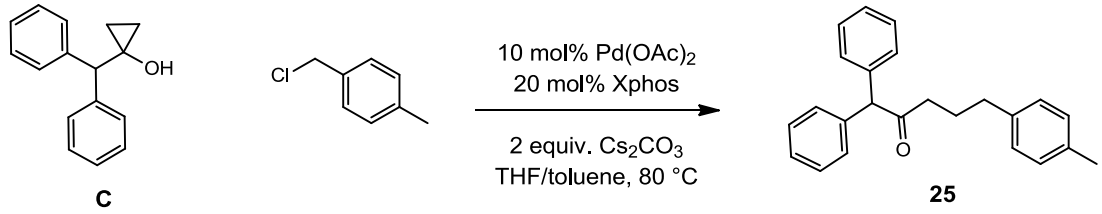
υ = 2918, 2849, 1713, 1511,1447,1375,1283, 1081, 1010, 808, 540, 482 cm^{-1}

m.p. 34 °C

HRMS TOF EI

Calculated for $[C_{18}H_{26}O]^+$ = 258.1984, found = 258.1978

Ketone **25**



C **25**

Following *General Procedure 1* cyclopropanol **C** (0.1 g, 0.45 mmol, 1 equiv.) was coupled to 4-methyl benzyl chloride (0.06 g, 0.45 mmol, 1 equiv.). Purification by flash column chromatography using 8% solution of EtOAc in hexanes (R_f = 0.34) afforded ketone **25** (0.10 g, 0.31 mmol) as yellow oil in 70% yield.

^{1}H NMR (400 MHz, CD_2Cl_2)

δ 7.34- 7.18 (m, 10 H), 7.02 (d, *J* = 7.6 Hz, 2 H), 6.94 (d, *J* = 7.6 Hz, 2 H), 5.08 (s, 1H), 2.52 (t, *J* = 7.2 Hz, 2 H), 2.47 (t, *J* = 7.2 Hz, 2 H), 2.26 (s, 3H), 1.83 (tt, *J* = 7.2, 7.2 Hz, 2 H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 208.35, 135.33, 132.44, 130.09, 129.05, 128.97, 128.70, 128.35, 127.21, 64.14, 42.12, 34.50, 25.55, 21.03

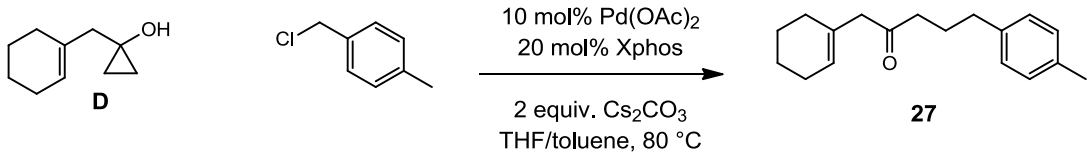
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 2923, 1715, 1657, 1494, 1276, 745, 696, 638, 545, 483 cm^{-1}

HRMS TOF EI

Calculated for $[C_{24}H_{24}O]^+$ = 328.1827, found = 328.1815

Ketone **27**



Following *General Procedure 1* cyclopropanol **D** (0.10 g, 0.66 mmol, 1 equiv.) was coupled to 4-methyl benzyl chloride (0.09 g, 0.66 mmol, 1 equiv.). Purification by flash column chromatography using 10% solution of EtOAc in hexanes (R_f = 0.41) afforded ketone **27** (0.12 g, 0.49 mmol) as yellow oil in 74% yield.

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.12 (d, *J* = 8.1 Hz, 2H), 7.08 (d, *J* = 8.1 Hz, 2H), 5.54 (s, 1H), 3.00 (s, 2H), 2.59 (t, *J* = 7.8Hz, 2H), 2.46 (t, *J* = 7.5Hz, 2H), 2.34 (s, 3H), 1.941 (s, 2H), 1.94-1.89 (m, 2H), 1.89 (tt, *J* = 7.5, 7.8 Hz, 2H), 1.62-1.60 (m, 4H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 209.51, 138.56, 135.29, 131.72, 128.99, 126.11, 52.50, 43.63, 40.83, 38.05, 34.59, 28.61, 25.35, 22.72, 21.97, 20.96

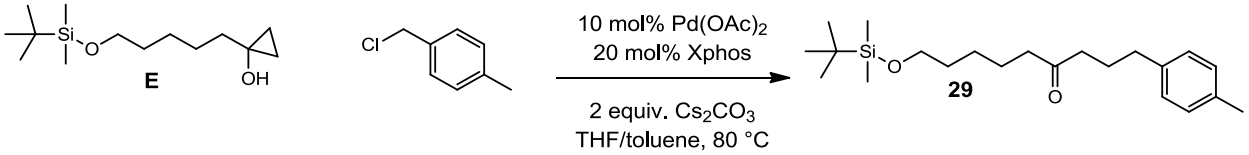
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3022, 2932, 2837, 2658, 1713, 1511,1437,1375,1137, 1036, 1010, 916, 876, 718, 639, 540, 482 cm^{-1}

HRMS TOF EI

Calculated for $[C_{17}H_{22}O]^+$ = 256.1827, found = 256.1836

Ketone **29**



Following *General Procedure 1* cyclopropanol **E** (0.10 g, 0.39 mmol, 1 equiv.) was coupled to 4-methyl benzyl chloride (0.05 g, 0.39 mmol, 1 equiv.). Purification by flash column chromatography using 6% solution of EtOAc in hexanes (R_f = 0.40) afforded Ketone **29** (0.10 g, 0.28 mmol) as yellow oil in 72% yield.

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.12 (d, *J* = 8.2 Hz, 2H), 7.08 (d, *J* = 8.2 Hz, 2H), 3.62 (t, *J* = 6.6 Hz, 2H), 2.60 (t, *J* = 7.5 Hz, 2H), 2.42 (t, *J* = 7.2 Hz, 2H), 2.40 (t, *J* = 7.5 Hz, 2H), 2.34 (s, 3H), 1.91 (tt, *J* = 7.2, 7.5 Hz, 2H), 1.62- 1.51 (m, 4H), 1.37- 1.31 (m, 2H), 0.91 (s, 9H), 0.07 (s, 6H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 210.91, 138.51, 135.29, 129.01, 128.31, 62.94, 42.78, 41.88, 34.65, 32.59, 25.95, 25.48, 25.32, 23.59, 20.96, 18.32, -5.31

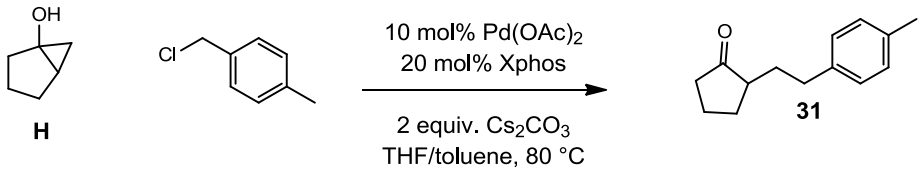
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 2928, 2856, 1714, 1515, 1471, 1253, 1096, 833, 809, 773 cm^{-1}

HRMS TOF EI

Calculated for $[C_{22}H_{38}O_2Si]^+H^+$ = 363.27138, found = 363.27153

Ketone **31**



Following *General Procedure 1* cyclopropanol **H** (0.10 g, 1.0 mmol, 1 equiv.) was coupled to 4-methyl benzyl chloride (0.14 g, 1.0 mmol, 1 equiv.). Purification by flash column chromatography using 8% solution of EtOAc in hexanes (R_f = 0.35) afforded ketone **31** (0.16 g, 0.81 mmol) as yellow oil in 79% yield.

^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.11 (s, 4H), 2.73- 2.56 (m, 2H), 2.31 (S, 3H), 2.28- 2.22 (m, 2H), 2.16- 1.99 (m, 4H), 1.79- 1.74 (m, 1H), 1.57- 1.53 (m, 2H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 221.28, 138.49, 135.33, 129.02, 128.27, 48.31, 38.15, 33.15, 31.45, 29.68, 20.96, 20.69

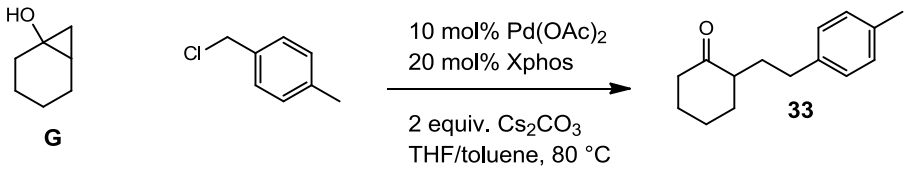
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 2922, 2859, 1733, 1514, 1453, 1405, 1152, 805, 547, 488 462 cm^{-1}

HRMS TOF EI

Calculated for $[C_{14}H_{18}O]^+$ = 202.1358, found = 202.1365

Ketone **33**



Following *General Procedure 1* cyclopropanol **G** (0.07g, 0.62 mmol, 1 equiv.) was coupled to 4-methyl benzyl chloride (0.09 g, 0.624 mmol, 1 equiv.). Purification by flash column chromatography using 8% solution of EtOAc in hexanes (R_f = 0.35) afforded ketone **33** (0.09 g, 0.41 mmol) as yellow oil in 66% yield.

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.09 (s, 4H), 2.60 (t, *J* = 7.9 Hz, 2H), 2.42-2.28 (m, 6H), 2.19- 2.03 (m, 3H), 1.88-1.82 (m, 1H), 1.75- 1.61 (m, 2H), 1.54- 1.40 (m, 2H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 213.23, 139.06, 135.16, 128.99, 128.26, 49.78, 42.09, 33.99, 32.72, 31.26, 28.05, 24.88, 20.97

IR Alpha-Platinum ATR, Bruker, diamond crystal

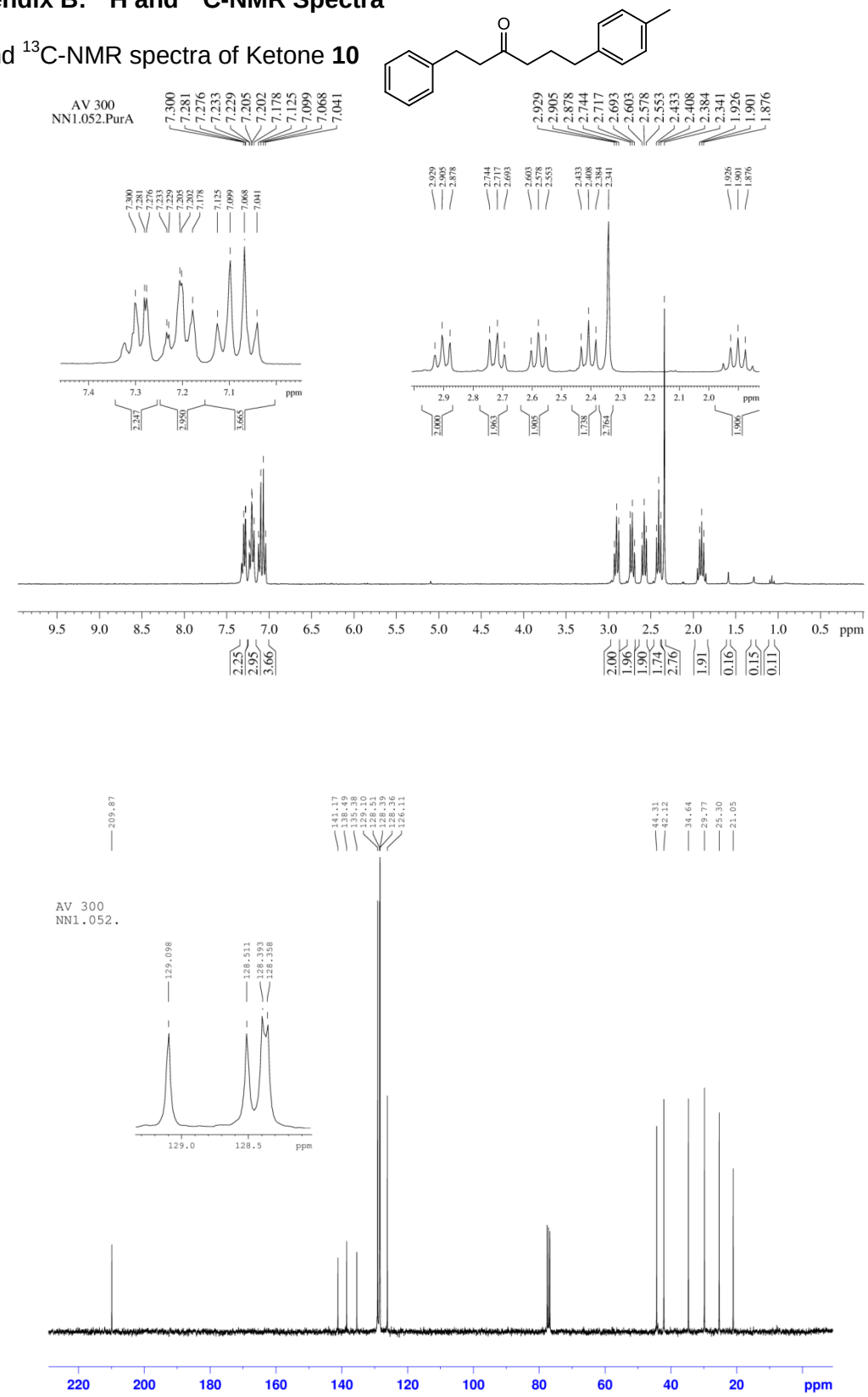
υ = 2930, 2862, 1730, 1515, 1457, 1412, 1153, 807, 542, 493, 454 cm^{-1}

HRMS TOF EI

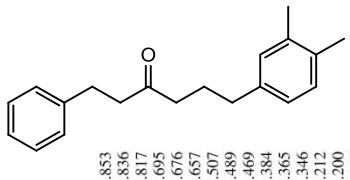
Calculated for $[C_{15}H_{20}O]^+$ = 216.1514, found = 216.1506

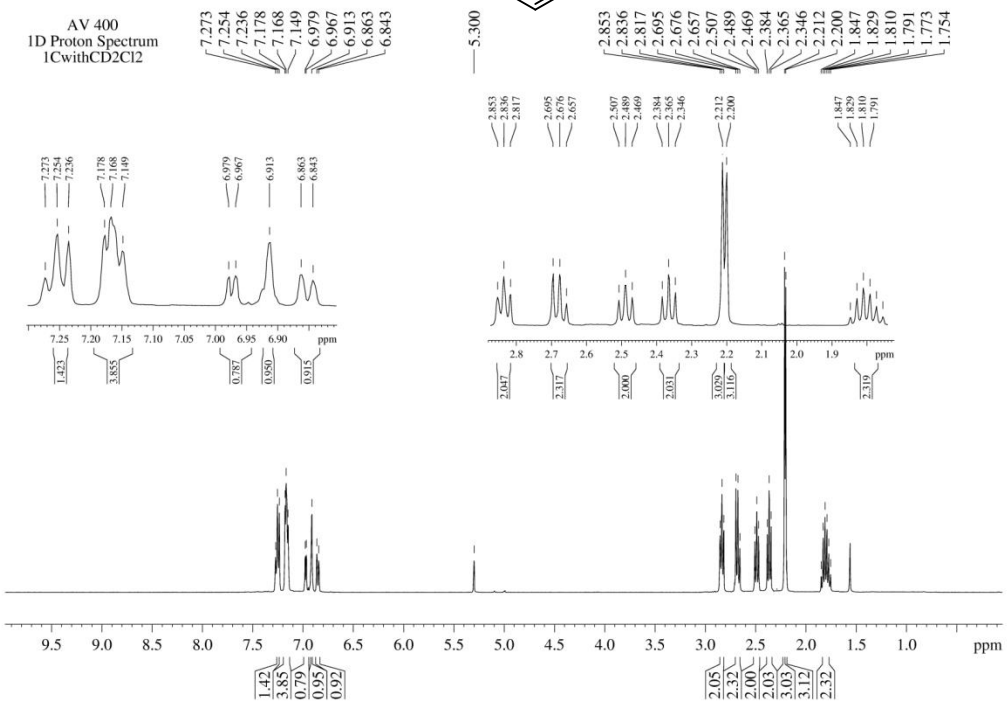
Appendix B: ^{1}H and ^{13}C-NMR Spectra

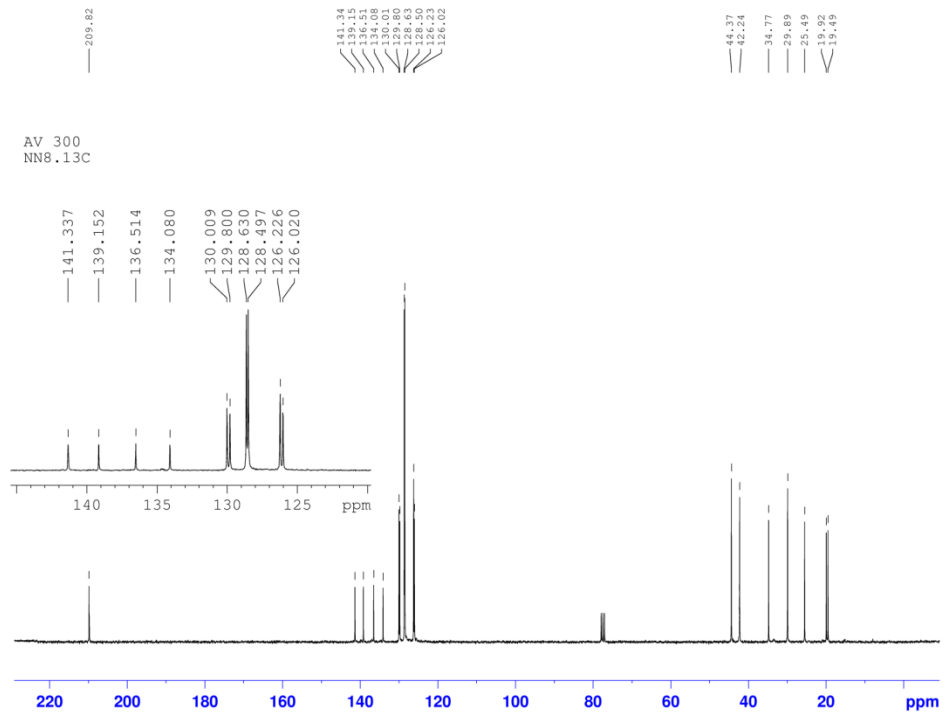
^{1}H and ^{13}C-NMR spectra of Ketone **10**



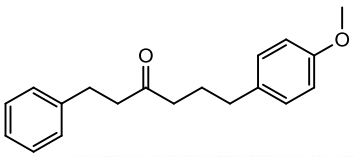
^{1}H and ^{13}C-NMR spectra of Ketone **17**

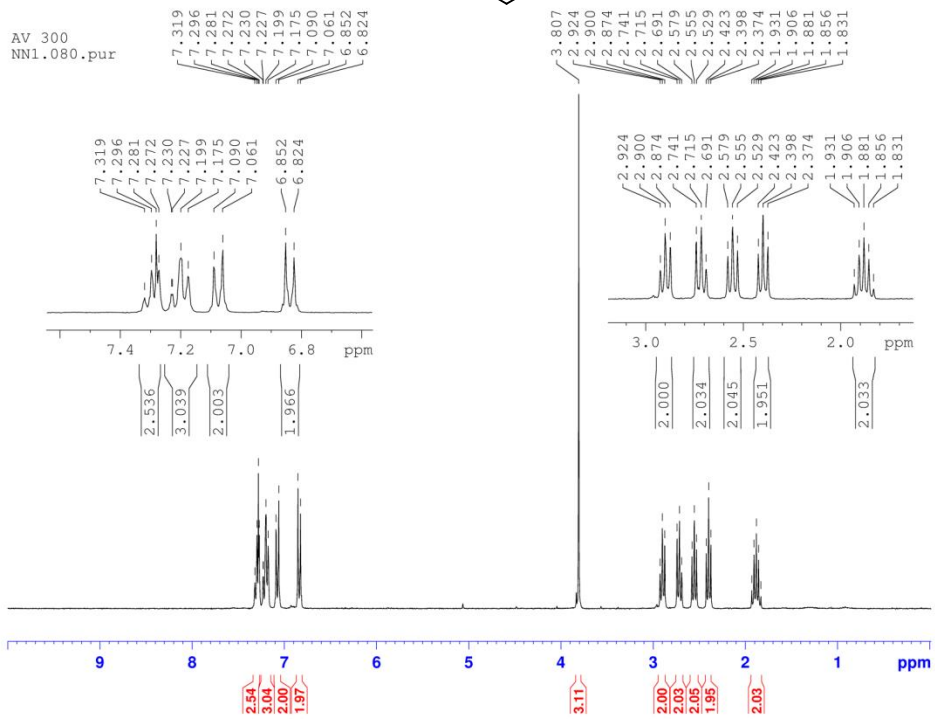


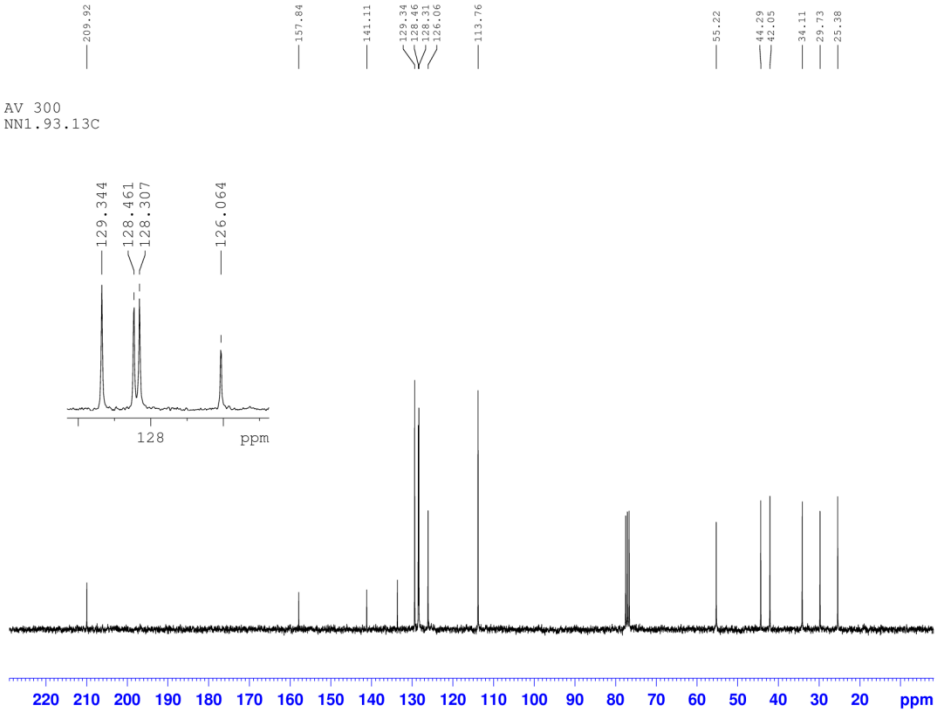




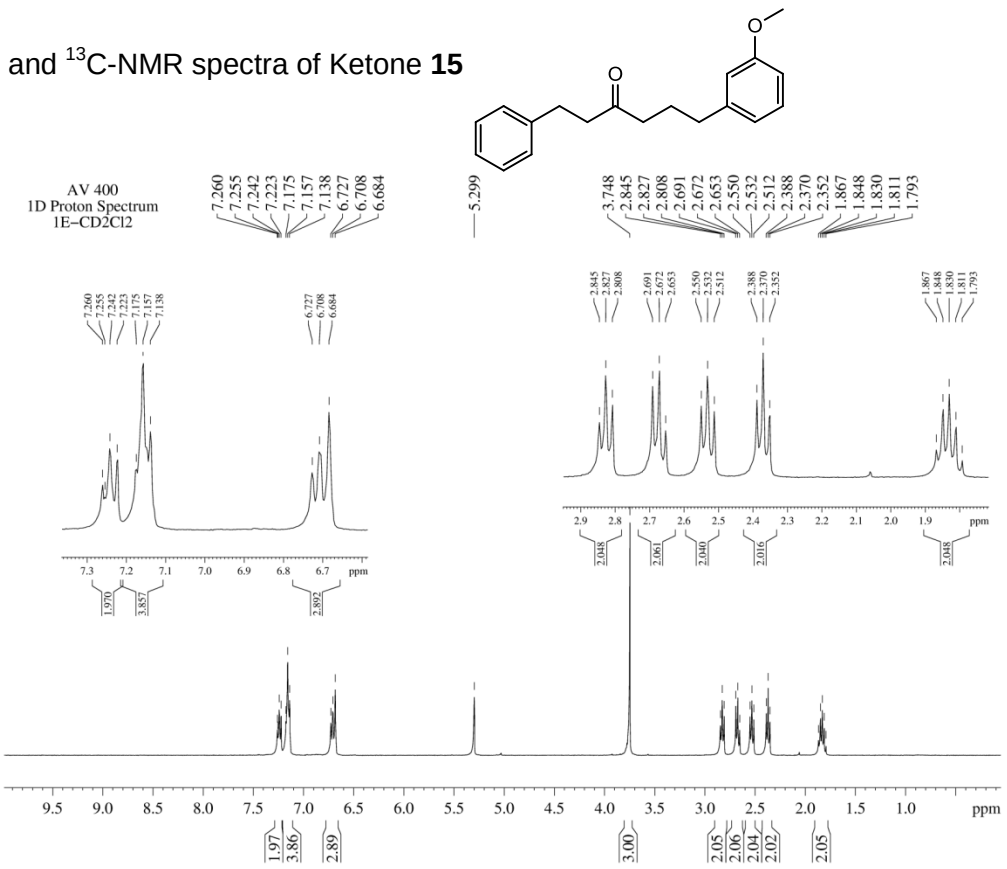
^{1}H and ^{13}C-NMR spectra of Ketone **11**

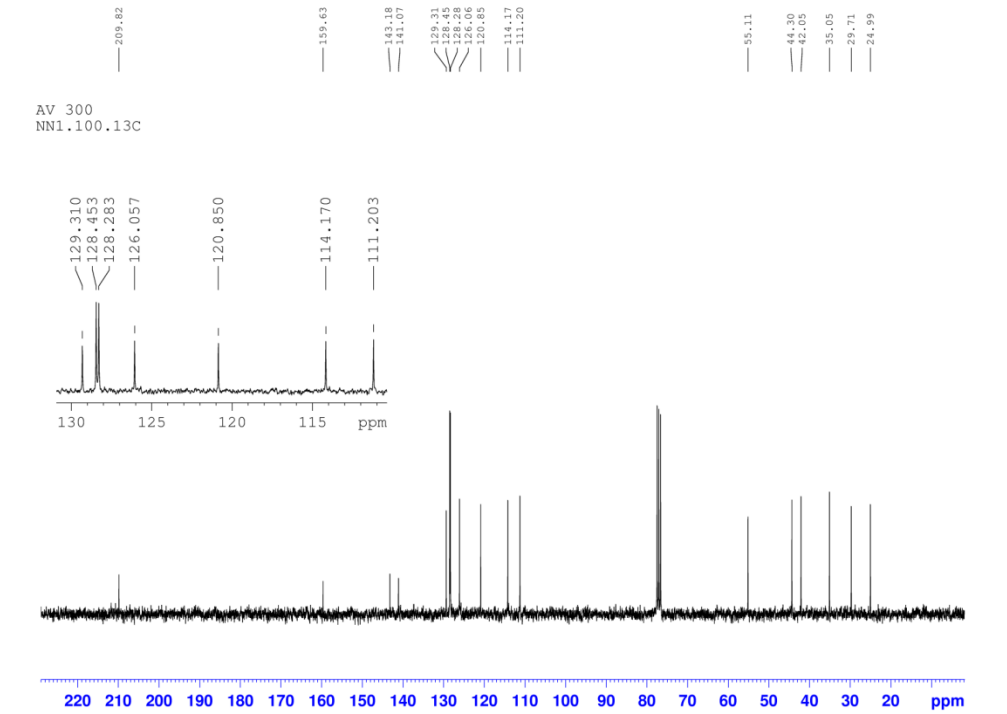




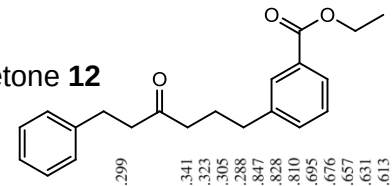


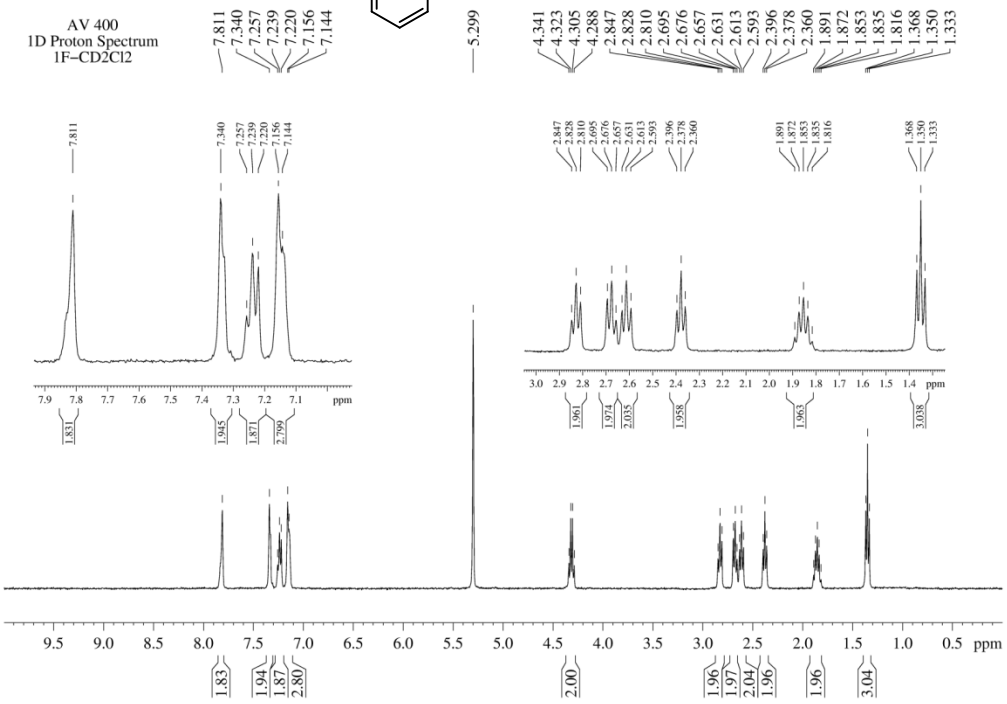
^{1}H and ^{13}C-NMR spectra of Ketone **15**

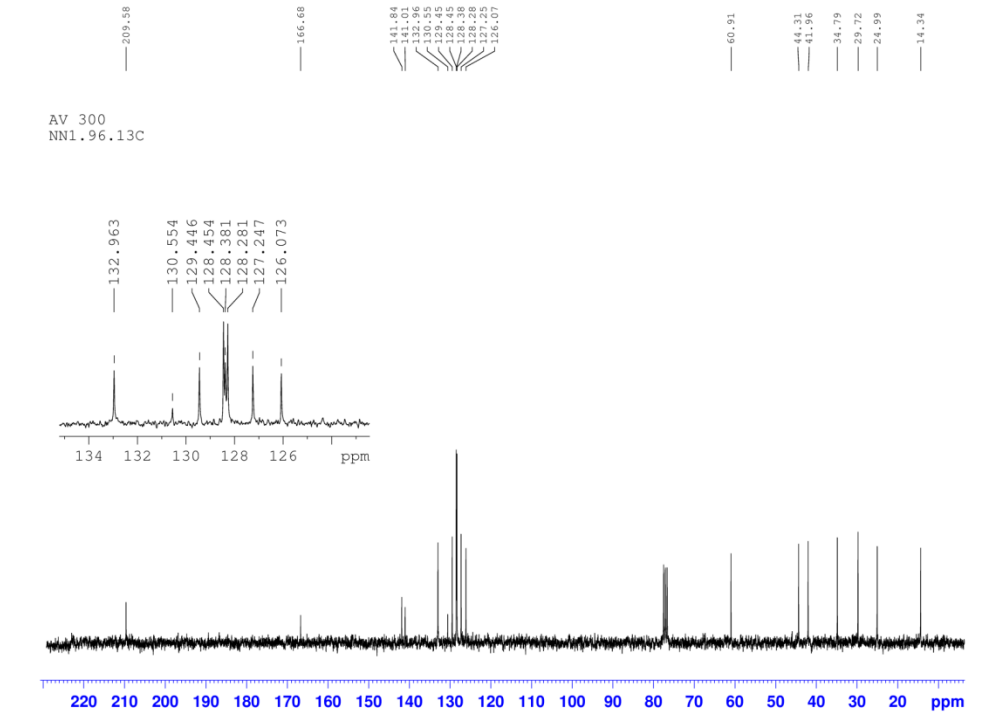




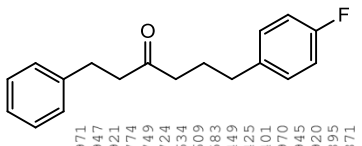
^{1}H and ^{13}C-NMR spectra of Ketone **12**

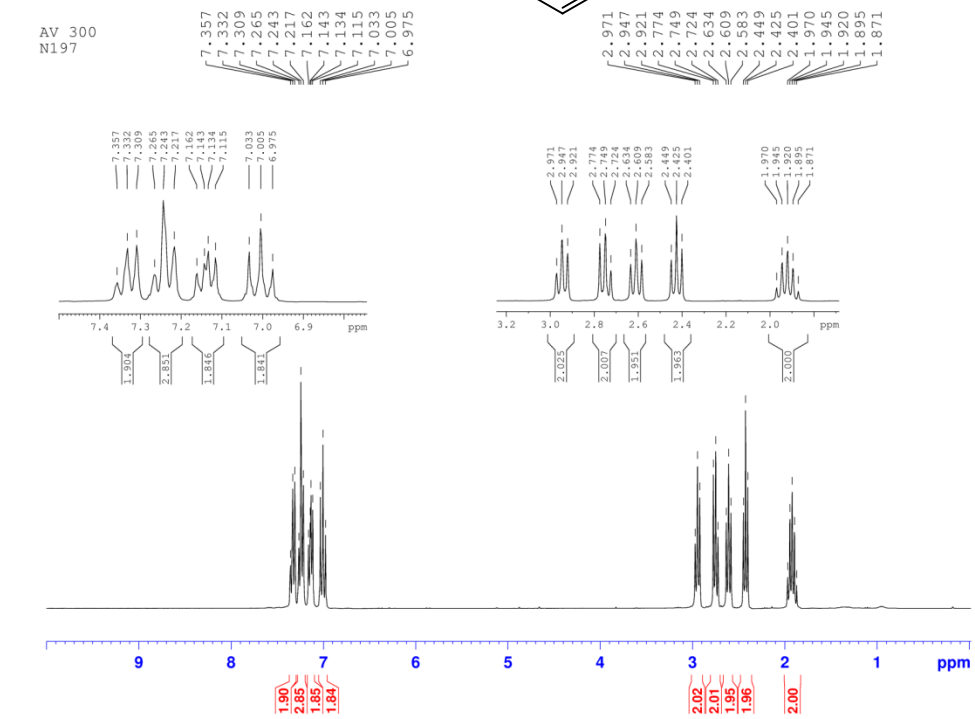


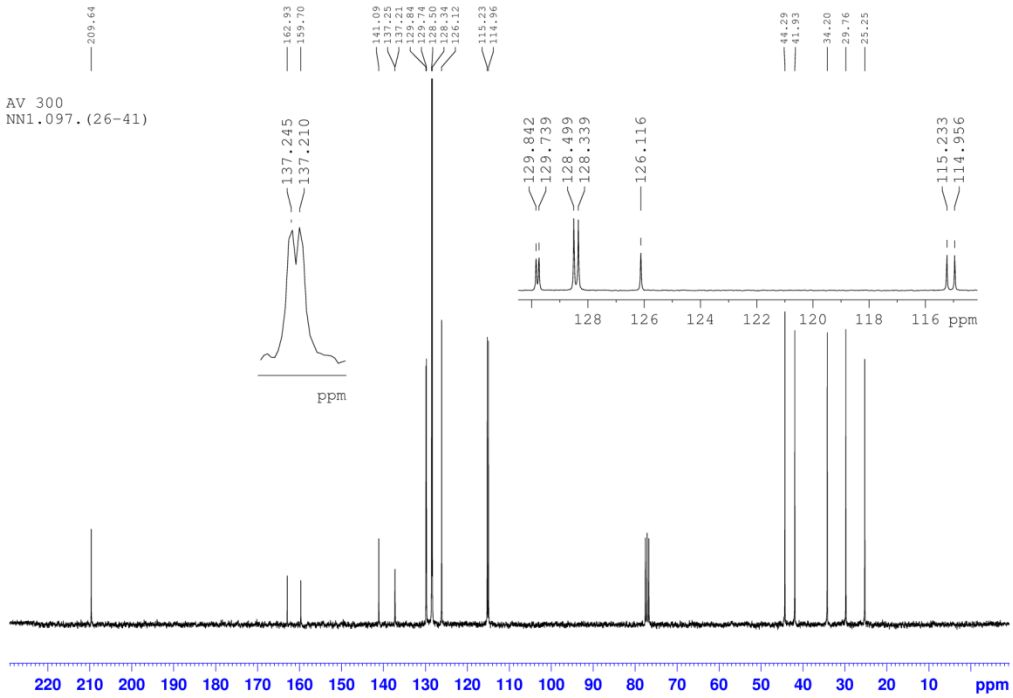


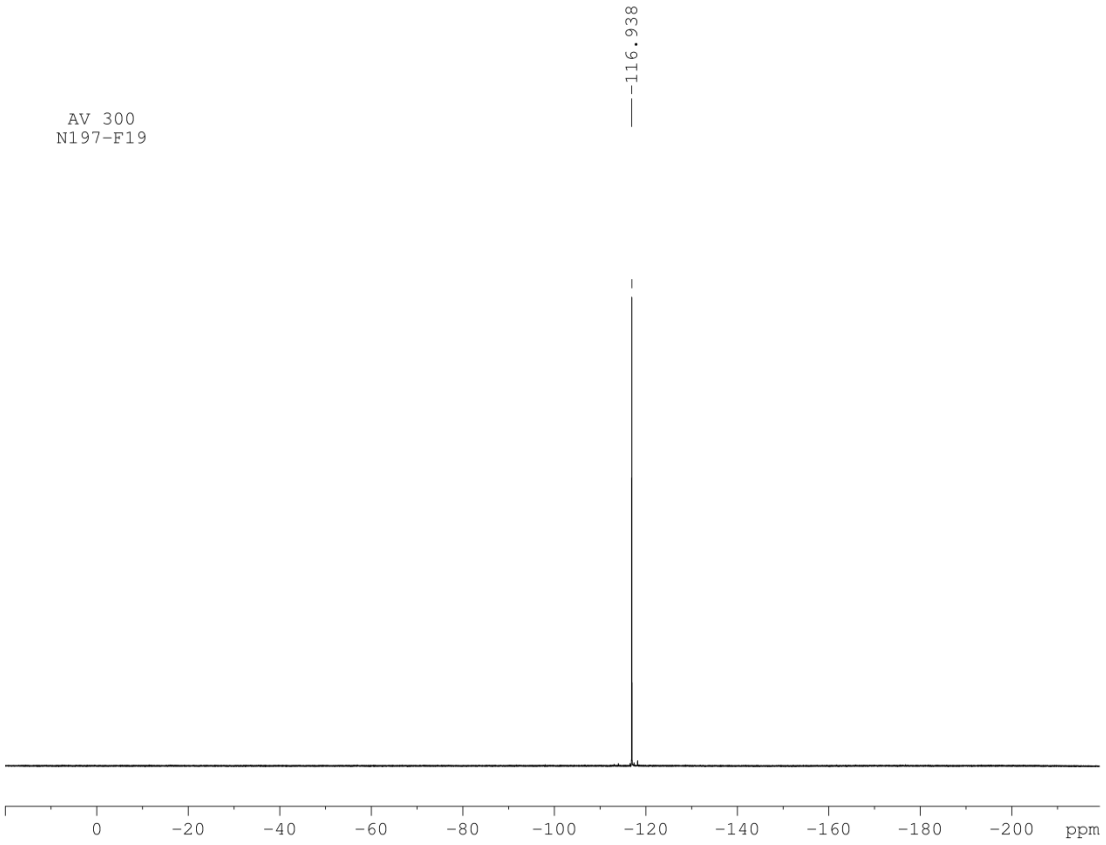


^{1}H, ^{13}C and ^{19}F-NMR spectra of Ketone **18**





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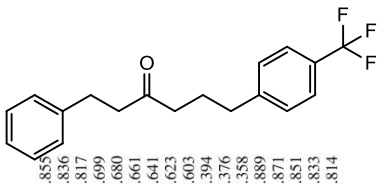
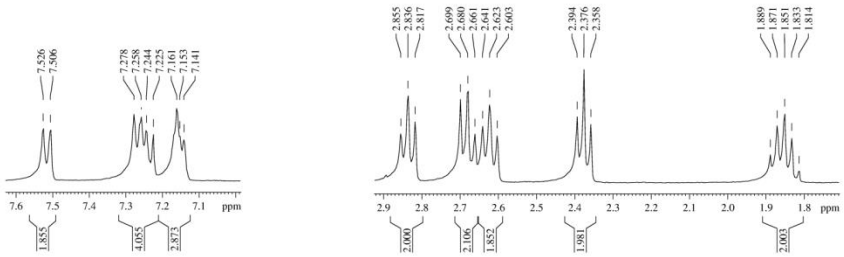
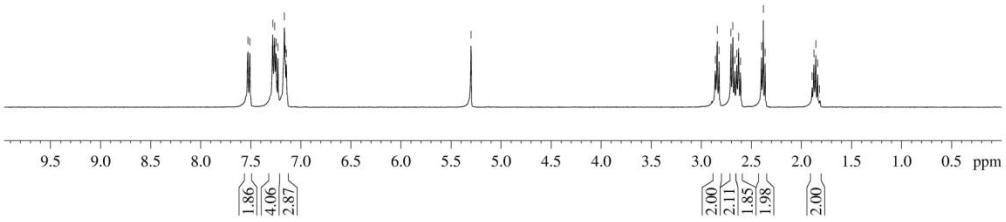
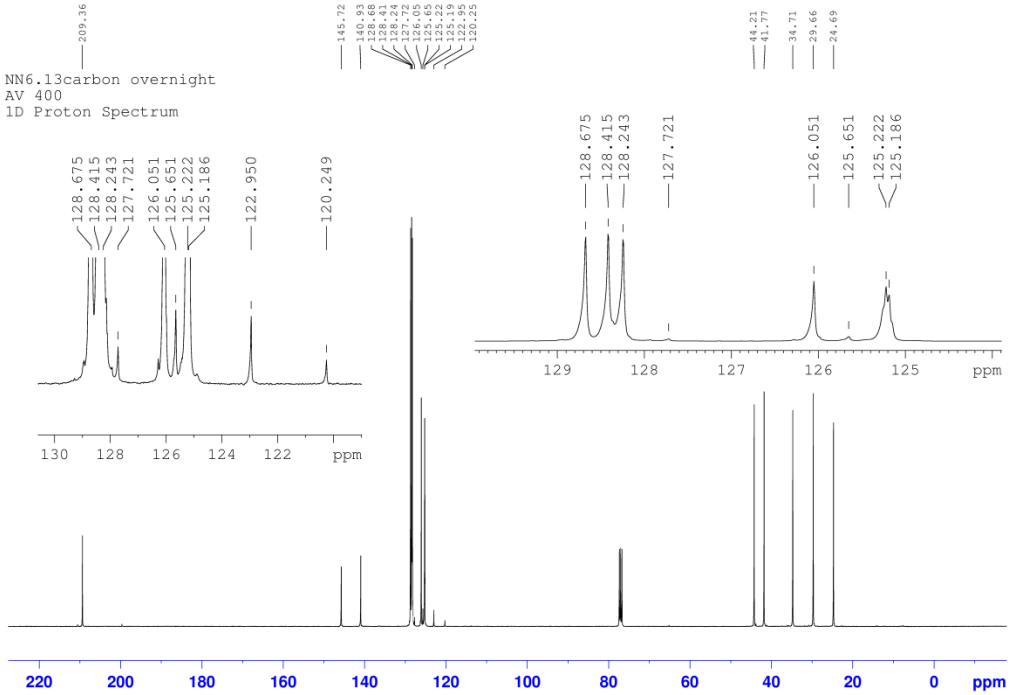
ppm

^{1}H, ^{13}C and ^{19}F-NMR spectra of Ketone **13**

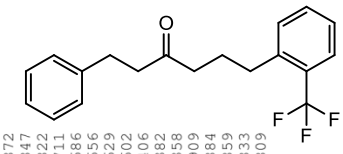


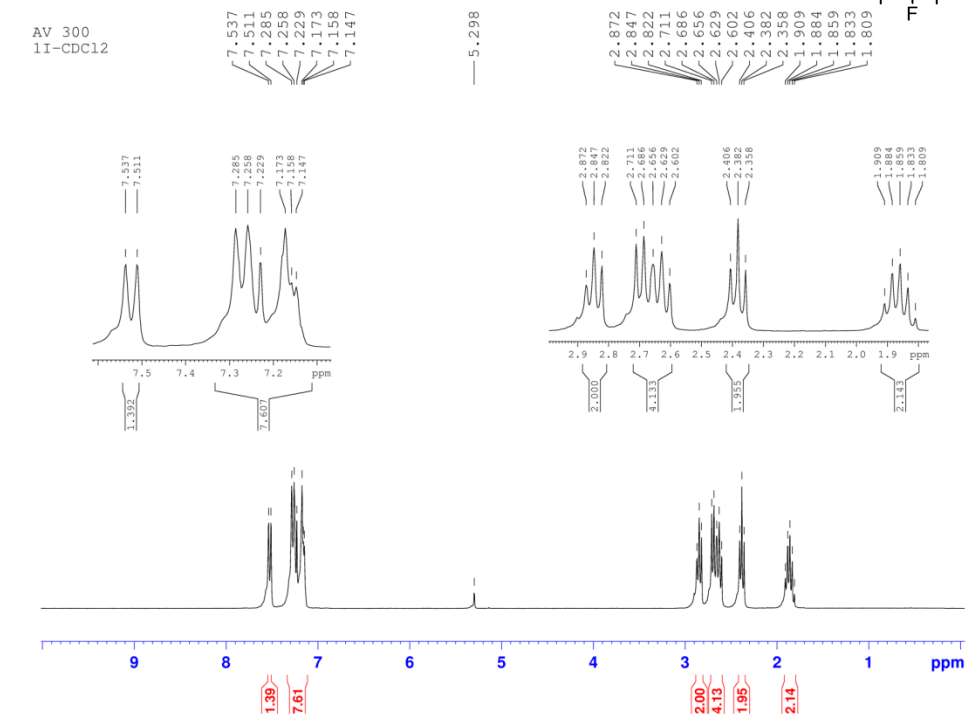


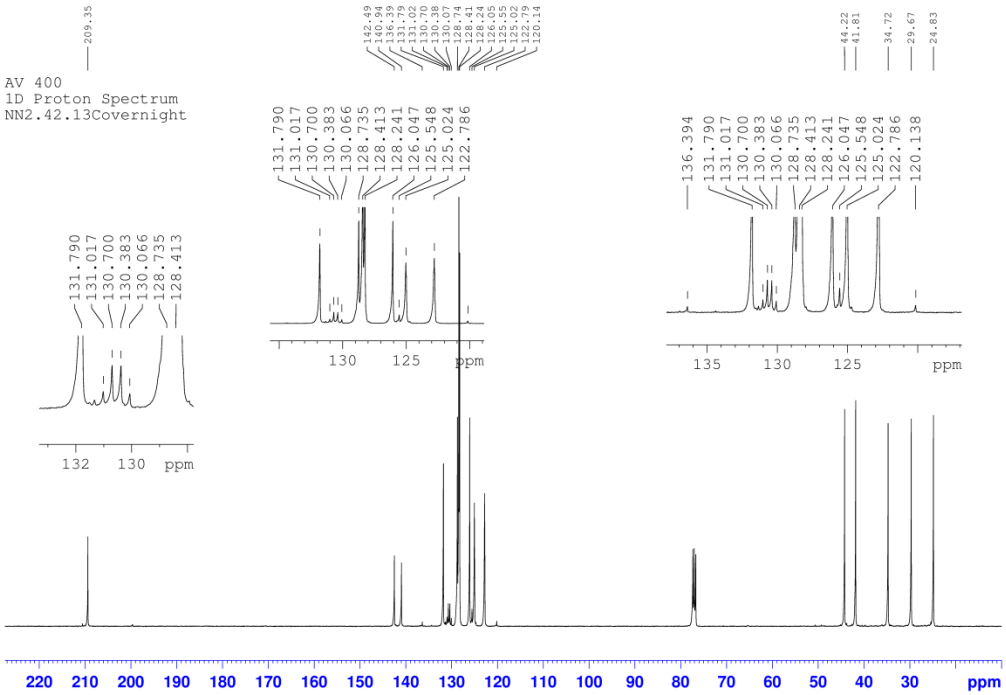


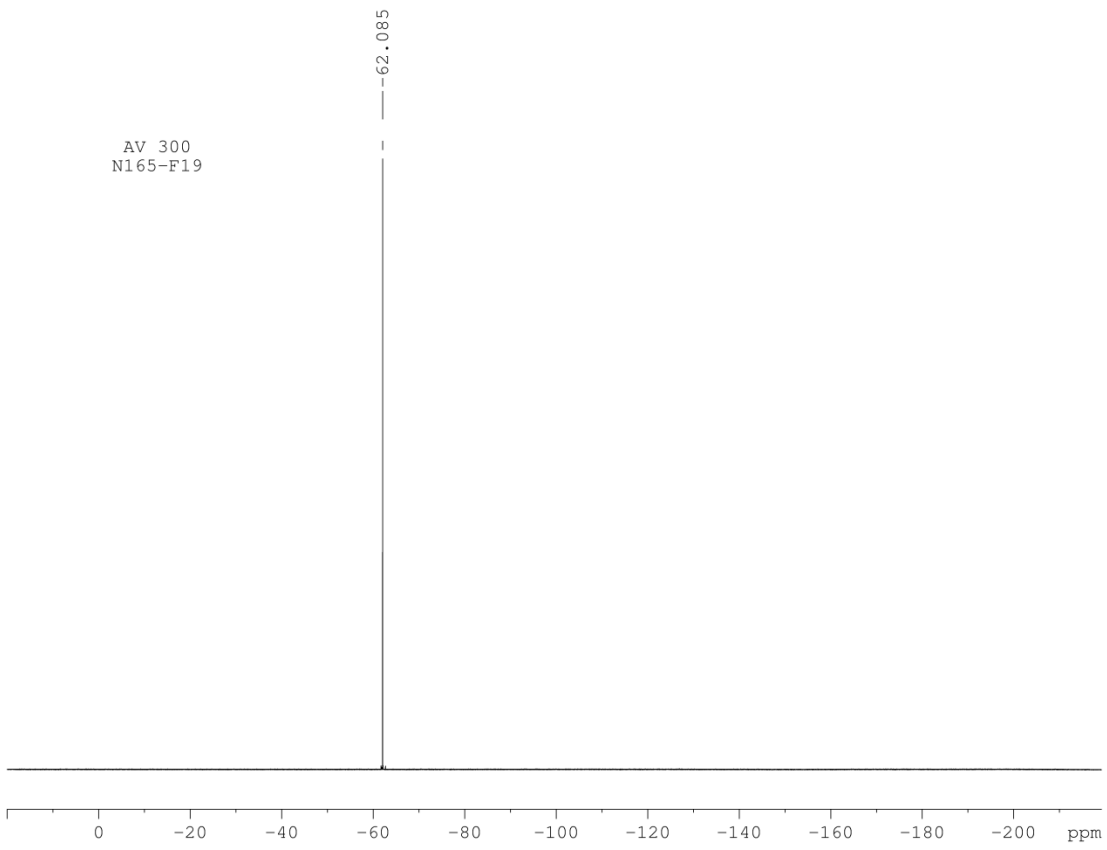


^{1}H, ^{13}C and ^{19}F-NMR spectra of Ketone **19**





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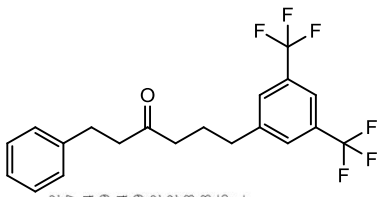
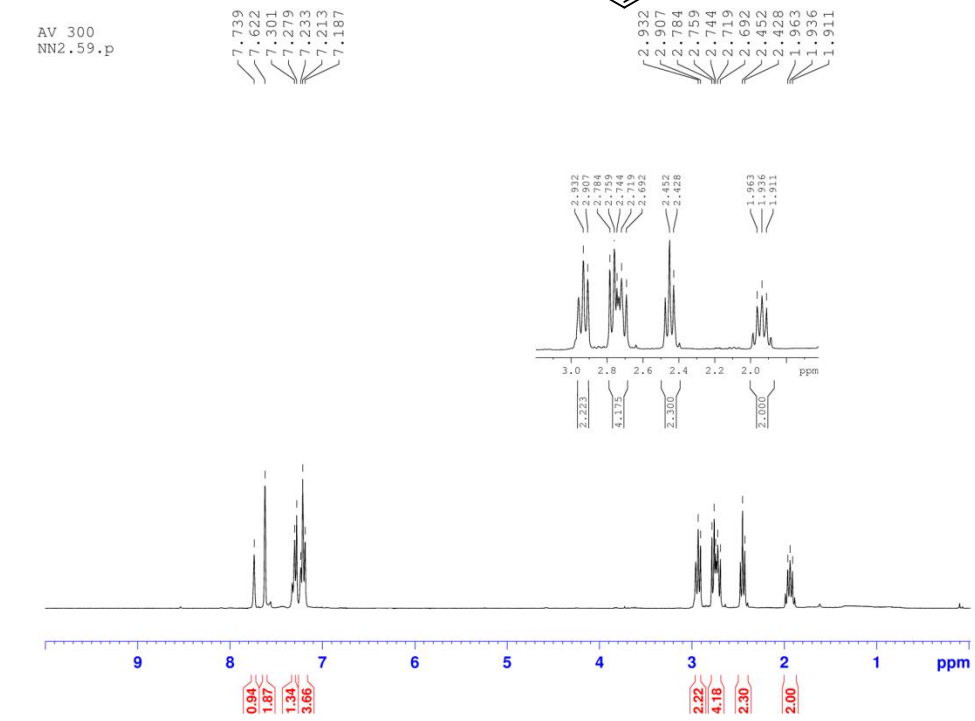
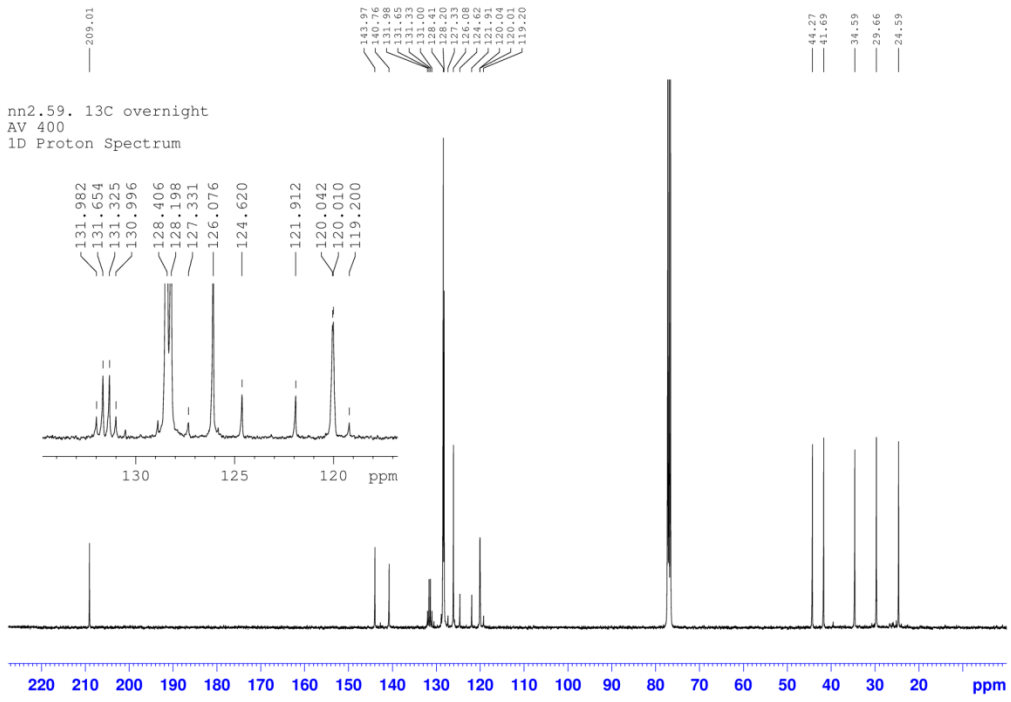
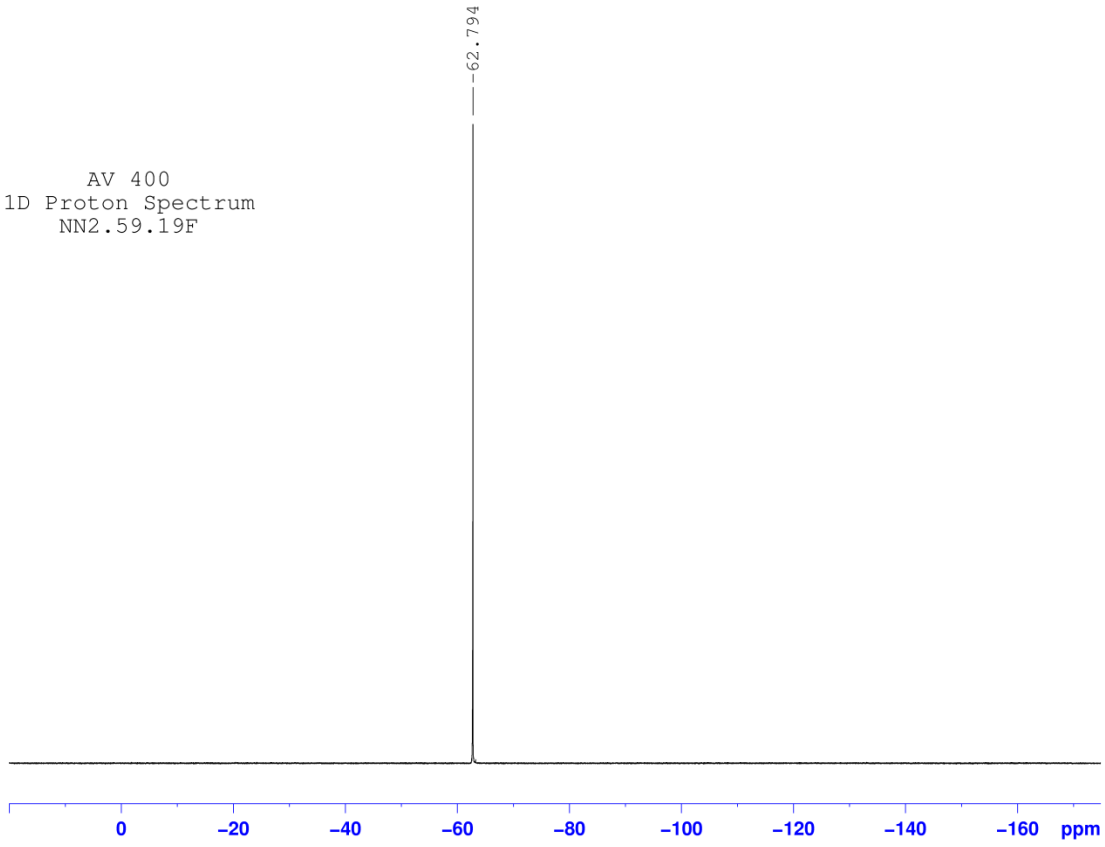
^{1}H, ^{13}C and ^{19}F-NMR spectra of Ketone **20**





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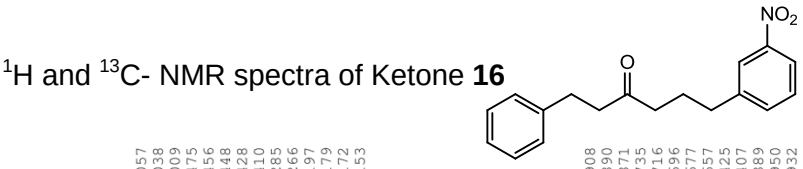
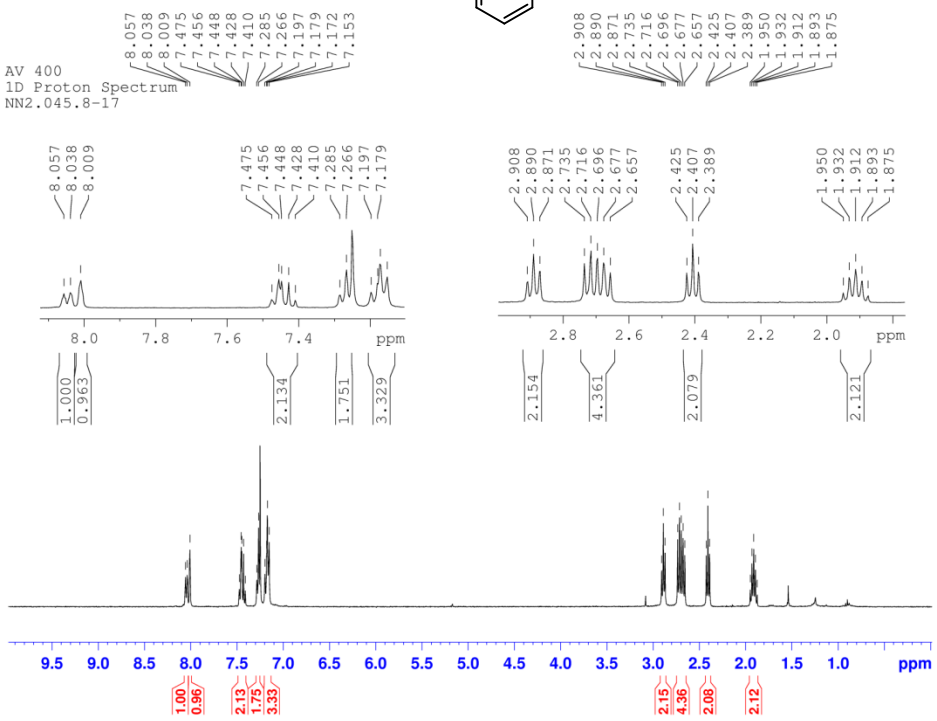
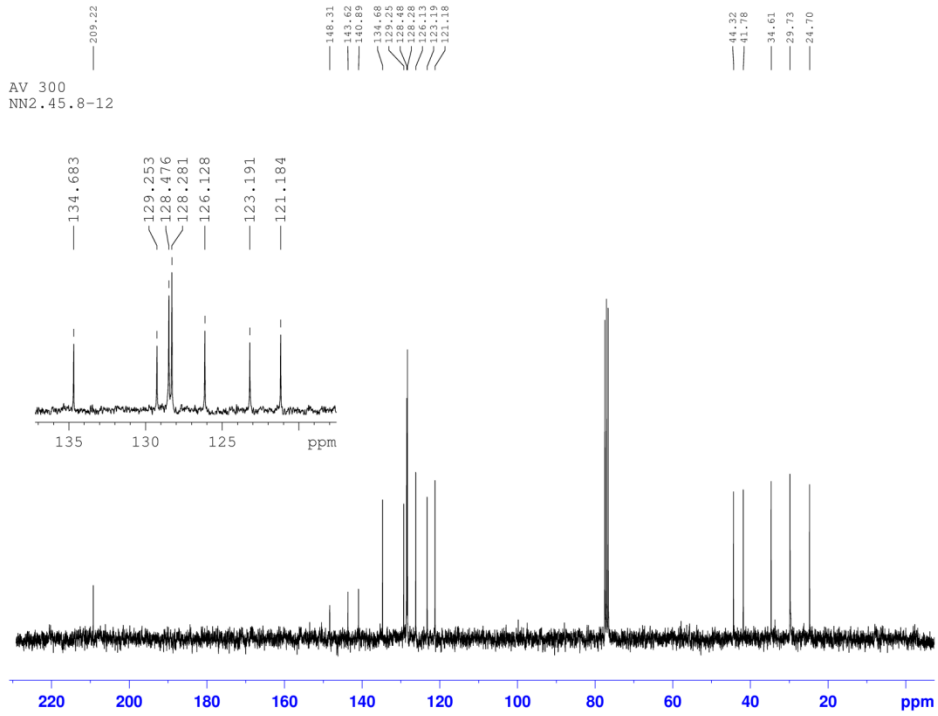
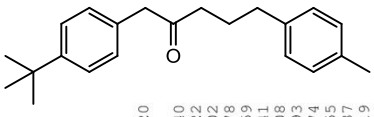
^{1}H and ^{13}C- NMR spectra of Ketone **16**

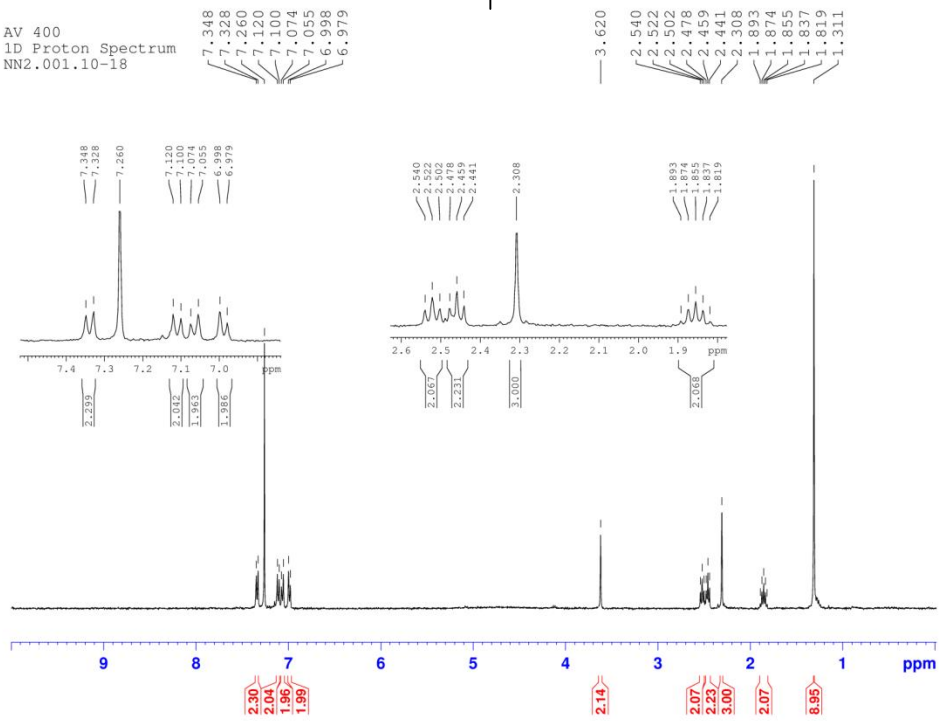


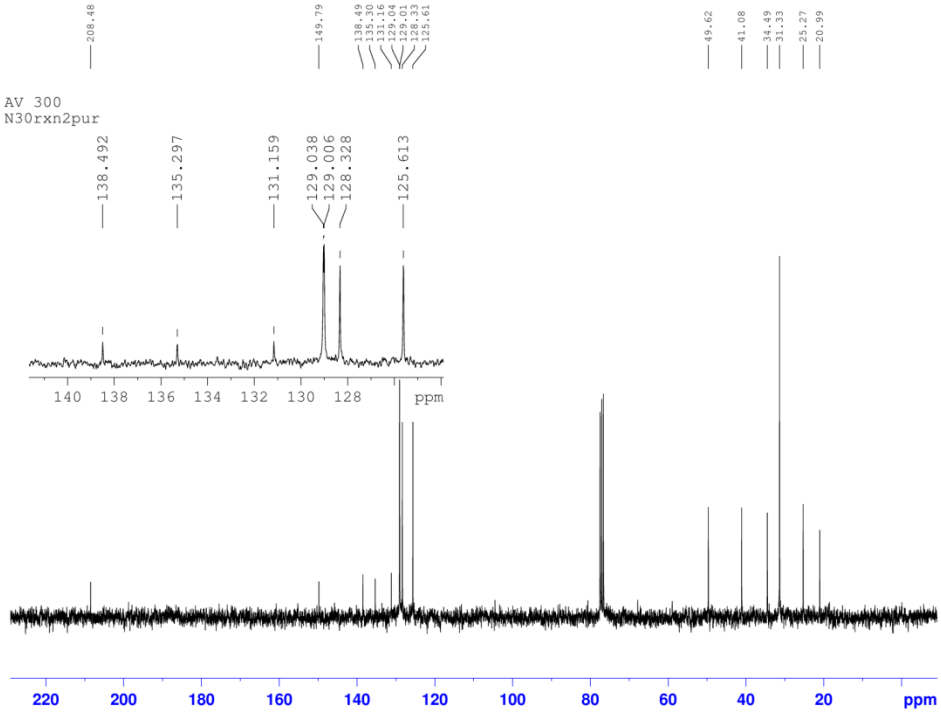




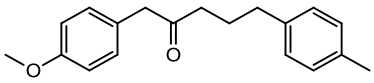
^{1}H and ^{13}C- NMR spectra of Ketone **2**

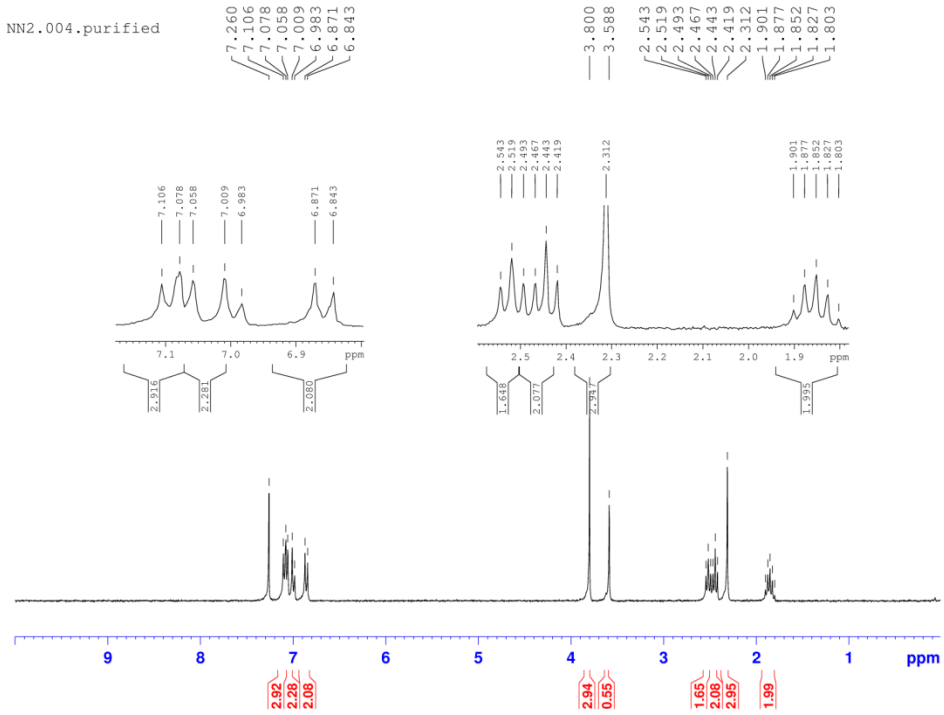


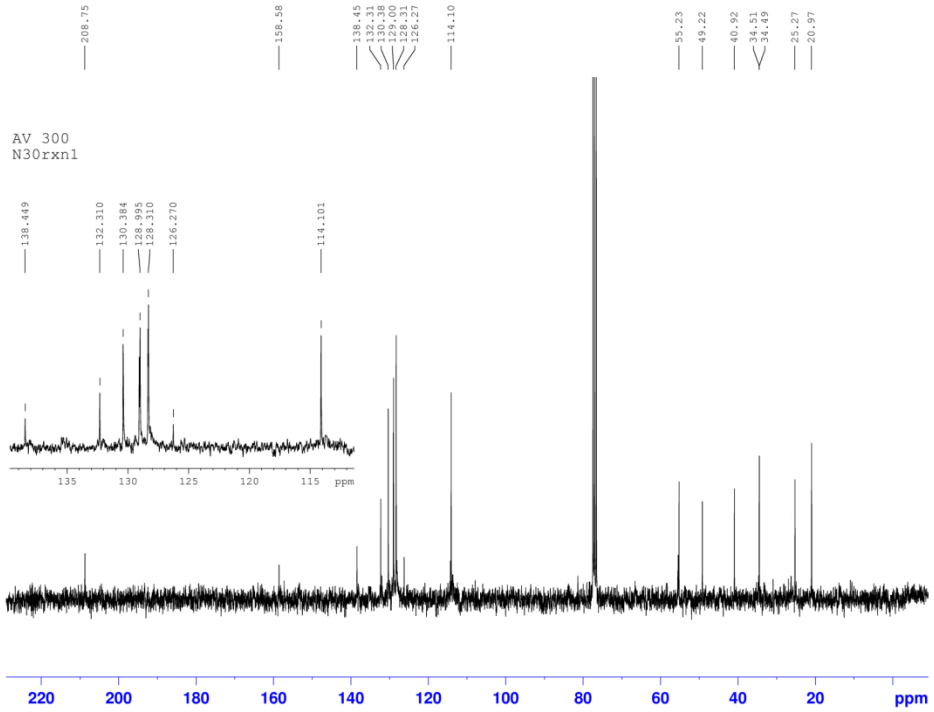




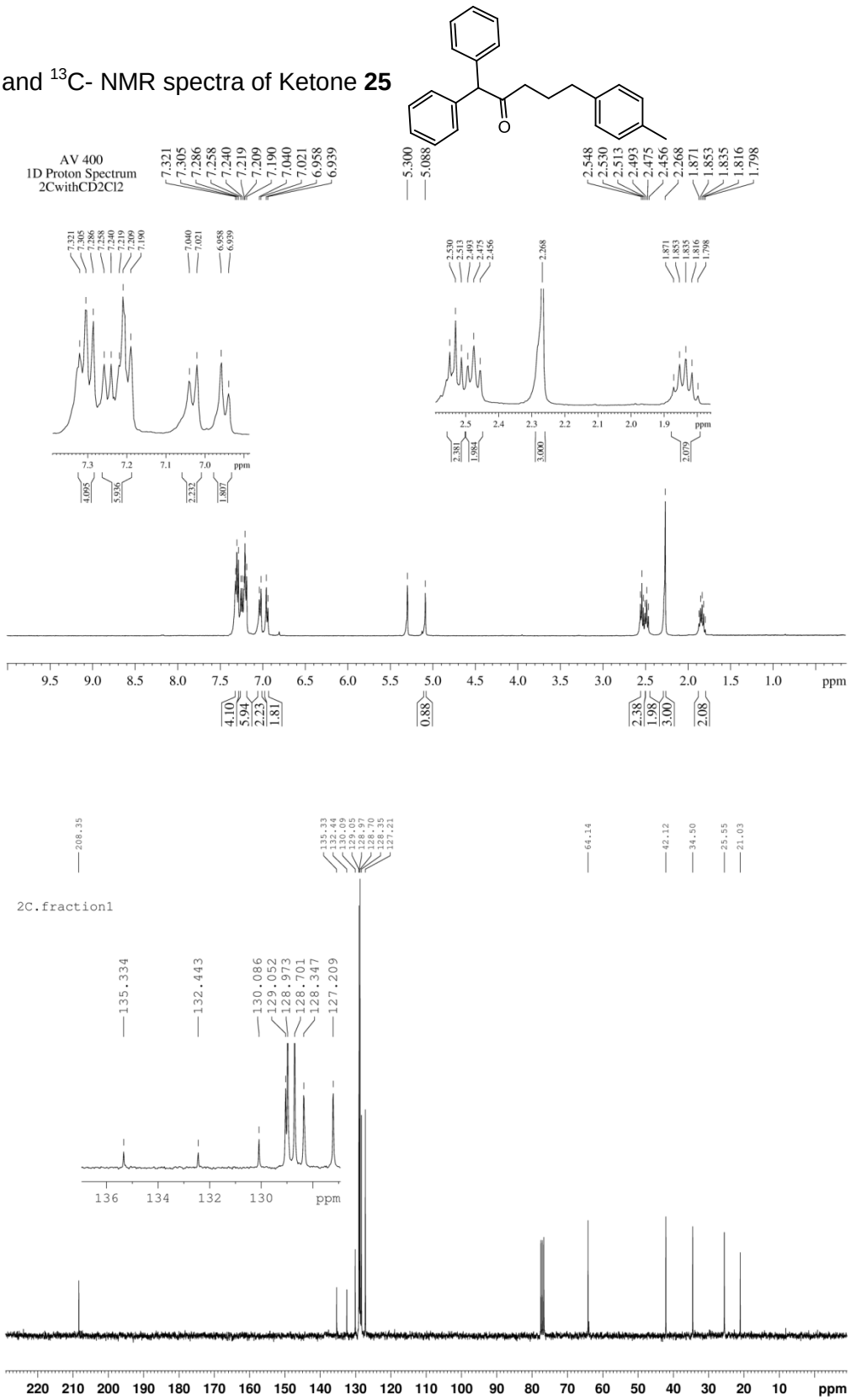
^{1}H and ^{13}C- NMR spectra of Ketone **5**



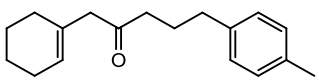


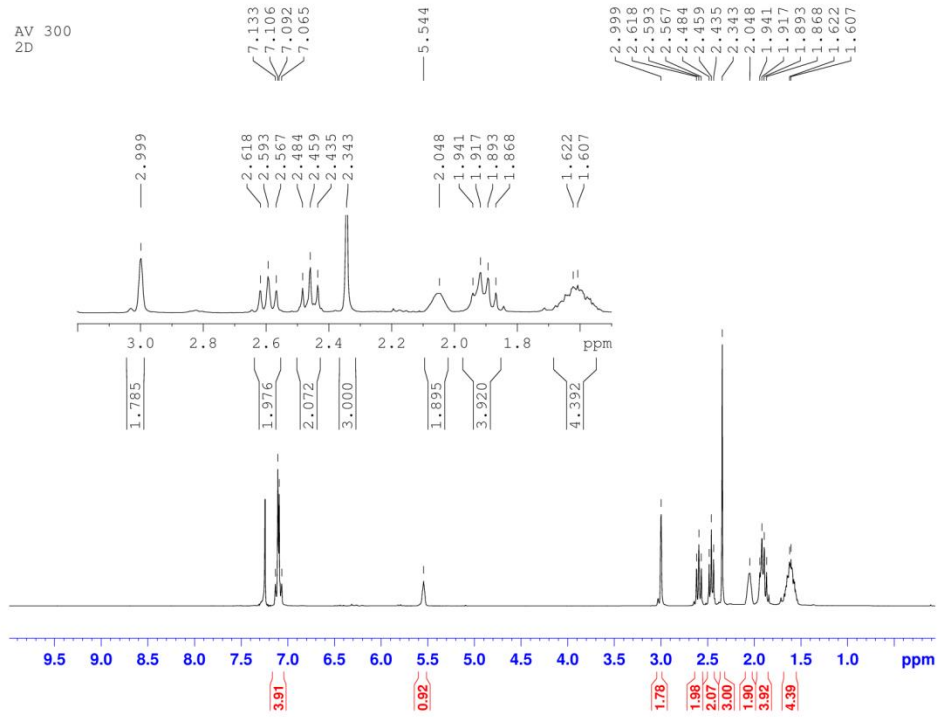


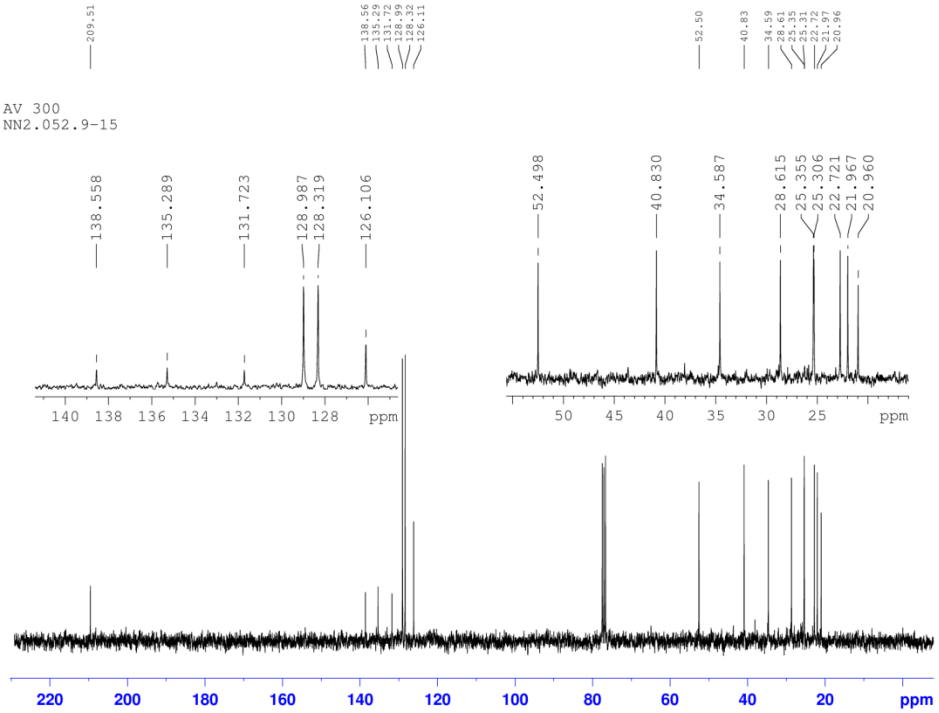
^{1}H and ^{13}C- NMR spectra of Ketone **25**



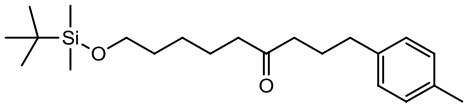
^{1}H and ^{13}C- NMR spectra of Ketone **27**

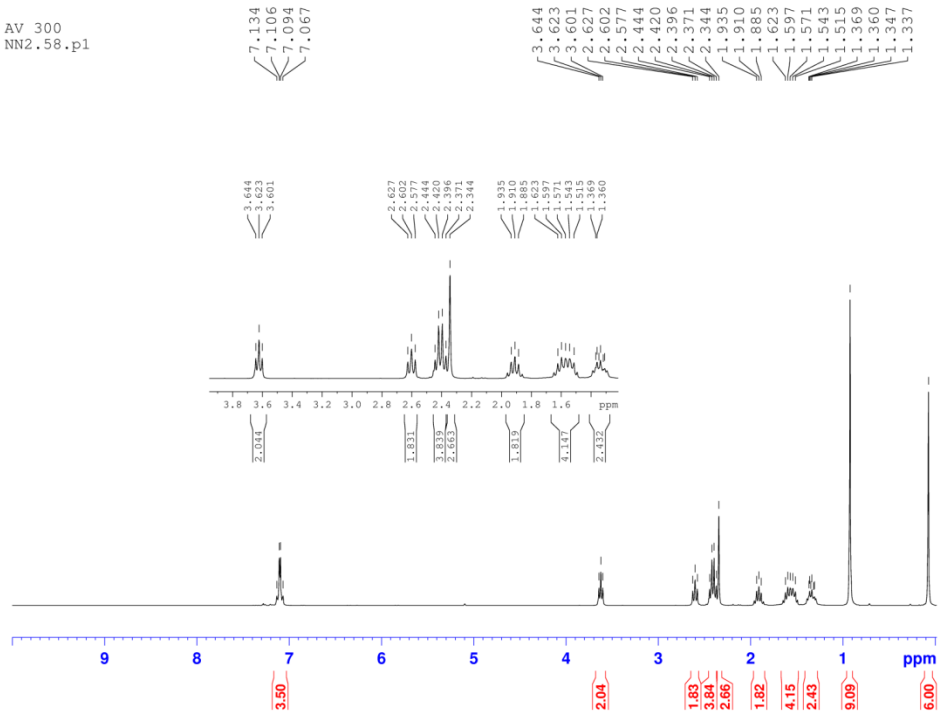


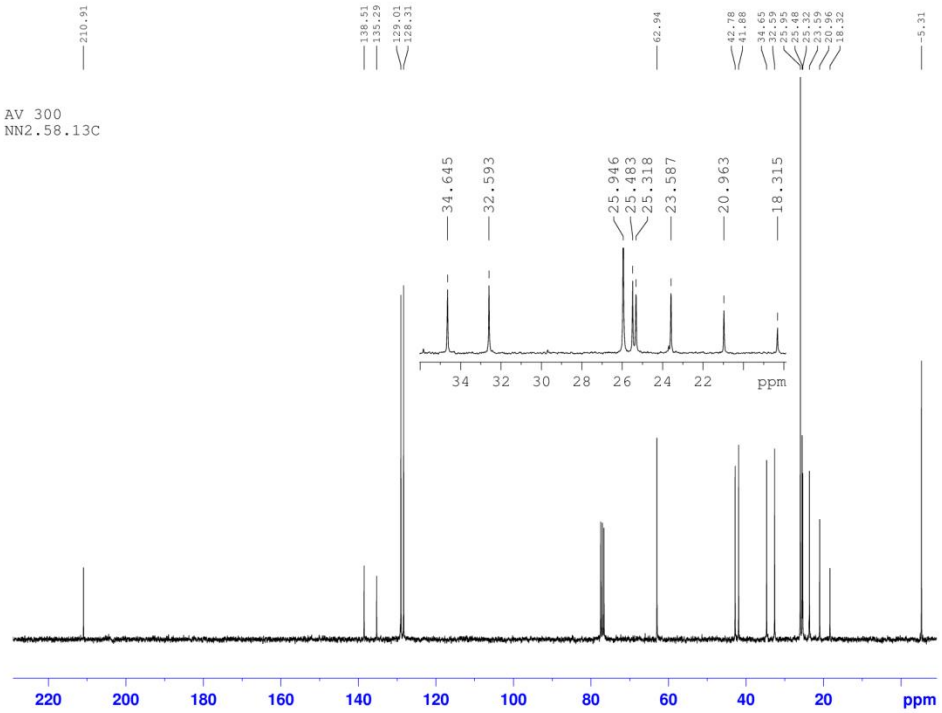




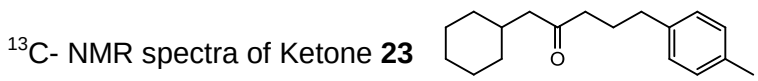
^{1}H and ^{13}C- NMR spectra of Ketone **29**

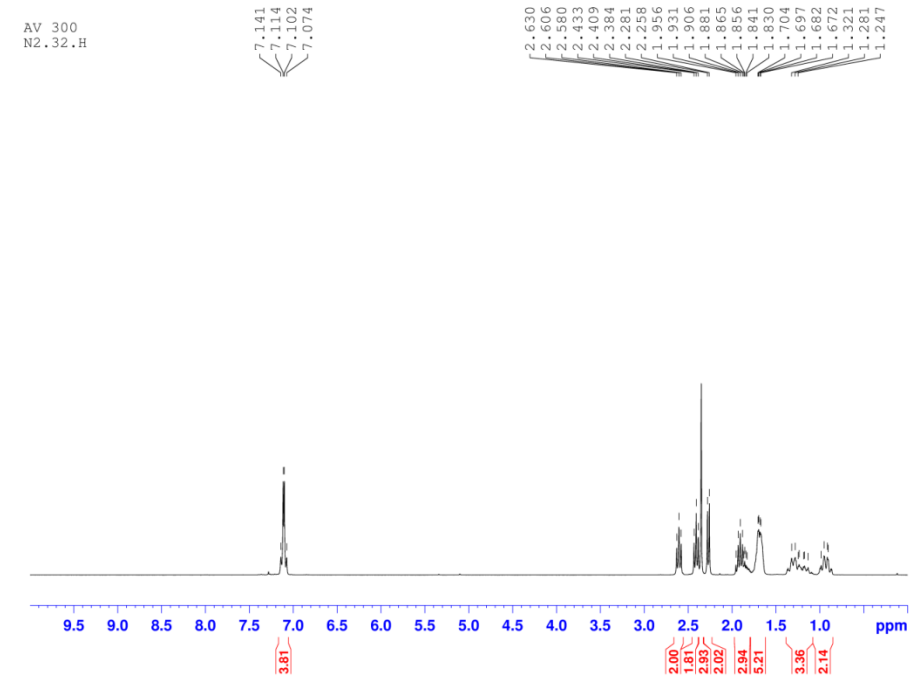


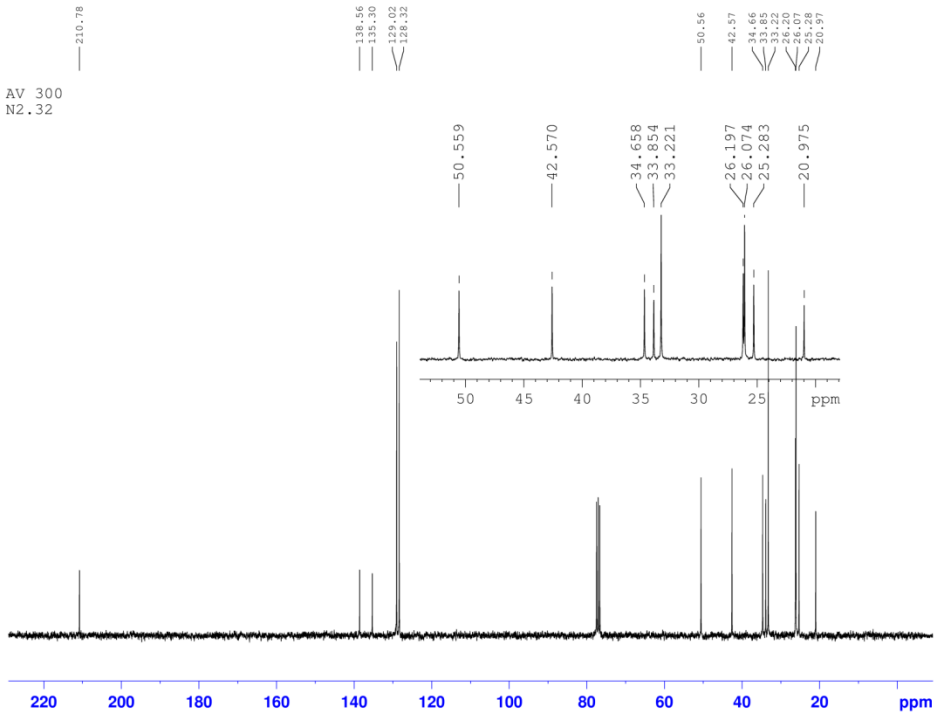




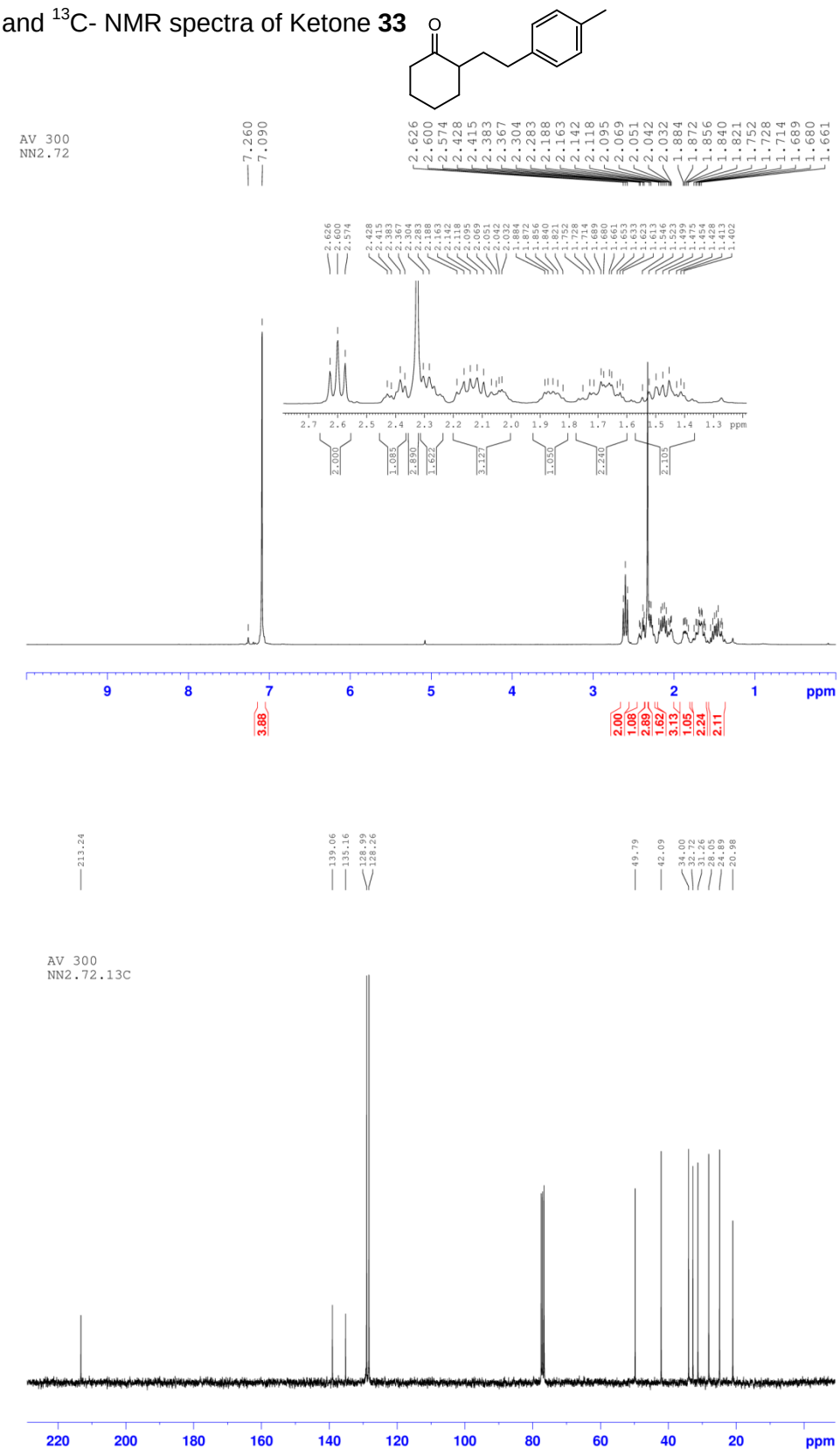
^{1}H and ^{13}C- NMR spectra of Ketone **23**







^{1}H and ^{13}C- NMR spectra of Ketone **33**



^{1}H and ^{13}C- NMR spectra of Ketone **31**