Palladium Mediated Synthesis of Substituted Phenols from Acyclic Ketones

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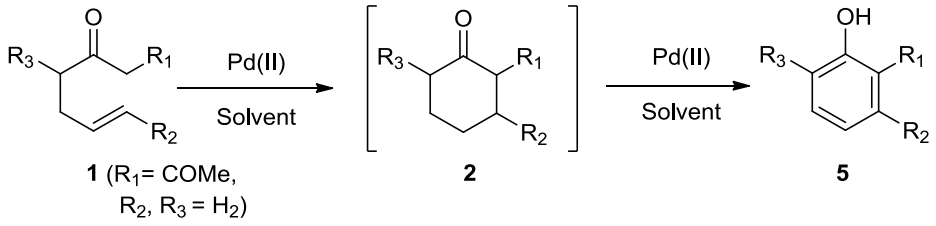
Abstract

The direct functionalization of phenols at the *ortho* and *para* position is generally facilitated by the electron-donating nature of the hydroxyl group. Accessing *meta* substituted phenols, on the other hand, often requires lengthy synthetic sequences. Here, we report a conceptually different method for the one-pot synthesis of substituted phenols by using a pre-functionalization strategy whereby the functional group is installed on the substrate, an acyclic unsaturated ketone, before a cyclization/aromatization reaction. Hence, the functionality is present during the palladium(II) catalyzed reaction. To develop this process we first identified practical reaction conditions for the cyclization of γ,δ-unsaturated ketone **1** (oct-7-ene-2,4-dione) using catalytic amounts of $PdCl_2(CH_3CN)_2$, HCl and $CuCl_2$ in dioxane at 70 °C. With cyclic ketone **2** (2-acetylcyclohexanone) in hand we next explored oxidation using chloranil as an optimal oxidant for the oxidation of the $PdCl_2(CH_3CN)_2$. Combination of these two steps results in formation of phenol **5** (1-(2-hydroxyphenyl)ethanone) from acyclic ketone **1** in one pot process (Scheme 1). This transformation leads to the formation of various mono-, di-, and trisubstituted phenols with substituents at various positions.



Scheme 1: Palladium catalyzed aromatization of acyclic substrate.

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ACS	american chemical society
AMS	anthraquinone-2-sulfonic acid sodium salt
Bpy	bipyridine
BQ	benzoquinone
CDI	carbonyldiimidazole
Co(Slp)	cobalt salophen
DAF	diazafluorene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DG	directing group
DIAD	diisopropyl azodicarboxylate
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
DOM	directed *ortho*-metalation
EAS	electrophilic aromatic substitution reaction
equiv.	equivalents
ETM	electron transfer mediator
EtOAc	ethyl acetate
EWG	electron withdrawing group
Fe(Pc)	iron(II) phtalocyanine
HQ	hydroquinone
HRMS	high resolution mass spectrometry
L_n	ligand(s) (n = number of ligands)
LDA	lithium diisopropyl amide

MeCN	acetonitrile
m.p.	melting point
MS	mass spectrometery
n-BuLi	*n*-butyllithium
N.R.	no reaction
OAc	acetate
OTf	trifluoromethanesulfonate (triflate)
OTs	tosylate
Ph	phenyl
rt	room temperature
TBAF	tetra-*n*-butylammonium fluoride
TBSCl	*t*-butyldimethylsilylchloride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMSCl	trimethylsilylchloride

Chapter 1: Introduction

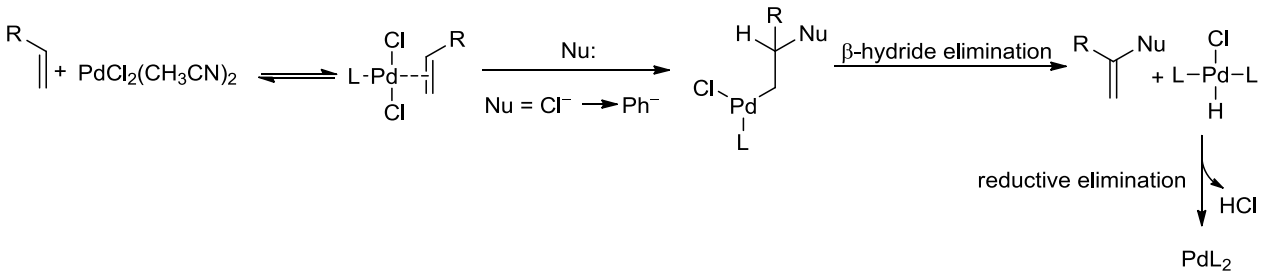
1.1 General introduction

The use of transition metal-catalyzed reactions in organic synthesis has been widely established.[1] Transition metal catalysis represents one of the key methods for chemical transformations today; this is due to transition metals having a wide range of readily accessible oxidation states, and also their ability to undergo oxidation-reduction reactions. Transition metal complexes promote a range of transformations which are otherwise difficult to achieve (e.g. palladium catalyzed sp^2-sp^2 carbon-carbon bond formation in Suzuki-Miyaura coupling).[2] Transition metals can readily coordinate to organic functional groups, resulting in a change of electron density and hence altering the reactivity of the functional group. Moreover, the high selectivity of many transition metal-catalyzed reactions reduces the need to use protecting groups. Another advantage of transition metals is their ability to form multiple bonds in cascade reactions.[3] Among the transition metal catalysts currently used in organic reactions, palladium complexes are perhaps the most widely used both industrially and academically.[4] This is due to the ability of palladium complexes to catalyze a wide range of organic reactions, the availability of various palladium compounds, and the relatively low cost of palladium compared to other transition metals such as rhodium and gold.[5] Palladium(0) complexes catalyze a variety of coupling reactions including the Mizoroki-Heck reaction,[6] Stille-Migita coupling,[7] and Suzuki-Miyaura coupling,[2] in contrast, palladium(II) complexes catalyze a number of transformations including the Wacker reaction.[8]

1.2 Properties of palladium

Palladium is the 46th element in the periodic table and has an electron count of [Kr] $4d^{10}$. Palladium-mediated processes have countless applications in the syntheses of natural products, polymers, and pharmaceuticals.[9] Palladium can exist in a variety of oxidation states including 0, +1, +2, +3, and +4.[10] However, the most common oxidation states are 0, +2, and therefore Pd(0) and Pd(II)

complexes are by far the most widely used in transition metal catalyzed reactions. Pd(0) tends to form 18 electron tetrahedral d^{10} complexes, while Pd(II) tends to form 16 electron square planar d^8 complexes. Pd(II) compounds such as $PdCl_2$ and $Pd(OAc)_2$ are air-stable and commercially available species. In contrast, palladium(0) complexes must be protected from air to avoid their oxidation. Palladium(II) salts are known to coordinate to olefins thereby significantly altering the reactivity pattern by directing the electron density toward the metal and away from the π orbitals of the alkene.[11] This leads to activation of the coordinated alkene towards attack by nucleophiles.[12] A wide range of nucleophiles can attack activated olefin complexes. Trans nucleophilic attack to palladium-coordinated olefin complexes results in new carbon-nucleophile σ sigma bond formation. Other elementary steps, such as β-hydride elimination can occur subsequently, depending on the reaction conditions and the nature of the catalyst (Scheme 2).



Scheme 2: General scheme showing attack of a nucleophile on a palladium olefin complex.

1.3 Ligands on palladium

Palladium(II) chloride without any additional ligands on it, $PdCl_2$, exists in a polymeric structure; and is not soluble in common organic solvents and water. In order to make this compound a more effective catalyst it must be converted to a more soluble complex. Therefore, different types of monodentate and bidentate ligands such as phosphorous ligands, nitrogen based ligands, and other neutral ligands containing group 14 and 16 elements were combined with palladium chloride in order to disrupt the polymeric structure and improve solubility in a broad range of solvents. In addition, the

use of ligands can also affect the palladium centre by altering the electronic properties of the metal which in turn affects reactivity with different functional groups. Monodentate phosphine ligands (e.g. triphenylphosphine) are commonly used with palladium as they can stabilize the palladium source through a combination of σ-donor and π-acceptor interactions. The steric effects imparted on the palladium center by the ligands are also important in palladium catalyzed reactions. In the case of monodentate phosphine ligands the steric effect is determined by the Tolman cone angle parameter that shows the degree of steric bulk around the metal centre. The cone angle is defined as an angle formed by the metal at the vertex and hydrogen atoms of the ligand at the perimeter of the cone (Figure 1).[13] An increase in cone angle can result in facile dissociation of phosphine ligands from coordinatively saturated palladium(0) complexes.

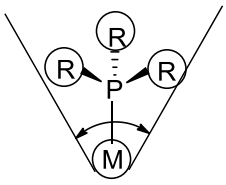
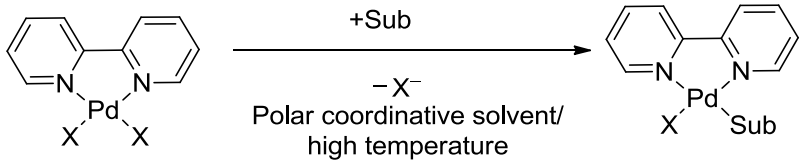


Figure 1: Cone angle.

However, phosphine ligands are generally not suitable ligands for palladium catalyzed oxidation reactions, as strong σ-donating phosphine ligands reduce the oxidizing ability of the palladium catalyst and, also can be oxidized themselves.

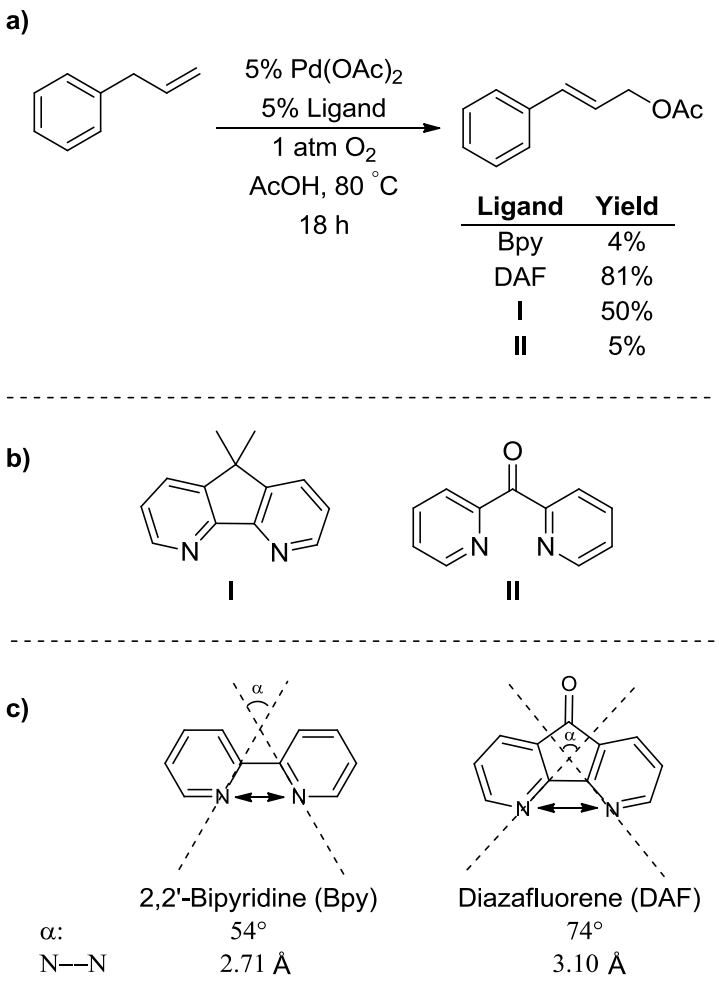
A significant challenge is posed when selecting a suitable ligand system for palladium(II) catalyzed oxidative reactions, on one hand a ligand that will effectively stabilize the palladium(II) centre is desirable, on the other hand, the ligand should not inhibit any steps in the catalytic cycle. In this regard, nitrogen ligands are the most commonly used, and unlike phosphine ligands the electronic properties of the nitrogen-containing ligands don't have an inhibiting effect on the oxidation/reduction ability of the metal centre.[14] The most common Pd complexes containing nitrogen donor atoms are $Cl_2Pd(MeCN)_2$ and $Cl_2Pd(PhCN)_2$. These complexes are readily prepared by

reaction of $PdCl_2$ with the corresponding nitrile under reflux conditions. The monodentate nitrogen ligand increases the solubility of the palladium species in organic solvents thus facilitating improved catalytic activity. Bidentate nitrogen ligands are also commonly used in palladium catalyzed oxidation/reduction chemistry.[14] Bidentate ligands generally form a stronger bond to the metal due to the chelate effect, which stabilizes the palladium complex and inhibits decomposition. Indeed, studies show[15] that substrates can successfully coordinate to bidentate Pd–N complexes in the presence of more polar coordinating solvent or at higher reaction temperature (Scheme 3).



Scheme 3: Properties of bidentate nitrogen ligands.

In the case of Pd–N complexes the geometry of the bidentate ligand is another factor that can affect the reactivity of the Pd complexes. The impact of different types of nitrogen based bidentate ligands in palladium catalyzed allylic acetoxylation was investigated by Stahl and co-workers (Scheme 4, a).[16] Initially, it was believed that the differences in the electronic properties of the diazafluorene (DAF) ligand relative to a 2,2'-bipyridine (bpy) ligand were responsible for the greater yields observed when DAF was used. Stahl postulated that the carbonyl group on the ligand backbone could promote back bonding from the palladium(II) centre and favouring reductive elimination. However, control experiments failed to support this theory. For example, when the carbonyl group in diazafluorene (DAF) was replaced with two methyl substituents as for ligand **I** a moderate yield (50%) was observed, whereas use of di-2-pyridyl ketone (**II**) which is capable of back-bonding, afforded the allylic acetoxylation product in a very low yield (5%) (Scheme 4, a, and b). Therefore, Stahl concluded that the difference in reactivity is due to the geometric properties of the ligand, specifically the nitrogen-metal-nitrogen bite angle, of diazafluorene (DAF) compared to bpy (Scheme 4, c).[16]



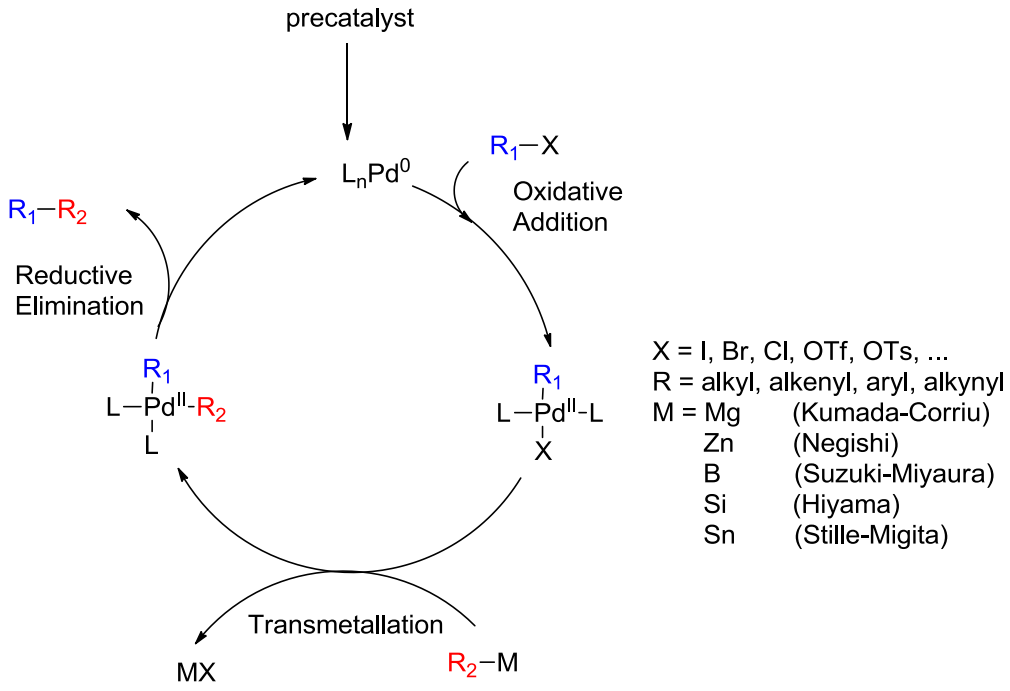
Scheme 4: The effect of ligand geometry on reactivity of palladium complexes.

1.4 Palladium catalyzed methods for the construction of carbon–carbon and carbon–heteroatom bonds

1.4.1 Pd– cross– coupling methodologies

Cross-coupling reactions are one of the most common and versatile methods for palladium catalyzed C-C bond formation. The cross coupling of Grignard reagents was first developed in 1972, by Kumada and Tamao using a Ni catalyst that enabled the formation of C-C bonds.[17] In 1975, Murahashi and co-workers were the first to report a Kumada–Tamao–Corriu reaction using a

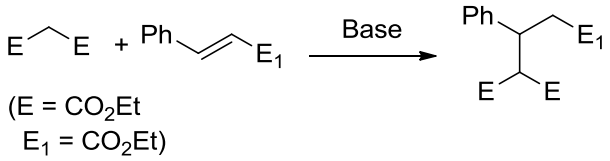
palladium catalyst. $Pd(PPh_3)_4$ that allowed for the formation of C-C bonds between sp^2 and sp^3 hybridized carbon atoms.[18] Cross coupling reactions follow a general catalytic cycle which begins with oxidative addition of palladium(0) into a carbon-halide or *pseudo*-halide bond. The resultant palladium(II) species can then undergo transmetallation with a suitable organometallic or main group organic species to generate a second palladium(II) species, with a metal halide or *pseudo*-halide produced as a by-product. In the last step, reductive elimination gives rise to cross coupled product and regenerates the palladium(0) catalyst (Scheme 5). Palladium(0) species are air sensitive so an inert atmosphere is required for their handling and storage. Therefore, palladium(0) is typically generated *in situ* by reduction of a palladium(II) complex.



Scheme 5: General catalyst cycle of cross-coupling reactions.

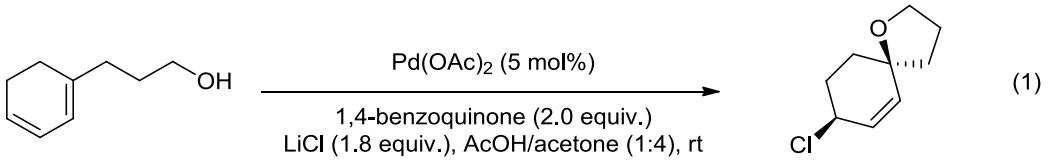
1.4.2 Other Pd catalyzed carbon–carbon and carbon–heteroatom bond formation

The formation of carbon-carbon bonds is one of the fundamental challenges in organic synthesis. The regioselective addition of a carbon nucleophile to an olefin bearing an electron-withdrawing group (e.g. Michael addition; see Scheme 6) is one of the known methods for the mild formation of C-C bonds. However, this method is limited to activated olefins. In this regard, transition metals have received considerable attention owing to their ability to promote a wide variety of C-C bond formation processes.



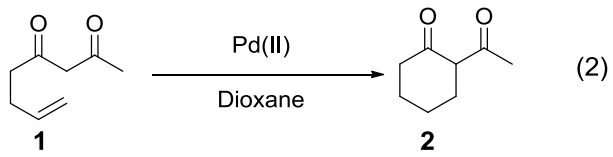
Scheme 6: Michael addition of diethyl malonate to ethyl 3-phenylacrylate.

Palladium has been shown to promote the formation of C-C bonds between carbon nucleophiles (e.g. enolates) and unactivated olefins.[19] Furthermore, palladium has played a dominant role in the formation of cyclic ethers and amines, often giving products in excellent yields and high selectivity. For instance palladium(II) acetate can coordinate to olefins, making them sufficiently electrophilic to enable the intramolecular formation of oxygen heterocycles by nucleophilic attack of an alcohol (Equation 1).[20] Initially, palladium coordinates to one face of the diene and promotes intramolecular attack by the alcohol on the opposite face. The resulting σ complex can form a π-allyl complex with the palladium on the lower face. Finally, nucleophilic attack of chloride from the lithium chloride proceeds from the opposite face to the palladium. Stoichiometric amounts of palladium are avoided by using benzoquinone as the stoichiometric oxidant to regenerate the catalytic palladium species.



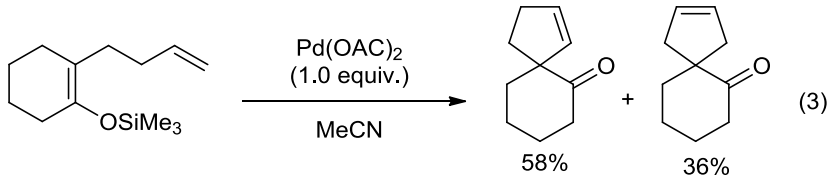
73% yield; 99:1 syn:anti

Due to palladium ability to π-coordinate to an alkene, methods for the intramolecular hydroalkylation of β-diketones using palladium have been previously reported by Widenhoefer.[21] However a mild and general route to the cyclized product is yet to be established (Equation 2).



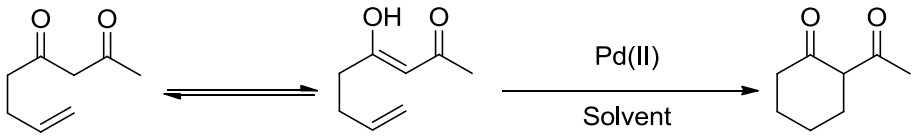
1 **2** (2)

Widenhoefer postulated that β-diketones such as **1** may co-ordinate to Pd in a similar way to silyl enol ethers, as silyl enol ethers can react as nucleophiles in intramolecular reactions with unactivated olefins in the presence of palladium (Equation 3).[22]

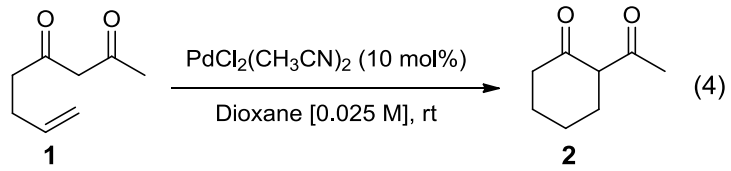


(3)

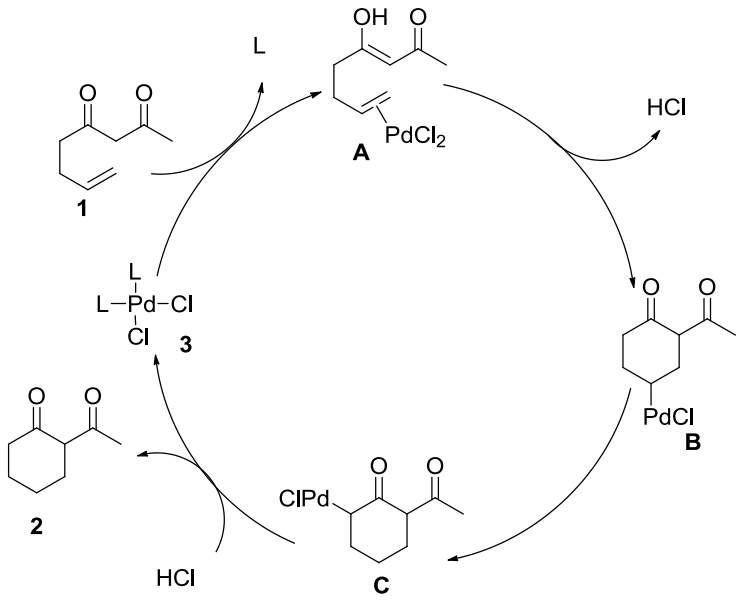
Since β-diketones exist predominantly in their enol form at room temperature[19] (Scheme 7), they may react with olefins in a similar manner (Equation 4). In a model reaction Widenhoefer found that treatment of a very dilute solution of **1** [0.025 M in 1, 4-dioxane] with a catalytic amount of $PdCl_2(MeCN)_2$ (10 mol %) at room temperature for 16 h led to the isolation of **2** in 80% yield (Equation 4).



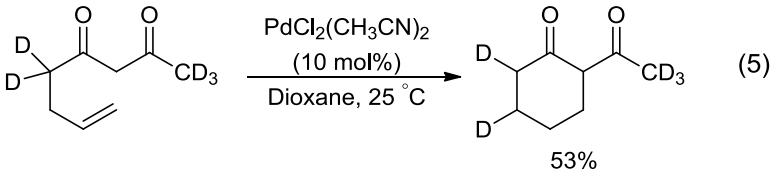
Scheme 7: Keto/enol tautomerization and cyclization of oct-7-ene-2,4-dione.



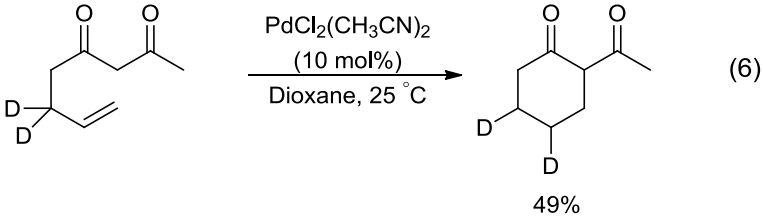
A plausible catalytic cycle for this transformation would involve initial coordination of the palladium to the terminal olefin of substrate **1** to generate complex **A**. Intramolecular attack of the pendant enol on the palladium complex olefin of intermediate **A**, followed by loss of HCl to form the palladium cyclohexyl intermediate **B**. Deuterium labelling studies suggest that palladium undergoes successive β-hydride elimination and insertion steps to generate intermediate **C** (Equations 5-7).[21] Furthermore, it is believed that the HCl generated in the first step re-enters the catalytic cycle, and facilitates proto-demetalation of intermediate **C** to re-generate the catalyst **3** and release **2** (Scheme 8).[21]



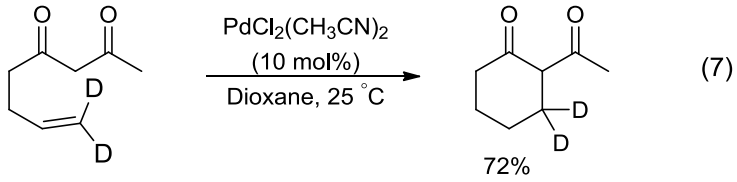
Scheme 8: Plausible catalytic cycle for the cyclization of oct-7-ene-2,4-dione to 2-acetylcyclohexanone, adapted from ref 21.



(5)

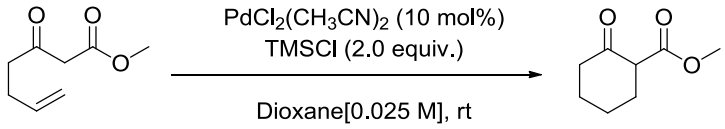


(6)



(7)

In addition to β-diketones, alkenyl β-keto esters can also undergo cyclization in the presence of $PdCl_2(MeCN)_2$ (Equation 8). However, by comparing the pK_a values it is obvious that alkenyl β-keto esters (pKa of 14.2 in DMSO at room temperature) are significantly less reactive than β-diketones (pKa of 13.3 in DMSO at room temperature).[23, 24] As shown in Scheme 8, the substrate is required to be in the enol form in order to undergo cyclization.[25] The use of TMSCl is therefore essential in this reaction, as this leads to the formation of the silyl enol ether *in situ* from the β-keto ester. This increases the nucleophilicity of the β-keto ester (Equation 8).

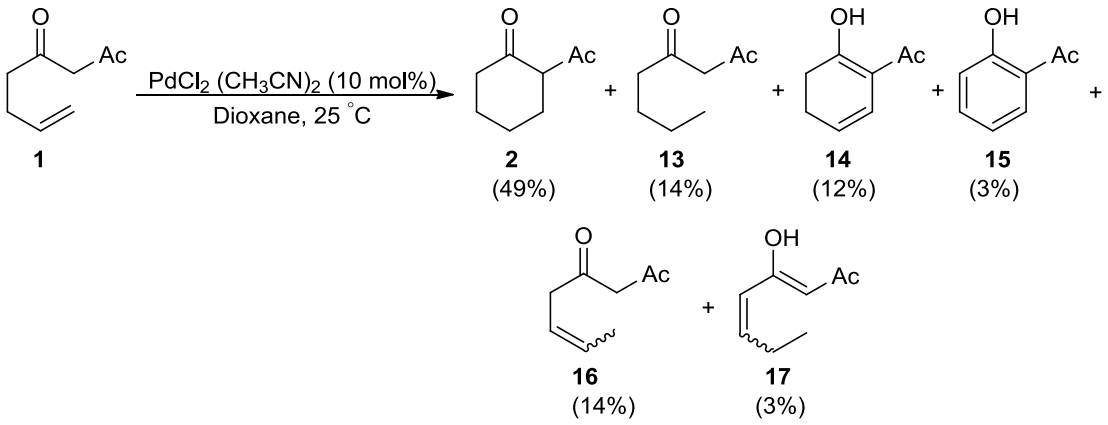


(8)

3 **4**

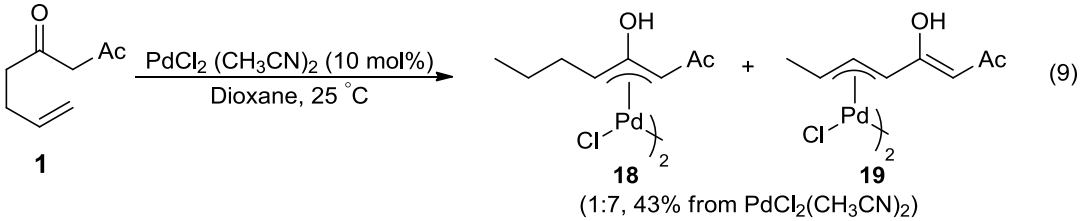
From the studies by Widenhoefer, it was determined that a dilute substrate solution (25 mM) in dioxane, with $PdCl_2(MeCN)_2$ as the catalyst, were the optimal reaction conditions for the conversion of **1** to **2** and **3** to **4**. Low concentrations were found to be critical for high yielding reactions, whereas reactions at high concentration (250 mM) resulted in the formation of undesired byproducts and lower yields (49%) of **2** (Scheme **8**). Detailed studies were conducted by the Widenhoefer group to elucidate the source of byproduct formation for reactions carried out at high concentrations. Initially,

organic byproducts formed at higher concentrations were identified from reaction mixtures by GC analysis. The main byproducts identified were 2,4-octanedione **13**, 2-acyl-1-hydroxy-1,3-hexadiene **14**, and 2-acetylphenol **15**, (E)- and (Z)-6-octene-2,4-dione **16**, and (E)- and (Z)-4-hydroxy-3,5-octadien-2-one **17** (Scheme 9).



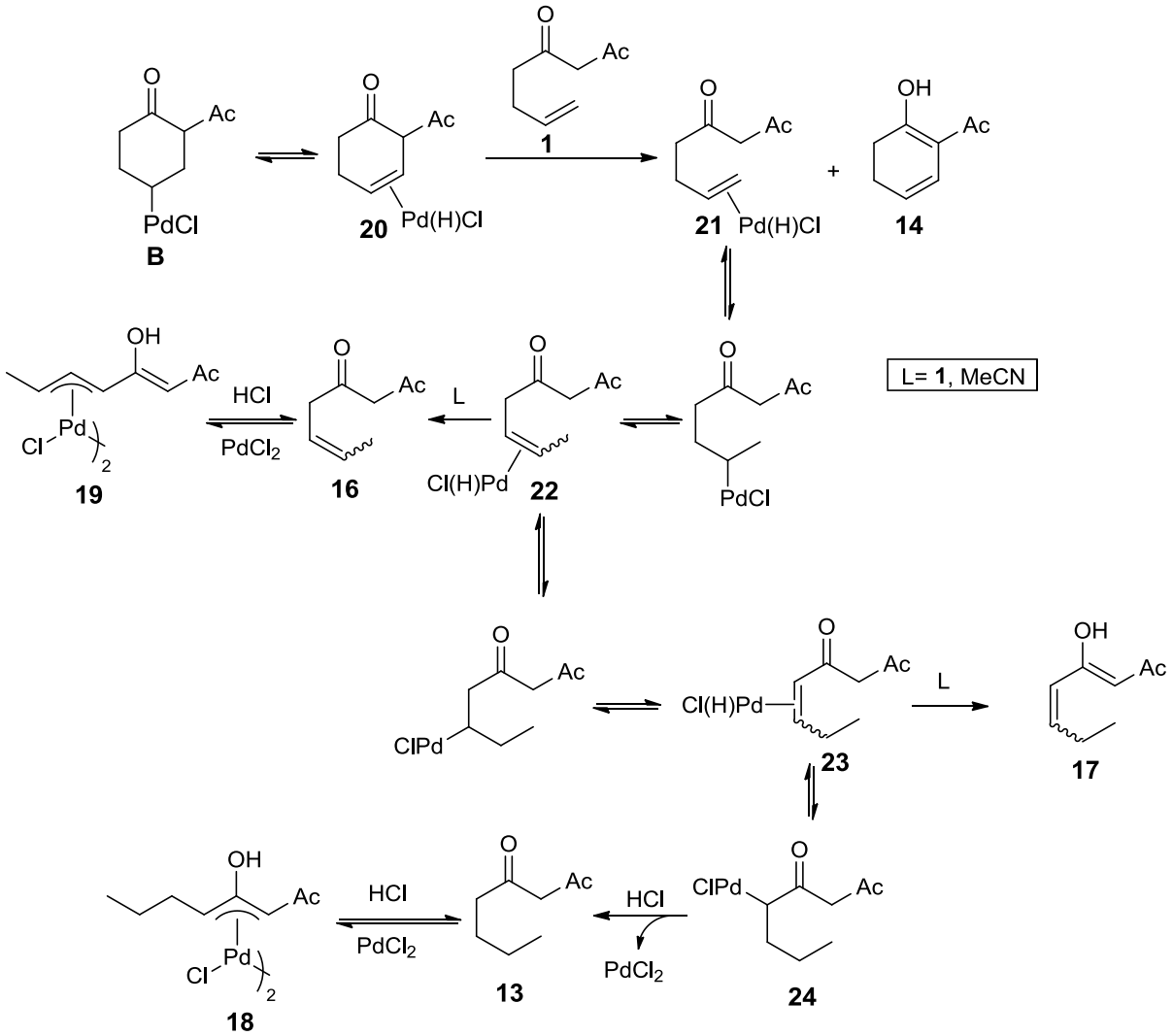
Scheme 9: Characterized products from the reaction of **1** with $PdCl_2(CH_3CN)_2$.

The fate of the organometallic complex was also investigated and two main organopalladium species, **18** and **19** were isolated by addition of pentane to the crude reaction mixture resulting in precipitation of the organopalladium species as yellow powders (Equation 9).



A comprehensive mechanism was proposed to account for the formation of the organic byproducts and unproductive palladium complexes observed in this reaction (Scheme 10). It appears that complex **B** which is an intermediate in the cyclization of oct-7-ene-2,4-dione **1** to 2-acetylcyclohexanone **2** leads to the formation of complex **20**. Formation of complex **20** as an intermediate in the migration of palladium from the C_4 carbon atom of **B** to the C_3 carbon atom is

consistent with the observation of byproduct **14**. Associative olefin displacement from palladium olefin complex **20** with the olefin in starting material **1** would lead to byproduct **14** and palladium complex **21**. In a series of β-hydride elimination and insertion steps complex **21** is converted to palladium complexes **22**, **23**, and **24**. Olefin displacement on intermediates **22**, and **23** would generate byproducts **16** and **17** respectively. Protonation of palladium enolate complex **24** would generate byproduct **13**. Subsequent reaction of the starting palladium complex $PdCl_2(CH_3CN)_2$ with byproducts **13** and **16** would lead to the formation of complexes **18** and **19** respectively. These organopalladium species act as a sink for the palladium since they are very stable to protonolysis.

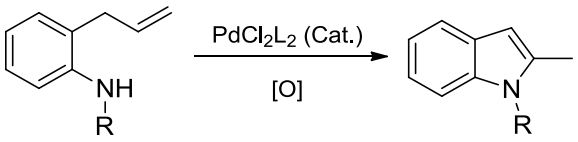


Scheme 10: Mechanism of byproduct formation in cyclization of **1** to **2**.

It is clear from the mechanism that the key step for the deactivation of palladium involves a biomolecular olefin displacement of **20** with olefin **1**, which is concentration dependent. Therefore, at higher concentrations the palladium deactivation pathway is more likely to occur.[26]

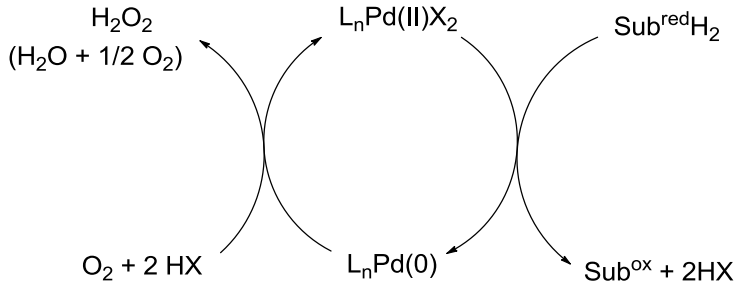
1.5 Palladium catalyzed oxidation reactions

One of the weaknesses of palladium(II) catalyzed reactions is the formation of palladium(0) species which cause an incomplete catalytic cycle. There are two solutions to this problem. A stoichiometric amount of palladium(II) complex could be used which is not practical unless the reaction is performed on a small scale. Another solution is to use an external oxidant to regenerate palladium(II) so that the cycle can continue (Equation 10).



(10)

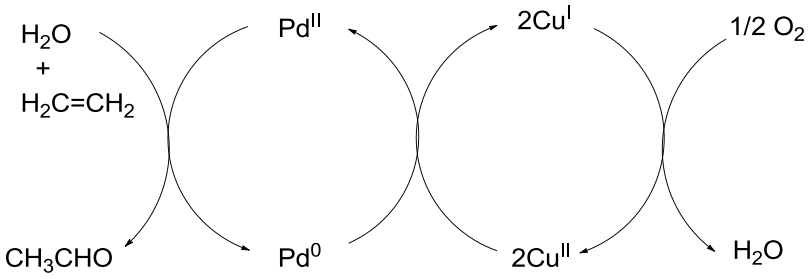
Oxidations are key reactions in organic chemistry and there is currently a demand for more efficient oxidation protocols that have a higher selectivity and are environmentally friendly.[27] Using molecular oxygen is one of the most environmentally friendly ways of performing oxidation reactions. Recently, O_2 has been used as a stoichiometric oxidant in a wide variety of Pd catalyzed reactions.[28] The catalytic cycle for the aerobic oxidation of organic substrates by Pd complexes consists of oxidation by Pd(II) and re-oxidation of palladium(0) back to palladium(II) by O_2 (scheme 11).



Scheme 11: The catalytic cycle of Pd-catalyzed aerobic oxidation reactions.

One of the major problems of using O_2 as the oxidant in Pd catalyzed reactions is a competitive decomposition pathway through Pd-aggregation.[28] As a result, active Pd molecules are converted to an inactive species. Formation of palladium precipitate, palladium black, can be prevented by using ligands that can stabilize the palladium(0) which will be generated during the reaction, additionally electron transfer mediators (ETM's) that can rapidly oxidize palladium(0) back to palladium(II) also inhibit the formation of palladium black. Electron transfer mediators are often transition metal complexes that can oxidize palladium(0) to palladium(II); subsequently, the reduced form of the ETM will be re-oxidized by a stoichiometric amount of an external oxidant. However, in some cases, examined by Stahl, and co-workers, mixing palladium(0) with O_2 resulted in the formation of a catalytically active palladium(II) species.[28]

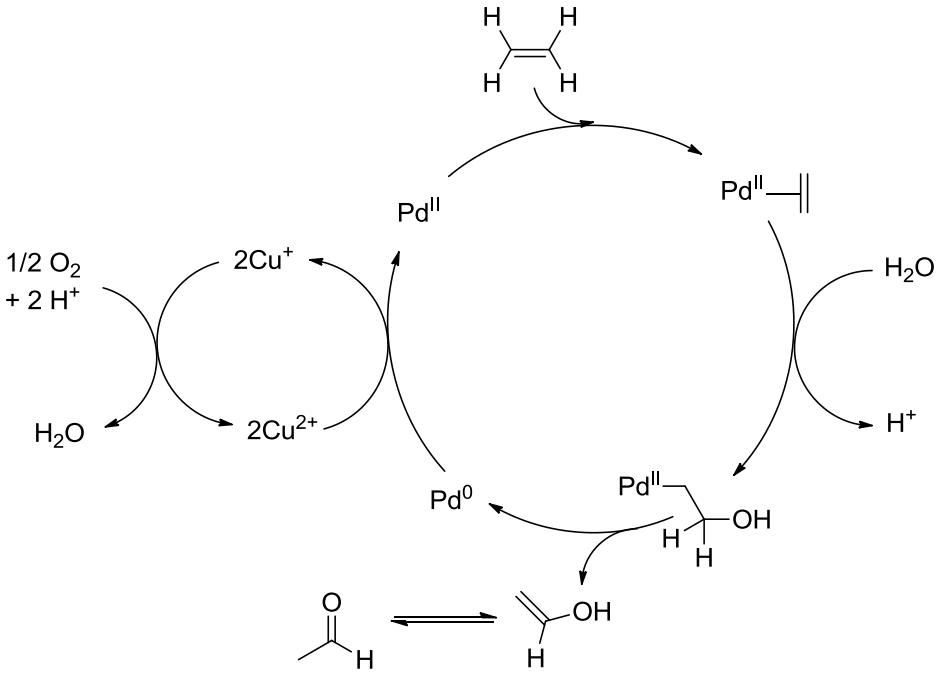
The Wacker reaction[29] illustrates the use of electron transfer mediators. In this reaction, oxygen is used to oxidize palladium(0) back to palladium(II) by using copper as a co-catalyst. Direct oxidation of palladium(0) back to palladium(II) with molecular oxygen mostly fails because of the higher energy barrier of the electron transfer than that for catalyst decomposition. Hence, using $CuCl_2$ as an electron transfer agent can be an effective way to transfer electrons from palladium(0) to molecular oxygen. This is due to the lower energy barrier of electron transfer between palladium and copper and also the ease of electron transfer between CuCl and molecular oxygen (Scheme 12).



Scheme 12: Wacker oxidation process.

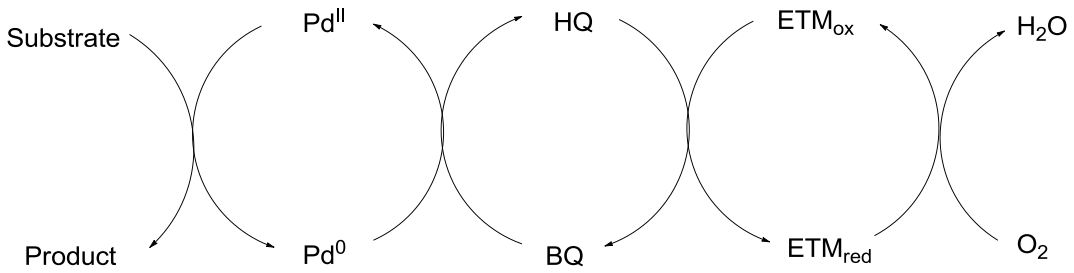
The crucial step in the Wacker reaction is believed to involve nucleophilic attack of a water molecule on a π-bound alkene. This leads to formation of the desired C–O bond. Numerous attempts have

also been made to extend the scope of this reaction to cover the successful formation of various C–C, C–N, and other C–O bonds simply by varying the nucleophile.[30] The formation of C–O bonds in the Wacker reaction occurs *via* attack of a water nucleophile on a Pd-coordinated alkene followed by β-hydride elimination of alkylpalladium species. Re-oxidation of palladium(0) back to palladium(II) occurs in the presence of $CuCl_2$ as a co-oxidant. The reduced CuCl reacts with molecular oxygen and an equivalent of acid produced during the reaction to regenerate the co-oxidant (Scheme 13).

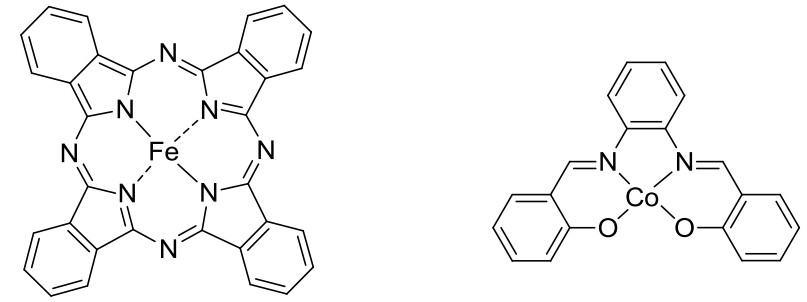


Scheme 13: Catalytic cycle for Wacker reaction.

Quinone is also commonly used as an oxidant in stoichiometric amounts or catalytically in Pd-catalyzed reactions. Since there is a high energy barrier for transferring electrons between hydroquinone and molecular oxygen, the presence of an electron transfer mediator is required if a catalytic amount of quinone is used (Scheme 14).[31] The success of the ETM system is based on stepwise electron transfer cycles with low energy barriers. Therefore employing oxygen-activating catalysts such as Co(salophen), or Iron(II) phtalocyanine (Fe(Pc)) (Figure 2), could indirectly oxidize palladium(0) to palladium(II) in the presence of a catalytic amount of quinone.



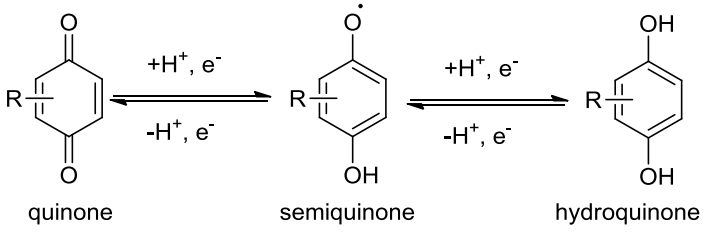
Scheme 14: Aerobic oxidation facilitated by electron transfer mediator (ETM).



Iron(II) phtalocyanine Fe(Pc) Cobalt salophen (Co(slp))

Figure 2: Structures of Fe(Pc) and Co(slp).

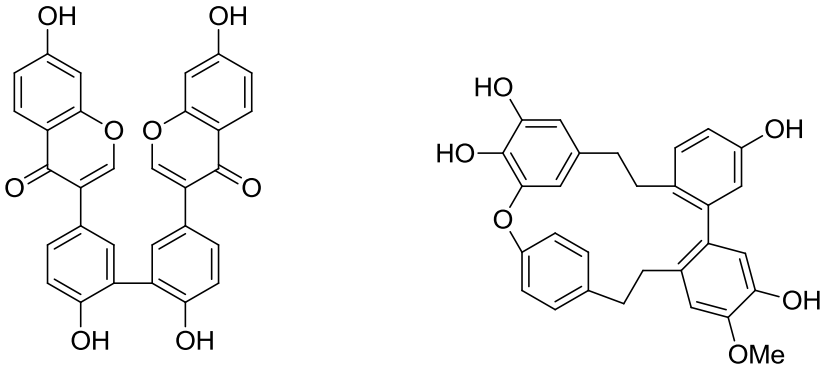
The mechanism for the reduction of quinone involves single electron transfer. Initially fully oxidized quinone is reduced to semiquinone before further reduction leads to the formation of two-electron reduced hydroquinone (Scheme 15).[31]



Scheme 15: Reduction of quinone species.

1.6 The importance of phenols in organic synthesis

Phenols are valuable structural elements found in naturally occurring substrates and drug-like molecules including kuduisoflavone A, and plagiochin B (Figure 3).[32] Due to the presence of phenolic motifs in a number of pharmaceutically active compounds, numerous synthetic methods have been developed for the preparation of substituted phenols.



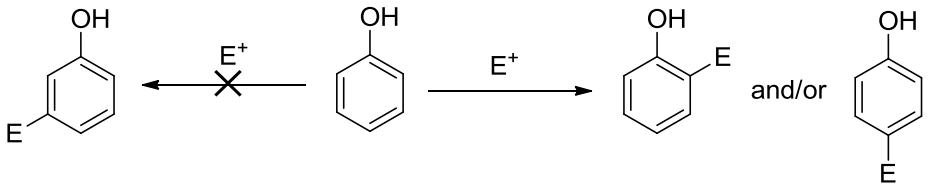
Kuduisoflavone A
(Antibacterial)

Plagiochin B
(Liverwort)

Figure 3: Natural phenolic compounds.

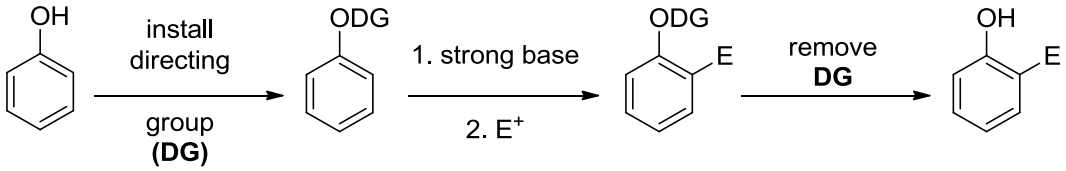
1.7 Common methods for the preparation of substituted phenols

Different methods employed in the preparation of phenol derivatives have been shown to lead to a different pattern of substitution on the ring. Electrophilic aromatic substitution reactions (EAS) are one the most straightforward methods for making *ortho*- and *para*-substituted phenols. Since phenols behave as an enols, they are more reactive than a benzene ring in EAS reactions (e.g. Friedel-Crafts, and bromination).[33] The hydroxyl group on phenol is said to be *ortho*-, and *para*- directing towards electrophiles, however no substitution happens at either *meta*- positions. Furthermore, a mixture of *ortho*-, and *para*- products are observed due to double or triple substitution; this gives rise to mixtures of products which are often not easy to separate (Scheme 16).



Scheme 16: Electrophilic aromatic substitution reaction.

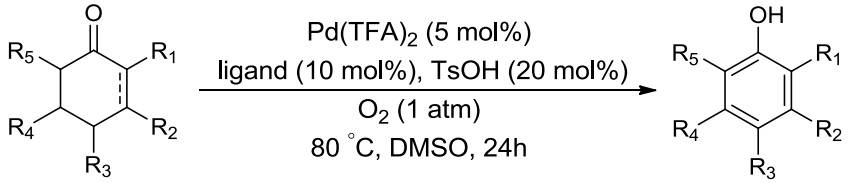
Directed *ortho*-metalation[34] (DOM) is an alternative to electrophilic aromatic substitution, in which the electrophile is added *ortho* to a hydroxyl group. The principle of this reaction involves installation of a directing group (DG), followed by treatment with an alkyllithium reagent, resulting in deprotonation at the position *ortho* to the directing group. Subsequent addition of an electrophile, followed by removal of the directing group, gives rise to an *ortho*-substituted phenol product (scheme 17).[34] Compared to electrophilic aromatic substitution, this reaction has complete regioselectivity. On the other hand, this method is not suitable for the formation of *para*- and *meta*-substituted phenols. Moreover, this reaction requires the installation and removal of a directing group, which might affect the yield of the reaction, and reduce the atom economy.



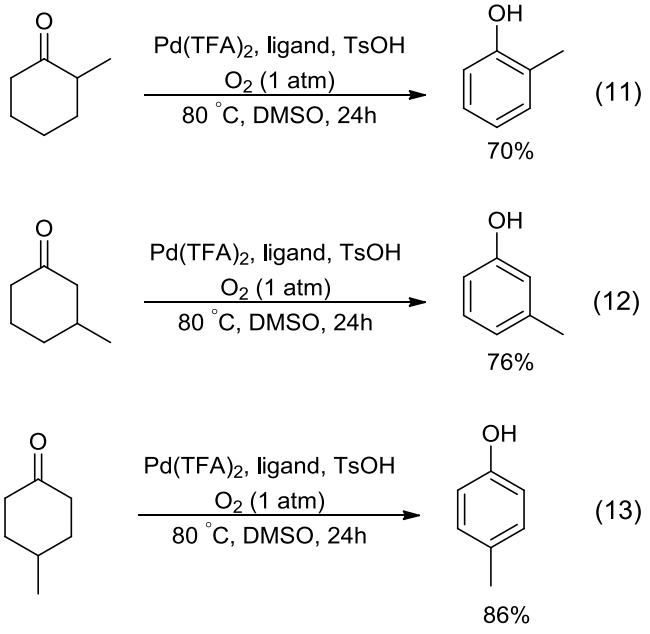
Scheme 17: Directed *ortho*-metallation reaction.

The oxidation of substituted cyclohexanones with palladium has been postulated as an alternative route for the preparation of substituted phenols, which can be substituted at the *ortho, meta* or *para* positions. Stahl and co-workers have investigated the oxidation of cyclohexanones, and cyclohexenones (Scheme 18).[35] Good yields of the substituted phenol could be obtained from 2-methylcyclohexanone, 3-methylcyclohexanone and 4-methylcyclohexanone, respectively (Equations 11, 12, and 13). This method overcomes the limitation of having to install and then subsequently

remove a directing group, as in directed *ortho* metalation (DOM). Another advantage of this strategy is that the substitution pattern in the starting cyclohexanone is carried through to the product. Therefore, this route overcomes the main limitation of electrophilic aromatic substitution reactions where over-substitution at the *ortho* and *para* positions becomes an issue (Equations 11, 12, and 13).

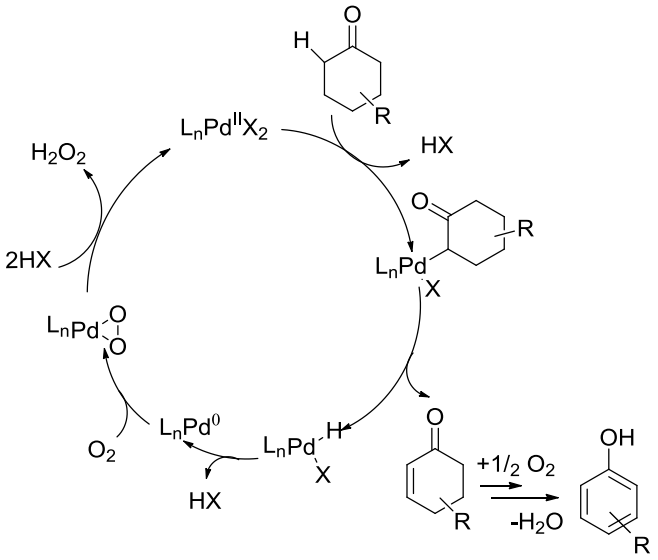


Scheme 18: Palladium-catalyzed aerobic dehydrogenation of cyclic ketones as reported by Stahl.[35]



This reaction involves initial dehydrogenation of cyclohexanone derivatives to cyclohexenone; the initial Pd^{II} catalyst is converted to Pd nanoparticles that catalyze subsequent dehydrogenation reactions to generate the desired phenol product.[15] Scheme 19 shows a plausible catalytic cycle for the mechanism of dehydrogenation of a substituted cyclohexanone. This transformation would

involve palladium insertion followed by β-hydride elimination to give the cyclohexenone and Pd-hydride. Reductive elimination of HX gives palladium(0) which is oxidized to palladium(II) through aerobic oxidation. Cyclohexenone is converted to phenol following the same cycle. This strategy is appealing since molecular oxygen can be used as an external oxidant to oxidize palladium hydride intermediates formed during reaction.

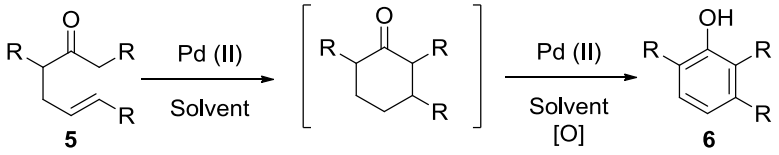


Scheme 19: Proposed mechanism for Pd-catalyzed dehydrogenation of cyclohexanones.

1.8 Proposal

The aim of this project is to find a conceptually different method for the preparation of poly-substituted phenols. In this method, substituents on the phenol can be pre-installed on an acyclic ketone that is then cyclized to give an intermediate cyclohexanone. The cyclohexanone is then oxidized and aromatized to give the desired phenol. Importantly, this methodology overcomes the problems with EAS and DOM, especially in the case of *meta*- substituted phenols, which are hard to make through other means (Section 1.8). We intend to start from γ,δ-unsaturated ketone **5** employing a single palladium catalyst to generate phenol **6** in one pot. We anticipate that through the use of a

single palladium catalyst we can first carry out the cyclization of γ,δ-unsaturated ketone **5**, and then subsequently catalyze the oxidation of the resulting cyclohexanone to a substituted phenol by employing an appropriate oxidant (Scheme 20).



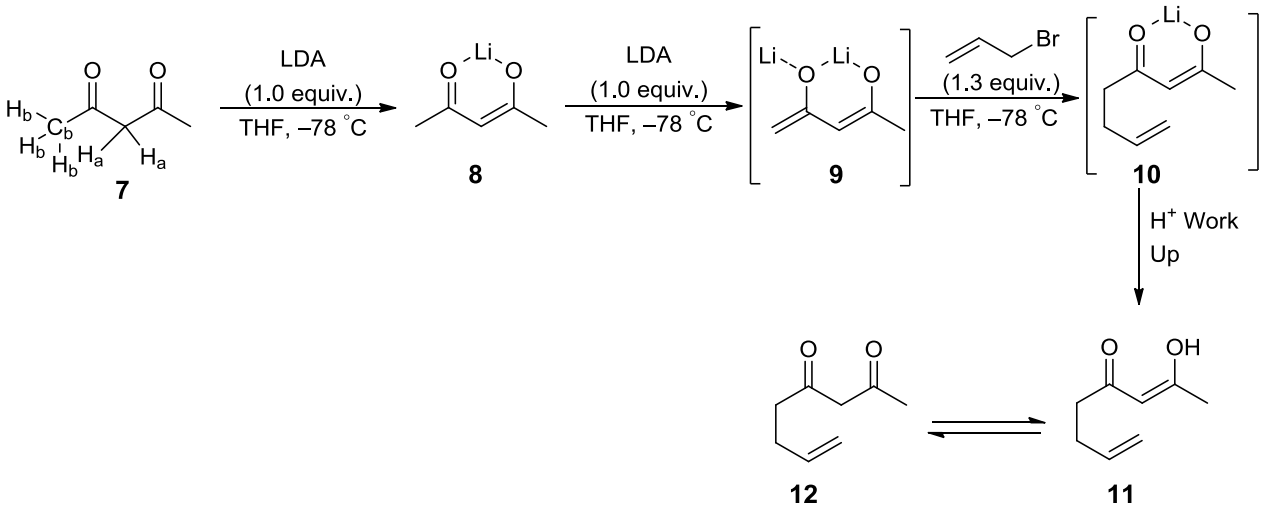
Scheme 20: Palladium catalyzed cyclization and aromatization of acyclic ketone.

Our strategy for developing this reaction was to first identify optimized conditions for the cyclization and aromatization reaction independently employing the same metal catalyst for each of the two-steps, and then combine them in a one-pot process. For the initial cyclization step we intended to re-examine the studies previously conducted by Widenhoefer and coworkers (Scheme 8).[21] In these reports γ,δ-unsaturated ketones were cyclized to give cyclohexanones in the presence of a palladium catalyst. However, the reported reactions were carried out under high dilution conditions (0.025 M), which due to the large quantities of solvent required relative to the reagents are not ideal for large-scale reactions. To address this limitation, we plan to evaluate a number of palladium(II) salts in combination with bidentate nitrogen ligands which we believe will inhibit the formation of the byproducts outlined in Scheme 10. Once we establish the optimal conditions for the cyclization reaction we will next investigate oxidants and reaction conditions for the oxidation step. The Stahl group established the mechanism for aromatization of cyclohexanones to phenols using palladium(II) trifluoroacetate as their palladium source and molecular oxygen as the oxidant (Scheme 19).[35] We plan to aromatize our cyclohexanone derivatives using a similar approach as the Stahl group. Finally, upon determining the optimal conditions for both steps we will conduct the reaction in one pot using a single palladium catalyst to initially cyclize and then aromatize our acyclic ketone.

Chapter 2: Results and discussion

2.1 Preparation of model substrate

To test the proposed palladium-catalyzed cyclization and aromatization of unsaturated ketones we decided to synthesize oct-7-ene-2,4-dione **12** as a model substrate. Substrate **12** was obtained on a gram scale by following the protocol developed by Weiler and coworkers, as shown in Scheme 21.[33] This route relies on the efficient generation of dianion **9** followed by alkylation with allyl bromide. Treatment of diketone **7** with 2 equivalants. of base is required due to the difference in pK_a values between H_a and H_b (11 vs 25). If **7** is treated with 1 equivalent of LDA initial deprotonation occurs at the most acidic position (H_a), which when allylated gives rise to undesired product. In order to avoid this, two equivalents of LDA are required to generate the dianion **9** and obtain allylation at the desired carbon centre (C_b). Gratifyingly, this approach was successful and delivered the model substrate in multi-gram quantities from cheap, commercially available pentane-2,4-dione.

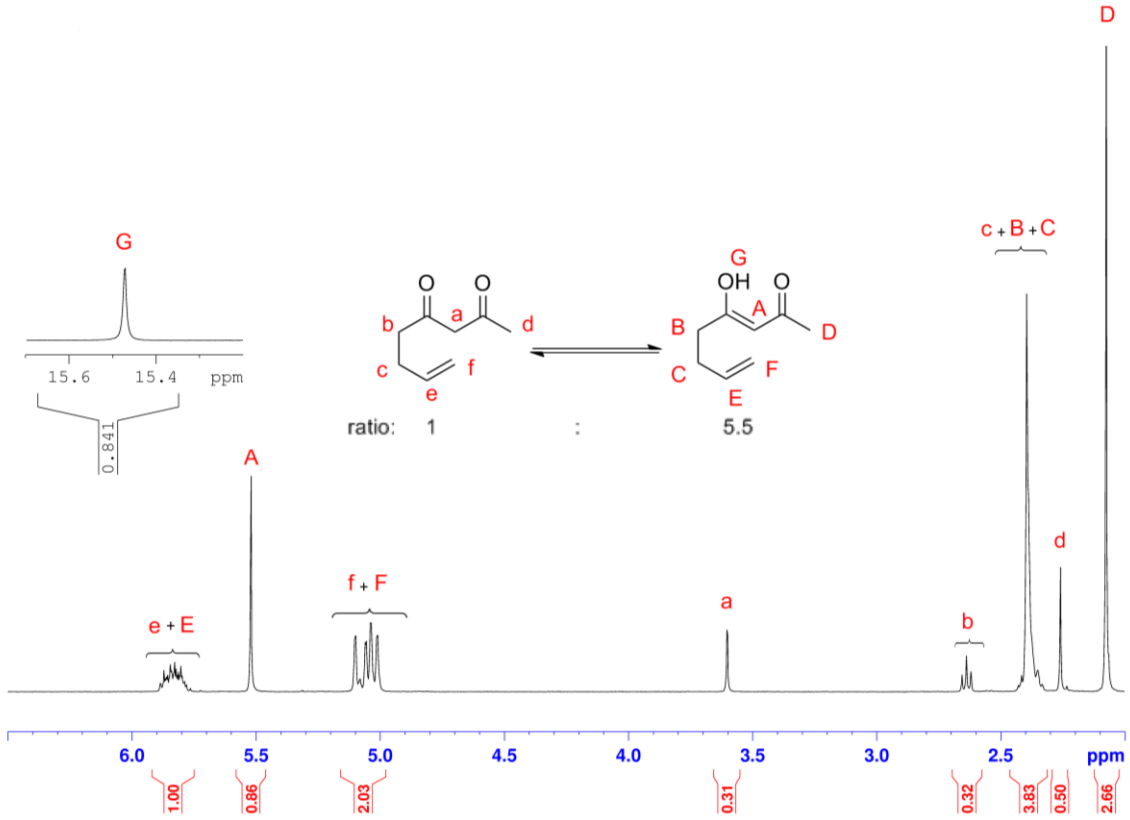


Scheme 21: Synthesis of oct-7-ene-2,4-dione **12**.

Interestingly, the ^{1}H NMR spectrum of **12** shows tautomerization between species **11** and **12**. The ratio of enol to ketone can be easily calculated, and has been shown to be solvent dependent. The ratio of enol to ketone increases in $CDCl_3$ (ketone: enol 1: 5.5) (Figure 4, a); by contrast, switching

the solvent to CD_3CN gives more distinct peaks with a reduced ratio of enol to ketone (ketone: enol 1: 1.4) (Figure 4, b). This result is valuable for the initial cyclization step, as this reaction proceeds *via* the enol tautomer (Scheme 8)

a)



b)

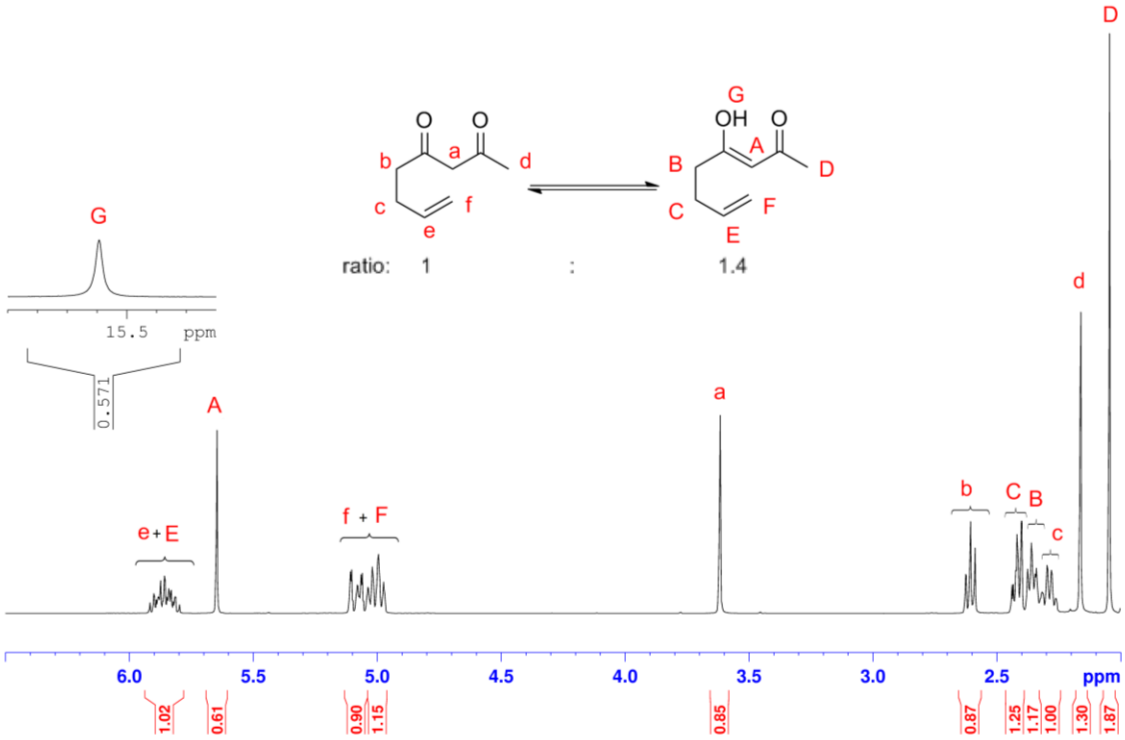
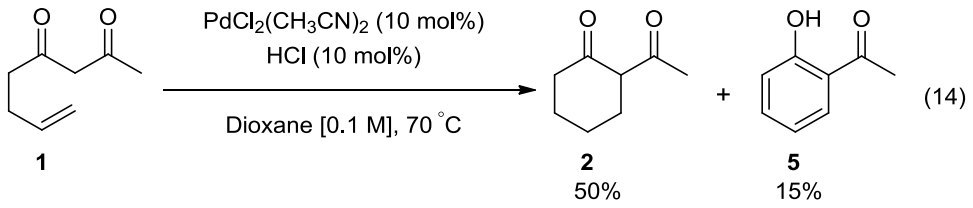


Figure 4: a) ^{1}H-NMR spectrum of compound **12** collected on a 400 MHz spectrometer ($CDCl_3$) and b) ^{1}H-NMR spectrum of compound **12** collected on a 400 MHz spectrometer (CD_3CN).

2.2 Proof of principle experiment

With model substrate **17** in hand, we were eager to test the feasibility of our palladium catalyzed cyclization/aromatization reaction (Equation 14). Initially, bis(acetonitrile)palladium(II)dichloride, was chosen as the palladium(II) source. The reaction was carried out in dioxane at 70 °C in the presence of a catalytic amount of HCl; the reaction was found not to proceed in the absence of HCl (Scheme 8). Purification of the crude mixture furnished two compounds: **2** (50% yield) and phenol **5** (15% yield). Based on these results, we were optimistic that we could increase the yield of desired phenol by optimization of the reaction conditions, which in this case would involve the use of an appropriate oxidant.



2.3 Part I: Palladium-catalyzed cyclization of alkenyl β-diketones

Further to the study of the method developed by Widenhoefer for cyclization of γ,δ-unsaturated ketones (Scheme 8),[21] the next goal of the project was to optimize the reaction conditions. As discussed previously, these reactions required a high catalyst loading and very dilute conditions. It was suggested that formation of an off-cycle, unproductive palladium(II) complex (Scheme 10) was responsible for the lower catalytic activity at higher concentrations. One way to prevent the palladium deactivation problem is to use bidentate ligands, which occupy a free coordination site on palladium with the underlying logic that the chelating bidentate ligands would be unlikely to dissociate completely from the metal centre during the catalytic cycle. As a result, bidentate nitrogen ligands stabilise palladium centre and prevent the formation of byproducts and off-cycle palladium complex at higher concentration (Scheme 10). Furthermore, we intended to use a palladium source with labile ligands so that the bidentate ligand can readily coordinate to the metal. Thus, our first effort was to re-investigate the conditions of the cyclization step using a variety of palladium(II) salts along with bidentate ligands (Table 1).

As a starting point, reactions were carried out under an atmosphere of argon, using a 0.1 M concentration of the substrate. We decided to screen a range of different nitrogen based bidentate ligands with palladium(II) sources, keeping the rest of the conditions identical to those in equation 4. Ligand choice was informed by the requirement to have a ligand that wouldn't interfere with the subsequent aromatization step. Since the goal of this project was to carry out both cyclization and aromatization in one pot, the same source of Pd (II) species was going to be used for both reaction processes. As previously discussed in section 1.3 using strong σ-donor ligands such as phosphines

is not appropriate due to the second step of the reaction involving oxidation chemistry. As a result, we sought to use bidentate nitrogen ligands instead of phosphine ligands. Initial experiments (Table 1, entries 1-4) revealed that none of the palladium catalysts screened were effective at room temperature in dioxane with any of the bidentate ligands we employed (Figure 5). Since no reaction occurred at room temperature, we decided to increase the reaction temperature to 70 °C. Under these conditions $PdCl_2(CH_3CN)_2$ proved to be a more effective catalyst than $Pd(OAc)_2$, $Pd(NCMe)_2(OTs)_2$, or $Pd(TFA)_2$ (see Table 1, entry 8). Among the ligands tested only 2,2'-pyridil (L_1) led to formation of product (Table 1, entry 8). However, using an excess (20 mol%) amount of ligand (L_1) inhibits formation of the desired cyclohexanone derivative (Table 1, entry 10). Since L_1 is the most effective ligand we carried out further screening experiments with this ligand-metal combination.

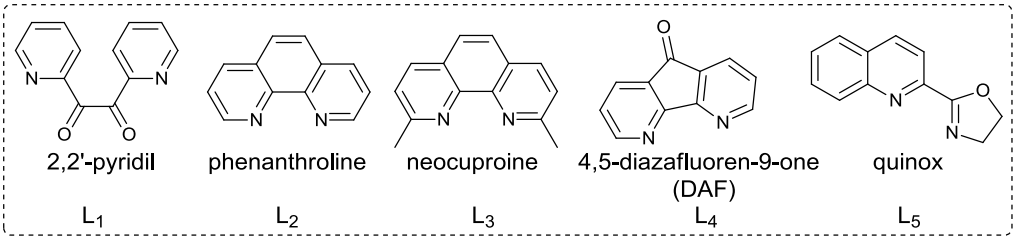
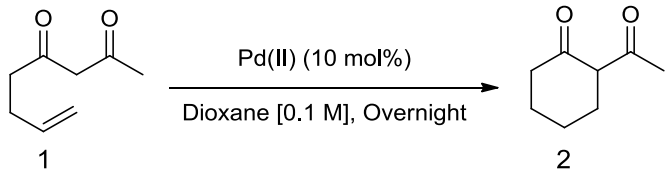


Figure 5: Bidentate ligands employed.

Table 1: Optimization of reaction conditions – Palladium and ligand screen.[a]



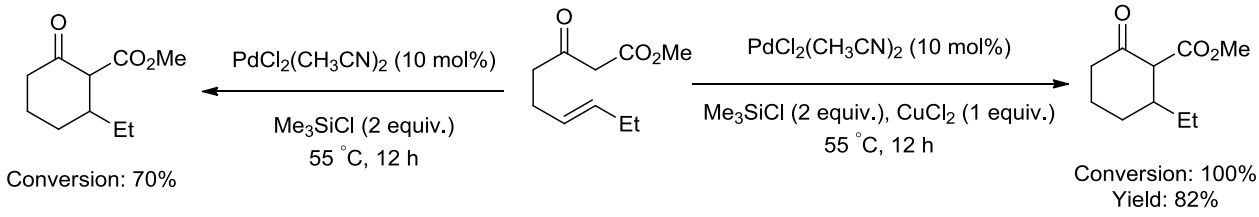
1 2

Entry	Pd(II)	Ligand[b]	Temperature (°C)	Yield (%)
1	$PdCl_2(CH_3CN)_2$	----, L_1, L_2, L_3, L_4, L_5	rt	0
2	$Pd(NCMe)_2(OTs)_2$	----, L_1, L_2, L_3, L_4, L_5	rt	0
3	$Pd(TFA)_2$	----, L_1, L_2, L_3, L_4, L_5	rt	0
4	$Pd(OAc)_2$	----, L_1, L_2, L_3, L_4, L_5	rt	0
5	$Pd(NCMe)_2(OTs)_2$	----, L_1, L_2, L_3, L_4, L_5	70	0
6	$Pd(TFA)_2$	----, L_1, L_2, L_3, L_4, L_5	70	0
7[c]	$PdCl_2(CH_3CN)_2$	----, L_1, L_2, L_3, L_4, L_5	70	0
8[d]	$PdCl_2(CH_3CN)_2$	L_1	70	10
9	$Pd(OAc)_2$	----, L_1, L_2, L_3, L_4, L_5	70	0
10[e]	$PdCl_2(CH_3CN)_2$	L_1	70	0

a) Unless stated otherwise, all reactions have been carried out under argon atmosphere with Pd (II) (10 mol%), 10 mol% of the ligand in 0.1 M of solvent overnight. b) Either 5 mol% or 10 mol% of L_1 was used, c) 10 mol% of L_1 was used, d) 5 mol% of L_1 was used, e) 20 mol% of ligand was used.

Considering that the conditions developed previously by Widenhoefer [21] involved high dilution with respect to the substrate (Equation 4) we subsequently shifted our efforts towards optimizing the yield of our reactions whilst increasing the concentration of the ene-dione **1**. As the substrate is required to be in the enol form in order to undergo cyclization (Scheme 8), we decided to employ additives in order to increase formation of the enol tautomer. Therefore, we decided to explore a combination of

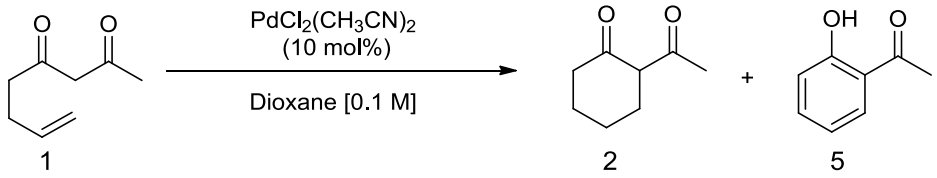
HCl [4 M, in dioxane] and $CuCl_2$ using the same conditions that Widenhoefer and co-workers employed.[36] In these reactions, HCl was used as a Brønsted acid to increase the formation of the enol tautomer relative to the ketone, which in turn should result in higher conversion and higher yields of the desired product. Additionally, the exact role of $CuCl_2$ in this reaction is at present not fully understood however there are similar examples in which $CuCl_2$ is used as an oxidant to prevent palladium decomposition that might occur at higher temperature by oxidizing it (Scheme 22).[37]



Scheme 22: $CuCl_2$ effect on cyclization of unsaturated keto ester.

We speculate that it might be possible that in our case $CuCl_2$ acts as a Lewis acid. Interestingly, in our reaction full consumption of substrate **1** was observed (as determined by ^1H NMR spectroscopy of the crude reaction mixture) when 0.3 equivalents of $CuCl_2$ were used in combination with a catalytic amount of HCl [4 M, in dioxane] (Table 2, entry 1). However, the isolated yield was only 65%, with the rest of the material being unidentified side products. The same result was observed in the absence of ligand (Table 2, entry 2). However, a lower yield was observed when $CuCl_2$ was used in the absence of HCl [4 M, in dioxane] (Table 2, entry 3). Attempts to carry out the reaction at room temperature resulted in recovery of the starting material (Table 2, entry 4). As Table 2 indicates, the loading of $CuCl_2$ could be reduced from 30 mol% to 10 mol% without a significant decrease in conversion or yield of the reaction (Table 2, entries 1, and 5). Moreover, it was found that the same yield could be obtained without the use of a bidentate ligand, 2,2'-pyridil (L_1) (Table 2, entry 6) so it was decided not to use any ligand for this reaction in further screening experiments. Additionally, it was observed that the fully aromatized product could also be obtained, albeit in low yield, using these reaction conditions.

Table 2: Optimization of reaction conditions – Additives screen.[a]

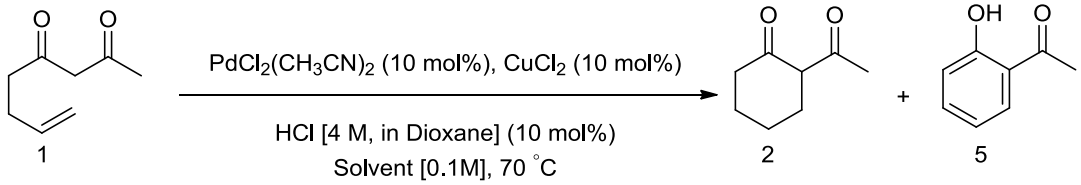


Entry	HCl (mol%)	$CuCl_2$ (mol%)	Ligand[b]	Temperature (°C)	Time (h)	Conversion[c] (%)	Yield[d] 2 : 5 (%)
1	10	30	L_1	70	15	100	50 : 15
2	10	30	-----	70	15	100	51 : 15
3	------	30	L_1	70	20	95	39 : 10
4	10	30	L_1	r.t.	20	0	-----
5	10	10	L_1	70	15	100	51 : 15
6	10	10	-----	70	15	100	53 : 16

a) Dioxane [0.1 M], $PdCl_2(CH_3CN)_2$ (10 mol%.), 70 °C, 15 or 20h, b) 5 mol% of L_1 was used, c) Conversion is based on consumption of substrate in crude ^{1}H-NMR spectroscopy. d) Isolated yield.

In an effort to combine the palladium catalyzed cyclization and aromatization processes, we next investigated conditions that would enable us to carry out the two steps in a one-pot procedure. A solvent screen was conducted using a catalytic amount of HCl [4 M, in dioxane] and $CuCl_2$ as additives under otherwise identical reaction conditions (Table 3, entry 6). The use of more polar solvents like DMF and DMSO (Table 3, entries 3 and 4) did not give any cyclic product **2**. A small increase in the yield of **2** was achieved using toluene, however the yield of phenol **5** decreased from 15 % to 5 % (Table 3, entry 2).

Table 3: Optimization of reaction conditions – Solvent screen.[a]

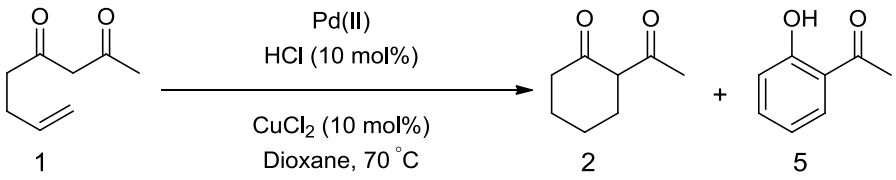


Entry	Solvent	Time (h)	Conversion[b] (%)	Yield[c] 2 : 5 (%)
1	Dioxane	15	100	53 : 16
2	Toluene	15	100	60 : 5
3	DMF	20	0	-----
4	DMSO	20	0	-----

a) All reactions have been carried out under argon atmosphere with $PdCl_2(CH_3CN)_2$ (10 mol%), HCl[4 M in dioxane] (10 mol%), $CuCl_2$ (10 mol%), in 0.1 M of solvent overnight. b) Conversion is based on consumption of substrate in crude ^{1}H-NMR spectroscopy. c) Isolated yield.

Attempts were then made to lower the catalyst loading in order to improve reaction efficiency. Decreasing the catalyst loading from 10 mol% to 1 mol% did not have a significant impact on the yield of the reaction or alter the product ratio (Table 4, entry 2). Additionally, a control experiment run in the absence of a Pd catalyst confirms that palladium is crucial for the reaction to proceed as no detectable cyclization product was observed after 20 h (Table 4, entry 3). A 1 mol% loading of $PdCl_2(CH_3CN)_2$ was found to be the optimum amount of catalyst giving the highest yield of cyclohexanone **2** and phenol **5**. It is important to note that phenol derivative **5** was still observed even at low catalyst loading.

Table 4: Optimization of reaction conditions – Catalyst loading.[a]

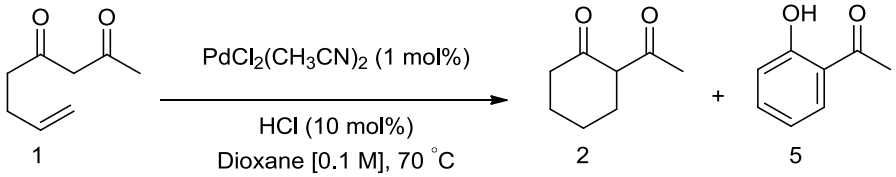


Entry	$PdCl_2(CH_3CN)_2$ (mol%)	Time (h)	Conversion[b] (%)	Yield[c] 2 : 5 (%)
1	10	15	100	53 : 16
2	1	15	100	52 : 15
3	-----	20	0	-----

a) All reactions have been carried out under argon atmosphere with Pd (II) (X mol%), HCl[4 M in dioxane] (10 mol%), $CuCl_2$ (10 mol%), in 0.1 M of solvent overnight. b) Conversion is based on consumption of substrate in crude ^{1}H-NMR spectroscopy. c) Isolated yield.

Next, we decided to decrease the amount of $CuCl_2$. Interestingly, we found that this reaction does not require the addition of $CuCl_2$ to proceed. In fact, the same yield could be obtained without $CuCl_2$ (Table 5, entry 2).

Table 5: Optimization of reaction conditions – $CuCl_2$ loading.[a]



Entry	$CuCl_2$ (mol%)	Conversion[b] (%)	Yield[c] 2 : 5 (%)
1	10	100	52 : 15
2	------	100	48 : 15

a) All reactions have been carried out under argon atmosphere with Pd (II) (1 mol%), HCl[4 M in dioxane] (10 mol%), in 0.1 M of solvent overnight. b) Conversion is based on consumption of substrate in crude ^{1}H-NMR spectroscopy. c) Isolated yield.

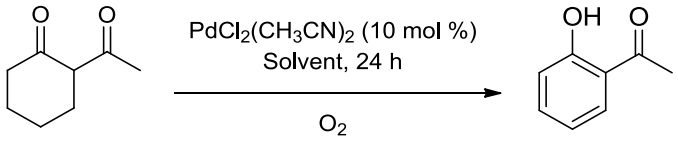
With the initial cyclization step optimized, we then went on to examine conditions for the aromatization reaction using $PdCl_2(MeCN)_2$ as the palladium source.

2.4 Part II: Synthesis of phenols from acyclic substrates

In order to establish the conditions required to be able to carry out both cyclization and aromatization in one-pot, we chose to explore the aromatization step in isolation from the cyclization reaction, using the same catalyst. A number of different oxidants and solvent systems were screened for their effectiveness in the aromatization of 2-acetylcyclohexanone.

When conducting the aromatization reaction under catalytic conditions, the introduction of an oxidant to the system is required in order to regenerate the palladium catalyst. As a starting point, reactions were carried out under an atmosphere of molecular oxygen. Oxygen was the oxidant of choice because of its ease of use and environmentally benign nature. However, oxidation of 2-acetylcyclohexanone under O_2 pressure at 80 °C in dioxane failed to produce *o*-acetylphenol (Table 6, entry 1). Increasing the temperature to 100 °C also did not lead to any of the desired product (Entry 2). Additionally switching the solvent from dioxane to toluene did not result in desired product formation (Entry 3 and 4). It became apparent that our palladium source is not able to transfer electrons to oxygen directly. These results indicate that the use of a co-oxidant other than O_2 is essential in this process.

Table 6: Optimization of reaction conditions – Solvent screen.[a]

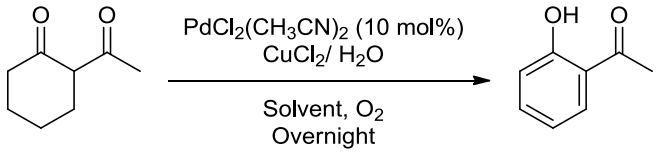


Entry	Solvent	Temperature (°C)	Yield (%)
1	Dioxane	80	0
2	Dioxane	100	0
3	Toluene	80	0
4	Toluene	100	0

a) All reactions have been carried out under oxygen atmosphere with $PdCl_2(CH_3CN)_2$ (10 mol%), in 0.1 M of solvent.

The use of $CuCl_2$ as an electron transfer mediator (ETM), analogous to the Wacker oxidation, was also investigated (refer to section 1.6 in introduction). However, extensive efforts to synthesize aromatized products through the Wacker process, wherein different ligands, solvents, additives, and reaction temperatures were evaluated, ultimately did not lead to desired product (Table 7, entry 1, 2 and 3). Even the use of a stoichiometric amount of $CuCl_2$ only resulted in 10 % conversion (see Table 7, entry 4). The formation and stabilization of palladium nanoparticles, which might be generated in our reaction, may be facilitated by the ligand, reaction solvent or other additives. Ammonium salts, strong acids, solvents with high dielectric constants (e.g. DMSO), and Lewis bases such as sulfoxides,[15,39] are known to promote the formation and stabilization of Pd nanoparticles. Therefore, we chose to use a mixture of DMSO/dioxane in order to generate and stabilize Pd nanoparticles formed in our reaction; moreover, the high boiling point of DMSO allowed us to carry out the reaction at a higher temperature. However, no product was observed by employing a DMSO/1,4-dixoane (1:1) solvent system under a positive oxygen pressure (Entry 5, table 7). A mixture of dioxane/ethylene glycol was also not productive (Entry 6). The use of additives such as anthraquinone-2-sulfonic acid sodium salt (AMS), commonly used as a means of generating palladium nanoparticles, does not lead to formation of the desired product (Entry 7).

Table 7: Optimization of reaction conditions – Solvent screen.[a]

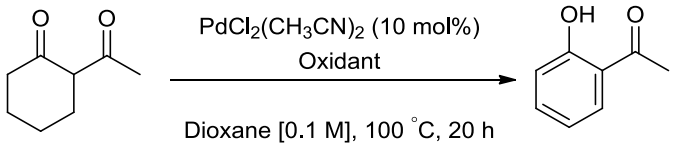


Entry	$CuCl_2$ (equiv.)	Additives (equiv.)	Solvent	Temperature (°C)	Product (%)
1	0.1	----	Dioxane	80	N.R.
2	0.1	----	Toluene	110	N.R.
3	0.1	----	Acetonitrile	80	N.R.
4	1.0	----	Dioxane	100	10[c]
5	0.1	----	Dioxane: DMSO (1:1)	110	N.R.
6	0.1	----	Dioxane: Ethylene glycol (1:1)	90	N.R.
7	----	AMS[b] (0.09)	Dioxane	80	N.R.
8	----	AMS[b] (0.09)	Dioxane: DMSO (1:1)	80	N.R.

a) All reactions have been carried out under oxygen atmosphere with $PdCl_2(CH_3CN)_2$ (10 mol%), in 0.1 M of solvent. b) AMS= Anthraquinone-2-sulfonic acid sodium salt. c) Isolated yield.

The Wacker oxidation process also did not facilitate the reoxidation of Pd^0, so cheap and commercially available benzoquinone derivatives were investigated as oxidants in our system. The selection of quinone as an oxidant for palladium is based on the fact that quinones are well-known oxidants and electron carriers in palladium-catalyzed oxidation reactions (refer to section 1.6 in the introduction). First, we examined 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as an ETM.[31] When 1.1 equivalents of DDQ was used in the reaction at 100 °C (Table 8, entry 1), incomplete conversion of 2-acetylcyclohexanone to 2-acetylphenol was observed. Similarly, the reaction in the presence of diisopropyl azodicarboxylate (DIAD) gave only 25% conversion after 24 hours (Table 8, entry 2). A similar result was observed when benzoquinone (BQ) was used as an oxidant (Table 8, entry 3). Improved results were obtained by using tetrachloro-1,4-benzoquinone where a conversion of 54% was observed; however, the isolated yield of the reaction was only 30% (Table 8, entry 4). Attempts to use molecular oxygen in tandem with the quinone oxidant failed to increase the yield of the reaction (Table 8, entry 5). The use of silver carbonate as an oxidant also failed to give the desired phenol product (Table 8, entry 6).

Table 8: Optimization of reaction conditions – Oxidant screen.



Entry	Oxidant (equiv.)	O_2	Conversion[b] (%)
1	DDQ(1.1)	--	43
2	DIAD (1.1)	--	25
3	BQ (1.1)	--	38
4	Chloranil (1.1)	--	54 (30)[a]
5	Chloranil (1.0)	✓	55 (30)[a]
6	Ag_2CO_3 (1.5)	✓	No product observed

a) Isolated yield. b) Conversion was determined by crude ^{1}H-NMR spectroscopy.

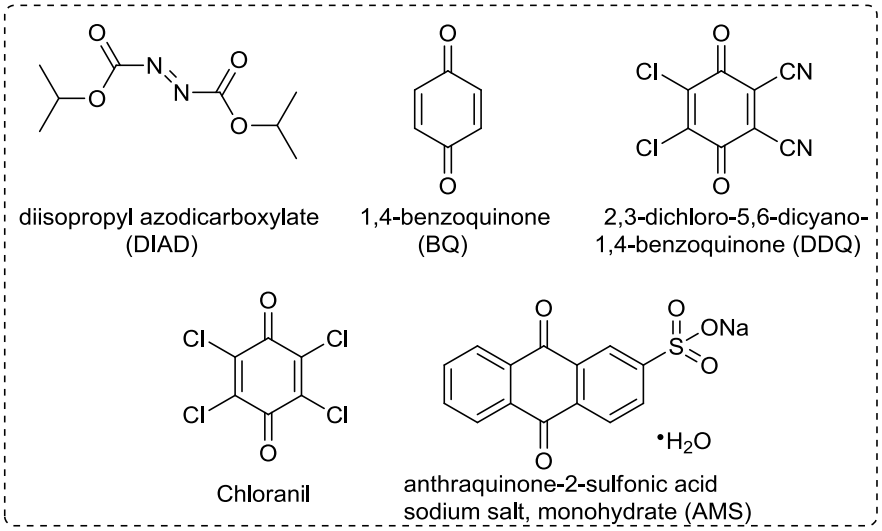
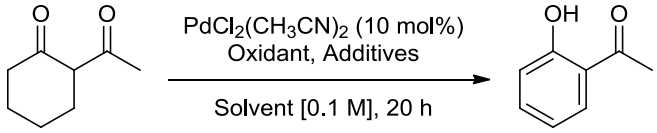


Figure 6: Structures of oxidants and additives.

Based on these results, we decided to increase the amount of oxidant used. The best results were obtained by using 2 equivalents of chloranil, in which full conversion was observed and a good isolated yield of 68 % was obtained (Table 9, entry 1). As a means of reducing the amount of oxidant employed, we screened a number of different quinone and metal co-catalyst systems that had previously been used for the re-oxidation of Pd^0 using O_2 as terminal oxidant.[31] Since it is not possible to directly re-oxidize the hydroquinone formed with molecular oxygen, we lowered the

amount of tetrachloro-1,4-benzoquinone to ~0.5 equivalents and used an additional ETM as a co-oxidant to re-oxidize the hydroquinone formed during the reaction. Iron(II) phtalocyanine (Fe(Pc)) and cobalt salophen (Co(Slp)) were investigated as ETM's, with the reactions carried out under O_2 pressure. Unfortunately, all of our efforts to find a system in which we could use a catalytic amount of tetrachloro-1,4-benzoquinone in the presence of a co-oxidant failed to give the aromatized product in acceptable yield (Entry 2, 3, 4, and 6). Addition of acetic acid as a 1:1 co-solvent with dioxane was found to significantly increase the overall conversion by solubilizing the Iron(II) phtalocyanine; however, a yield of only 30% was observed (Entry 5).

Table 9: Optimization of reaction conditions – Oxidant loading.



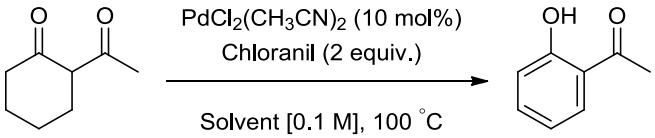
Entry	Oxidant (equiv.)	Additives (equiv.)	temperature (°C)	O_2	Solvent	Conversion[a] (%)	Yield[b] (%)
1	Chloranil (2.0)	------	100	--	Dioxane	100	68
2	BQ (0.4)	Fe(Pc) (0.1)	r.t	✓	Dioxane	-----	0
3	BQ (0.4)	Fe(Pc) (0.1)	80	✓	Dioxane	-----	0
4	Chloranil (0.1)	Fe(Pc) (0.1)	100	✓	Dioxane	-----	0
5	Chloranil (0.4)	Fe(Pc)[c] (0.1)	100	✓	Dioxane: AcOH (1:1)	100	30
6	Chloranil (0.4)	Co(Slp)[c] (0.2)	100	✓	Dioxane: AcOH (1:1)	-----	0

a) Conversion is based on consumption of substrate in crude ^{1}H-NMR spectroscopy b) Isolated yield. c) Fe(Pc) = Iron(II) phtalocyanine, Co(Slp) = cobalt salophen.

With an effective oxidant in hand, the reaction conditions were further optimized by screening different solvents. Since the cyclization reaction works both in dioxane and toluene, we decided to employ the same solvents for the aromatization step. The use of dioxane provided the title compound

in 68% isolated yield (Table 10, entry 1). However, switching the solvent from dioxane to toluene resulted in poor conversion (Table 10, entry 2).

Table 10: Optimization of reaction conditions – Solvent screen.

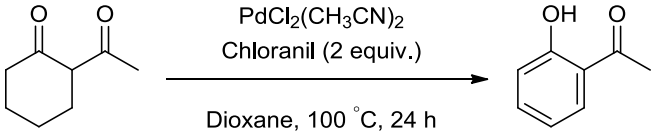


Entry	Solvent	Time (h)	Conversion[a] (%)
1	Dioxane	18	100 (68)[b]
2	Toluene	24	15

a) **)** Conversion is based on consumption of substrate in crude ^{1}H-NMR spectroscopy b) Isolated yield.

Next, we attempted to decrease the catalyst loading. In contrast to the initial cyclization step, running the aromatization reaction with a low loading of $PdCl_2(CH_3CN)_2$ failed to give full conversion (Table 11, entry 2). A control experiment showed that no *o*-acetylphenol was observed in the absence of $PdCl_2(CH_3CN)_2$ which indicates the role of Pd^{II} as a catalyst in the aromatization reaction (Table 11, entry 3).

Table 11: Optimization of reaction conditions – Catalyst loading.



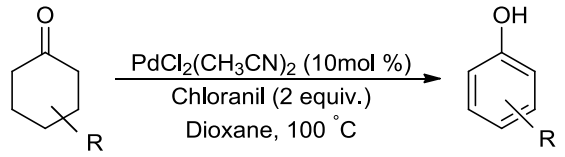
Entry	$PdCl_2(CH_3CN)_2$ (mol%)	Conversion[a] (%)
1	10	100 (68)[b]
2	5	40
3	-----	0

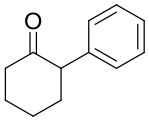
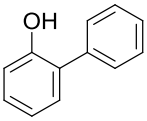
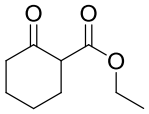
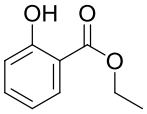
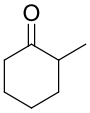
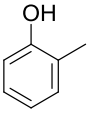
a) **)** Conversion is based on consumption of substrate in crude ^{1}H-NMR spectroscopy. b) Isolated yield.

Upon finding conditions that led to the full conversion of 2-acetylcyclohexanone to the corresponding phenol, we examined different substrates. The yield of the reaction dramatically improved by changing the substrate to 2-phenylcyclohexanone giving an excellent yield of 100% (see Table 12, entry 1). Aromatization of methyl cyclohexanone-2-carboxylate (Table 12, entry 2) also results in an

excellent yield. In contrast, a low yield was observed for aromatization of 2-methylcyclohexanone (Table 12, entry 3).

Table 12: Aromatization of substituted cyclohexanone.

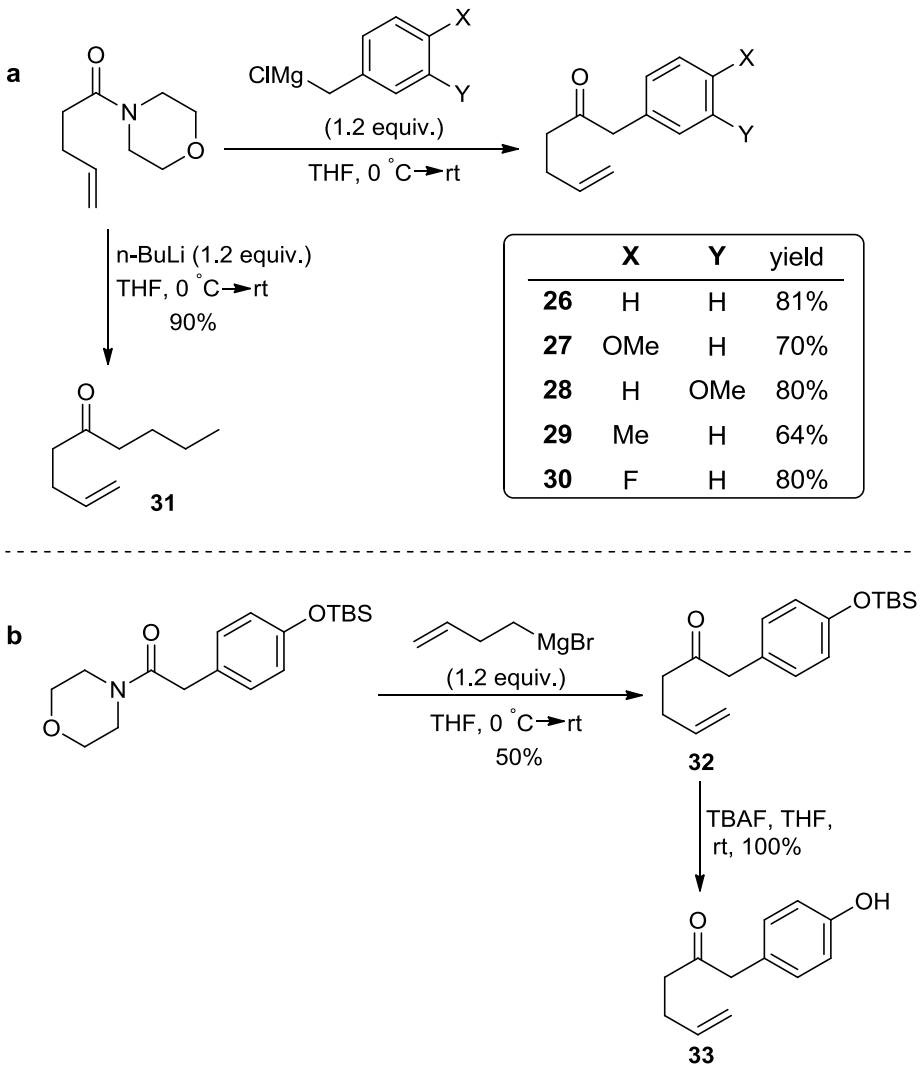


Entry	Cyclohexanone	Phenol	Yield[a]
1			100%
2			95%
3			34%

a) Isolated yield.

2.5 Preparation of acyclic unsaturated ketones

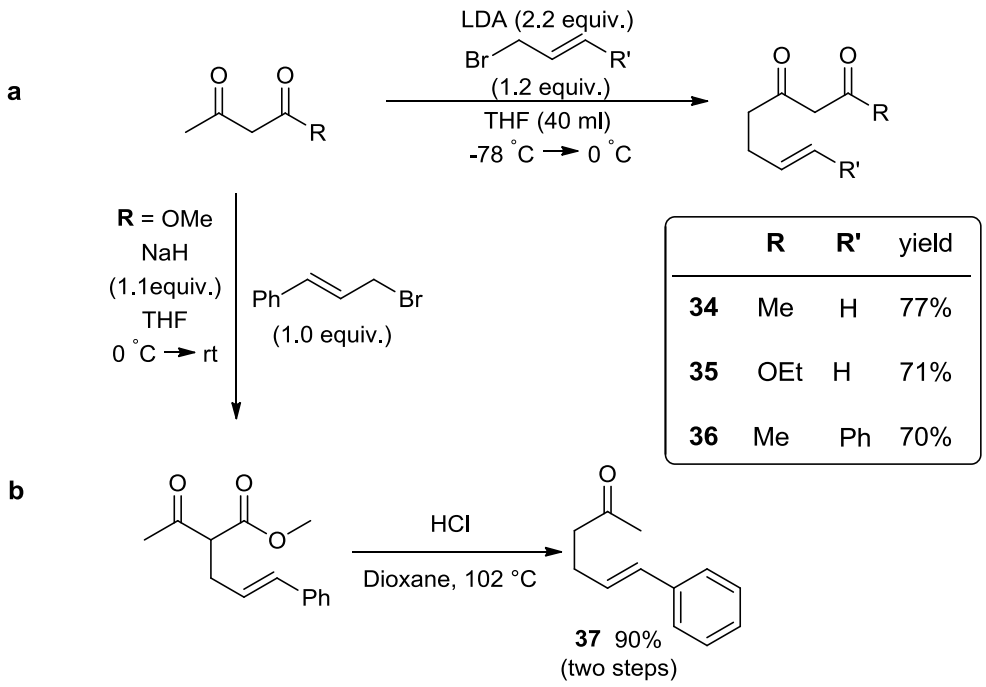
Having identified suitable conditions for the cyclization and aromatization steps, we next prepared a number of substrates that would lead to substituted phenols in a single process. A number of routes to γ,δ-unsaturated ketones were explored including addition of the corresponding Grignard or alkyllithium reagents to morpholine amides (Scheme 23, a, and b).



	X	Y	yield
26	H	H	81%
27	OMe	H	70%
28	H	OMe	80%
29	Me	H	64%
30	F	H	80%

Scheme 23: Strategies for the preparation of substituted γ,δ-unsaturated acyclic ketones **26**-**33**.

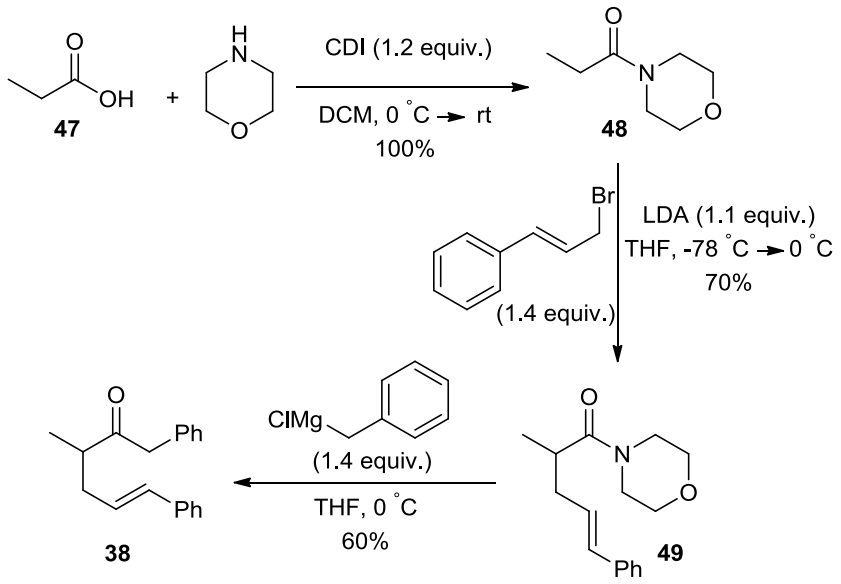
Additionally, unsaturated diketones or β-ketoesters were synthesized by Weiler alkylation of dienolates (Scheme 24, a, substrates 34-36). Similarly, ketone **37** was prepared by alkylation and decarboxylation of β-ketoesters (Scheme 24, b, substrate 37).



	R	R'	yield
34	Me	H	77%
35	OEt	H	71%
36	Me	Ph	70%

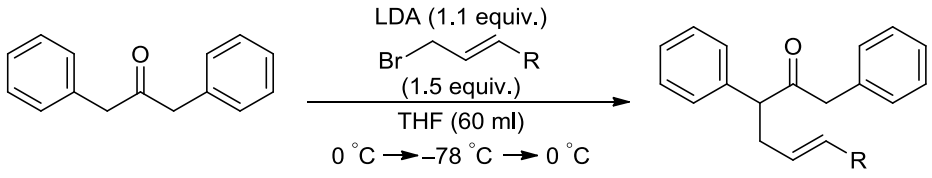
Scheme 24: Strategies for the preparation of substituted γ,δ-unsaturated acyclic ketones **34**-**37**.

Substrate **38** was prepared using a three-step procedure. In the first step, morpholine amide **48** was prepared from propionic acid using CDI and morpholine. **48** was then reacted with LDA and cinnamyl bromide in THF at –78 °C to give substituted morpholine amide **49**. Lastly, addition of the benzylmagnesium chloride to morpholine amide **49**, yielded the desire product (Scheme 25).



Scheme 25: Strategies for the preparation of substituted γ,δ-unsaturated acyclic ketone **38**.

The last two unsaturated ketone substrates were synthesized by deprotonation of diphenylpropanone, followed by addition of an alkyl bromide electrophile (Scheme 26).



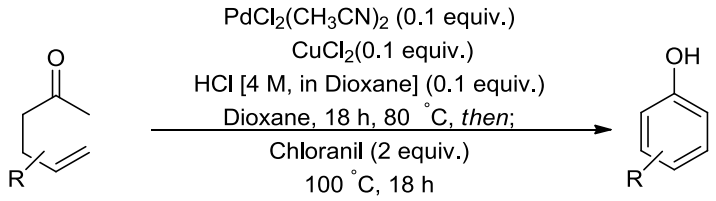
	R	yield
39	H	80%
40	Ph	80%

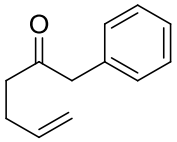
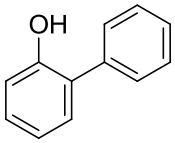
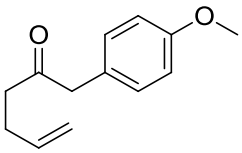
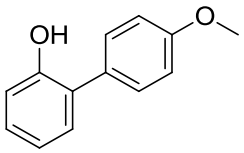
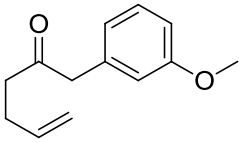
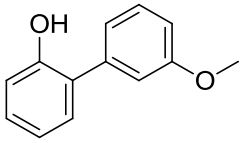
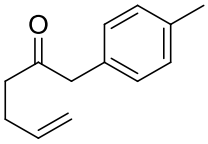
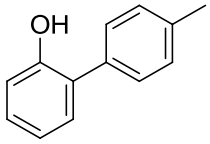
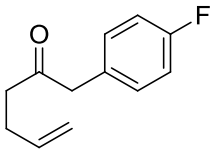
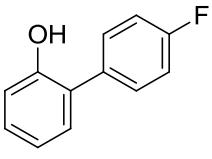
Scheme 26: Strategies for the preparation of substituted γ,δ-unsaturated acyclic ketones **39**, and **40**.

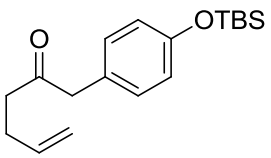
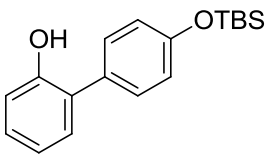
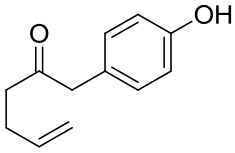
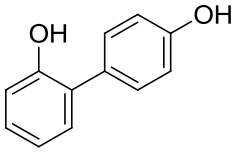
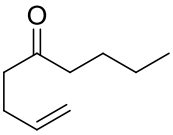
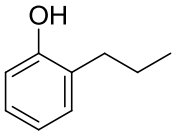
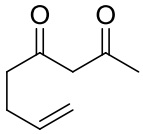
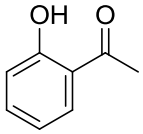
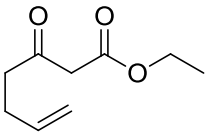
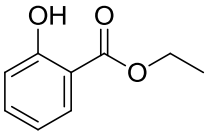
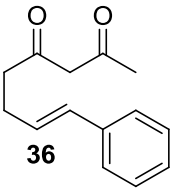
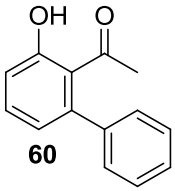
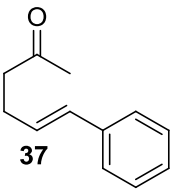
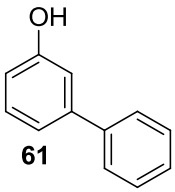
2.6 Scope of reaction

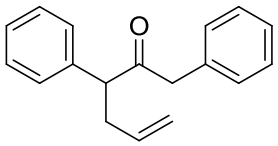
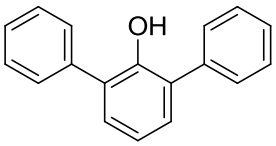
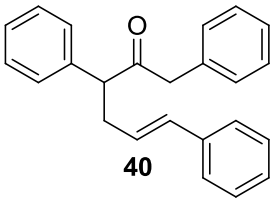
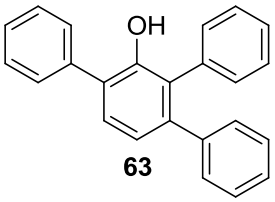
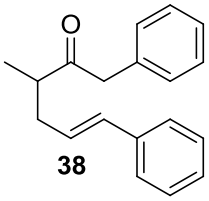
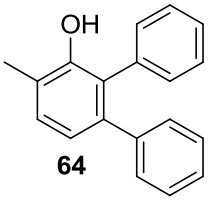
With fifteen substrates in hand, the scope of the reaction was explored next (Table 13). Initially, the cyclization of ethyl 3-oxohept-6-enoate and 1-phenylhex-5-en-2-one was explored (Table 13, entries 1 and 10) using our optimal conditions in section 2.3 (10 mol% $PdCl_2(CH_3CN)_2$ in the presence of HCl [4 M, in dioxane] at 80 °C for 18 h followed by addition of chloranil (2 equiv.) at 100 °C in dioxane for 18 h.). For these substrates the yield of phenol product was low (50% for substrate **26** and 43% for substrate **35**). In order to overcome this, it was found that the addition of $CuCl_2$ significantly increased the reaction yield, contrary to what was observed in our initial optimization studies (Tale 13, entries 1, and 10). In addition to 1-phenylhex-5-en-2-one **26**, a range of functionalized allyl ketones aromatized in the presence of $PdCl_2(CH_3CN)_2$ (10 mol%) to form the desired substituted phenols. A range of unsaturated acyclic ketones with various different aromatic substitutions (Entries 1-7, table 13) were successfully aromatized to form the corresponding phenols in good to excellent yield. These high yields may reflect the fact that a conjugated nucleophilic enol is readily formed prior to cyclization. In contrast, substrate **31** gave low yields of the corresponding phenol under these conditions, and this may reflect the diminished acidity of the ketone, resulting in a low concentration of the enol required for cyclization (Tale 3, entry 8). Furthermore, unsaturated diketone and keto-ester substrates provided the corresponding phenols in moderate yields (Entries 9, 10, and 11) that are consistent with those observed in our optimization experiments. Substrate **37**, bearing a methyl ketone group, allows for the direct formation of a meta-substituted phenol, which would be harder to access. Under the optimized reaction conditions this substrate yields the expected phenol product in modest yield, which might be due to the low concentration of the enol tautomer required for the cyclization step. Finally, substrates **38**, **39**, and **40**, with increased bulk about the carbonyl group can react to give the desired substituted phenols in acceptable yield (see table 13, entries 13, 14, 15).

Table 13: Synthesis of phenols through one-pot cyclization and aromatization.



Entry	Acyclic ketone	Phenol	Yield
1	 **26a** **26b**	 **50**	80% 50%[a]
2	 **27**	 **51**	78%
3	 **28**	 **52**	89%
4	 **29**	 **53**	71%
5	 **30**	 **54**	78%

6	 **32**	 **55**	90%
7	 **33**	 **56**	88%
8	 **31**	 **57**	28%
9	 **34**	 **58**	51%
10	 **35a** **35b**	 **59**	60% 43%[a]
11	 **36**	 **60**	41%
12	 **37**	 **61**	50%

13	 **39**	 **62**	81%
14	 **40**	 **63**	57%
15	 **38**	 **64**	60%

) Reaction is done in absence of $CuCl_2$

2.7 Conclusion

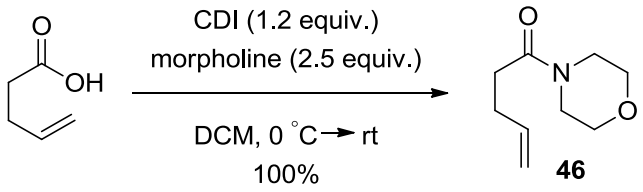
In conclusion, we have developed an effective methodology for the preparation of various mono-, di-, and trisubstituted phenols in a one pot process employing a single palladium(II) catalyst. Initial, cyclization of γ,δ-unsaturated ketones with $PdCl_2(CH_3CN)_2$ (10 mol%) in the presence of HCl (10 mol%) and $CuCl_2$ (10 mol%) leads to the intermediate cyclohexanones, which were subsequently converted *in situ* to the corresponding phenols upon addition of chloranil. This is an alternative approach to traditional methods for the preparation of phenols. In this approach, we proposed a conceptually different method for the preparation of substituted phenols, especially in the case of *meta*- substituted phenols, which are challenging to prepare through other means. By preprogramming the substituents on the ring from the very beginning a wide range of substituted phenols could be effectively synthesized, in good to excellent yield, in a single reaction step from simple acyclic ketones.

Chapter 3: General experimental

All reactions were conducted in flame- or oven-dried glassware under an atmosphere of argon using freshly distilled solvents unless specified otherwise. Dichloromethane (DCM), and toluene were distilled from CaH_2 prior to use. Tetrahydrofuran (THF) was distilled from sodium/benzophenone. Commercial reagents were used as received. Thin-layer chromatography was performed on Merck silica gel 60 F_{254} plates. Visualisation was carried out using UV light (254 nm) and/or $KMnO_4$, $(NH_4)_2Ce(NO_3)_6$ solutions. Hexanes (ACS grade) and ethyl acetate (ACS grade) were used as received. Flash column chromatography was carried out using Aldrich silica gel (230-400 mesh, 40-63 µ, 60 Å pore size). ^{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). Spectra recorded using chloroform was calibrated to 7.28 ppm ^{1}H and 77.23 ppm ^{13}C. ^{19}F-NMR spectra were recorded on Bruker 400 AV spectrometer (^{1}H decoupled) in chloroform-d (99.8 % deuterated) using α,α,α -trifluorotoluene as an external standard. Chemical shifts (δ) are reported in ppm and multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet), br (broad). Coupling constants *J* are reported in Hertz (Hz). Infrared (IR) spectra were recorded as thin films (neat) using Alpha-Platinum ATR, Bruker, diamond crystal FT-IR instrument.

3.1 Experimental procedures and data

1-(4-morpholinyl)-4-penten-1-one 46



A flame-dried round-bottomed flask equipped with a magnetic stir bar was charged with 4-pentenoic acid (3.01 g, 30.0 mmol, 1.0 equiv.) and placed under an atmosphere of argon. Freshly distilled CH_2Cl_2 was added to prepare a 0.5 M solution of the acid, and the solution was cooled to 0 °C. Carbonyldiimidazole (CDI, 5.84 g, 36.0 mmol, 1.20 equiv.) was added and the reaction mixture was stirred for 30 minutes, then morpholine (6.53 g, 75.0 mmol, 2.50 equiv.) was added. The mixture was warmed to room temperature and stirred for 4 h. The resulting mixture was treated with 1M aqueous HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*, to give morpholine amide **46** as colorless oil (5.09 g, 30.0 mmol, 100% yield) that was used in the next step without further purification.

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

δ 5.91-5.84 (m, 1 H), 5.08 (d, *J* = 18.0 Hz, 1 H), 5.02 (d, *J* = 10.0 Hz, 1 H), 3.70-3.64 (m, 6 H), 3.50-3.47 (m, 2 H), 2.42 (m, 4 H).

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

δ 170.4, 137.1, 114.9, 66.5, 66.2, 45.6, 41.5, 31.8, 28.8.

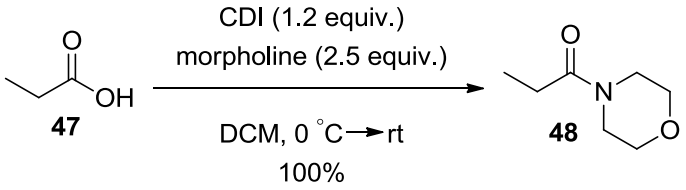
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 2900, 2854, 1635, 1224, 1112, 1026, 911 cm^{-1}

HRMS TOF EI

Calculated for $[C_9H_{15}NO_2]^+$ = 169.1103, found = 169.1100

1-morpholinopropan-1-one 48



In a flame-dried flask under an atmosphere of argon, propionic acid **47** (2.22g, 30.0mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (60 mL) and cooled to 0 °C. Carbonyldiimidazole (CDI) (5.83 g, 36.0 mmol, 1.20 equiv.) was added and the reaction mixture was stirred at 0 °C for 30 minutes, followed by the addition of morpholine (6.53 g, 74.9 mmol, 2.50 equiv.). The reaction mixture was warmed to room temperature and stirred for 4 h. The resultant mixture was treated with 1 M aqueous HCl and extracted with ethyl acetate. The organic layers were collected and washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give morpholine amide **48** (4.29 g, 30.0 mmol, 100% yield) as a colorless oil that was used in the next step without further purification. Spectral data for this compound is consistent with that reported by Williams and coworkers.[59]

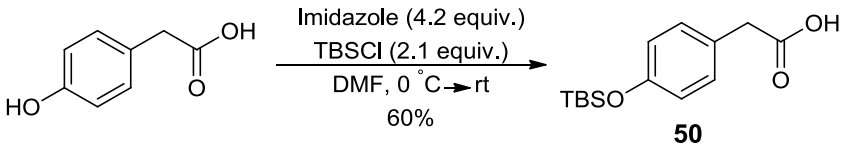
^{1}H NMR (300 MHz, $CDCl_3$)

δ 3.70-3.64 (m, 6 H), 3.47 (dd, *J* = 4.6, 4.6 Hz, 2 H), 2.35 (q, *J* = 7.5 Hz, 2 H), 1.17 (t, *J* = 7.5 Hz, 3 H).

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

δ 172.2, 66.6, 66.4, 45.6, 41.7, 26.0, 9.1.

2-(4-((tert-butyldimethylsilyl)oxy)phenyl)acetic acid 50



50

To a stirred solution of *p*-hydroxyphenylacetic acid (2.00 g, 13.1 mmol, 1.0 equiv.) and imidazole (3.76 g, 55.2 mmol, 4.20 equiv.) in DMF (30.0 mL) was added *t*-butyldimethylsilylchloride (4.17 g, 27.6 mmol, 2.10 equiv.) at 0 °C. The reaction mixture was allowed to warm to room temperature. After 6 h, the reaction mixture was diluted with ethyl acetate, washed with 0.1 N HCl and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography using 20% solution of EtOAc in hexanes (R_f = 0.22) to give 2-(4-((tert-butyldimethylsilyl)oxy)phenyl)acetic acid **50** as a yellow oil (2.10 g, 7.89 mmol, 60% yield). Spectral data for this compound is consistent with that reported by Young and coworkers.[60]

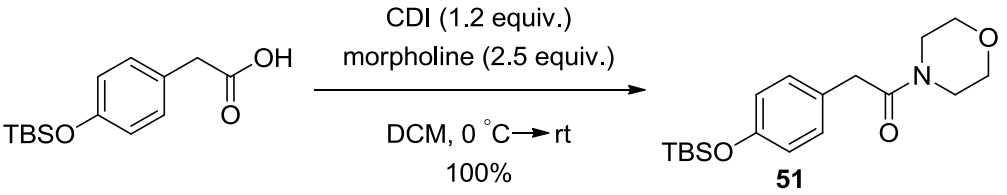
^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.16 (d, *J* = 8.2 Hz, 2 H), 6.81 (d, *J* = 8.2 Hz, 2 H), 3.59 (s, 2 H), 1.00 (s, 9 H), 0.21 (s, 6 H).

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

δ 178.0, 154.8, 130.2, 125.8, 120.0, 40.1, 25.6, 18.0, –4.6.

2-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-1-(4-morpholinyl) ethanone 51



51

2-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)acetic acid (1.00 g, 3.75 mmol, 1.0 equiv.) was added to a flame-dried round-bottomed flask equipped with a magnetic stir bar. The flask was placed under an atmosphere of argon and dry CH_2Cl_2 (30 mL) was introduced. The solution was cooled to 0 °C and carbonyldiimidazole (0.730 g, 4.50 mmol, 1.20 equiv.) was added. The reaction mixture was stirred for 30 minutes at 0 °C, prior to the addition of morpholine (0.815 g, 9.35 mmol, 2.50 equiv.). The mixture was warmed to room temperature and stirred for 4 h. The resultant mixture was treated with 1M aqueous HCl and extracted with DCM. The combined organics were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*, to give the corresponding morpholine amide **51** as a yellow oil (1.25 g, 3.75 mmol, 100% yield).

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

δ 7.11 (d, *J* = 8.0 Hz, 1 H), 6.81 (d, *J* = 8.0 Hz, 2 H), 3.68 (s, 2 H), 3.65 (br, 4 H), 3.66 (br, 4 H), 1.00 (s, 9 H), 0.20 (s, 6 H).

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

δ 169.9, 154.4, 129.4, 127.3, 120.3, 66.7, 66.3, 47.1, 46.4, 42.0, 40.0, 25.5, 18.1, –4.6.

IR Alpha-Platinum ATR, Bruker, diamond crystal

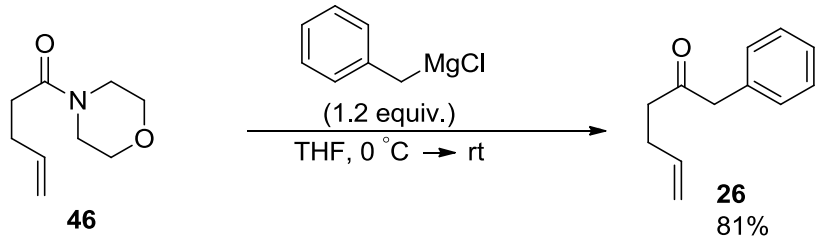
υ = 3030, 2930, 1635, 1599, 1224, 1112, 1029, 964 cm^{-1}

HRMS TOF EI

Calculated for $[C_{18}H_{29}NO_3Si]^+$ = 335.1917, found = 335.1911.

***General Procedure 1**: <u>Synthesis of ketones by addition of Grignard or organolithium reagents to morpholine amides.</u>*

1-Phenyl-5-hexen-2-one (ketone **26**)



46 **26** 81%

To a cold (0 °C) solution of 1-(4-morpholinyl)-4-penten-1-one (1.40 g, 8.27 mmol, 1.0 equiv.) in THF (25.0 mL) was added benzylmagnesium chloride (9.92 mmol, 1.20 equiv.). After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred for 6 h. The resulting mixture was treated with saturated aqueous NH_4Cl and extracted with ethyl acetate (3 x 30 mL). The organics layer were combined and washed with brine, dried with anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on SiO_2 using a 20% solution of EtOAc in hexanes (R_f = 0.25) to give ketone **26** as a colorless oil (1.17 g, 6.70 mmol, 81%). Spectral data for this compound is consistent with that reported by Shipman and coworkers.[40]

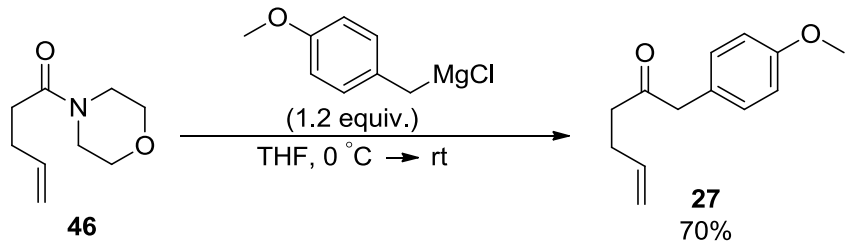
^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.37-7.34 (m, 2 H), 7.31-7.28 (m, 1 H), 7.22 (d, *J* = 7.2 Hz, 2 H), 5.83-5.75 (m, 1 H), 5.00 (d, *J* = 17.6 Hz, 1 H), 4.97 (d, *J* = 10.4 Hz, 1 H), 3.71 (s, 2 H), 2.57 (t, *J* = 7.2 Hz, 2 H), 2.32 (td, *J* = 7.2, 6.0 Hz, 2 H)

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

δ 207.3, 136.9, 134.2, 129.3, 128.6, 126.9, 115.2, 50.1, 40.9, 27.6.

1-(4-methoxyphenyl)-5-hexen-2-one (ketone **27)**



Following *General Procedure 1*, 1-(4-morpholinyl)-4-penten-1-one (0.250 g, 1.47 mmol, 1.0 equiv.) was reacted with 4-methoxybenzylmagnesium chloride (1.76 mmol, 1.20 equiv.) to give ketone **27**. Purification of the crude product by column chromatography using a 20% solution of EtOAc in hexanes (R_f = 0.21) afforded ketone **27** (0.210 g, 1.03 mmol, 70%) as a yellow oil. Spectral data for this compound is consistent with that reported by Schmittel and coworkers.[41]

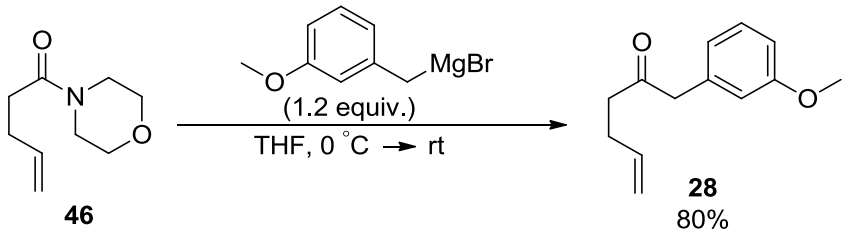
^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.14 (d, *J* = 8.0 Hz, 2 H), 6.89 (d, *J* = 8.0 Hz, 2 H), 5.83-5.73 (m, 1 H), 5.00 (d, *J* = 18 Hz, 1 H), 4.97 (d, *J* = 10.4 Hz, 1 H), 3.81 (s, 3 H), 3.64 (s, 2 H), 2.56 (t, *J* = 7.2 Hz, 2 H), 2.32 (td, *J* = 7.2, 6.0 Hz, 2 H).

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

δ 207.3, 159.7, 138.5, 129.6, 121.6, 115.2, 114.9, 55.1, 50.2, 40.8, 27.6.

1-(3-methoxyphenyl)-5-hexen-2-one (ketone **28**)



46 **28** 80%

Following *General Procedure 1*, 1-(4-morpholinyl)-4-penten-1-one (0.250 g, 1.47 mmol, 1.0 equiv.) was reacted with 3-methoxybenzylmagnesium bromide (1.76 mmol, 1.20 equiv.) to give ketone **28**. Purification by column chromatography using 20% solution of EtOAc in hexanes (R_f = 0.22) afforded ketone **28** (0.230 g, 1.17 mmol, 80%) as a yellow oil.

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

δ 7.27 (dd, *J* = 7.6, 7.2 Hz, 1 H), 6.83 (d, *J* = 7.6 Hz, 1 H), 6.81 (d, *J* = 7.2 Hz, 1 H), 6.77 (s, 1 H), 5.82-5.73 (m, 1 H), 5.00 (d, *J* = 18.4 Hz, 1 H), 4.97 (d, *J* = 10.4, 1 H), 3.82 (s, 3 H), 3.68 (s, 2 H), 2.57 (t, *J* = 7.2 Hz, 2 H), 2.32 (td, *J* = 7.0, 6.8 Hz, 2 H).

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

δ 207.3, 159.7, 136.9, 135.5, 129.6, 121.7, 115.1, 114.9, 112.4, 55.1, 50.2, 40.8, 27.6.

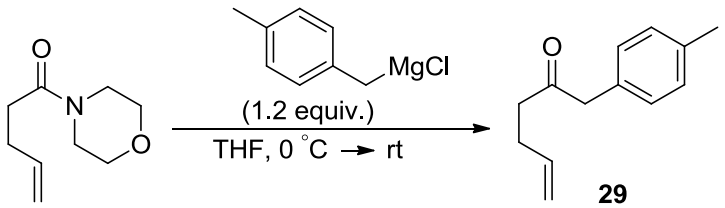
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 2909, 2836, 1710, 1611, 1509, 1244, 998 cm^{-1}

HRMS TOF EI

Calculated for $[C_{13}H_{16}O_2]^+$ = 204.1150, found = 204.1158

1-(4-methylphenyl)-5-hexen-2-one (ketone **29**)



46 **29** 64%

Following *General Procedure 1*, 1-(4-morpholinyl)-4-penten-1-one (1.39 g, 8.21 mmol, 1.0 equiv.) was reacted with 4-methylbenzylmagnesium chloride (9.85 mmol, 1.20 equiv.) to give ketone **29**. Purification by column chromatography using a 5% solution of EtOAc in hexanes (R_f = 0.33) afforded ketone **29** (0.980 g, 5.25 mmol, 64%) as a colorless oil. Spectral data for this compound is consistent with that reported by Widenhoefer and coworkers.[42]

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

δ 7.17-7.10 (m, 4 H), 5.77 (ddt, *J* = 17.6, 10.4, 7.2 Hz, 1 H),

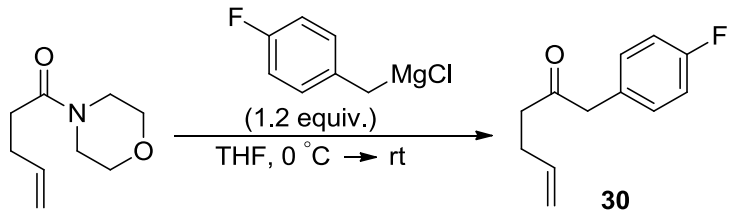
5.00 (d, *J* = 17.6 Hz, 1 H), 4.97 (d, *J* = 10.4 Hz, 1 H), 3.67 (s, 2 H),

2.56 (t, *J* = 7.2 Hz, 2 H), 2.36 (s, 3 H), 2.32 (td, *J* = 7.2, 7.2 Hz, 2 H).

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

δ 207.7, 137.0, 136.5, 131.1, 129.3, 129.2, 115.1, 49.7, 40.8, 27.6, 21.0.

1-(4-fluorophenyl)-5-hexen-2-one (ketone **30**)



46 **30** 80%

Following *General Procedure 1*, 1-(4-morpholinyl)-4-penten-1-one (0.599 g, 3.53 mmol, 1.0 equiv.) was reacted with (4-fluorobenzyl)magnesium chloride (3.88 mmol, 1.10 equiv.) to give ketone **30**. Purification by column chromatography using an 8% solution of EtOAc in hexanes (R_f = 0.21) afforded ketone **30** (0.561 g, 2.80 mmol, 80%) as a yellow oil. Spectral data for this compound is consistent with that reported by Widenhoefer and coworkers.[21]

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

δ 7.20-7.16 (m, 2 H), 7.04 (dd, $^3J_{H-H}$ = 8.4 Hz, $^3J_{H-F}$ = 8.4 Hz, 2 H),
5.79 (ddt, *J* = 14.7, 8.7, 6.4 Hz, 1 H), 5.02 (d, *J* = 14.7 Hz, 1 H),
4.98 (d, *J* = 8.7 Hz, 1 H), 3.69 (s, 2 H), 2.58 (t, *J* = 7.2 Hz, 2 H),
2.33 (td, *J* = 7.2, 6.4 Hz, 2 H).

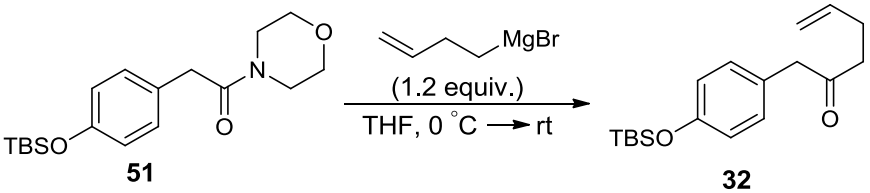
^{13}C NMR (100 MHz, $CDCl_3$)

δ 207.0, 163.0, 160.6 (d, $^1J_{C-F}$ = 240 Hz), 136.8, 130.9 (d, $^3J_{C-F}$ = 8.0 Hz),
129.8 (d, $^4J_{C-F}$ = 3.0 Hz), 115.4 (d, $^2J_{C-F}$ = 21 Hz), 115.2, 48.9, 41.0, 27.5.

^{19}F NMR (282 MHz, $CDCl_3$)

δ –115.8.

1-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-5-hexen-2-one (ketone **32**)



51 **32**
50%

Following *General Procedure 1*, to a solution of morpholine amide **51** (0.998 g, 2.98 mmol, 1.0 equiv.) in THF (25.0 mL) was added 3-butenylmagnesium bromide (3.58 mmol, 1.20 equiv.) at 0 °C. When the addition was complete, the reaction mixture was allowed to warm to room temperature over 6 h. The resulting mixture was treated with saturated aqueous NH_4Cl and extracted with EtOAc. The organic layers were combined and washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography using a 5% solution of EtOAc in hexanes (R_f = 0.33) to give ketone **32** as yellow oil (0.449 g, 1.49 mmol, 50%).

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

δ 7.07 (d, *J* = 8.0 Hz, 2 H), 6.81 (d, *J* = 8.0 Hz, 2 H),

5.77 (ddt, *J* = 16.4, 9.6, 7.2 Hz, 1 H), 4.99 (d, *J* = 16.4 Hz, 1 H),

4.96 (d, *J* = 9.6 Hz, 1 H), 3.63 (s, 2 H), 2.55 (t, *J* = 7.2 Hz, 2 H),

2.31 (td, *J* = 7.2, 7.2 Hz, 2 H), 1.00 (s, 9 H),

0.21 (s, 6 H).

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

δ 207.7, 154.6, 136.9, 130.3, 126.8, 120.2, 115.1, 49.3, 40.6, 27.6, 25.6, 18.1,

–4.5.

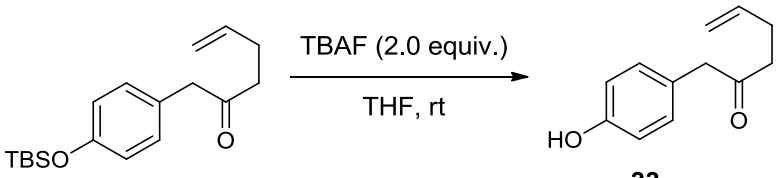
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3529, 2928, 1711, 1640, 1513, 997, 911 cm^{-1}

HRMS TOF EI

Calculated for $[C_{18}H_{28}O_2Si]^+$ = 304.1859, found = 304.1852.

1-(4-hydroxyphenyl)-5-hexen-2-one (ketone **33**)



32 **33**
100%

To a solution of 1-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-5-hexen-2-one (ketone **32**, 0.026 g, 0.085 mmol, 1.0 equiv.) in THF (2M) was added TBAF (1M in THF, 0.171 mmol, 2.0 equiv.). After stirring for 20 minutes at ambient temperature the reaction mixture was diluted with ethyl acetate and washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*, The residue was purified by column chromatography using a 15% solution of EtOAc in hexanes (R_f = 0.25) to give ketone **33** (0.016 g, 0.085 mmol) in 100% yield.

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

δ 7.08 (d, *J* = 8.4 Hz, 2 H), 6.81 (d, *J* = 8.4 Hz, 2 H),

5.78 (ddt, *J* = 16.8, 11.6, 7.2 Hz, 1 H), 5.00 (d, *J* = 16.8 Hz, 1 H),

4.97 (d, *J* = 11.6 Hz, 1 H) 3.64 (s, 2 H), 2.57 (t, *J* = 7.2 Hz, 2 H),

2.32 (td, *J* = 7.2, 7.2 Hz, 2 H).

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

δ 209.7, 155.0, 136.7, 130.5, 125.5, 115.7, 115.3, 49.2, 40.9, 27.6.

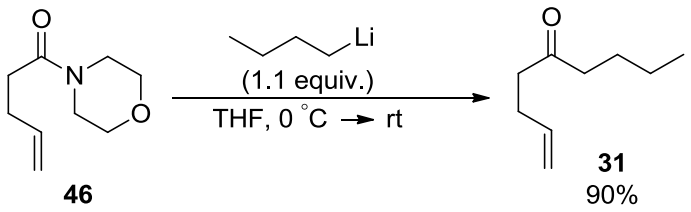
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3351, 3032, 2919, 1716, 1644, 1496, 910, 990 cm^{-1}

HRMS TOF EI

Calculated for $[C_{12}H_{14}O_2]^+$ = 190.0994, found = 190.0990.

1-Nonen-5-one (ketone **31**)



46 **31** 90%

Following *General Procedure 1*, a flame-dried round-bottomed flask equipped with a magnetic stir bar was charged with 1-(4-morpholinyl)-4-penten-1-one (1.01 g, 5.90 mmol, 1.0 equiv.) and placed under an atmosphere of argon. Freshly distilled THF was introduced into the flask to prepare a 0.5 M solution, which was then cooled to −78 °C. *n*-BuLi (1.6 M in hexanes, 1.10 equiv.) was added and the reaction mixture was stirred for 8 h at 0 °C. The resulting mixture was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography using a 6% solution of EtOAc in hexanes (R_f = 0.30) to give ketone **31** (0.745 g, 5.31 mmol) as a colorless oil in 90% yield. Spectral data for this compound is consistent with that reported by Thomas and coworkers.[43]

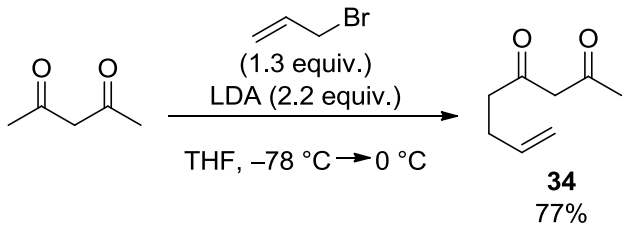
^{1}HNMR (400 MHz, $CDCl_3$)

δ 5.83 (ddt, *J* = 17.2, 10.4, 6.8 Hz, 1 H), 5.05 (d, *J* = 17.2 Hz, 1 H), 4.99 (d, *J* = 10.4 Hz, 1 H), 2.52 (t, *J* = 7.2 Hz, 2 H), 2.42 (t, *J* = 7.6 Hz, 2 H), 2.34 (dt, *J* = 7.2, 6.8 Hz, 2 H), 1.58 (tt, *J* = 7.6, 7.6 Hz, 2 H), 1.33 (tq, *J* = 7.6, 7.2 Hz, 2 H), 0.92 (t, *J* = 7.2 Hz, 3 H).

^{13}CNMR (100 MHz, $CDCl_3$)

δ 210.4, 137.1, 115.0, 42.5, 41.6, 27.7, 25.8, 22.2, 13.7.

7-Octene-2,4-dione (1,3-diketone **34**)



34
77%

To a solution of freshly distilled diisopropylamine (4.66 mL, 33.0 mmol, 2.20 equiv.) in THF (35.0 mL) was added *n*-BuLi (1.6 M in hexanes, 20.6 mL, 33.0 mmol, 2.20 equiv.) at 0 °C. The solution was stirred at 0 °C for 30 minutes. To this solution was added acetylacetone (1.52 g, 15.0 mmol, 1.0 equiv.). After stirring for 30 min at 0 °C, a solution of allylbromide (2.36 g, 19.5 mmol, 1.30 equiv.) in THF (0.5M) was added. The solution was stirred at −78 °C for 1 h and 0 °C for 1 h. The resultant mixture was treated with 1 M aqueous HCl and extracted with ethyl acetate. The organic layers were collected and washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography using a 10% solution of EtOAc in hexanes (R_f = 0.25) to give ketone **34** as a yellow oil (1.62 g, 11.5 mmol, 77%) (observed as 1.4:1 of enol/ketone tautomers by ^{1}H NMR spectroscopy in CD_3CN). Spectral data for this compound is consistent with that reported by Widenhoefer and coworkers.[21]

Ketone:

^{1}H NMR (400 MHz, CD_3CN)

δ 5.91-5.78 (m, 1 H), 5.11-4.97 (m, 2 H), 3.62 (s, 2 H), 2.61 (t, *J* = 7.2 Hz, 2 H), 2.29 (td, *J* = 7.2, 6.8 Hz, 2 H), 2.16 (s, 3 H).

Enol:

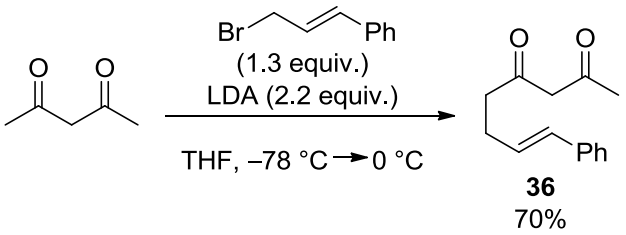
^{1}H NMR (400 MHz, CD_3CN)

δ 15.59 (s, 1 H), 5.91-5.78 (m, 1 H), 5.64 (s, 1 H), 5.11-4.97 (m, 2 H), 2.29 (td, *J* = 7.2, 6.4 Hz, 2 H), 2.36 (t, *J* = 7.2 Hz, 2 H), 2.05 (s, 3 H).

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

δ 203.2, 201.9, 193.4, 190.9, 136.7, 136.4, 115.4, 115.3, 99.4, 57.8, 42.6, 37.4, 30.8, 29.3, 27.2, 24.7.

8-Phenyl-(7*E*)-7-octene-2,4-dione (diketone **36**)



36
70%

To a solution of freshly distilled diisopropylamine (4.66 mL, 33.0 mmol, 2.20 equiv.) in THF (35 mL) was added *n*-BuLi (1.6 M in hexanes, 20.6 mL, 33.0 mmol, 2.20 equiv.) at 0 °C. The solution was stirred at 0 °C for 30 minutes. To this solution was added acetylacetone (1.50 g, 15.0 mmol, 1.0 equiv.). After stirring for 30 min at 0 °C, a solution of cynnamyl bromide (3.84 g, 19.5 mmol, 1.30 equiv.) in THF (0.5M) was added. The solution was stirred at −78 °C for 1 h and 0 °C for 1 h. The resultant mixture was treated with 1 M aqueous HCl and extracted with ethyl acetate. The organic layers were collected and washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by flash column chromatography using 10% solution of EtOAc in hexanes (R_f = 0.25) afforded mixture of ketone **36** (2.27 g, 10.5 mmol, 70%) and enol **36** (0.460 g, 2.13 mmol, 14%) as a colorless oil (observed as 5 : 1 mixture of enol/ketone tautomers by ^{1}H NMR spectroscopy in $CDCl_3$). Spectral data for this compound is consistent with that reported by Widenhoefer and coworkers.[21]

Ketone:

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

δ 7.34-7.17 (m, 5 H), 6.40 (d, *J* = 15.9 Hz, 1 H), 6.18 (dt, *J* = 15.9, 6.3 Hz, 1 H), 3.59 (s, 2 H), 2.69 (t, *J* = 7.2 Hz, 2 H), 2.55-2.49 (m, 2 H), 2.23 (s, 3 H)

Enol:

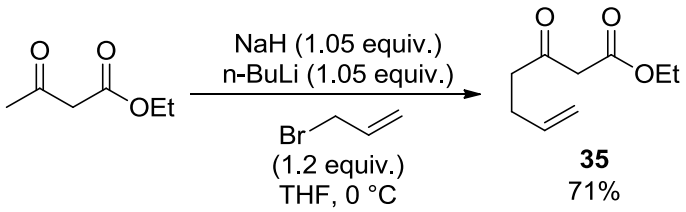
^{1}H NMR (300 MHz, $CDCl_3$)

δ 15.46 (s, 1 H), 7.34-7.17 (m, 5 H), 6.42 (d, *J* = 15.9 Hz, 1 H) , 6.18 (dt, *J* = 15.9, 6.3 Hz, 1 H), 5.51(s, 1 H), 2.55-2.49 (m, 4 H), 2.05 (s, 3 H).

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

δ 203.2, 201.9, 193.4, 190.9, 137.3, 130.8, 128.5, 128.5, 127.1, 126.0 99.9, 57.8, 43.1, 37.9, 30.8, 28.7, 26.7, 24.7.

ethyl 3-oxohept-6-enoate (ketoester **35**)



To a solution of NaH (60 % dispersion in mineral oil, 0.630 g, 15.8 mmol, 1.05 equiv.) in THF (35 mL) was added 3-oxobutanoate (1.95 g, 15.0 mmol, 1.0 equiv.) at 0 °C. The solution was stirred at 0 °C for 30 minutes. To this solution was added *n*-BuLi (1.6 M in hexanes, 9.87 mL, 15.8 mmol, 1.05 equiv.). After stirring for 30 min at 0 °C, a solution of allylbromide (2.17 g, 18.0 mmol, 1.20 equiv.) in THF (0.5M) was added. The solution was stirred at 0 °C for 2 h. The resultant mixture was treated with 1M aqueous HCl and extracted with ethyl acetate. The organic layers were collected and washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography using 10% solution of EtOAc in hexanes (R_f = 0.22) afforded ketone **35** (1.81 g, 10.6 mmol, 71%) as a yellow oil (observed as mixture of enol/ketone tautomers by ^{1}H NMR spectroscopy in $CDCl_3$). Spectral data for this compound is consistent with that reported by Widenhoefer and coworkers.[21]

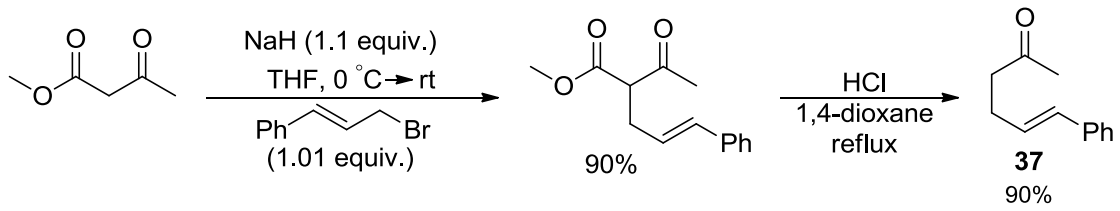
^{1}H NMR (400 MHz, $CDCl_3$)

δ 12.1 (s, 1 H), 5.81 (ddt, *J* = 17.2, 9.6, 6.8 Hz, 1 H), 5.05 (d, *J* = 17.2 Hz, 1 H), 5.00 (d, *J* = 9.6 Hz, 1 H), 4.19 (q, *J* = 7.2 Hz, 2 H), 3.44 (s, 2 H), 2.66 (t, *J* = 7.2 Hz, 2 H), 2.31 (dt, *J* = 7.2, 6.8 Hz, 2 H), 1.29 (t, *J* = 7.2 Hz, 3 H).

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

δ 201.8, 166.9, 136.4, 115.2, 61.0, 49.0, 41.7, 27.1, 13.8.

6-Phenyl-(5*E*)-5-hexen-2-one (ketone **37**)



Methyl acetoacetate (4.32 mL, 40.0 mmol, 2.0 equiv.) was added dropwise to a suspension of 60% NaH (0.880 g, 22.0 mmol, 1.10 equiv.) in dry THF (45 mL) at 0 ºC. A solution of 3-bromo-1-phenyl-1-propene (4.14 g, 21.0 mmol, 1.01 equiv.) in dry THF (5 mL) was added at 0 ºC. The reaction mixture was stirred at 0 ºC for 30 minutes and then at room temperature for an additional 18 hours. The reaction was quenched by addition of water (50 mL) at 0 ºC and the THF was removed *in vacuo*. The aqueous phase was extracted with EtOAc and the combined organic layers was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography using a 9% solution of EtOAc in hexanes (R_f = 0.22) to give the pure methyl 2-acetyl-5-phenylpent-4-enoate (4.18 g, 18.0 mmol, 90%) as yellow oil. Spectral data for this compound is consistent with that reported by Tsuji and coworkers.[44]

^{1}HNMR (400 MHz, $CDCl_3$)

δ 7.33-7.23 (m, 5 H), 6.48 (d, *J* = 15.9 Hz, 1 H), 6.13 (dt, *J* = 15.9, 7.2 Hz, 1 H), 3.79 (s, 3 H), 3.63 (t, *J* = 7.2 Hz, 1 H), 2.78 (t, *J* = 7.2 Hz, 2 H), 2.28 (s, 3 H).

^{13}CNMR (100 MHz, $CDCl_3$)

δ 202.3, 169.6, 136.9, 132.7, 128.4, 127.3, 126.2, 126.1, 59.2, 52.4, 31.4, 29.2.

The alkylated ketoester (4.75 g, 20.4 mmol) was dissolved in a 2M HCl (aq.)/dioxane (4:1) mixture (50 mL) and heated at reflux for 18 hours. After cooling to room temperature the reaction was adjusted to pH = 6-7 using 2 M NaOH and extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography using a 10% solution of EtOAc in hexanes (R_f = 0.30) to give ketone **37** (3.21 g, 18.4 mmol, 90%) as a yellow oil. Spectral data for this compound is consistent with that reported by Bäckvall and coworkers.[45]

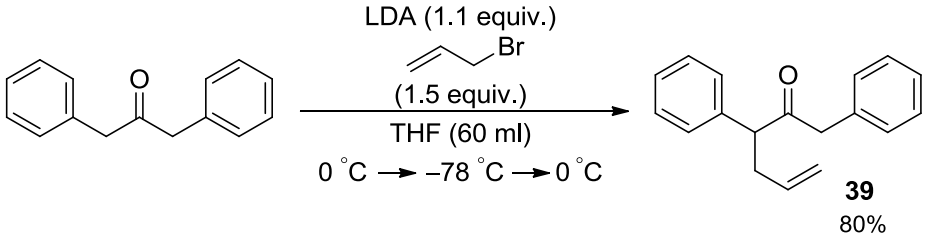
^{1}HNMR (400 MHz, $CDCl_3$)

δ 7.36-7.28 (m, 4 H), 7.22 (t, *J* = 7.2 Hz, 1 H), 6.43 (d, *J* = 15.6 Hz, 1 H), 6.22 (dt, *J* = 15.6, 6.8 Hz, 1 H), 2.64 (t, *J* = 7.4 Hz, 2 H), 2.50 (td, *J* = 7.4, 6.8 Hz, 2 H), 2.20 (s, 3 H).

^{13}CNMR (100 MHz, $CDCl_3$)

δ 207.9, 137.3, 130.6, 128.7, 128.4, 127.0, 125.9, 43.0, 29.9, 27.0.

1,3-diphenyl-5-hexen-2-one (ketone **39**)



39
80%

A flame-dried round-bottomed flask equipped with a magnetic stirrer was charged with diisopropylamine (0.786 mL, 5.61 mmol, 1.10 equiv.), freshly distilled THF (10 mL), and purged with argon. The resulting solution was cooled to −78 °C and *n*-BuLi (1.6 M in hexanes, 3.50 mL, 5.61 mmol, 1.10 equiv.) was added. To this solution was added 1,3-diphenylpropan-2-one (1.07 g, 5.10 mmol, 1.0 equiv.), and the resulting solution was stirred at 0 °C for 2 h. After this time, the solution was cooled to −78 °C, and allylbromide (0.925 g, 7.65 mmol, 1.50 equiv.) was added. After stirring at this temperature for 4 h, the reaction was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The organic layers collected and washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude material was purified by column chromatography using a 3% solution of EtOAc in hexanes (R_f = 0.28) to give ketone **39** (1.01 g, 4.08 mmol, 80%) as a colorless oil. Spectral data for this compound is consistent with that reported by Mori and coworkers.[46]

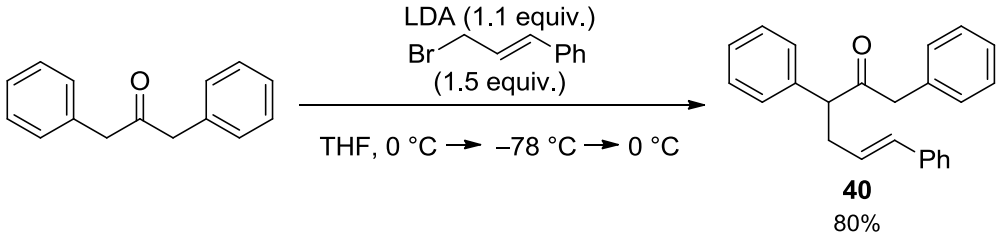
^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.37-7.32 (m, 2 H), 7.32-7.25 (m, 4 H), 7.21 (d, *J* = 7.6 Hz, 2 H),
7.06 (d, *J* = 7.6 Hz, 2 H), 5.61 (dddd, *J* = 18.0, 10.8, 7.2, 6.8 Hz, 1 H),
4.95 (d, *J* = 18.0 Hz, 1 H), 4.92 (d, *J* = 10.8 Hz, 1 H),
3.82 (dd, *J* = 7.4, 7.4 Hz, 1 H), 3.65 (s, 2 H), 2.78 (ddd, *J* = 14.2, 7.2, 7.2 Hz, 1 H),
2.44 (ddd, *J* = 14.2, 7.2, 6.8 Hz, 1 H).

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

δ 206.7, 138.1, 135.6, 134.0, 129.5, 128.9, 128.5, 128.5, 127.4, 126.8, 116.6, 57.7, 48.7, 36.4.

1,3,6-triphenyl-(5*E*)-5-hexen-2-one (ketone **40**)



40
80%

A flame-dried round-bottomed flask equipped with a magnetic stirrer was charged with diisopropylamine (1.47 mL, 10.5 mmol, 1.10 equiv.), freshly distilled THF (10.0 mL), and purged with Argon. The resulting solution was cooled to −78 °C and *n*-BuLi (1.6 M in hexanes, 6.56 mL, 10.5 mmol, 1.10 equiv.) was added. To this solution was added 1,3-diphenylpropan-2-one (1.99 g, 9.50 mmol, 1.0 equiv.), and the resulting solution was stirred at 0 °C for 2 h. After this time, the solution was cooled to −78 °C, and cinnamyl bromide (2.82 g, 14.3 mmol, 1.50 equiv.) was added. After stirring at this temperature for 4 h, the reaction was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The organic layers collected and washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification by column chromatography using a 5% solution of EtOAc in hexanes (R_f = 0.30) afforded ketone **40** (2.48 g, 7.61 mmol, 80%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$)
δ 7.39-7.20 (m, 13 H), 7.07 (d, *J* = 6.8 Hz, 2 H), 6.32 (d, *J* = 15.6 Hz, 1 H), 5.97 (dt, *J* = 15.6, 7.2 Hz, 1 H), 3.89 (t, *J* = 7.4 Hz, 1 H), 3.66 (s, 2 H), 2.95 (ddd, *J* = 14.0, 7.4, 7.2 Hz, 1 H), 2.55 (ddd, *J* = 14.0, 7.0, 6.8 Hz, 1 H).

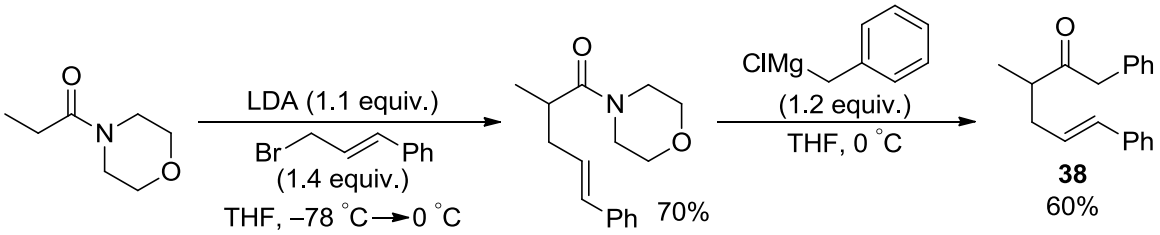
^{13}C NMR (100 MHz, $CDCl_3$)
δ 206.7, 138.2, 137.4, 134.0, 131.9, 129.6, 129.1, 128.6, 128.5, 128.4, 127.5, 127.4, 127.1, 126.9, 126.1, 57.9, 48.9, 35.9.

IR Alpha-Platinum ATR, Bruker, diamond crystal
υ = 3022, 2889, 1710, 1597, 1490, 935, 750 cm^{-1}

M.P. 90-95 °C

HRMS TOF EI
Calculated for $[C_{24}H_{22}O]^+$ = 326.1671, found = 326.1670

3-Methyl-1,6-diphenyl-(5*E*)-5-hexen-2-one (ketone **38**)



To a cold (0 °C) solution of diisopropylamine (0.777 g, 7.68 mmol, 1.10 equiv.) in freshly distilled THF (20 mL) was added *n*-BuLi (1.6 M in hexanes, 4.79 mL, 7.68 mmol, 1.10 equiv.), and the reaction was stirred for 30 minutes. The reaction was then cooled to −78 °C and a solution of 1-(4-morpholinyl)-1propanone (1.04 g, 6.98 mmol, 1.0 equiv.) in distilled THF (10.0 mL) was added. The mixture was warmed to 0 °C and stirred at this temperature for 1h, and then cooled to −78 °C. A solution of cinnamyl bromide (1.93 g, 9.77 mmol, 1.40 equiv in THF (10.0 mL) was then added. After the addition was complete, the mixture was warmed to 0 °C and stirred for 4 h. The reaction was quenched with 1 M aqueous HCl and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude material was purified by column chromatography using a 5% solution of EtOAc in hexanes to give 1-(4-morpholinyl)-2-methyl-5-phenyl-(4*E*)-4-penten-1-one (1.25 g, 4.87 mmol, 70%) as a colorless oil.

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

δ 7.36-7.21 (m, 5 H), 6.51 (d, *J* = 16.0 Hz, 1 H),

6.19 (ddd, *J* = 16.0, 7.2, 7.2 Hz, 1 H), 3.66 (m, 6 H), 3.54 (m, 2 H),

2.82 (ddq, *J* = 6.8 Hz, 6.8, 6.8 Hz, 1 H), 2.61 (ddd, *J* = 14.0, 7.2, 6.8 Hz, 1 H),

2.33 (ddd, *J* = 14.0, 7.2, 6.8 Hz, 1 H), 1.20 (d, *J* = 6.8 Hz, 3 H).

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

δ 174.2, 137.2, 131.8, 128.4, 127.5, 127.0, 125.9, 66.8, 66.6, 45.9, 42.0, 37.3, 35.4, 17.4.

IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3026, 2930, 1635, 1599, 1224, 1112, 1029, 964 cm^{-1}

HRMS TOF EI

Calculated for $[C_{16}H_{21}NO_2]^+$ = 259.1572, found = 259.1579

To a cold (0 °C) solution of 1-(4-morpholinyl)-2-methyl-5-phenyl-(4*E*)-4-penten-1-one (1.01 g, 3.89 mmol, 1.0 equiv.) in freshly distilled THF(30 mL) was added benzylmagnesium chloride (4.66 mmol, 1.20 equiv.) as a solution in THF (15 mL). The reaction mixture was allowed to warm to room temperature and was stirred for 6 h. The reaction was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography using a 5% solution of EtOAc in hexanes (R_f = 0.21) to give ketone **38** (0.616 g, 2.33 mmol, 60%) as a colorless oil.

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

δ 7.36-7.20 (m, 10 H), 6.39 (d, *J* = 15.6 Hz, 1 H),

6.07 (ddd, *J* = 15.6, 7.2, 7.2 Hz, 1 H), 3.78 (s, 2 H),

2.82 (ddq, *J* = 6.9 Hz, 6.9, 6.9 Hz 1 H), 2.58 (ddd, *J* = 14.1, 7.2, 6.9 Hz, 1 H),

2.27 (ddd, *J* = 14.1, 7.2, 6.9 Hz, 1 H), 1.16 (d, *J* = 6.9 Hz, 3 H).

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

δ 210.9, 137.2, 134.0, 132.0, 129.5, 128.6, 128.4, 127.2, 127.1, 126.9, 126.0, 48.8, 45.3, 36.3, 16.4.

IR Alpha-Platinum ATR, Bruker, diamond crystal

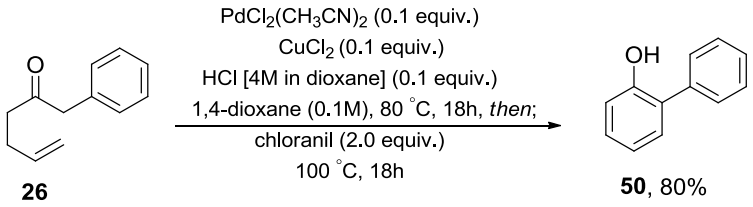
υ = 3026, 2967, 2930, 1708, 1599, 1029, 964, 692 cm^{-1}

HRMS TOF EI

Calculated for $[C_{19}H_{20}O]^+$ = 264.1514, found = 264.1510

***General Procedure 2**: Synthesis of phenols by palladium-catalyzed cyclization and oxidation*

[1,1'-Biphenyl]-2-ol (phenol **50**)



26 **50**, 80%

A suspension of 1-phenyl-5-hexen-2-one **26** (0.100 g, 0.574 mmol, 1.0 equiv), HCl [4 M in dioxane, 0.144 mL, 0.10 equiv.], $PdCl_2(MeCN)_2$ (0.015 g, 0.057 mmol, 0.10 equiv.), and $CuCl_2$ (0.008 g, 0.057 mmol, 0.10 equiv) in 1,4-dioxane (5.71 mL) was stirred at 80 °C. After 18h of stirring, chloranil (0.283 g, 1.15 mmol, 2.0 equiv) was added and the reaction mixture was stirred for 18h at 100 °C. Upon cooling, the reaction mixture was filtered through a pad of celite® using EtOAc as an eluent, and concentrated *in vacuo*. Flash column chromatography of the crude product using a 10% solution of ethyl acetate in hexanes (Rf = 0.33) afforded phenol **50** as a brown solid (0.079 g, 0.470 mmol) in 80% yield. Spectral data for this compound is consistent with that reported by Stahl and coworkers.[47]

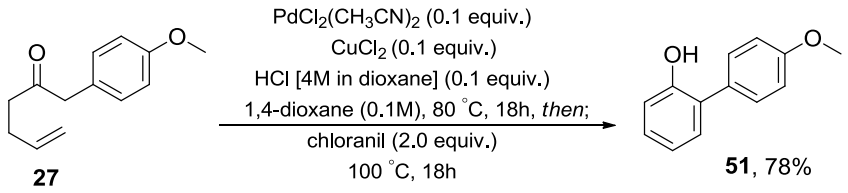
^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.54-7.43 (m, 5 H), 7.31-7.26 (m, 2 H), 7.04-7.00 (m, 2 H), 5.19 (s, 1 H)

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

δ 152.4, 137.2, 130.4, 129.2, 129.2, 128.2, 127.8, 120.9, 116.0.

4’-Methoxy-[1,1’-biphenyl]-2-ol (phenol **51**)



Following *General Procedure* 2, 1-(4-methoxyphenyl)-5-hexen-2-one **27**(0.100 g, 0.489 mmol, 1.0 equiv.) was converted to 4’-Methoxy-[1,1’-biphenyl]-2-ol. Purification by flash column chromatography using 15% solution of EtOAc in hexanes (R_f = 0.20) afforded phenol **51** (0.076 g, 0.381 mmol, 78%) as a pale brown solid. Spectral data for this compound is consistent with that reported by Contreras and coworkers.[48]

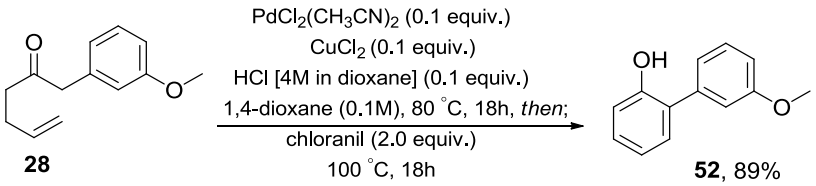
^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.42 (d, *J* = 8.4 Hz, 2 H), 7.26-7.23 (m, 2 H), 7.05 (d, *J* = 8.4 Hz, 2 H), 7.02-6.99 (m, 2 H), 5.17 (s, 1H), 3.89 (s, 3 H).

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

δ 159.2, 152.4, 130.2, 130.1, 129.0, 128.7, 127.7, 120.7, 115.5, 114.6, 55.3.

3’-Methoxy-[1,1’-biphenyl]-2-ol (phenol **52**)



28 **52**, 89%

Following *General Procedure* 2, ketone **28** (0.100 g, 0.489 mmol, 1.0 equiv.) was coverted to 3’-Methoxy-[1,1’-biphenyl]-ol. Purification by flash column chromatography using 15% solution of EtOAc in hexanes (R_f = 0.20) afforded phenol **52** (0.086 g, 0.430 mmol, 89%) as a red solid. Spectral data for this compound is consistent with that reported by Schmidt and coworkers.[49]

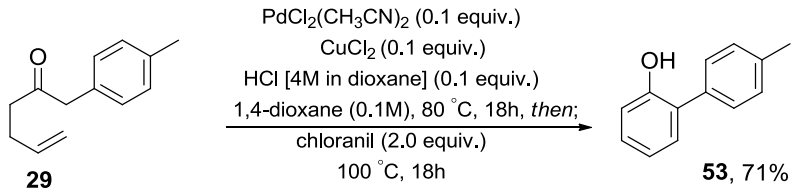
^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.43 (dd, *J* = 7.6, 7.6 Hz, 1 H), 7.31-7.27 (m, 2 H), 7.07 (d, *J* = 7.6 Hz, 1 H), 7.01-6.96 (m, 4 H), 5.30 (s, 1 H), 3.87 (s, 3 H)

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

δ 160.2, 152.3, 138.3, 130.3, 129.9, 129.1, 127.8, 121.0, 120.6, 115.7, 114.4, 113.5, 55.2.

4’-Methyl-[1,1’-biphenyl]-2-ol (phenol **53**)



Following *General Procedure* 2, ketone **29** (0.100 g, 0.531 mmol, 1.0 equiv.) was converted to 4’-Methyl-[1,1’-biphenyl]-2-ol. Purification by flash column chromatography using 5% solution of EtOAc in hexanes (R_f = 0.30) afforded phenol **53** (0.069 g, 0.377 mmol, 71%) as a colorless solid. Spectral data for this compound is consistent with that reported by Uemura and coworkers.[50]

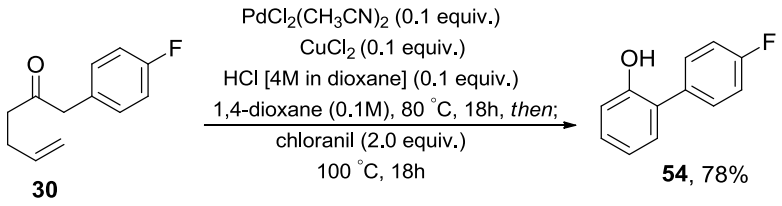
^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.38 (d, *J* = 8.0 Hz, 2 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 7.26-7.24 (m, 2 H), 7.02-6.99 (m, 2 H), 5.22 (s, 1 H), 2.44 (s, 3 H).

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

δ 152.5, 137.7, 134.0, 130.2, 130.0, 128.9, 128.9, 128.1, 120.8, 115.7, 21.2.

4’-Fluoro-[1,1’-biphenyl]-2-ol (phenol **54**)



30 **54**, 78%

Following *General Procedure* 2 ketone **30** (0.100 g, 0.520 mmol, 1.0 equiv) was converted to 4’-Fluoro-[1,1’-biphenyl]-2-ol. Purification by flash column chromatography using 5% solution of EtOAc in hexanes (R_f = 0.25) afforded phenol **54** (0.076 g, 0.406 mmol, 78%) as a white oil. Spectral data for this compound is consistent with that reported by Manabe and coworkers.[51]

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

δ 7.49-7.46 (m, 2 H), 7.30-7.18 (m, 4 H), 7.04-6.98 (m, 2 H), 5.04 (s, 1 H).

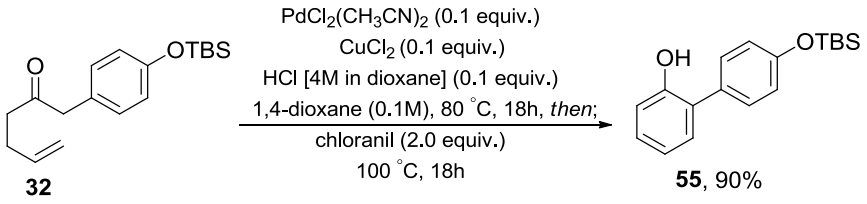
^{13}C NMR (100 MHz, $CDCl_3$)

δ 162.3 (d, $^{1}J_{C\text{-}F}$ = 246 Hz), 152.3, 133.0 (d, $^{4}J_{C\text{-}F}$ = 3 Hz), 130.8 (d, $^{3}J_{C\text{-}F}$ = 8 Hz), 130.2, 129.1, 127.1, 120.9, 116.1 (d, $^{2}J_{C\text{-}F}$ = 22 Hz), 115.8.

^{19}F NMR (282 MHz, CDCl3)

δ –114.2.

4'-(*tert*-butyldimethylsilyl)oxy-[1,1'-biphenyl]-2-ol (phenol **55**)



Following *General Procedure* 2 ketone **32** (0.100 g, 0.328 mmol, 1.0 equiv.) was converted to phenol **55**. Purification by flash column chromatography using 10% solution of EtOAc in hexanes (R_f = 0.35) afforded phenol **55** (0.088 g, 0.293 mmol, 90%) as a yellow oil.

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

δ 7.34 (d, *J* = 8.4 Hz, 2 H), 7.25-7.22 (m, 2 H), 6.99 (dd, *J* = 8.8, 8.8 Hz, 4 H) 5.21 (s, 1 H), 1.03 (s, 9 H), 0.27 (s, 6 H).

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

δ 155.5, 152.4, 130.1, 129.5, 128.7, 127.8, 120.8, 120.6, 115.5, 29.6, 25.5, 18.1, –4.5.

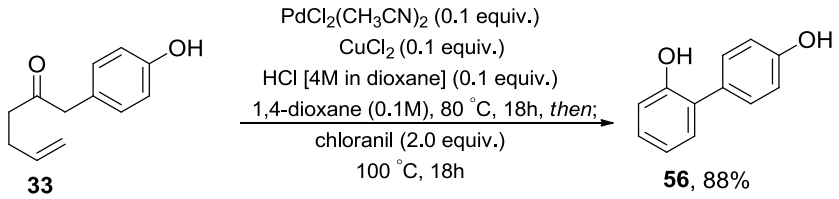
IR Alpha-Platinum ATR, Bruker, diamond crystal

υ = 3529, 2928, 1474, 1100cm^{-1}

HRMS TOF EI

Calculated for $[C_{18}H_{24}O_2Si]^+$ = 300.1546, found = 300.1539.

[1,1'-Biphenyl]-2,4'-diol (phenol **56**)



Following *General Procedure* 2 ketone **33** (0.100 g, 0.526 mmol, 1.0 equiv.) was converted to [1,1'-Biphenyl]-2,4'-diol. Purification by flash column chromatography using 10% solution of EtOAc in hexanes (R_f = 0.25) afforded phenol **56** (0.086 g, 0.462 mmol, 88%) as a white solid. Spectral data for this compound is consistent with that reported by Schmidt and coworkers.[49]

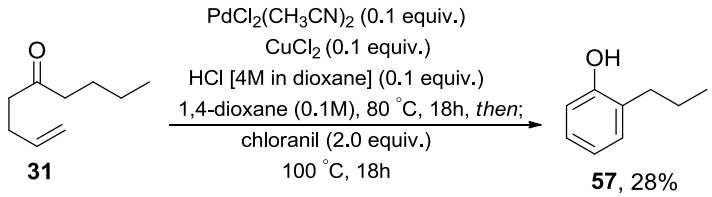
^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.37 (d, *J* = 8.4 Hz, 2 H), 7.24 (dd, *J* = 8.0, 8.0 Hz, 2 H), 7.01-6.97 (m, 4 H), 5.17 (s, 1 H), 4.97 (s, 1 H).

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

δ 155.2, 152.3, 130.4, 130.1, 129.3, 128.7, 127.6, 120.7, 116.0, 115.6.

2-Propylphenol (phenol **57**)



Following *General Procedure* 2 Ketone **31** (0.100 g, 0.713 mmol, 1.0 equiv) was converted to 2-propylphenol. Purification by flash column chromatography using 10% solution of EtOAc in hexanes (R_f = 0.25) afforded phenol **57** (0.027 g, 0.199 mmol, 28%) as a colorless oil. Spectral data for this compound is consistent with that reported by Brunel and coworkers.[52]

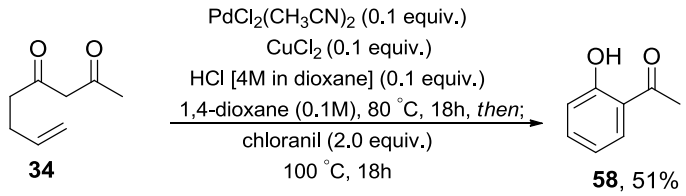
^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.16-7.09 (m, 2 H), 6.90 (dd, *J* = 7.6, 7.2 Hz, 1 H), 6.80 (d, *J* = 7.6 Hz, 1 H), 4.71 (s, 1 H), 2.62 (t, *J* = 7.6 Hz, 2 H), 1.68 (tq, *J* = 7.6, , *J* = 7.2 Hz, 2 H), 1.00 (t, *J* = 7.2 Hz, 3 H).

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

δ 153.6, 130.5, 129.2, 127.2, 121.0, 115.6, 32.2, 23.2, 14.1.

2-Acetylphenol (phenol **58**)



Following *General Procedure* 2 ketone **34** (0.100 g, 0.713 mmol, 1.0 equiv.) was converted to 2-acetylphenol. Purification by flash column chromatography using 5% solution of EtOAc in hexanes (R_f = 0.25) afforded phenol **58** (0.049 g, 0.356 mmol, 50%) as a solid in 50% yield. Spectral data for this compound is consistent with that reported by Takale and coworkers.[53]

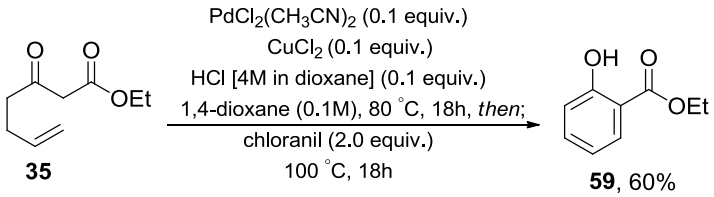
^{1}H NMR (400 MHz, $CDCl_3$)

δ 12.29 (s, 1 H), 7.76 (d, *J* = 7.8 Hz, 1 H), 7.50 (dd, *J* = 7.8, 7.8 Hz, 1 H), 7.00 (d, *J* = 7.8 Hz, 1 H), 6.93 (dd, *J* = 7.8, 7.8 Hz, 1 H), 2.66 (s, 3 H).

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

δ 204.4, 162.0, 136.0, 130.6, 119.3, 118.6, 117.8, 26.0.

Ethyl salicylate (phenol **59**)



35 **59**, 60%

Following *General Procedure* 2 ketone **35** (0.100 g, 0.588 mmol, 1.0 equiv.) was converted to ethyl salicylate. Purification by flash column chromatography using 10% solution of EtOAc in hexanes (R_f = 0.26) afforded phenol **59** (0.059 g, 0.353 mmol, 60%) as a yellow oil. Spectral data for this compound is consistent with that reported by Magano and coworkers.[54]

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

δ 10.87 (s, 1 H), 7.88 (dd, *J* = 8.0, 1.6 Hz, 1 H),

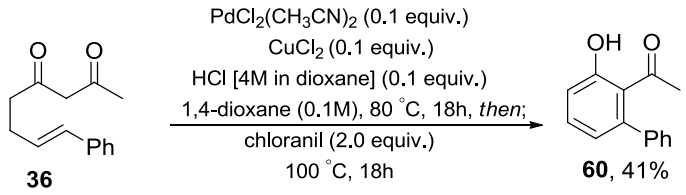
7.47 (ddd, *J* = 8.0, 8.0, 1.6 Hz, 1 H), 7.00 (d, *J* = 8.0 Hz, 1 H),

6.90 (dd, *J* = 8.0, 8.0 Hz, 1 H), 4.43 (q, *J* = 7.2 Hz, 2 H), 1.44 (t, *J* = 7.2 Hz, 3 H).

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

δ 170.0, 161.6, 135.4, 129.7, 118.9, 117.3, 112.4, 61.2, 14.0.

2-Acetyl-3-phenylphenol (phenol **60**)



36 **60**, 41%

Following *General Procedure* 2 ketone **36** (0.100 g, 0.462 mmol, 1.0 equiv.) was converted to 2-Acetyl-3-phenylphenol. Purification by flash column chromatography using 5% solution of EtOAc in hexanes (R_f = 0.23) afforded phenol **60** (0.041 g, 0.189 mmol, 41%) as a yellow solid. Spectral data for this compound is consistent with that reported by Mendez and coworkers.[55]

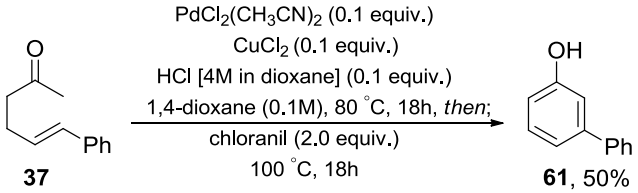
^{1}H NMR (300 MHz, $CDCl_3$)

δ 11.64 (s, 1 H), 7.46-7.45 (m, 4 H), 7.37-7.35 (m, 2 H), 7.02 (d, *J* = 8.4 Hz, 1 H), 6.87 (d, *J* = 7.2 Hz, 1 H), 1.87 (s, 3 H).

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

δ 209.5, 162.5, 145.2, 143.7, 134.0, 130.0, 128.9, 128.1, 122.4, 120.8, 117.7, 32.1.

m-Phenylphenol (phenol **61**)



37 **61**, 50%

Following *General Procedure* 2 ketone **37** (0.100 g, 0.573 mmol, 1.0 equiv.) was converted to *m*-phenylphenol. Purification by flash column chromatography using 15% solution of EtOAc in hexanes (R_f = 0.22) afforded phenol **61** (0.049 g, 0.287 mmol, 50%). Spectral data for this compound is consistent with that reported by Stahl and coworkers.[28]

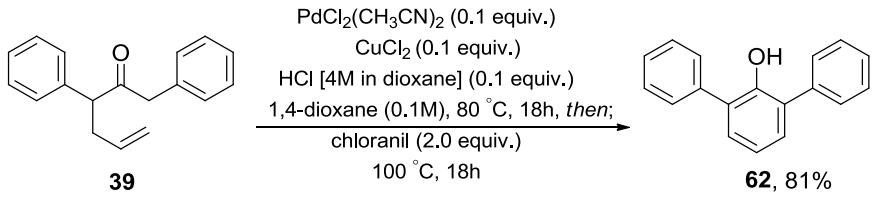
^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.60 (d, *J* = 7.2 Hz, 2 H), 7.46 (dd, *J* = 7.6, 7.6 Hz, 2 H), 7.39-7.32 (m, 2 H), 7.20 (d, *J* = 7.2 Hz, 1 H), 7.09 (s, 1 H), 6.85 (d, *J* = 7.2 Hz, 1 H), 4.80 (s, 1 H).

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

δ 155.7, 143.0, 140.7, 130.1, 128.8, 127.5, 127.1, 119.8, 114.4, 114.2.

2,6-Diphenylphenol (phenol **62**)



39 **62**, 81%

Following *General Procedure* 2 ketone **39** (0.100 g, 0.399 mmol, 1.0 equiv.) was converted to 2,6-diphenylphenol. Purification by flash column chromatography using 5% solution of EtOAc in hexanes (R_f = 0.34) afforded phenol **62** (0.080 g, 0.324 mmol, 81%) as a white oil. Spectral data for this compound is consistent with that reported by Lee and coworkers.[56]

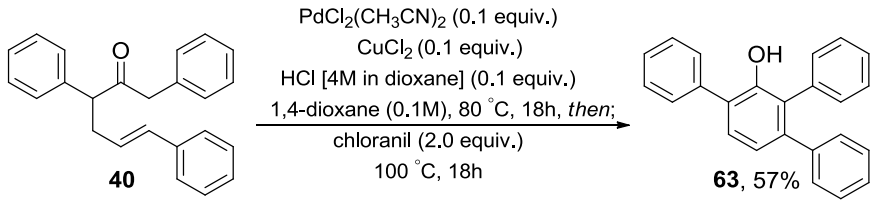
^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.59 (d, *J* = 7.6 Hz, 4 H), 7.51 (dd, *J* = 7.6, 7.6 Hz, 4 H), 7.42 (dd, *J* = 7.6, 7.6 Hz, 2 H), 7.31 (d, *J* = 7.2 Hz, 2 H), 7.10 (t, *J* = 7.6 Hz, 1 H), 5.43 (s, 1 H)

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

δ 149.2, 137.5, 129.9, 129.3, 128.7, 128.7, 127.5, 120.6.

2,3,6-triphenylphenol (phenol **63**)



Following *General Procedure* 2 ketone **40** (0.100 g, 0.306 mmol, 1.0 equiv.) was converted to 2,3,6-triphenylphenol. Purification by flash column chromatography using 10% solution of EtOAc in hexanes (R_f = 0.35) afforded phenol **63** (0.056 g, 0.175 mmol, 57%) as a white solid. Spectral data for this compound is consistent with that reported by Kim and coworkers.[57]

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

δ 7.66 (d, *J* = 7.6 Hz, 2 H), 7.50 (dd, *J* = 7.6, 7.6 Hz, 2 H),

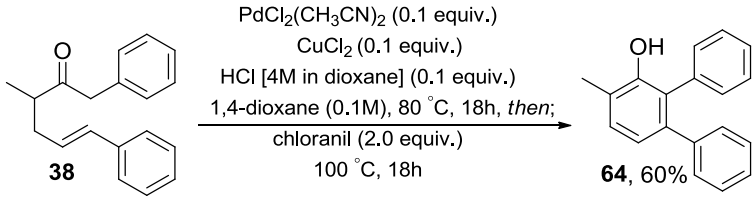
7.41 (d, *J* = 7.6 Hz, 2 H), 7.40-7.31 (m, 3 H), 7.24 (d, *J* = 7.2 Hz, 2 H),

7.20-7.18 (m, 3 H), 7.13 (d, *J* = 7.6 Hz, 3 H), 5.34 (s, 1 H).

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

δ 149.7, 141.6, 140.9, 137.8, 135.3, 131.1, 129.7, 129.6, 129.3, 128.8, 128.5, 127.6, 127.3, 126.4, 122.3.

6-methyl-2,3-diphenylphenol (phenol **64**)



Following *General Procedure* 2 ketone **38** (0.100 g, 0.378 mmol, 1.0 equiv.) was converted to 6-methyl-2,3-diphenylphenol. Purification by flash column chromatography using 10% solution of EtOAc in hexanes (R_f = 0.30) afforded phenol **64** (0.059 g, 0.227 mmol, 60%) as an orange solid. Spectral data for this compound is consistent with that reported by Huguet and coworkers.[58]

^{1}H NMR (700 MHz, $CDCl_3$)

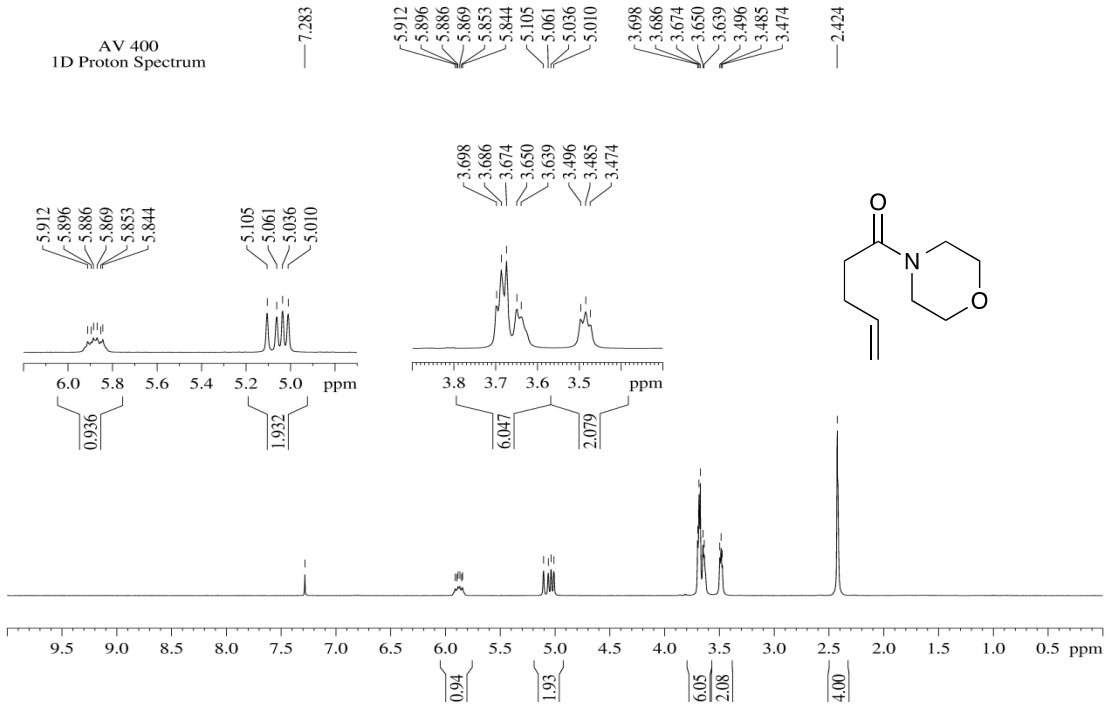
δ 7.35 (ddd, *J* = 7.2, 7.2, 0.7 Hz, 2 H), 7.31-7.28 (m, 1 H), 7.23 (d, *J* = 7.7 Hz, 1 H), 7.19 (dd, *J* = 7, 1.4 Hz, 2 H), 7.16-7.15 (m, 3 H), 7.08-7.07 (m, 2 H), 6.96 (d, *J* = 7.7 Hz, 1 H), 5.18 (s, 1 H), 2.37 (s, 3 H).

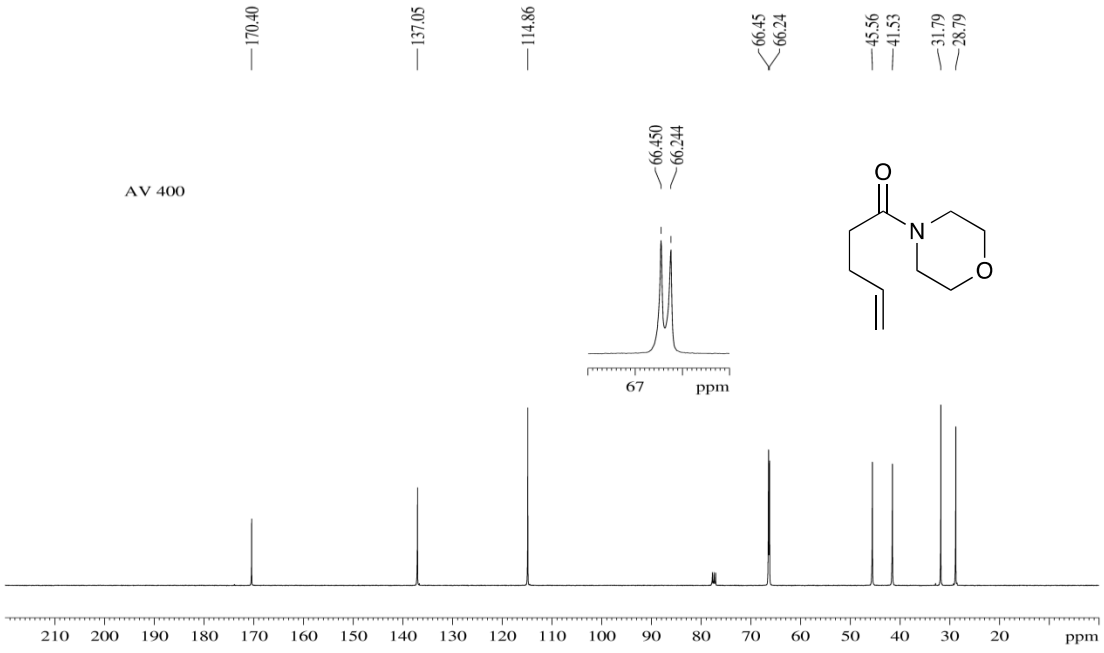
^{13}C NMR (176 MHz, $CDCl_3$)

δ 150.9, 141.2, 139.7, 135.3, 131.0, 130.0, 129.6, 129.1, 127.7, 127.6, 126.2, 126.1, 123.5, 121.7, 16.2.

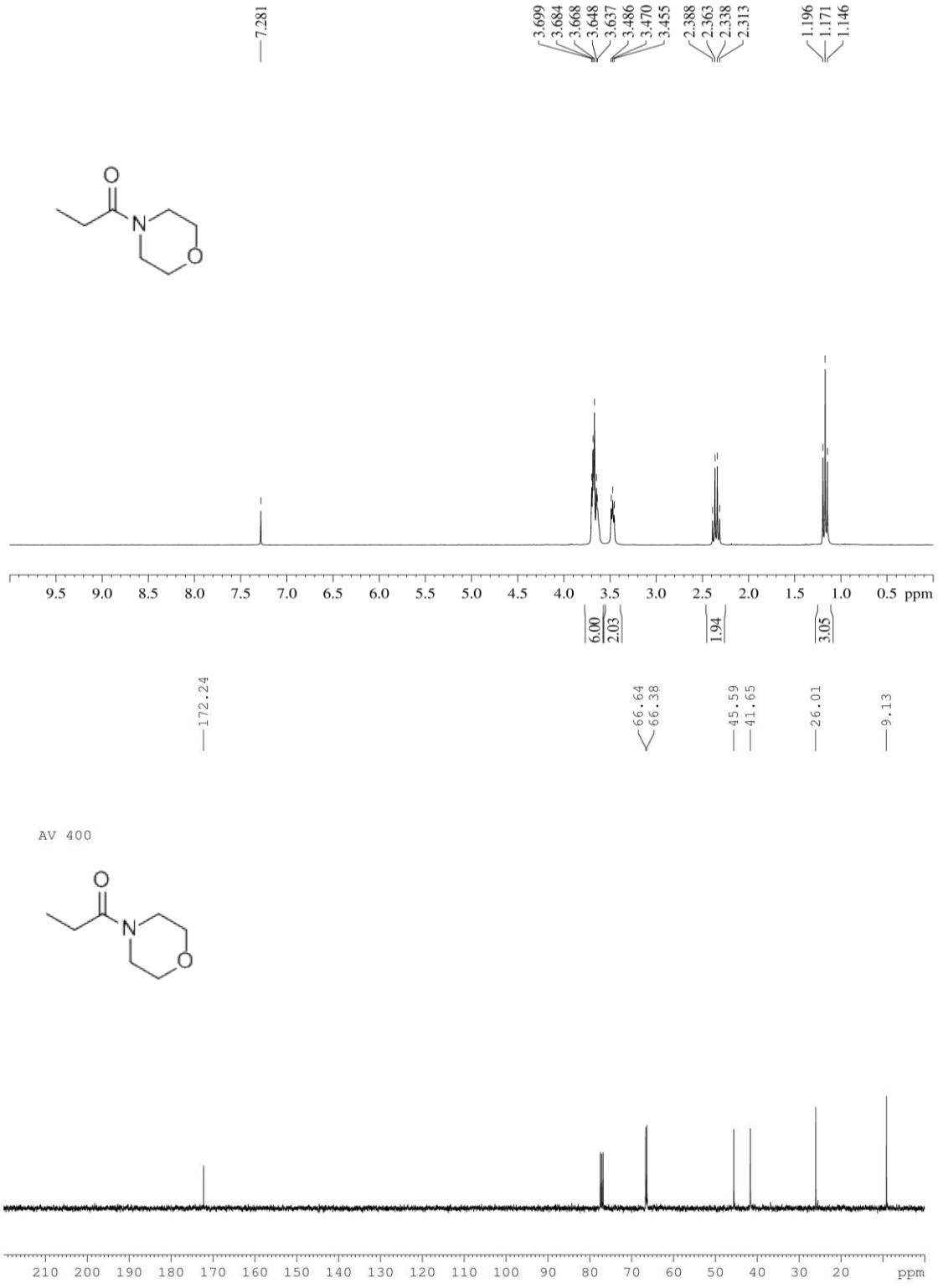
3.2 NMR spectra

^{1}H and ^{13}C-NMR spectra of 1-(4-morpholinyl)-4-penten-1-one **46**

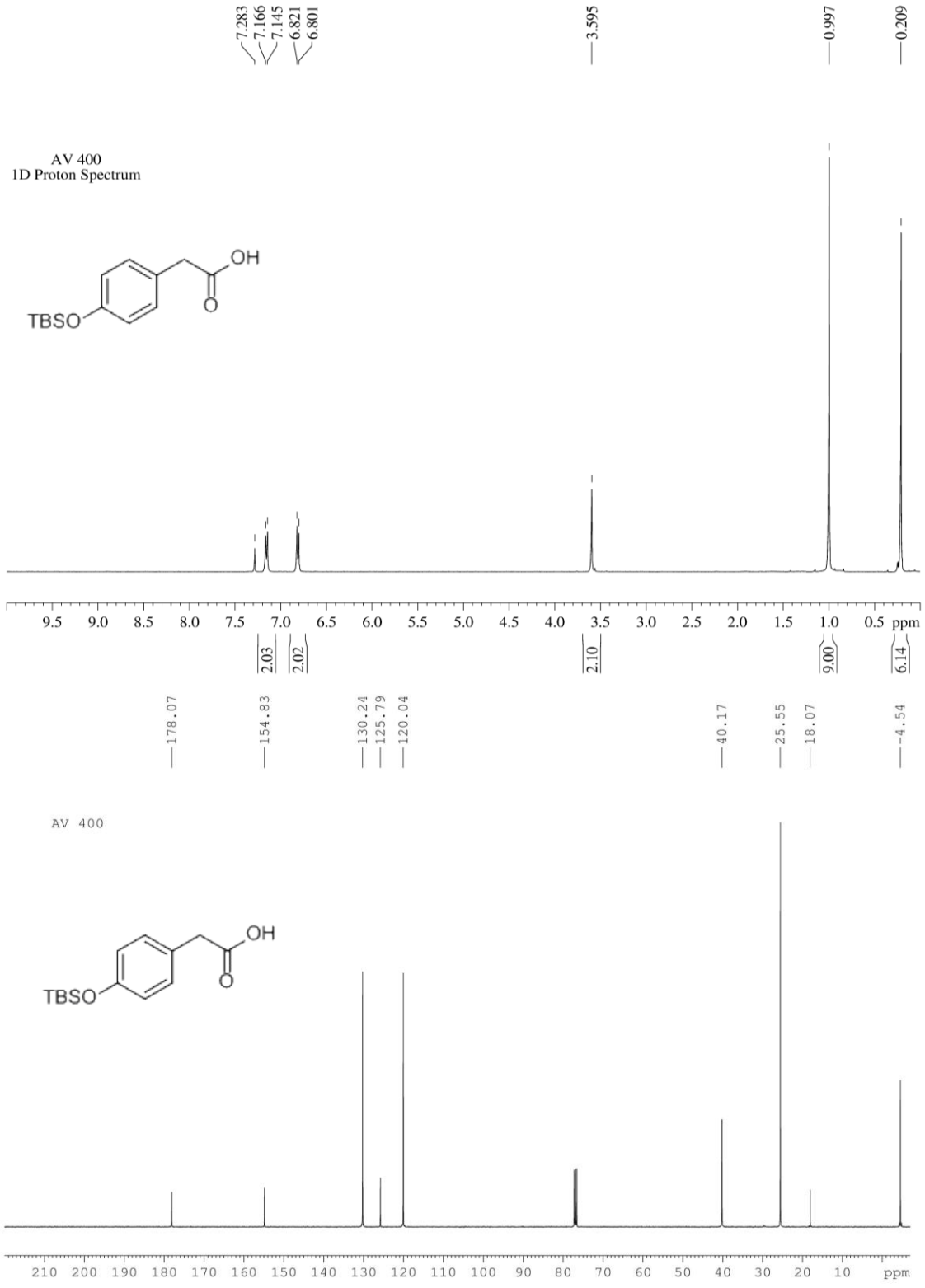




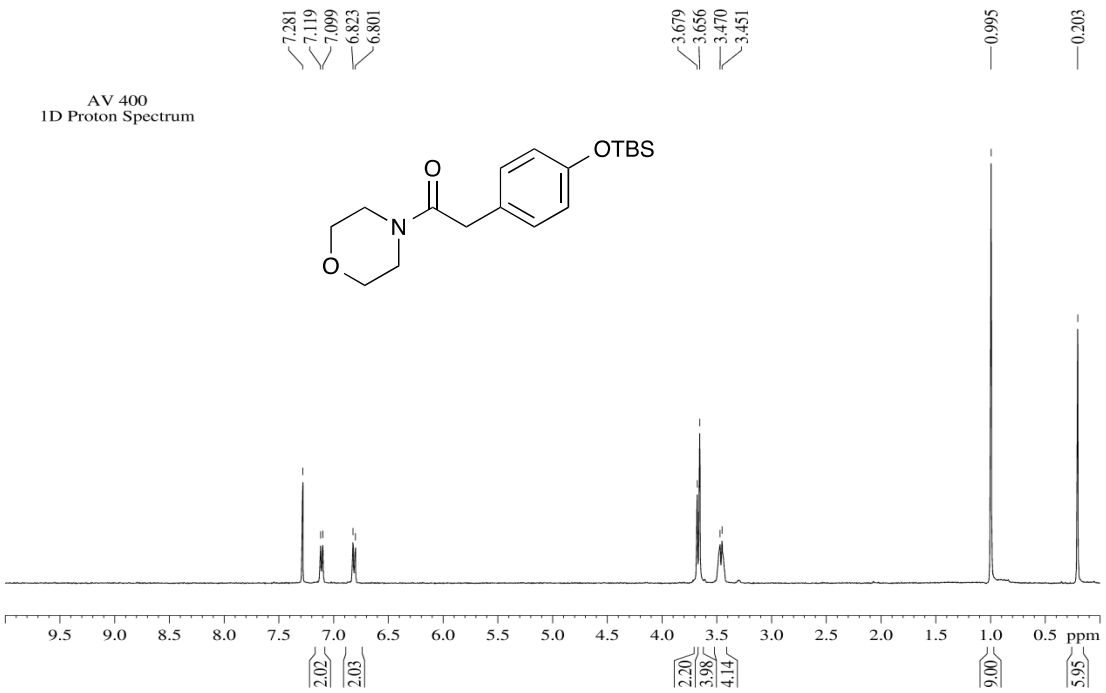
^{1}H and ^{13}C-NMR spectra of 1-morpholinopropan-1-one **48**

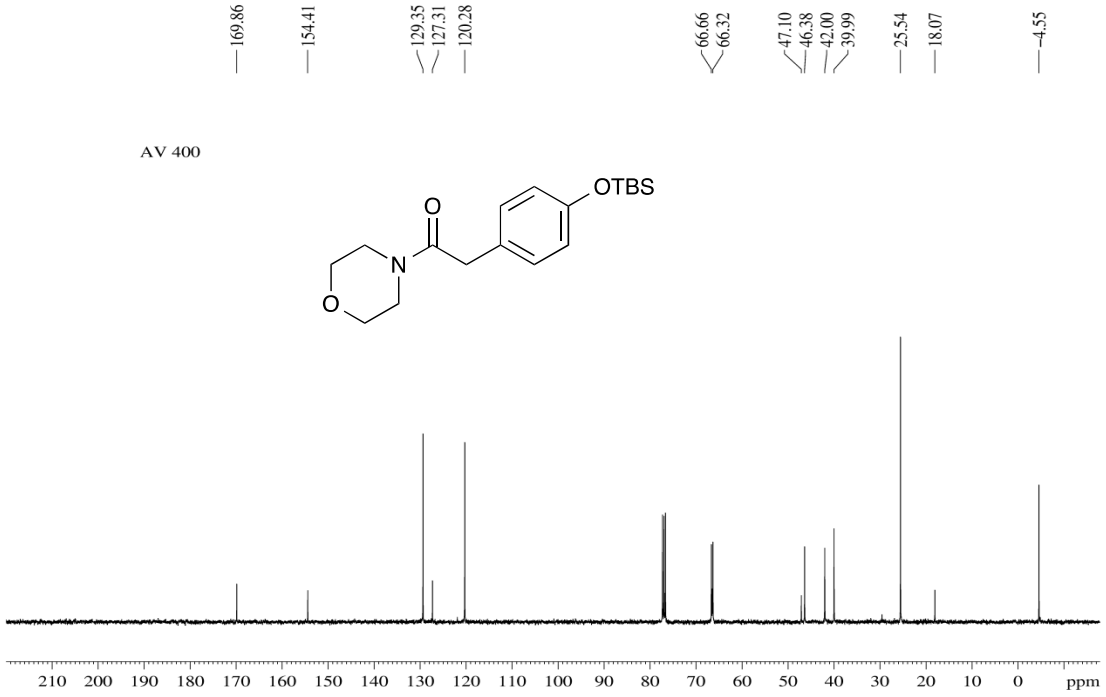


^{1}H and ^{13}C-NMR spectra of 2-(4-((tert-butyldimethylsilyl)oxy)phenyl)acetic acid **50**

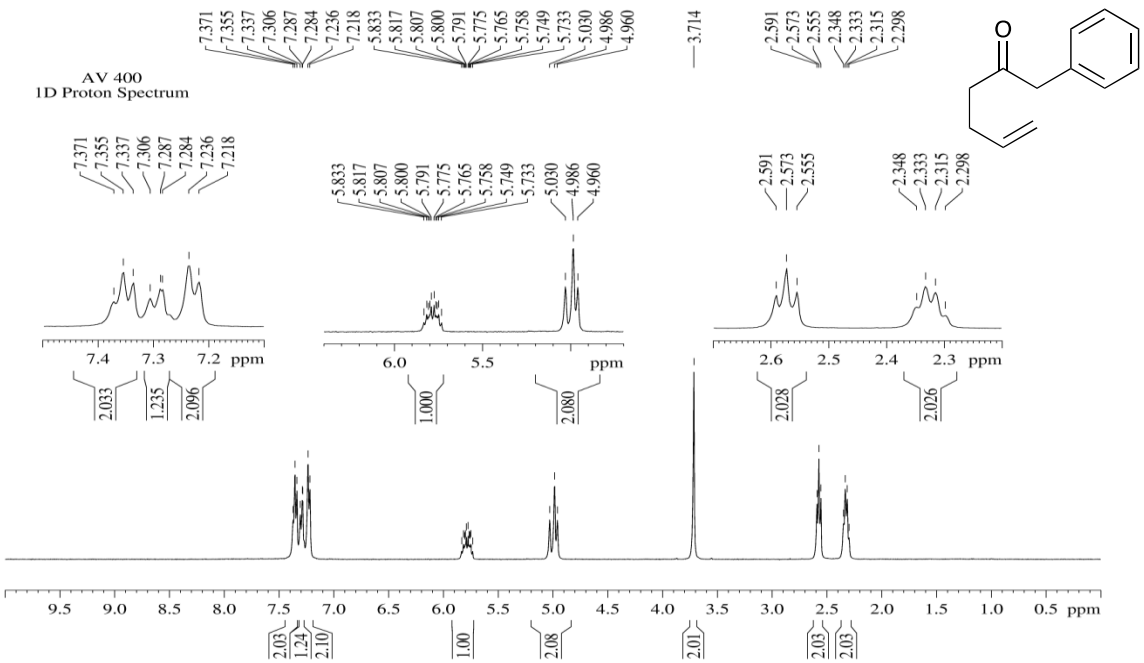


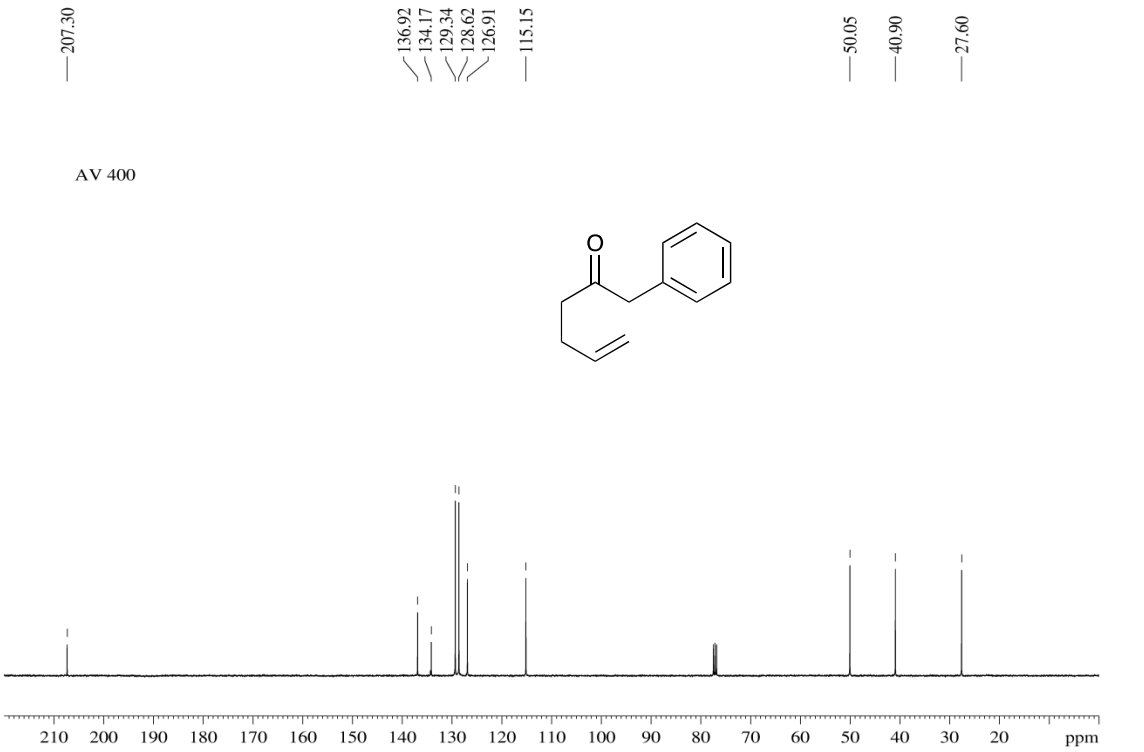
^{1}H and ^{13}C-NMR spectra of 2-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-1-(4-morpholinyl)ethanone**51**



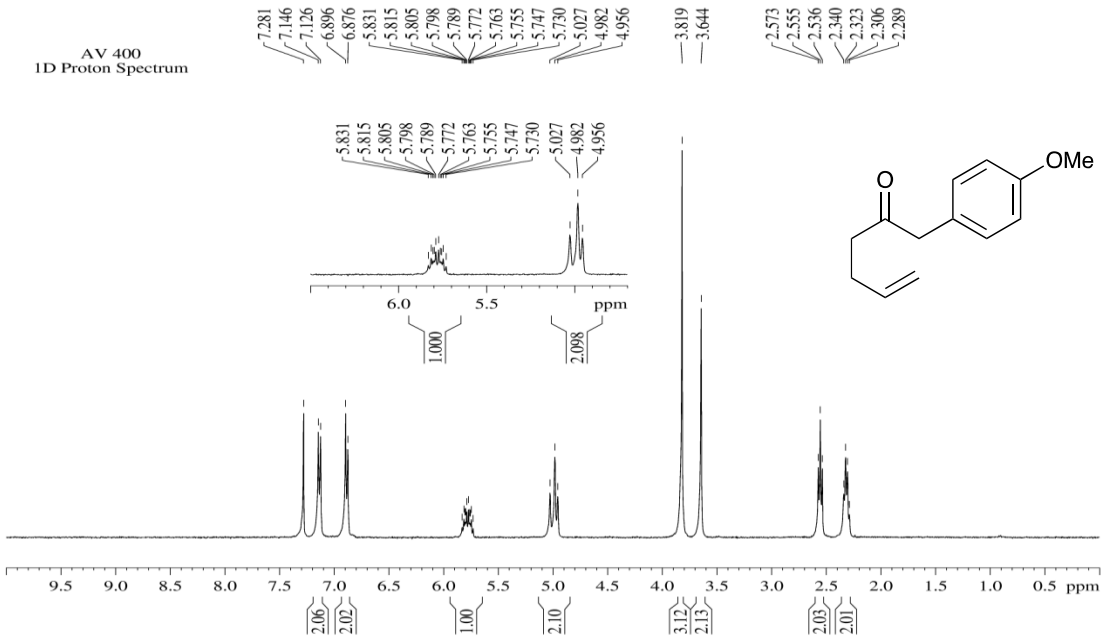


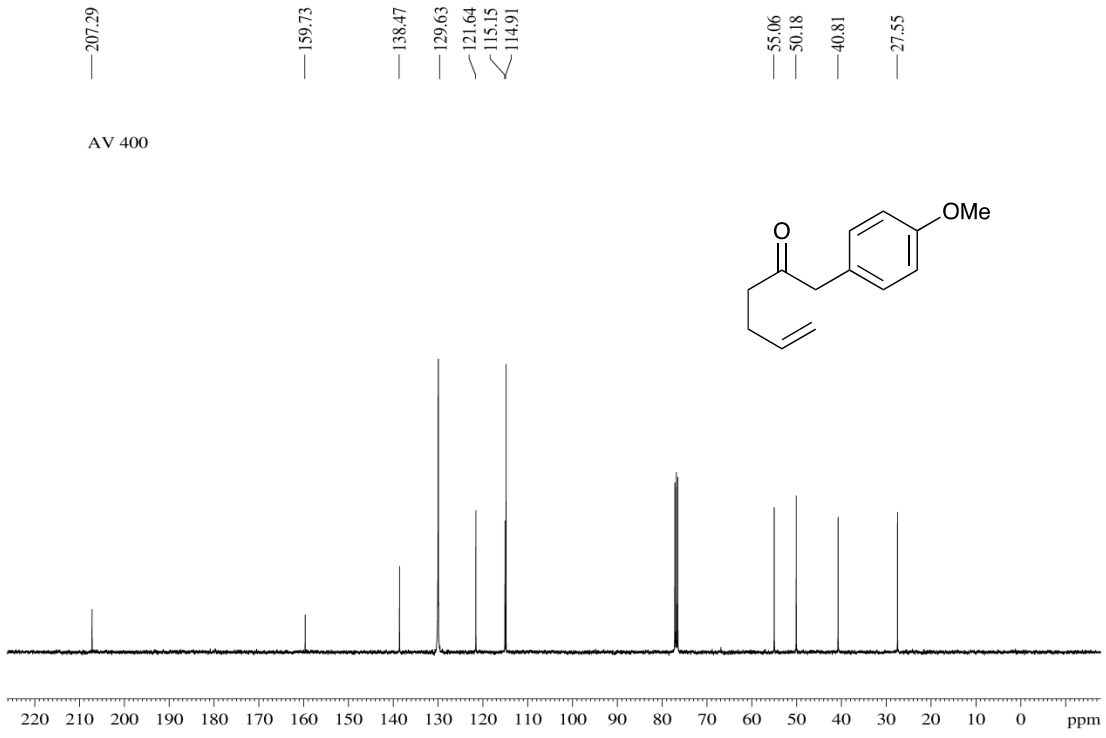
^{1}H and ^{13}C-NMR spectra of 1-Phenyl-5-hexen-2-one **26**



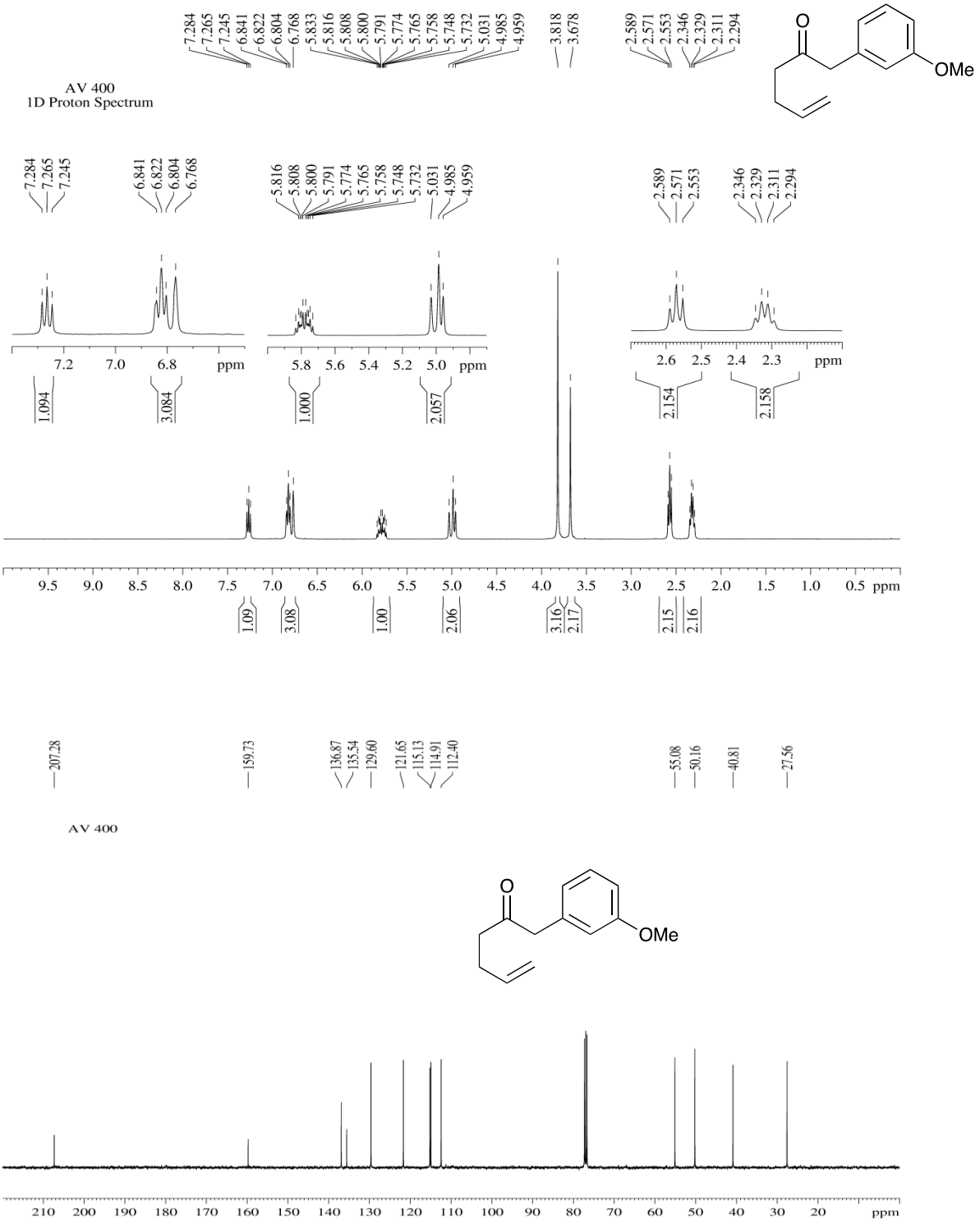


^{1}H and ^{13}C-NMR spectra of 1-(4-methoxyphenyl)-5-hexen-2-one **27**

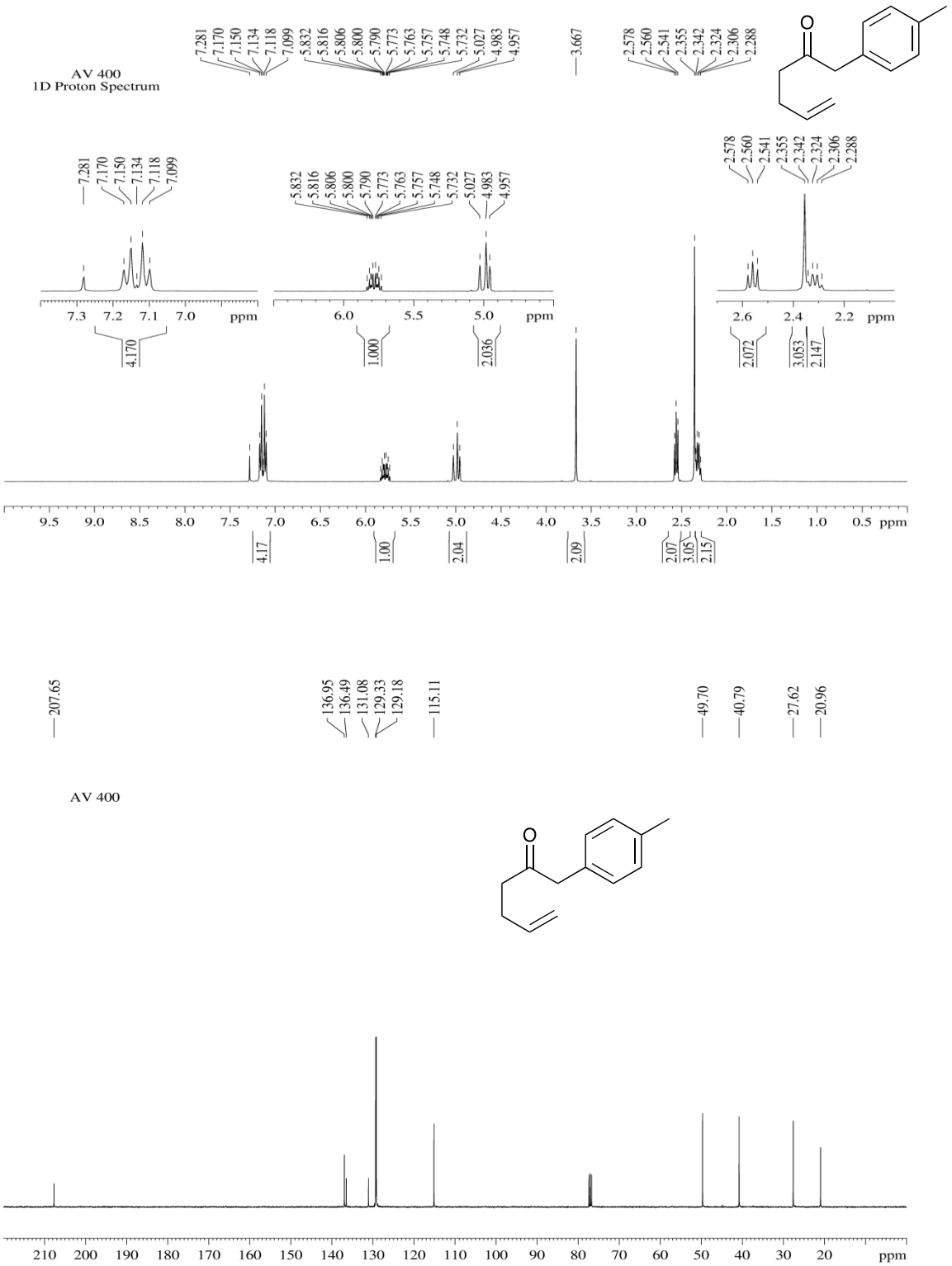




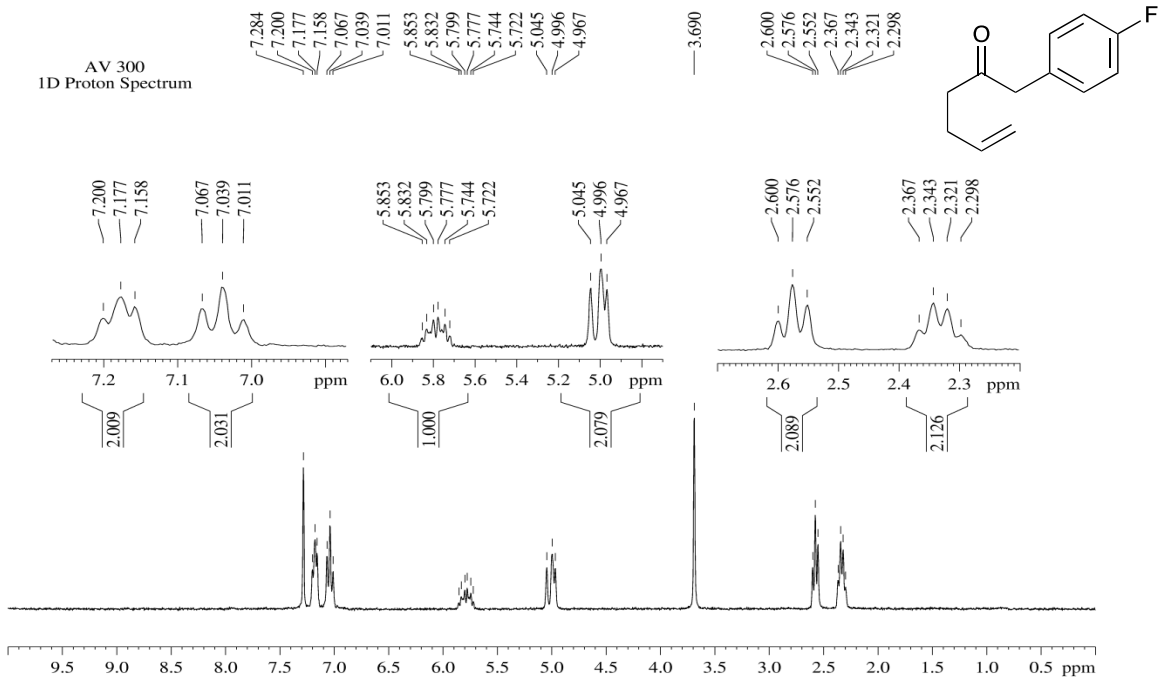
^{1}H and ^{13}C-NMR spectra of 1-(3-methoxyphenyl)-5-hexen-2-one **28**

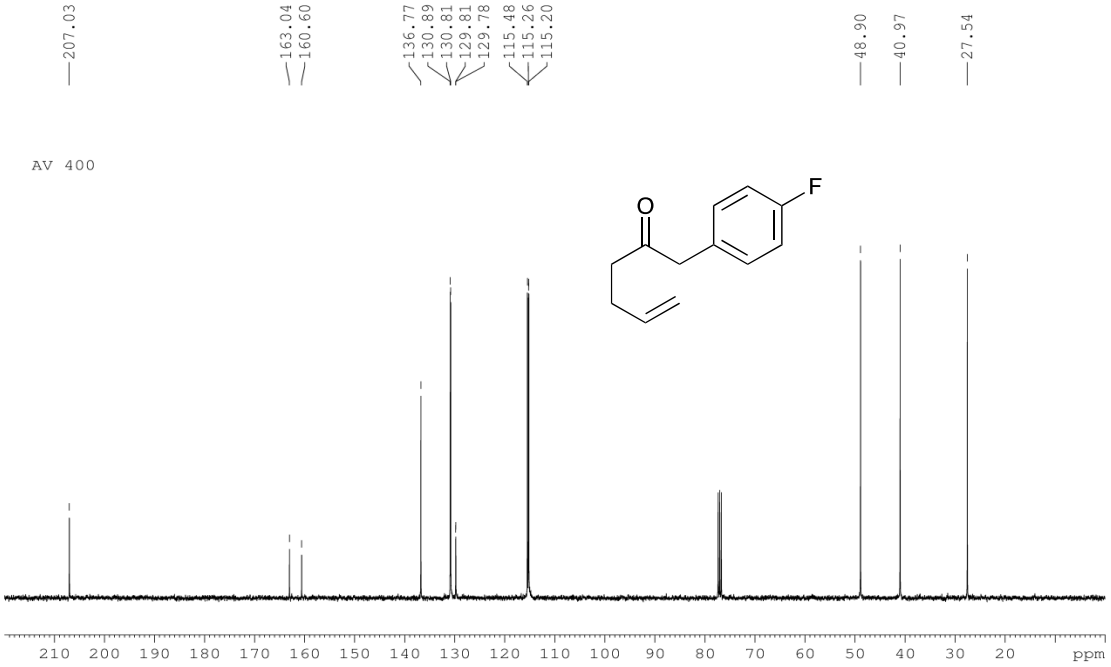


^{1}H and ^{13}C-NMR spectra of 1-(4-methylphenyl)-5-hexen-2-one **29**

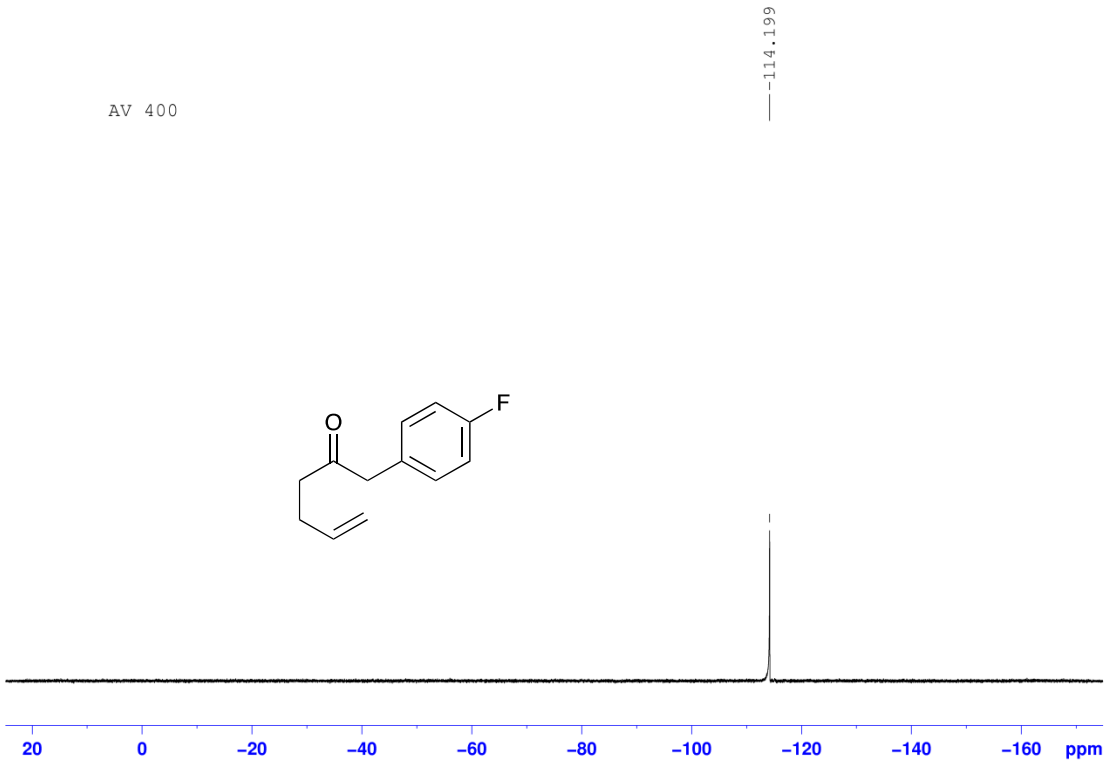


^{1}H and ^{13}C-NMR spectra of 1-(4-fluorophenyl)-5-hexen-2-one **30**

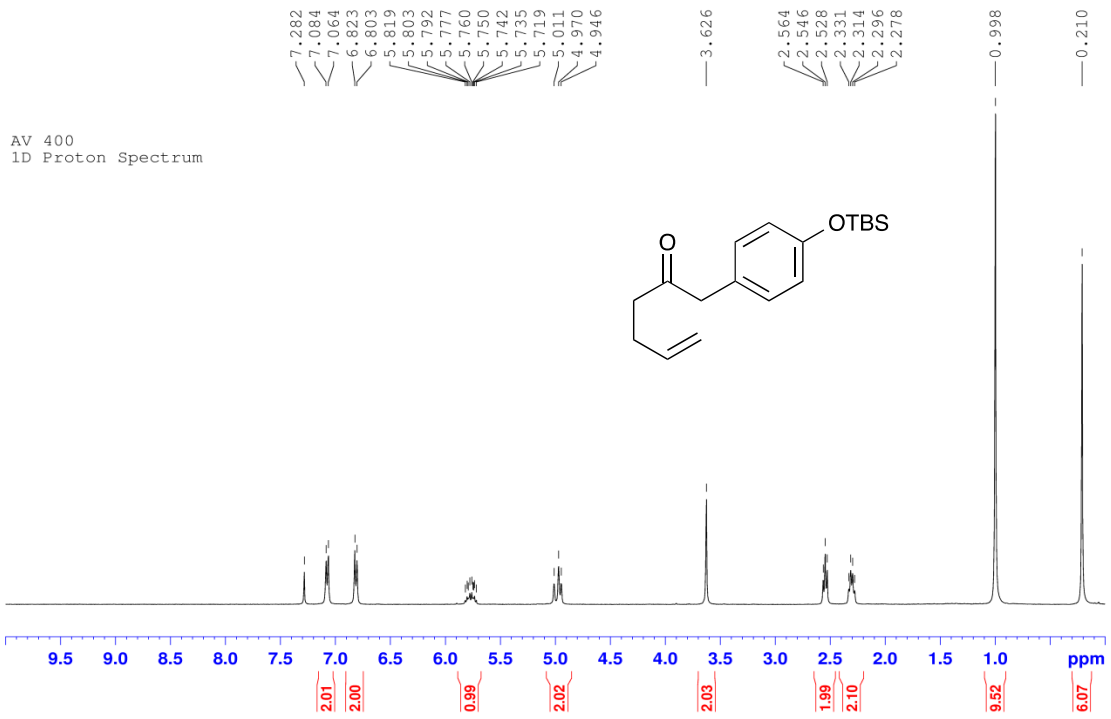


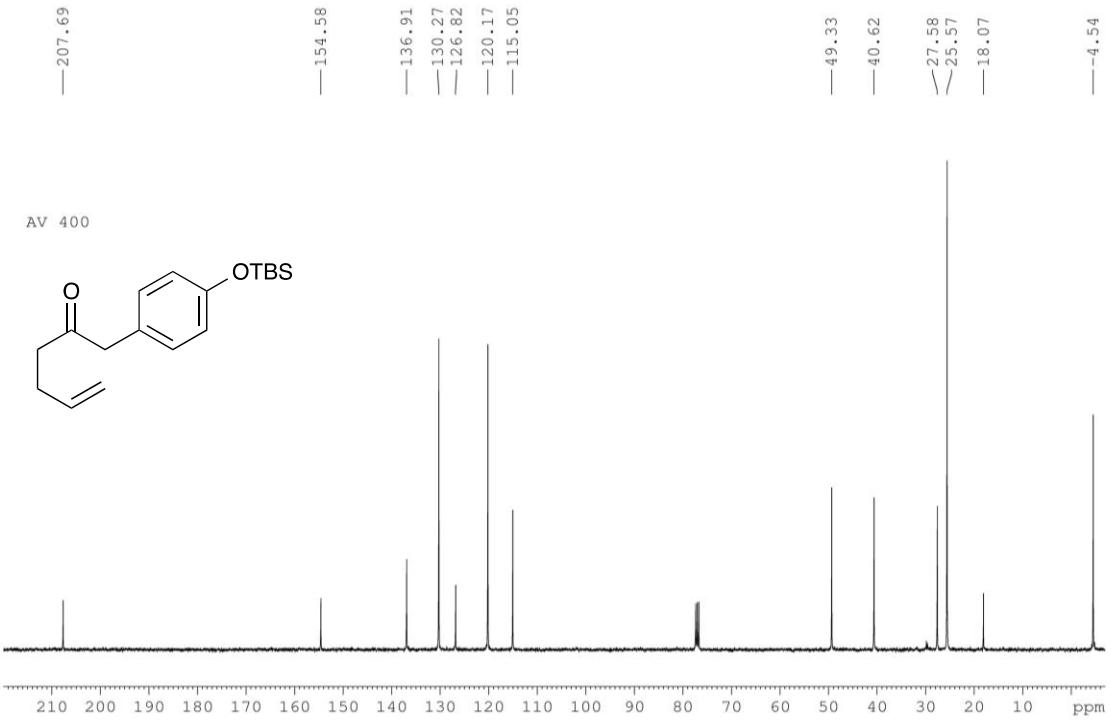


^{19}F-NMR spectra of 1-(4-fluorophenyl)-5-hexen-2-one **30**

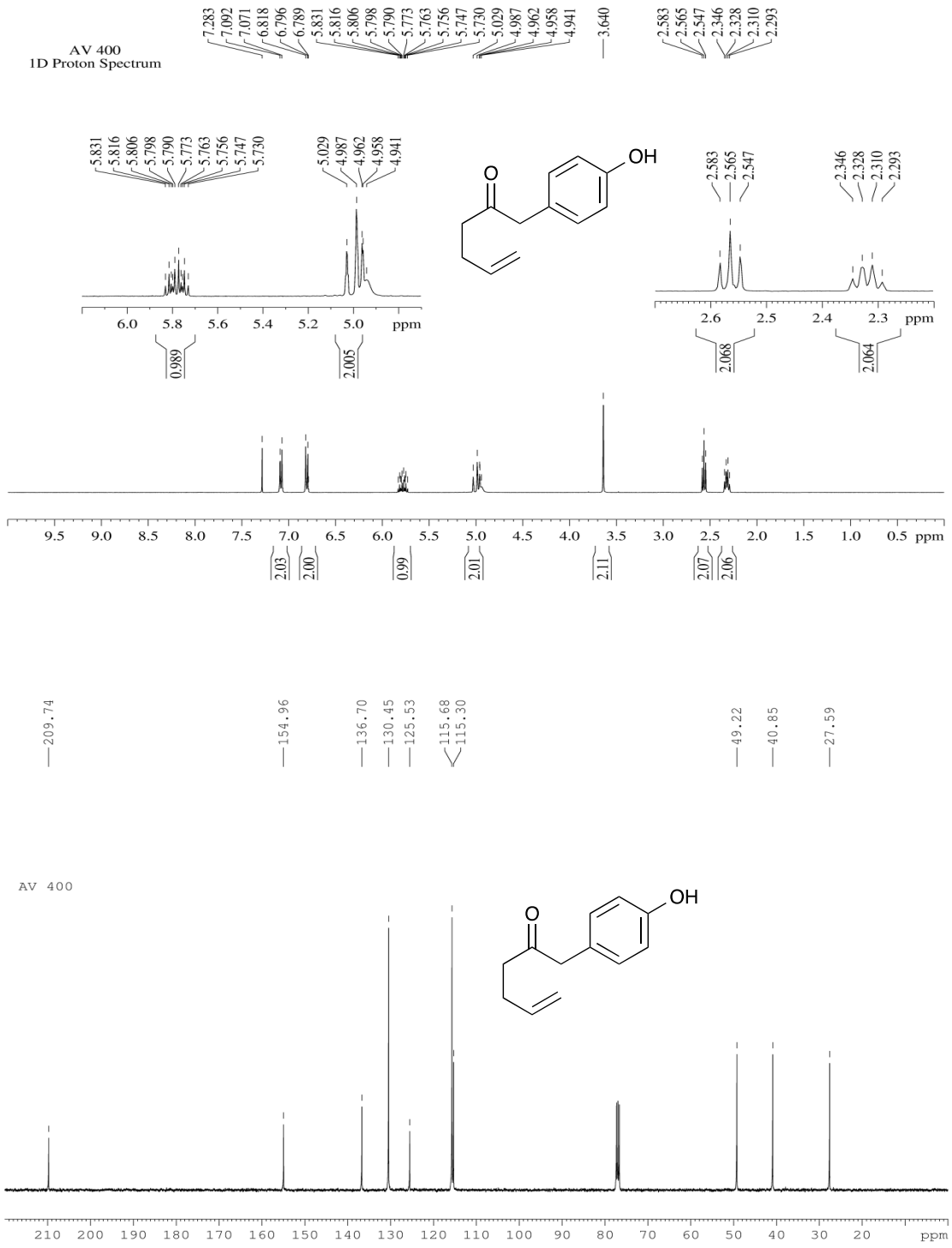


^{1}H and ^{13}C-NMR spectra of 1-(4-((*tert*-butyldimethylsilyl)oxy)phenyl)-5-hexen-2-one **32**

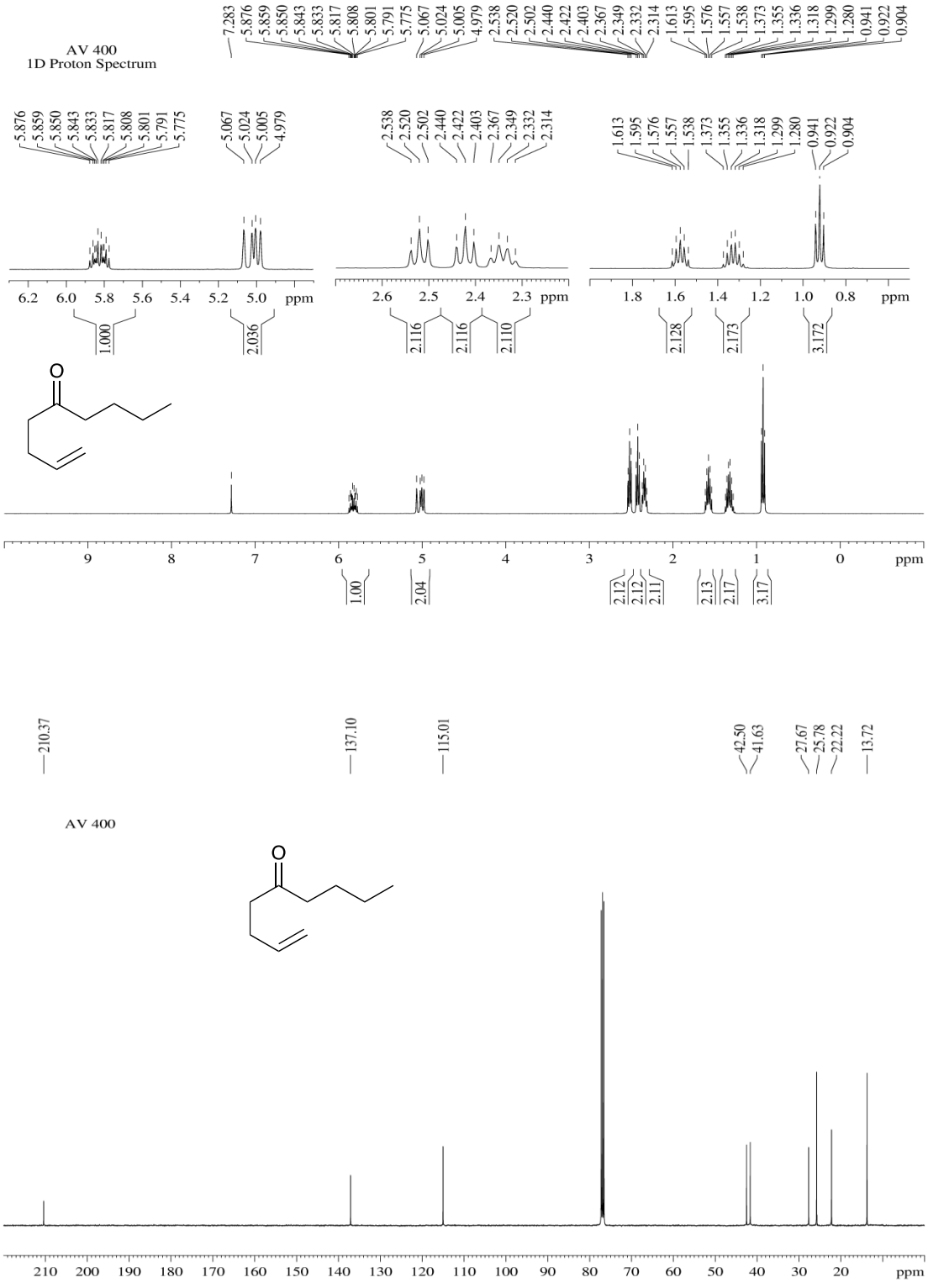




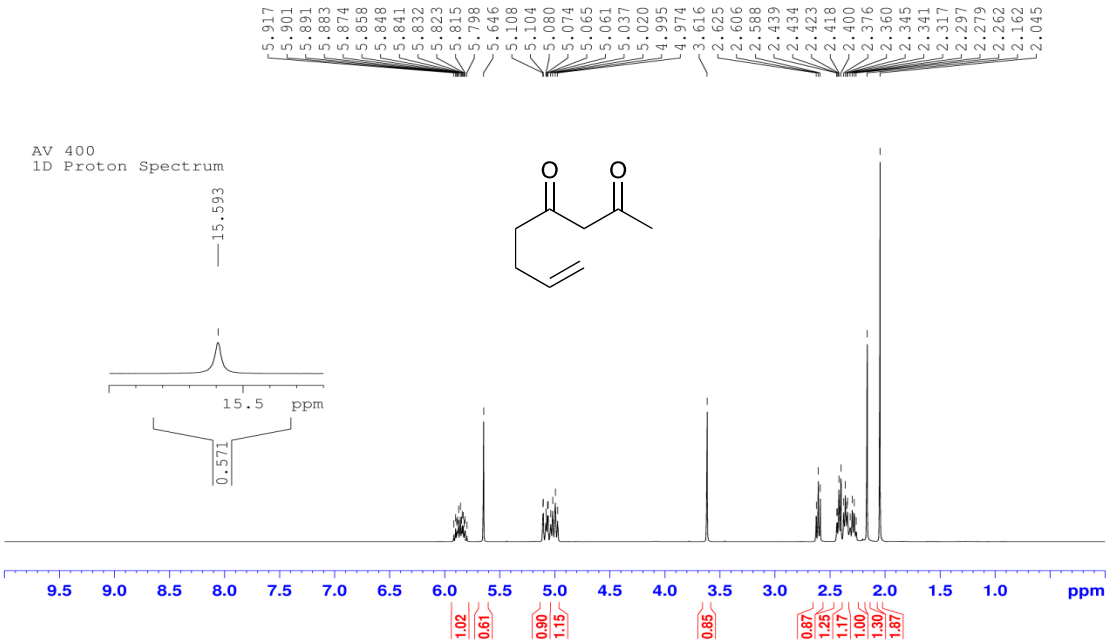
^{1}H and ^{13}C-NMR spectra of 1-(4-hydroxyphenyl)-5-hexen-2-one **33**

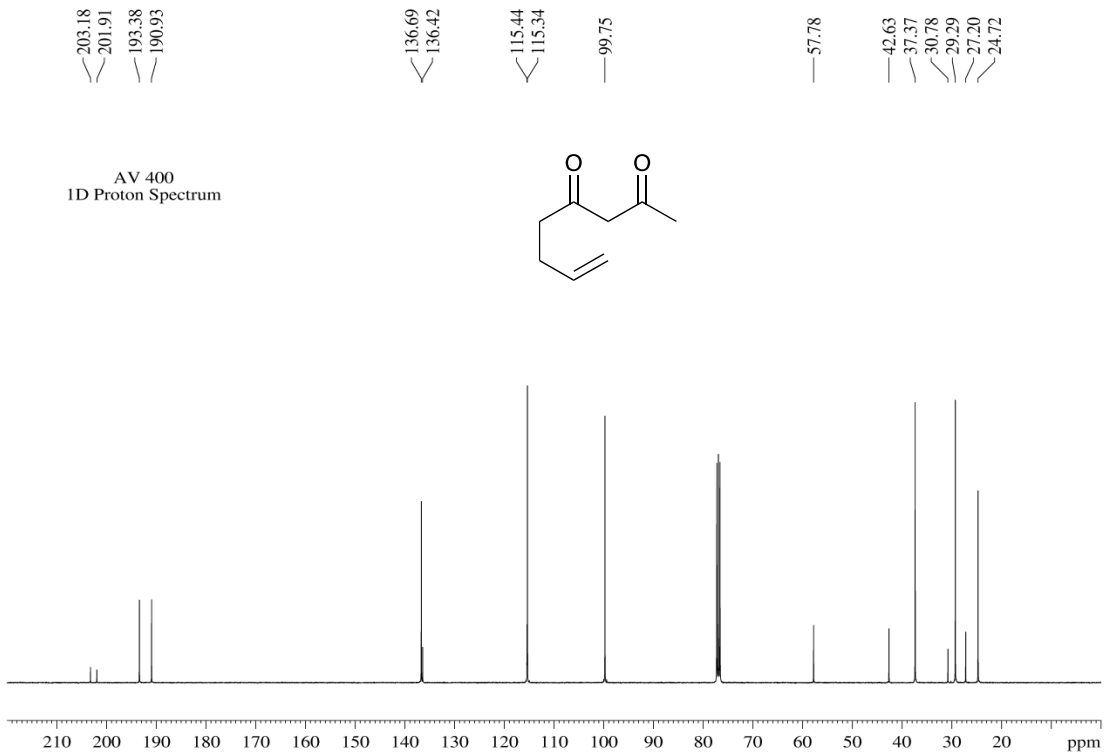


^{1}H and ^{13}C-NMR spectra of 1-nonen-5-one **31**

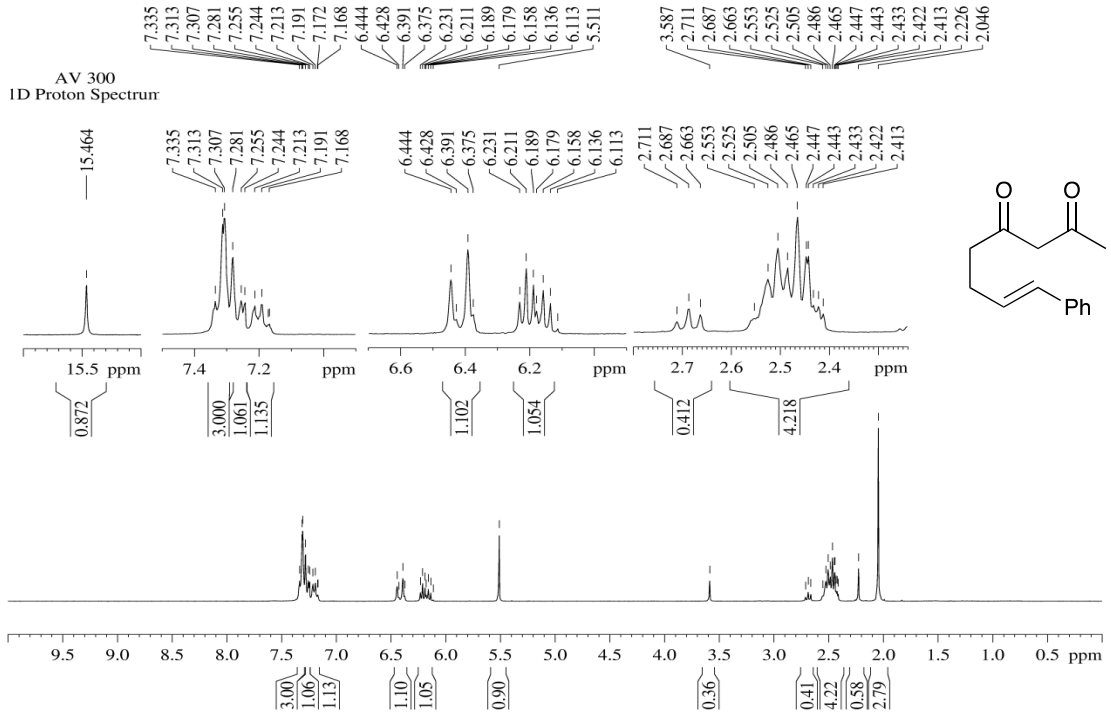


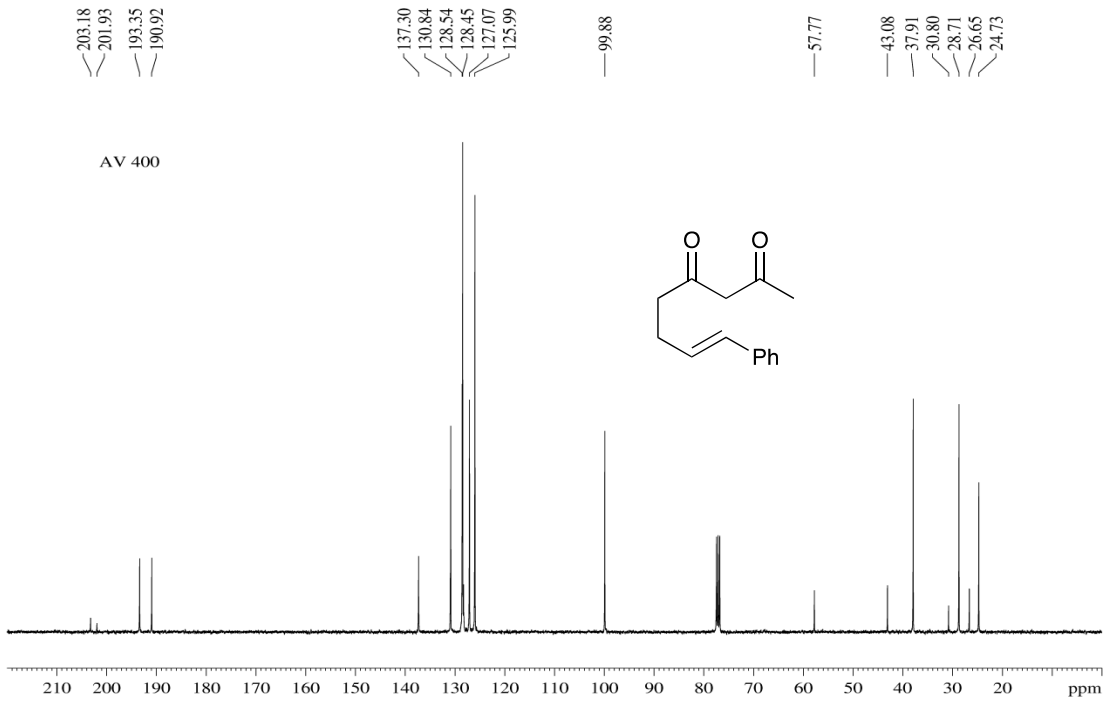
^{1}H and ^{13}C-NMR spectra of 7-octene-2,4-dione **34**



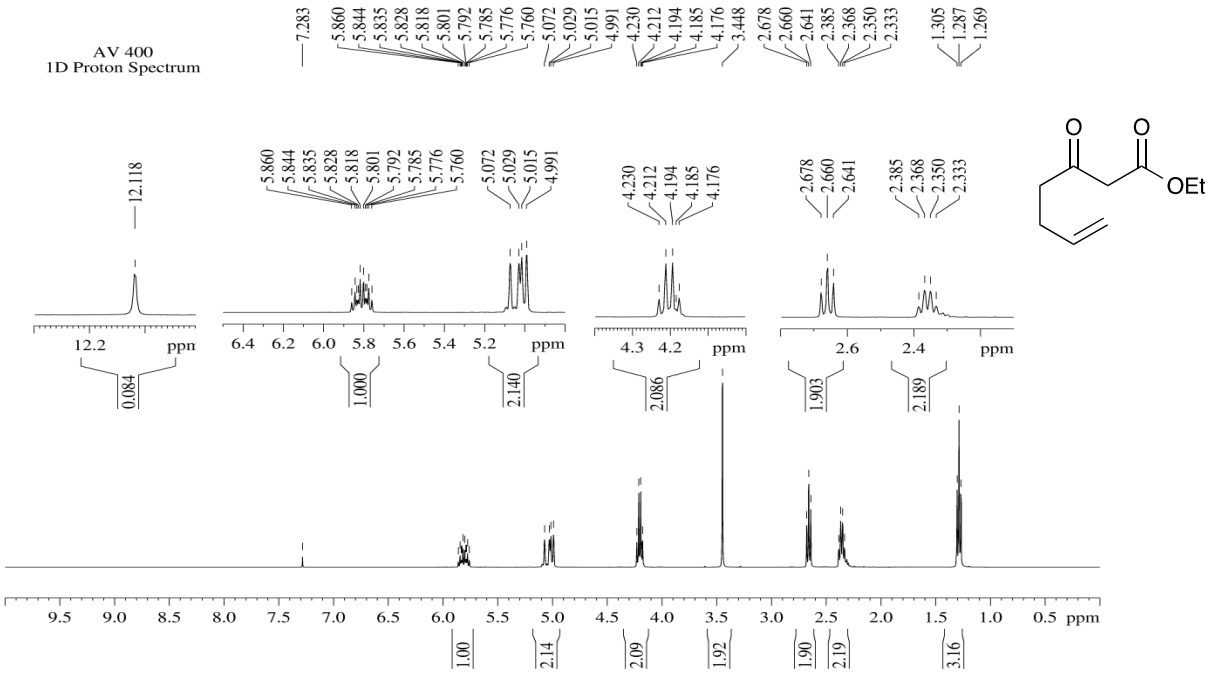


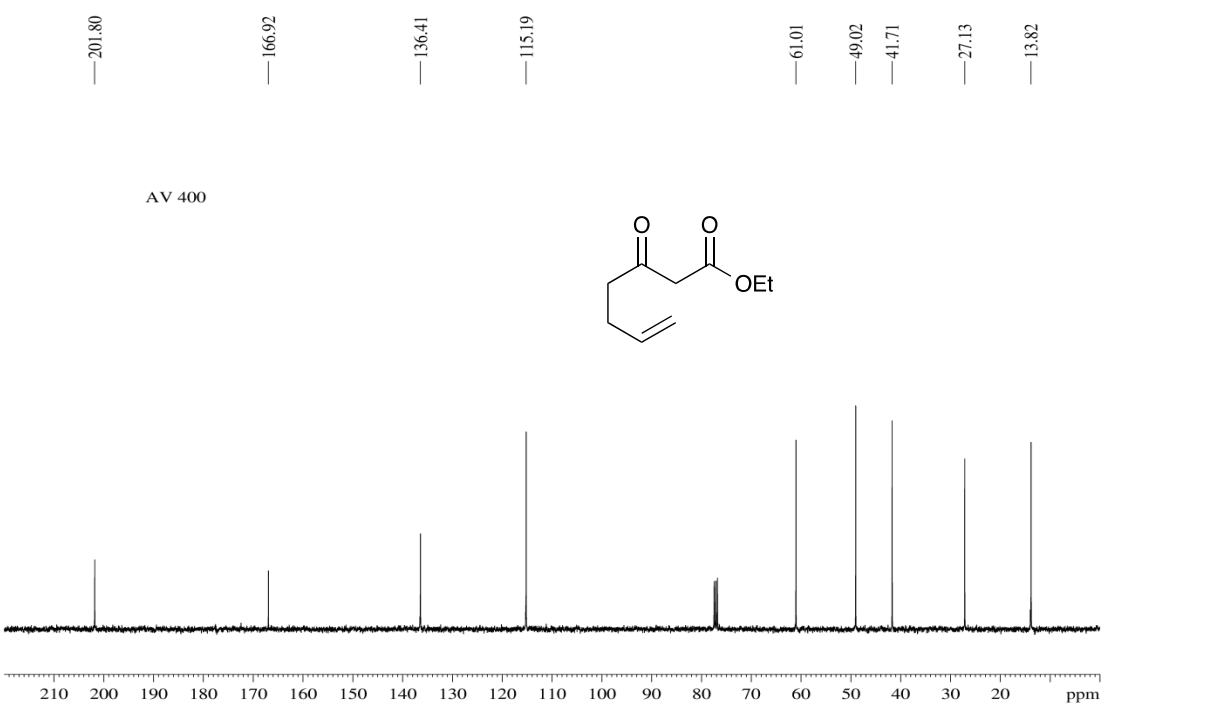
^{1}H and ^{13}C-NMR spectra of 8-phenyl-(7*E*)-7-octene-2,4-dione **36**



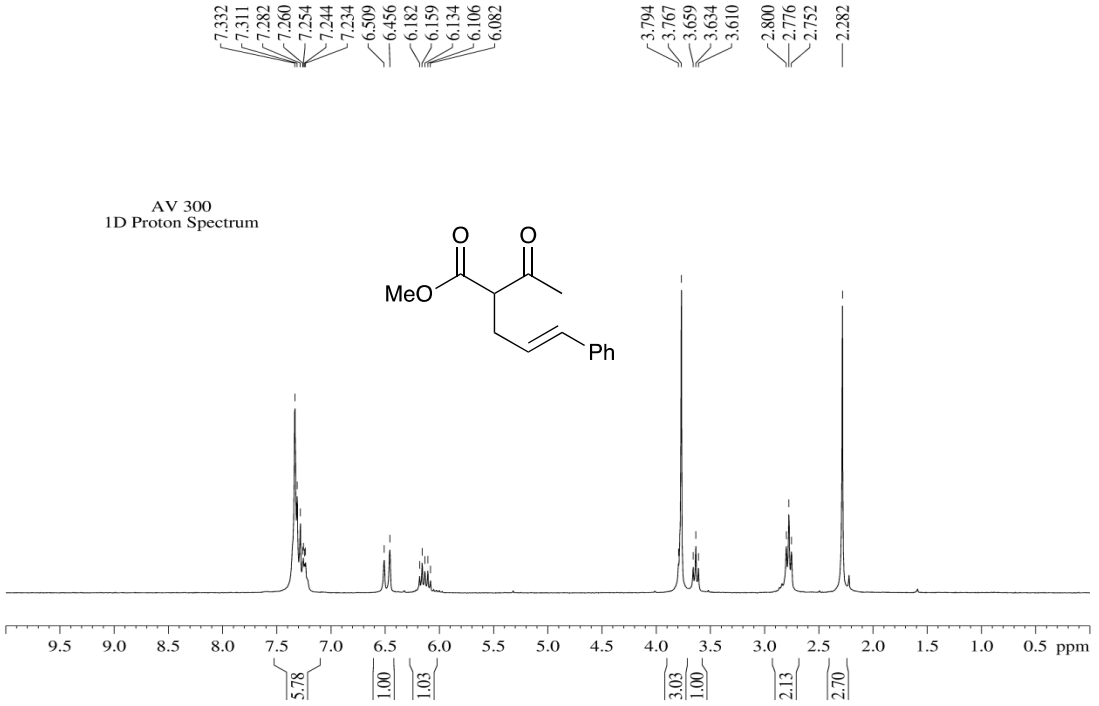


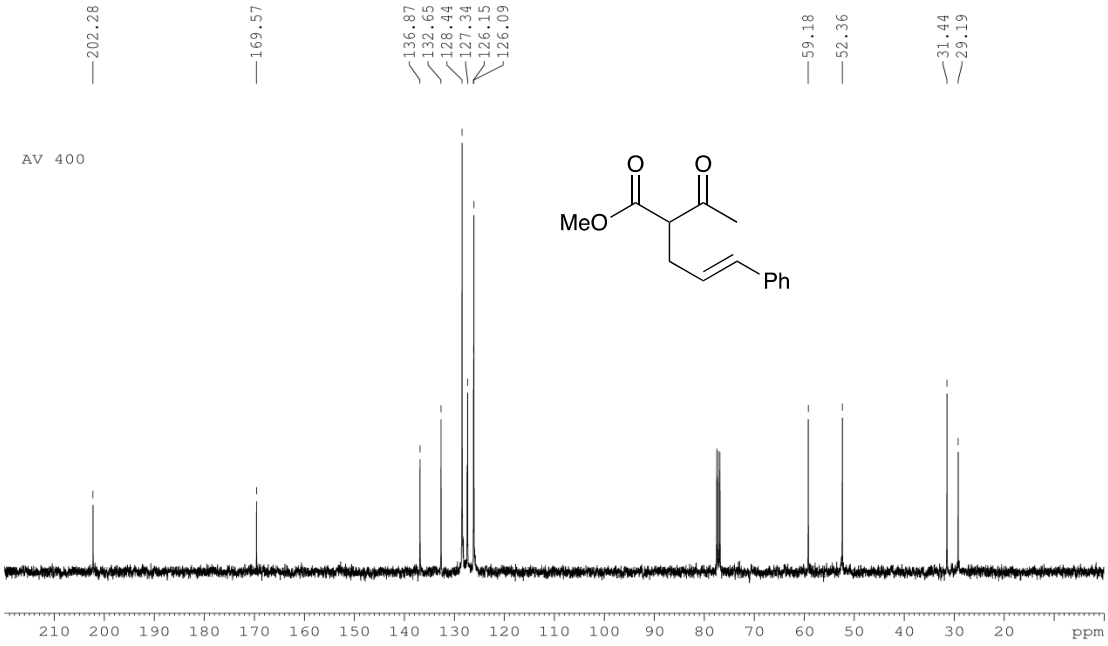
^{1}H and ^{13}C-NMR spectra of 3-oxo-6-heptenoic acid ethyl ester **35**



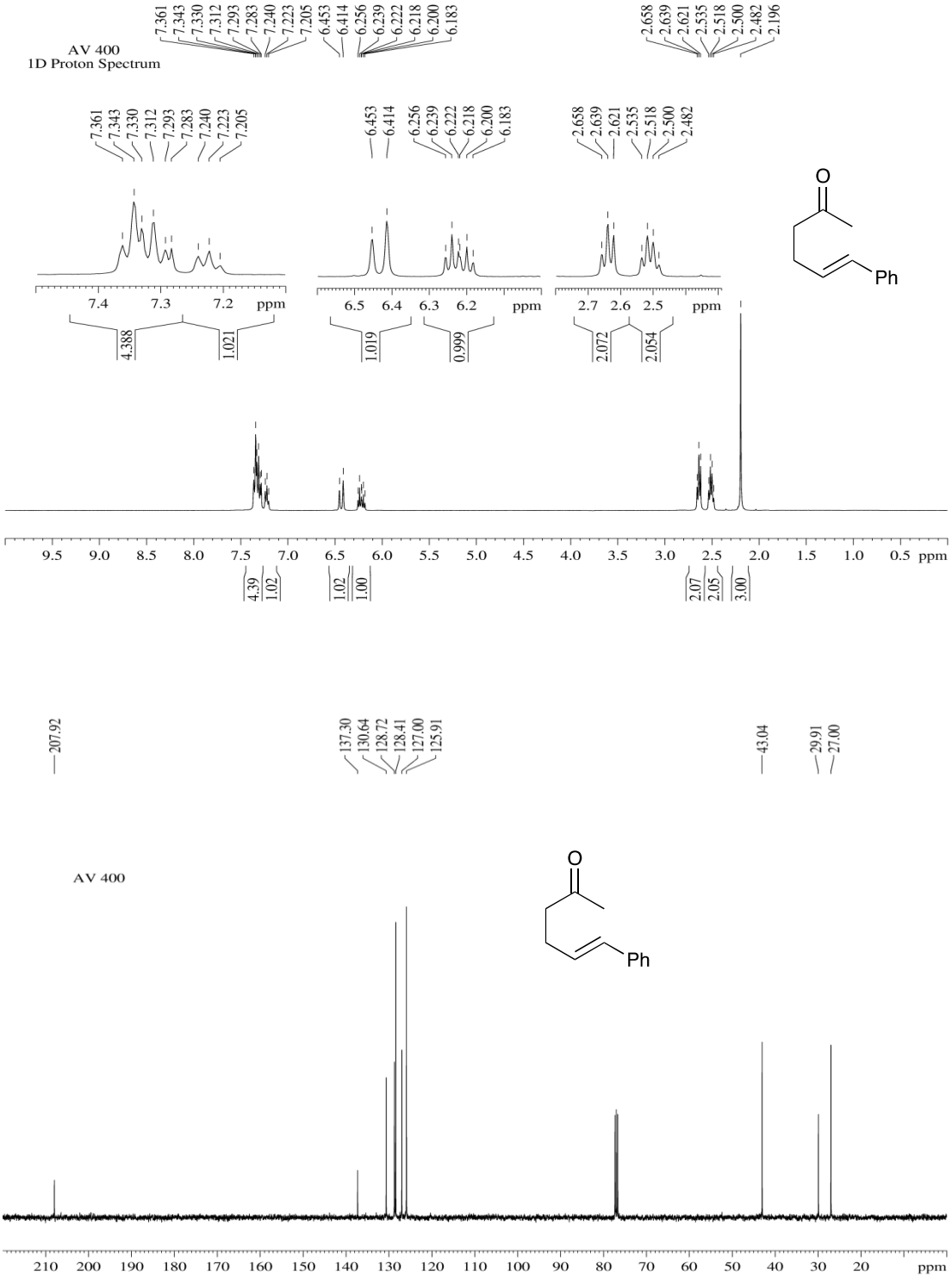


^{1}H and ^{13}C-NMR spectra of methyl 2-acetyl-5-phenylpent-4-enoate

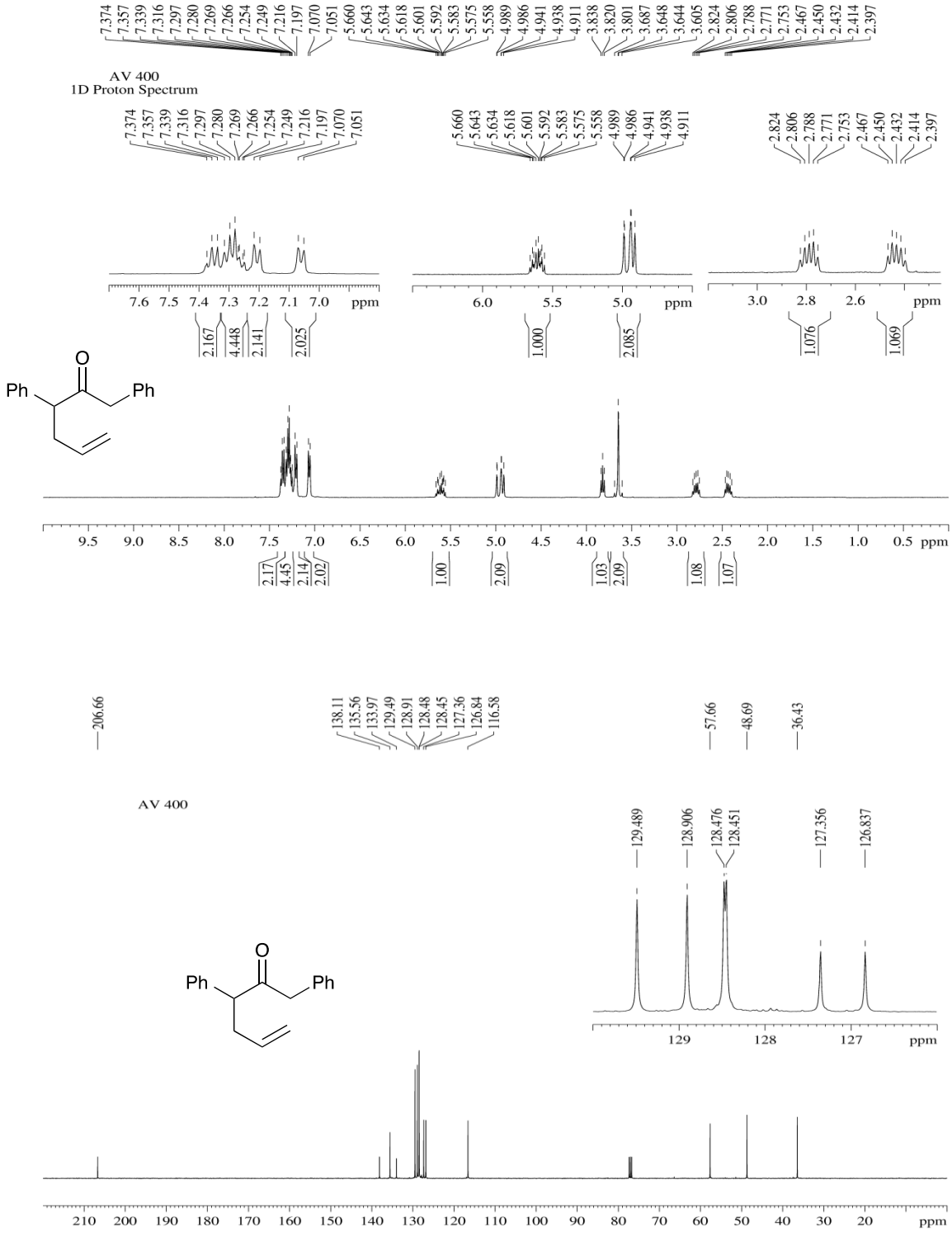




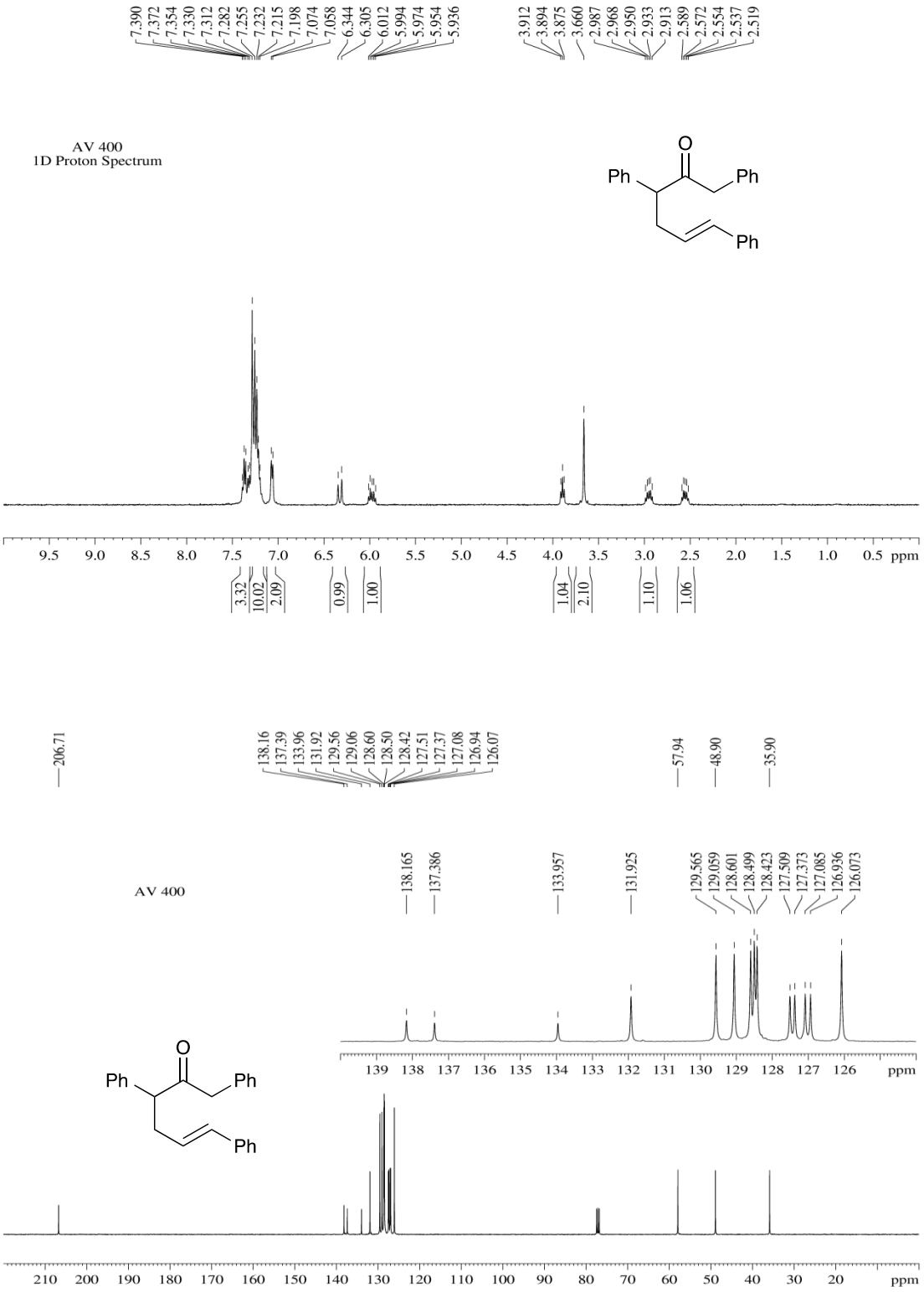
^{1}H and ^{13}C-NMR spectra of 6-phenyl-(5*E*)-5-hexen-2-one **37**



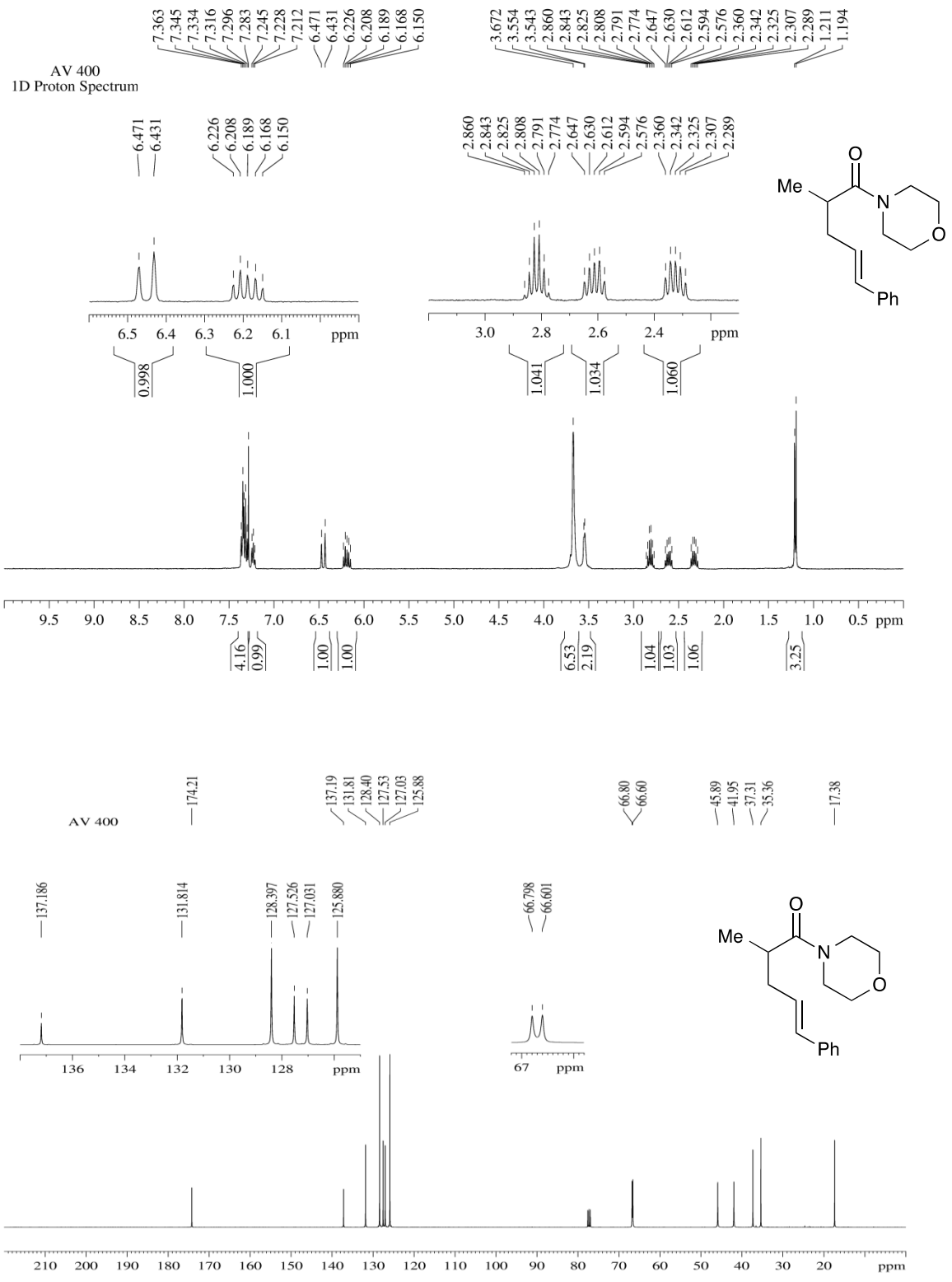
^{1}H and ^{13}C-NMR spectra of 1,3-diphenyl-5-hexen-2-one **39**



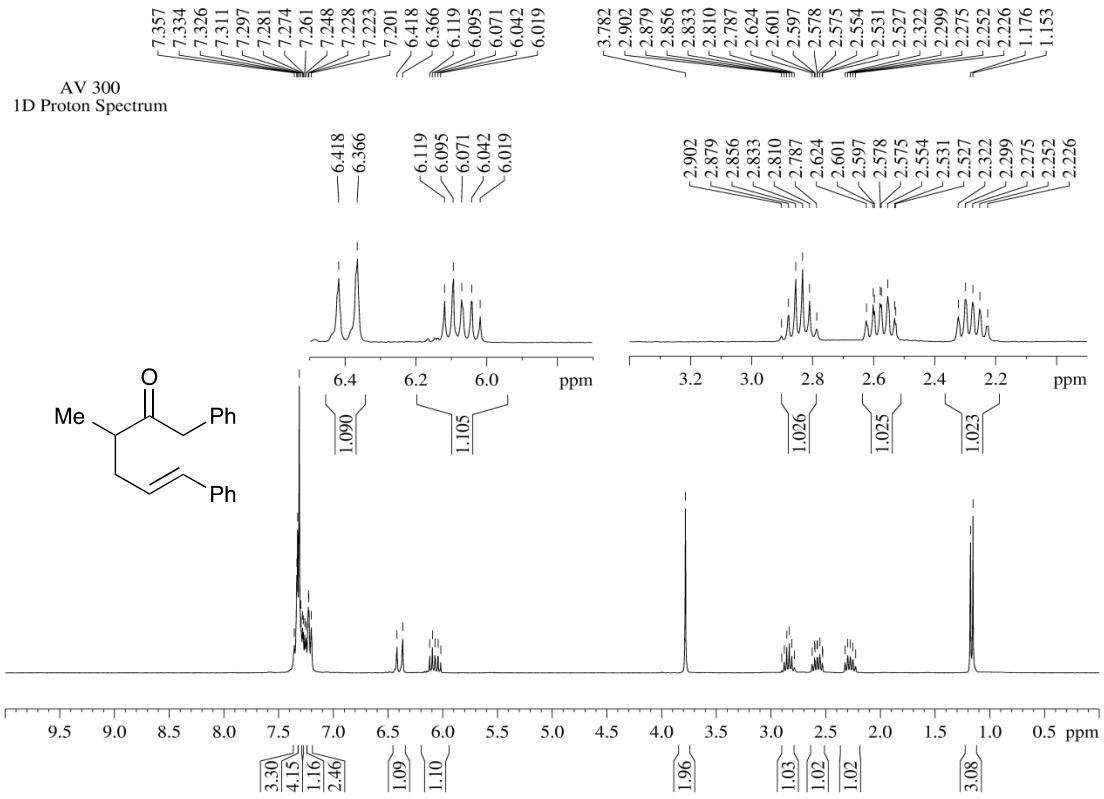
^{1}H and ^{13}C-NMR spectra of 1,3,6-triphenyl-(5*E*)-5-hexen-2-one **40**

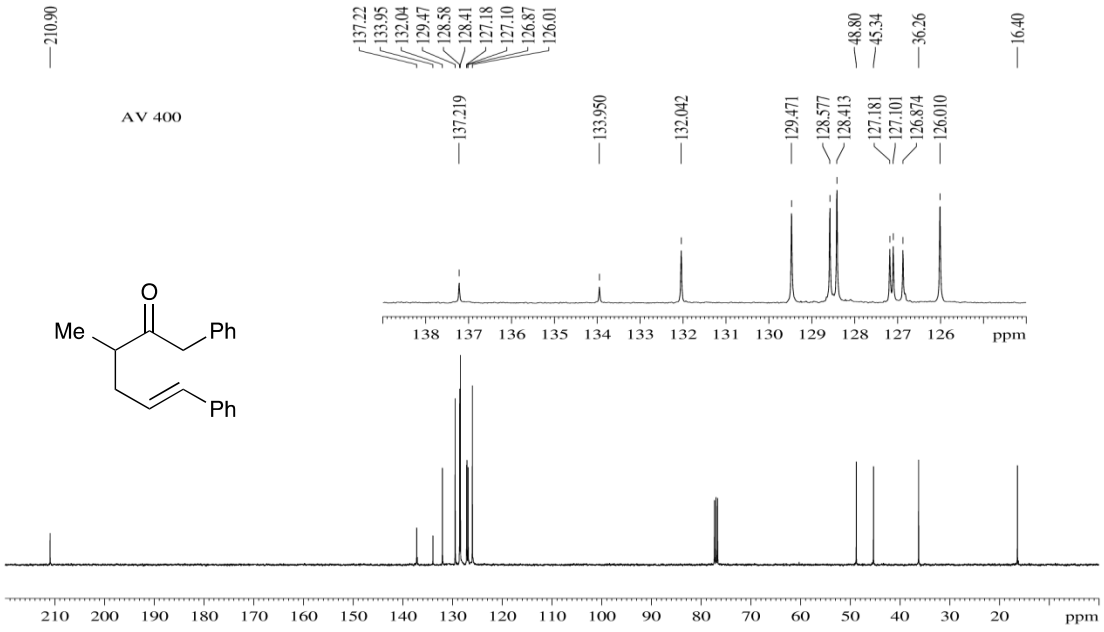


^{1}H and ^{13}C-NMR spectra of 1-(4-morpholinyl)-2-methyl-5-phenyl-(4*E*)-4-penten-1-one

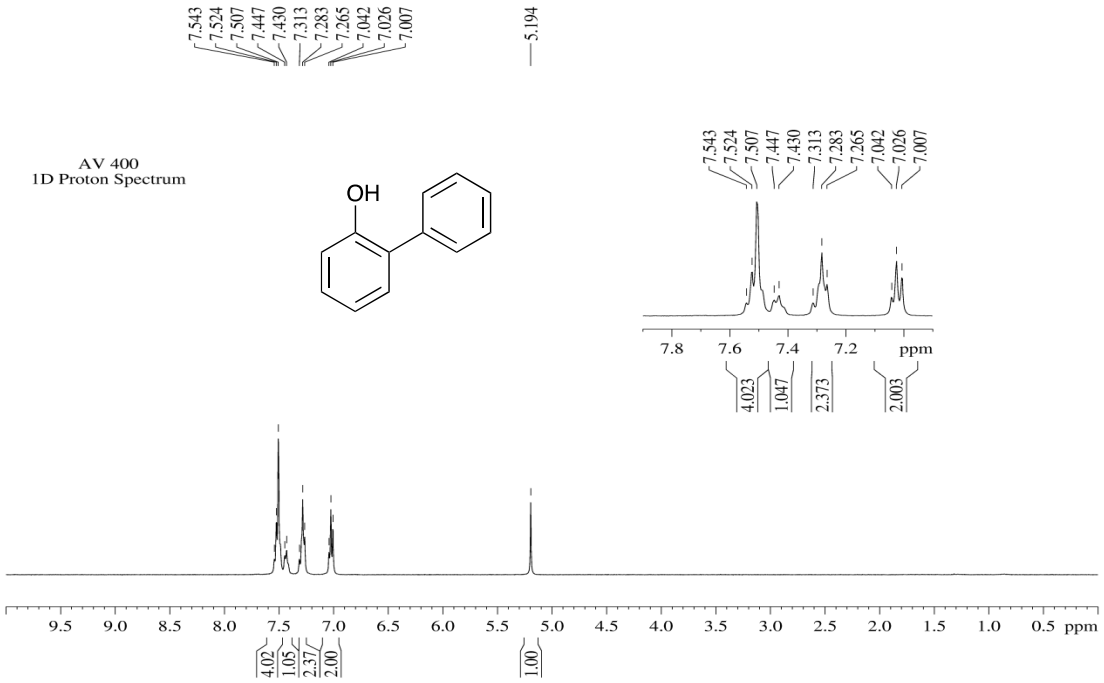


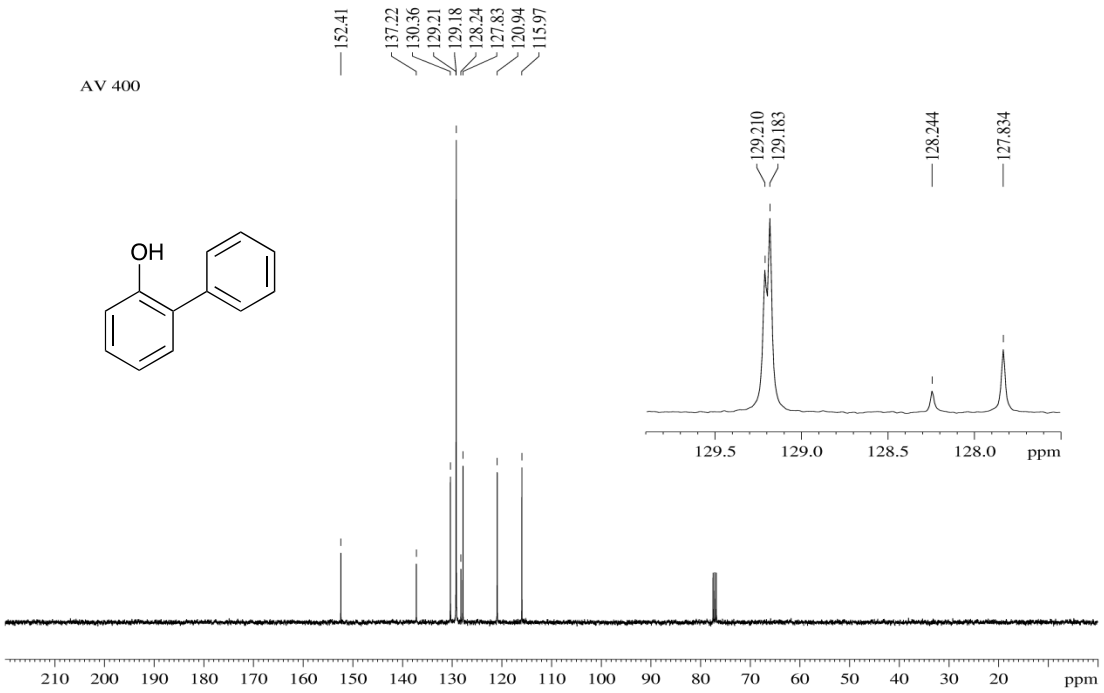
^{1}H and ^{13}C-NMR spectra of 3-methyl-1,6-diphenyl-(5*E*)-5-hexen-2-one **38**



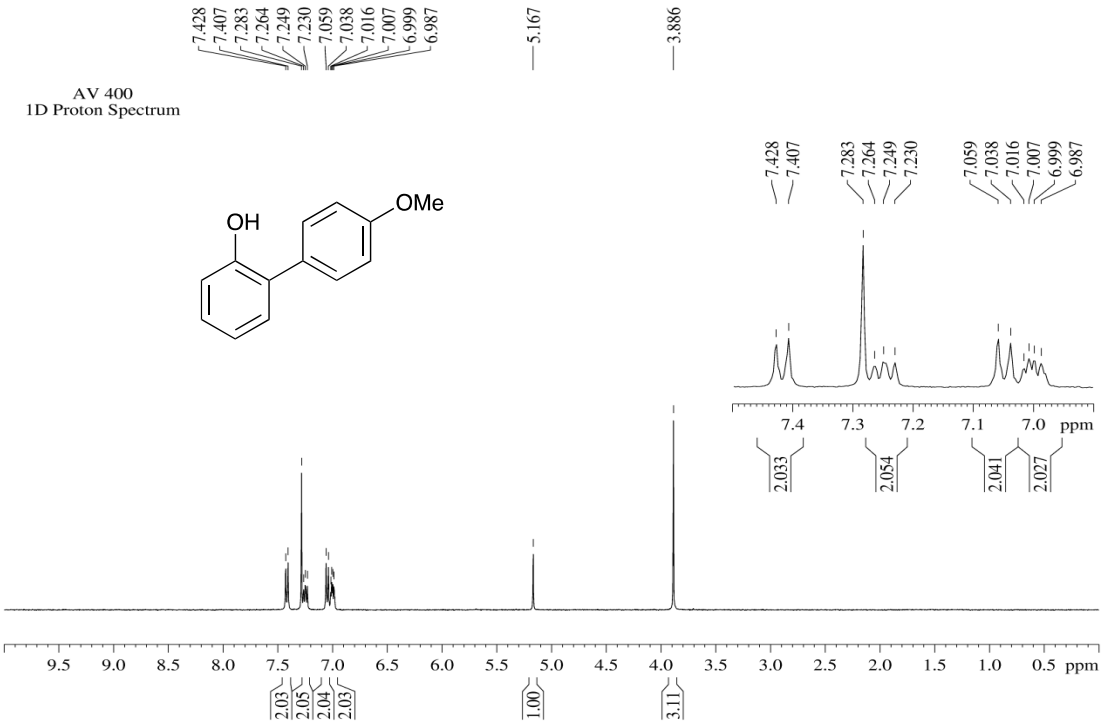


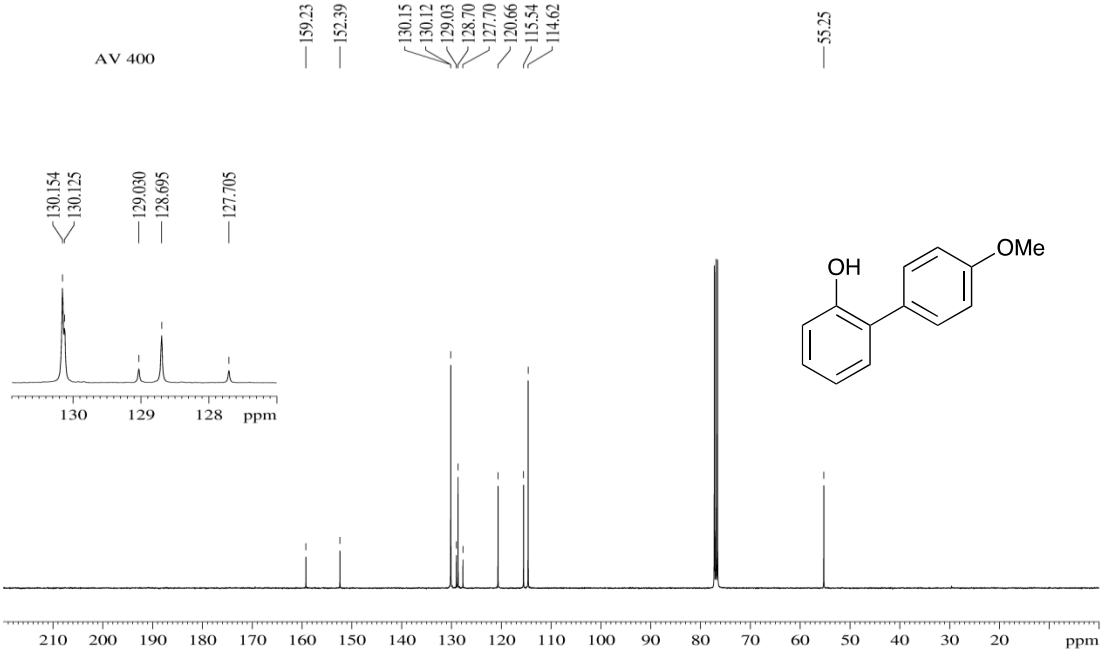
^{1}H and ^{13}C-NMR spectra of [1,1'-biphenyl]-2-ol **50**





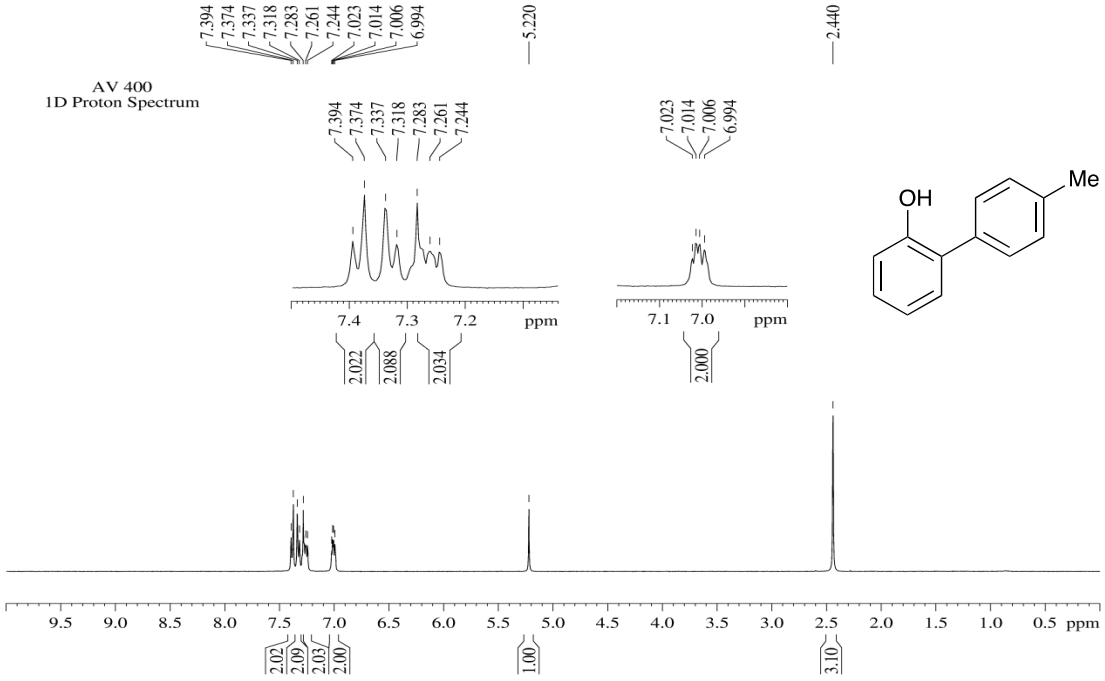
^{1}H and ^{13}C-NMR spectra of 4'-methoxy-[1,1'-biphenyl]-2-ol **51**

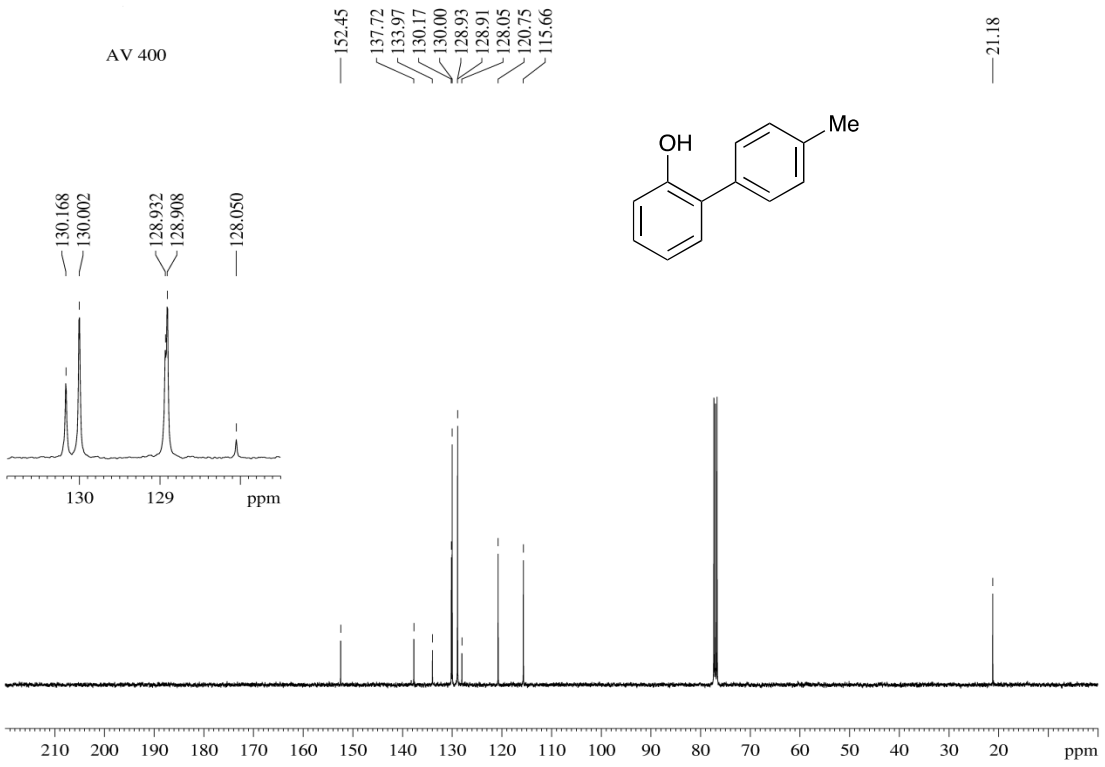




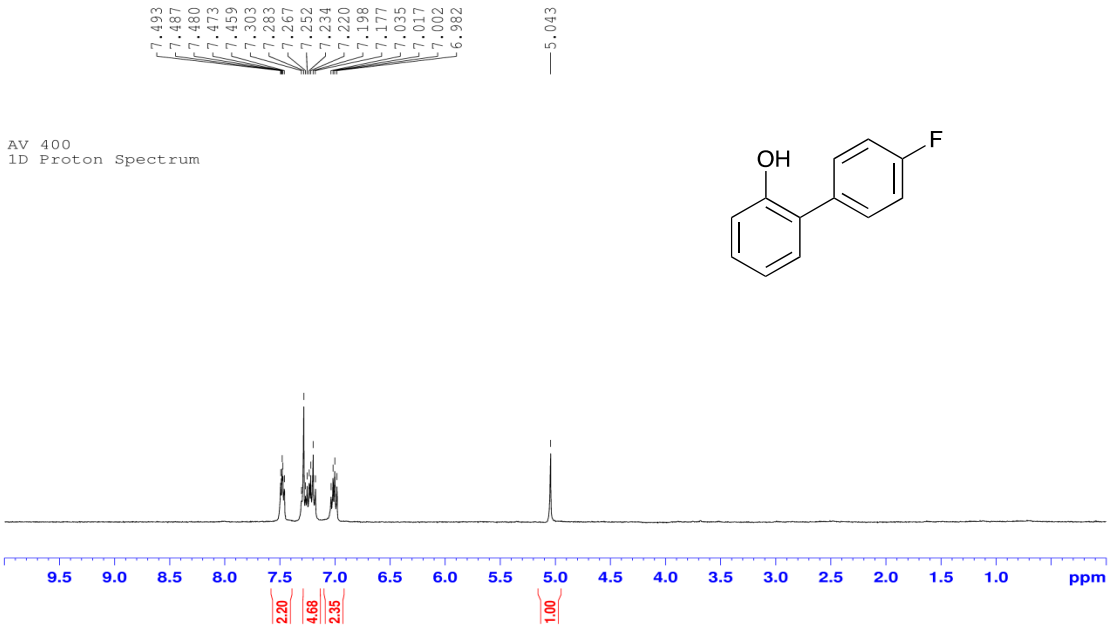
^{1}H and ^{13}C-NMR spectra of 3'-methoxy-[1,1'-biphenyl]-2-ol **52**

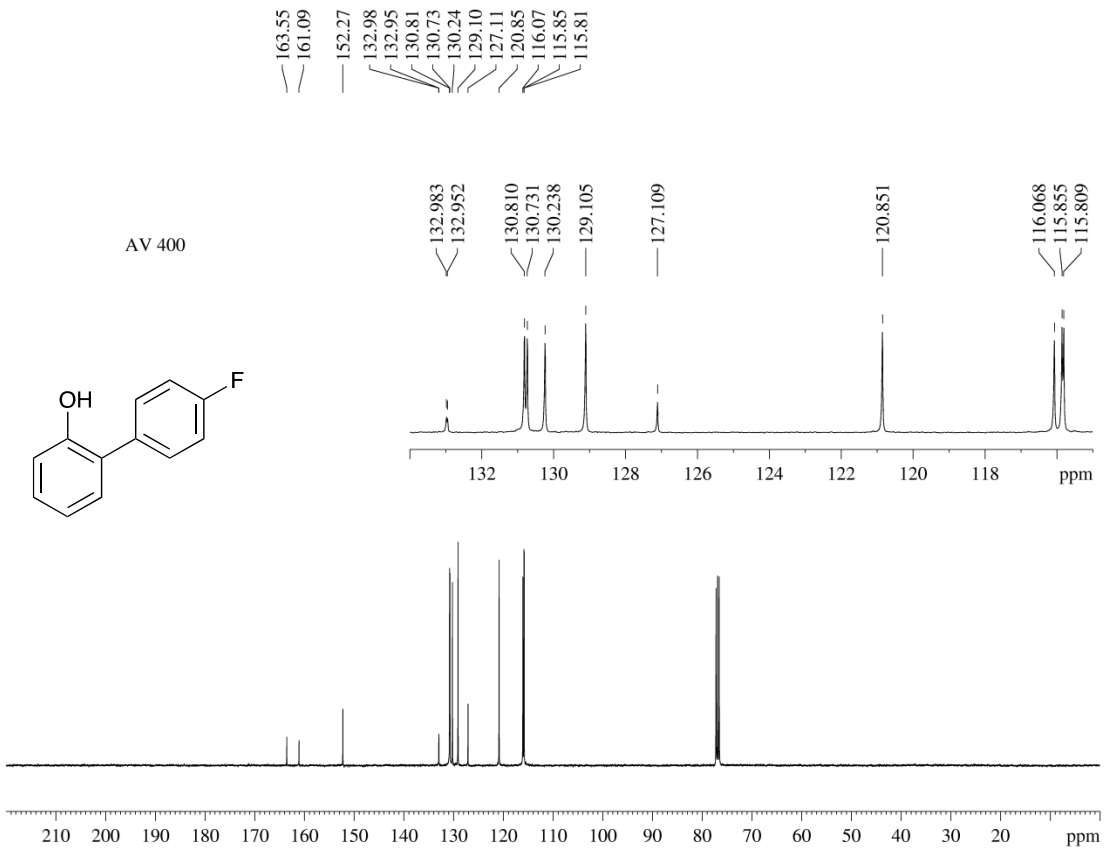
^{1}H and ^{13}C-NMR spectra of 4'-methyl-[1,1'-biphenyl]-2-ol **53**



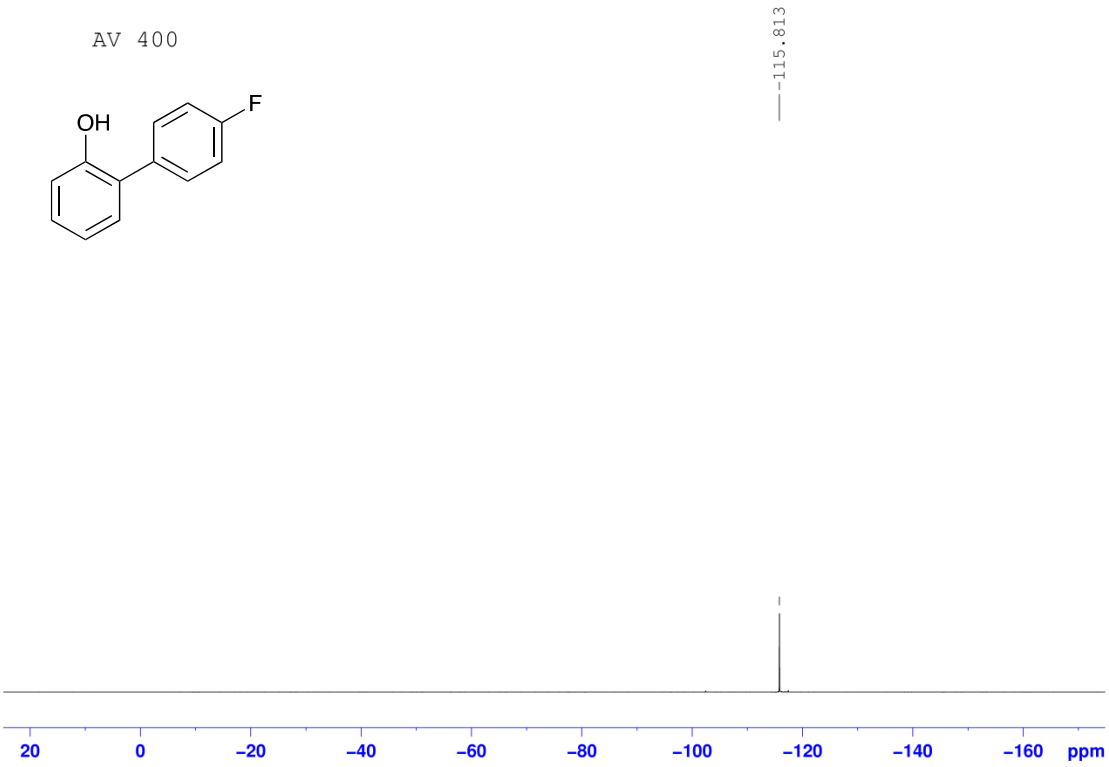


^{1}H and ^{13}C-NMR spectra of 4'-fluoro-[1,1'-biphenyl]-2-ol **54**

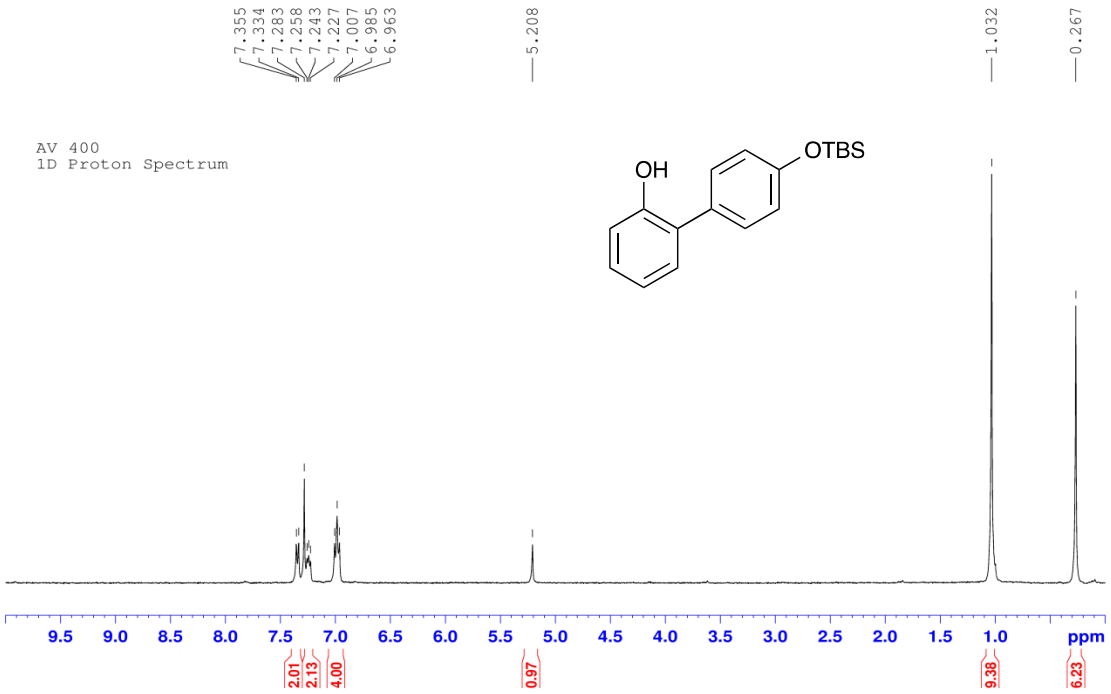


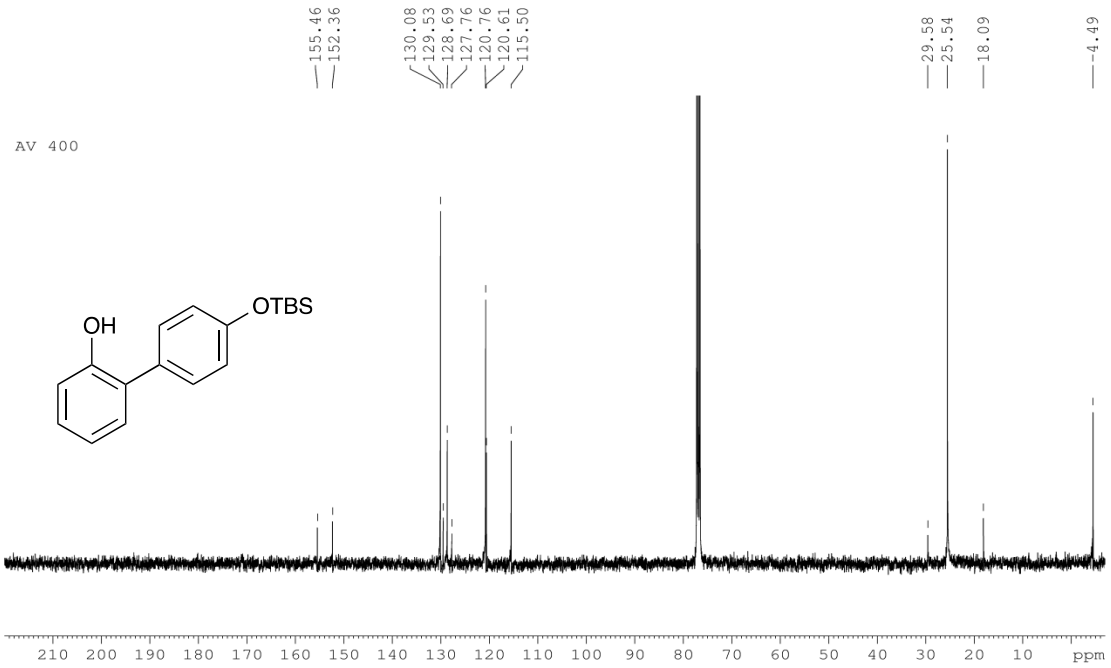


^{19}F-NMR spectra of 4'-fluoro-[1,1'-biphenyl]-2-ol **54**

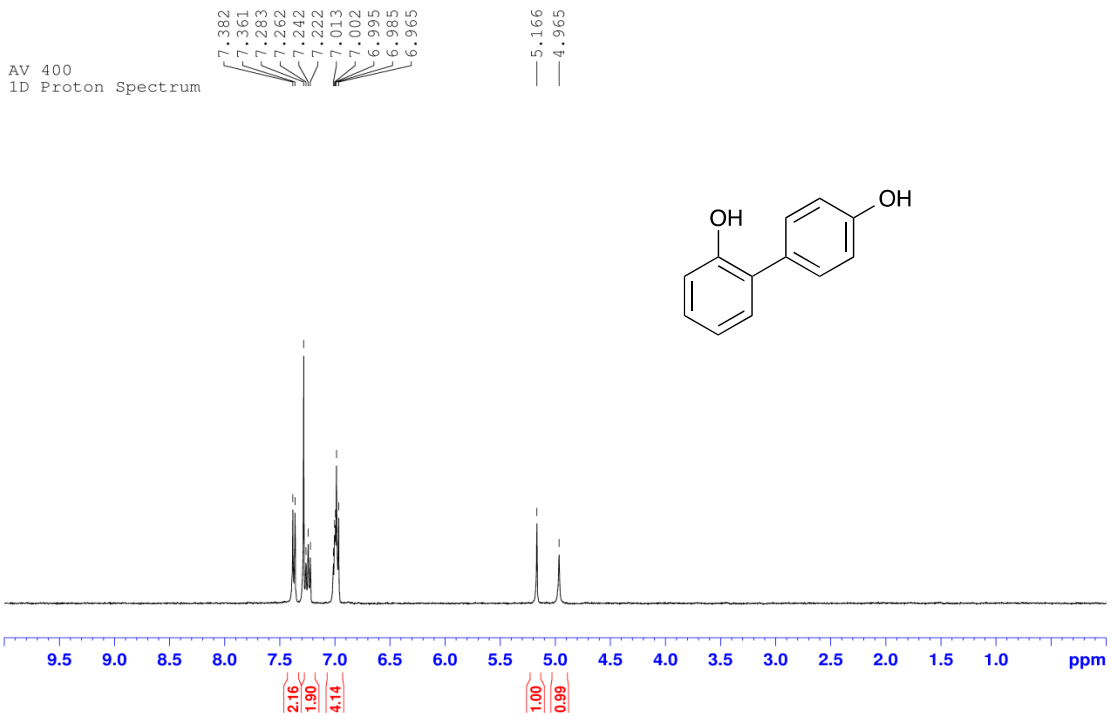


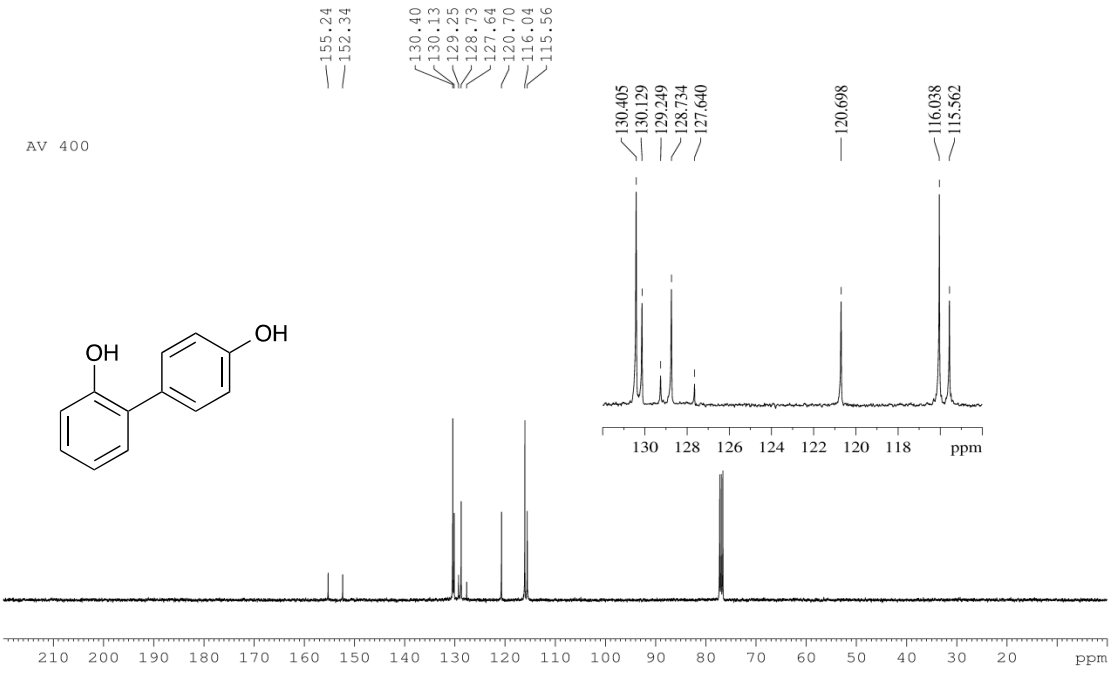
^{1}H and ^{13}C-NMR spectra of 4'-(*tert*-butyldimethylsilyl)oxy-[1,1'-biphenyl]-2-ol **55**



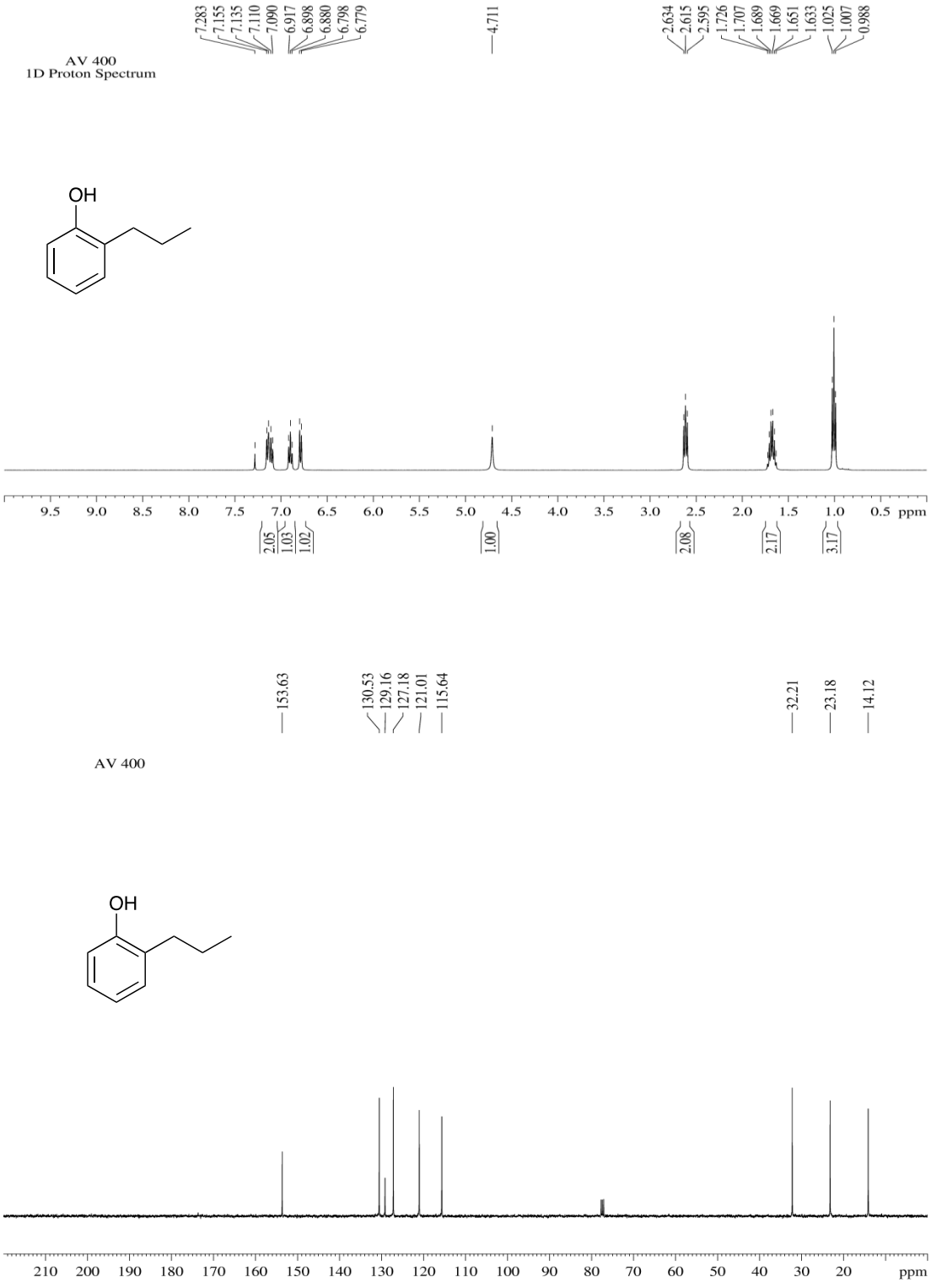


^{1}H and ^{13}C-NMR spectra of [1,1'-biphenyl]-2,4'-diol **56**

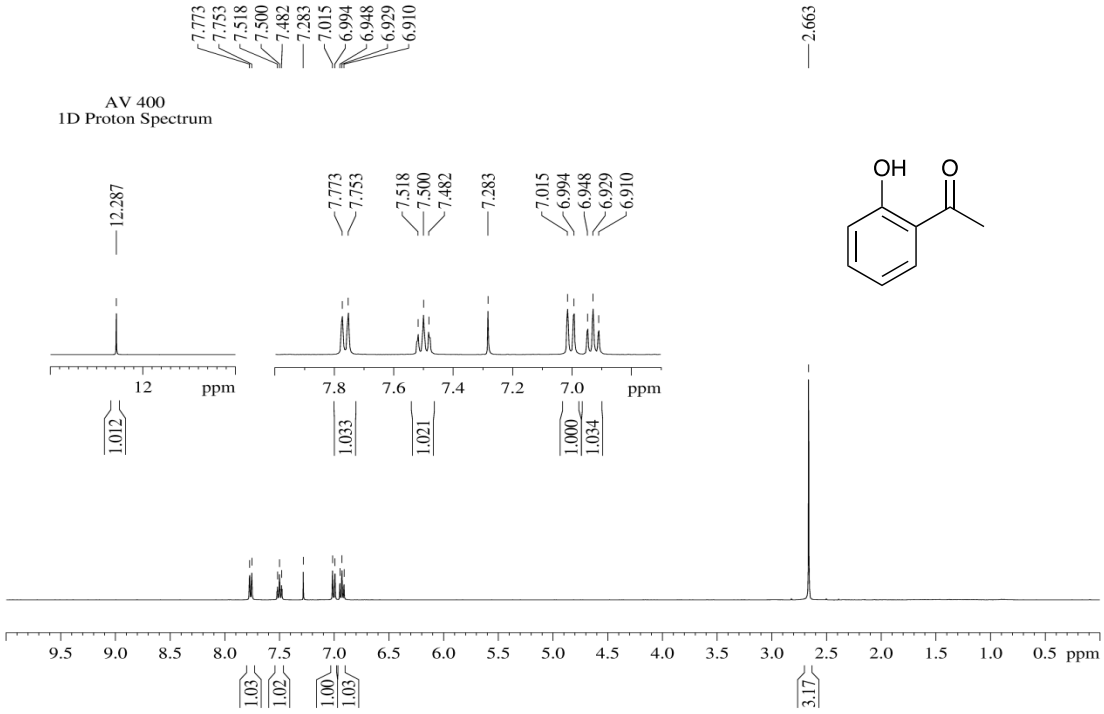


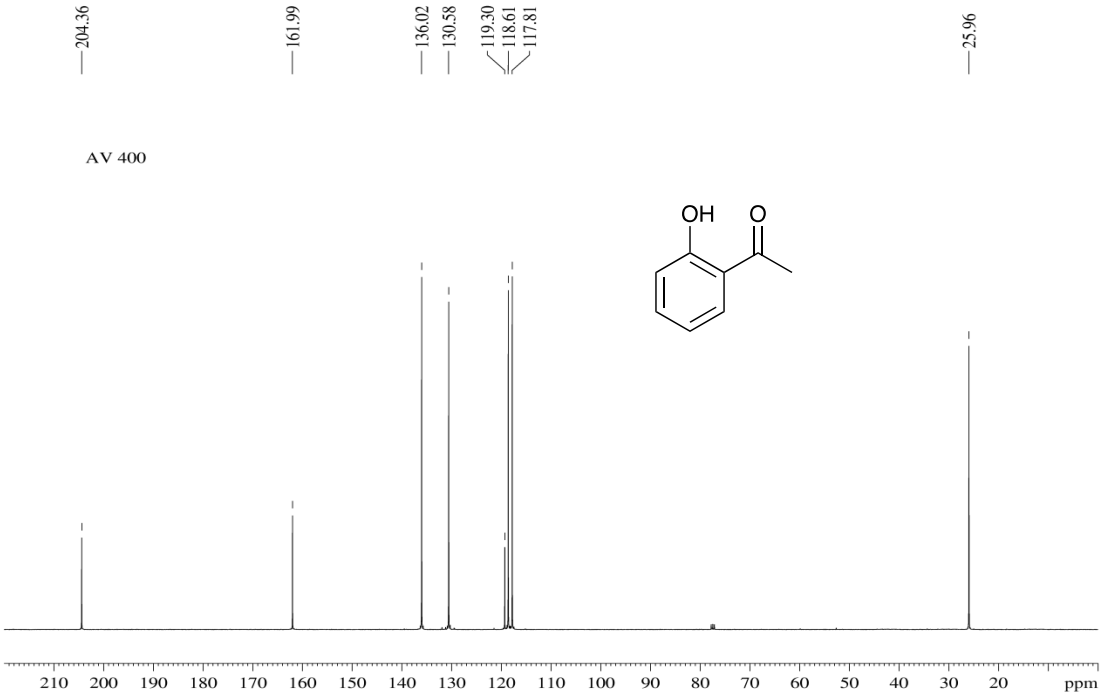


^{1}H and ^{13}C-NMR spectra of 2-propylphenol **57**

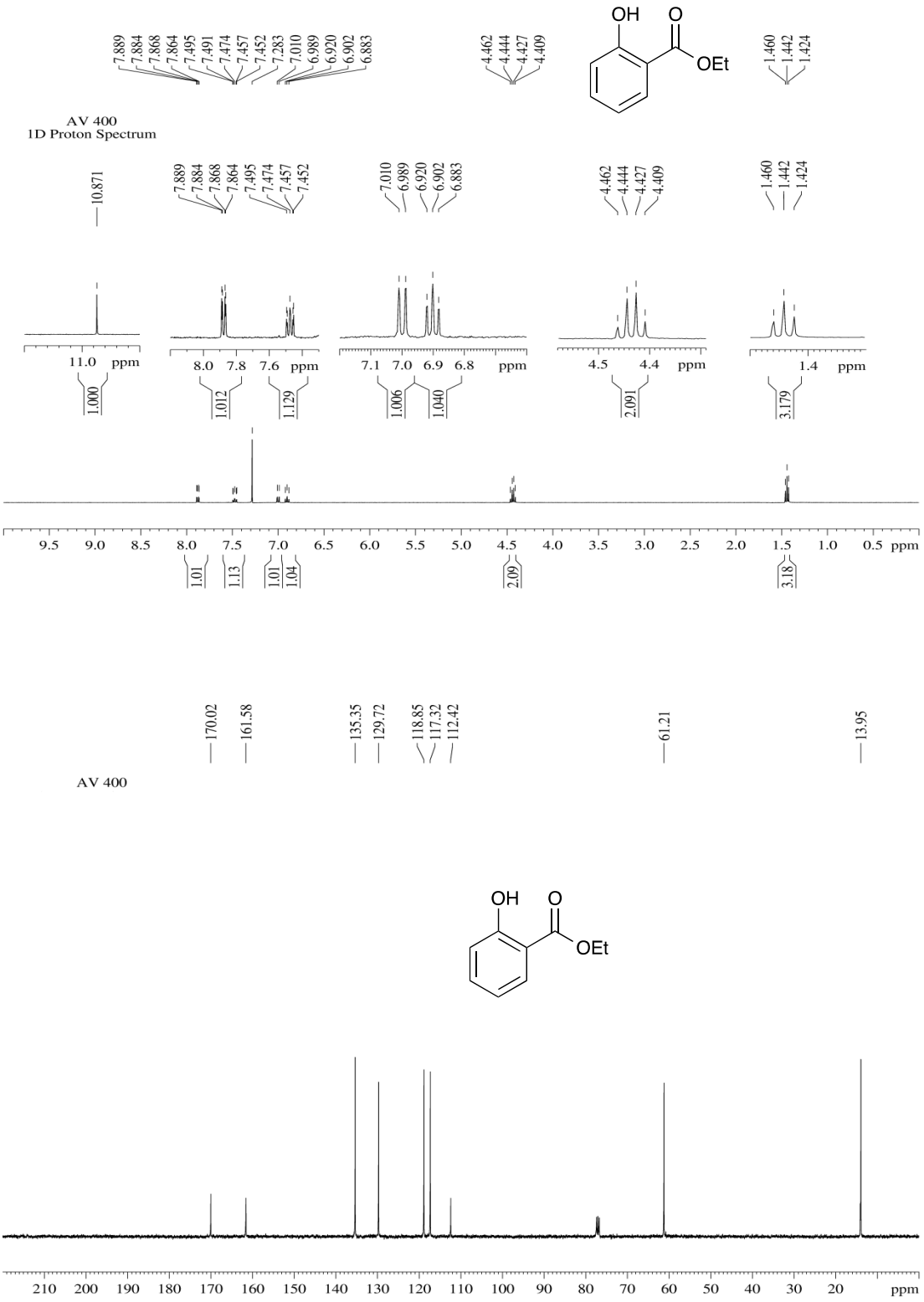


^{1}H and ^{13}C-NMR spectra of 2-acetylphenol **58**

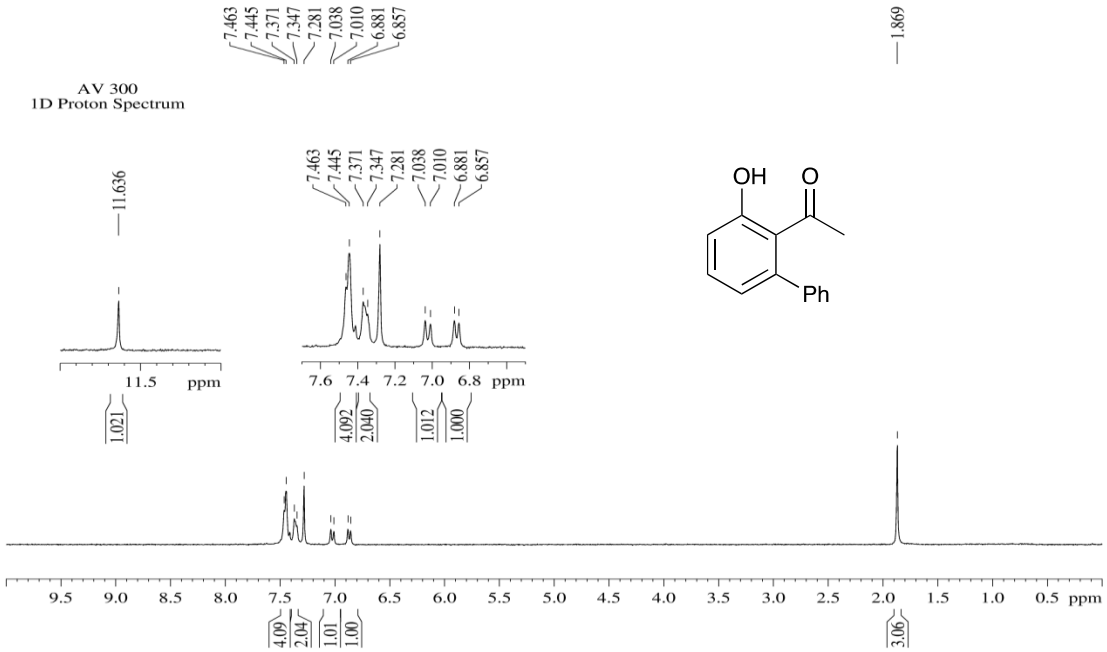


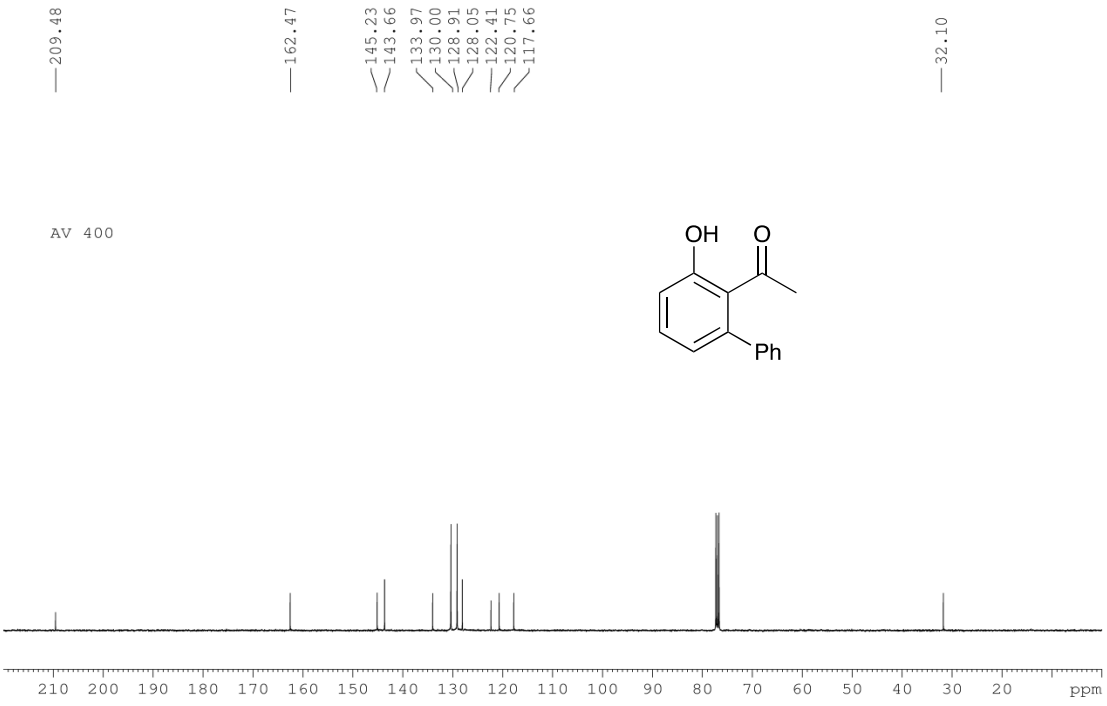


^{1}H and ^{13}C-NMR spectra of ethyl salicylate **59**

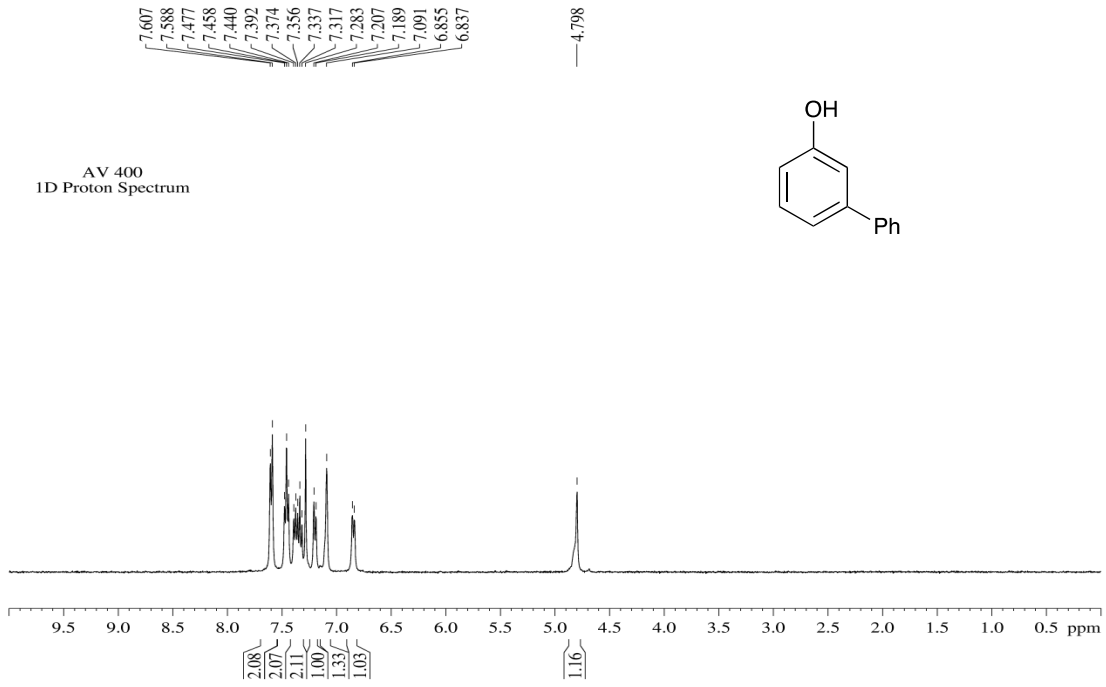


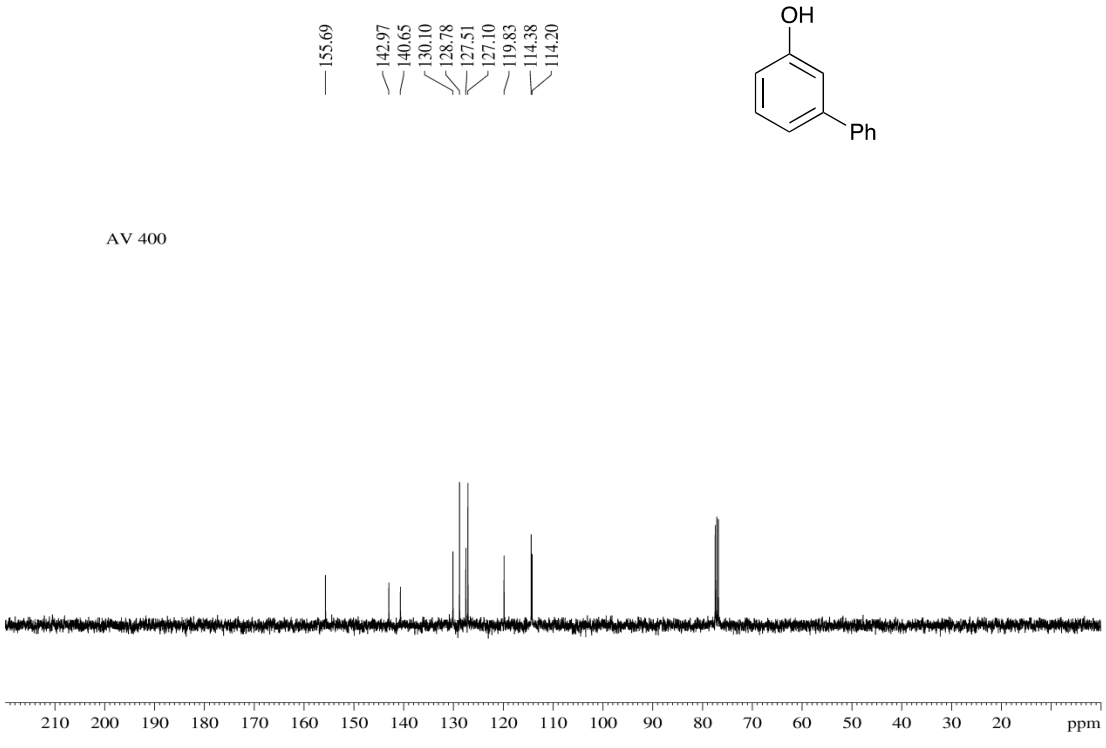
^{1}H and ^{13}C-NMR spectra of 2-acetyl-3-phenylphenol **60**



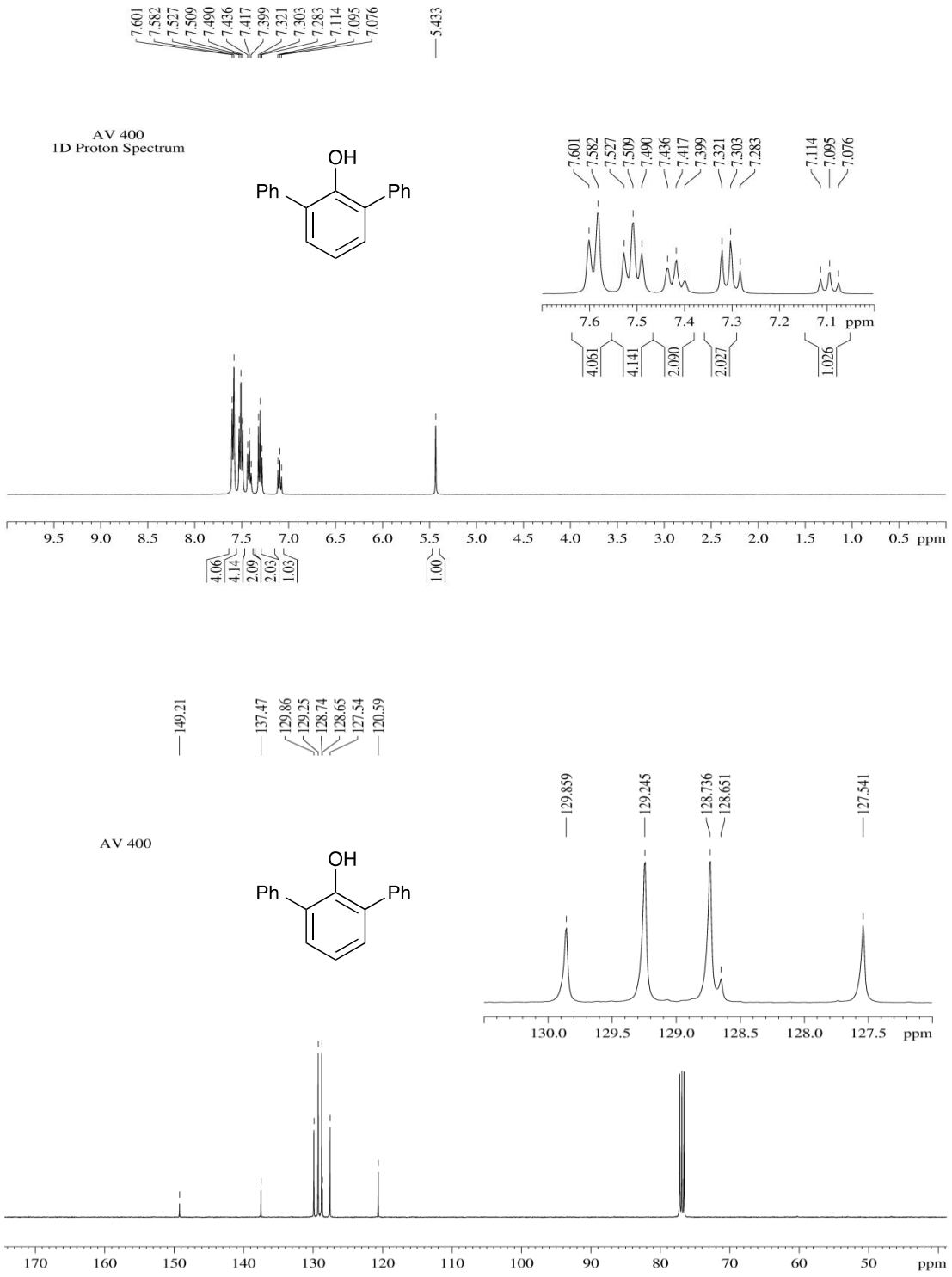


^{1}H and ^{13}C-NMR spectra of *m*-phenylphenol **61**

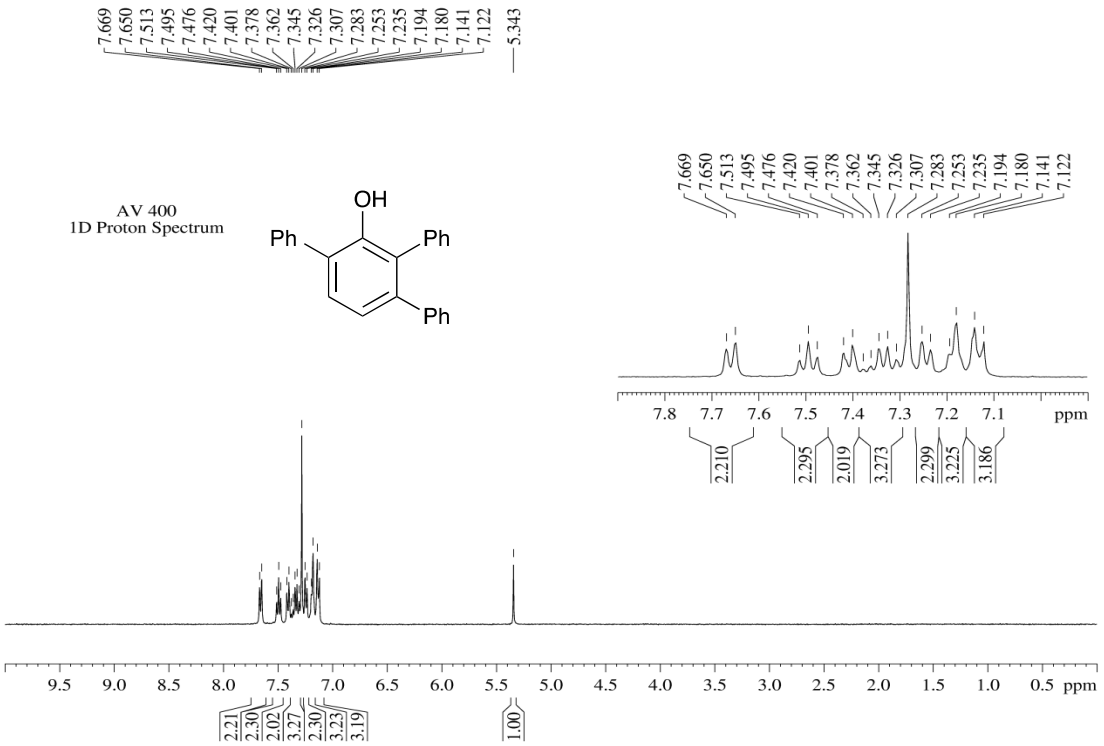


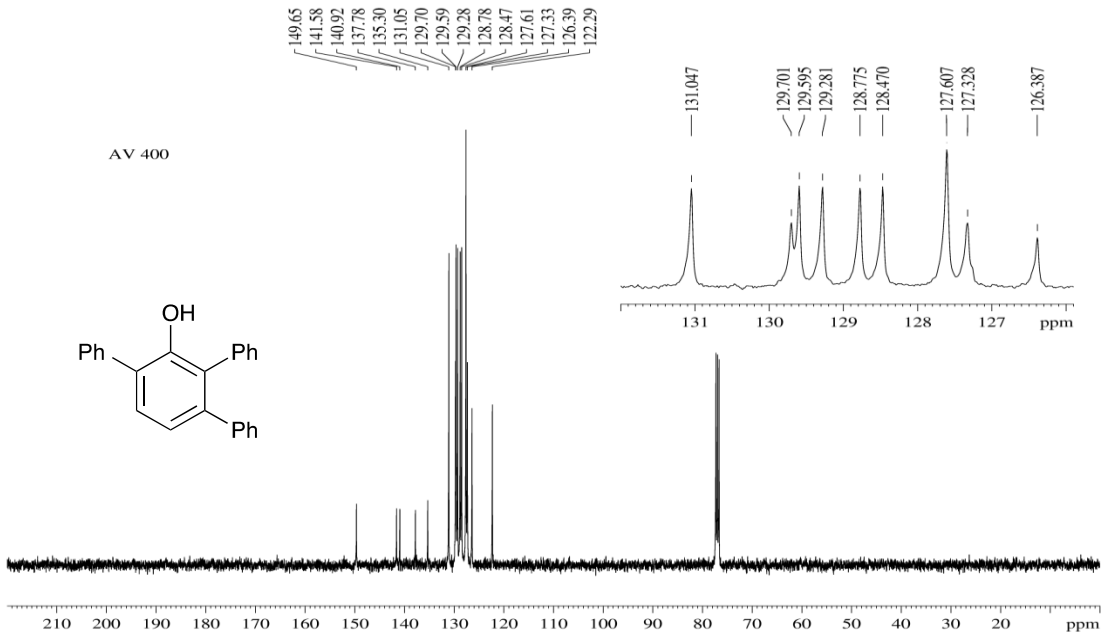


^{1}H and ^{13}C-NMR spectra of 2,6-diphenylphenol **62**

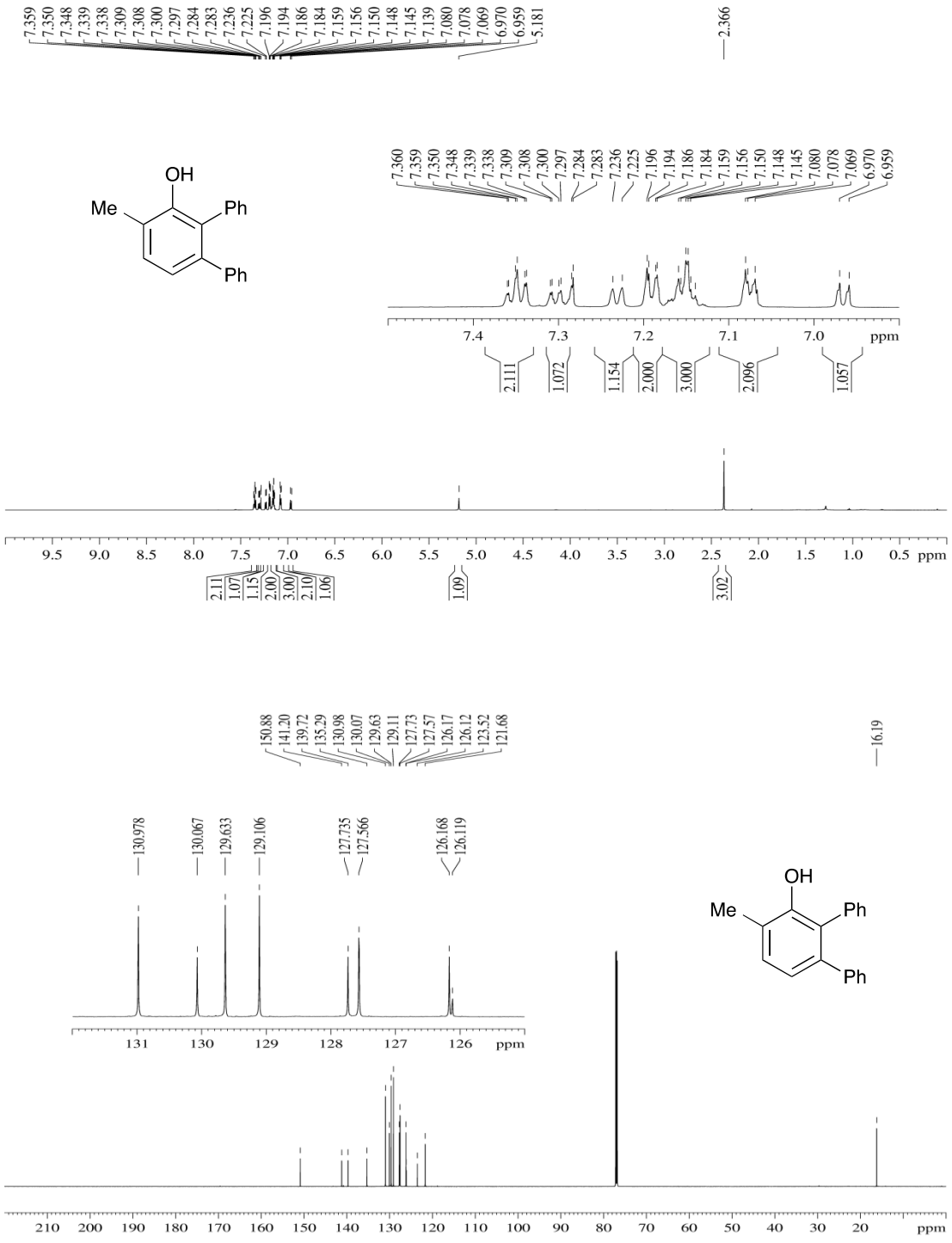


^{1}H and ^{13}C-NMR spectra of 2,3,6-triphenylphenol **63**





^{1}H and ^{13}C-NMR spectra of 6-methyl-2,3-diphenylphenol **64**



References

[1] Denmark, S. E.; Ober, M. H. *Palladium-Catalyzed Cross-Coupling Reactions of Substituted Aryl(dimethyl)silanols*, *Adv. Synth. Catal*. **2004**, *346*, 1703 –1714.

[2] Miyaura, N.; Suzuki, A. *Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds*, *Chem. Rev*. **1995**, *95*, 2457–2483.

[3] Hegedus, L. S. *In Transition Metals in the Synthesis of Complex Organic Molecules, 2nd Edition,* University Science Books: Mill Valley, CA, **1999**, pp 1–2.

[4] Shu, J.; Grandjean, B.; Neste, A.; Kaliaguine, S. *Catalytic palladium-based membrane reactors*, *Can. J. Chem. Eng*. **1991**, *69*, 1036–1060.

[5] Tsuji, J. *Palladium Reagents and Catalysts*, 2nd Edition. Vol. 9. (Ed.: Evans, A.), Tokyo Institute of Technology, Japan*,* **2004**, pp 656.

[6] Dieck, H. A.; Heck, R. F. *Organophosphinepalladium Complexes as Catalysts for Vinylic Hydrogen Substitution Reactions*, *J. Am. Chem. Soc.* **1974**, *96*, 1133–1136.

[7] Stille, J. K. *The Palladium-Catalyzed Cross-Coupling Reactions of Organotin Reagents with Organic Electrophiles [New Synthetic Methods (58)]*, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508–524.

[8] Smidt, J.; Hafner, W.; Jira, R.; Sieber, R.; Sedlmeier, J.; Sabel, A. *The Oxidation of Olefins with Palladium Chloride Catalysts*, *Angew. Chem. Int. Ed. Engl*.**1962**, *1*, 80–88.

[9] Roy, R. *Palladium in Restorative Dentistry*, *Platinum Metals Rev*. **2004**, *48*, 15–31.

[10] Dick, A. R.; Kampf, J. W.; Sanford. M. S. *Unusually Stable Palladium(IV) Complexes: Detailed Mechanistic Investigation of C-O Bond-Forming Reductive Elimination*, *J. Am. Chem. Soc*., **2005**, 127, 12790–12791.

[11] Minami, T.; Nishimoto, A.; Hanaoka, M. *Formal synthesis of nitidine through palladium-catalyzed isocoumarin synthesis*, *Tetrahedron Lett*. **1995**, *36*, 9505.

[12] Semmelhack, M. F.; Kim, C. R.; Dobler, W.; Meier, M. *Controlled beta-hydride elimination during tetrahydropyran formation with Pd(II); diastereoselective formation of the tetrahydropyran ring of tetronomycin*, *Tetrahedron Lett*. **1989**, *30*, 4925–4928.

[13] Tolman, C. A. *Steric Effects of Phosphorus Ligands in Organometallic Chemistry and Homogeneous Catalysis*, *Chem. Rev*. **1977**, *77*, 313–48.

[14] Sonogashira, K. Pd(0) and Pd(II) Complexes Containing Phosphorus and Other Group 15 Atom Ligands. in *Handbook of Organopalladium Chemistry for Organic Synthesis*, 1st Edition. Vol 2. (Ed.: Negishi, E.), Wiley–VCH, New York, **2002**, pp 47–65

[15] Diao, T.; Stahl, S. S. *Aerobic Dehydrogenation of Cyclohexanone to Phenol Catalyzed by $Pd(TFA)_2$/2-Dimethylaminopyridine: Evidence for the Role of Pd Nanoparticles*, *J. Am. Chem. Soc.* **2013**, *135*, 8213–8221.

[16] Campbell, A.; White, P.; Guzei, I.; Stahl, S. S. *Allylic C−H Acetoxylation with a 4,5-Diazafluorenone-Ligated Palladium Catalyst: A Ligand-Based Strategy To Achieve Aerobic Catalytic Turnover*, *J. Am. Chem. Soc*. **2010**, *132*, 15116–15119.

[17] (a) Tamao, K.; Sumitani, K.; Kumada, M. *Selective carbon-carbon bond formation by cross-coupling of Grignard reagents with organic halides. Catalysis by nickel-phosphine complexes*, *J. Am. Chem. Soc.* **1972**, *94*, 4374–4376. (b) Corriu, R. J. P.; Masse, J. P. *Activation of Grignard reagents by transition-metal complexes. A new and simple synthesis of trans-stilbenes and polyphenyls*. *J. Chem. Soc. Chem. Commun*. **1972**, 144a–144a.

[18] Yamamura, M.; Moritani, I.; Murahashi, S. *The reaction of σ-vinylpalladium complexes with alkyllithiums. Stereospecific syntheses of olefins from vinyl halides and alkyllithiums*, *J. Organomet. Chem*. **1975**, *91*, C39–C42.

[19] Backvall, J.; Andersson, P. G. *Stereocontrolled Oxaspiroxyclization of Conjugated Dienes via Palladium Catalysis*. *J. Org. Chem*. **1991**, *56*, 2274–2276.

[20] Hosokawa, T.; Murahashi, S. I. *New aspects of oxypalladation of alkenes*, *Acct. Chem. Res*. **1990**, *23*, 49–54.

[21] (a) Pei, T.; Widenhoefer, R. A. *Palladium-catalyzed cyclization of alkenyl β-keto esters in the presence of chlorotrimethylsilane*, *Chem. Commun.* **2002**, *6*, 650–651. (b) Qian, H.; Widenhoefer, R. A. *Mechanism of the Palladium-Catalyzed Intramolecular Hydroalkylation of 7-octene-2,4-dione*, *J. Am. Chem. Soc.* **2003**, *125*, 2056–2057.

[22] Kende, A. S.; Roth, B.; Sanfdippo, P. J. *Facile, Palladium(II)-Mediated Synthesis of Bridged and Spirocyclic Bicycloalkenones*, *J. Am. Chem. Soc.* **1982**, *104*, 1784–1785.

[23] In DMSO at room temperature, the pKa (K enol / ketone) of β-diketone, β-keto ester, benzyl ketone, and dialkyl ketone is 13.3 (3.2), 14.2 (0.9), 19.9 (8×10^{-5}), and 24.8 (5×10^{-9}), respectively.

[24] (a) Bordwell, F. G. *Equilibrium acidities in dimethyl sulfoxide solution*, *Acc. Chem. Res.* **1988**, *21,* 456–463. (b) Guthrie, J. P. *Can. The enol content of simple carbonyl compounds: an approach based upon pK_a estimation*, *Can. J. Chem.* **1979**, *57*, 1177–1185.

[25] The lower reactivity of alkenyl β-keto esters relative to β-diketones is evidenced by low acidity and lower $K_{enol/ketone}$ of a β-keto esters relative to a β-diketones. Han, X.; Wang, X.; Pei, T.; Widenhoefer, R. A. *Palladium-Catalyzed Intramolecular Hydroalkylation of Alkenyl- β-Keto Esters, α-Aryl Ketones, and Alkyl Ketones in the Presence of Me_3SiCl or HCl*, *Chem. Eur . J.* **2004**, *10*, 6333–6342.

[26] Qian, H.; Pei, T.; Widenhoefer, R. A. *Development, Scope, and Mechanism of the Palladium-Catalyzed Intramolecular Hydroalkylation of 3-Butenyl β-Diketones*, *Organometallics.* **2005**, *24*, 287–301.

[27] Sheldon, R.; Arends, I.; Brink, G.; Ten, J.; Dijksman, A. *Green, catalytic oxidations of alcohols*, *Acc Chem Res*. **2002**, 35, 774–781.

[28] Diao, T.; Stahl, S. S. *Aerobic Dehydrogenation of Cyclohexanone to Cyclohexenone Catalyzed by $Pd(DMSO)_2(TFA)_2$: Evidence for Ligand-Controlled Chemoselectivity*, *J. Am. Chem. Soc.* **2013**, *135*, 8205–8212.

[29] Bäckvall, J.-E.; Akermark, B.; Ljunggren, S. O. *Stereochemistry and Mechanism for the Palladium(II)-catalyzed Oxidation of Ethene in Water*, *J. Am. Chem. Soc*. **1979**, *101*, 2411–2416.

[30] McDonald, R. I.; Liu, G. S.; Stahl, S. S. *Palladium(II)-Catalyzed Alkene Functionalization via Nucleopalladation: Stereochemical Pathways and Enantioselective Catalytic Applications*, *Chem. Rev.* **2011**, *111*, 2981–3019.

[31] Piera, J.; Bäckvall, J.-E.Catalytic *Oxidation of Organic Substrates by Molecular Oxygen and Hydrogen Peroxide by Multistep Electron Transfer—A Biomimetic Approach*, *Angew. Chem. Int. Ed*. **2008**, *47*, 3506–3523.

[32] Tyman, J. H. P. *Synthetic and natural phenols*, 1st Edition. Vol. 52. Elsevier, Amsterdam, **1996**, pp 560–610.

[33] Groves, J. K. *The Friedel–Crafts Acylation of Alkenes*, *Chem. Soc. Rev.* **1972***, 1*, 73–97.

[34] Anctil, E. J.-G.; Snieckus, V. *in Metal-Catalyzed Cross-Coupling Reactions*, 2nd Edition. Vol 2. (Eds.: De Meijere, A; Diederich, F.), Wiley-VCH: Weinheim, Germany, **2004**, pp.761–813.

[35] Izawa, Y.; Pun, D.; Stahl, S. S. *Palladium-catalyzed aerobic dehydrogenation of substituted cyclohexanones to phenols*. *Science*. **2011**, 333, 209–213.

[36] Wang, X.; Pei, T.; Han. X.; Widenhoefer, R. A. *Palladium-Catalyzed Intramolecular Hydroalkylation of Unactivated Olefins with Dialkyl Ketones*, *Org. Lett.* **2003**, *9*, 2699–2701.

[37] Pei, T.; Widenhoefer, R. A. *Palladium-Catalyzed Intramolecular Hydroalkylation of Alkenyl- β-Keto Esters, α-Aryl Ketones, and Alkyl Ketones in the Presence of Me_3SiCl or HCl*, *Chem. Eur . J.* **2004**, *10,* 6333–6342.

[38] Huckin, S.; Weiler, L. *Alkylation of Dianions of .Beta.-Keto Esters*, *J. Org. Chem.* **1974**, *4*, 1082–1087.

[39] Man, R. W. Y.; Brown, A. R. C.; Wolf, M. O. *Mechanism of Formation of Palladium Anoparticles: Lewis Base Assisted, Low-Temperature Preparation of Monodisperse Nanoparticles*, *Angew. Chem. Int*. *Ed*. **2012**, *51*, 11350–11353.

[40] Hayes, J.; Shipman, M.; Twin. H. *Multicomponent Reactions Involving 2-Methyleneaziridines: Rapid Synthesis of 1,3-Disubstituted Propanones*, *J. Org. Chem*. **2002**, *67*, 935–942.

[41] Schmittle, M.; Levis, M. *Electron Transfer Induced Deprotection of Benzyl Substituted 1,3-Dithianes with Iron(III)phenanthroline Complexes*, *Synlett.* **1996**, *4*, 315–316.

[42] Pei, T.; Widenhoefer, R. A. *Palladium-Catalyzed Intramolecular Hydroalkylation of Alkenyl- β-Keto Esters, α-Aryl Ketones, and Alkyl Ketones in the Presence of Me_3SiCl or HCl*, *Chem. Eur . J.* **2004**, *10,* 6333–6342.

[43] Thomas, E. J.; Vickers, C. F. *An approach to an asymmetric synthesis of stemofoline*, *Tetrahedron: Asymmetry* **2009**, *20*, 970–979.

[44] Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y.; Sugiura, T. *Allylic Carbonates. Efficient Allylating Agents of Carbonucleophiles in Palladium-Catalyzed Reactions under Neutral Conditions*, *J. Org. Chem*. **1985**, *11*, 1523–1529.

[45] Warner, M. C.; Bäckvall, J. E. *Racemization of Olefinic Alcohols by a Carbonyl(cyclopentadienyl)ruthenium Complex: Inhibition by the Carbon–Carbon Double Bond*, *Eur. J. Org. Chem*. **2015**, *11*, 2388–2393.

[46] Mori, M.; Akashi, M.; Hori, M. *Synthesis of Heterocycles Using Molecular Nitrogen as a Nitrogen Source*, *Bull. Chem. Soc. Jpn*. **2004**, *77*, 1655–1670.

[47] Izawa, Y.; Zheg, C.; Stahl, S. S. *Oxidative Heck/Dehydrogenation Reactions of Cyclohexenones: Efficient Access to* meta-*Substituted Phenols*, *Angew. Chem . Int. Ed.* **2013**, *52,* 3672–3675.

[48] Contreras-Celedón, C. A.; Mendoza-Rayo, D.; Rincón-Medina, J. A.; Chacón-García, L. *Novel 4-Aminoantipyrine-Pd(II) Complex Catalyzes Suzuki–Miyaura Cross-Coupling Reactions of Aryl Halides*, *Beilstein J. Org. Chem.* **2014**, *10*, 2821–2826.

[49] Schmidt, B.; Riemer, M. *Suzuki–Miyaura Coupling of Halophenols and Phenol Boronic Acids: Systematic Investigation of Positional Isomer Effects and Conclusions for the Synthesis of Phytoalexins from Pyrinae*, *J. Org. Chem*. **2014**, *79*, 4104−4118.

[50] Ohe, K.; Yokoi, T.; Miki, K.; Nishino, F.; Uemura, S. *Chromium- and Tungsten-Triggered Valence Isomerism of cis-1-Acyl-2-ethynylcyclopropanes via [3,3]Sigmatropy of (2-Acylcyclopropyl)vinylidene−Metal Intermediates*, *J. Am. Chem. Soc.* **2002**, *124*, 526–527.

[51] Ishikawa, S.; Manabe, K. Ortho-*Selective Cross-Coupling of Fluorobenzenes with Grignard Reagents: Acceleration by Electron-Donating* Ortho-*Directing Groups*, *Synthesis*, **2008**, *16*, 2645–2649.

[52] Brunel, J. M. *Scope, Limitations and Mechanistic Aspects in the Selective Homogeneous Palladium-Catalyzed Reduction of Alkenes under Transfer Hydrogen Conditions*, *Tetrahedron*, **2007***, 63*, 3899–3906.

[53] Takale, B. S.; Telvekar, V. N. *Oxidation of Dihydrazones of Diaryl α-Diketones to Diarylacetylenes Using Sodium Periodat, Chem. Lett.* **2010**, *39*, 1279–1280.

[54] Magano, J.; Chen, M. H.; Clark, J. D.; Nussbaumer, T. *2-(Diethylamino)ethanethiol, a New Reagent for the Odorless Deprotection of Aromatic Methyl Ethers*, *J. Org. Chem,* **2006**, *71*, 7103–7105.

[55] Tejedor, D.; Mendez, G.; Cotos, L. *A Microwave-Assisted Domino Rearrangement of Propargyl Vinyl Ethers to Multifunctionalized Aromatic Platforms*, *Chem. Eur. J.* **2011**, *17*, 3318–3321.

[56] Lee, D. H.; Jin, M. *An Extremely Active and General Catalyst for Suzuki Coupling Reaction of Unreactive Aryl Chlorides*, *Org. Lett*. **2011**, *13*, 252–255.

[57] Kim, W.; Hay, A. *Synthesis of Soluble Poly(ether imides) from bis(ether anhydrides) Containing Bulky Substituents*, *Macromolecules,* **1993**, *26*, 5275–5280.

[58] Huguet, N.; Lebœuf, D.; Echavarren, A. M. *Intermolecular Gold(I)-Catalyzed Cyclization of Furans with Alkynes: Formation of Phenols and Indenes*, *Chem. Eur. J*. **2013**, *19*, 6581–6585.

[59] Davulcu, S.; Allen, C.; Milne, K.; Williams, M. J. *Catalytic Conversion of Nitriles into Secondary- and Tertiary Amides*, *ChemCatChem*. **2013**, *2*, 435–438.

[60] Chen, G.; Arns, S.; Young, R. *Determination of the Rat in Vivo Pharmacokinetic Profile of a Bone-Targeting Dual-Action Pro-Drug for Treatment of Osteoporosis*, *Bioconjugate Chem*. **2015**, *26*, 1095−1103.