PALLADIUM(II)-MEDIATED TRANSFORMATION: EXPLORING SYNTHETIC METHODOLOGY FOR THE SYNTHESIS OF CYCLOPENTENONES FROM TERTIARY-CYCLOBUTANOLS

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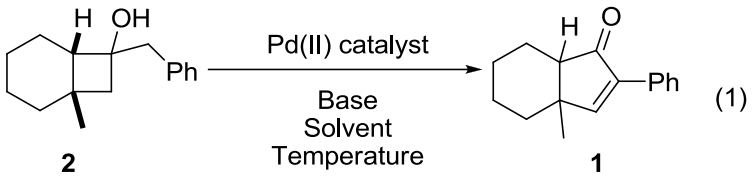
Abstract

A new method for the synthesis of ring-fused cyclopentenone (**1**, Eq. 1) is described. The method utilizes the built-in strain of tertiary cyclobutanol (**2**, Eq.1) to drive the palladium(II)-catalyzed rearrangement to the corresponding ring-fused cyclopentanone followed by Saegusa-Ito reaction to furnish final cyclopentenone product.



(1)

Synthesis of cyclopentenone **1** from tertiary-cyclobutanol **2.**

Extensive efforts to transform this reaction into a catalytic process by screening various palladium(II) sources, ligands, oxidants, bases, solvents and reaction temperatures failed. Interesting and unexpected results were however obtained while exploring copper(II) chloride and copper(II) bromide as potential oxidants.

Acknowledgements

I want to begin by thanking my family in particular my Mom and Dad, to whom I owe everything. Your love, support and consideration throughout all these years allowed me to be where I am. You have motivated me to work hard in order to make you proud. Although life is full of ups and downs, we always find way to be strong and move on together.

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List of Abbreviations

Ac	acetyl
Atm	atmosphere
COD	1, 5-cyclooctadiene
Dba	dibenzylideneacetone
DCM	dichloromethane
DDQ	2, 3-dichloro-5, 6-dicyanobenzoquinone
DMA	dimethylacetamide
DMSO	dimethylsulfoxide
Equiv	equivalents
IR	infrared
L_n	ligand(s) (n = number of ligands)
MS	mass spectrometry
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
O_h	octahedral point group symmetry
Pd(II)L_n	palladium(II) catalyst with n ligands
Piv	pivaloyl
Ph	phenyl
r.t.	room temperature
SET	single electron transfer
D_{4h}	square planar point group symmetry
TBHP	*tert*-butyl hydroperoxide
t-Bu	*tert*-butyl
T_d	tetrahedral point group symmetry
TBAF	tetra-*n*-butylammonium fluoride
TLC	thin layer chromatography
Tf	trifluoromethanesulfonyl

TMANO	trimethylamine N-oxide
IMes	1,3-bis(2,4,6-trimethylphenyl)imidazole-2-ylidene

Chapter 1: Introduction

1.1 Transition Metal Chemistry

Transition metal chemistry involves the d-block elements, spanning from group 3 to group 12 on the periodic table. Transition metals are different from the main-group elements in many ways. The distribution of the d-electrons around the metal center depends largely on the geometry around the metal and on the coordinated ligands. Transition metals unlike main-group elements can either be diamagnetic or paramagnetic, the former has no unpaired electrons while the latter has at least one. Transition metals also exhibit variable geometries, with many adopting octahedral, tetrahedral and square-planar structures. Alfred Werner was the first to propose octahedral structures for cobalt ammine complexes in 1893 (Figure 1). [1] He later went on to win the Nobel Prize in 1913 for his contribution to coordination chemistry. Years later, theories such as the Crystal Field Theory and the Ligand Field Theory were developed to help rationalize both the magnetism and the geometry of the complexes. Unlike the inorganic complexes, organometallic complexes are based on coordination of carbon-based ligands to transition metals and similar to inorganic complexes have broad applications in organic synthesis.

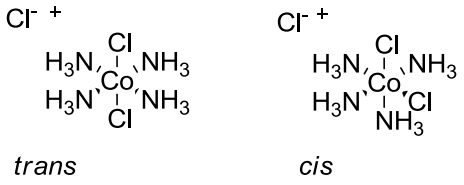
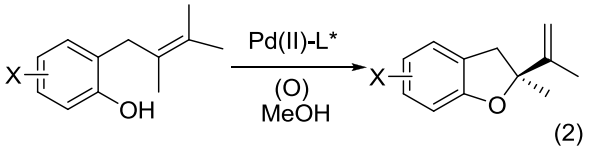


Figure 1: *cis* and *trans* cobalt ammines.

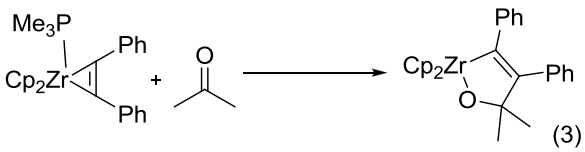
1.2 Transition Metals in the Synthesis of Organic Molecules

Nearly every organic functional group can undergo coordination to transition metals, resulting in redistribution of the electronics around the functional group, thereby imparting its reactivity. For example, upon coordination of an alkene to Pd(II), there is an electron density shift from the alkene to the Pd(II) center, rendering the alkene electron deficient and subject to nucleophilic attack (Eq. 2).[2] In contrast, low valent, early transition metals such as Zr(II) being electropositive, render alkenes and alkynes electron rich and capable of reacting with electrophiles (Eq. 3).[3]



(2)

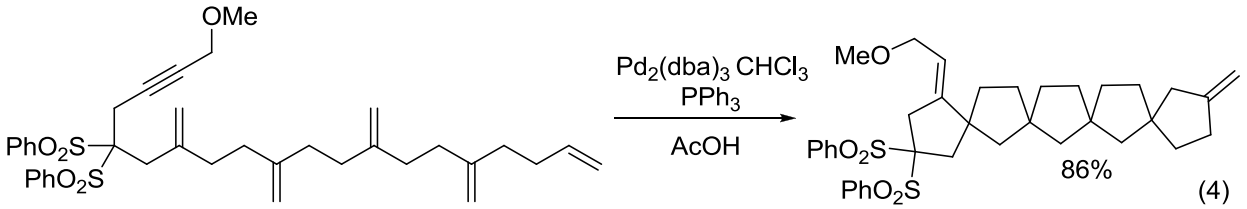
Pd(II) catayzed dihydrobenzofuran derivative synthesis *via* alkene activation.



(3)

Nucleophilic activation of alkyne by low valent Zr(II).

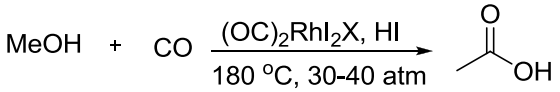
Hence, with careful choice of the transition metal, one can achieve different modes of reactivity. Another useful feature of transition metals is their ability to stabilize reactive organic species, which can potentially be used in organic synthesis in a predictable and controlled manner. For example, cyclobutadiene is unstable and dimerizes even at 35^{o} K, but when coordinated to transition metals, it forms isolable complexes.[42] Many organometallic reactions are specific to certain functional groups and show great functional group tolerance. This avoids the use of protecting groups in some cases and this reduces number of synthetic steps.[43] Another unique characteristic of transition metal catalysts is their ability to facilitate a series of steps in one pot in order to achieve complex molecule synthesis that would otherwise be very challenging. For example, hexacyclic spiro product was achieved *via* palladium catalyzed multiple 1,2-insertions (Eq. 4). [4]



Transition metal promoted tandem reaction.

Although some of the transition metals employed in organic synthesis are used in a stoichiometric amount, most can be used in a catalytic manner. This is less wasteful as compared to traditional reagents used in organic synthesis, which are required in stoichiometric amount or in excess. In addition to low catalyst loading, some transition metal catalysts enable some reactions to proceed with nearly 100% atom economy. For example, the Monsanto process which uses Rh(I) catalyst, produces more than

1 000 000 tons of acetic acid yearly



Monsanto process

(Eq. 5). [5] It is clear that transition metals show excellent properties as catalysts in organic synthesis. Transition metals also allow for non-intuitive retrosynthetic disconnections to be made, and this has significantly changed the way synthesis is carried out today.

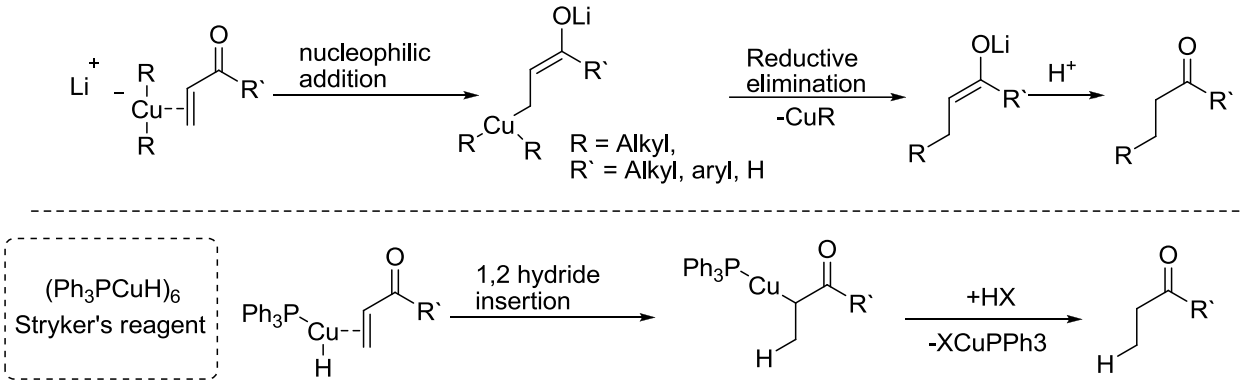
1.3 Palladium Catalysis in Organic Synthesis

Most transition metals have found use in organic synthesis. For example, electropositive early transition metals (e.g., Ti, Zr, Sc.etc.) usually act as Lewis acids while middle and late transition metals are generally better suited for metathesis, hydrogenation and cross-coupling reactions. Although there are many transition metals used in organic synthesis for carbon-carbon bond formation, none are as widely used as palladium. Palladium is a group 10 transition metal and is redox active with various accessible oxidation states such as 0, +1, +2, +3 and +4.[6] However, most palladium catalysis is based on Pd(0)/Pd(II) redox where palladium is oxidized and reduced by 2 electrons. Unlike many transition metals, palladium shows wide scope of reactivity, and can be made to display great stereo-, regio-, and chemo-selectivity. Palladium is also considered to be “soft” with relatively high electronegativity of 2.2 on the Pauling scale, which imparts covalency in bonding to carbon-based organic ligand, which are also considered ``soft``. In general, palladium is the metal of choice because of its predictable reactivity, the ease of handling, greater tolerance for moisture and air as compared to other transition metals, low toxicity, and relatively low cost as compared to Os, Rh, Ru, Au and Pt metals.

1.4 Copper Catalysis in Organic Synthesis

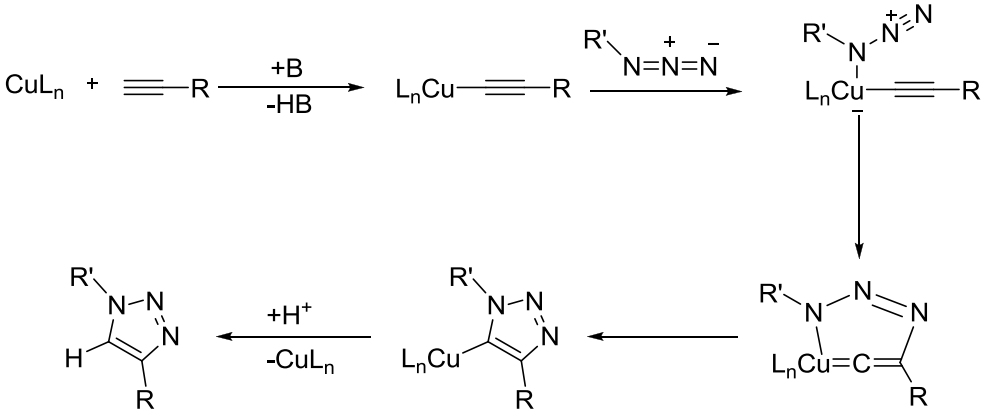
Similar to palladium, copper is another widely used transition metal in organic synthesis. Today, copper finds widespread use in synthesis and most copper salts are air and moisture stable, inexpensive and relatively non-toxic. In addition, copper-mediated

reactions also show great chemo- and regioselectivity. For example, a selective 1,4-reduction and 1,4-alkylation can be achieved with the use of Stryker's reagent and lithium dialkyl cuprates respectively, without reduction or alkylation of the carbonyl moiety (Scheme 1).[7]



Scheme 1: Regio and chemoselective copper-mediated 1,4-addition

Another highly regio- and chemoselective reaction based on copper catalyst is the azide-alkyne Huisgen cycloaddition (Scheme 2).[8]



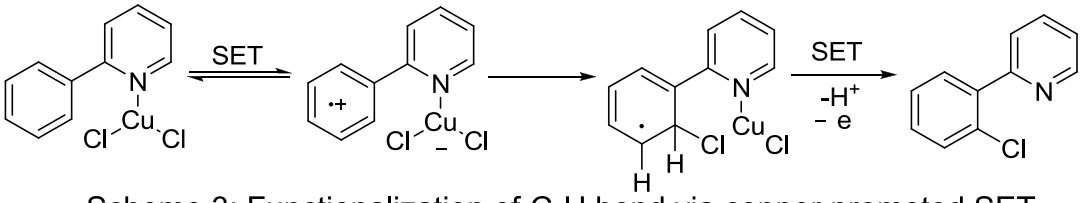
Scheme 2: Azide-alkyne Huisgen cycloaddition

1,3-Dipolar cycloaddition reactions have poor regio-selectivity,[45] but with the use of copper salts, excellent regio-selectivity can be achieved.[8] This demonstrates the

advantage of using transition metals to improve selectivity in synthesis of organic molecules as well as versatility of carbon-heteroatom and carbon-carbon bond formations. Unlike palladium, which most often undergoes 2 electron redox couple, copper is known to undergo single electron transfer, where it is oxidized or reduced by one electron at a time.

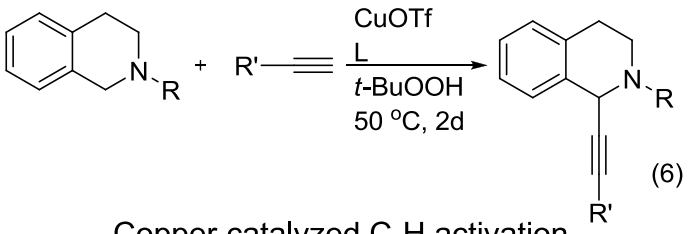
1.5 Single Electron Transfer (SET)

Transition metals are known to undergo single electron redox.[44] Single electron transfer is a very fast process and sometimes is diffusion controlled owing to the wave-particle duality of electrons. When an electron is transferred from a neutral organic molecule to a metal, it generates cationic radical with interesting reactivity that is useful for organic synthesis. Yu and others have shown that copper (II) chloride can be an efficient electron transfer reagent for organic synthesis, allowing for functionalization of ortho C-H bonds via a cationic radical intermediate (Scheme 3).[9]



Scheme 3: Functionalization of C-H bond via copper promoted SET

Similarly, Li and others reported an unusual functionalization of tertiary-amines at α-C-H bond proposed to proceed via copper-mediated SET at nitrogen (Eq. 6).[10]



(6)

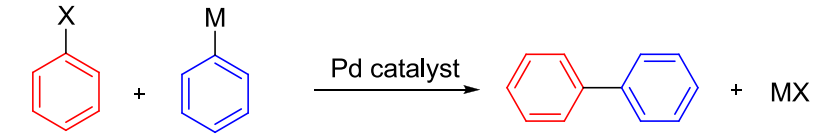
Copper catalyzed C-H activation

1.6 Cross-Coupling Reactions

Carbon-carbon bond formation is of great importance in organic synthesis. Traditional methods require prefunctionalization of the substrate and use stoichiometric reagents, which increases waste and decreases atom economy. Transition metal-catalyzed cross-coupling facilitates carbon-carbon bond formation using a catalytic amount of the metal, thus reducing waste and increasing atom economy. Traditional carbon-carbon bond formation is usually an S_N1 or S_N2 reaction between a nucleophilic sp^3, sp^2 or sp carbon and an electrophilic sp^3 carbon. However, S_N1 and S_N2 reactions between two sp^2 carbon atoms does not occur and thus is one of the most challenging bond formations using non-transition metal catalysis. Ullmann was the first to introduce sp^2-sp^2 cross-coupling in 1902. The reaction is based on copper-catalyzed coupling of aryls, although high temperatures were necessary.[11] Since then, improved and efficient methods have been developed.[46] Introduction of transition metal catalyzed cross-coupling allows easy access to sp^2-sp^2 carbon-carbon bond formation. This greatly simplified the synthesis of biaryl compounds that would otherwise be difficult to make.

Today, cross-coupling chemistry is dominated by palladium catalysis.[46] Palladium catalyzed cross-coupling is highly versatile and allows sp^2-sp^2, sp^2-sp, sp^2-sp^3 and sp^3-sp^3 carbon-carbon bond formation. There are many named cross-coupling reactions and some of which are summarized in Table 1.

Table 1: Summary of named reactions used in traditional cross-coupling.

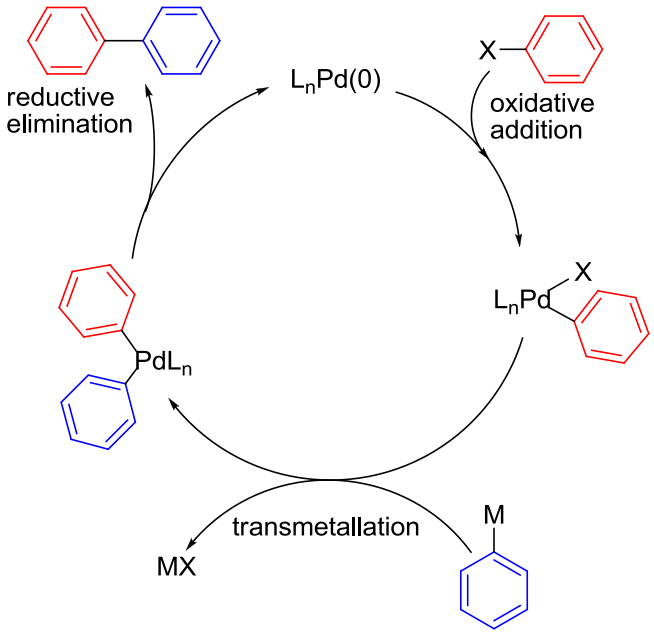


X = Cl, Br, I, tosylate, triflate etc.

M = Zn, Si, Mg, B, or Sn.

Name reaction	Metal (M)
Stille	SnR_3
Suzuki	$B(OR)_3$
Kumada	MgX
Hiyama	SiR_3
Negishi	ZnX

In traditional cross-coupling, an electrophilic partner such as aryl halide or aryl pseudohalide (triflate or tosylate) and an organometallic reagent arene are stitched together by palladium, forming an sp^2-sp^2 carbon-carbon sigma bond. The mechanism of this transformation is shown in a general catalytic cycle (Scheme 4). The catalytic cycle begins with oxidative addition of a weak carbon-halogen or carbon pseudohalogen bond to palladium(0). In this process, palladium is formally oxidized by 2 electrons. Next, transmetallation of the preactivated metal based arene to the aryl-palladium(II) complex takes place. In the last step, reductive elimination, an sp^2-sp^2 carbon-carbon sigma bond of the biaryl is formed, palladium is reduced by 2 electrons and re-enters the catalytic cycle.



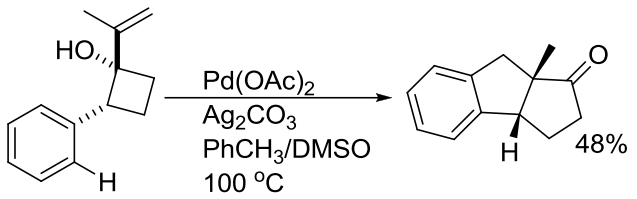
Scheme 4: General catalytic cycle for palladium-catalyzed biaryl synthesis

Although cross-coupling is a versatile method for carbon-carbon bond formation it has some disadvantages. The main disadvantage is the requirement for stoichiometric prefunctionalized metal-based cross-coupling partner, which increases waste generated and decreases atom economy. Various synthetic protocols have been developed to improve atom economy and efficiency.[12] For example, one alternative to traditional cross-coupling reaction involves palladium-catalyzed ring opening of cyclopropanols and cyclobutanols *via* β-carbon-elimination followed by C-H activation.

1.7 Palladium Promoted β-Carbon -Elimination of Strained Rings

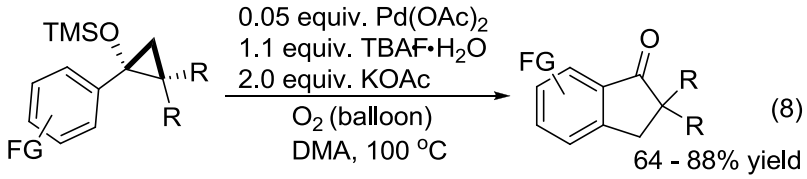
Open-chain organic molecules are able to minimize torsional and angle strain due to flexibility in the structure as compared to cyclic molecules. The number of degrees of freedom is greatly reduced in cyclic molecules and this increases angle and torsional strain, hence strained ring molecules have intrinsic destabilization. Strain raises the energy content of the molecule and increases its reactivity. Cyclopropane and

cyclobutane have high strain energies of 27.5 and 26.5 kcal/mol, respectively. The high reactivity of cyclopropane and cyclobutane is exploited in palladium catalyzed ring expansion of cyclopropanols and cyclobutanols (Eqs. 7 and 8).[12,13,47,48]



(7)

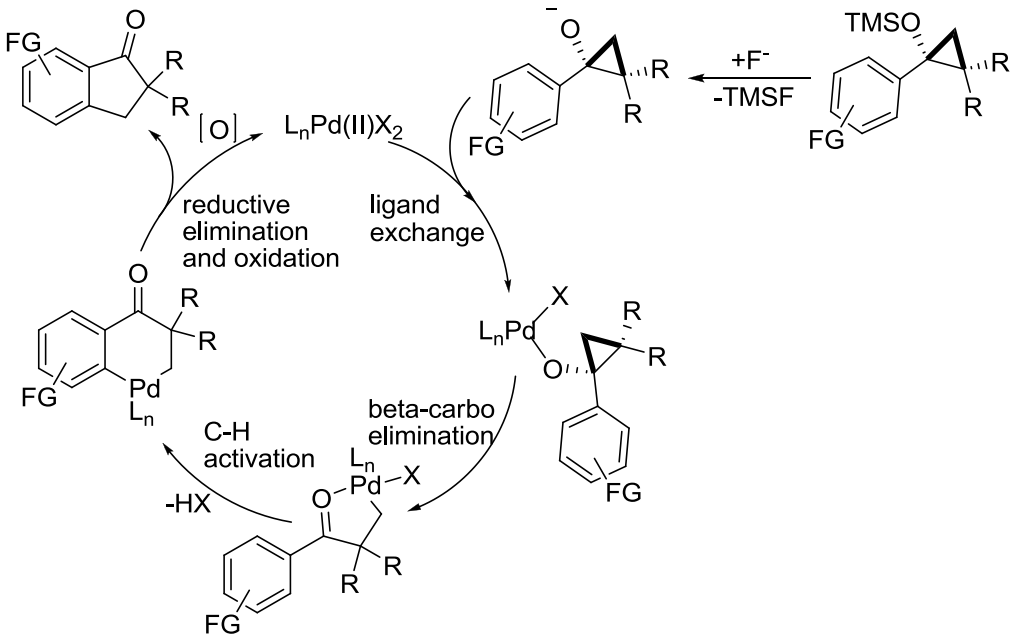
Palladium catalyzed ring expansion of cyclobutanol and C-H activation.



(8)

Palladium catalyzed ring expansion of cyclopropanol and C-H activation.

These examples of non-traditional cross-coupling reactions utilize the C-H bond as the cross-coupling partner. Formation of the alkoxy-palladacycle intermediate *via* β-carbon-elimination is the key step in the catalytic cycle after which C-H activation and reductive elimination complete the cycle (Scheme 5).



Scheme 5: Palladium catalyzed synthesis of alpha-indanones *via* beta-carbon-limination and direct arylation.

This is an efficient method which utilizes ring-strain of cyclopropanols for synthesis of ring systems such as indanones and bicyclic five-membered rings. A significant advantage of these reactions is that functionality is retained in the product since the tertiary alcohol is transformed to a ketone and can further be used in synthetic transformations.

1.8 *Occurrence and Biological Activity of Cyclopentenones*

Cyclopentenones are common structures within naturally occurring molecules including prostaglandin A2, cucumin H, pentenomycin, punaglandin, methylenomycin B, trichodenone A, (-)(4S,5S)-isoterrein, myrothenone A, prostaglandin A1, and *cis*-jasmone (Figure 2). Some of these molecules are important due to their biological activity. Prostaglandins are biologically active molecules with many different physiological effects

such as regulating the contraction and relaxation of smooth muscle tissue, control of cell growth, and control of hormone regulation.[14] Myrothenone A and trichodenone A are isolated from marine derived fungus Myrothecium and show a tyrosinase inhibitory activity.[15] Jasmone is an extract from jasmine flowers and naturally occurs as both *cis* and *trans* isomers both of which are used in perfumes and cosmetics.[16]

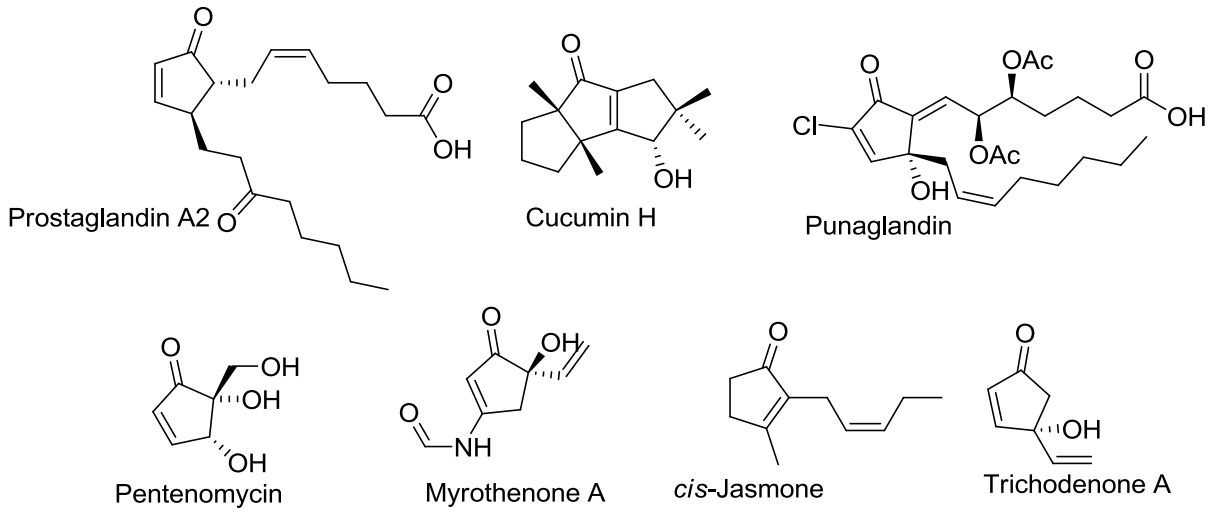


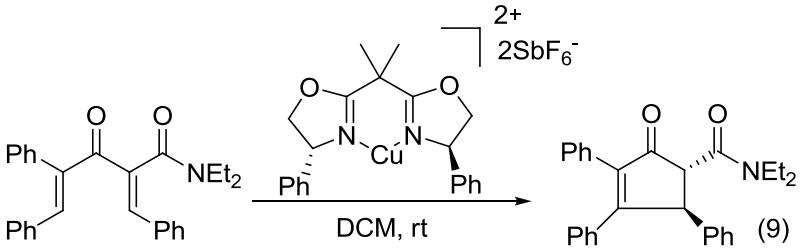
Figure 2: Naturally occuring molecules containing cyclopentenone structure.

Most of these biologically active molecules are isolated from natural sources such as plants and marine sponges on a milligram scale. However, due to their importance and demand in the pharmaceutical discovery there been various synthetic protocols developed to allow cyclopentenone synthesis to be carried out in a laboratory on the larger scale.[17,19] Current synthetic methods for cyclopentenone synthesis although useful are far from ideal.

1.9 Common Synthetic Strategies for the Preparation of Cyclopentenones

1.9.1 The Nazarov-Cyclization

Ivan Nikolaevich Nazarov discovered the Nazarov-Cyclization reaction in 1949 and today it is a common method for synthesis of cyclopentenones (Eq. 9).[17]



Copper(II) promoted Nazarov cyclization.

This is a pericyclic reaction that requires either a Bronsted or a Lewis acid or heat to drive the 4-π conrotatory cyclization of divinyl ketones. The driving force for this reaction is the formation of a new sigma bond and loss of a π bond. This method is a valuable tool in organic synthesis and is the key step in many natural product synthesis (e.g. rocaglamide Figure 3).[18] Although this method is well established and is a common way to install cyclopentenone, it has its drawbacks. The reaction often requires several equivalents of a strong Lewis acid to which other functional groups might be sensitive, limiting the substrate scope. Installation of an α,β-unsaturation via loss of a proton is not usually regioselective and produces isomers that are often difficult to separate. Enolate protonation (tautomerization) is not usually streoselective and produces mixture of epimers.

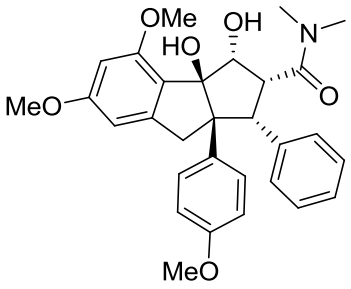
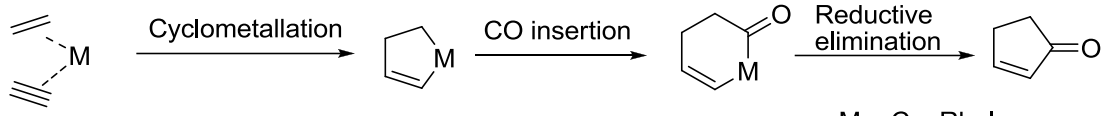


Figure 3: Structure of rocaglamide

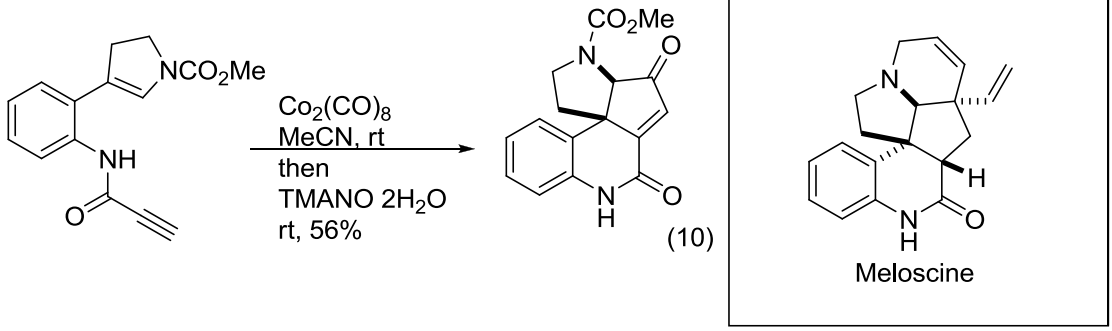
1.9.2 Pauson-Khand Reaction

Pauson-Khand method is a transition-metal catalyzed cyclopentenone forming reaction via (2+2+1) cycloaddition. The 2 + 2 refers to a transition metal catalyzed oxidative-coupling of an alkene to an alkyne and 1 refers to carbon monoxide insertion (Scheme 6).



Scheme 6: Elementary steps of Pauson-Khand reaction.

The reaction was first carried out using stoichiometric dicobalt octacarbonyl in the presence of carbon monoxide but later catalytic variants were developed using other transition metals. This method is highly versatile and is a key step in the synthesis of many natural products, including (±)-meloscine (Eq. 10).[19]

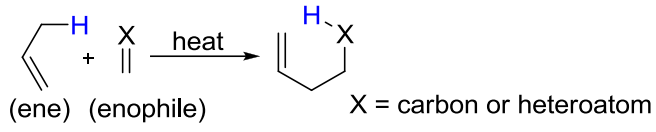


Pauson-Khand reaction used in synthesis of natural product, meloscine.

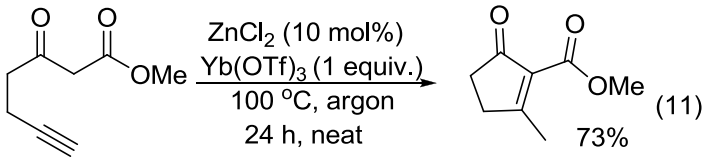
Although this method is versatile, it has disadvantages. It often requires dicobalt octacarbonyl in stoichiometric amounts, high CO pressure, has poor regioselectivity for internal alkynes and does not work well for alkenes containing strong electron-withdrawing groups.

1.9.3 Lewis Acid Promoted Conia-Ene Reaction

A classic Alder-ene reaction is a concerted pericyclic transformation between an olefin containing an allylic proton (ene) and a multiple bond (enophile) (Scheme 7). The Conia-ene reaction is similar to Alder-ene process but is limited to intramolecular reactions that contain carbonyl functional groups.[20] This method is heat-promoted or Lewis acid-catalyzed cyclization and provides access to various ring sizes. Using the Conia-ene reaction, Li and others have developed a protocol to generate cyclopentenone derivatives using Lewis acid catalysis (Eq. 11).[20] While this method works well for terminal alkynes containing 1,3-dicarbonyl functional group, internal alkynes form cyclohexenones or a mixture of cyclopentenone and cyclohexenone. The limited scope of this reaction due to substrate specificity and requirement of highly oxophilic Ln(III) metal makes this method non-ideal.



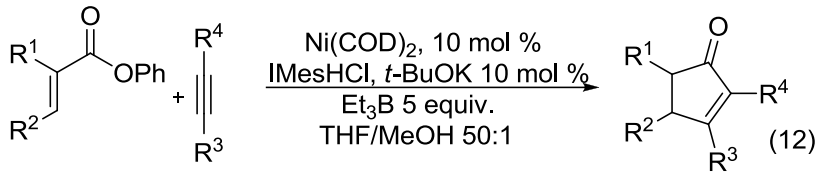
Scheme 7: Alder-ene reaction.



Conia-ene reaction used for synthesis of cyclopentenone.

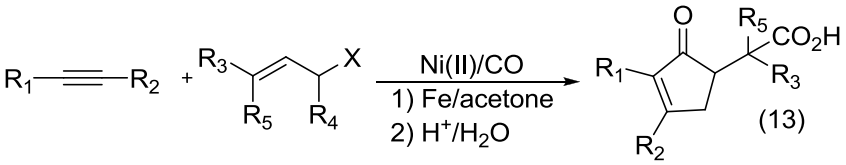
1.10 Other Methods for the Preparation of Cyclopentenones

Montgomery and co-workers have developed a protocol based on Ni(0) catalysis.[21] This synthetic method gives access to substituted cyclopentenones from phenyl enoates and alkynes in the presence of triethyl borane as both the Lewis acid and reducing agent (Eq. 12).[21] This methodology is limited to phenyl enoates and shows significant decrease in yield for R^1 other than hydrogen. This significantly limits the scope and utility of this method.



Nickel(0) catalyzed cyclopentenone formation.

Another method based on nickel was introduced by Moreto and others and they suggest that the catalytic cycle operates under Ni(I)/Ni(III) redox (Eq. 13).[22]



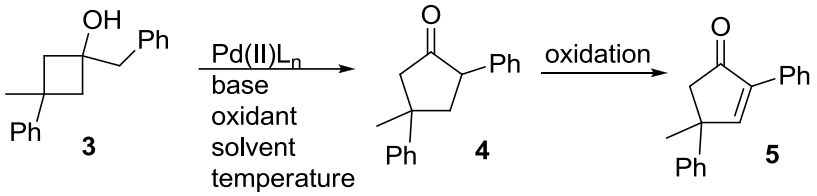
Ni(I) catalyzed cyclopentenone synthesis.

This method requires Fe(0) to reduce Ni(II) to Ni(I) and initiate Ni(I)/Ni(III) redox cycle. This method is far from being ideal and the major disadvantage is the need for the Fe(0) as the reducing agent, which can potentially reduce sensitive functional groups.

1.11 *Proposal*

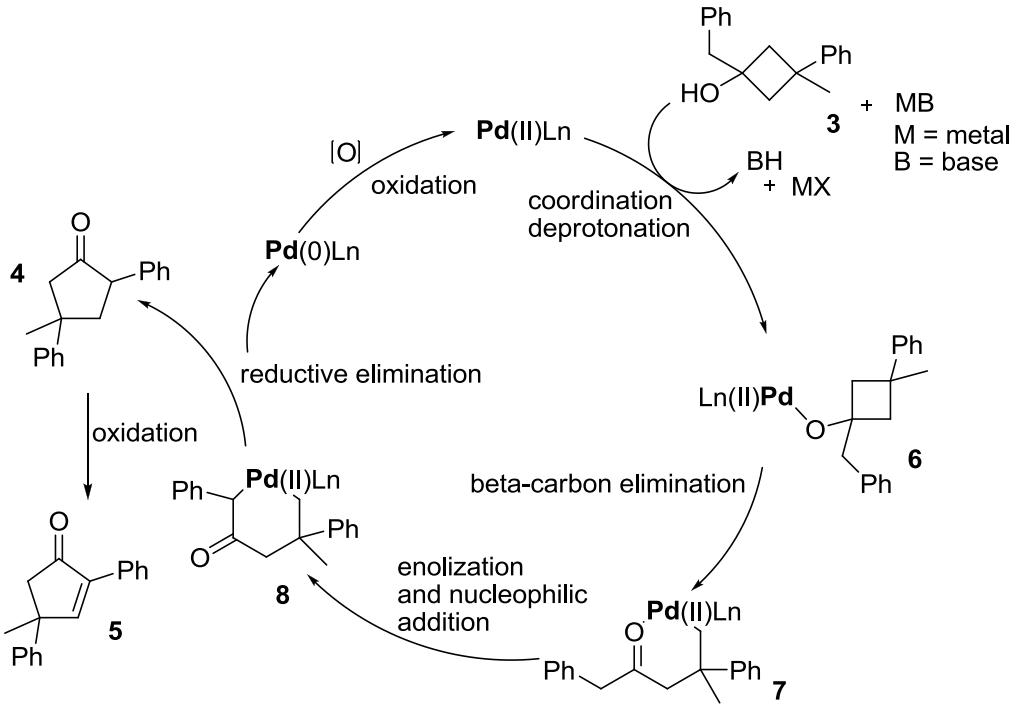
Exploring a New Palladium-Catalyzed Rearrangement of Tertiary-Cyclobutyl Alcohols to α,β-Unsaturated Cyclopentanones

Aware of the common synthetic methods for cyclopentenone synthesis and their limitations, we turned our attention to utilising the ring strain of tertiary-cyclobutanols (**3**, Scheme 8) to access cyclopentanones (**4,** Scheme 8) *via* a palladium(II) catalyzed rearrangement with β-carbon-elimination as the key step.[49, 50, 51] It was envisioned that cyclopentanone **4** can be oxidized to cyclopentenone (**5,** Scheme 8) by the palladium catalyzed Saegusa-Ito oxidation in the same pot and under the same conditions.



Scheme 8: Proposed synthesis of cyclopentenone from tertiary-cyclobutanol.

The feasibility of this transformation will be explored using a stoichiometric amount of palladium(II) sources. Optimization of reaction conditions such as base, ligand, oxidant, solvent and temperature should render this transformation catalytic. A catalytic cycle for the transformation is proposed (Scheme 9). Coordination and deprotonation of the alcohol is expected to generate palladium(II) alkoxide **6,** and this should undergo strain releasing β-carbon-elimination, generating palladacycle **7**.



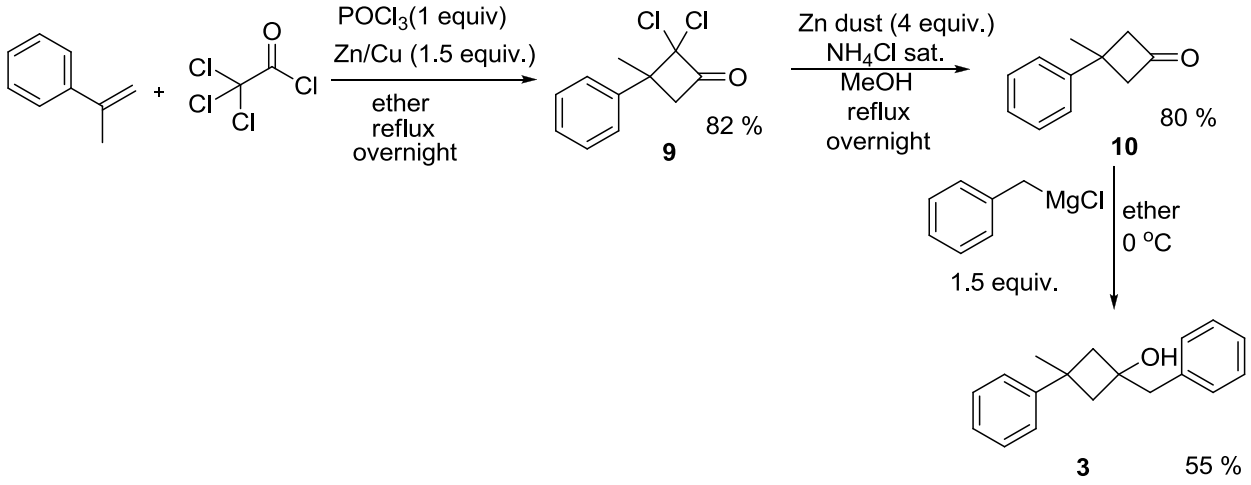
Scheme 9: Proposed catalytic cycle for palladium(II) catalyzed cyclopentenone formation.

Upon coordination of the carbonyl moiety to palladium, the pKa of the α-protons is lowered and allows the formation of palladium(II) enolate **8**, reductive elimination then yields cyclopentenone **4**. The catalytic cycle should be completed by reoxidation of palladium(0) to palladium(II). The final product **5** should be formed via oxidation of cyclopentanone **4**, via Saugusa-Ito reaction. Upon successful development of this method, the generality of the reaction will be examined using various tertiary-cyclobutanols.

Chapter 2: Results and Discussion

2.1 Substrate Synthesis: Synthesis of Model Substrate 3

Initially, our focus was towards the synthesis of 1-benzyl-3-methyl-3-phenyl-*tert*-cyclobutanol **3** in order to explore the plausibility of the proposed cyclopentenone synthesis. Benzyl cyclobutanol **3** was chosen as a model substrate since it is readily synthesized and easily analyzed by ^{1}H-NMR spectroscopy due to symmetry. Also, we began to explore our synthetic strategy using substrate containing unsubstituted benzyl group. (Scheme 10).



Scheme 10: Preparation of 3-methyl-phenyl substituted benzyl cyclobutanol **3**.

The preparation of benzyl cyclobutanol **3** (Scheme 10) was carried out *via* a three-step synthetic protocol starting with α-methylstyrene. In the first step, the 2,2-dichlorocyclobutanone **9** was synthesized *via* a (2+2) cycloaddition of *in-situ* generated dichloro-ketene with α-methylstyrene according to a literature procedure.[23] Next, the reduction of 2,2-dichlorocyclobutanone **9** to cyclobutanone **10** (Scheme 10) was

carried out in the presence of zinc powder in refluxing anhydrous methanol saturated with ammonium chloride.[23] Compound **3** (Figure 4) was isolated in 55% yield as single diastereomer and used for the next step without establishing relative configuration.

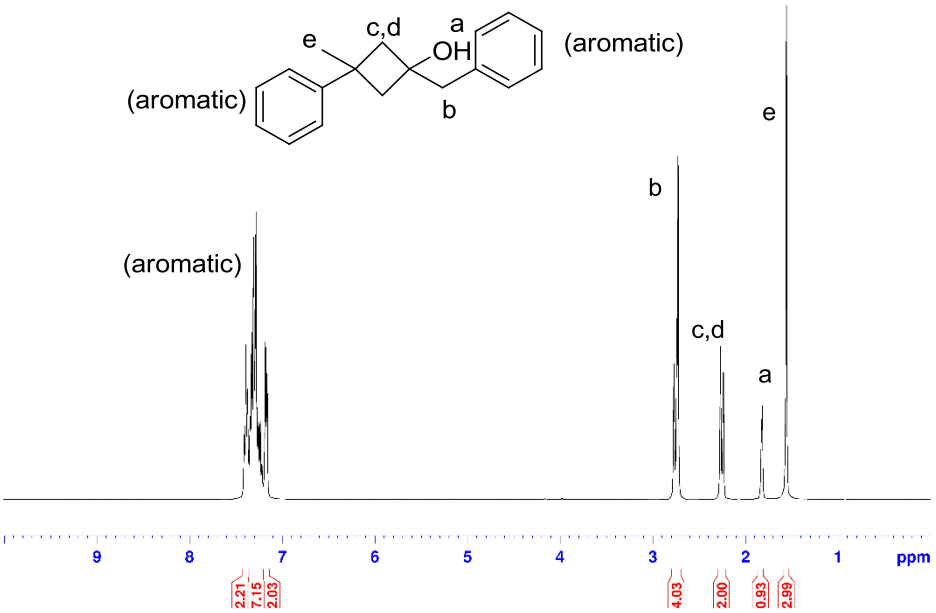


Figure 4: ^{1}H-NMR spectrum for compound **3** collected on 300 MHz spectrometer ($CDCl_3$).

2.2 Substrate Synthesis: Synthesis of Model Substrate 2

(±)-7-benzyl-1-methylbicyclo[4.2.0]octan-7-ol **2** was synthesized as a second model substrate for our study (Scheme 11). Compared to cyclobutane, fused bicyclic structures have greater ring strain, which is due to the increase in angle and torsional strains as a consequence of increased rigidity (Figure 5).[24,25,27] Therefore, benzyl cyclobutanol **2** was thought to have a greater propensity to undergo β-carbon-elimination. As before, we wanted to explore our synthetic strategy using substrate containing unsubstituted benzyl group.

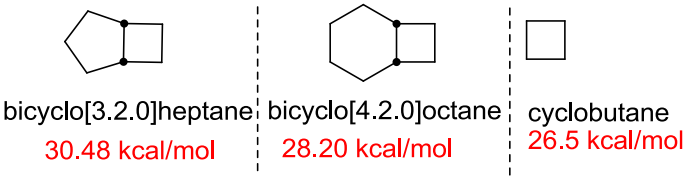
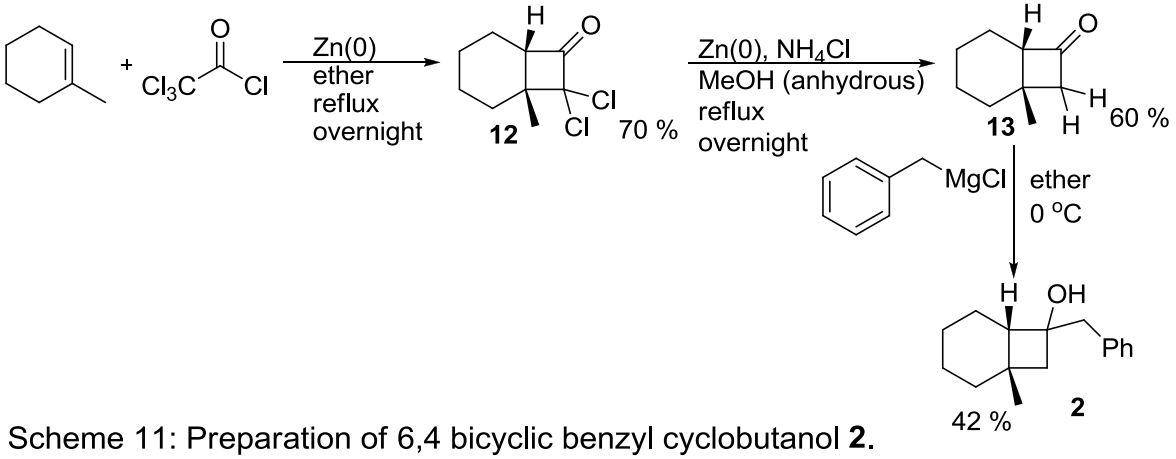


Figure 5: Ring strain energies of 5,4 and 6,4 fused rings as compared to cyclobutane.



Scheme 11: Preparation of 6,4 bicyclic benzyl cyclobutanol **2.**

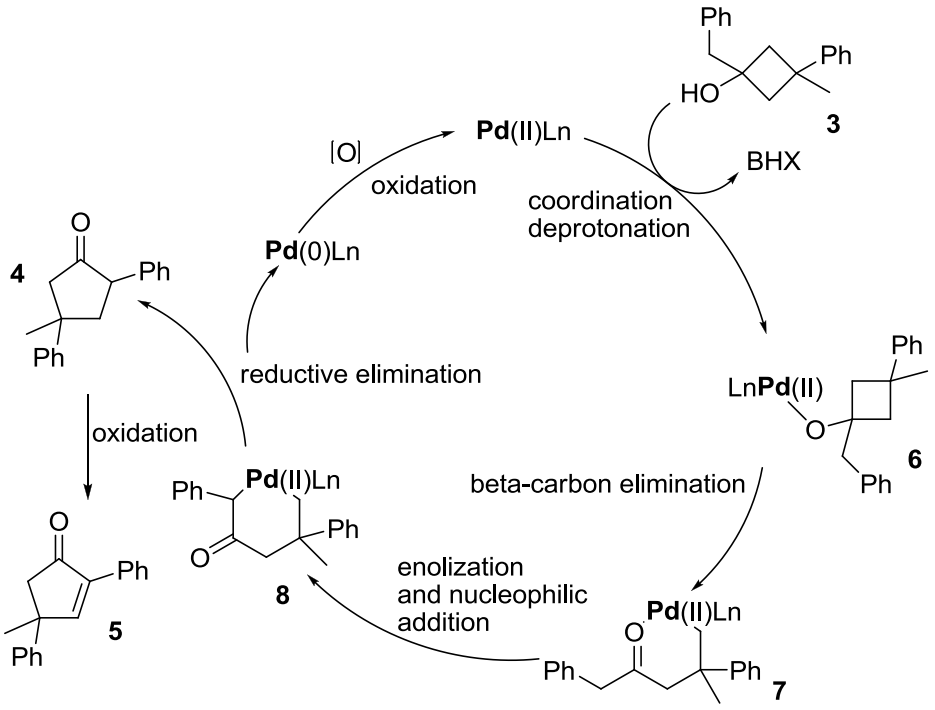
The synthesis of benzyl cyclobutanol **2** was carried out *via* a three step synthetic protocol starting with 1-methyl-1-cyclohexene. In the first step, the 2,2-dichlorocyclobutanone **12** was synthesized *via* (2+2) cycloaddition of dichloro-ketene with 1-methyl-1-cyclohexene according to literature procedure.[26,41] According to ^{1}H-NMR spectrum, **12** was the only regioisomer formed. Next, the reduction of 2,2-dichlorocyclobutanone **12** to

cyclobutanone **13** was achieved in 60% using zinc powder in refluxing anhydrous methanol saturated with ammonium chloride. Lastly, benzyl cyclobutanol **2** was generated in 42%, by addition of benzylmagnesium chloride to cyclobutanone **13**. The proton NMR spectrum of the isolated cyclobutanol **2** showed a multiplet at δ 7.33-7.23 (m, 5 H), an AB type signal consisting of a set of leaning doublets at δ 2.89 (d, *J* = 13.2 Hz, 1 H) and δ 2.82 (d, *J* = 13.2 Hz, 1 H), doublet at δ 2.07 (d, *J* = 7.2 Hz, 1 H), another set of AB type signal at δ 1.99 (d, J = 12.4 Hz, 1 H) and δ 1.85 (d, 12.4 Hz, 1 H) followed by multiplet at δ 1.55-1.15 (m, 8 H) and methyl group at δ 1.13 (s, 3 H). Additional spectroscopic evidence based on IR and ^{13}C-NMR spectroscopy further confirmed the structure of **2**.

2.3 Establishing Proof of Concept Using Stoichiometric Palladium(II)

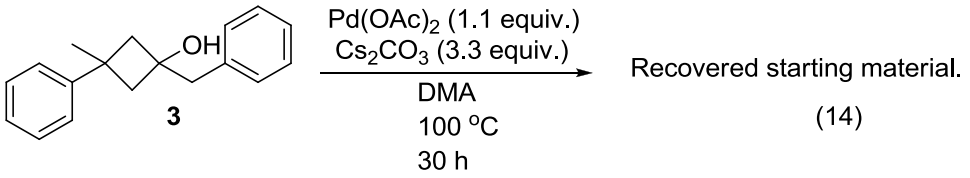
2.3.1 Establishing Proof of Concept using Substrate 3

With the model substrate **3** in hand, we were set to explore the feasibility of the proposed cyclopentenone synthesis *via* β-carbon-elimination as the key step, under palladium(II) catalysis. We hypothesised that model substrate (**3**, Scheme 9), would form a palladium alkoxide complex (**6**, Scheme 9), promoting the strain-releasing β-carbon-elimination of benzyl cyclobutanol **3** to intermediate (**7**, Scheme 9). Further, we envisioned that coordination of the carbonyl moiety to palladium(II) would lower the pKa of the α-benzylic protons and promote enolate formation in the presence of mild base and that would generate palladacycle (**8**, Scheme 9). This intermediate would in turn reductively eliminate the cyclopentanone (**4**, Scheme 9) and form cyclopentenone *via* Saegusa-Ito oxidation in one pot. Using a catalytic amount of palladium, generation of palladium(0) at the end of catalytic cycle would require introduction of an oxidant to regenerate palladium(II) catalyst.



Scheme 9: Proposed catalytic cycle for palladium(II) catalyzed cyclopentenone formation.

Initially, we chose to explore the reactions using stoichiometric amounts of palladium(II) acetate and 3 equivalents of base in DMA solvent at 100 ^{o}C (Eq. 14). This initial set of conditions did not yield the cyclopentenone product and instead resulted in complete recovery of the starting cyclobutanol; the use of other bases, such as potassium carbonate, silver carbonate and various acetates also showed recovery of starting material.



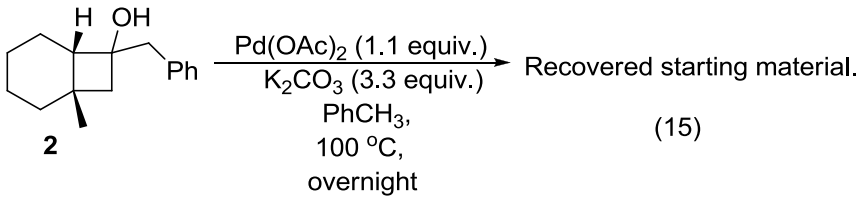
Initial reaction with stoichiometric palladium (Substrate 3).

At this stage, we hypothesized that it was difficult for cyclobutanol **3** to coordinate to palladium(II) acetate, possibly arising from lack of free coordination site. We envisioned that switching to palladium(II) trifluoroacetate, bearing more labile ligands, would facilitate coordination since the trifluoroacetate ligands should dissociate from palladium. However, switching palladium(II) acetate to palladium(II) trifluoroacetate did not yield the desired product and full recovery of starting material was confirmed by ^{1}H-NMR spectroscopy. We then decided to introduce the cationic tetrakis(acetonitrile)palladium(II) tetrafluoroborate salt in an effort to make the palladium center more electrophilic in order to promote coordination of cyclobutanol **3**. However, no cyclopentenone product (**5**, Scheme 9) was formed and complete recovery of starting material was confirmed by ^{1}H-NMR spectroscopy.

After many attempts, using various solvents, palladium(II) sources and bases, no satisfactory results could be achieved and it was concluded that cyclobutanol **3** does not coordinate efficiently to palladium(II) source or is not strained enough.

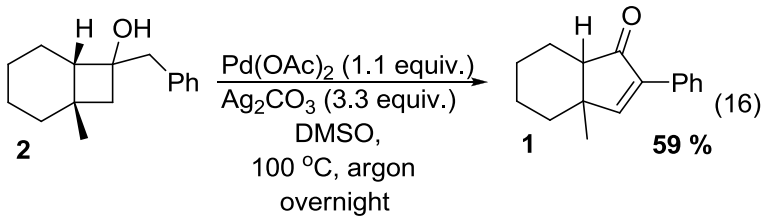
2.3.2 Establishing Proof of Concept using Substrate 2

Considering the increased ring-strain of the bicyclo[4.2.0]octane (28.2 kcal/mol) ring system as compared to cyclobutane (26.5 kcal/mol), we were optimistic that model substrate (**2**, Eq. 15) would have greater propensity to undergo strain-driven β-carbon-elimination with palladium(II) catalyst. As an initial set of conditions, we chose to use stoichiometric amounts of palladium(II) acetate and toluene as the solvent at 100 ^{o}C (Eq. 15).



Initial reaction with stoichiometric palladium (Substrate 2).

These conditions did not yield the cyclopentenone product and complete recovery of the starting cyclobutanol (**2**, Eq. 15) was confirmed by ^{1}H-NMR spectroscopy. Next, we investigated pyridine as base and observed the same result. After considerable effort, we discovered that palladium(II) acetate, silver carbonate, and DMSO at 100 ^{o}C was the appropriate combination towards cyclopentenone **1** synthesis (Eq. 16). The experiment demonstrated the feasibility of the proposed method as a desired product was isolated in moderate yield with ^{1}H-NMR spectroscopic data consistent with cyclopentenone **1**.



Cyclopentenone synthesis with stoichiometric palladium.

The proton spectrum of compound **1** showed the characteristic singlet peak at δ 7.58 ppm, owing to the proton attached to the deshielded β-carbon of the alkene. This chemical shift matched closely to the chemical shift of structurally similar compound 2-phenylcyclopent-2-enone.[46] The doublet of doublets at δ 2.24 ppm with *J* coupling constants of 6.0 Hz and 6.6 Hz was characteristic of the α proton to the carbonyl group (Figure 6).

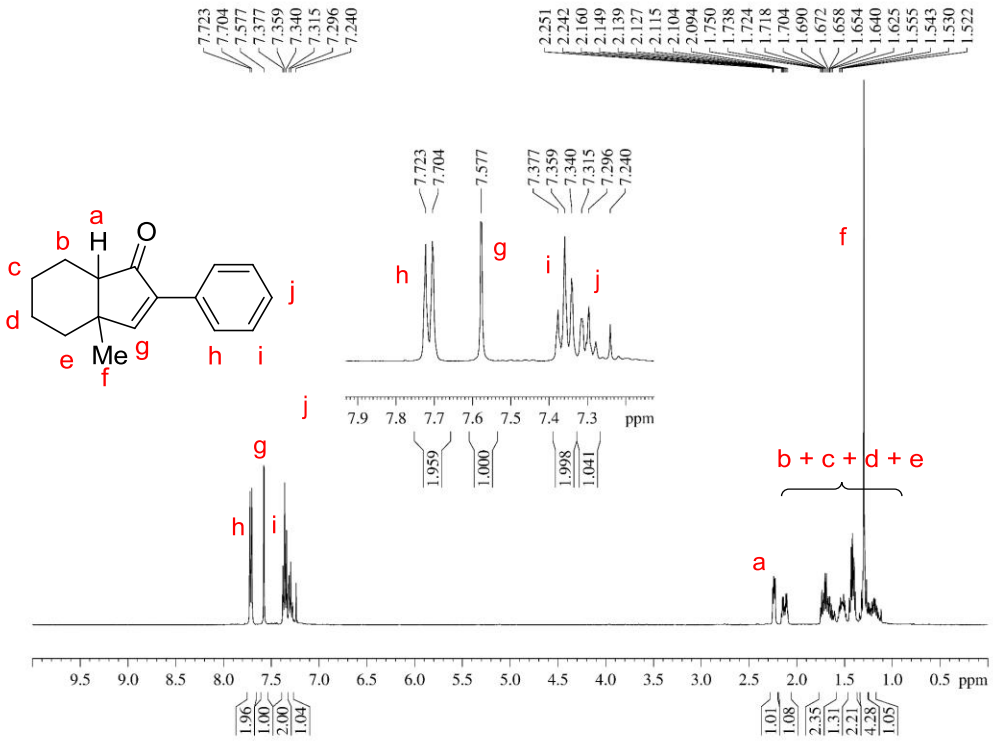


Figure 6: ^{1}H-NMR spectrum of cyclopentenone **1** collected on 600 MHz spectrometer ($CDCl_3$).

To obtain further evidence for the desired target molecule **1**, ^{13}C-NMR and IR spectra were recorded, which were consistent with the proposed structure. The ^{13}C NMR spectrum showed the characteristic peaks for the carbonyl carbon at 208.5 ppm and for the β-carbon of the alkene at 166.0 ppm. The IR spectrum of the compound showed an intense carbonyl stretch at 1704 cm^{-1} and alkene stretch at 1685 cm^{-1}. A GC-MS spectrum ($M^{+\cdot}$ = m/z 226.14) provided additional evidence for the proposed structure.

2.4 Making Reaction Catalytic in Palladium

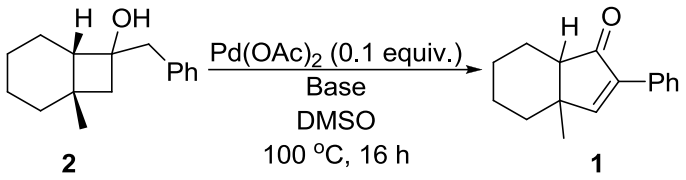
Having gathered enough spectroscopic evidence, we were certain that the isolated compound was cyclopentenone **1** and focused our efforts to optimization of reactions conditions and turning this method catalytic in palladium.

2.4.1 Base Screen

Since the reaction is under catalytic conditions, it is essential to regenerate the palladium(II) catalyst, hence an oxidant is required. Our initial screen of bases were carried out under an atmosphere of molecular oxygen. Oxygen is an ideal oxidant mainly due to its low cost and water as a major by-product.

When potassium phosphate (Entry 1, Table 2) was used as the base with 10 mol % palladium acetate and DMSO as solvent at 100 ^{o}C no product formation could be observed. Next we introduced sodium and potassium carbonates and observed the same result. Then we switched to silver carbonate (Ag_2CO_3) (Entry 4, Table 2) the formation of cyclopentenone **1** in < 5% yield was observed. As a comparison, we decide to explore acetate bases. When potassium acetate (Entry 5, Table 2) was used with 10 mol % palladium acetate and DMSO as solvent at 100 ^{o}C, no product formation was observed. Moving forward, we switched the base for silver(I) acetate and observed complete recovery of the starting material. Continuing our exploration of the acetate bases, we introduced potassium pivalate (Entry 7, Table 2) and observed the formation of cyclopentenone **1** in < 5% yield. Next, we increased the catalyst loading from 0.1 to 0.5 equivalents and the amount of product isolated did not exceed the mole percentage of

catalyst used. Based on this, we concluded that the reaction was stoichiometric in palladium and molecular oxygen was not an efficient oxidant under these conditions.



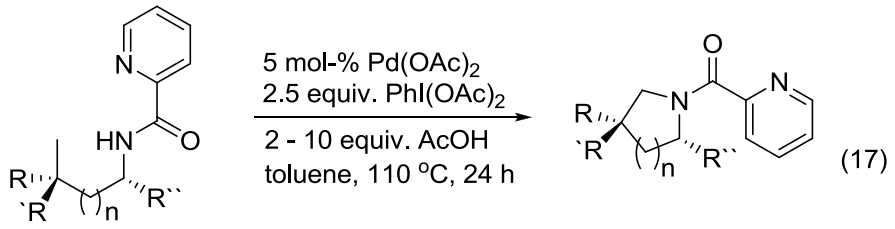
2 **1**

Table 2: Summary of the Base Screen using Cyclobutanol **2** as Substrate.

Entry (% yield of 1)						
1(0%)	2(0%)	3(0%)	4(< 5%)	5(0%)	6(0%)	7(< 5%)
K_3PO_4(3.3) O_2 (1 atm)	K_2CO_3(3.3) O_2 (1 atm)	Na_2CO_3(3.3) O_2 (1 atm)	Ag_2CO_3(3.3) O_2 (1 atm)	KOAc(3.3) O_2 (1 atm)	AgOAc(3.3) O_2 (1 atm)	KOPiv(3.3) O_2 (1 atm)

2.4.2 Oxidant Screen

Considering that molecular oxygen was an ineffective oxidant, we turned our attention to other oxidants using DMSO at 100 °C as solvent. Chen and co-workers demonstrated the utility of (diacetoxyiodo)benzene (Entry 1, Table 3) as viable oxidant for palladium(II) catalysis (Eq. 17).[28]



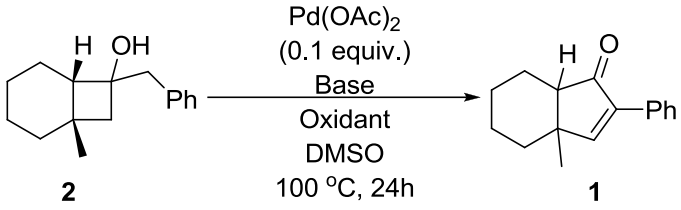
(17)

(Diacetoxyiodo)benzene used as terminal oxidant for palladium.

Muniz and others also showed the potential of (diacetoxyiodo)benzene as terminal oxidant for palladium.[29] However, when (diacetoxyiodo)benzene was used as an oxidant,

we observed complete recovery of starting material, as confirmed by ^{1}H-NMR spectroscopy.

Silver(I) salts have been shown to act as oxidants in oxidative palladium catalyzed reactions.[30] When stoichiometric silver(I) additives such as silver carbonate (entry 2, Table 3), silver acetate (entry 3, Table 3) and silver tetrafluoroborate (entry 4, Table 3) were used as oxidants, only minor product formation could be observed < 5%. Next, we decided to investigate organic oxidants. We began with stoichiometric amount of benzoquinone, potassium pivalate in DMSO at 100 ^{o}C (entry 5, Table 3). The cyclopentenone product could not be observed and starting material was recovered. Similar results were obtained with DDQ and tetrafluoro-1,4-benzoquinone (entries 6 and 7, table 3).

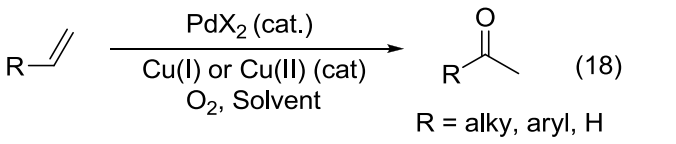


2 **1**

Table 3: Summary of the Oxidant Screen.

Entry	Base/Oxidant (equiv.) (%yield of 1)	Entry	Base/Oxidant (equiv.) (%yield of 1)
1	KOPiv (3.3) (diacetoxyiodo)benzene (1.1 equiv.) (< 5%)	7	KOPiv (3.3) tetrafluoro-1,4-benzoquinone (1.1 equiv.) (0%)
2	KOPiv (3.3) silver carbonate (1.1 equiv.) (< 5%)	8	KOPiv (3.3)/O_2 copper(I) chloride (2.2 equiv.) (0%)
3	KOPiv (3.3) silver acetate (2.2 equiv.) (< 5%)	9	KOPiv (3.3)/O_2 copper(I) bromide (2.2 equiv.) (0%)
4	KOPiv (3.3) silver tetrafluoroborate (2.2 equiv) (0%)	10	KOPiv (3.3) copper(II) acetate (2.2 equiv.) (0%)
5	KOPiv (3.3) benzoquinone (1.1 equiv.) (0%)	11	KOPiv (3.3) copper(II) chloride (2.2 equiv) (see text)
6	KOPiv (3.3) DDQ (1.1 equiv) (0%)	12	KOPiv (3.3) copper(II) bromide (2.2 equiv.) (see text)

In effort to find a viable oxidant for this protocol, we decided to explore copper(I) and copper(II) salts *via* Wacker-Tsuji type oxidation conditions (Eq.18).[31] Wacker-Tsuji oxidation is an important industrial method for oxidation of ethylene and terminal alkenes to aldehydes and ketones. Mechanistic studies indicate that oxygen is the terminal oxidant and regenerates copper(II) catalyst, while copper(II) is the secondary oxidant and regenerates



(18)

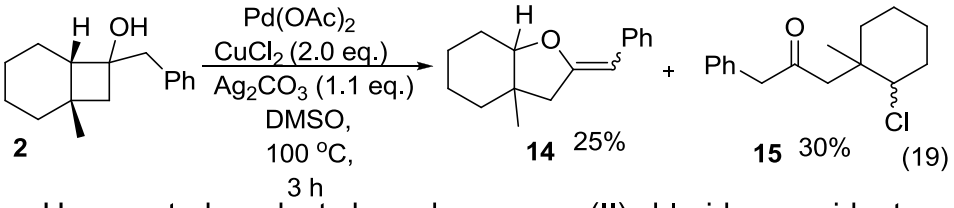
R = alky, aryl, H
X = Cl, Br, TFA, OAc,

Wacker-Tsuji reaction conditions.

palladium(II) catalyst, allowing for copper(II) and palladium(II) to be used in catalytic amounts .[33]

Optimistic about this method, we wanted to explore its application to our protocol. For our initial conditions we chose stoichiometric copper(I) chloride (entry 8, Table 3), potassium pivalate base, and DMSO at 100 ^{o}C under oxygen atmosphere. The result after 16 h, was complete recovery of starting material. Similar result was obtained using copper(I) bromide/O_2 and copper(II) acetate (entries 9 and 10, table 3).

Next, we wanted to investigate, copper(II) chloride and copper(II) bromide as viable oxidants for palladium. Initial reaction conditions (Entries 11, 12, Table 3) showed recovery of starting material. When silver carbonate was used instead of potassium pivalate we observed complete consumption of starting alcohol **2** after 3 h. However, two new and unexpected products were formed rather than the desired enone **1** (Eq. 19).



Unexpected products based on copper(II) chloride as oxidant.

The unexpected products were 2-benzylidene-3-methyloctahydrobenzofuran **14** and 1-(2-chloro-1-methylcyclohexyl)-3-phenylpropan-2-one **15**. Compound **14** was unstable and decomposed over time. The proton spectrum of compound **14** showed two doublets at δ 2.60 ppm and δ 2.46 ppm with large geminal coupling constants of 15.2 Hz, which is characteristic for a methylene group with diastereotopic protons. The aromatic region showed a doublet at δ 7.59 ppm with a *J* coupling constant of 8.0 Hz and doublet of doublets at δ 7.29 ppm with coupling constants of 8.0 Hz and 7.2 Hz and a doublet of

doublets at δ 7.09 ppm with coupling constants of 7.6 Hz and 7.2 Hz. The proton α to the ether oxygen was abserved as doublet of doublets at δ 4.09 ppm with a *J* coupling constants of 2.8 Hz and 2.8 Hz. The methyl group was observed as a singlet at δ 1.14 ppm. The alkenyl proton was observed as a singlet at δ 5.22 ppm. The remaining aliphatic protons were observed as multiplet from δ 2.12-1.30 ppm (Figure 7).

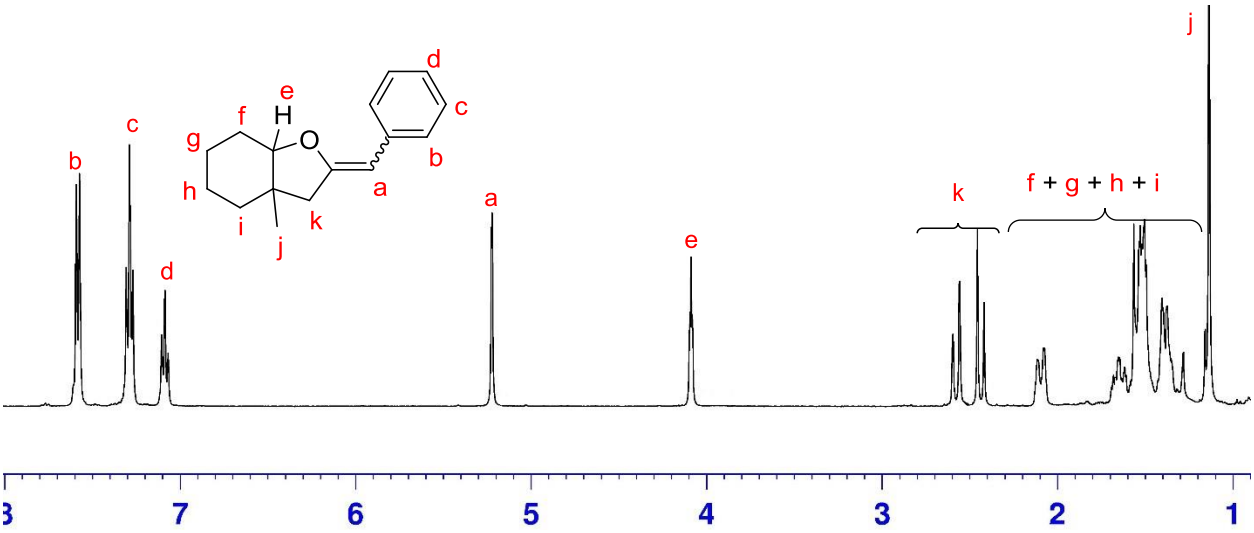


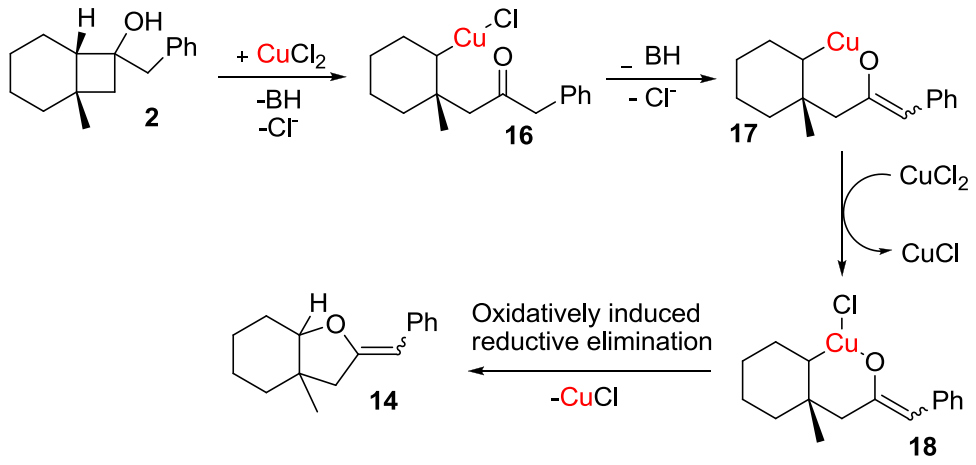
Figure 7: ^{1}H-NMR spectrum of unexpected compound **14** collected on 400 MHz spectrometer ($CDCl_3$).

To obtain further evidence for the identity of the molecule **14**, a ^{13}C NMR spectrum was recorded and the number of carbons and their chemical shifts were consistent with the molecule **14**. The IR spectrum of the compound showed an intense alkenyl stretch at 1672 cm^{-1} and HRMS confirmed the mass as 228.1523 g mol^{-1}.

In a control experiment, palladium(II) acetate was removed from the reaction and the same product distribution was observed with similar yields. Hence we ruled out any

participation of palladium. Interestingly, when 1 equivalent of copper(II) chloride was used, 50% of cyclobutanol **2** was recovered.

Compound **14** is thought to be formed *via* copper(II) promoted ring expansion of *tert*-cyclobutanol **2** (Scheme 12). We envision that cyclobutanol **2** coordinates to the copper(II) center and undergoes ring-opening which generates intermediate **16**, this is followed by subsequent enolization to form intermediate **17.** Considering that 2 equivalents of copper(II) chloride are required for full conversion, we believe that the second equivalent of copper(II) chloride is a terminal oxidant and facilitates the formation of intermediate **18**, *via* single-electron oxidation of copper(II) to copper(III).[32] Reductive elimination from copper(III) center is facile, owing to the electron deficiency of the metal.[34] Vinyl-ether **14** is thought to be formed from metallacycle **18** upon reductive elimination.



Scheme 12: Proposed mechanism for the formatoin of the vinyl ether **14.**

Compound **15** was isolated as an inseparable mixture of the two diastereomers in roughly 1:1 mixture. The proton spectrum of the isolated mixture **15** showed a multiplet at δ 7.37-

7.20 ppm, 4 doublets at δ 2.83 ppm, δ 2.68 ppm, δ 2.56 ppm and δ 2.48 ppm with large germinal coupling constants of 16.4 Hz and 16 Hz consistent with the nonbenzylic α carbonyl protons. For one of the diastereomers, the proton α to the chlorine atom appeared as doublet of doublets at δ 4.29 ppm with coupling constants of 11.4 Hz and 4.8 Hz while a broad singlet at δ 4.88 ppm for the other and reflects axial and equatorial α proton positions. The benzylic protons appeared as an apparent doublet at δ 3.72 ppm. The methyl groups appeared at δ 1.19 ppm and δ 1.09 ppm and the rest of the aliphatic protons were between 2-1 ppm (Figure 8).

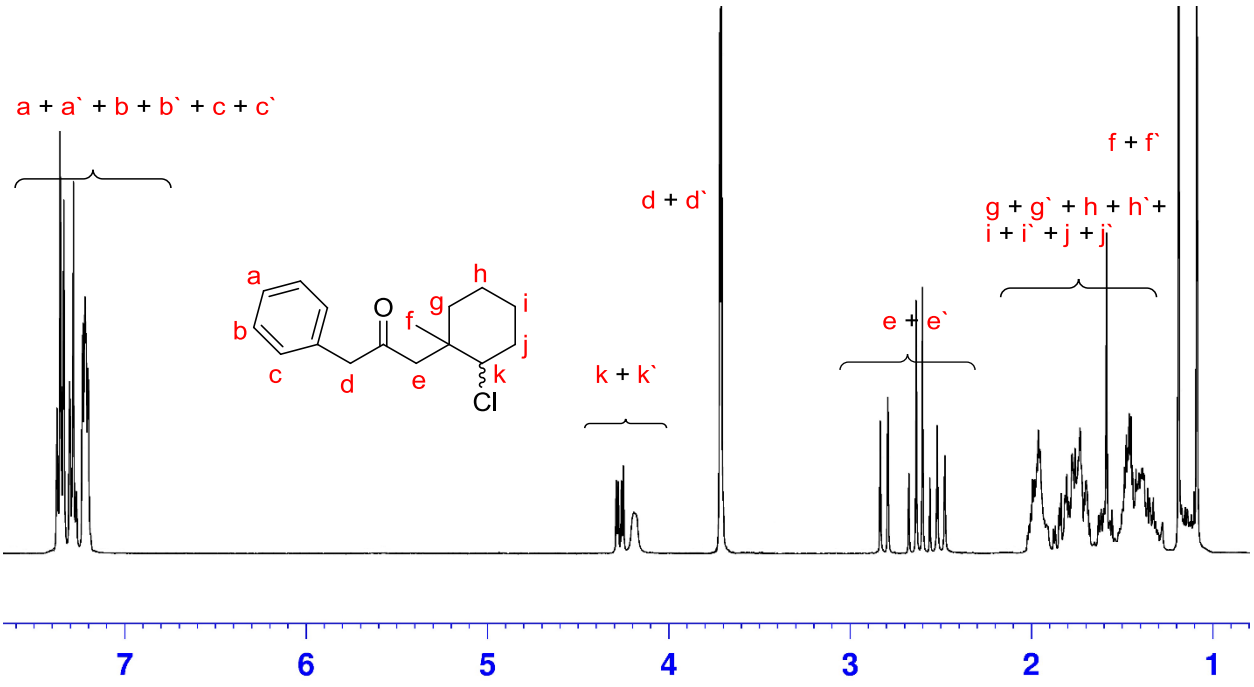


Figure 8: ^{1}H-NMR spectrum of unexpected compound **15** as mixture of diastereomers collected on 400 MHz spectrometer ($CDCl_3$).

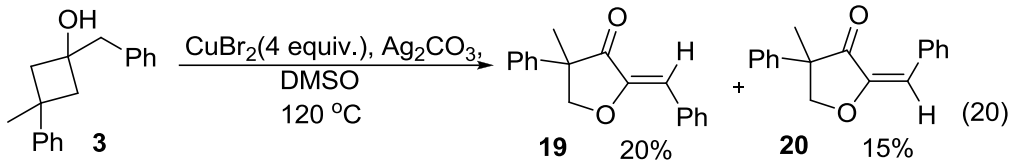
Further evidence for the identity of the proposed structure **15** was obtained from a ^{13}C spectrum that showed two characteristic carbonyl peaks at δ 207.4 and δ 207.3 ppm. The IR spectrum showed an intense carbonyl stretch at 1718 cm^{-1} with the MS with M^+ at 264.1281 and 266.1251 in about 3:1 ratio. Next we subjected *tert*-cyclobutanol **3** (Scheme 10) to similar conditions and observed complete recovery of **3** by ^1H-NMR spectroscopy (Table 4).

Table 4: Summary of The Copper(II) Salts and their Equivalents with **3**.[a]

Entry	Copper(II) Salt	Equivalents	Result
1	$Cu(OH)_2$	2	Recovery of cyclobutanol 3
2	$Cu(NO_3)_2$	2	Recovery of cyclobutanol 3
3	$CuSO_4$	2	Recovery of cyclobutanol 3
4	$CuSO_4$ H_2O	2	Recovery of cyclobutanol 3
5	$CuCO_3$	2	Recovery of cyclobutanol 3
6	$CuCl_2$	2	Complex Mixture
7	$CuBr_2$	2	About 50 % conversion of cyclobutanol 3
8	$CuBr_2$	4	Almost 100 % conversion of cyclobutanol 3 (Eq. 19)

[a]Unless stated otherwise, reactions have been carried out with DMSO as solvent and Ag_2CO_3 as base at 120 ^oC.

Thorough exploration of different copper(II) oxidants led to the formation of 1.3:1 Z:E mixture of unexpected ketone products (Z)-2-benzylidene-4-methyl-4-phenyldihydrofuran-3(2H)-one **19** (Eq. 20) along with E isomer **20** as inseparable mixture with starting material and unknown impurities.



Unexpected ketone products **19** and **20** based on copper(II) bromide salt.

It was noted that 4 equivalents of copper(II) bromide were essential for full conversion and that in absence of DMSO as solvent, this reaction gave complex mixture or recovery of starting alcohol.

The proton spectrum of compound **19** showed a doublet at δ 7.83 ppm with coupling constant of 7.6 Hz, multiplet at δ 7.44-7.28 ppm, an alkenyl singlet proton at δ 6.46 ppm, two doublets at δ 4.97 ppm and δ 4.56 ppm with geminal coupling constants of 9.2 Hz, and a singlet methyl peak at δ 1.67 ppm (Figure 9).

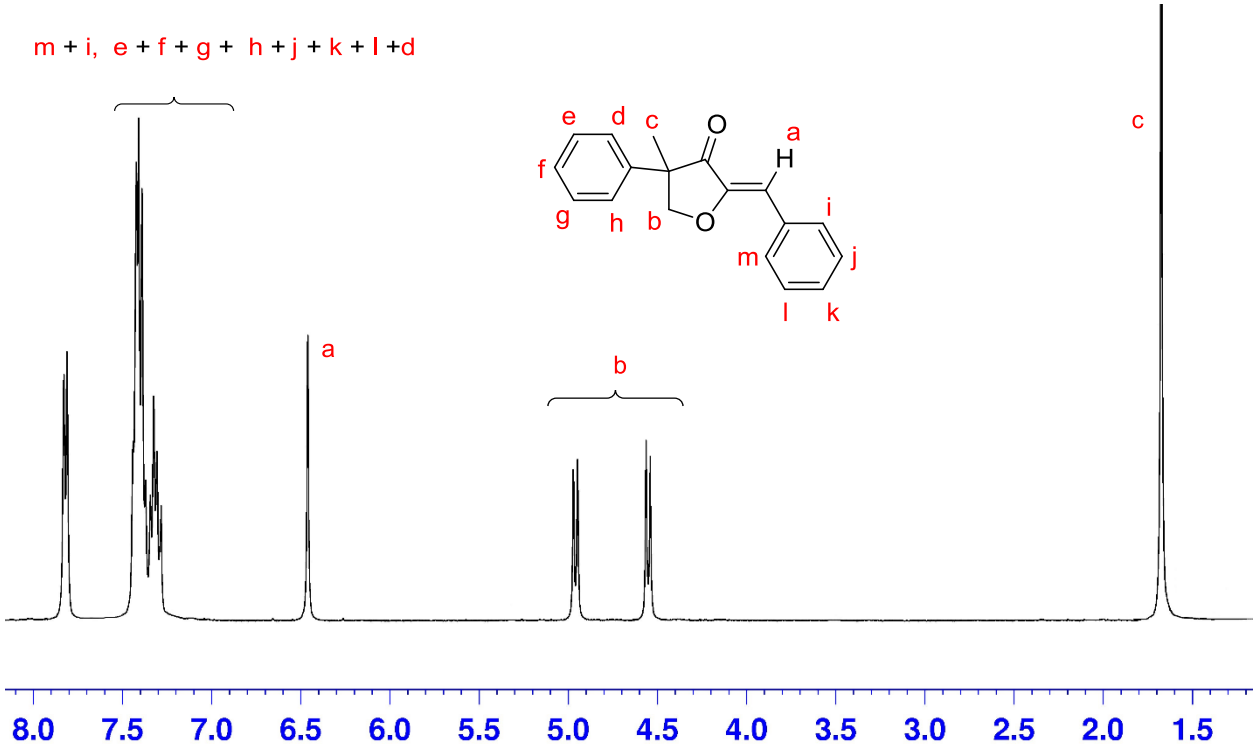


Figure 9: ^{1}H-NMR spectrum of unexpected compound **19** collected on 400 MHz spectrometer ($CDCl_3$).

The geometry of the double bond was established based on the comparison to a chemical shift of proton a in a similar molecule synthesized by Chen and co-workers (Figure 10).[35]

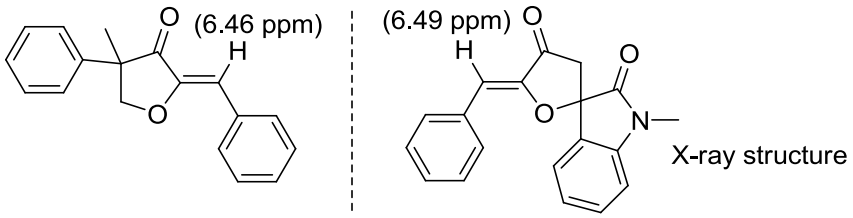
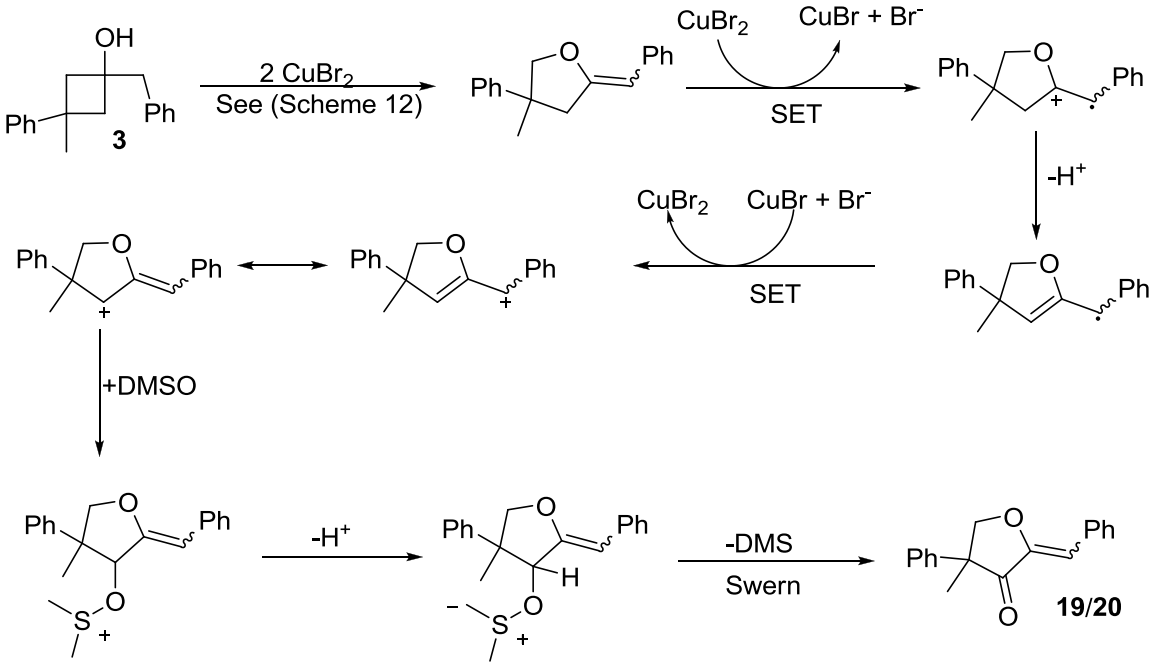


Figure 10: Alkene bond geometry of compound **19** based on similar literature molecule.

Although no mechanistic studies were carried out, we propose the formation of compound **19** could be explained by a copper(II) bromide-promoted ring expansion similar to (Scheme 12), followed by successive single-electron transfer (SET) steps and by oxidation with DMSO (Scheme 13).[36]



Scheme 13: Proposed mechanism for the formation of ketones **19** and **20** *via* multiple single electron transfer steps.

The mechanism outlined in (Scheme 13) accounts for the 4 equivalents of copper(II) bromide and explains the formation of the ketones **19** and **20**.

2.4.3 Solvent Screen

In effort to make cyclopentenone synthesis protocol catalytic in palladium, we wanted to investigate various solvents in combination with oxidants 1-10 (Table 3) using silver carbonate as base and cyclobutanol **2** as substrate. After a thorough screen of oxidants with various solvents we were unable to achieve a catalytic reaction, since the amount of product isolated did not exceed the mole percentage of catalyst used (Table 5).

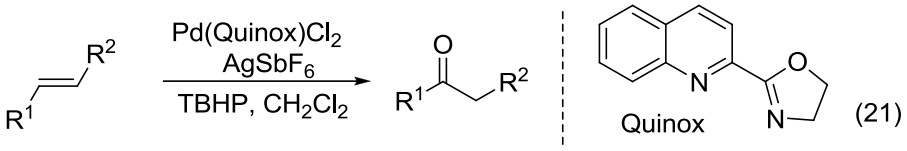
Table 5: Summary of the Solvent Screen with Various Oxidants with Substrate **2**.[a]

	Solvent				
Oxidant	DMA	DMF	NMP	DMSO	$PhCH_3$
DIB (1.1 equiv.)	< 5%	< 5%	< 5%	< 5%	Recovery of **2**
Ag_2CO_3 (1.1 equiv.)	< 5%	< 5%	< 5%	< 5%	Recovery of **2**
AgOAc (2.2 equiv.)	< 5%	< 5%	< 5%	< 5%	Recovery of **2**
$AgBF_4$ (2.2 equiv)	< 5%	< 5%	< 5%	< 5%	Recovery of **2**
BQ (1.1 equiv.)	< 5%	< 5%	< 5%	< 5%	Recovery of **2**
DDQ (1.1 equiv.)	< 5%	< 5%	< 5%	< 5%	Recovery of **2**
TFBQ (1.1 equiv.)	< 5%	< 5%	< 5%	< 5%	Recovery of **2**
CuCl (2.2 equiv.)	< 5%	< 5%	< 5%	< 5%	Recovery of **2**
CuBr (2.2 equiv.)	< 5%	< 5%	< 5%	< 5%	Recovery of **2**
$Cu(OAc)_2$ (2.2 equiv.)	< 5%	< 5%	< 5%	< 5%	Recovery of **2**
$CuCl_2$ (2.2 equiv)	Complex mixture	Complex mixture	Complex mixture	See Equation 19	Recovery of **2**
$CuBr_2$ (2.2 equiv.)	Complex mixture	Complex mixture	Complex mixture	Complex mixture	Recovery of **2**

[a]Unless stated otherwise, reactions have been carried out using Ag_2CO_3 (3.3 equiv.) as base and $Pd(OAc)_2$ (0.1 equiv.) as palladium source.

2.4.4 Ligand Screen

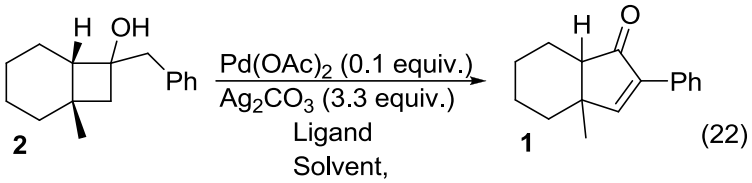
Nitrogen based ligands have been shown to be efficient in oxidative palladium(II) chemistry.[37] Therefore we investigated whether such ligands could be used for our transformation. The group of Sigman has shown the great utility of quinox ligand and its derivatives as efficient additive for palladium(II) catalyzed transformations under oxidative conditions (Eq. 21).[38,39,40]



(21)

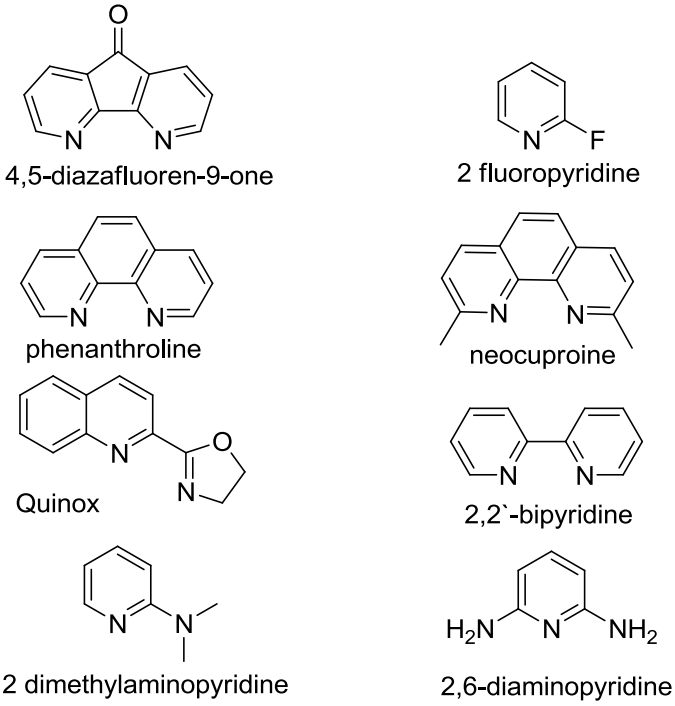
Wacker-type reaction developed by Sigman.

When we used quinox ligand, in DMSO as solvent and with silver carbonate as the base, no product formation was observed. We then screened a variety of mono and bi-dentate nitrogen based ligands along with different solvents (Table 6). However, after many attempts, it was evident that turning this protocol catalytic in palladium proved to be more challenging than anticipated.



Attempted cyclopentenone synthesis with catalytic amount of palladium and variable solvents and ligands.

Table 6: Summary of the Nitrogen Based Ligands.[a,b]



[a]Unless stated otherwise, reactions have been carried out under O_2 atmosphere, Ag_2CO_3 as base and screen of DMSO, $PhCH_3$, xylene, DMA and DMF solvents for every ligand. [b]The yields did not exceed the mole % of catalyst.

2.5 Conclusions and Comments

In conclusion, we have developed a new protocol to access six-membered ring-fused cyclopentenone, using stoichiometric palladium(II) acetate by a strain-driven ring expansion of benzyl cyclobutanol **2** as the key step. Turning this protocol catalytic proved to be more challenging than expected. After a thorough screen of bases, oxidants, solvents and ligands, the amount of product isolated did not exceed the mole percentage of catalyst used, likely owing to inefficient re-oxidation of palladium(0) back to palladium(II). Exploring copper(II) chloride and copper(II) bromide as potential oxidants, furnished unexpected compounds **14**, **15**, **19** and **20** believed to be formed via copper(II) mediated single electron transfer.

Chapter 3: Experimental

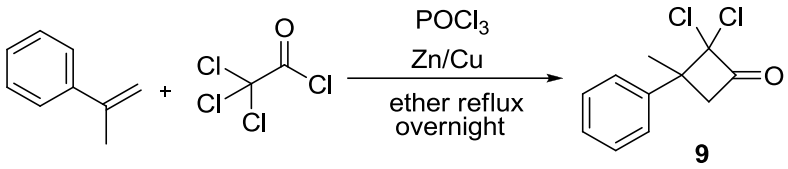
3.1 General Experimental

Reactions were conducted in flame- or oven-dried glassware under an atmosphere of argon or oxygen using freshly distilled solvents unless specified otherwise. Commercial reagents were used as received. Anhydrous dimethylacetamide, dimethylformamide and dimethyl sulfoxide were used as received. Thin-layer chromatography was performed on Merck silica gel 60 F_{254} plates. Visualisation was carried out using UV light (254nm) and/or $KMnO_4$, anisaldehyde or $(NH_4)_2Ce(NO_3)_6$ solutions. Hexanes (ACS grade) and ethyl acetate (ACS grade) were used as received. Flash column chromatography was carried out using Aldrich silica gel (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, Bruker 300 AV or Bruker 600 AV spectrometer in chloroform-*d* (99.8 % deuterated), and using chloroform (7.24 ppm ^{1}H and 77.23 ppm ^{13}C) as a reference. Chemical shifts (δ) are reported in ppm and multiplicities are indicated by s (singlet), d (doublet), q (quartet), t (triplet) m (multiplet), br (broad). Coupling constants *J* are reported in Hertz (Hz). Infrared (IR) spectra were recorded as thin films (neat) in NaCl cells using a Mattson Genesis II FT-IR instrument.

3.2 Experimental Procedures and Data

*Synthesis of α,α-dichlorocyclobutanone **9**.*

α,α-Dichlorocyclobutanone **9** was prepared using the procedure reported by Stoltz.[23]



9

Purification by flash column chromatography using a 6% solution of EtOAc in hexanes provided α,α-dichlorocyclobutanone **9** as clear oil in 82% yield.

Data for **9**

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

δ 7.51-7.34 (m, 5 H), 4.08 (d, *J* = 16.5 Hz, 1 H), 3.17 (d, *J* = 16.5 Hz, 1 H), 1.71 (s, 3 H)

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

δ 191.9, 141.4, 128.7, 127.7, 126.4, 92.3, 52.5, 50.4, 29.4

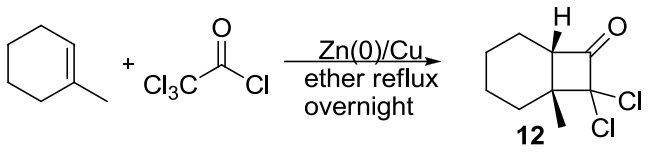
IR (thin film, NaCl)

υ = 3056, 2911, 2866, 1805, 1604, 1580, 1413, 1015, 831 cm^{-1}

GC-MS Calculated for $C_{11}H_{10}Cl_2O$ (M^+) *m/z* 228.01, 230.00, 232.00, found 228.08, 230.01, 232.02.

*Synthesis of dichlorocyclobutanone **12**.*

α,α-Dichlorocyclobutanone **12** was prepared using the procedure reported by Cortese.[41]



α,α-Dichlorocyclobutanone **12** was prepared from 1-methyl-1-cyclohexene following *Procedure 2*. Purification by flash column chromatography using a 5% solution of EtOAc in hexanes provided α,α-dichlorocyclobutanone **12** as clear yellow oil in 70% yield.

Data for **12**

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

δ 3.48 (d, *J* = 6.9 Hz, 1 H), 2.00 (d, *J* = 14.7 Hz, 1 H), 1.75-1.55 (m, 4 H), 1.44 (s, 3 H), 1.41-1.12 (m, 3H)

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

δ 194.9, 92.2, 57.8, 43.7, 33.7, 22.0, 21.1, 19.8, 19.4

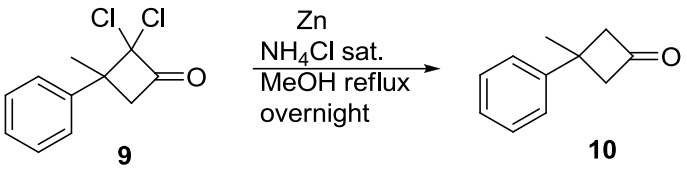
IR (thin film, NaCl)

υ = 2911, 2866, 1802, 1580, 1413, 1015, 831 cm^{-1}

GC-MS Calculated for $C_9H_{12}Cl_2O$ (M^+) *m/z* 206.03, 208.02 and 210.02 found 206.00, 208.04 and 210.05.

*Synthesis of cyclobutanone **10**.*

Cyclobutanone **10** was prepared using the procedure reported by Stoltz.[23]



9 **10**

Purification by flash column chromatography using a 10% solution of EtOAc in hexanes provided cyclobutanone **10** as clear yellow oil in 80% yield.

Data for **10**

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

δ 7.42-7.24 (m, 5 H), 3.50 (d, *J* = 18.9 Hz, 2 H), 3.15 (d, *J* = 18.9 Hz, 2 H), 1.62 (s, 3 H)

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

δ 206.3, 148.3, 128.6, 126.3, 125.7, 59.2, 33.9, 31.1

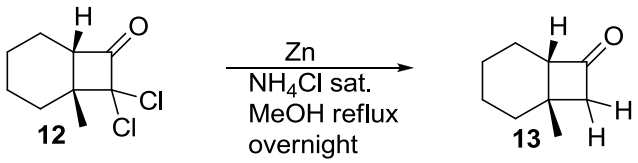
IR (thin film, NaCl)

υ = 3102, 2958, 2866, 1784, 1601, 1496, 1445, 1381, 1080, 764, 701 cm^{-1}

GC-MS Calculated for $C_{11}H_{12}O$ (M^+) *m/z* 160.09 found 160.09

Synthesis of cyclobutanone **13***.*

Cyclobutanone **13** was prepared using the procedure reported by Cortese.[41]



Purification by flash column chromatography using an 8% solution of EtOAc in hexanes provided cyclobutanone **13** as clear yellow oil in 60% yield.

Data for **13**

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

δ 2.86 (d, *J* = 4.3 Hz 1 H), 2.76 (d, *J* = 16.0 Hz, 1 H), 2.57 (d, *J* = 16.0 Hz, 1 H), 1.90-1.50 (m, 4 H), 1.37 (s, 3 H), 1.3-1.1 (m, 4 H)

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

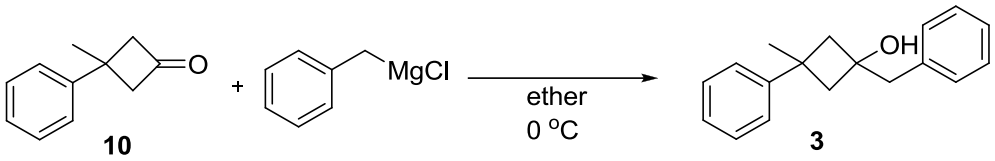
δ 208.8, 62.2, 58.6, 35.8, 28.2, 26.6, 22.3, 21.1, 20.4

IR (thin film, NaCl)

υ = 2901, 2875, 1779, 1588, 1587, 1460, 1419, 1344, 1010, 1020, 822 cm^{-1}

GC-MS Calculated for $C_9H_{14}O$ (M^+) *m/z* 138.10 found 138.11

Synthesis of tert-benzylcyclobutanol **3***.*



A flame-dried round-bottomed flask equipped with a stir bar and a rubber septum was charged with 200 mg (1.25 mmol, 1.0 equiv.) of cyclobutanone **10** followed by 6 mL of dry ether solvent and placed under an atmosphere of argon and cooled to 0 °C. Benzylmagnesium chloride was then added 1.88 mL (1.88 mmol, 1.5 equiv.) dropwise as a 1 M solution in THF. The reaction was monitored by TLC. After TLC analysis showed complete conversion, the reaction was quenched with saturated aqueous ammonium sulfate. Organic and aqueous layers were separated. The aqueous phase was washed with ethyl acetate 3 times. The combined organic phase was washed with brine, dried using magnesium sulfate and concentrated *in vacuo*. The crude product was purified by flash column chromatography, using a 15% solution of EtOAc in hexanes provided *tert*-cyclobutanol **3** as white solid in 55% yield.

Data for **3**

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

δ 7.38-7.15 (m, 10 H), 2.76 (d, *J* = 12.4 Hz, 1 H), 2.72 (s, 2 H), 2.26 (d, *J* = 12.4 Hz, 1 H), 1.79 (s, 1 H), 1.55 (s, 3 H)

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

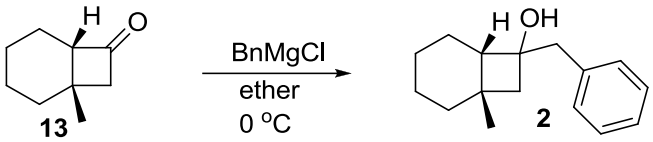
δ 151.0, 136.9, 129.7, 128.4, 128.2, 126.6, 125.4, 125.3, 70.7, 47.5, 47.4, 35.4, 33.8

υ = 3510, 3444, 3050, 2950, 2904, 2820, 1599, 1430, 1180, 881, 800 cm^{-1}

HRMS (HREI) Calculated for $C_{18}H_{20}O$ (M^+) *m/z* 252.1514 found 252.1519.

Melting point: 95-96 °C

Synthesis of bicyclo[4.2.0] tert-benzylcyclobutanol **2***.*



A flame-dried round-bottomed flask equipped with a stir bar and a rubber septum was charged with 200 mg (1.25 mmol, 1.0 equiv.) of cyclobutanone **13** followed by 6 mL of dry ether solvent and placed under an atmosphere of argon and cooled to 0 °C. Benzylmagnesium chloride was then added 1.88 mL (1.88 mmol, 1.5 equiv.) dropwise as a 1 M solution in THF. The reaction was monitored by TLC. After TLC analysis showed complete conversion, the reaction was quenched with saturated aqueous ammonium sulfate. Organic and aqueous layers were separated. The aqueous phase was washed with ethyl acetate 3 times. The combined organic phase was washed with brine, dried using magnesium sulfate and concentrated *in vacuo*. The crude product was purified by flash column chromatography, using a 10% solution of EtOAc in hexanes provided *bicyclo[4.2.0] tert*-cyclobutanol **2** as clear yellow oil in 42% yield.

Data for **2**

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

δ 7.33-7.23 (m, 5 H), 2.89 (d, *J* = 13.2 Hz, 1 H), 2.82 (d, *J* = 13.2 Hz, 1 H), 2.07 (d, *J* = 7.2 Hz, 1 H), 1.99 (d, *J* = 12.4 Hz, 1 H), (d, *J* = 12.4 Hz, 1 H) 1.55-1.15 (m, 8 H), 1.13 (s, 3 H)

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

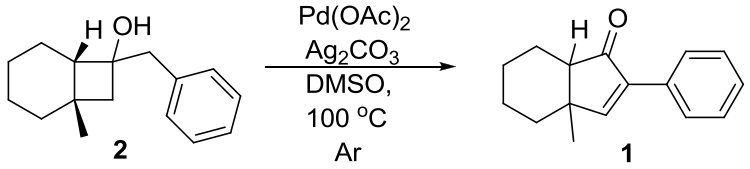
δ 137.3, 129.7, 128.3, 126.4, 75.3, 49.6, 48.1, 47.2, 35.8, 31.5, 28.4, 22.3, 20.9, 20.3

IR (thin film, NaCl)

υ = 3522, 3455, 3080, 2995, 2900, 2810, 1601, 1456, 1178, 888, 805 cm^{-1}

HRMS (HREI) Calculated for $C_{16}H_{22}O$ (M^+) *m/z* 230.1671 found 230.1679.

Procedure 6: *Synthesis of cyclopentenone* **1***.*



A flame-dried test tube equipped with a stir bar was charged with $Pd(OAc)_2$ (102.4 mg, 0.456 mmol, 1.1 equiv.), Ag_2CO_3 (125.8 mg, 0.456 mmol, 1.1 equiv.), *tert*-cyclobutanol **2** (100 mg, 0.415 mmol, 1 equiv.) and 4 mL of DMSO solvent. The reaction mixture was placed into an oil bath preheated to 100 °C. The reaction progress was monitored by TLC and showed complete consumption of the starting material within 1 hour. The reaction was quenched with saturated aqueous ammonium chloride and diluted with ethyl acetate. The organic and aqueous layers were separated. The aqueous phase was washed with ethyl acetate 3 times. The combined organic phase was washed with brine, dried using magnesium sulfate and concentrated *in vacuo*. The crude product was purified by flash column chromatography using a 10% solution of EtOAc in hexanes, provided the desired product **1** as clear oil in 59% yield.

Data for **1**

^{1}H NMR (600 MHz, $CDCl_3$)

δ 7.71 (d, *J* = 7.2 Hz, 2 H), 7.58 (s, 1 H), 7.37-7.30 (m, 3 H), 2.25 (dd, *J* = 6.6 Hz, 3.6 Hz, 1 H), 2.15 (m, 1 H), 1.74-1.40 (m, 5 H), 1.30 (s, 3 H), 1.23-1.16 (m, 3 H)

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

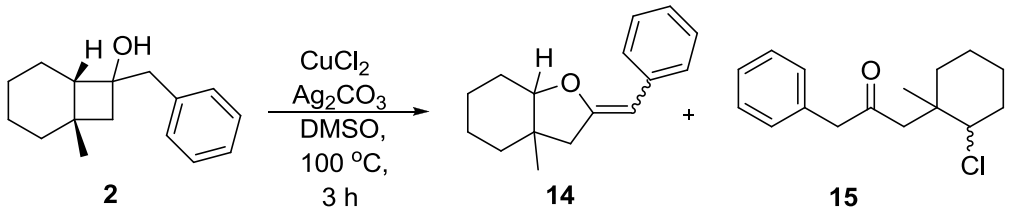
δ 208.5, 166.1, 139.5, 131.7, 128.3, 128.2, 127.0, 54.6, 41.3, 35.9, 25.2, 21.5, 21.1, 19.8

IR (thin film, NaCl)

υ = 3088, 2960, 2840, 1704, 1685, 1600, 1522, 904 cm^{-1}

HRMS (HREI) Calculated for $C_{16}H_{18}O$ (M^+) *m/z* 226.1358 found 226.1365.

Procedure 7: *Synthesis of vinyl-ether* **14** *and ketone* **15***.*



2 **14** **15**

A flame-dried test tube equipped with a stir bar was charged with $CuCl_2$ (122.7 mg, 0.912 mmol, 2.2 equiv.), Ag_2CO_3 (125.8 mg, 0.456 mmol, 1.1 equiv.), *tert*-cyclobutanol **2** (100 mg, 0.415 mmol, 1 equiv.) and 4 mL of DMSO solvent. The reaction mixture was placed in an oil bath preheated to 100 °C. The reaction progress was monitored by TLC and showed complete consumption of the starting material within 3 hours. The reaction was quenched with saturated aqueous ammonium chloride and diluted with ethyl acetate. Organic and aqueous layers were separated. The aqueous phase was washed with ethyl acetate 3 times. The combined organic phase was washed with brine, dried using magnesium sulfate and concentrated *in vacuo*. The crude product was purified by flash column chromatography using a 7% solution of EtOAc in hexanes, provided products **14** and **15** as clear oils in 25% and 30% yields respectively.

Data for **14**

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

δ 7.60 (d, *J* = 7.6 Hz, 2 H), 7.29 (dd, *J* = 8 Hz, 7.6 Hz, 2 H), 7.09 (dd, *J* = 7.6 Hz, 7.6 Hz, 1 H), 5.22 (s, 1 H), 4.09 (dd, *J* = 2.8 Hz, 2.8 Hz,1 H), 2.60 (d, *J* = 16.2 Hz, 1 H), 2.46 (d, *J* = 16.2 Hz, 1 H), 2.12 (dd, *J* = 14 Hz, 2.4 Hz, 1 H), 1.70-1.20 (m, 7 H), 1.14 (s, 3 H)

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

δ 137.2, 128.0, 127.1, 126.9, 124.4, 97.7, 86.1, 47.1, 37.9, 32.2, 26.1, 21.5, 21.3, 20.1

IR (thin film, NaCl)

υ = 3120, 2985, 2944, 2833, 1672, 1602, 1500, 1455, 1250, 1160, 1030, 894cm^{-1}

HRMS (HREI) Calculated for $C_{16}H_{20}O$ (M^+) *m/z* 228.1514 found 228.1523

Data for **15** (mixture of 2 diastereomers)

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

δ 7.37-7.20 (m, 10 H), 4.30 (dd, *J* = 11.4 Hz, 4.8 Hz,1 H), 4.19 (s, 1 H), 3.72 (s, 4 H), 2.83 (d, *J* = 16.4 Hz,1 H), 2.68 (d, *J* = 16.0 Hz, 1 H), 2.60 (d, *J* = 16.0 Hz, 1 H), 2.52 (d, *J* = 16.4 Hz,1 H), 2.00-1.20 (m, 16 H), 1.19 (s, 3 H), 1.09 (s, 3 H)

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

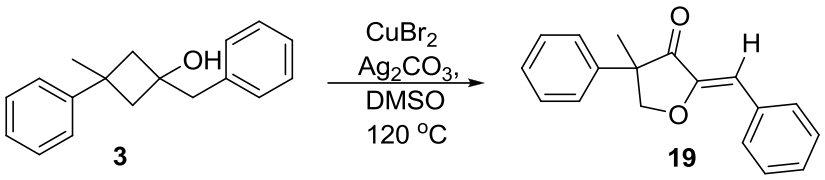
δ 207.4, 207.3, 134.0, 133.9, 129.4, 128.5, 126.9, 126.9, 69.5, 67.8, 52.0, 51.8, 51.2, 39.6, 38.5, 35.9, 34.1, 32.3, 31.2, 26.0, 24.1, 23.0, 20.8, 20.7, 18.2

IR (thin film, NaCl)

υ = 3345, 2995, 2950, 2930, 1718, 1612, 1515, 1230, 1020 cm^{-1}

HRMS (HREI) Calculated for $C_{16}H_{21}ClO$ (M^+) *m/z* 264.1281 found 264.1271.

Synthesis of ketone **19***.*



A flame-dried test tube equipped with a stir bar was charged with $CuBr_2$ (370.5 mg, 1.66 mmol, 4.0 equiv.), Ag_2CO_3 (125.8 mg, 0.456 mmol, 1.1 equiv.) followed by the *tert*-cyclobutanol **3** (100 mg, 0.396 mmol, 1 equiv.) and 4 mL of DMSO solvent. The reaction mixture was placed into an oil bath preheated to 120 °C. The reaction progress was monitored by TLC and showed complete consumption of the starting material within 2 hours. The reaction was quenched with saturated aqueous ammonium chloride and diluted with ethyl acetate. The layers were separated and the aqueous phase was washed with ethyl acetate 3 times. The combined organic phase was washed with brine, dried using magnesium sulfate and concentrated *in vacuo*. The crude product was purified by flash column chromatography using a 35% solution of DCM in hexanes, provided product **19** as white solid in 20% yield.

Data for **19**

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

δ 7.83 (d, *J* = 7.6 Hz, 2 H), 7.44-7.31 (m, 8 H), 6.46 (s, 1 H), 4.97 (d, *J* = 9.2 Hz,1 H), 4.56 (d, *J* = 9.2 Hz,1 H), 1.67 (s, 3 H)

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

δ 201.2, 146.4, 140.1, 133.6, 130.2, 128.8, 128.5, 128.3, 127.4, 126.1, 107.3, 80.2, 50.4, 21.7

IR (thin film, NaCl)

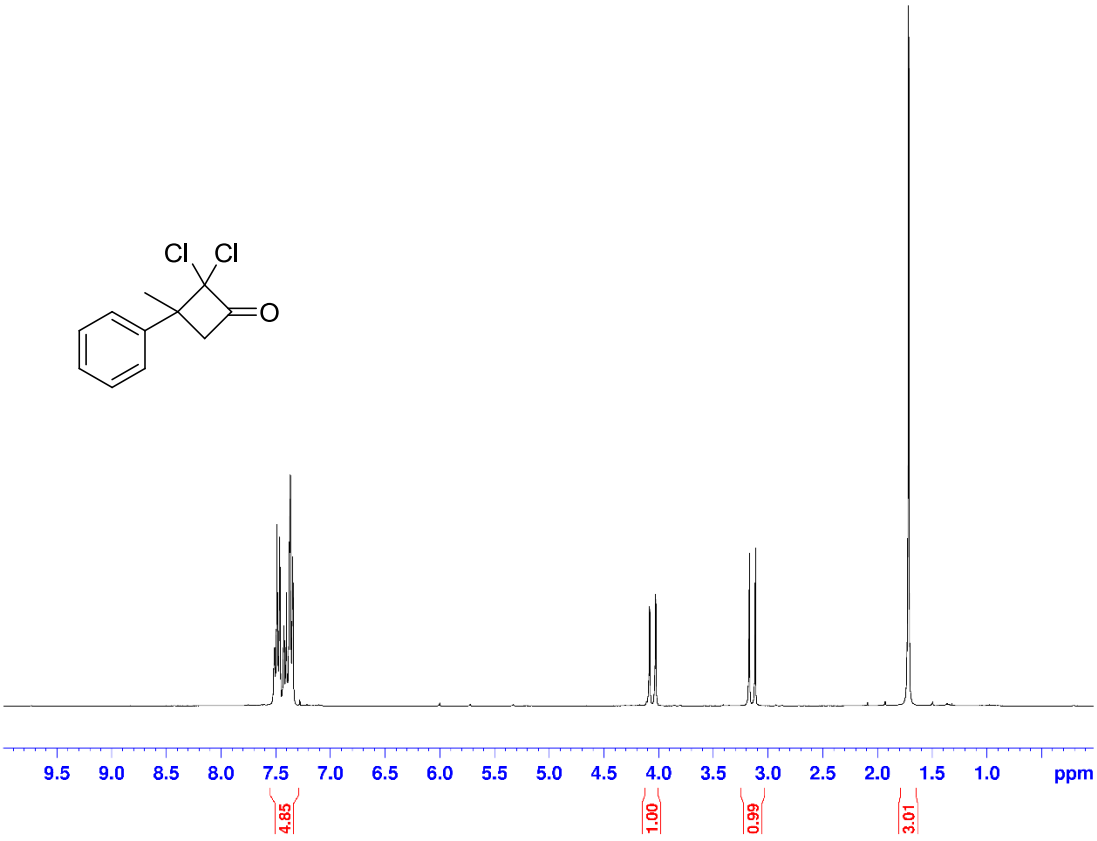
υ = 3052, 2956, 2840, 1725, 1610, 1522, 904, 829 cm^{-1}

HRMS (HREI) Calculated for $C_{18}H_{16}O_2$ (M^+) *m/z* 264.1150 found 264.0039.

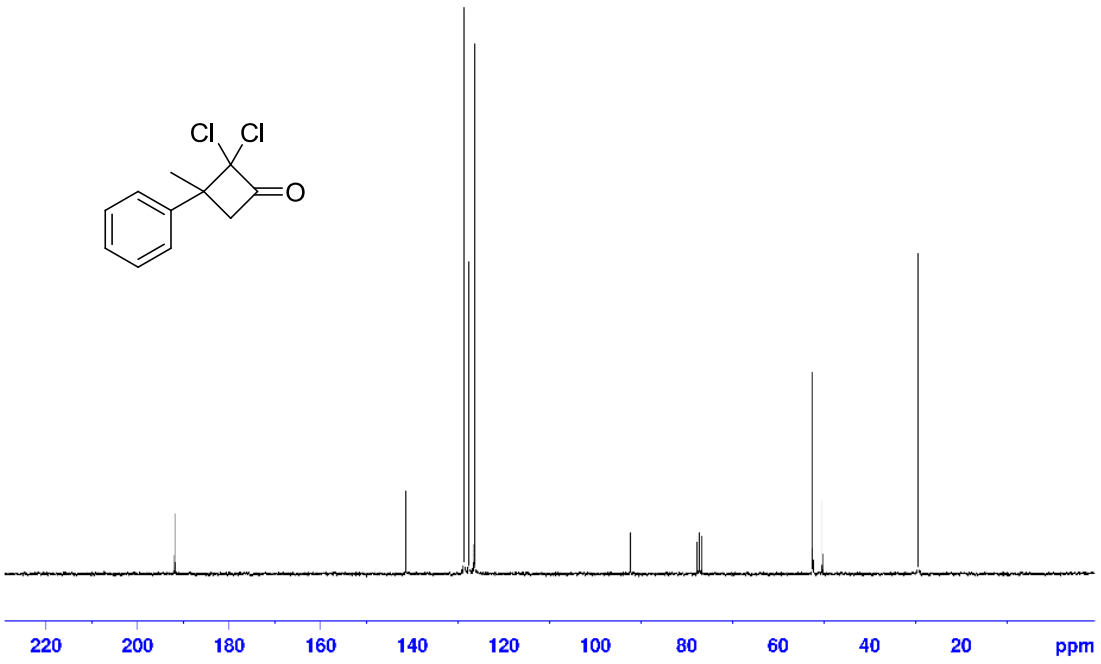
Melting point: 55-56 ^oC

3.3 ^{1}H and ^{13}C-NMR Spectra

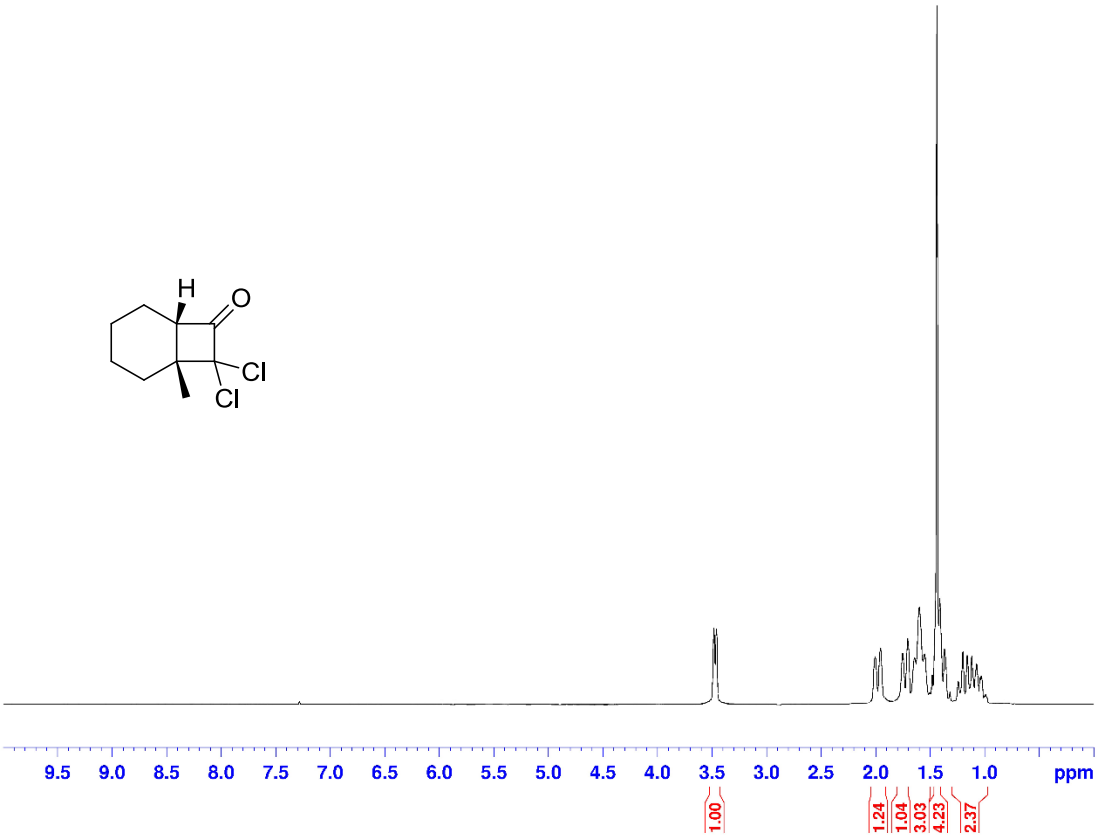
^{1}H-NMR data for compound **9** Recorded on 300 MHz spectrometer ($CDCl_3$)



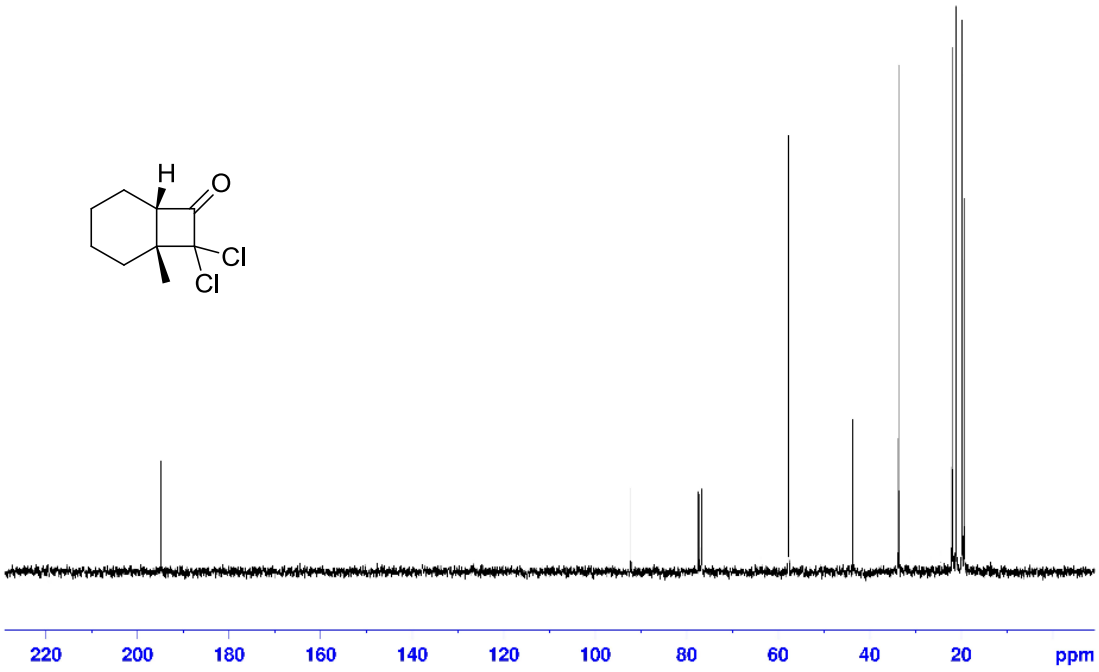
^{13}C-NMR data for compound **9** Recorded on 300 MHz spectrometer ($CDCl_3$)



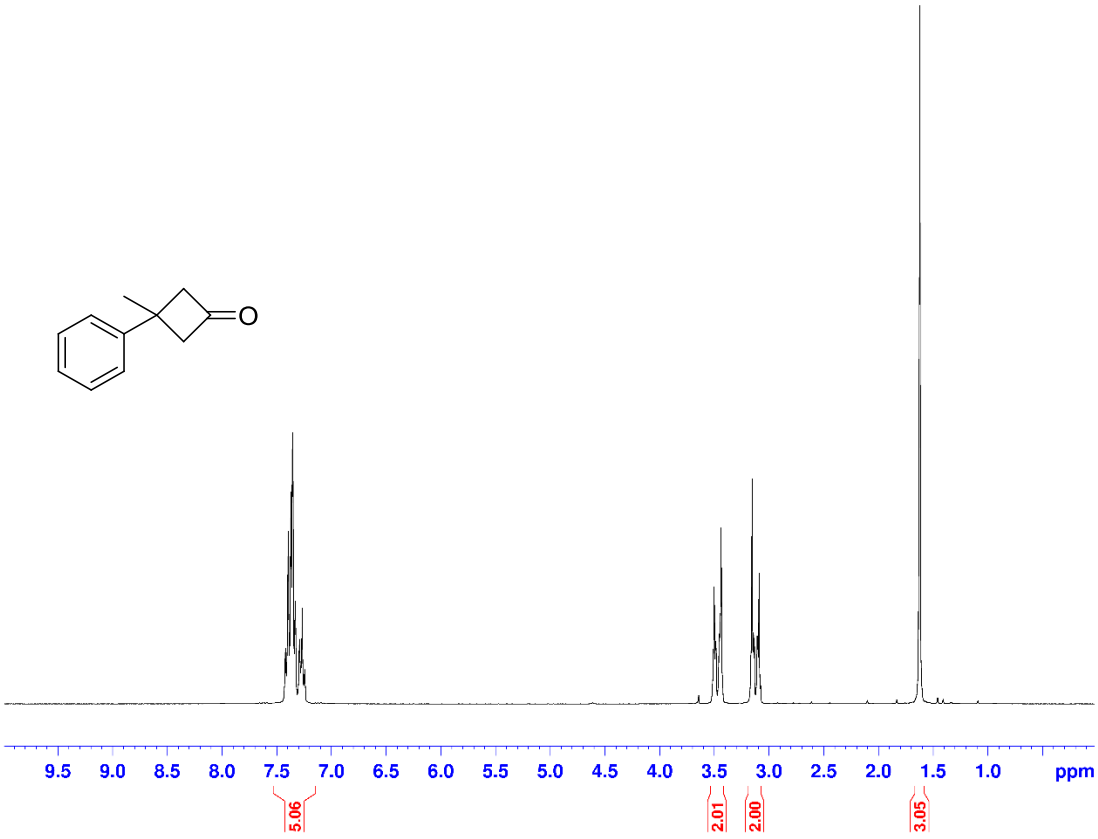
^{1}H-NMR data for compound **12** Recorded on 300 MHz spectrometer ($CDCl_3$)



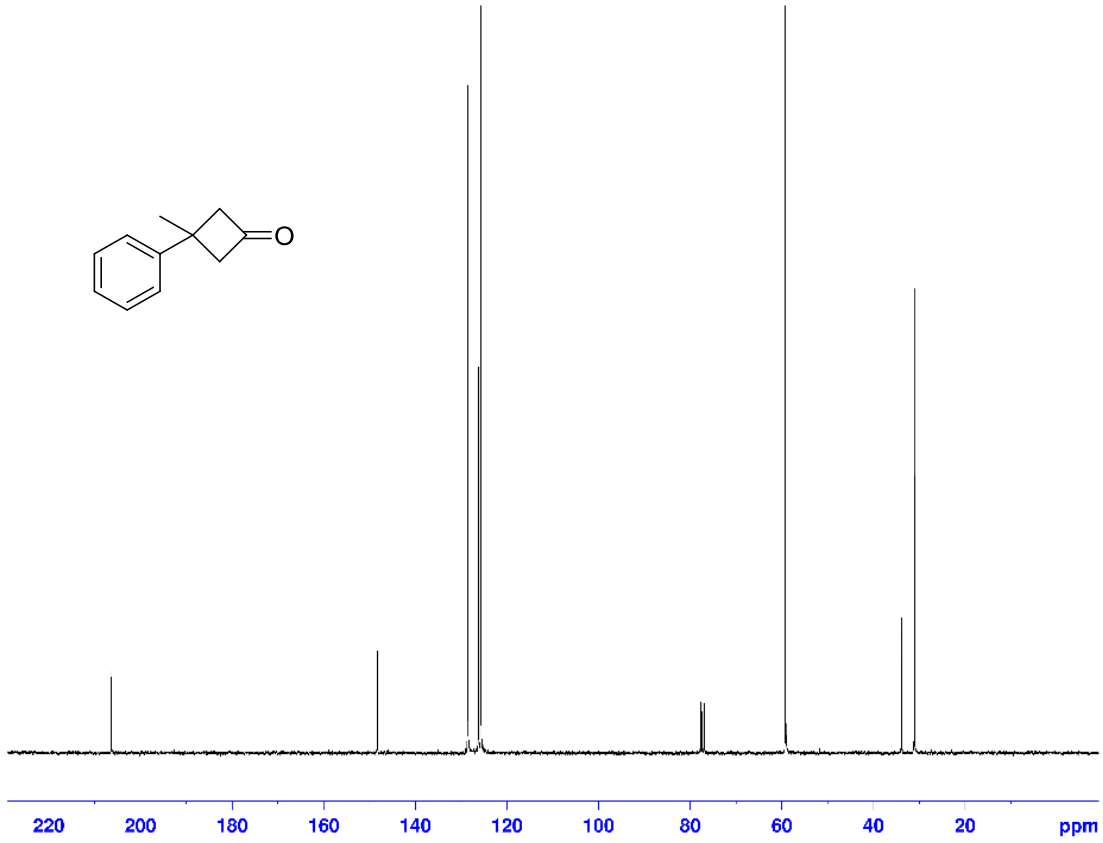
^{13}C-NMR data for compound **12** Recorded on 300 MHz spectrometer ($CDCl_3$)



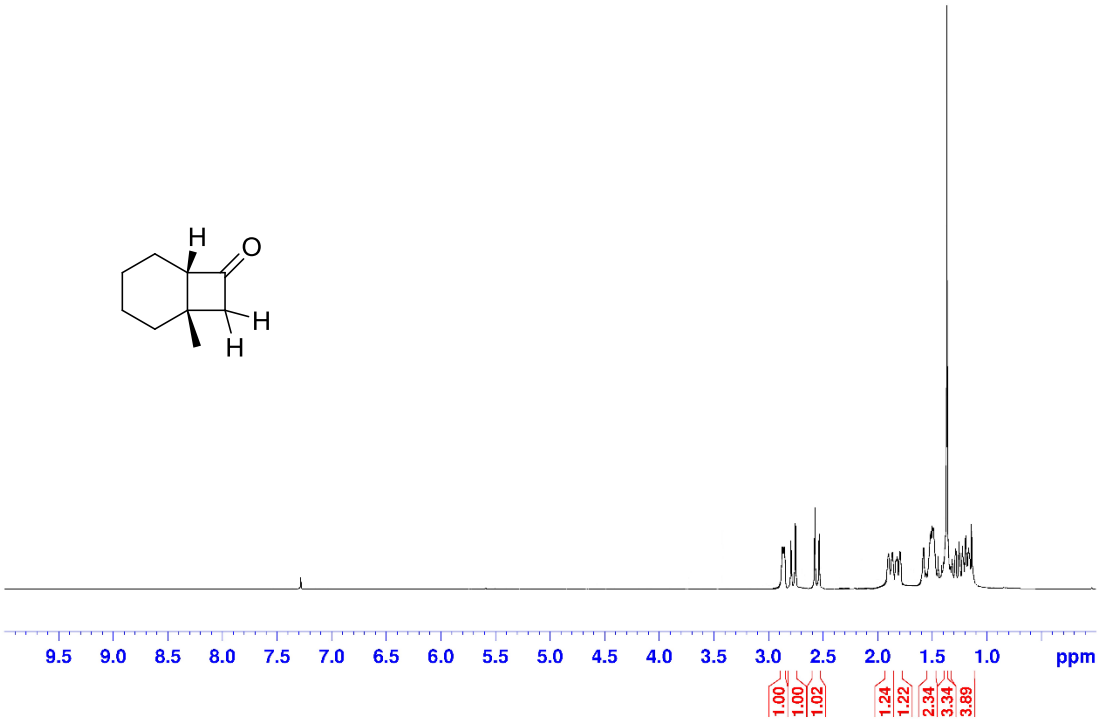
^{1}H-NMR data for compound **10** Recorded on 300 MHz spectrometer ($CDCl_3$)



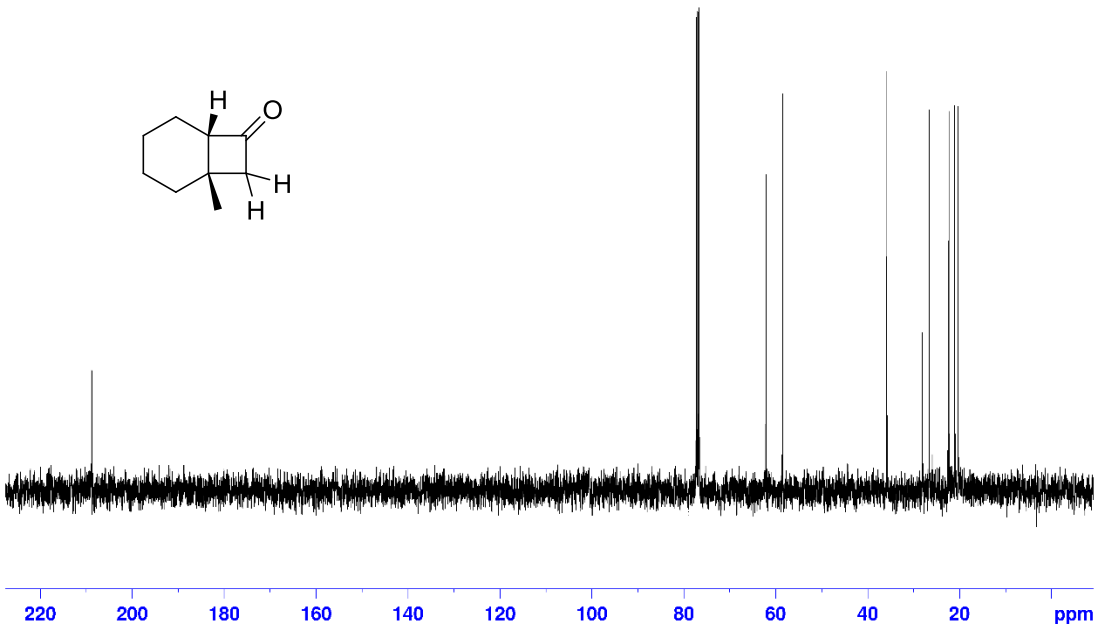
^{13}C-NMR data for compound **10** Recorded on 300 MHz spectrometer ($CDCl_3$)



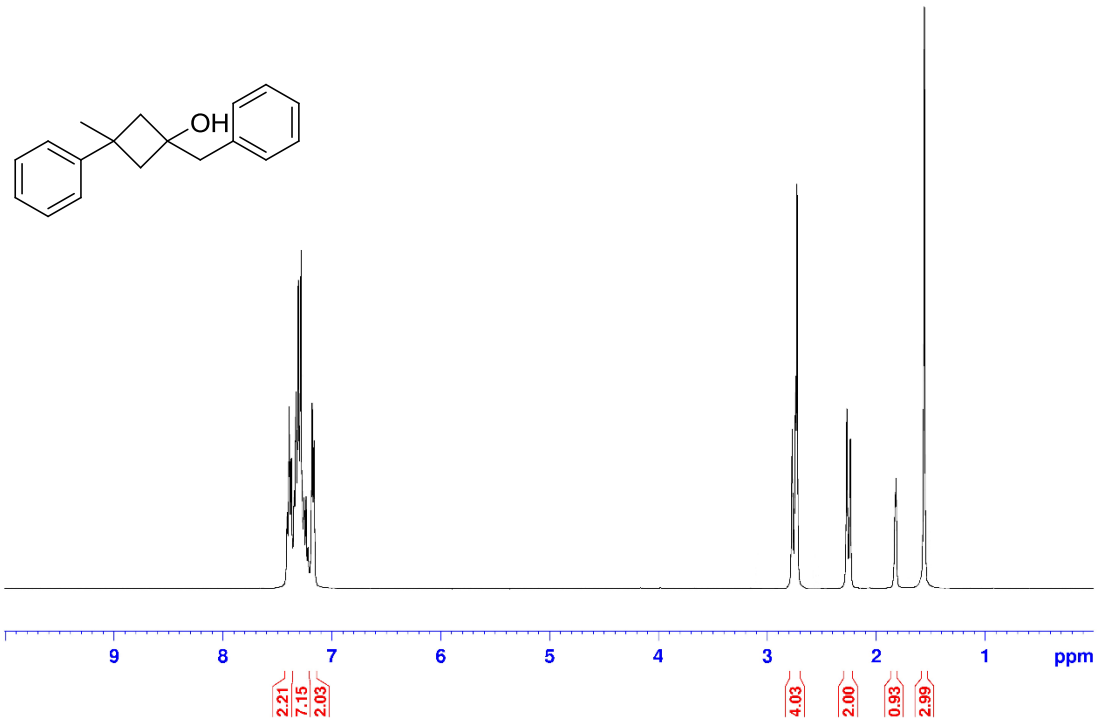
^{1}H-NMR data for compound **13** Recorded on 400 MHz spectrometer ($CDCl_3$)



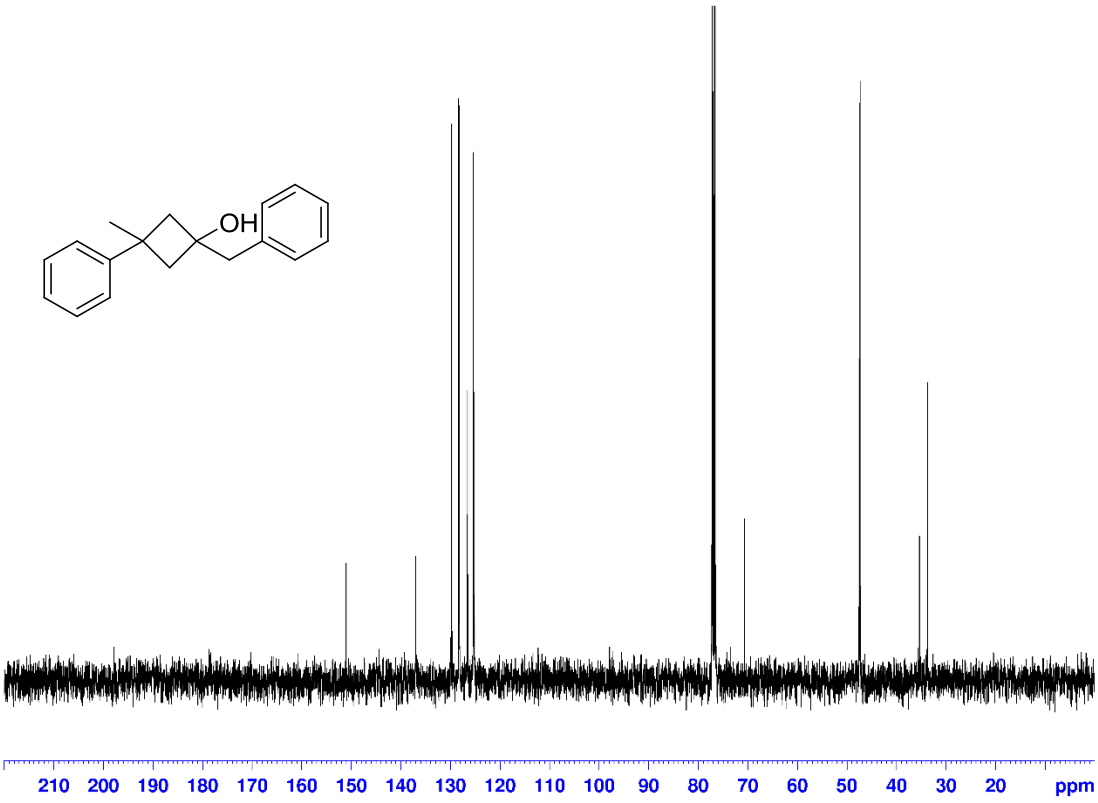
^{13}C-NMR data for compound **13** Recorded on 400 MHz spectrometer ($CDCl_3$)



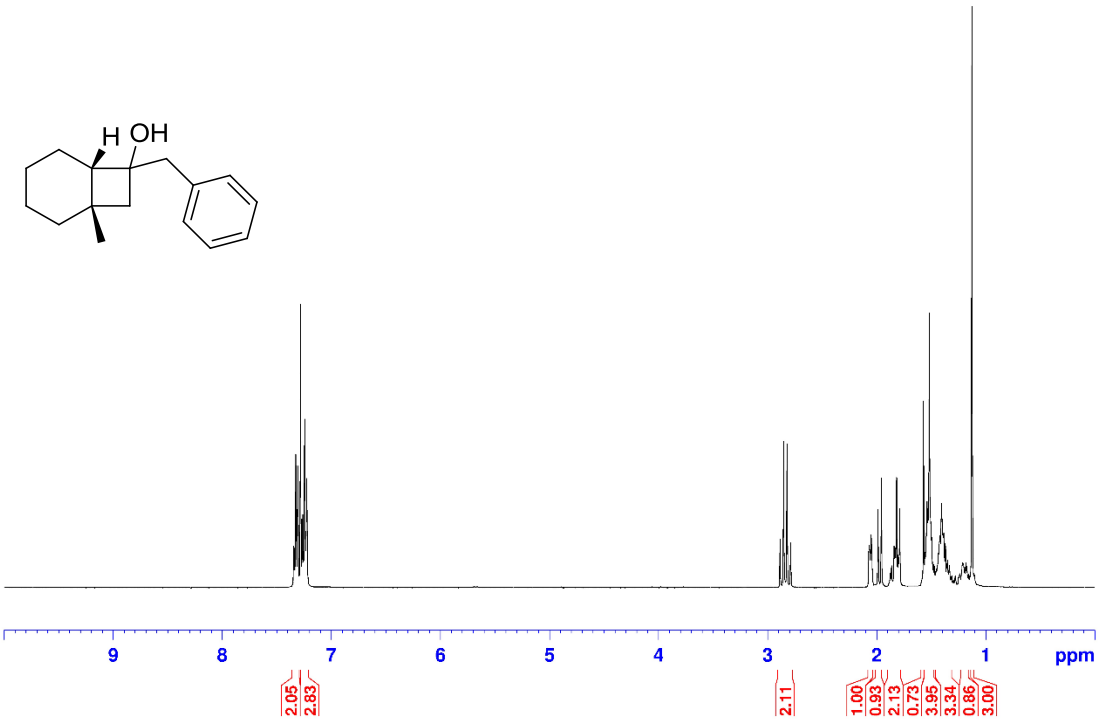
^{1}H-NMR data for compound **3** Recorded on 400 MHz spectrometer ($CDCl_3$)



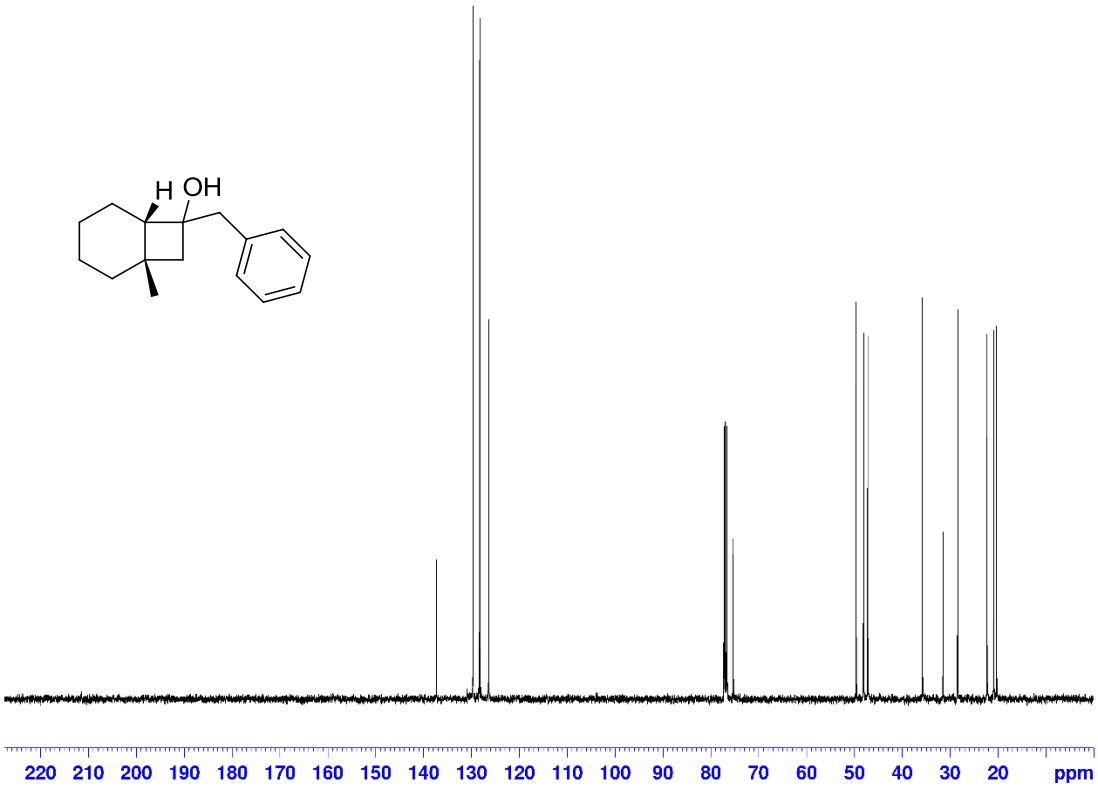
^{13}C-NMR data for compound **3** Recorded on 400 MHz spectrometer ($CDCl_3$)



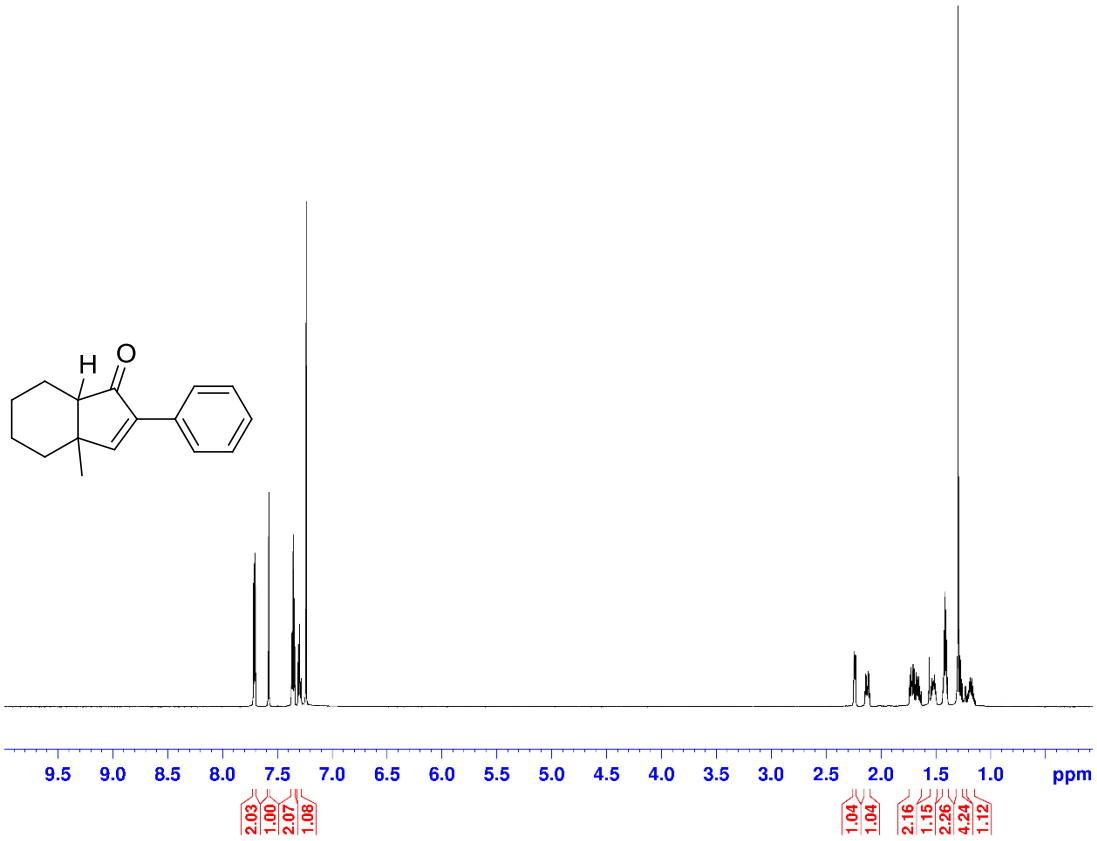
^{1}H-NMR data for compound **2** Recorded on 400 MHz spectrometer ($CDCl_3$)



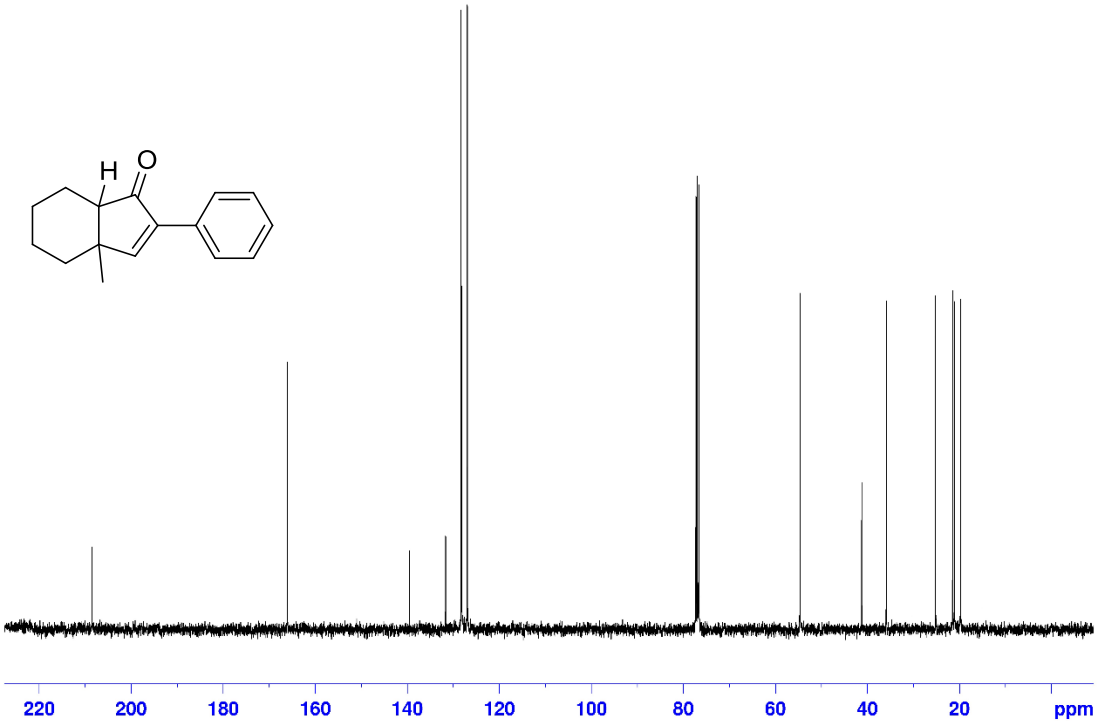
^{13}C-NMR data for compound **2** Recorded on 400 MHz spectrometer ($CDCl_3$)



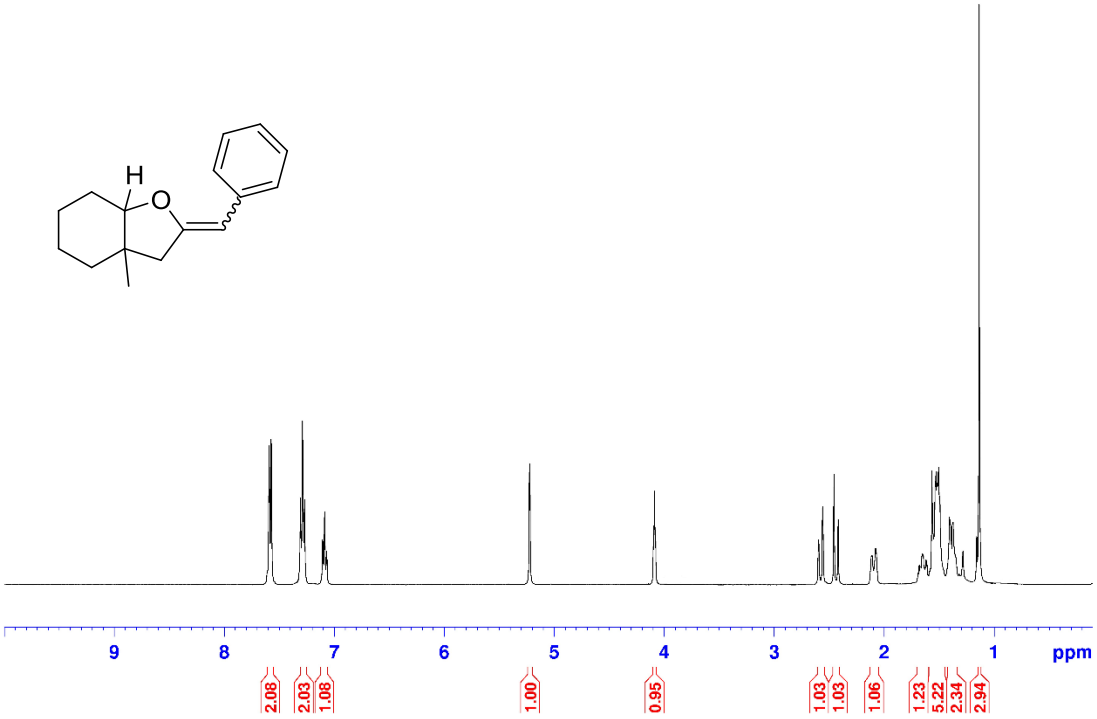
^{1}H-NMR data for compound **1** Recorded on 600 MHz spectrometer ($CDCl_3$)



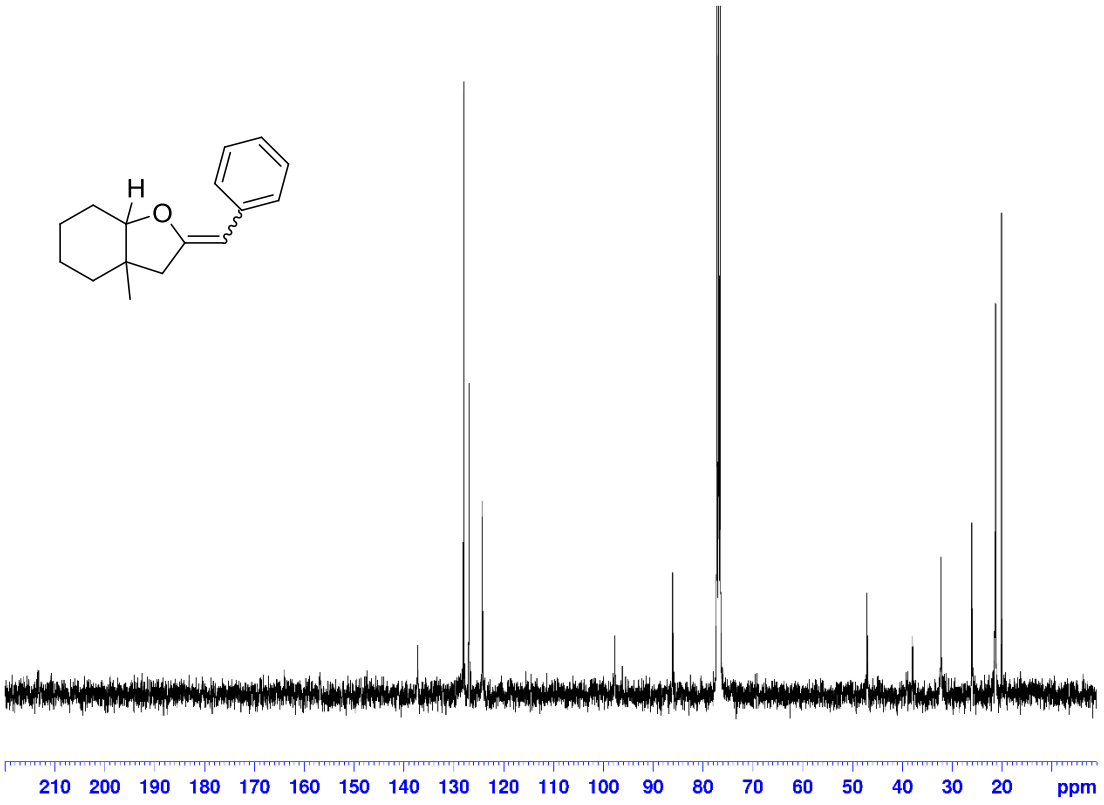
^{13}C-NMR data for compound **1** Recorded on 600 MHz spectrometer ($CDCl_3$)



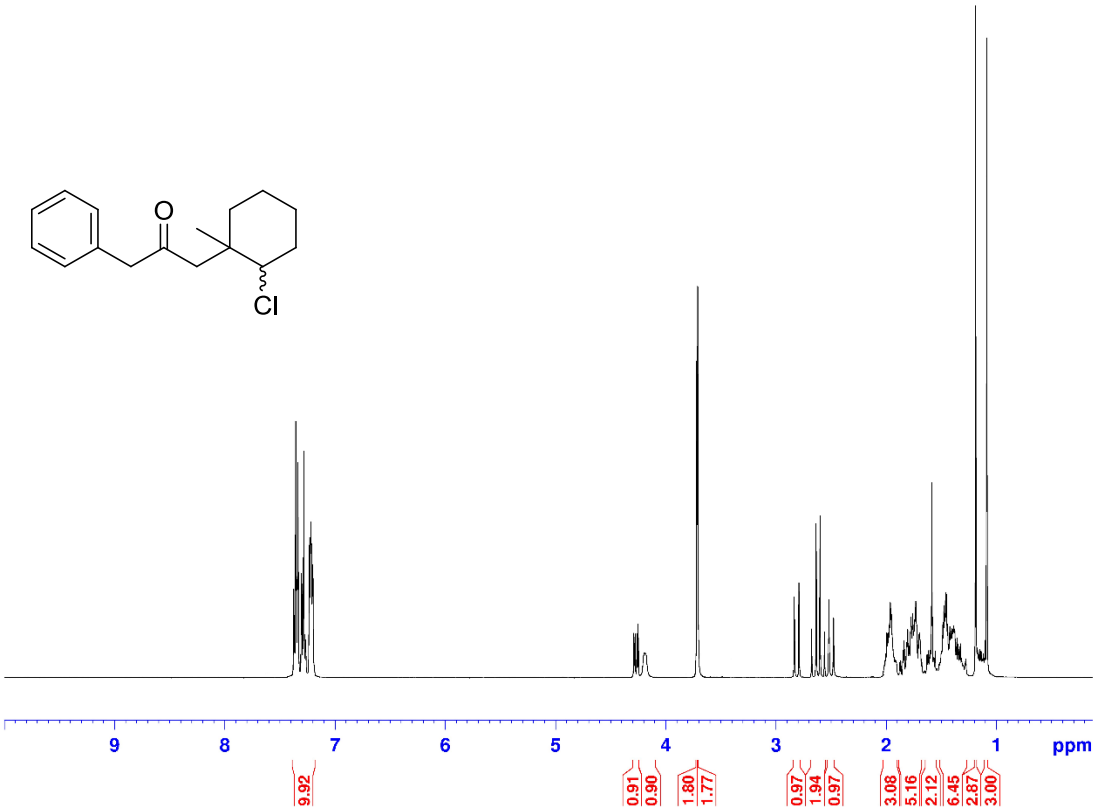
^{1}H-NMR data for compound **14** Recorded on 400 MHz spectrometer ($CDCl_3$)



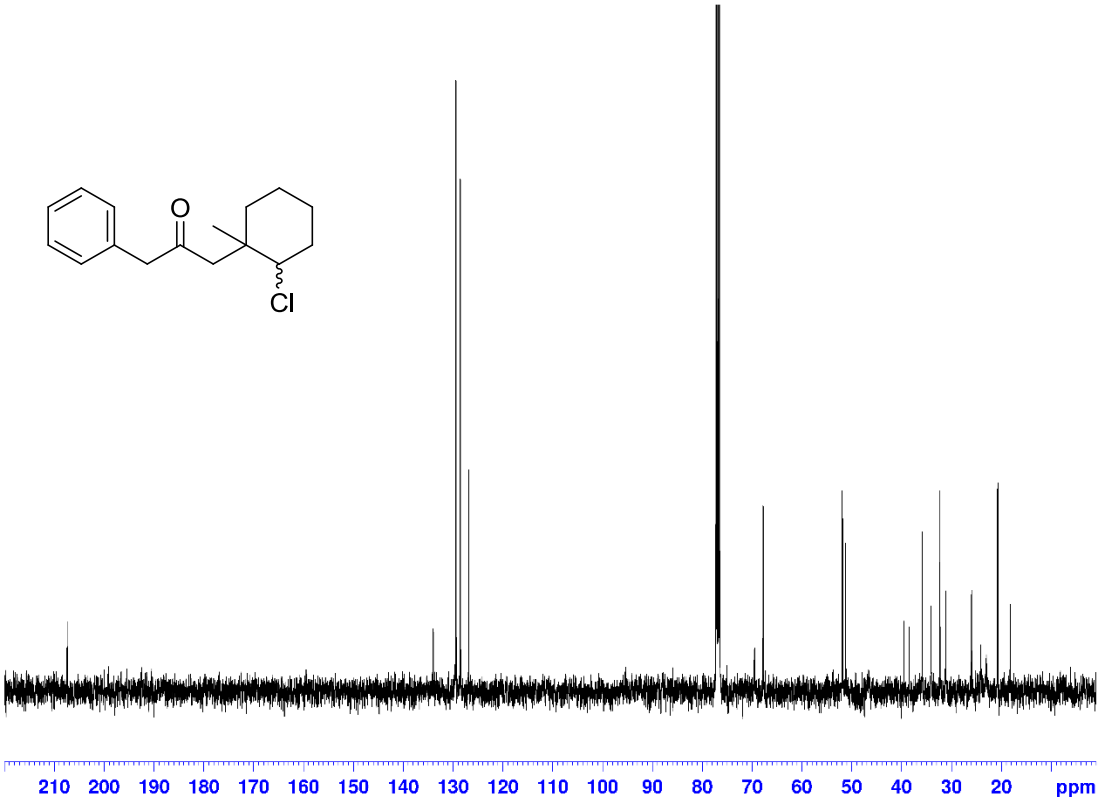
^{13}C-NMR data for compound **14** Recorded on 400 MHz spectrometer ($CDCl_3$)



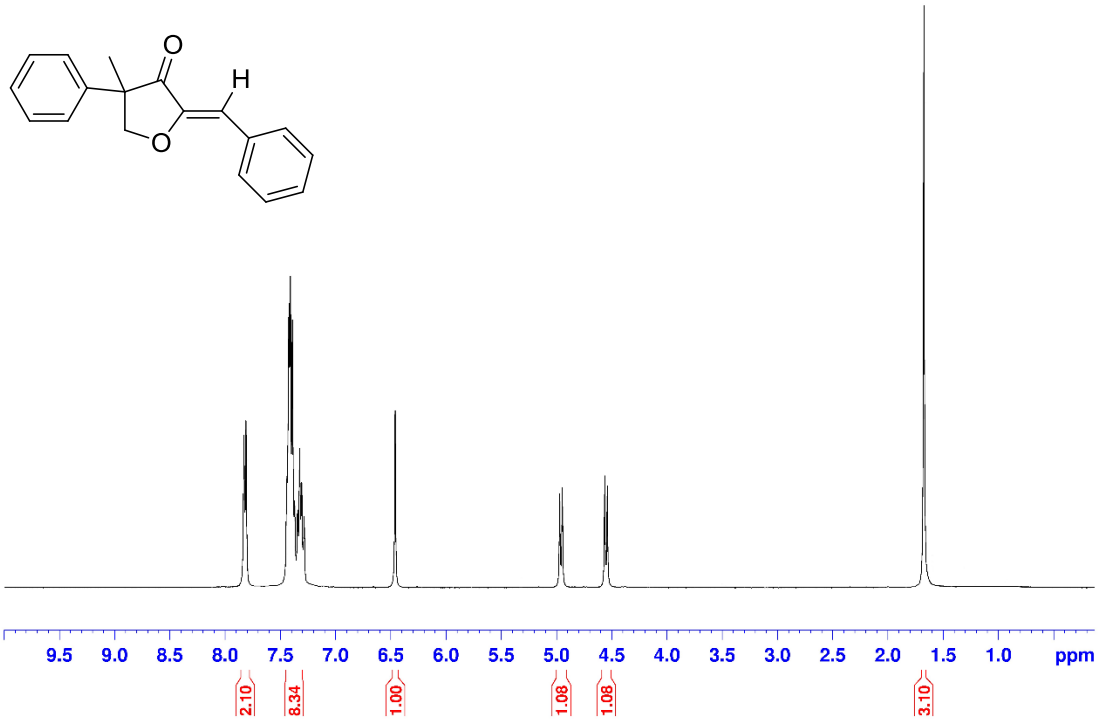
^{1}H-NMR data for compound **15** (mixture of diastereomers) Recorded on 400 MHz spectrometer ($CDCl_3$)



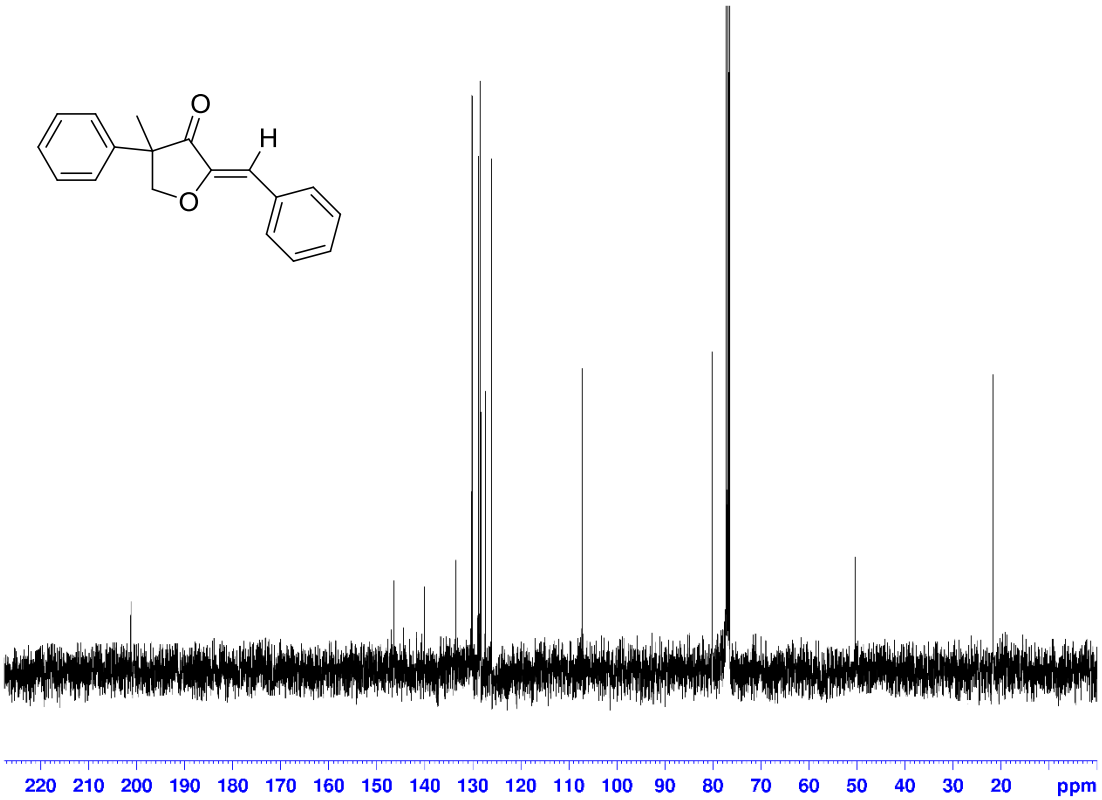
^{13}C-NMR data for compound **15** (mixture of diastereomers) Recorded on 400 MHz spectrometer ($CDCl_3$)



^{1}H-NMR data for compound **19** Recorded on 400 MHz spectrometer ($CDCl_3$)



^{13}C-NMR data for compound **19** Recorded on 400 MHz spectrometer ($CDCl_3$)



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