Towards the Understanding of Palladium-Catalyzed Tandem Cyclopropanol Opening-Direct Arylation Reactions

Bojan Dragisic

A thesis submitted to the Faculty of Graduate Studies in
partial fulfillment of the requirements
for the degree of
Master of Science

Graduate Program in Chemistry
York University
Toronto, Ontario

December 2012

Abstract

Insight into the stereoelectronic requirements for intramolecular direct arylation reactions is presented. Substrates were designed and synthesized with the goal of elucidating the steric, electronic, and conformational requirements for the concerted metalation-deprotonation process in intramolecular direct arylation reactions.

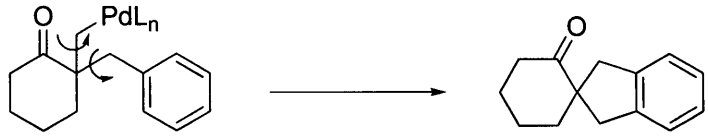


Figure 1: Rotational constraints in CMD

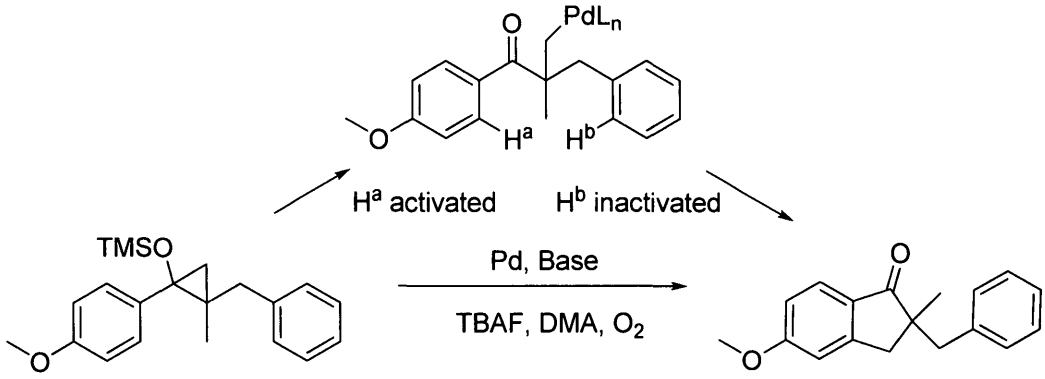


Figure 2: Selectivity in direct arylation

Poor conversions and yields were obtained with rotationally-constrained systems not possessing electron-withdrawing, or activating, groups on the aryl ring (Figure 1). Systems containing both activated and unactivated protons participating in CMD showed full selectivity for the activated protons (Figure 2).

Dedication

I would like to dedicate the entirety of this thesis to Martins Oderinde, who has been a guide through this process and has helped me on countless occasions with reactions, lab techniques, theory, and especially because he was a great friend.

Acknowledgements

I would like to thank…

Professor Muhammad Yousaf for his help in the completion of this thesis and degree.

York University and the Chemistry Department for granting me the Queen Elizabeth II Graduate Scholarship in Science and Technology.

Caitlin Matthew for her support and friendship during the latter half of my studies.

Andrei Nikolaev for the long discussions on orbital and NMR theory and for his humor throughout much of my time in the laboratory.

Paul O'Brien for his friendship and help with the thesis and presentation.

Professor Pierre Potvin for his help and advice.

Table of Contents

List of Abbreviations

Ar	Aryl
Bn	Benzyl
Bu	Butyl
CMD	Concerted Metalation-Deprotonation
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DFT	Density Functional Theory (computational method)
DMA	Dimethylacetamide
Equiv	Equivalents
IR	Infrared
KIE	Kinetic Isotope Effect
L_n	Ligand (s) (n = number of ligands)
M	Molarity (Mol/L)
m	Complex Multiplet
NMR	Nuclear Magnetic Resonance
Ph	Phenyl
ppm	Parts Per Million
q	Quartet
r.t.	Room Temperature (298 K)
s	Singlet
t	Triplet
THF	Tetrahydrofuran
TMS	Trimethylsilyl
TLC	Thin-layer Chromatography

List of Tables

List of Figures

List of Schemes

List of Equations

Chapter 1: Introduction and Proposal

1.1 General introduction

A catalyst is defined[1] as a species or compound which increases the rate at which a chemical reaction reaches equilibrium, by providing "an alternate pathway" (Figure 3), without itself being consumed in the reaction.

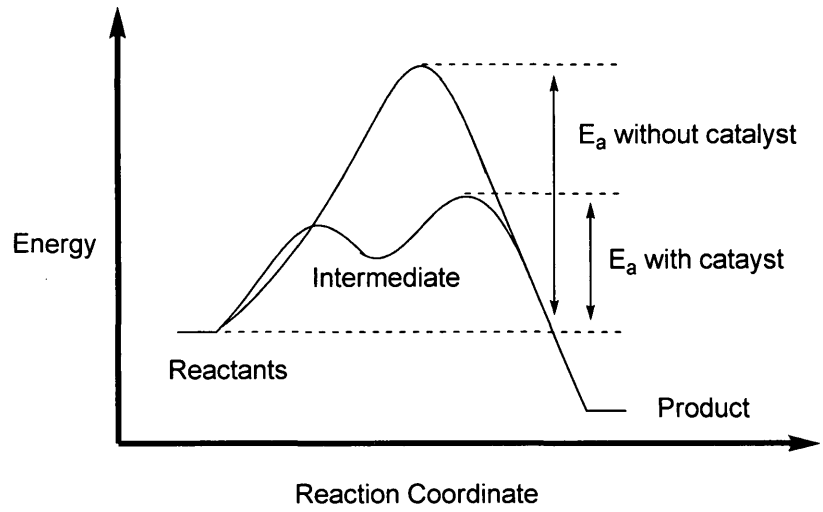
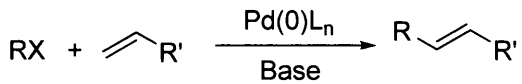


Figure 3: Energy profiles of catalyzed and uncatalyzed reactions

Since the 1960s, palladium[2] catalysis has rapidly expanded and has become an essential component in carbon-carbon bond forming reactions, which now encompasses the Negishi[3], Suzuki[4,5], Stille[6,7] and Sonogashira[8,9], and Heck,[10,11,12] cross-coupling reactions, as well as many variants and subdivisions based on additives and the scope of reaction. Nickel is also capable of catalyzing a number of the processes palladium catalyzes. However, palladium offers certain advantages over nickel, such as lower toxicity and inability to undergo radical processes, producing fewer side-products. In

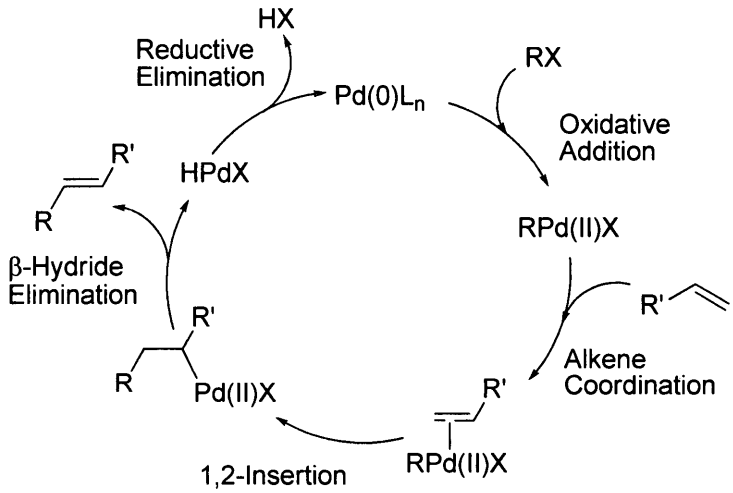
2010, the Nobel Prize in chemistry was awarded to Akira Suzuki, Ei-ichi Negishi, and Richard Heck for palladium-catalyzed cross-coupling reactions.

Traditional C-C bond forming reactions catalyzed by palladium, namely the Heck (Equation 1), Suzuki (Equation 2), Sonogashira (Equation 3), Stille (Equation 4), and Negishi (Equation 5) reactions, all have in common the fact that the coupling partners need to be pre-functionalized. In the case of the Suzuki reaction, one coupling partner needs to have a boronic acid or ester substituent and the other has to be a C-X-containing species, where X is a halide or pseudohalide such as a tosylate. Similarly, in the case of the Stille reaction, one coupling partner consists of a C-Sn functionality and the other of a C-X functionality. The Heck reaction (Equation 1) couples an aryl or alkyl halide to a terminal olefin using palladium catalysis.



Equation 1: Heck cross-coupling reaction

The mechanism of the Heck reaction (Scheme 1) involves the initial oxidative addition of palladium across a C-H bond followed by an olefin coordination. 1,2-insertion joins the two R groups, at the terminal olefin position to form the carbopalladium complex. *Beta*-hydride elimination produces a palladium hydride species and restores the unsaturation in the product. HX then eliminates to restore the catalyst.



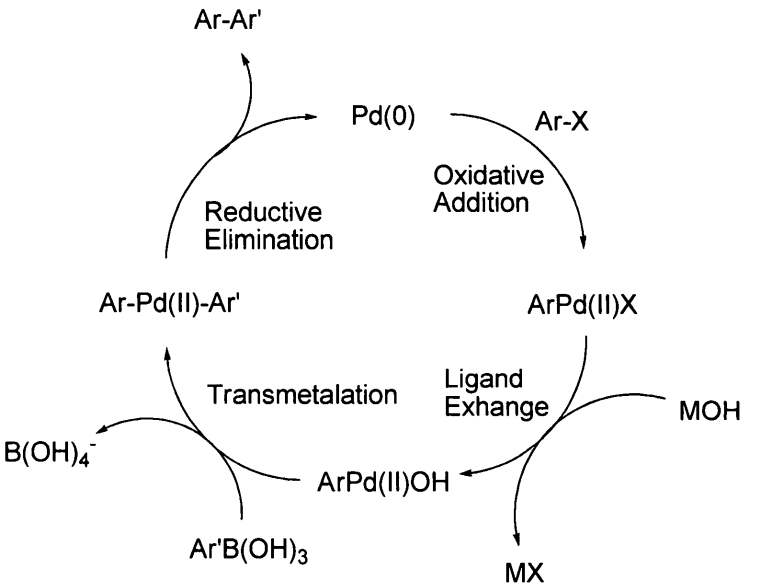
Scheme 1: Heck cross-coupling reaction mechanism

The Suzuki reaction (Equation 2) essentially couples two aryl systems to form a variety of biaryl species. More recent expansions[13] to the reaction scope allowed for the alkyl-aryl and alkyl-alkyl couplings.

$$Ar\text{-}BR_2 + Ar\text{-}X \xrightarrow[Base]{PdL_n} Ar\text{-}Ar$$

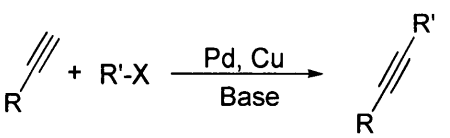
Equation 2: Suzuki cross-coupling reaction

The first step of the Suzuki reaction mechanism (Scheme 2) is an oxidative addition of an electron-rich palladium(0) species across an aryl halide C-X bond, much like in the Heck reaction. It is proposed that Ligand exchange then replaces the halide with a hydroxyl and a transmetalation of another alkyl or aryl group from a boronic acid or ester onto palladium follows to produce the dialkylpalladium species which then reductively eliminates, although this step is still in question and there is significant debate as to what precisely occurs.



Scheme 2: Suzuki cross-coupling reaction mechanism

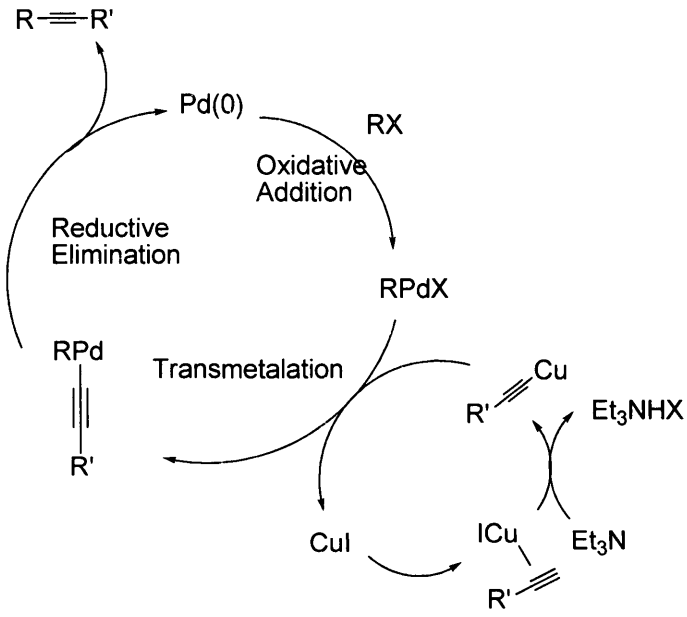
The Sonogashira reaction (Equation 3), is a useful method for preparing alkynes substituted with other $C(sp^2)$ or $C(sp^3)$ functionalities using palladium-catalyzed cross-coupling.



Equation 3: Sonogashira cross-coupling mechanism

The Sonogashira reaction mechanism (Scheme 3), much like the Suzuki or Heck reactions mechanisms, begins with an oxidative addition of palladium across a C-X bond. However, in the next step there is transmetalation of a terminal alkyne from the organocuprate reagent onto palladium. The role of the triethylamine is to deprotonate the cooper-coordinated alkyne while bound to copper, so that it may bind to copper in the

anionic state. Once both the alkyl and alkynyl groups are on palladium, reductive elimination occurs to produce the substituted alkyne.



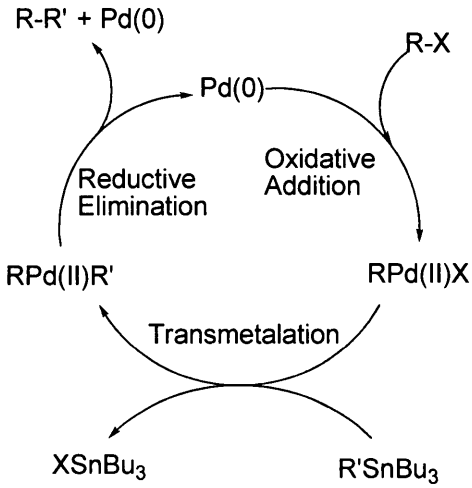
Scheme 3: Sonogashira cross-coupling reaction mechanism[14]

The Stille reaction[15] (Equation 4) uses organostannanes to transmetalate organic groups to palladium for reductive elimination to occur. Though these reactions offer a variety of applications, tin is often toxic and hazardous to the environment.

$$RSn(R'_3) + R''\text{-}X \xrightarrow[\text{Additives}]{Pd(0)L_n} R\text{-}R''$$

Equation 4: Stille cross-coupling reaction

The Stille reaction mechanism (Scheme 4) resembles the mechanistic pathways of the Suzuki and Sonogashira couplings except that it uses tin as a transmetalating agent.



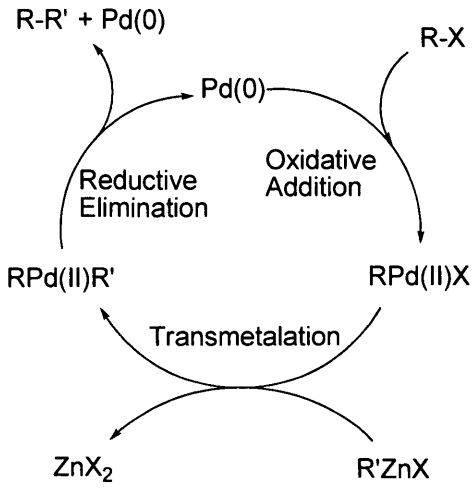
Scheme 4: Stille cross-coupling reaction mechanism[16,17]

The Negishi reaction (Equation 5) is an effective method of accomplishing a variety of various carbon-carbon couplings, including $C(sp^3)$-$C(sp^3)$ and $C(sp^3)$-$C(sp^2)$. It is substantially less toxic than the Stille protocol as it utilizes organozinc instead of organotin.

$$RX + R'ZnX \xrightarrow[\text{Additives}]{Pd(0)L_n} R\text{-}R'$$

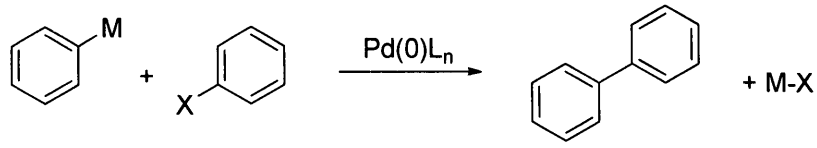
Equation 5: Negishi cross-coupling reaction

The key step of the Negishi reaction mechanism, after the initial oxidative addition, is the transmetalation of the organozinc reagent onto palladium to yield an alkyl- or alkenylpalladium intermediate which then reductively eliminates to form the coupled product.



Scheme 5: Negishi cross-coupling reaction mechanism

The need for coupling partners to be pre-functionalized before the coupling reactions, as is the case for the five cross-coupling reaction previously discussed, implies that additional steps may be required before the coupling is carried out. It also suggests the need for the use of additional reagents to prepare the pre-functionalized coupling partners. Once those groups are synthesized, they will be discarded during the coupling reaction. Indeed, this is a significant issue in most traditional coupling reactions, as is demonstrated below.



M= Zn, Mg, Sn, B

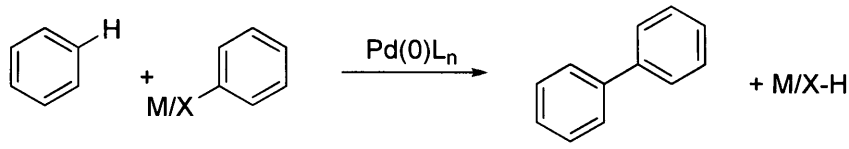
Equation 6: Generic palladium-catalyzed cross-coupling reaction

It can be seen from equation 6 that an organometallic reagent, such as a Grignard, organotin, or organozinc reagent, must be prepared separately prior to the coupling

reaction. Depending upon the complexity of the aryl halide, it may itself require several steps to synthesize, which in turn adds to the length and material requirements of the synthesis. Ideally, synthesis would be achieved through minimal preparation of substrates, without discarding groups (better atom economy) and by preserving functional groups after coupling steps.

1.2 Direct Arylation Methods and Concerted Metalation-Deprotonation

The aim of direct arylation reactions (Equation 7)[26] in general is to limit or avoid the pre-functionalization of one or more coupling partners. Ideally, simple arenes would constitute coupling partners, but before this objective can be realized, certain obstacles must be overcome.



Equation 7: Generic palladium-catalyzed direct arylation reaction

One such obstacle is the difficulty of C-H bond activation and another is selectivity between several available C-H bonds in a molecule. Several operative mechanisms have been proposed for direct arylation reactions, many which mirror traditional cross-coupling reactions (Figure 8). C-H bond activation has also been studied using both kinetic[18,19,20,21] mechanistic studies as well as computational[22,23] modelling, as it plays a key role in direct arylation reactions.

Each path in figure 4 initially begins with the oxidative addition of palladium(0) across a C-X bond. In path A, a carbopalladation, or a potential electrophilic aromatic substitution,

occurs before the reductive elimination which yields the coupled product. Path B involves the oxidative addition of palladium(0) across the C-H bond, producing a palladium(IV) species as an intermediate, known for its lack of stability. Path C treats the double bond on the arene as a localized double bond, which coordinates to palladium so that the first arene could insert. *Beta*-hydride elimination occurs to restore aromaticity and to yield the coupled product. Paths D and E are similar to path A except that the hapticity of the aryl ligand changes as well as the processes that ensue to yield the coupled product.

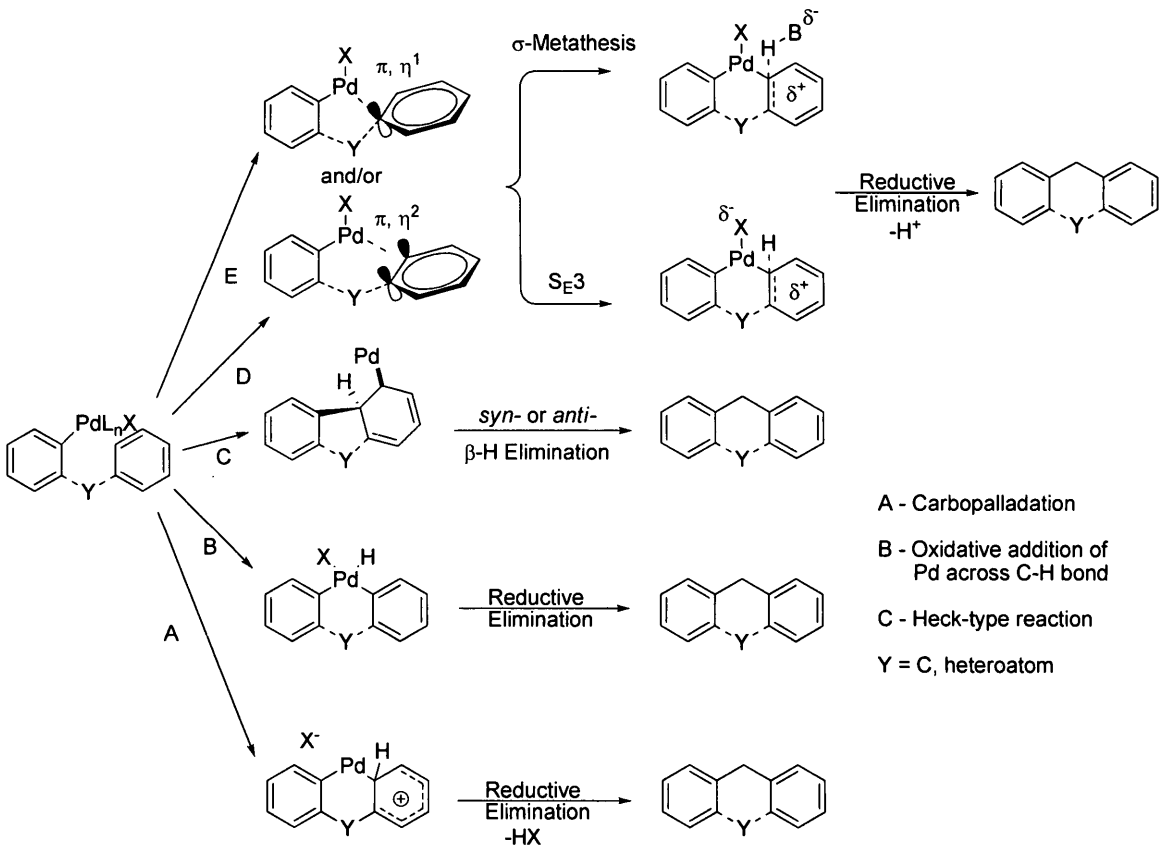


Figure 4[24]: Proposed direct arylation pathways

The pathways shown in figure 4 include aryl groups as both coupling partners. $C(sp^2)$-$C(sp^3)$ coupling, on the other hand, is more difficult to achieve. C-H bonds of sp^3-

hybridized carbon atoms are far more inert to the insertion of palladium and in cases where they do occur, are at risk for decomposition via β-hydride elimination if a methylene group is present adjacent to the palladated carbon. One way of accessing Pd-C(sp^3) coupling functionality is through the use of high-energy small molecules, such as cyclopropanols or cyclobutanols. Such molecules often readily ring-open to yield the corresponding metal homoenolate and the adjacent *beta-* center is quaternary, rendering decomposition through *beta*-hydride elimination impossible. The path of a reaction seems to depend on the nature of the substrate as well as other reaction conditions, such as the use of base. Another possible pathway, if base is present, is the concerted metalation-deprotonation pathway.[25,26]

The concept of concerted metalation-deprotonation dates back to 1955.[27] Winstein and Traylor discovered that the addition of acetic acid to a diphenylmercury complex would produce phenylmercury acetate and benzene, going through a proposed cationic intermediate (Figure 5a). The intermediate structure was not clear at first and further research was done by George Olah, who used NMR studies to propose a different intermediate (Figure 5b).

Sigma Complex
Winstein and Traylor, 1955

Pi Complex
Olah, 1980

Figure 5: Proposed intermediates for phenylmercury complexes

In 1968 Davidson and Triggs observed similarities between the way that palladium formed complexes with benzene and the way mercury did.[28] For palladium-catalyzed C-

H activation, palladium acetate was found to be the preferred palladium salt. The acetate ligand played several roles. First, it was found to better facilitate the solvation of reaction intermediates than other counter-ions. Second, acetate improved the electrophilicity of the palladium center due to its ability to act as either a mono- or bidentate ligand. Third, acetate stabilizes the palladium(II) center as a result of its electron-donating ability. Acetate was also found to play a key role as a base while acting as a ligand, which could accomplish the deprotonation in a concerted fashion. Ryabov *et al.* performed detailed mechanistic studies[29] on the palladation of N,N-dimethylbenzylamine. Hammett studies indicated that the palladium center was electrophilic in nature and further mechanistic studies determined the reaction to have a positive normal KIE. It was found that the reaction profile had a negative entropy of activation, which implied that the transition state was highly ordered. From these studies it was deduced that deprotonation occurred in an intramolecular fashion, likely facilitated by the acetate.

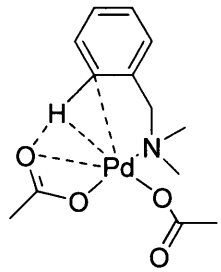


Figure 6[30]: Acetate-assisted CMD of dimethylbenzylamine

Indeed, mechanistic work by Davies and MacGregor using DFT modelling[30] seemed to also suggest that there was an agostic interaction between the *ortho* proton and palladium, which helped to polarize the C-H bond. Hydrogen bonding between the acetate base and the *ortho* proton, along with the enhanced acidity due to the agostic

interaction (denoted as the Pd-H dashed bond in figure 6), lead to a six-membered cyclic transition state in which the deprotonation occurs.

1.3 Beta-Carbon Elimination

When an alkyl palladium species, with a hydrogen atom beta to the metal, is generated as in intermediate in an organometallic reaction, the complex has the potential to undergo *beta*-hydride elimination to form the resulting metal hydride and alkene. This process occurs through the donation of palladium *d* orbital electrons into the C-H antibonding orbitals (Figure 7).

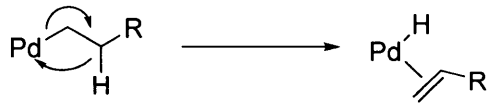


Figure 7: *beta*-hydride elimination

Beta-Carbon elimination parallels *beta*-hydride elimination, shown in figure 8, in that palladium *d* orbital electrons are donated into C-C antibonding orbitals and the result is a double bond. However, the process occurs less readily and usually requires some sort of driving force, such as molecular strain (Figure 8).

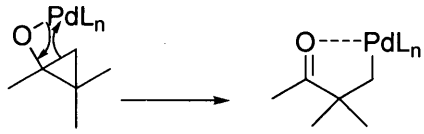


Figure 8: *beta*-carbon elimination

In figure 8, *beta*-carbon elimination occurs due to the inherent angle strain of the cyclopropane ring. The resulting molecule is a ketone (which is analogous to the alkene in *beta*-hydride elimination), and what is essentially a palladium homoenolate. From

Figure 8 it can be observed that new reactivity (namely the homoenolate) is accessed. Also observable is the fact that a functional group is still available after the coupling.

1.4 Strained Tertiary Alcohols

Small cyclic molecules[31,32] are often associated with inherent ring strain. This strain is usually comprised of angle strain due to the fact that sp^3-hybridized carbon atoms are not at their preferred bond angle of 109.5°, as well as torsional strain, owing to *gauche* eclipsing interactions, as well as strain due to 1,3-interactions. Ring strain is often compared to a reference, cyclohexane, which has little or no strain overall. Strain energies grouped by ring size are shown below.

Table 1: Ring strain energy according to ring size

Entry	Ring	Strain (kcal/mol)
1		27.5
2		55.2
3		26.5
4		6.5
5		~0

The higher the strain of a molecule, the higher is its energy content. This concept directly follows from the extent to which a certain conformation or set of bond angles is disfavored. Cyclopropane bond angles, forming an equilateral triangle, deviate significantly from the preferred 109.5° and are found to be 60°. This is apparent in the calculated strain energy of the molecule (Table 1, entry 1). Cyclopropene has approximately twice the strain energy of cyclopropane due the presence of an internal olefin, whose bond angles are far from the preferred 120°. Cyclobutane has less strain energy because the bond angles are approximately 88°, closer to the preferred 109.5°.

Cyclobutane is non-planar, which in turn causes 'flagpole' steric interactions, as well as torsional strain (*gauche* interactions), which place its strain energy close to that of cyclopropane. In cyclopropanols,[33] the energy content and the molecule's propensity to ring-open is even greater, mainly due to the ability of the oxygen atom to donate lone pairs into C-C antibonding orbital. If a source of protons is present upon ring opening, the homoenolate (carbanion) that forms is quenched to produce a ketone. However, metal salts such as various palladium(II) salts may be added to trap the homoenolate and make it available for coupling reactions. This process differs from the acid-mediated ring opening in that the metal may first coordinate to the oxygen and trigger *beta*-carbon elimination. Studies by Cha *et al.* have shown that in most cases, cleavage of the less substituted bond occurs.[34]

1.5 Cross-Coupling with Cyclopropanol-Derived Homoenolates

α,β-unsaturated ketones, commonly referred to as enones, are electrophilic at the ketone carbon as well as the *beta*-carbon, shown in figure 9. Indeed, this is shown numerous times in literature containing examples of 1,4-conjugate additions to enones, such as Michael additions. The beta-carbon in most of these cases is, however, restricted to being solely electrophilic. Being able to access a nucleophilic character on the *beta*-carbon opens doors to a wide variety of new retrosynthetic disconnections through a reversal of typical polarity, also known as '*umpolung*'.[35]

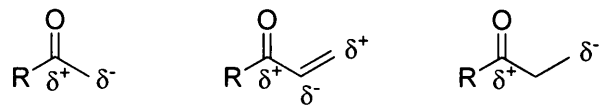
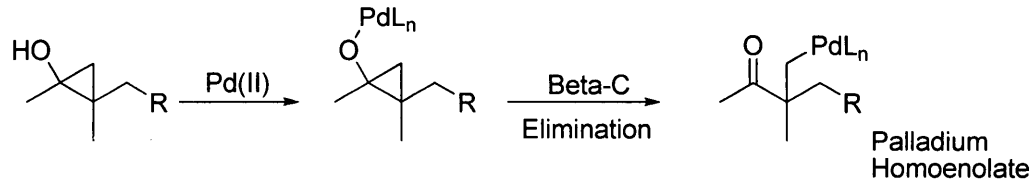


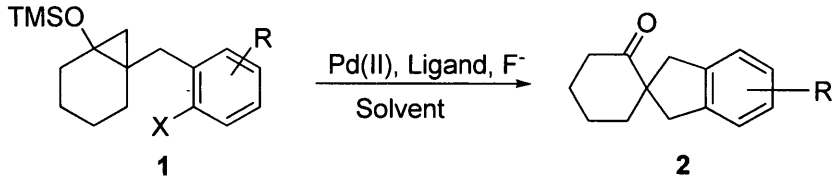
Figure 9: Comparison of unsaturated functionalities

Palladium homoenolates may be accessed through the reaction of a cyclopropanol with a palladium salt, such as palladium(II) acetate (Scheme 7). The formation of the homoenolate is proposed to be initiated by the coordination of palladium(II) to the cyclopropanol, although this is not known with certainty. This is then followed by *beta*-carbon elimination to produce the palladium homoenolate.



Scheme 6: Formation of a palladium homoenolate from cyclopropanol

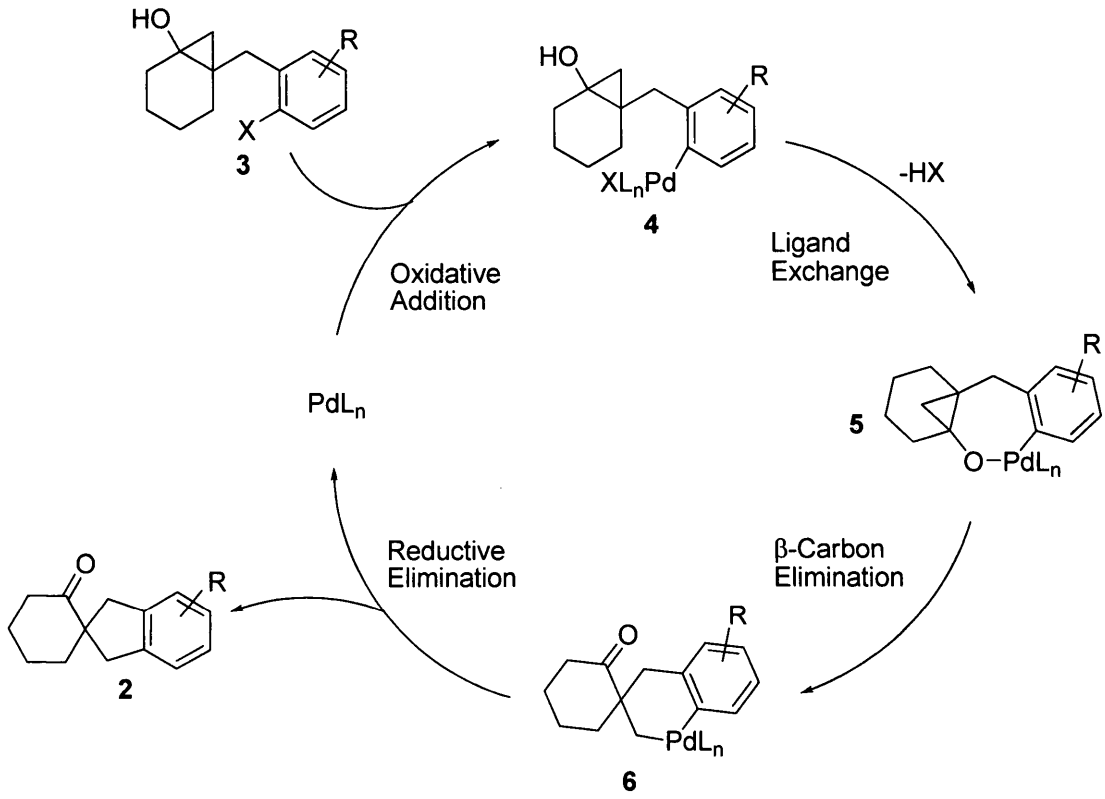
Work done by Rosa *et al.*[36] has exploited this process to achieve both inter- and intramolecular cross-coupling reactions. In the intramolecular example (Equation 8), a cyclopropanol protected with a trimethylsilyl group is subjected to fluoride and a palladium (II) source to form the palladium homoenolate. The solvent commonly used to facilitate such reactions is dimethylacetamide, notably good for its capacity for oxygen.



Equation 8: Cross-coupling reaction involving palladium-catalyzed ring opening

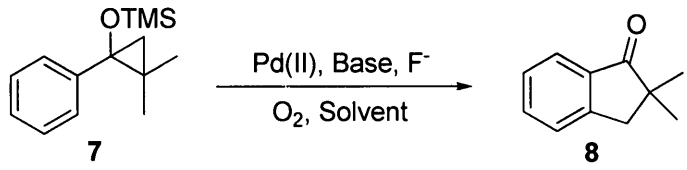
In the mechanism (Scheme 8), a palladium(0) source is necessary for initial oxidative addition across the C-X bond of **3** to form **4**. The hydroxyl group then coordinates to palladium to release HX and to form intermediate **5**, which then proceeds to undergo

beta-carbon elimination to form the palladium aryl homoenolate species **6**. Reductive elimination then occurs to afford the spirocyclic product **2**.



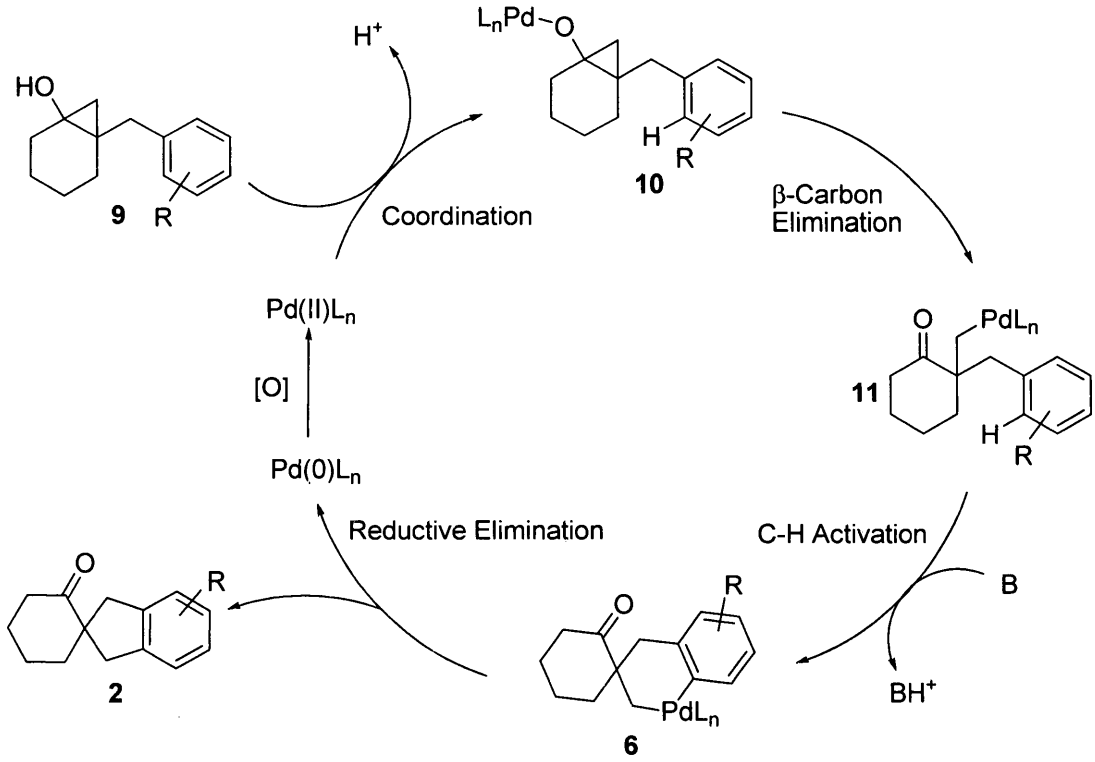
Scheme 7: Mechanism of cross-coupling involving palladium-catalyzed ring opening

Formation of the palladium homoenolate followed by concerted metalation-deprotonation has also been achieved. These reactions, unlike the examples where oxidative addition of palladium(0) across a C-X bond occurs first, start with the addition of a palladium(II) source, a base, and a fluoride source to the TMS-protected cyclopropanol. DMA and oxygen are the preferred solvent and oxidant, respectively (Equation 9).[37]



Equation 9: Direct arylation on activated substrate

The fluoride source is necessary to remove the silyl protecting group before the reaction can begin. The base, often an acetate, facilitates CMD. The mechanism is shown in scheme 9.



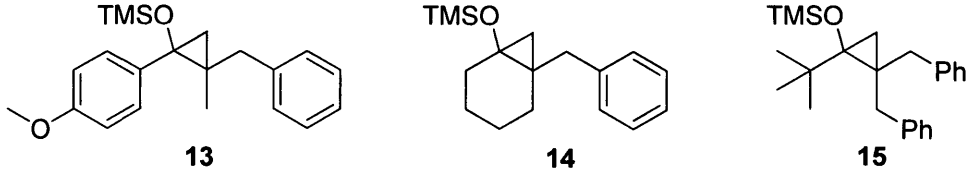
Scheme 8: Mechanism of direction arylation reaction

If the siloxycyclopropane is used for the reaction, TBAF removes the protecting group before palladium coordinates. If the hydroxycyclopropane is used instead, it first coordinates to the palladium and acetate removes the proton to form intermediate **9**. As

in the previous mechanism, *beta*-carbon elimination occurs to produce intermediate **6**. Acetate-facilitated concerted metalation-deprotonation is believed to be the operative mechanism that takes intermediate **11** to intermediate **16,** which then reductively eliminates to produce the spirocyclic product **2**. Work done by Schweinitz *et al.* utilizes cyclobutanols[38] to exploit the same process.

1.6 Proposal

Direct arylation reactions of cyclopropanols that exploit the concerted metalation-deprotonation step as a key mechanistic process are currently limited to systems which do not possess *beta*-hydrogen atoms in the alkylpalladium(II) intermediate which can partake in the competing *beta*-hydride elimination reaction. Also, relatively poorer results have been obtained in systems in which the aryl groups do not have an activating, or electron-withdrawing group, which makes the CMD-participating proton more acidic and thus labile. Several questions regarding the operative mechanism need to be answered: Is selectivity achieved in substrates containing both activated and unactivated aryls? What is the outcome if no activating group is present and how is the reaction affected? Does the rotational freedom or constraint of the palladium homoenolate play a role facilitating CMD? To answer these questions and to test the hypotheses, three model substrates were designed to be used in the direct arylation reaction (Figure 10).



13 **14** **15**

Figure 10: Proposed synthetic targets

To answer the first question, substrate **13** was designed so that it produces an *ortho*-electron-withdrawing group upon *beta*-carbon elimination on the methoxy-containing ring while still leaving the other aryl neutral, thus allowing reaction selectivity to be gauged (Figure 11).

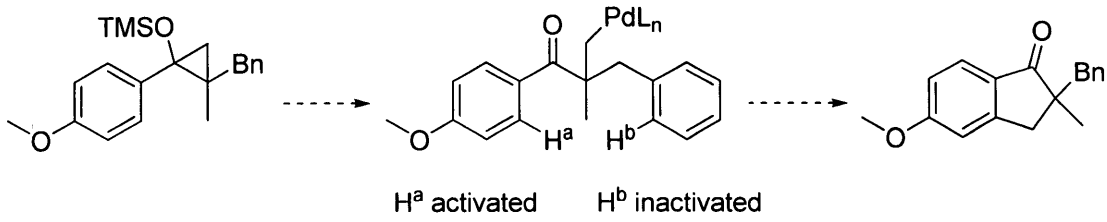


Figure 11: Selectivity in concerted metalation-deprotonation

Substrate **14** was designed with the purpose of providing the aryl group with no electron-withdrawing substituents that would make the *ortho*- proton more labile. Furthermore, once *beta*-carbon elimination occurs to form the palladium homoenolate intermediate, the degrees of freedom of the palladium are then restricted by the cyclohexyl ring (Figure 12).

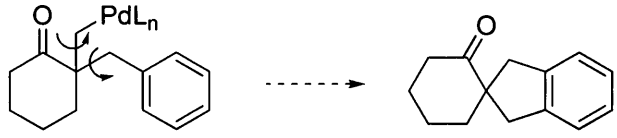


Figure 12: Rotational constrains of the alkylpalladium(II) intermediate

Substrate **15** was designed with the intention of allowing the palladium homoenolate free rotation while still maintaining neutrality on aryl rings. Significant difficulties with the synthesis of **15** that was envisioned were encountered, likely due to the bulk of the *tert*-butyl substituent. The dibenzylpinacolone proved resistant to enolization and to the

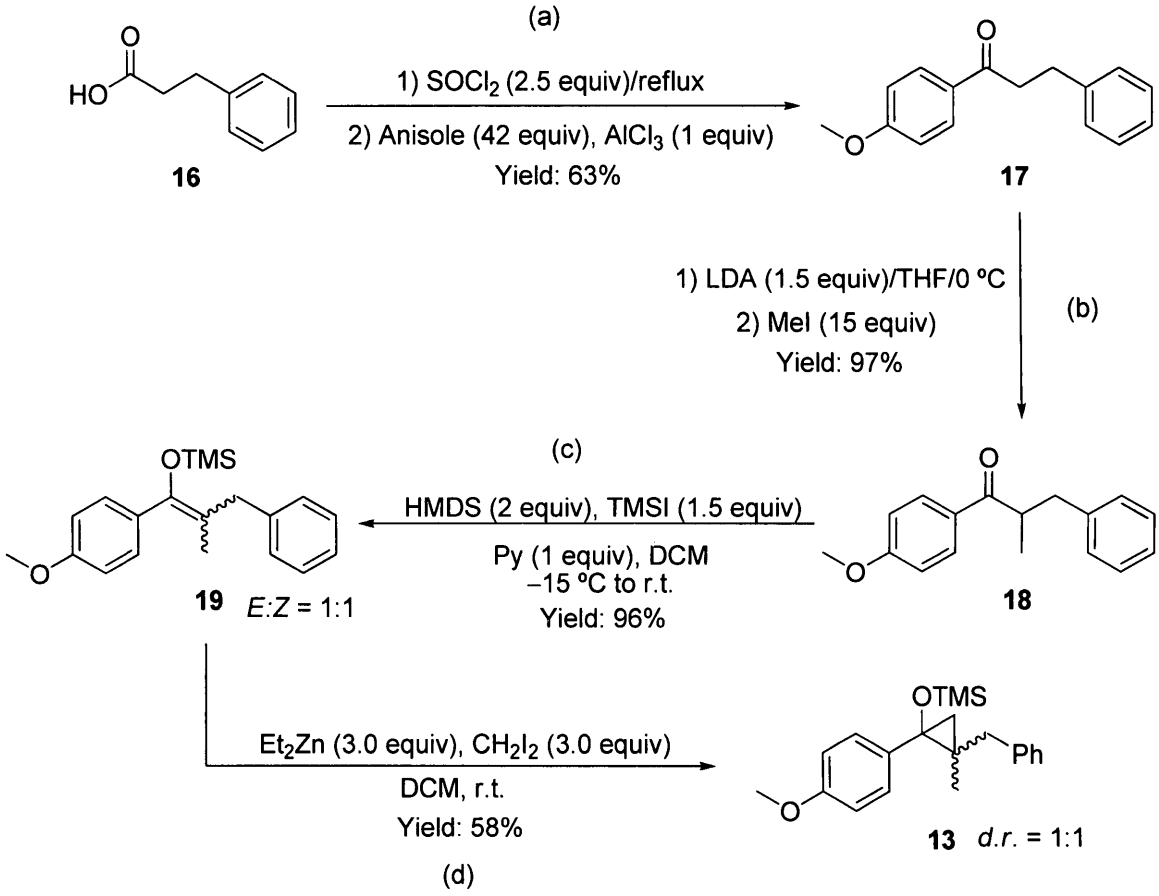
formation of the corresponding silyl enol ether. The synthesis and reaction results of substrates **13** and **14** are presented herein.

Chapter 2: Results and Discussion

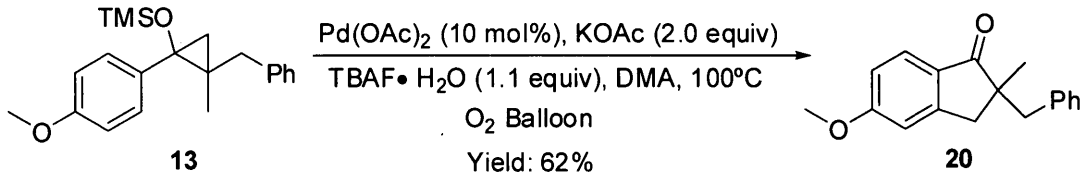
2.1 Synthesis of Substrate 13

An initial synthesis of **17** involved the deprotonation of 4-methoxyacetophenone with lithium diisopropylamide, followed by slow addition of benzyl bromide. After this synthesis failed to provide product **17**, a Friedel-Crafts[39,40] reaction was employed (Scheme 10a) in which hydrocinnamic acid **16** was first converted to the corresponding acid chloride *in*-situ, followed by electrophilic aromatic substitution with anisole, induced by aluminum chloride. α-methylation of ketone **17** initially consisted of using 1.1 equivalents of LDA and 1.5 equivalents of methyl iodide and it was observed that the result was a 1:1 mixture of starting material to product. The next trial involved 2.5 equivalents of LDA and 1.01 equivalents of methyl iodide. This reaction also showed significant starting material. The crude reactions with significant amounts of starting material present could not be taken to the enolization step, as **18** would form the silyl enol ether and the two would exist as an inseparable mixture, even throughout the cyclopropanation step. The next approach taken involved the addition of 1.5 equivalents of LDA and 4 equivalents of methyl iodide. It was observed from the first trial that excess LDA did not produce any dialkylated product, regardless of the amount of methyl iodide added. Keeping the equivalents of LDA consistent at 1.5, it was observed by proton NMR that the product to starting material ratio increased with increasing equivalents of methyl iodide, with no dialkylated by-product observed. The optimal amount of equivalents of methyl iodide was 15, to ensure nearly complete consumption of starting material **17** (Scheme 9b). Soft enolization[41] was carried out on **18** using the trimethylsilyl iodide, prepared according to the procedure of Olah *et al.*[42] as Lewis acid, pyridine, and

hexamethyl disilazane to afford silyl enol ether **19** (Scheme 9c). Due to its instability to silica gel, **19** was taken to the next step without further purification after workup. Substrate **19** was then subjected to the carbenoid[43] formed from combining neat diethyl zinc and diiodomethane and full conversion was achieved (Scheme 9d). It was also observed that higher yields could be achieved if the crude mixture was extracted with disodium EDTA rather than through the separation of the emulsion via separatory funnel alone.



Scheme 9: Synthetic route to substrate **13**



Equation 10: Palladium-catalyzed direct arylation reaction using substrate 13

13 was subjected to conditions optimized by Rosa *et al*[37]. The result was a single product, **20** (Equation 10), resulting from C-H activation of the aryl ring containing the acyl substituent. The observed selectivity suggests that activated *ortho* protons react more quickly (kinetic control) than unactivated protons.

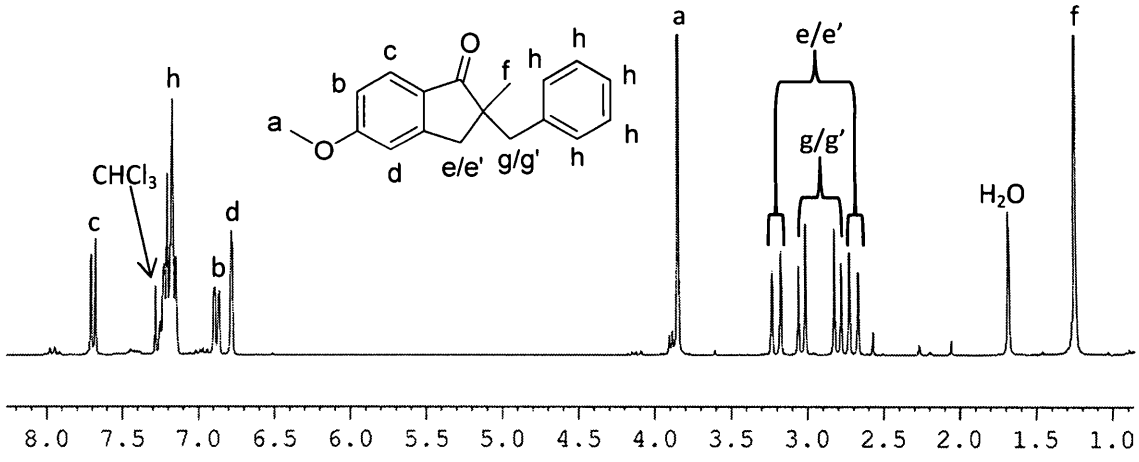
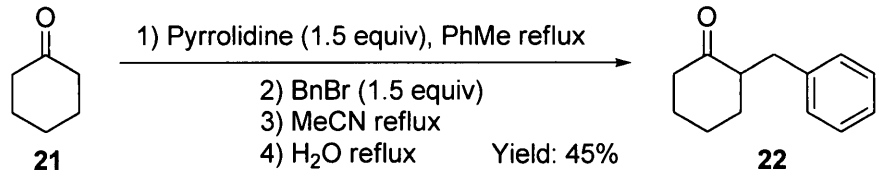


Figure 13: ^{1}H-NMR spectrum of **20**

The ^{1}H-NMR spectrum of **20** presents unknown impurities. Proton *d* is isolated on the molecule and presents as a singlet in the aromatic region. Proton *b*, *ortho* to the methoxy group, which is electron-donating through resonance to the *ortho* position, appears as the doublet furthest upfield. Proton *c* appears as the doublet furthest downfield. Diastereotopic protons *e* and *e'* appear as the doublet of doublets with a larger

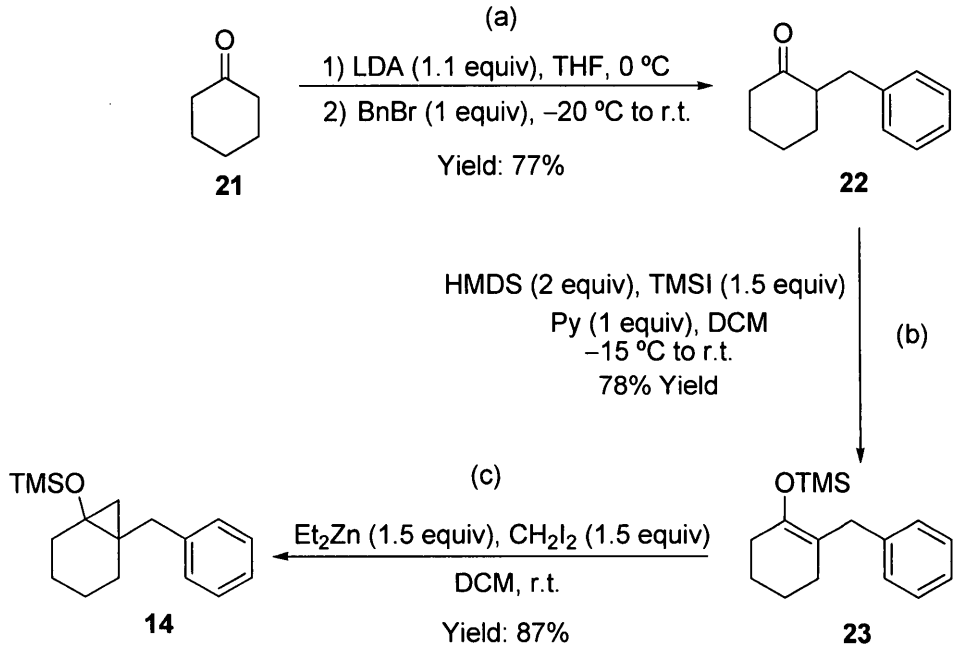
secondary coupling constant because their environments are significantly different depending upon the relative orientations of the methyl and benzyl groups. The leaning of the peaks is due to the germinal coupling of the two protons to each other. Proton *f* appears as a simple singlet. Protons *g* and *g'* also appear as a leaning doublet of doublets due to the fact that they are diastereotopic. Protons *h* appears as a multiplet in the aromatic region.

2.2 Synthesis of Substrate 14



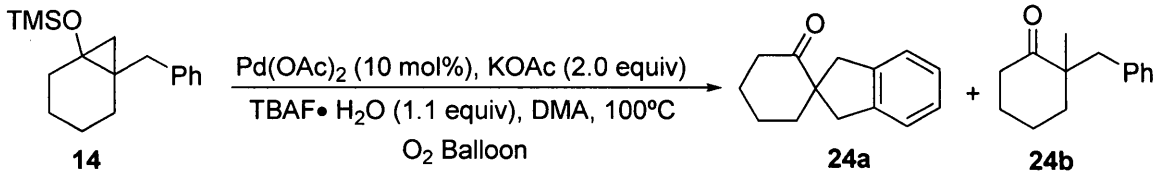
Equation 11: Enamine-based formation of **22**

Substrate **22** was initially synthesized through the formation of the enamine, which is then alkylated with benzyl bromide in the Stork reaction (Equation 11). Moderate product yields (45%) were obtained. An alternate synthesis was achieved through the deprotonation of cyclohexanone with lithium diisopropylamide at 0 °C, followed by alkylation with benzyl bromide, at a temperature range of - 20 °C to room temperature, to afford **22** in yields in excess of 75% (Scheme 10a). It was observed that if cyclohexanone was deprotonated at - 78 °C the yields were lower. The synthesis of **23** was carried out in the same fashion as that of **19** (Scheme 10b). No regioisomeric enolization by-product was observed. The cyclopropanation of **23** was carried out in the same fashion as that of **19**.



Scheme 10: Synthetic route to substrate **14**

Substrate **14** was then subjected to conditions optimized by Rosa *et al*[37] (Equation 12). Desired product **24a** was observed in trace quantities along with **24b**, the product resulting from a ring opening of the hydroxycyclopropanol. The ^{1}H-NMR spectrum on page 50 shows the **24a** + **24b** mixture as isolated from the crude reaction.

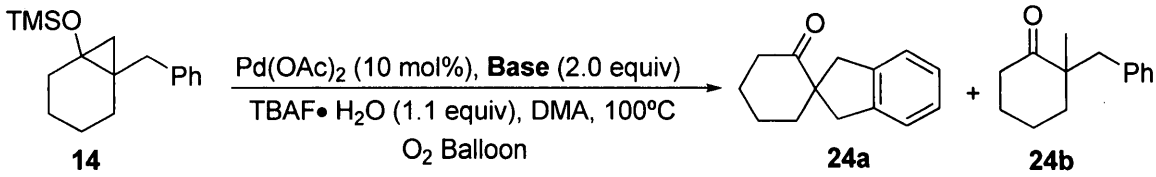


Equation 12: Direct arylation reaction on substrate **14**

Both products were isolated together, as an inseparable mixture, in less than 10% yield, which suggests that the reaction has difficulty proceeding even under optimized conditions. The palladium homoenolate conformation is locked to a significant extent by the cyclohexyl ring and for the reaction to occur, what must essentially take place is rotation about the benzyl bond. It is suggested that the reaction proceeds poorly due to the restricted degrees of freedom of the palladium homoenolate intermediate.

2.3 Base Screen

Table 2: Base screen



14 **24a** **24b**

Entry	**Base**	Product
1	LiOAc	Trace **24a** + **24b**
2	NaOAc	Trace **24a** + **24b**
3	KOAc	Trace **24a** + **24b**
4	CsOAc	Trace **24a** + **24b**
5	KO*t*Bu	100% **24b**
6	Pyridine	Trace **24a** + **24b**
7	TBAOAc	Trace **24a** + **24b**
8	KPiv	Trace **24a** + **24b**
9	DBU	-
10	Cs_2CO_3	-

A screen of bases for the test reaction on substrate **14** showed that changing bases had no significant effect on producing a single product or on increasing yields. In all cases where products were observed, except entry 5, the isolated yields of **24a** + **24b** mixtures were typically under 10 percent, based on crude NMR spectra. In entry 5, solely the ring-opened product was observed, as expected, due to the high basicity of the reaction and the presence of the cyclopropyl oxide, which spontaneously ring-opens to produce **24a**.

DBU and cesium carbonate produced neither product, indicating that the likely operative mechanism is an acetate-facilitated concerted metalation-deprotonation.

2.4 Conclusions and Future Work

In conclusion, we have synthesized two substrates for the purpose of determining the selectivity of direct arylation reactions for activated rings in the presence of inactivated rings, and determining how the rotational constraints of palladium homoenolates affect the outcome of the direct arylation reaction. We have discovered that direct arylation reactions involving CMD are fully selective for aryl rings containing an *ortho*- activating group in the presence of rings containing no electron-withdrawing groups. The free rotation of the palladium homoenolate intermediate has also been found to have a significant impact on the yield and efficiency of the reaction, showing negligible yields and formation of side products for rotationally-restricted species, while showing good yields and a single product for species that can undergo free rotation. Attempts to synthesize substrate **15** involved the dibenzylation of pinacolone using sodium amide and benzyl chloride. The subsequent step involved the enolization of dibenzylpinacolone, which failed to yield the desired silyl enol ether, likely due to the bulk of the *t*-butyl group. An alternate synthetic method is required to produce a substrate similar to **15**.

Chapter 3: Experimental

3.1 General Experimental

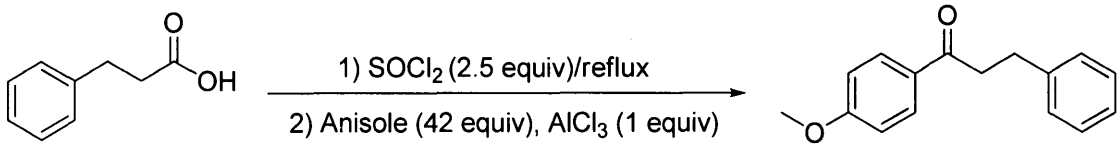
Reactions were conducted in flame- or oven-dried glassware in an atmosphere of argon using freshly-distilled solvents unless specified otherwise. Stainless steel needles were oven-dried, cooled in a desiccator, and purged with argon prior to the handling of dry solvents and reagents. Commercial reagents were used as received. Dichloromethane and toluene were distilled from CaH_2 prior to use. Tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone.

Thin-layer chromatography was performed on Merck silica gel 60 F_{254} plates. Visualization was carried out using UV light and $KMnO_4$ or anisaldehyde staining solutions. Hexanes and ethyl acetate (ACS grade) were used as received. Flash column chromatography was carried out using Silicycle® SilaFlash® P60 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 AV-400 or Bruker AV-300 spectrometer in chloroform-*d* (99.8% deuterated), and using chloroform (7.28 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), and br (broad). Coupling constants *J* are reported in Hertz (Hz). Infrared (IR) spectra were recorded as thin films in NaCl cells using a Mattson Genesis II FT-IR instrument or neat using a Bruker ALPHA FTIR spectrometer equipped with a ZnSe ATR crystal.

3.2 Experimental Procedures and Data

Synthesis of **17**:



16 **17**

Substrate **16** (5 g, 33.3 mmol, 1 equiv.) was added into a 250-mL flame-dried round-bottomed flask, purged with argon, containing a magnetic stir bar. Thionyl chloride (6.2 mL, 83.2 mmol, 2.5 equiv.) was added to the flask via syringe while the contents were vigorously stirred. The reaction mixture was heated at reflux for two hours. Afterwards, Thionyl chloride (6.2 mL, 83.2 mmol, 2.5 equiv.) was added to the flask via syringe while the contents were vigorously stirred. The reaction was refluxed for two hours. After two hours the stir bar was removed; the thionyl chloride was removed as well on the rotary evaporator under reduced pressure and a $NaHCO_3$ trap. Anisole (153 mL, 1.4 mol, 42 equiv) and aluminum chloride (4.45 g, 33.3 mmol, 1 equiv) were added to the flask and the reaction was heated to 80 °C for one hour, at which point the contents were dark brown in color. Upon completion of the reaction excess anisole was removed under reduced pressure at 70 °C. Absolute ethanol was added to the remaining viscous oil, at which point white crystals precipitated. The white crystals were collected via vacuum filtration and recrystallized twice from absolute ethanol to yield 5.008 g **17** (63% yield).

Data for **17**

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

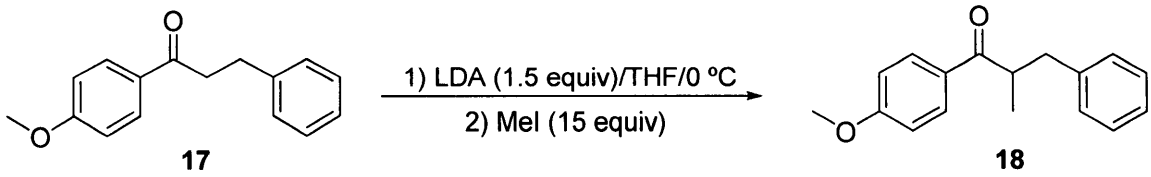
δ 7.97 (d, 2 H, J = 8.8 Hz), 7.28 (m, 5 H), 6.95 (d, 2 H, J = 8.8 Hz), 3.89 (s, 3 H), 3.28 (t, 2 H, J = 7.6 Hz), 3.09 (t, 2 H, J = 8 Hz) ppm

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

δ 197.7, 163.3, 141.4, 130.2, 129.8, 128.4, 128.3, 126.0, 113.6, 55.4, 40.0, 30.2 ppm

Spectra consistent with literature.[44]

Synthesis of **18**:



Diisopropylamine (0.44 mL, 3.12 mmol, 1.5 equiv) and 6 mL of THF were added into a 25-mL flame-dried round-bottomed flask, purged with argon, containing a magnetic stir bar.. The flask was cooled to 0 °C and *n*-butyllithium (1.95 mL, 3.12 mmol, 1.5 equiv) was added dropwise via syringe. The reaction mixture was stirred for 30 minutes and then **17** (0.5 g, 2.08 mmol, 1 equiv) was added as a THF solution, dropwise over five minutes. Upon the complete addition of **17**, the reaction was stirred for 30 minutes and MeI (1.94 mL, 31.2 mmol, 15 equiv) was added. The reaction mixture was subsequently stirred for one hour and then quenched with a saturated solution of $(NH_4)_2SO_4$. The reaction mixture was extracted twice with ethyl acetate, washed with brine and dried over anhydrous $MgSO_4$. The crude reaction mixture was chromatographed using 10 percent EtOAc in hexanes to afford 0.542 g **18** (97% yield).

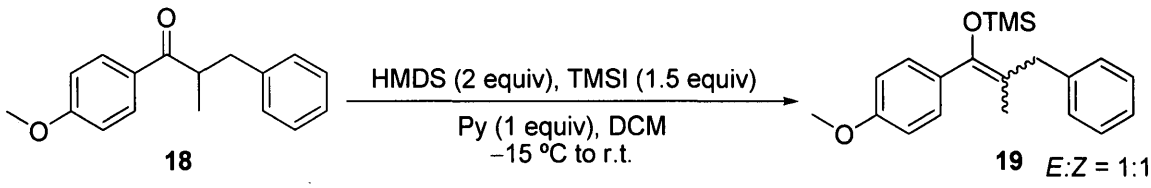
Data for **18**

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

δ 7.94 (d, 2 H, J = 9 Hz), 7.26 (m, 5 H), 6.94 (d, 2 H, J = 8.9 Hz), 3.88 (s, 3 H), 3.72 (m, 1 H), 3.16 (dd, 1 H, J = 20 Hz, 6.3 Hz), 2.70 (dd, 1 H, J = 21.6 Hz, J = 8.1 Hz), 1.21 (d, 3 H, J = 6.9 Hz) ppm

Spectrum consistent with literature.[45]

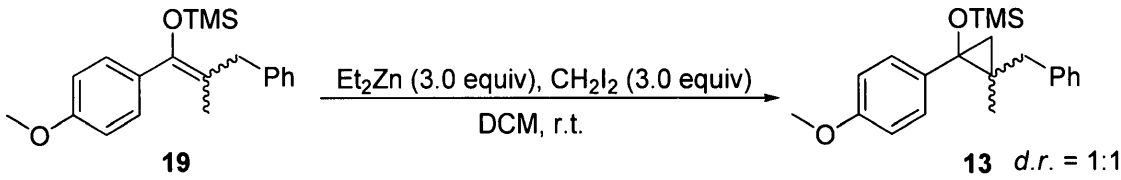
Synthesis of **19**:



Iodine (406 mg, 3.20 mmol, 1.5 equiv.) and hexamethyldisilane (0.35 mL, 3.20 mmol, 1.5 equiv.) were added into a 10-mL flame-dried round-bottomed flask, purged with argon, containing a magnetic stir bar and fitted with a condenser. The reaction was heated to 125 °C for 90 minutes. The contents were then cannulated to a 50-mL flame-dried round-bottomed flask, cooled to -20 °C, containing **18** (542 mg, 2.13 mmol, 1 equiv.), pyridine (0.17 mL, 2.13 mmol, 1 equiv.), and hexamethyldisilazane (0.89 mL, 4.26 mmol, 2 equiv.). The reaction was stirred for two hours and subsequently quenched with a saturated solution of $NaHCO_3$. The reaction was extracted twice with ethyl acetate, washed with brine and dried over anhydrous $MgSO_4$. The crude reaction mixture (0.670 g) was taken to the next step without purification.

Proton NMR spectrum is shown on page 47.

Synthesis of **4a**:



Substrate **19** (356 mg, 1.09 mmol, 1 equiv.), 20 mL of DCM, CH_2I_2 (0.3 mL, 3.27 mmol, 3 equiv.), and Et_2Zn (0.34 mL, 3.27 mmol, 3.0 equiv.) were added to a 50-mL flame-dried round-bottomed flask, purged with argon, containing a magnetic stir bar. The reaction was stirred for 16 hours and then quenched with a saturated solution of $(NH_4)_2SO_4$. The reaction was extracted twice with ethyl acetate, washed with a saturated solution of disodium EDTA, washed with brine, and dried over anhydrous $MgSO_4$. The crude reaction mixture was chromatographed using 2% EtOAc in hexanes to afford 0.217 g **13** (58% yield).

Data for **13**

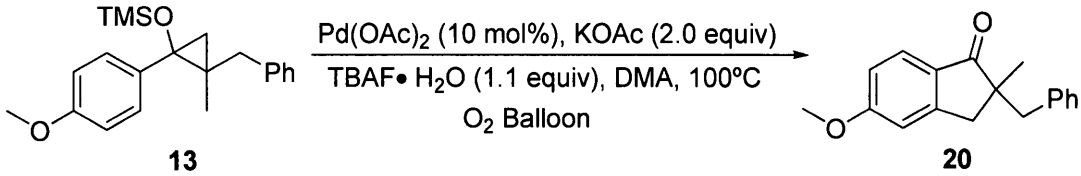
^{1}H-NMR (400 MHz, $CDCl_3$)

δ 7.52 – 6.88 (m, 18 H), 3.87 (s, 3 H), 3.84 (s, 3 H), 3.13 (d, 1 H, *J* = 13.6 Hz), 2.96 (d, 1 H, *J* = 14 Hz) 2.49 (d, 1 H, *J* = 14.4 Hz), 1.99 (d, 1 H, *J* = 14.4 Hz), 1.47 (d, 1 H, *J* = 6 Hz), 1.31 (s, 3 H), 1.19 (d, 1 H, *J* = 5.6 Hz), 0.99 (d, 1 H, *J* = 5.2 Hz), 0.80 (d, 1 H, *J* = 6 Hz), 0.61 (s, 3 H), 0.06 (s, 9 H), 0.03 (s, 9 H) ppm

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

δ 158.5, 158.4, 141.6, 140.6, 133.8, 133.5, 129.8, 129.7, 129.5, 129.0, 128.1, 128.0, 127.9, 125.6, 125.6, 113.4, 113.2, 113.1, 65.5, 65.2, 55.1, 55.0, 41.6, 39.8, 27.4, 27.3, 24.0, 23.3, 20.0, 17.6, 1.0, 0.9 ppm

Synthesis of **5a**:



13 **20**

Substrate **13** (50 mg, 0.15 mmol, 1 equiv), KOAc(29 mg, 0.29 mmol, 2 equiv), $Pd(OAc)_2$ (5 mg, 0.015 mmol, 10 mol%), TBAF•H_2O (46 mg, 0.16 mmol, 1.1 equiv) and 1.5 mL of DMA were added to a 25 mL test tube containing a magnetic stir bar. The test tube was capped with a rubber septum and was purged with oxygen from a balloon for 1 minute before the reaction was carried out. The test tube was heated to 100 °C and stirred for 16 hours. The crude reaction mixture was then filtered through a 3-cm silica plug using 2% EtOAc to afford 0.024 g **20** (62% yield).

Data for **20**

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

δ 7.70 (d, 1 H. *J* = 9 Hz), 7.22-7.15 (m, 5 H), 6.88 (dd, 1 H, *J* = 9 Hz, 1.8 Hz), 6.78 (s, 1 H), 3.85 (s, 3 H), 3.21 (d, 1 H, *J* = 18 Hz), 3.05 (d, 1 H, *J*= 15 Hz), 2.81 (d, 1 H, *J* = 15 Hz), 2.71 (d, 1 H, *J* = 18 Hz), 1.26 (s, 3 H) ppm

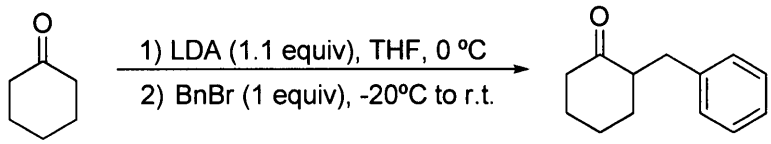
^{13}C-NMR (75 MHz, $CDCl_3$)

δ 109.0, 165.4, 155.4, 138.0, 130.2, 128.9, 128.0, 126.3, 125.9, 115.3, 109.6, 55.5, 50.5, 43.3, 38.9, 24.8 ppm

IR (thin film, NaCl)

v = 2368, 2341, 1699, 1598, 1492, 1453, 1264, 1144, 1104, 1088, 1027, 980 cm^{-1}

Synthesis of **1b**:



21 **22**

Diisopropylamine (4.53 mL, 32.1 mmol, 1.1 equiv) and 100 mL of THF were added into a 200-mL flame-dried round-bottomed flask, purged with argon, containing a magnetic stir bar. The flask was cooled to 0 °C and *n*-butyllithium (20.1 mL, 32.1 mmol, 1.1 equiv) was added dropwise via syringe. The reaction was stirred for 30 minutes and then cyclohexanone (3.18 mL, 30.7 mmol, 1.05 equiv) was added as a THF solution, dropwise over five minutes. Upon the complete addition of cyclohexanone **21**, the reaction mixture was stirred for 30 minutes and benzyl bromide (3.47 mL, 29.2 mmol, 1 equiv) was added. The reaction mixture was subsequently stirred for one hour and then quenched with a saturated solution of $(NH_4)_2SO_4$. The reaction mixture was extracted twice with ethyl acetate, washed with brine and dried over anhydrous $MgSO_4$. The crude reaction mixture was chromatographed using 10 percent EtOAc in hexanes to afford 4.552 g **22** (77% yield).

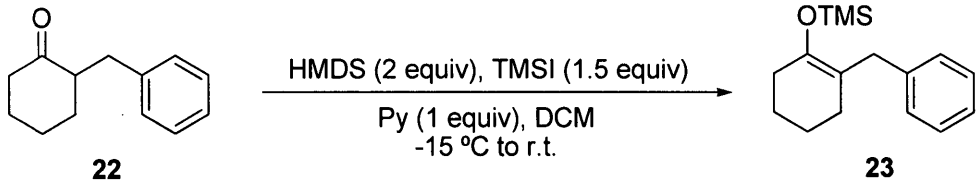
Data for **22**

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

δ 7.32-7.28 (m, 2 H), 7.23-7.17 (m, 3 H), 3.26 (dd, 1 H, *J* = 14 Hz, 4.8 Hz), 2.46-2.35 (m, 4 H), 2.08-2.06 (m, 2 H), 1.80-1.88 (m, 1 H), 1.55-1.78 (m, 2 H), 1.31-1.41 (m, 1 H) ppm

Spectrum consistent with literature.[46]

Synthesis of **2b**:



22 **23**

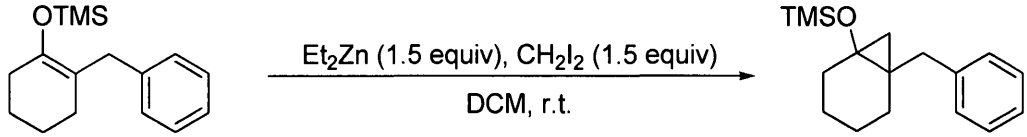
Iodine (1.523 g, 12.0 mmol, 1.5 equiv.) and hexamethyldisilane (1.21 mL, 12.0 mmol, 1.5 equiv.) were added into a 10-mL flame-dried round-bottomed flask, purged with argon, containing a magnetic stir bar and fitted with a condenser. The reaction was heated to 125 °C for 90 minutes. The contents were then cannulated to a 50-mL flame-dried round-bottomed flask, cooled to -20 °C, containing **22** (1.5 g, 7.97 mmol, 1 equiv.), pyridine (0.642 mL, 79.7 mmol, 1 equiv.), and hexamethyldisilazane (3.32 mL, 15.9 mmol, 2 equiv.). The reaction was stirred for two hours and subsequently quenched with a saturated solution of $NaHCO_3$. The reaction mixture was extracted twice with ethyl acetate, washed with brine, and dried over anhydrous $MgSO_4$. The crude reaction mixture (1.621 g) was taken to the next step without purification.

Data for **23**

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

δ 7.27 (d, 2 H, *J* = 7.5 Hz), 7.19 (d, 3 H, *J* = 7.2 Hz), 3.40 (s, 2 H), 2.13 (t, 2 H, *J* = 5.7 Hz), 1.89 (t, 2 H, *J* = 6 Hz), 1.69-1.65 (m, 2 H), 1.54-1.51 (m, 2 H), 0.18 (s, 9 H) ppm

Synthesis of **14**:



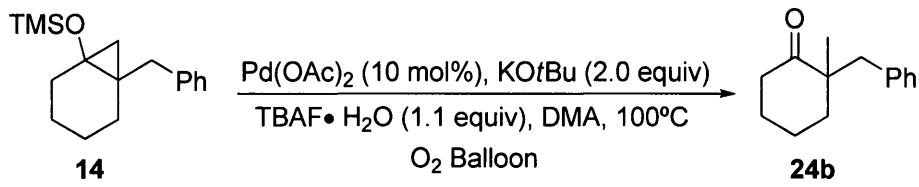
23 **14**

Substrate **23** (1.621 g, 6.22 mmol, 1 equiv.), 20 mL of DCM, CH_2I_2 (0.76 mL, 9.34 mmol, 1.5 equiv.), and Et_2Zn (0.96 mL, 9.34 mmol, 1.5 equiv.) were added to a 50-mL flame-dried round-bottomed flask, purged with argon, containing a magnetic stir bar. The reaction was stirred for 16 hours and then quenched with a saturated solution of $(NH_4)_2SO_4$. The reaction mixture was extracted twice with ethyl acetate, washed with a saturated solution of disodium EDTA, washed with brine, and dried over anhydrous $MgSO_4$. The crude reaction mixture was chromatographed using 10 percent EtOAc in hexanes to afford 1.489 g **14** (87% yield).

Data for **14**

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

δ 7.35-7.21 (m, 5 H), 2.81 (q, 2 H, *J* = 14.4 Hz), 2.11 (m, 1 H), 2.19 (m, 1 H), 2.17 (m, 1 H), 1.44 (m, 2 H), 1.15 (m, 3 H), 0.78 (d, 1 H, *J* = 4.5 Hz), 0.58 (d, 1 H, *J* = 4.6 Hz), 0.20 (s, 9 H) ppm



14 **24b**

Substrate **14** (50 mg, 0.18 mmol, 1 equiv), KO*t*Bu (45 mg, 3.64 mmol, 2 equiv), $Pd(OAc)_2$ (6 mg, 0.018 mmol, 10 mol%), TBAF•H_2O (56 mg, 0.20 mmol, 1.1 equiv) and 1.5 mL of DMA were added to a 25 mL test tube containing a magnetic stir bar. The test tube was capped with a rubber septum and purged with oxygen from a balloon for 1 minute before the reaction was carried out. The test tube was heated to 100 °C and stirred for 16 hours. The crude reaction mixture was then filtered through a 3-cm silica plug using 2% EtOAc to afford 0.024 g **24b** (66% yield).

Data for **24b**

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

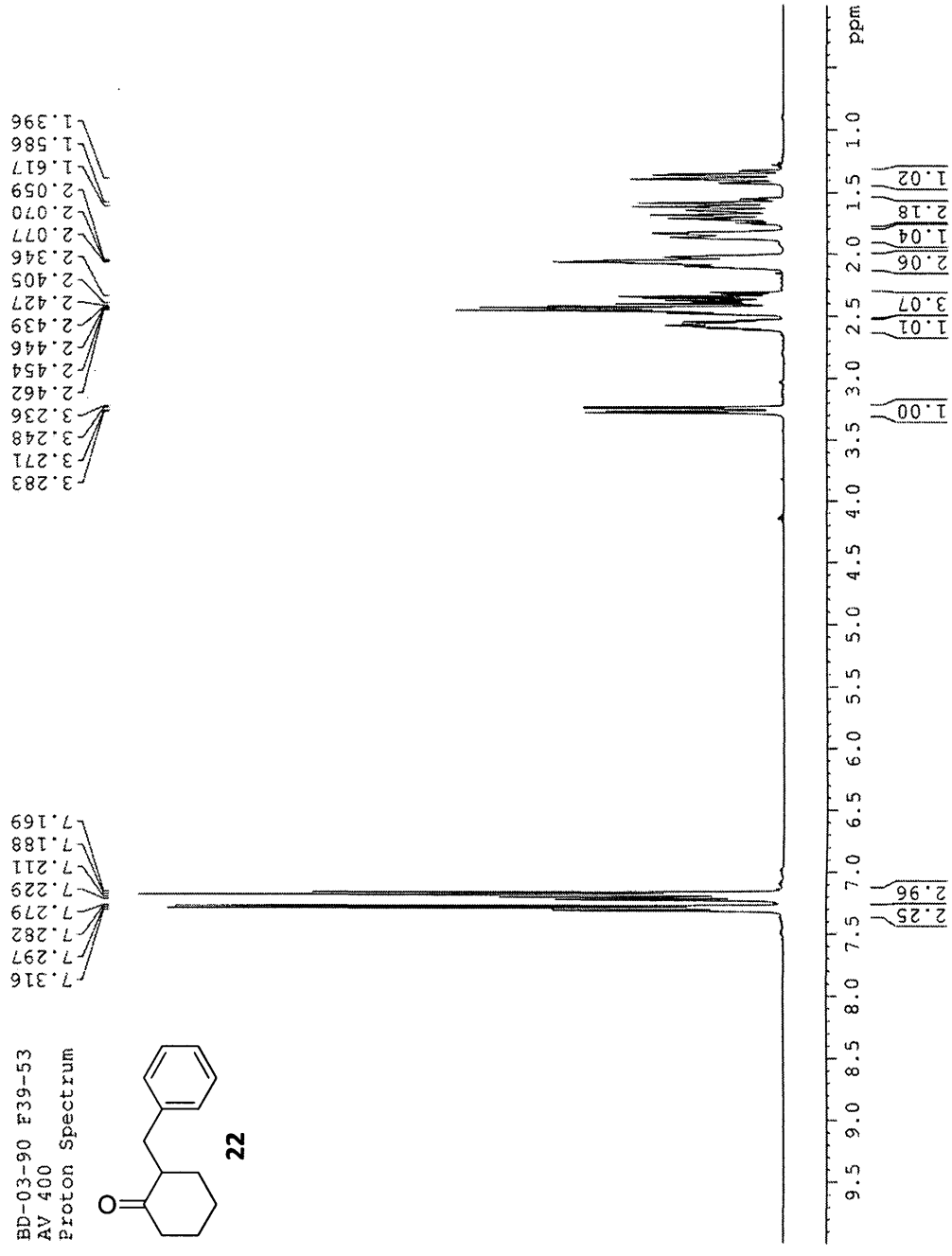
δ 7.12-7.28 (m, 5 H), 2.90 (s, 2 H), 2.53 (m, 2 H), 1.85 (m, 2 H), 1.83 (m, 5 H), 1.56 (m, 1 H), 1.05 (s, 3 H) ppm

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

δ 215.4, 137.6, 130.5, 127.9, 126.3, 49.3, 43.1, 38.8, 38.1, 27.3, 22.8, 21.1 ppm

Spectra consistent with literarure.[36]

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

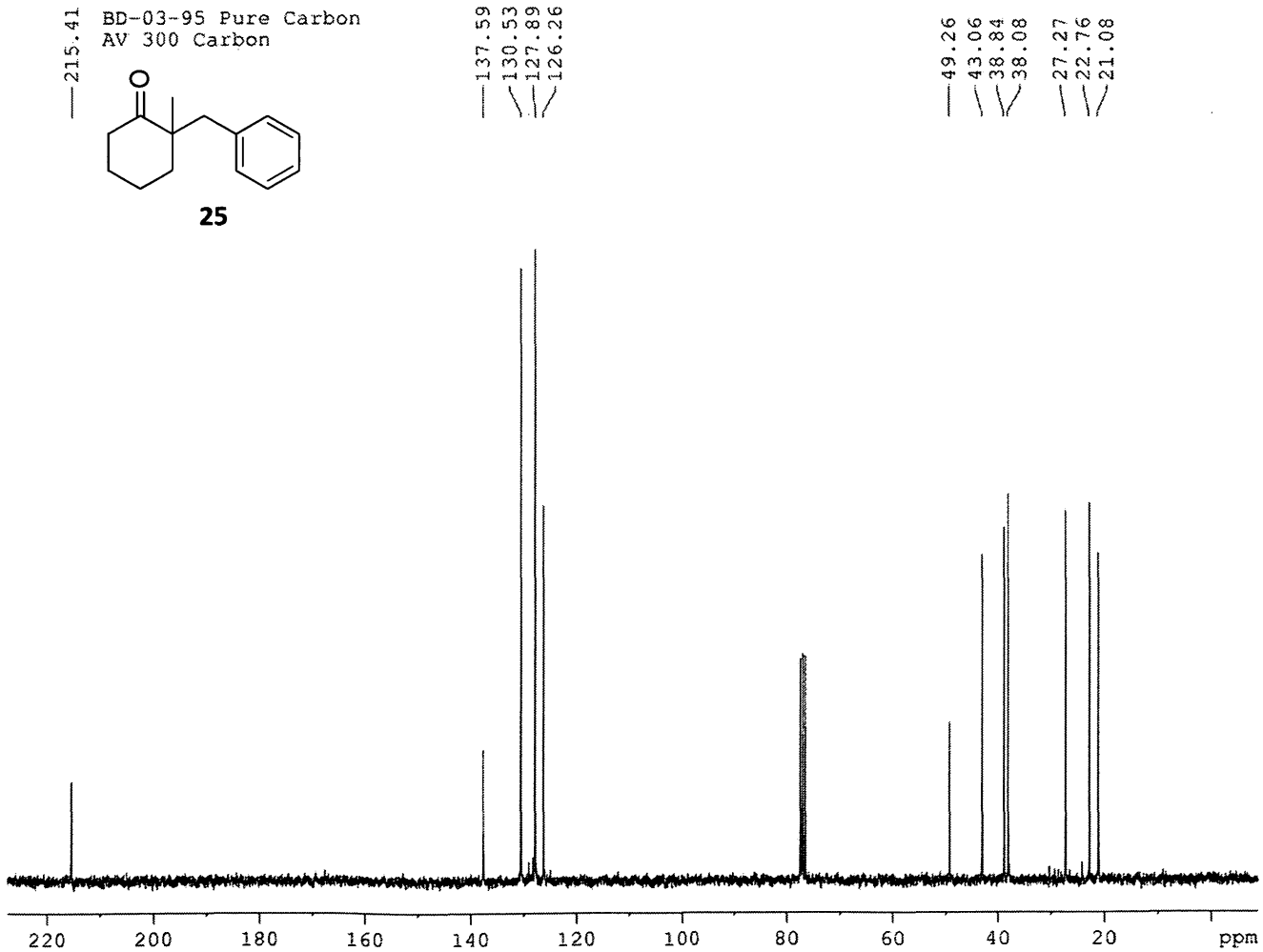


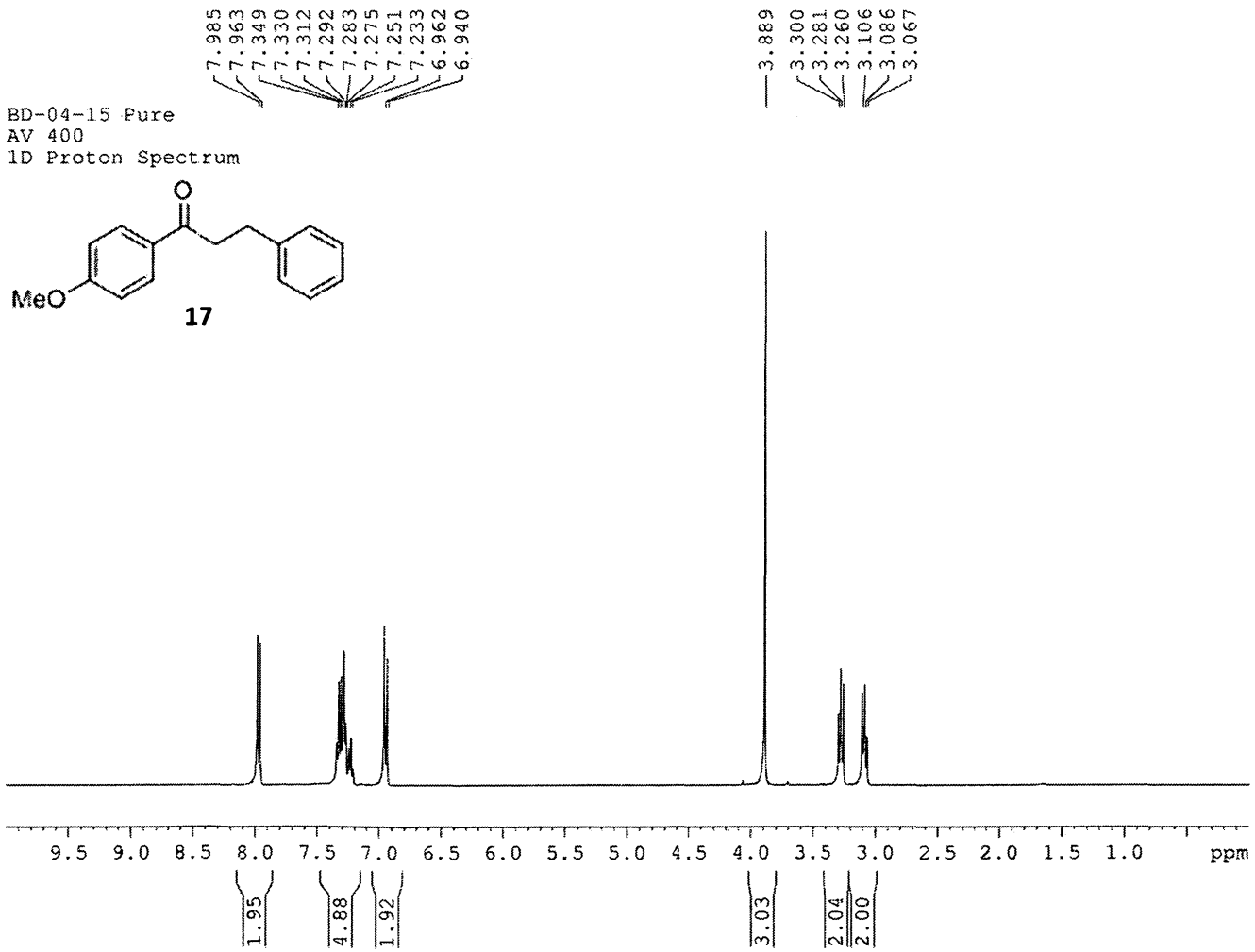
BD-03-92 Crude
AV 300 proton
OTMS
23
7.304
7.280
7.255
7.206
7.182
3.395
2.151
2.132
2.112
1.906
1.886
1.866
1.693
1.674
1.662
1.654
1.544
1.538
1.525
1.507
0.242
0.183
0.096
2.84
3.18
2.02
2.06
2.09
2.15
2.25
9.00
ppm

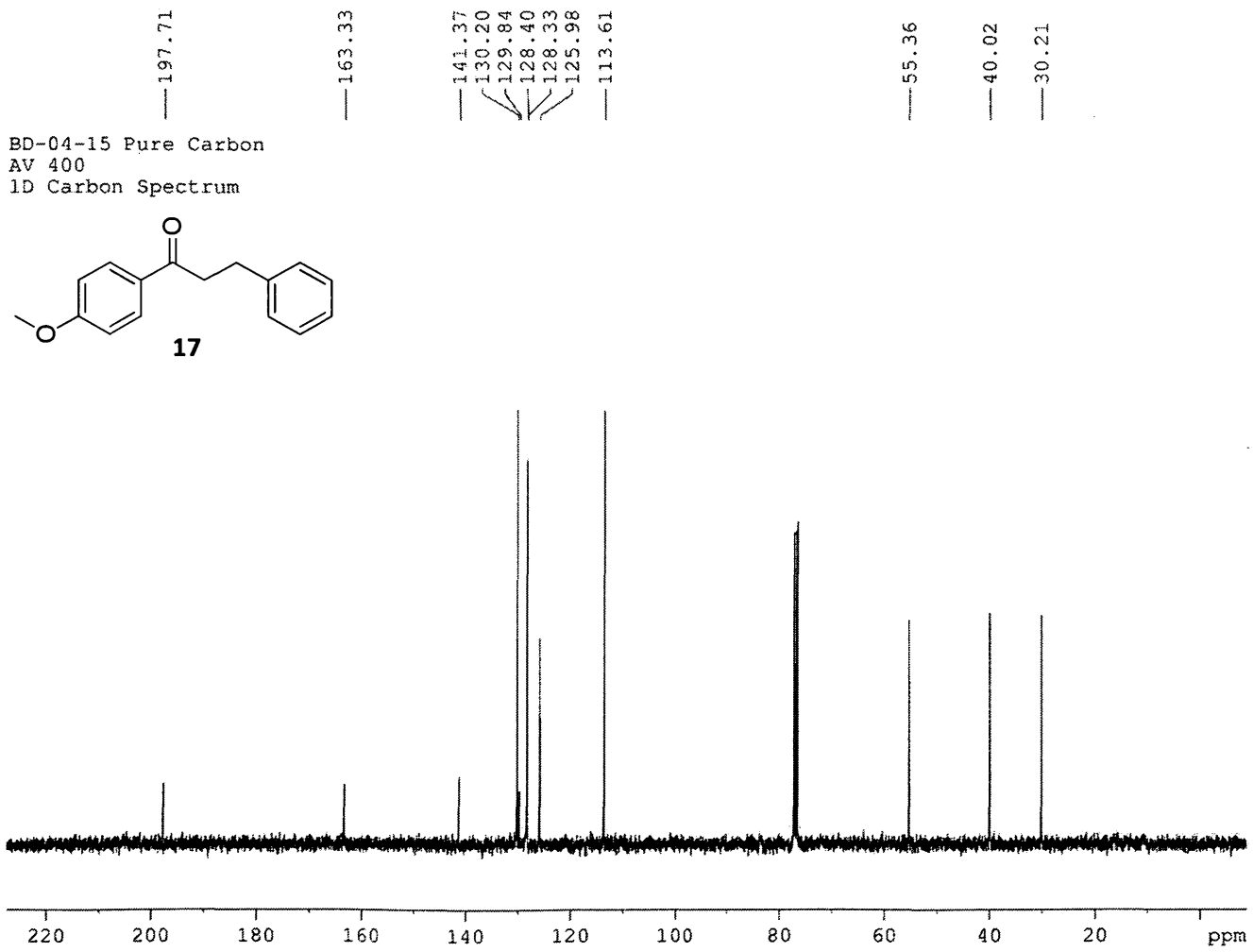
BD-03-93 Pure
AV 300 proton
TMSO
14
7.348
7.326
7.321
7.297
7.281
7.271
7.228
7.206
5.321
2.878
2.830
2.785
2.736
2.159
2.133
2.114
2.095
1.993
1.974
1.677
1.653
1.631
1.613
1.559
1.469
1.458
1.449
1.436
1.424
1.417
1.410
1.391
1.371
1.345
1.187
1.168
1.149
1.135
1.126
4.05
1.45
1.90
1.04
0.99
1.03
2.18
3.06
1.00
1.00
8.87
ppm

BD-03-97+98 Mix1
AV 300 Proton
24a
+
24b
7.260
7.237
7.174
7.157
7.146
7.129
7.124
7.116
3.486
3.433
2.880
2.848
2.795
2.515
2.494
2.471
1.908
1.884
1.862
1.844
1.829
1.812
1.797
1.255
1.031
8.90
2.65
1.00
2.72
3.76
10.96
1.64
ppm

BD-03-95 Pure
AV 300 proton
25
O
7.281
7.256
7.244
7.239
7.222
7.145
7.139
7.118
2.902
2.555
2.528
2.506
2.484
1.867
1.846
1.831
1.816
1.807
1.786
1.776
1.746
1.741
1.588
1.559
1.549
1.053
5.03
2.00
2.13
5.39
1.07
3.04
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm


215.41
BD-03-95 Pure Carbon
AV 300 Carbon
137.59
130.53
127.89
126.26
49.26
43.06
38.84
38.08
27.27
22.76
21.08
25
220
200
180
160
140
120
100
80
60
40
20
ppm


7.985
7.963
7.349
7.330
7.312
7.292
7.283
7.275
7.251
7.233
6.962
6.940
3.889
3.300
3.281
3.260
3.106
3.086
3.067
BD-04-15 Pure
AV 400
1D Proton Spectrum
O
MeO
17
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.95
4.88
1.92
3.03
2.04
2.00

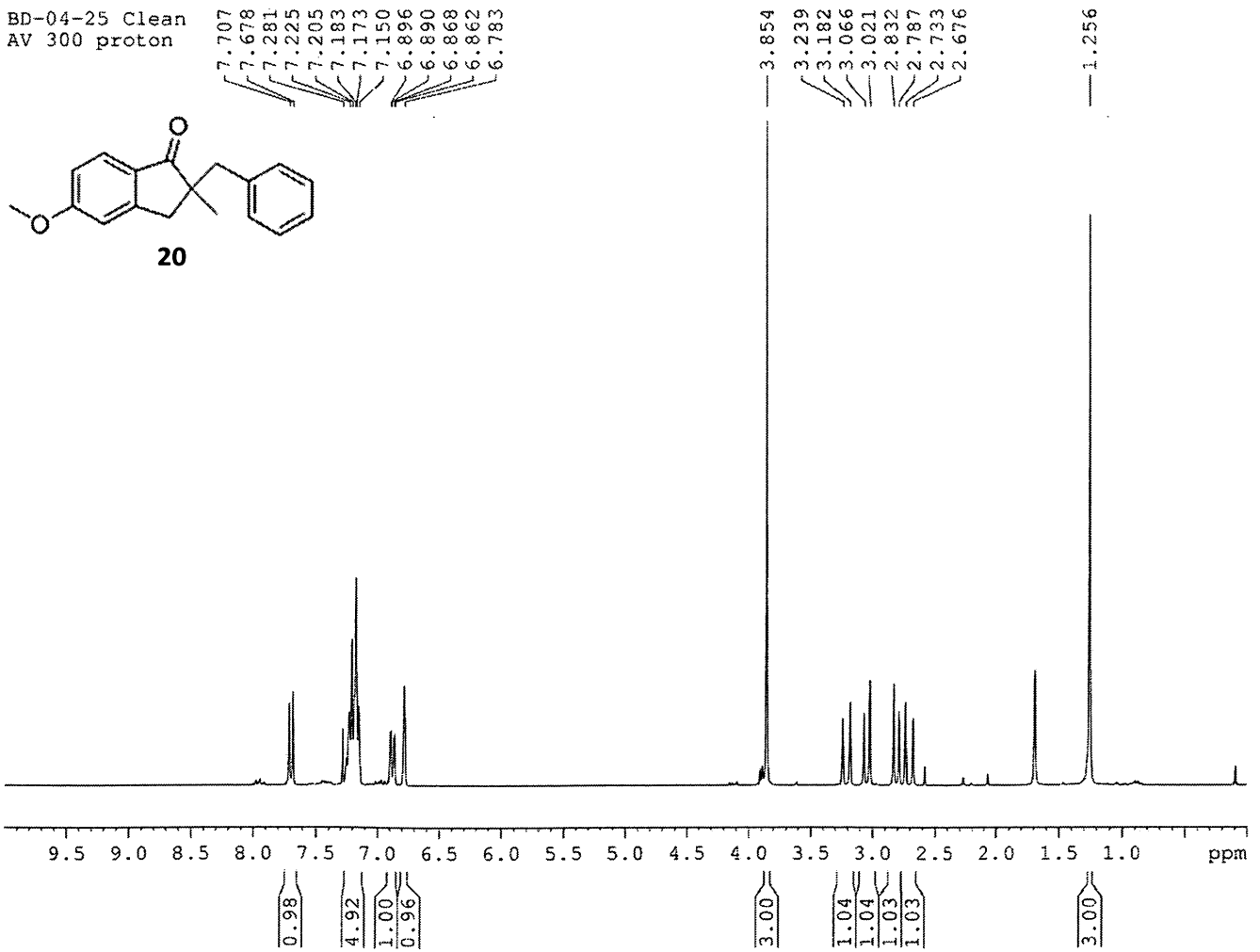

197.71
163.33
141.37
130.20
129.84
128.40
128.33
125.98
113.61
55.36
40.02
30.21
BD-04-15 Pure Carbon
AV 400
1D Carbon Spectrum
O
O
17
220
200
180
160
140
120
100
80
60
40
20
ppm

BD-04-19 Pure
AV 300 proton
18
7.959
7.929
7.286
7.282
7.261
7.230
7.221
7.206
6.956
6.931
6.927
3.882
3.736
3.712
3.209
3.188
3.163
3.142
2.740
2.713
2.694
2.668
1.283
1.223
1.200
1.91
5.17
2.00
3.03
1.00
0.09
0.92
0.11
0.95
2.88
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm

BD-04-20 Crude
AV 400
1D Proton Spectrum
MeO
OTMS
19
8.649
8.639
7.702
7.322
7.316
7.300
7.283
7.226
7.218
7.210
7.202
7.183
7.165
6.889
6.868
6.858
6.836
5.321
3.844
3.818
3.578
3.414
1.702
1.553
0.181
0.175
0.095
0.052
0.007
1.00
0.11
0.54
0.12
6.60
2.25
0.15
2.00
3.14
0.98
1.04
1.70
1.35
1.32
0.97
4.72
3.88
ppm

BD-04-24 Pure
AV 400
1D Proton Spectrum
MeO
TMSO
13
7.518
7.500
7.426
7.408
7.404
7.392
7.323
7.301
7.285
7.268
7.124
7.106
6.957
6.936
6.897
6.876
3.873
3.842
3.149
3.115
2.977
2.942
2.508
2.472
2.006
1.970
1.479
1.464
1.305
1.196
1.182
0.992
0.979
0.806
0.791
0.608
0.058
0.033
1.73
3.70
4.61
0.99
1.93
1.90
1.72
3.00
2.41
0.86
0.85
0.95
0.95
1.02
2.97
0.95
1.16
1.03
2.49
7.73
9.11
ppm

BD-04-24 Pure Carbon
AV 400
1D Proton Spectrum
MeO
TMSO
13
158.53
158.41
141.55
140.61
133.79
133.52
129.80
129.65
129.47
128.99
128.10
128.00
127.87
125.64
125.62
113.36
113.20
113.11
65.50
65.16
55.09
55.04
41.55
39.84
27.38
27.30
24.00
23.32
20.02
17.64
0.96
0.91
220
200
180
160
140
120
100
80
60
40
20
ppm


BD-04-25 Clean
AV 300 proton
7.707
7.678
7.281
7.225
7.205
7.183
7.173
7.150
6.896
6.890
6.868
6.862
6.783
3.854
3.239
3.182
3.066
3.021
2.832
2.787
2.733
2.676
1.256
20
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
0.98
4.92
1.00
0.96
3.00
1.04
1.04
1.03
1.03
3.00

BD-04-25 Clean Carbon
AV 300 Carbon
20
208.99
165.37
155.41
137.97
130.15
128.92
128.02
126.29
125.90
115.32
109.59
55.53
50.45
43.29
38.85
24.77
220
200
180
160
140
120
100
80
60
40
20
ppm

References

[1] Crabtree, R.H The Organometallic Chemistry of the Transition Metals; Wiley: New York, 2009.

[2] Nicolaou, K.C.; Bulger, P.G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442.

[3] King, A.O.; Okukado, N.; Negishi, E. *J. Am. Chem. Soc. Commun.* **1977**, *19*, 683.

[4] Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437.

[5] Miyaura, N.; Suzuki, A.; *Chem. Comm.* **1979**, *19*, 866.

[6] Milstein, D.; Stille, J.K. *J. Am. Chem. Soc.* **1978**, *100*, 3636.

[7] Kosugi, M.; Sasazawa, K.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 301.

[8] Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.

[9] Sonogashira, K. *J. Organomet. Chem.* **2002**, 653, 46.

[10] Heck, R.F. *J. Am. Chem. Soc.* **1969**, *91*, 6707.

[11] Heck, R.F.; Nolley, Jr., J.P. *J. Org. Chem.* **1972**, *37*, 2320.

[12] Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jap.* **1971**, *44*, 581.

[13] Miyaura, N.; Suzuki, A.; *Chem. Rev.* **1995**, *95*, 2457.

[14] Chinchilla, R.; Najera, C. *Chem. Rev.* **2007**, *107*, 874.

[15] Kosugi, M.; Sasazawa, K.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 301.

[16] Casado, A.L.; Espinet, P. *Organometallics.* **1998**, *17*, 954.

[17] Casado, A.L.; Espinet, P. *J. Am. Chem. Soc.* **1998**, *120*, 8978.

[18] Kleiman, J.; Dubeck, M. *J. Am. Chem. Soc.* **1963**, *85*, 1544.

[19] Cope, A.C.; Siekman, R.W. *J. Am. Chem. Soc.* **1965**, *87*, 3272.

[20] Cope, A.C.; Friedrich, E.C. *J. Am. Chem. Soc.* **1968**, *90*, 909.

[21] Lin, Z. Coord. *Chem. Rev.* **2007**, *251*, 2280.

[22] Balcells, D.; Clot, E.; Eisenstein, O. *Chem. Rev.* **2010**, *110*, 749.

[23] Gorelsky, S.I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848.

[24] Alberico, D.; Scott, M.E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174

[25] Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118.

[26] Lafrance, M.; Lapointe, D.; Fagnou, K. *Tetrahedron.* **2008**, *64*, 6015.

[27] Winstein, S.; Traylor, T.G. *J. Am. Chem. Soc.* **1955**, *77*, 3747.

[28] Davidson, J.M.; Triggs, C. *J. Chem. Soc. A.* **1968**, 1324.

[29] Ryabov, A.D.; Sakodinskaya, I.K.; Yatsimirsky, A.L. *J. Chem. Soc. Dalton Trans.* **1985**, 2629.

[30] Boutadla, Y.; Davies, D.L.; MacGregor, S.A.; Poblador-Bahamonde, A.I. *Dalton Trans.* **2009**, *30*, 5820.

[31] Roberts, J.D.; Chambers, V.C. *J. Am. Chem. Soc.* **1951**, *73*, 5030.

[32] Wiberg, K.B. *Angew. Chem. Int. Ed.* **1986**, *25*, 312.

[33] Roberts, J.D.; Chambers, V.C. *J. Am. Chem. Soc.* **1951**, *73*, 3176.

[34] Park, S.-B.; Cha, J.K. *Org. Lett.* **2000**, *2*, 147.

[35] Seebach, D. *Angew. Chemie. Int. Ed.* **1979**, *18*, 239.

[36] Rosa, D.; Orellana, A. *Org. Lett.* **2010**, *13*, 110.

[37] Rosa, D.; Orellana, A. *Chem. Commun.* **2012**, *48,* 1922.

[38] Schweinitz, A.; Chtchemelinine, A.; Orellana, A. *Org. Lett.* **2011**, *13*, 232.

[39] Johnston, K.M.; Shotter, R.G. *Tetrahedron.* **1974**, *30*, 4059.

[40] Boch, R.; Bohne, C.; Netto-Ferreira, J.C.; Scaiano, J.C. *Can. J. Chem.* **1991**, *69*, 2053.

[41] Miller, R.D.; McKean, D.R. *Synthesis.* **1979**, 730.

[42] Olah, G.A.; Narang, S.C. *Tetrahedron.* **1982**, *38*, 2225.

[43] Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron*, **1966**, *7*, 3353.

[44] Ruan, J.; Saidi, O.; Iggo, J.A.; Xiao, J. *J. Am. Chem. Soc.* **2008**, *130*, 10510.

[45] Samanta, S.; Mishra, B.K.; Pace, T.C.S.; Sathyamurthy, N.; Bohne, C.; Moorthy, J.N. *J. Org. Chem.***2006**, *71*, 4453.

[46] Han, X.; Wang, X.; Pei, T.; Widenhoefer, R.A. *Chem. Eur. J.* **2004**, *10*, 6333.