University of Alberta

Synthesis of Tetrakis(aryl)ethene Ligands

by

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Your file Votre référence
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To my Father David, my sister Belinda,

my lovely girlfriend Farahnaz and

The memory of my mother.

Abstract

A series of *ortho*-substituted diaryl ketones were subjected to McMurry conditions with the goal of producing tetrakis(2-methoxyaryl)ethenes that could be used as ligands. Most of the ketones tested did not produce the desired product possibly due to steric effects, however, bis(3-methoxy-2-naphthyl)methanone **59** coupled efficiently.

An important related synthetic target is tetrakis(2,6-dimethoxyphenyl)ethene **77** due to its ability to both coordinate to a metal and covalently bond to a silica surface. Barton-Kellogg olefination methodology was used in an attempt to synthesize **77**.

Attempts were made to make a thiol derivative of the tetrakis(2-methoxyphenyl)ethene ligand system. The scheme replied upon the reactivity of $AlCl_3$ and EtSH with a methoxy naphthyl compound. Unfortunately, this reaction did not work on sterically hindered structures.

Acknowledgements

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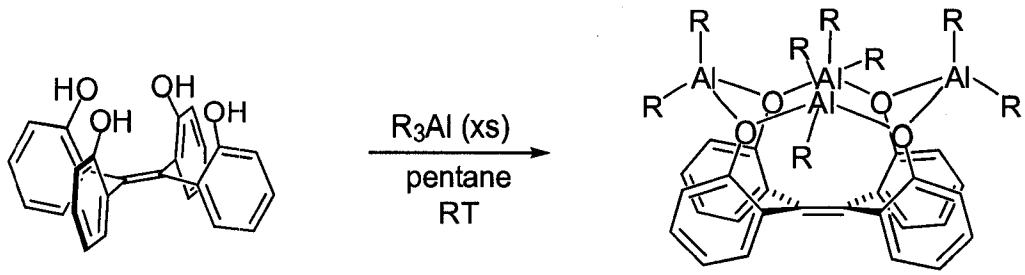
Chapter 1.1 Global Introduction

This project focused on the synthesis of structurally preorganized, multidentate ligands that bind to two or more metals and hold them in close proximity to each other. These ligands are also potentially useful in any catalytic process that involves a bimetallic mechanism. A flat portion of the "oxo" surface, typical of silica supported heterogeneous coordination catalysts, can be modeled by such structurally preorganized, multidentate ligands. The ligands are also potentially useful for chelation to metallic nanoparticles and general supramolecular chemistry.

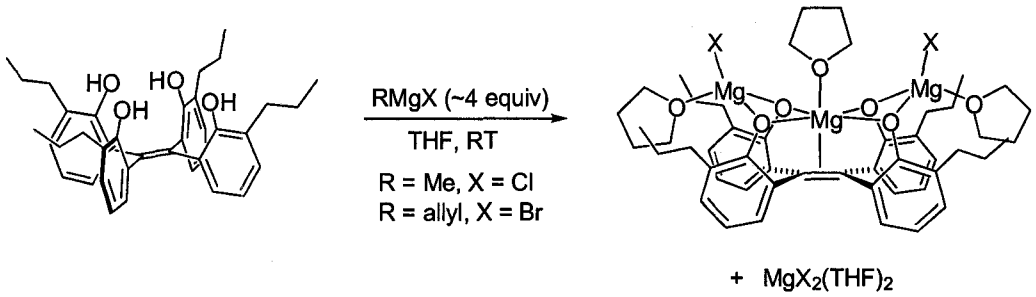
A silica surface contains many hydroxyl groups that can bind to metals producing supported metal catalysts. This silica surface has a random character and is difficult to characterize. The desired tetrahydroxy ligands serve as simple characterizable model for the silica surface as exemplified by the alkyl aluminum case (**Figure 1**).[11]

Figure 1. Tetrahydroxy Ligand Bonded to Aluminum

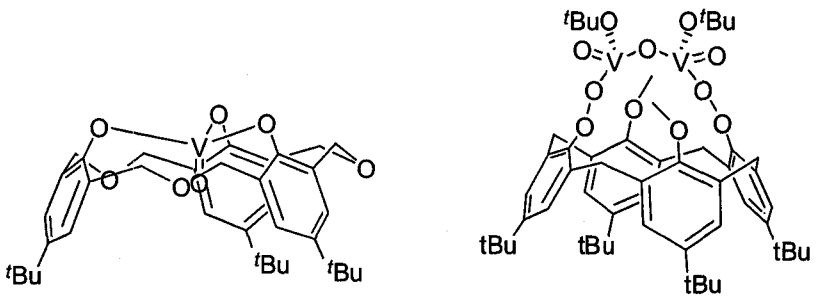


Variations in the ligands can demonstrate how changes in the steric bulk around the metal affect catalysis. For example propyl groups can be added to the 3-position (**Figure 2**).[11]

Figure 2. Tetrahydroxy Ligand Bonded to Magnesium



Calix[4]arenes are an important class of ligands with multiple binding sites that can bond to different metals. There is, however, a great deal of flexibility in the structural framework of calixarenes.[1] Vanadium oxacalix[3]arene complexes and vanadium calix[4]arene complexes were used in polymerization studies by Redshaw, *et al.*[2] In the following representative examples, two vanadium metals were complexed to a calix[4]arene **2** while only one vanadium metal complexed to an oxacalix[3]arene **1** (**Figure 3**).



1 **2**

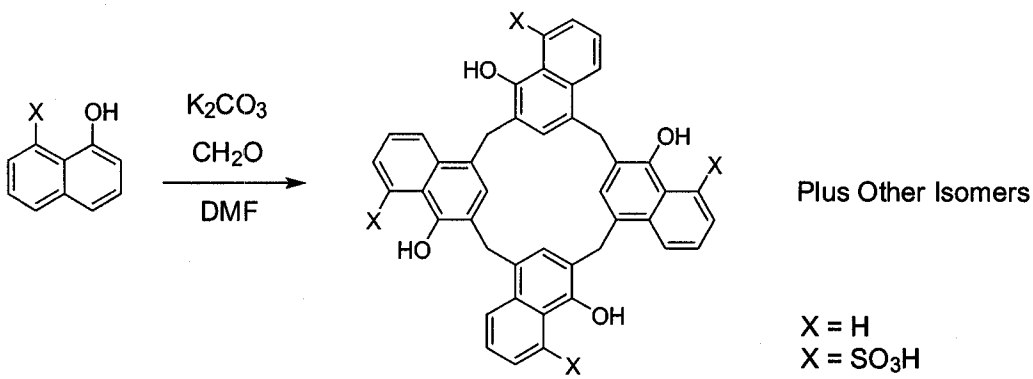
Figure 3. Vanadium Calixarene Complexes

These complexes were used with dimethylaluminumchloride (DMAC) and the reoxidizing agent ethyltrichloroacetate (ETA) to polymerize ethylene and copolymerize polypropylene.[2]

Some additional examples of metallic calix[4]arene complexes contain the metals tungsten,[3] molybdenum,[4] niobium,[5] and tantalum.[5] Of particular importance to polymerization are titanium calix[4]arene complexes.[6, 7]

One of the newer additions to the family of calix[4]arene ligands is the calix[4]naphthalene system. Calix[4]naphthalene compounds **3** have been synthesized from 1-methoxynaphthalene and formaldehyde in a condensation reaction (**Eq. 1**).[8] A new calix[4]naphthalene structured around 2-methoxynaphthalene was also synthesized.[9] Sulphonated calix[4]naphthalene compounds were prepared for improved water solubility.[10]

Equation 1. Synthesis of Calix[4]naphthalenes



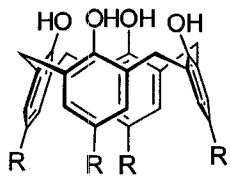
3

More recently the Stryker group has developed the tetrakis(2-hydroxyphenyl)ethene ligand system. The ligand is superficially similar to

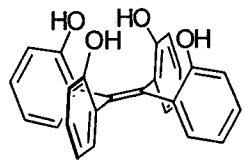
calix[4]arenes, except that all four phenols are rigidly bound to an ethene (**Figure 4**).[11] There is still free rotation of the phenyl groups, however, irrespective of whether the oxygen atoms are directed above or below the double bond, the oxygen atoms are always directed inwards towards the center of the compound. In the case of the calix[4]arene ligand, it is possible for the arene to twist and place some of the oxygen sites pointing away from the center of the ligand. Also, in a calix[4]arene ligand, the phenyl groups can pivot, giving "collapsed" chelating complexes with only one complexed metal or low nuclearity clusters.

In order for the sterically hindered environment around a double bond to be predictable, the double bond has to remain planar, that is, without significant diradical character that could distort the geometry of the ligand framework. Morton, et al., has shown that steric crowding around the double bond does not cause distortion of the double bond geometry. For example, Raman measurements of 1,2-diisopropyl-1,2-dimethylethene and tetraisopropylethene showed a very small shift of $\Delta\nu = 8$ cm^{-1} in the alkene stretching frequency, which is not a large enough shift to suggest significant distortion of the double bond.[12]

An additional advantage of the tetrakis(2-hydroxyphenyl)ethene ligand system is that fourfold substitution at the 3-position allows steric bulk to be introduced adjacent to the metal binding center. This creates a sterically isolated, well defined, binding site for the metals.



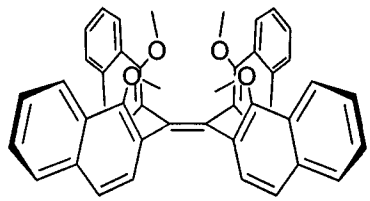
Calix[4]arene



Tetrakis(2-hydroxyphenyl)-ethene

Figure 4. Calix[4]arene vs. Tetrakis(2-hydroxyphenyl)ethene

We became interested in synthesizing tetrakis(hydroxynaphthyl)ethene variants of the tetrakis(2-hydroxyphenyl)ethene system. Of particular interest were compounds based on the tetrakis(1-methoxy-2-naphthyl)ethene ligand system, **4**, because the annulated benzene ring and the hydrogen at the 8-position provides some steric hindrance around the metal binding center (**Figure 5**).

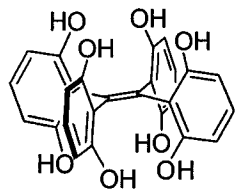


4

Figure 5. Tetrakis(1-methoxy-2-naphthyl)ethene **4**

Other interesting variants of the tetrakis(2-hydroxyphenyl)ethene ligand include ligands that incorporate nitrogen or sulphur binding sites instead of oxygen, which allows for the bonding of different metal systems. This methodology requires either nitrogen- or sulphur- substituted benzophenone compounds or a transformation that allows the substitution of nitrogen or sulphur for the oxygen on the tetrakis(hydroxynaphthyl)ethene ligand.

Another long standing interest in the Stryker group is the target tetrakis(2,6-dihydroxyphenyl)ethene, **5** (**Figure 6**).



5

Figure 6. Tetrakis(2,6-dihydroxyphenyl)ethene **5**

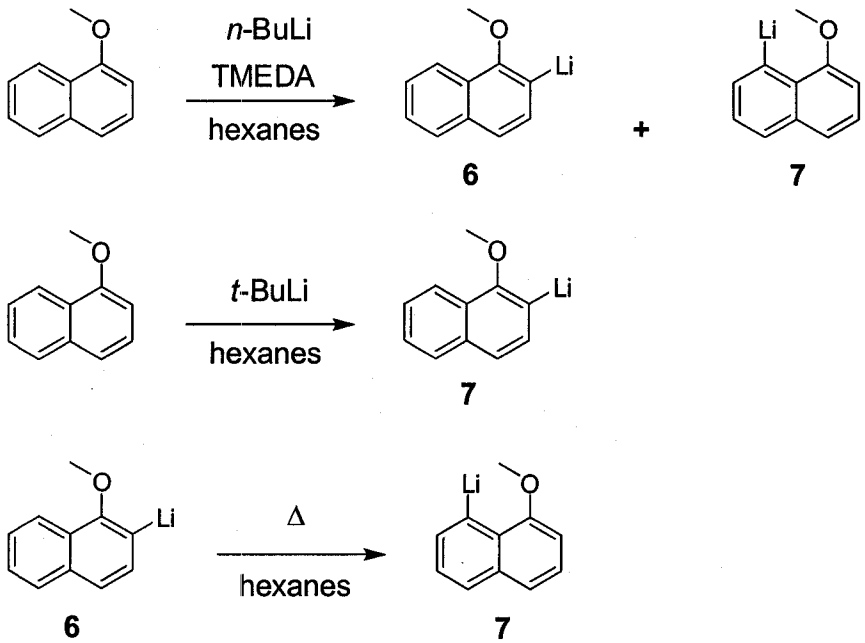
This compound allows connectivity with metals or an electrophilic surface both above and below the ethene. It is possible that the hydroxyl groups on one face of the double bond can react in a condensation reaction with a dehydrated silica surface, while the hydroxyl groups above the ethene bind to an array of metals. In the Stryker group, Dr. Chung has previously shown that this compound cannot be made via the McMurry reaction.

Chapter 1.2 Methods for the synthesis of diarylketones, sterically hindered ethenes, and other useful transformations

Irrespective of whether the McMurry reaction or some other olefination methodology is used to make the desired ligand, the required starting materials are the corresponding diaryl ketones. In most cases, these diaryl ketones are made from an organolithium reagent and the appropriate electrophile.[13] The selective lithiation of 1-methoxynaphthalene is required in order to produce the desired bis(1-methoxy-2-

naphthyl)methanone. Bauer and Betz studied the regioselective lithiation of 1-methoxynaphthalene (**Scheme 1**).[14]

Scheme 1. The lithiation of 1-methoxynaphthalene

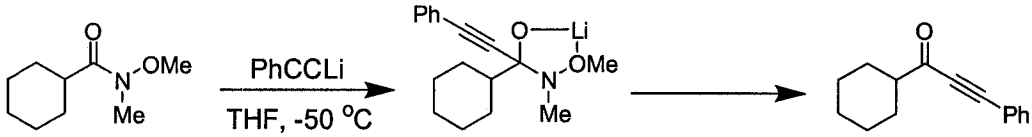


The lithiation of 1-methoxynaphthalene with *n*-BuLi predominantly produces lithio-1-methoxynaphthalene, **6**, over 8-lithio-1-methoxynaphthalene, **7**, while lithiation with *t*-BuLi produces **7** exclusively. Furthermore, the fact that **6** can be converted into **7** with heat suggested that **6** is the kinetic product while **7** is the thermodynamic product (**Scheme 1**). There is no kinetic isotope effect suggesting that deprotonation cannot be the rate determining step. Computational studies suggest that the rate determining step involves chelation with the TMEDA/*n*-BuLi complex.[14]

Synthesis of unsymmetrical diaryl ketones require a carboxylic acid derivative that can react with an organometallic reagent without over-reacting to give the

alcohol. When an organometallic reagent such as lithium phenyl acetylide reacts with a "Weinreb amide", the methoxy group stabilizes the intermediate, preventing the addition of a second equivalent of lithium phenyl acetylide (**Eq. 2**).[13] Unfortunately, this same intermediate, which prevents a second addition of lithium phenyl acetylide, also causes autoinhibition by forming cluster complexes with lithium phenyl acetylide, thus preventing the phenyl acetylide from reacting with the amide starting material.[13]

Equation 2. Using a Weinreb Amide to Make Ketones



The majority of the desired substrates for the McMurry reaction are symmetrical. The addition of two equivalents of an organolithium or Grignard reagent to an *N*-methoxy-urea allows the direct synthesis of a symmetrical ketone. This reagent produces similar intermediates as the previously discussed Weinreb amide (**Eq. 3**).[15]

Equation 3. Using a *N*-methoxy Urea Reagent to Make Ketones

X = OEt, CH_3NOCH_3, $N(CH_3)_2$

Tetrathiol ligands based on the tetraphenylethene framework would be highly desirable as a new ligand system. Work by Fujita, et al., suggests that a possible route to these tetrathiol ligands could involve the use of $AlCl_3$ to displace methoxy

groups on methoxynaphthalene compounds with a mercaptoethyl group (**Scheme 2**).[17] The use of $AlCl_3$ as both a Lewis acid and one electron oxidant allows ethanethiol to displace the methoxy functional group in methoxypolyaromatic compounds. This reaction was found serendipitously, as a mixture of $AlCl_3$ and EtSH had previously been used to deprotect anisoles. However, Fujita found that in the case of methoxynaphthalene, complete replacement of the methoxy functionality occurred (**Scheme 2**).[16] The difference in reactivity between methoxyphenyl and methoxynaphthalene is probably due to the fact that it is easier for naphthalene to lose aromaticity in one of the two aromatic rings than for a single benzene ring to lose its aromaticity (**Figure 7**).

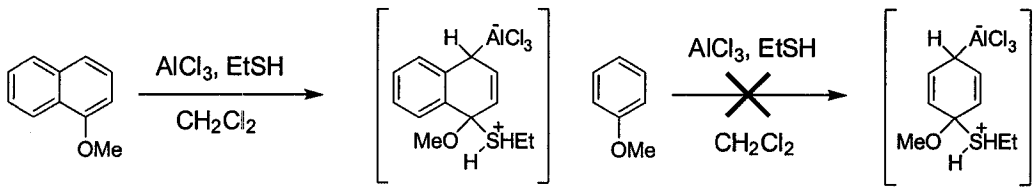
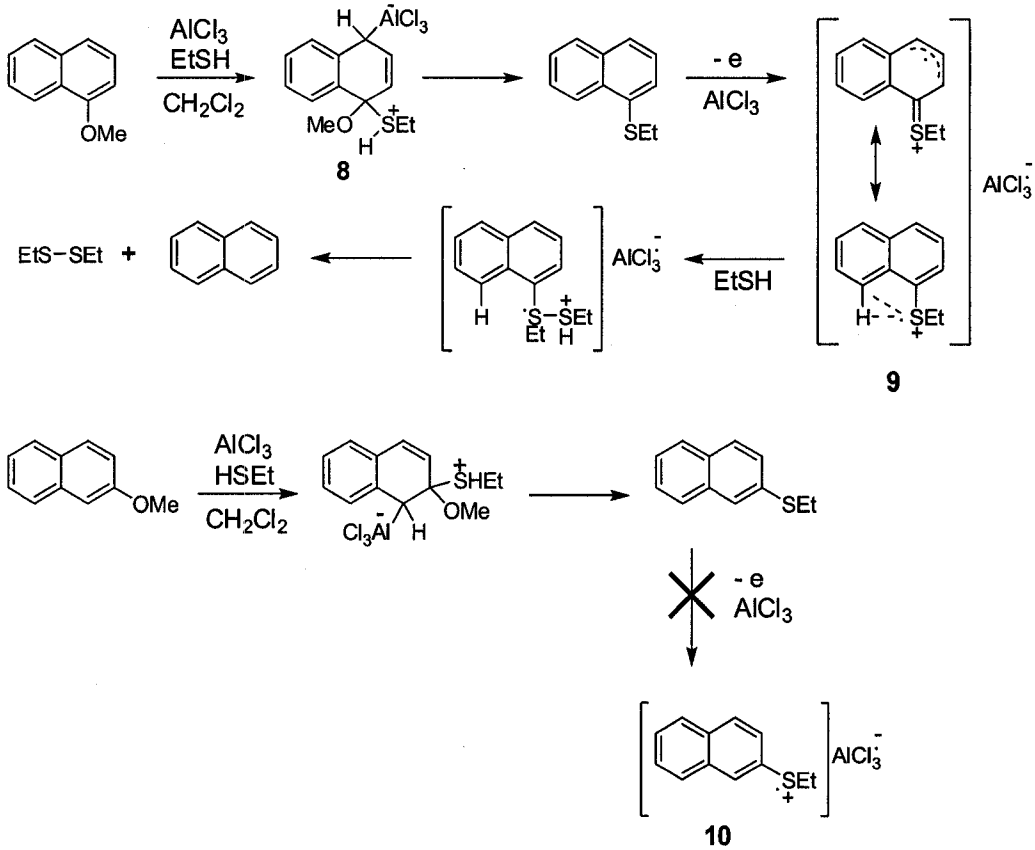


Figure 7. Methoxynaphthalene vs. anisol reactivity

In the case of 1-methoxynaphthalene, two equivalents of $AlCl_3$ alone with EtSH converts the starting material to naphthalene (**Scheme 2**).[17] The mechanism of this reaction involves $AlCl_3$ initially acting as a Lewis acid, allowing attack of the ethanethiol to the naphthalene to form the intermediate **8**. The authors propose that the radical cation **9** is stabilized by the neighbouring CH bond long enough for it to react with a second equivalent of EtSH. In the case of 2-methoxynaphthalene, there is no corresponding CH bond in the intermediate **10** to stabilize the radical cation, so

the reaction stops at ethyl 2-naphthyl sulfide and does not react further to form naphthalene (**Scheme 2**).[17]

Scheme 2. Mechanism: Methoxynaphthalene with $AlCl_3$ and ETSH[17]

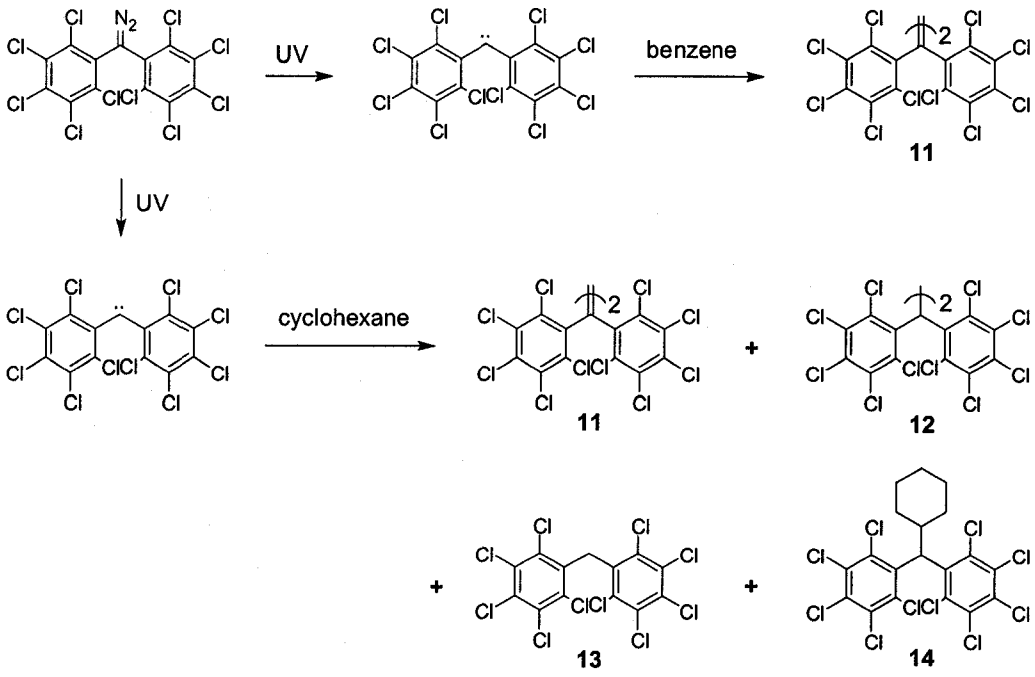


This suggests that this reaction might theoretically work better on tetrakis(3-methoxy-2-naphthyl)ethene **68** than tetrakis(1-methoxy-2-naphthyl)ethene **4**, which could potentially react completely to give tetranaphthylethene (**Equation 26**).

Another interesting method of forming very sterically hindered double bonds involves the use of carbenes. Tomioka, et al., has shown that uv irradiation of sterically hindered diaryldiazomethanes in benzene form diarylcarbene intermediates, which then couple to form ethenes in high yields (**Scheme 3**).[18] This carbene

dimerization chemistry was first introduced by Zimmerman, et al.[19] When the reaction was carried out in cyclohexane a mixture of products was isolated, including the ethene **11**, ethane **12**, methane **13** and a fourth product **14** produced via carbene insertion into a cyclohexane CH bond (**Scheme 3**).[18]

Scheme 3. The coupling of diaryl carbenes to form tetraaryl ethenes



Although it would be interesting to attempt this reaction on 1,1'-(diazomethylene)bis-(2-methoxybenzene) in benzene, the resulting carbene **15** would most likely insert into the methoxy functionality causing cyclization (**Figure 8**).

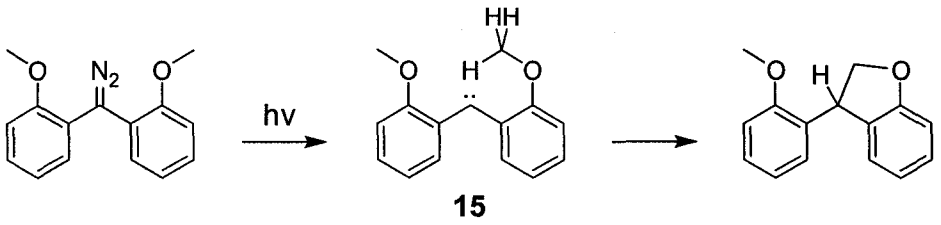
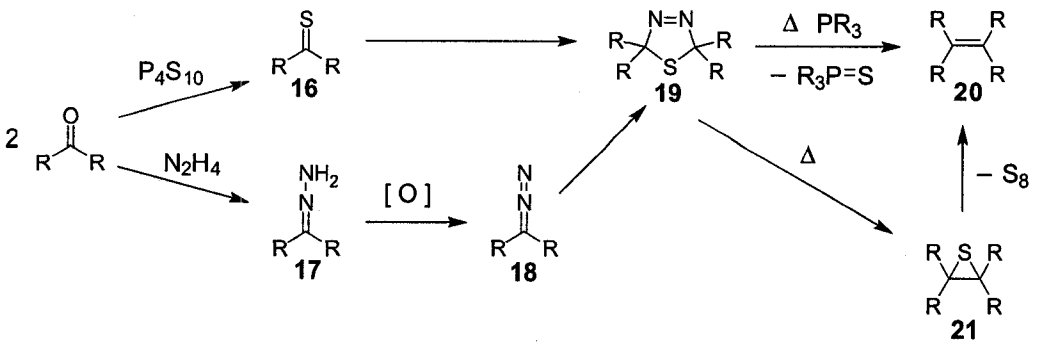


Figure 8. Proposed Unwanted Carbene Cyclization

Ever since the early 1970's the Barton-Kellogg olefination methodology has been known for its ability to make sterically hindered, highly substituted olefins (**Scheme 4**).[20, 21]

Scheme 4. Barton–Kellogg Methodology **1**



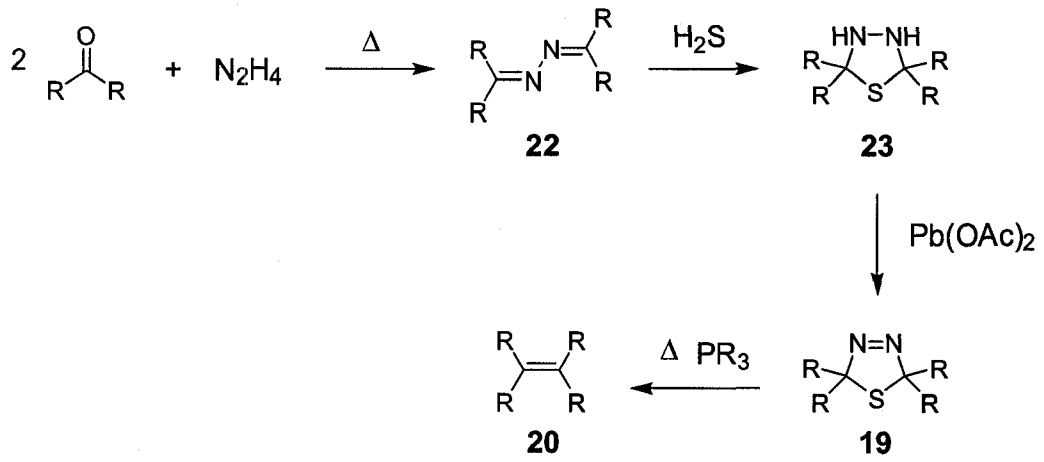
The general success of this methodology makes it attractive for the synthesis of the desired tetrakis(2,6-dihydroxyphenyl)ethene ligand; however, the drawback of this methodology is that more steps are required compared to the McMurry reaction. There are a large number of variations of this reaction, but they all involve the formation of a double bond via the collapse of a heterocyclic ring and the release of two small stable components. Often one of the released components is a gas such as

nitrogen or carbon dioxide and the other released component is an atom such as sulphur which aggregates further into its elemental form S_8.[20 21]

Reactions involving the loss of nitrogen are the most commonly used variants of the methodology; however, there are two common schemes used to form the needed 1,3,4-thiadiazoline five membered ring **19**. One method requires a diazo compound **18** and a thioketone **16**, which react to form the needed 1,3,4-thiadiazoline five membered ring **19**. A reaction between the ketone and P_4S_{10} forms the thioketone **16.** A separate reaction between a ketone and hydrazine forms the hydrazone **17** which is then oxidized to the corresponding diazo compound **18**. Combining the thioketone and the hydrazone forms the 1,3,4-thiadiazoline five membered ring **19**, which then reacts with a phosphine and heat to form the desired ethene **20**. If this last step is done without a phosphine then thiirane **21** is produced (**Scheme 4**).[20] This version of the Barton Kellogg methodology has been used to couple ketones of various different substitution patterns to form the desired olefins, but there is no control over which isomers are formed.[22]

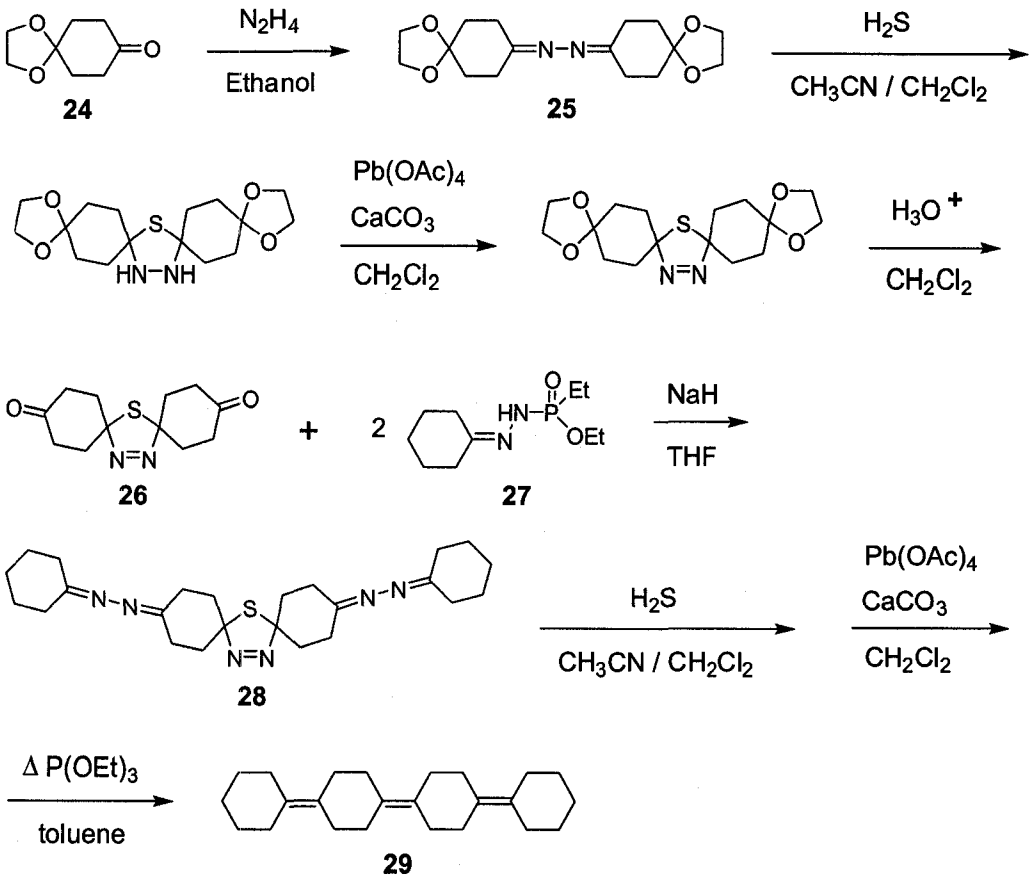
The second common method is to synthesize an azine **22** from two equivalents of a ketone and one equivalent of hydrazine.[23] A reaction between **22** and H_2S forms thiadiazolidine **23**. Thiadiazolidines **23** are oxidized to the desired thiadiazoline **19** with $Pb(OAc)_4$. The thiadiazoline then reacts thermally with a phosphine to produce the desired ethene **20**, similar to the former described method (**Scheme 5**).[23]

Scheme 5. Barton-Kellogg Methodology **2**



One practical example of this methodology has been used in the synthesis of oligo(cyclohexylidenes) (**Scheme 6**).[24] For example, Tetracyclohexylidene **29** was synthesized starting with a reaction between two equivalents of 1,4-cyclohexadione mono(ethylene ketal) **24** and hydrazine to make the corresponding azine **25**. This azine was treated with hydrogen sulfide, lead tetraacetate, and aqueous acid to make the deprotected thiadiazoline 7-thia-14,15-diazadispiro[5.1.5.2]pentadec-14-ene-3,11-dione **26**. This framework was extended by treating the thiadiazoline with two equivalents of cyclohexanone diethoxyphosphinylhydrazone **27** and NaH to produce 3,11-bis(cyclohexylidenehydrazono)-7-thia-14,15-diazadispiro[5.1.5.2]pentadec-14-ene **28**. This compound was then mixed with hydrogen sulfide, lead tetraacetate and triethylphosphite to produce the desired tetracyclohexylidene **29** (**Scheme 6**).[24] It is interesting to note that the last three reactions involve the enactment of three concurrent Barton-Kellogg reactions in the same molecule.

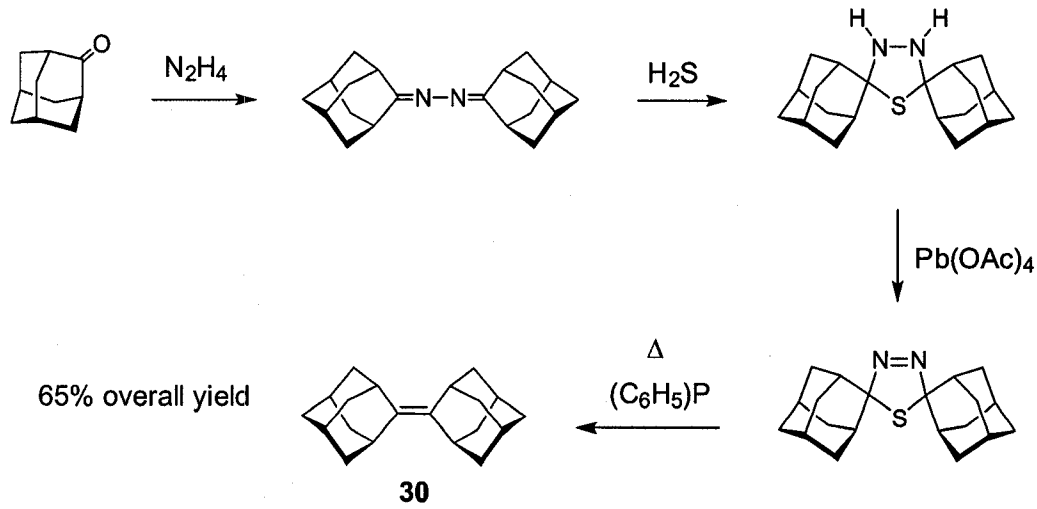
Scheme 6. Synthesis of tetracyclohexylidene **29**



24 **25** **26** **27** **28** **29**

The synthesis of the more sterically hindered adamantylideneadamantane **30** via this same variant of the Barton-Kellogg olefination shows the diversity of the reaction. It is particularly impressive because the yield is 65% over the four steps (**Scheme 7**).[23]

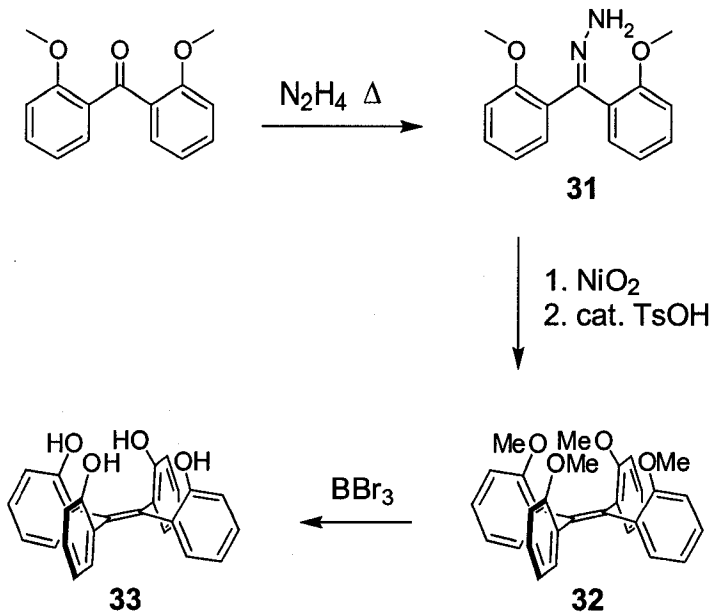
Scheme 7. Synthesis of Adamantylideneadamantane **30**



30

Stryker and coworkers initially described the synthesis of tetrakis(2-hydroxyphenyl)ethene ligands by the following series of reactions (**Scheme 8**).[11]

Scheme 8. Synthesis of Tetrakis(2-hydroxyphenyl)ethene **33**



31

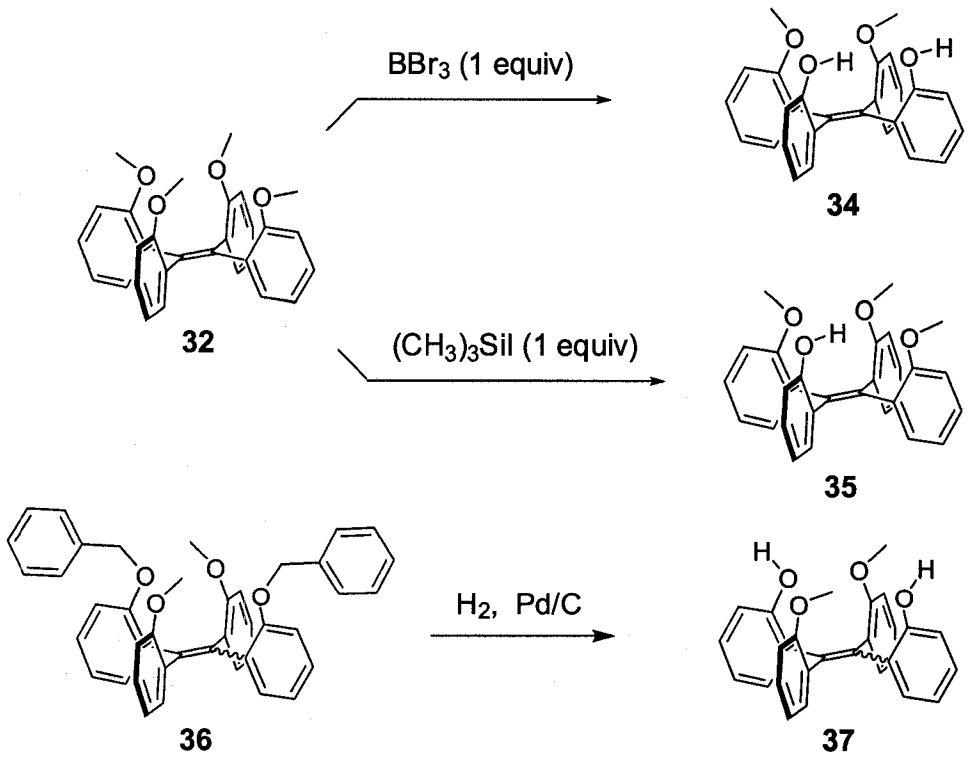
33

32

2,2'-Dimethoxybenzophenone was treated with hydrazine hydrate to form the corresponding hydrazone **31**. The hydrazone was oxidized to the corresponding diazo compound with NiO_2 and then further treated with catalytic TsOH to form the desired tetrakis(2-methoxyphenyl)ethene **32**. Deprotection using BBr_3 afforded the parent tetraphenol **33**. A limitation of this methodology is that benzophenone compounds with substitution ortho to the methoxy groups fail to form the hydrazone (**Scheme 8**).[11]

The (*E*)- and (*Z*)-1,2-disubstituted bis(ether) derivatives of tetrakis(2-hydroxyphenyl)ethene were also synthesized by Fujita and Qi in the Stryker group (**Scheme 9**).[25]

Scheme 9. Partial Deprotection of **32** and **36**



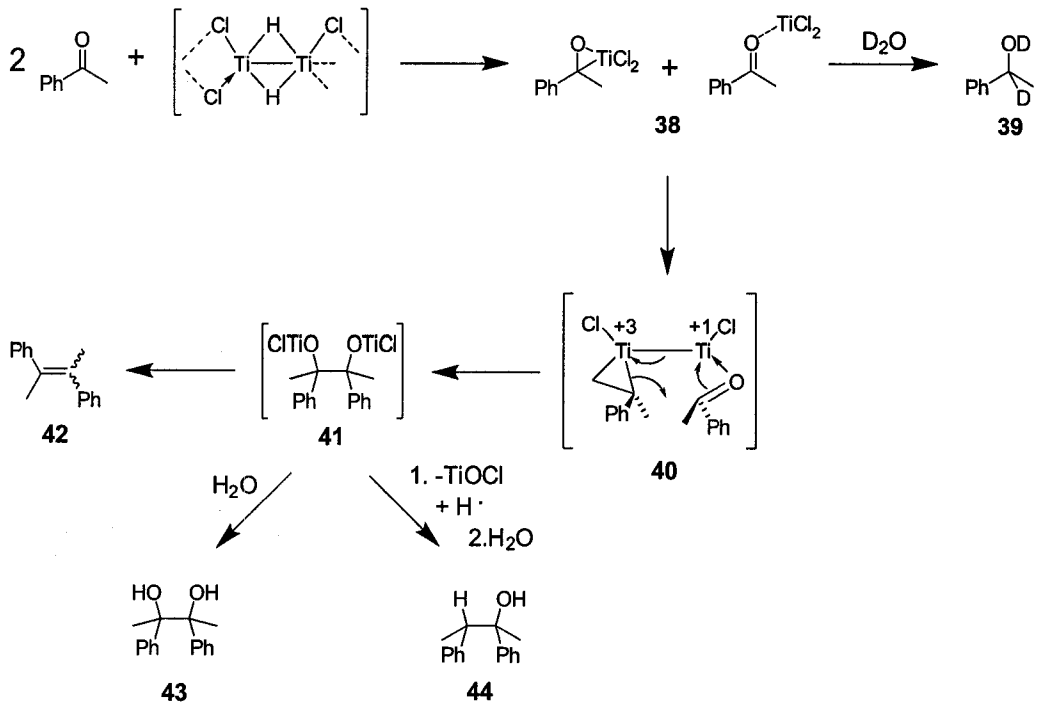
(*Z*)-1,2-bis(2-hydroxyphenyl)-bis(2-methoxyphenyl)ethene **34** was synthesized from tetrakis(2-methoxyphenyl)ethene **32** by using one equivalent of BBr_3. The tris (ether) derivative of tetrakis(2-hydroxyphenyl)ethene **35** was produced from tetrakis(2-hydroxyphenyl)ethene **32** by addition of one equivalent of TMSI, although with poor conversion. A mixture of (*E*)- and (*Z*)-bis(2-benzyloxyphenyl)-bis(2-methoxyphenyl)ethene **36** produced by the method shown in Scheme 8 reacts with hydrogen over Pd/C to produce predominantly the (*E*) isomer of the bis(ether) derivative of tetrakis(2-hydroxyphenyl)ethene **37** (**Scheme 9**).[25]

The synthesis of the ligands through the hydrazone intermediate (**Scheme 8**) proceeds in moderate to good yields, but requires several steps from the ketone.[11] The McMurry reaction has the advantage of requiring only one step for the synthesis of the carbon-carbon double bond from the ketone, but this reaction was, until recently, not successful in the case of 2,2-disubstituted benzophenoness.[33]

Chapter 1.3 A Review of the McMurry Olefination Reaction

Much of the mechanistic elucidation of the McMurry olefination reaction performed with $TiCl_3$ and Zn/Cu has been reported by Bogdanovi and Bolte.[26] The authors were able to make and characterize the McMurry reagent, $[HTiCl(THF)_{0.5}]_x$, by the reaction of $TiCl_3(THF)_3$ with MgH_2. The reaction of $[HTiCl(THF)_{0.5}]_x$ and acetophenone produced 2,3-diphenyl-2-butene **42** in 70% yield (**Scheme 10**).

Scheme 10. McMurry Reaction: A Nucleophilic Mechanism



Quenching the reaction with D_2O after a short reaction time produced dideutero-1-phenylethanol, **39**, supporting the concept of $TiCl_3$ binding side-on to the ketone.[26] Also, when the reaction is quenched with H_2O at a later time, the pinacol **43** is produced, suggesting that the bis(alkoxide) **41** is an intermediate on the mechanistic pathway to the ethene.[26]

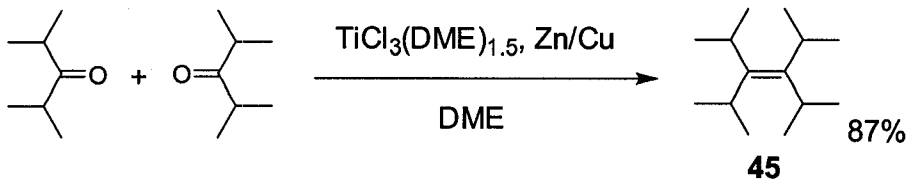
The side-on intermediate for the ketone/$TiCl_3$ complex suggests a nucleophilic possibility for the coupling of two ketones in the McMurry reaction, as shown in the transition state "structure" **40** (**Scheme 10**).[26]

An interesting side product produced from the coupling of acetophenone was 2,3-diphenyl-2-butanol, **44,** which is formed by over-reduction (**Scheme 10**).[26] This would require the replacement of a titanium alkoxide moiety complex by a hydrogen atom, presumably by a free radical process.

Bogdanović and Bolte also studied mechanistic aspects of the McMurry reaction conducted by using $TiCl_3(DME)_{1.5}$ and Zn/Cu.[26] They found that after heating a mixture of $TiCl_3(DME)_{1.5}$ and Zn/Cu in DME for 20 hours, the powder X-ray diffraction of the "product" revealed only unreacted starting materials.[26] This shows that $TiCl_3(DME)_{1.5}$ and Zn/Cu do not react in the absence of a soluble ketone substrate, which is not surprising as two heterogeneous solids generally do not react efficiently with each other. This is further exemplified by comparisons of the reduction potential of Ti (III) (E_o = - 1.62 V) compared to some of the reducing agents used: Zn (E_o = - 0.76 V), Fe (E_o = - 0.44 V), and Sn (E_o = - 0.14), none of which are strong enough to reduce Ti(III).[26] However, these reducing agents are apparently, strong enough to reduce the ketone Ti(III) complex.

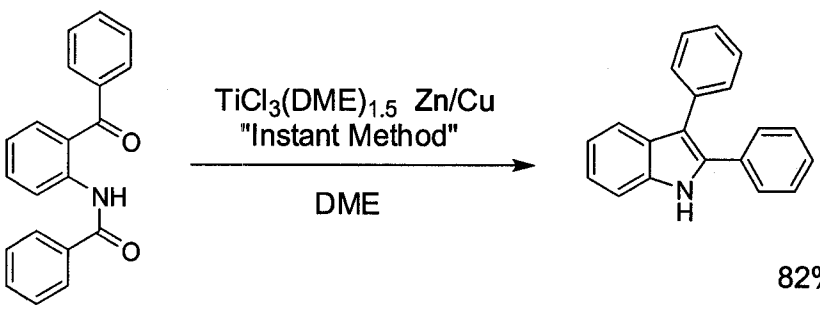
Because the McMurry reaction has had a problematic history of technical challenge and results that are difficult to reproduce, McMurry, *et al.*, published an optimized procedure for reactions that use $TiCl_3(DME)_{1.5}$, Zn/Cu, and DME.[27] In this optimized procedure, the McMurry reagent mixture is heated in DME at reflux before the ketone is added to the reaction mixture. An advantage of this procedure is that all of the reagents involved can be freshly prepared. The McMurry reaction can also be quite sensitive to the quality of the titanium compound. The $TiCl_3(DME)_{1.5}$ is made from titanium powder and $TiCl_4$ in DME, while the Zn/Cu can be made from Zn (s) and $CuSO_4$ in H_2O. A great example of this methodology is the synthesis of the very sterically hindered tetraisopropylethene **45** from diisopropyl ketone in excellent yields (**Equation 4**).[27] above

Equation 4. Tetraisopropylethene **45**



In 1994 Fürstner, *et al.*, published a new variant of the optimized McMurry reaction in which the ketone, $TiCl_3(DME)_{1.5}$, and Zn/Cu are all mixed together from the very beginning of the reaction, inspiring the label "Instant Method" (**Equation 5**).[28]

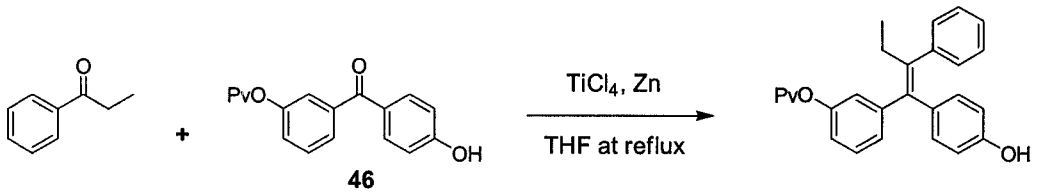
Equation 5. "Instant Method" McMurry olefination



This variation allows for the intramolecular synthesis of indole compounds from an oxo amide. The authors speculate that complexation of the ketone prior to reduction improves the overall performance of the reaction (**Equation 5**).[28]

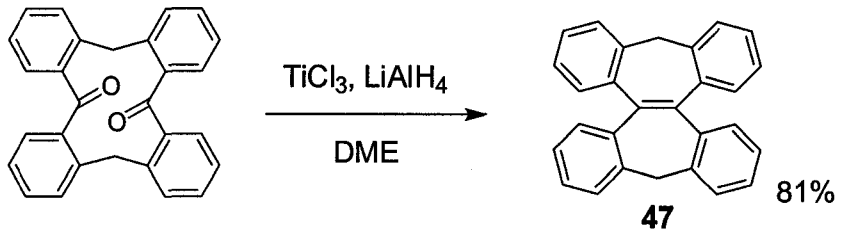
Using a large excess of McMurry reagent, Gauthier, et al., were able to accomplish a cross McMurry olefination reaction involving a benzophenone compound that has an unprotected hydroxyl group at the para position **46** (**Equation 6**).[29] Perhaps the excess of McMurry reagent made up for the fact that one of the substrates had an acidic phenolic functional group.

Equation 6. McMurrry Reaction with a Phenolic Substrate



Lee, *et al.,* performed a McMurry reaction on a 2,2' bridged dibenzophenone compound **47** and obtained an 81% yield (**Equation 7**).[30]

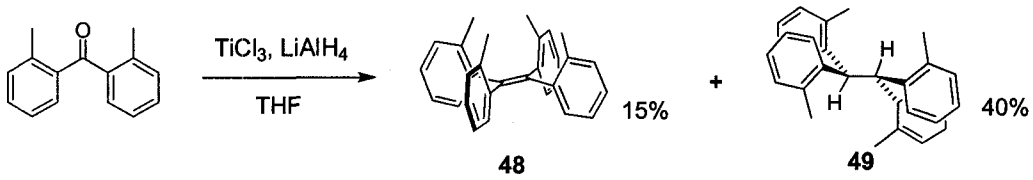
Equation 7. An ortho-bridged Tetraphenylethene



The synthesis of the coupled product was merely an afterthought. The synthesis of this ethene via the McMurry reaction is an example of constructing a hindered ethene from ortho substituted benzophenones. However, in this intramolecular case, the two carbonyl groups are already forced into close proximity to each other, aiding the reaction.[30]

Geise, *et al.*, performed a McMurry reaction on 2,2'-dimethylbenzophenone using $TiCl_3$, $LiAlH_4$ and cyclohexene, producing 15% of tetrakis(2-tolyl)ethene **48** and 40% of tetrakis(2-tolyl)ethane **49** (**Equation 8**).[31] Unlike the previous example, this intermolecular reaction does not benefit from a proximity effect and thus gave substantially lower yields.

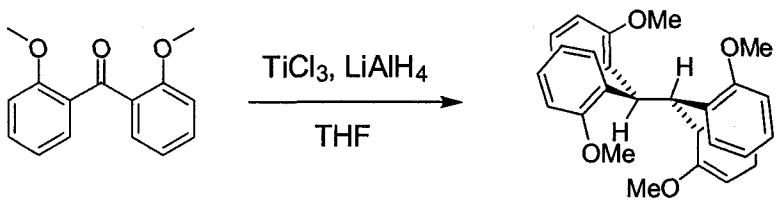
Equation 8. Tetrakis(2-tolyl)ethene **48** and Tetrakis(2-tolyl)ethane **49**



48 49

Vögtle, *et al.*, reported that the reaction of 2,2'-dimethoxybenzophenone with $TiCl_3/LiAlH_4$ results only in the formation of tetrakis(2-methoxyphenyl)ethane **50** (**Equation 9**).[32]

Equation 9. Tetrakis(2-methoxyphenyl)ethane **50**

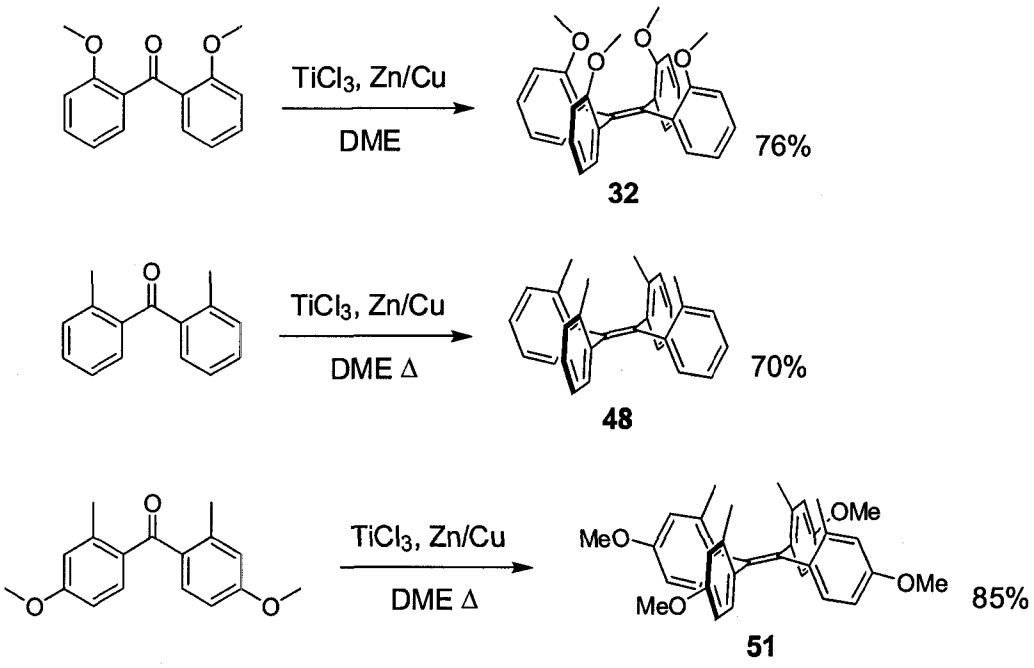


50

By itself, this reaction would suggest that the McMurry olefination reaction cannot be used to make the desired tetrakis(2-methoxyphenyl)ethene. This reaction probably suffered from the use of a hydride source like $LiAlH_4$ instead of Zn/Cu and the use of a relatively good radical hydrogen atom donor THF instead of DME as solvent.[32]

Dr. G. Qi in the Stryker group has reproduced the exact conditions reported by Vögtle and found that a small amount of the desired ethene is being produced. Dr. M. Chung followed this lead and improved this reaction by using $TiCl_3$ and Zn/Cu to produce the desired ethene in high yield and excellent selectivity (**Equation 10**).

Equation 10. McMurry Reaction and Electron Donating groups

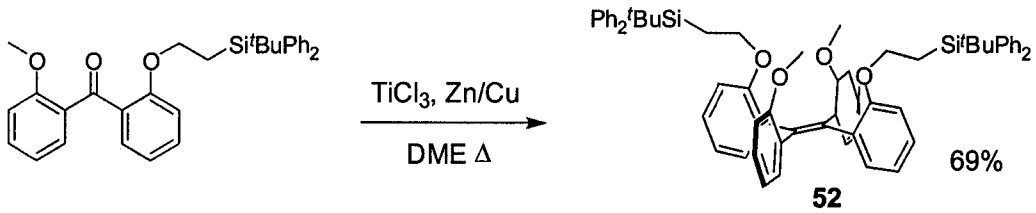


By investigating a series of compounds, Dr. Chung showed that benzophenone compounds with electron-donating substituents at the *ortho-* or *para-* positions produce high yields when subjected to this McMurry methodology. For example, 2,2'-dimethoxybenzophenone reacts smoothly to form tetrakis(2-methoxyphenyl)ethene, **32**, using the instant McMurry reaction conditions. 2,2'-dimethylbenzophenone and 4,4'-dimethoxy-2,2'-dimethylbenzopheneone also react smoothly to form tetrakis(2-tolyl)ethene, **48**, and tetrakis(4-methoxy-2-methylphenyl)ethene, **51**, respectively, but these substrates require reflux temperatures due to the ortho-methyl rather than methoxy substituents.[33]

Dr. Chung also developed a better method for producing partially deprotected derivatives of tetrakis(2-methoxyphenyl)ethene.[34] This work focused on a series of benzophenone compounds substituted with a methoxy group at the 2-position and a

different alkoxy functional group at the 2'-position. The intention was that the group at the 2'-position be deprotected using methodology that does not affect the methoxy group. The majority of these substrates were silicon based protecting groups that were deprotected with fluoride. For example, the doubly silyloxyethyl- protected tetraphenylethene **52** was synthesized in good yields via the McMurry reaction (**Equation 11**).[34] This compound could then be deprotected with fluoride to release ethene and the silylfluoride compound.[34] This technology has been supplanted by simpler methodology, as will be described in Chapter 2.

Equation 11. Silica Protected Tetraphenylethene **52**



Chapter 2 Results and Discussion

Chapter 2.1 Diaryl Ketone synthesis

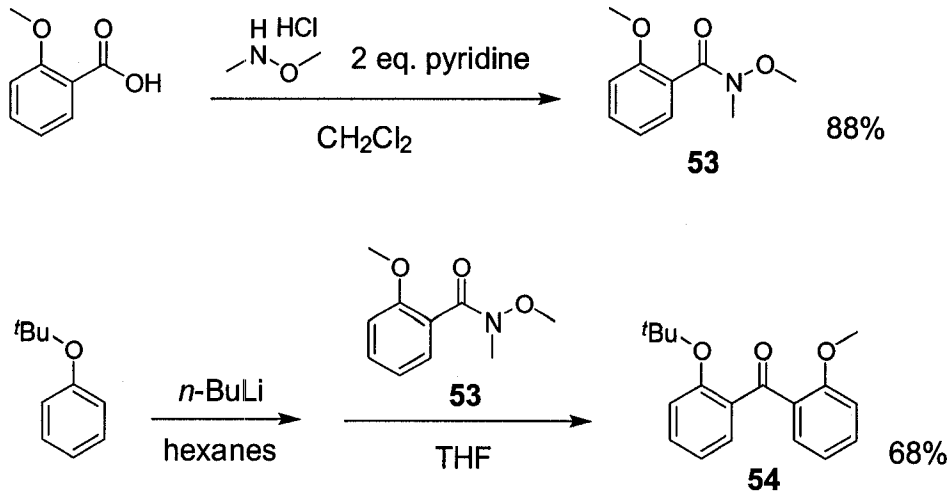
A series of 2,2'-substituted benzophenone compounds have been synthesized and subjected to McMurry reaction conditions. Symmetrical ketones were typically synthesized using a Grignard reagent or a lithioaryl reagent with half an equivalent of dimethylcarbamoyl chloride.[15] Other routes used to prepare the diaryl ketones involved the synthesis of the corresponding alcohols and subsequent oxidation.

Towards the synthesis of the unsymmetrical ketone 2-methoxy-2'-*tert*-butoxybenzophenone, **54**, *tert*-butoxybenzene was synthesized from bromobenzene with potassium *tert*-butoxide and *tert*-butanol in DMSO. Many other attempts were made to make *tert*-butoxybenzene from phenol by using various literature methods; however, 4-*t*-butylphenol was always produced instead. *N*,2-dimethoxy-*N*-methylbenzamide, **53** was prepared from 2-methoxybenzoic acid, methoxymethylamine·HCl, and two equivalents of pyridine (**Scheme 11**).

2-Lithio-*tert*-butoxybenzene was prepared *in situ* from *tert*-butoxybenzene and *n*-BuLi in hexanes and then treated with *N*,2-dimethoxy-*N*-methylbenzamide to produce the desired ketone, 2-methoxy-2'-*tert*-butoxybenzophenone, **54** (**Scheme 11**).

The ^{1}H NMR spectrum of *N*,2-dimethoxy-*N*-methylbenzamide, **53** contained three singlet peaks integrating to 3 hydrogen atoms in the region of 3 ppm. Two of these peaks were very broad, which is characteristic of a methyl group or a methoxy group connected to a nitrogen atom, as expected for an *N*-methoxy-*N*-methylamide (3.56 ppm, 3H), (3.31 ppm, 3H).

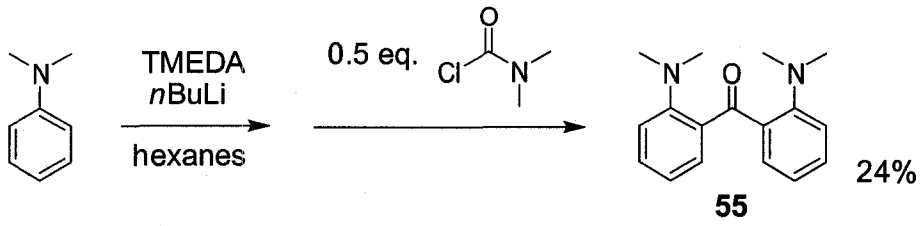
Scheme 11. 2-Methoxy-2'-*tert*-butoxybenzophenone **54**



The ^{1}H NMR spectrum of 2-methoxy-2'-*tert*-butoxybenzophenone, **54** contains multiple peaks corresponding to 8 hydrogen atoms in the aromatic region (7.60 – 6.91 ppm), as well as a methoxy peak (3.68 ppm, 3H) and a *tert*-butyl group peak (1.08 ppm, 9H).

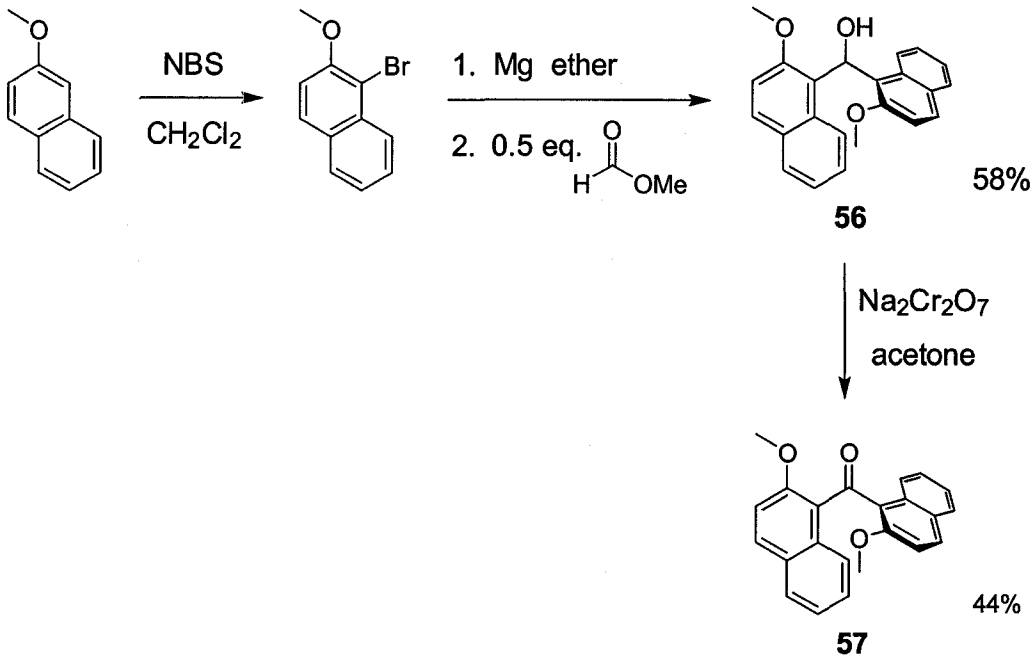
To prepare bis(2-*N*,*N*-dimethylamino-1-phenyl)methanone *N*,*N*-dimethylaniline was metallated using *n*-BuLi in hexanes and quenched with *N*,*N*-dimethylcarbamoyl chloride, to form bis(2-*N*,*N*-dimethylamino-1-phenyl)methanone, **55** in poor but serviceable yields (**Equation 12**). The poor yield is most likely due to the poor metallation-directing ability of the dimethylamino group and potential competition with direct deprotection of the methyl group. In some ways, the poor lithiation of this compound is surprising, as *N*,*N*-dimethylbenzylamine is a very good system for ortho-metallation.[35]

Equation 12. Bis(2-*N*,*N*-dimethylamino-1-phenyl)methanone **55**



The ^{1}H NMR spectrum of bis(2-*N*,*N*-dimethylamino-1-phenyl)methanone **55** contains four aromatic peaks, two apparent doublets and two apparent triplets, characteristic of a 1,2-substituted benzene ring (7.47 – 6.77 ppm). There was also a peak characteristic of two symmetric dimethylamino groups (2.82 ppm, 12H).

Scheme 12. Synthesis of Bis(2-methoxy-1-naphthyl)methanone **57**



Both bis(2-methoxy-1-naphthyl)methanone **57** and bis(3-methoxy-2-naphthyl)methanone **59** were synthesized using 2-methoxynaphthalene as a starting

material. Treatment of 2-methoxynaphthalene with NBS as a brominating agent yielded 2-methoxy-3-bromonaphthalene in good yield (**Scheme 12**).[36]

The Grignard reagent derived from 2-methoxy-3-bromonaphthalene was produced using magnesium turnings in ether and then quenched with half an equivalent of methylformate to produce bis(2-methoxy-1-naphthyl)methanol **56**. The oxidation of this alcohol with $Na_2Cr_2O_7$ in acetone produced the desired ketone bis(2-methoxy-1-naphthyl)methanone **57** (**Scheme 12**).

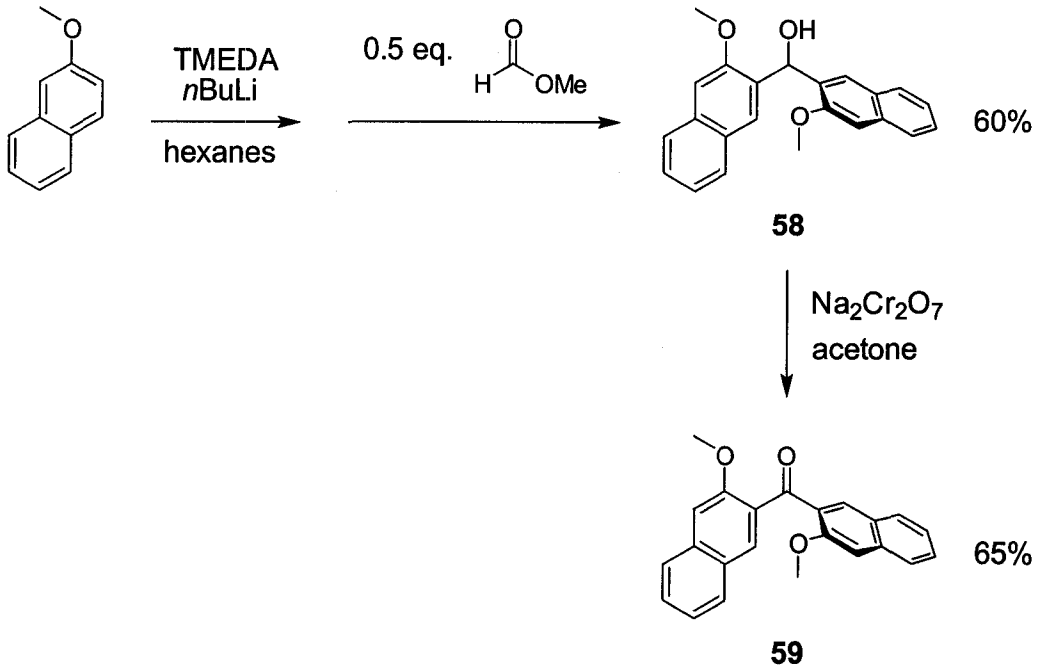
The ^{1}H NMR spectrum of bis(2-methoxy-1-naphthyl)methanol **56** shows the expected four doublets and two triplets in the aromatic region. The doublet at 6.05 ppm corresponds to the aliphatic hydrogen. The singlet at 3.77 ppm corresponds to the methoxy group.

The ^{1}H NMR spectrum of bis(2-methoxy-1-naphthyl)methanone **57** shows the expected four doublets and two triplets in the aromatic region. A correlated ^{1}H NMR spectrum shows a correlation between two of the doublets (7.89 $\leftrightarrow$ 7.16) suggesting two interacting, but otherwise isolated doublets. Correlations between the other two doublets (8.18 and 7.82 ppm) and the two triplets (7.52 and 7.40 ppm) suggest four aromatic hydrogens in a correlation consistent with a 1,2 aromatic ring (8.18 $\leftrightarrow$ 7.52, 7.40 $\leftrightarrow$ 7.82, 7.52). All of these correlations suggest the 1,2-disubstituted naphthalene ring. In the ^{13}C NMR spectrum of the compound is the peak at 199.8 ppm, characteristic of a carbonyl carbon. Compound **57** was previously synthesized by a different methodology.[37]

For the purpose of synthesizing bis(3-methoxy-2-naphthyl)methanone, **59,** the *in situ* conversion of 2-methoxynaphthalene to 2-methoxy-8-lithionaphthalene was

achieved by metallation of 2-methoxynaphthalene with *n*-BuLi, followed by the addition of half an equivalent of methyl formate to afford bis(3-methoxy-2-naphthyl)methanol **58**. Bis(3-methoxy-2-naphthyl)methanol was then oxidized with $Na_2Cr_2O_7$ in acetone to produce bis(3-methoxy-2-naphthyl)methanone **59** (**Scheme 13**).

Scheme 13. Bis(3-methoxy-2-naphthyl)methanone **59**



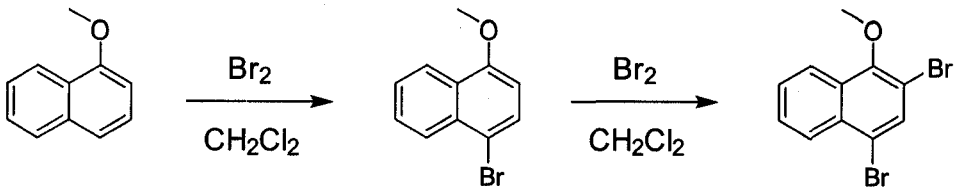
The ^{1}H NMR spectrum of bis(3-methoxy-2-naphthyl)methanol **58** contains the expected two singlets (7.68 and 7.18 ppm), two doublets (7.75 and 7.70 ppm), and two triplets (7.43 and 7.32 ppm) in the aromatic region of the spectrum as well as a methoxy peak (3.94 ppm) and central methine and hydroxyl doublet peaks (6.62 and 3.47 ppm). The correlated ^{1}H NMR spectrum clearly shows that the doublets and triplets are that of a 1,2-disubstituted benzene ring (7.75 ↔ 3.47, 7.70; 7.70 ↔ 7.32),

suggesting that the molecule contains a 2,3-disubstituted naphthalene ring. A correlation between the two doublets (6.62 ↔ 3.47) indicates that the methine hydrogen atom and hydroxyl group are geminal to each other.

The ^{1}H NMR spectrum of bis(3-methoxy-2-naphthyl)methanone, **59**, is similar to that of bis(3-methoxy-2-naphthyl)methanol, **58**. The ^{13}C NMR spectrum contains a resonance 194.8 ppm, indicating the presence of the carbonyl functionality.

To prepare the isomeric bis(1-methoxy-2-naphthyl)methanone requires metallation or halogenation at the 2-position of 1-methoxynaphthalene. Unfortunately, the literature shows that the reaction of 1-methoxynaphthalene and one equivalent of a brominating agent produces 4-bromo-1-methoxynaphthalene, **60**.[38] A second equivalent of a brominating agent produces 2,4-dibromo-1-methoxynaphthalene, **61** (**Equation 13**).[39]

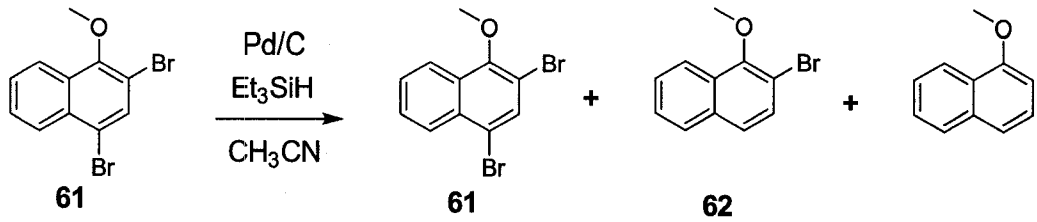
Equation 13. Synthesis of **60** and **61**



60 **61**

Using 2,4-dibromo-1-methoxynaphthalene, **61**, as a starting material, two different routes to bis(1-methoxy-2-naphthyl)methanone, **66**, were attempted. 2,4-Dibromo-1-methoxynaphthalene, **61**, was treated with Pd/C and one equivalent of triethylsilane, based on a literature procedure for 2-bromo-1-methoxynaphthalene (**Equation 14**).[40]

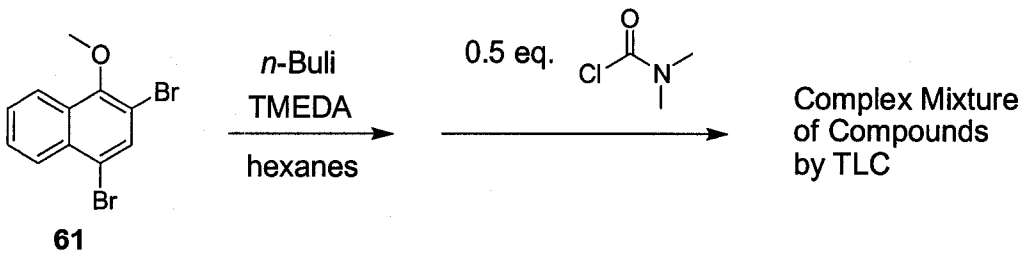
Equation 14. Debrominating 2,4-dibromo-1-methoxynaphthalene **61**



Unfortunately, the reaction produced a complex mixture consisting of 2,4-dibromo-1-methoxynaphthalene, **61**, 2-bromo-1-methoxynaphthalene, **62** and 1-methoxynaphthalene (**Equation 14**). These three compounds were very difficult to separate from each other. In the literature, microwave irradiation was used to facilitate the debromination, perhaps accounting for the greater selectivity reported.[40]

An attempt was made to selectively metallate 2,4-dibromo-1-methoxynaphthalene, **61**, with one equivalent of *n*-BuLi, followed by the addition of dimethylcarbamoyl chloride. This unfortunately produced an intractable mixture of compounds. (**Equation 15**).[39]

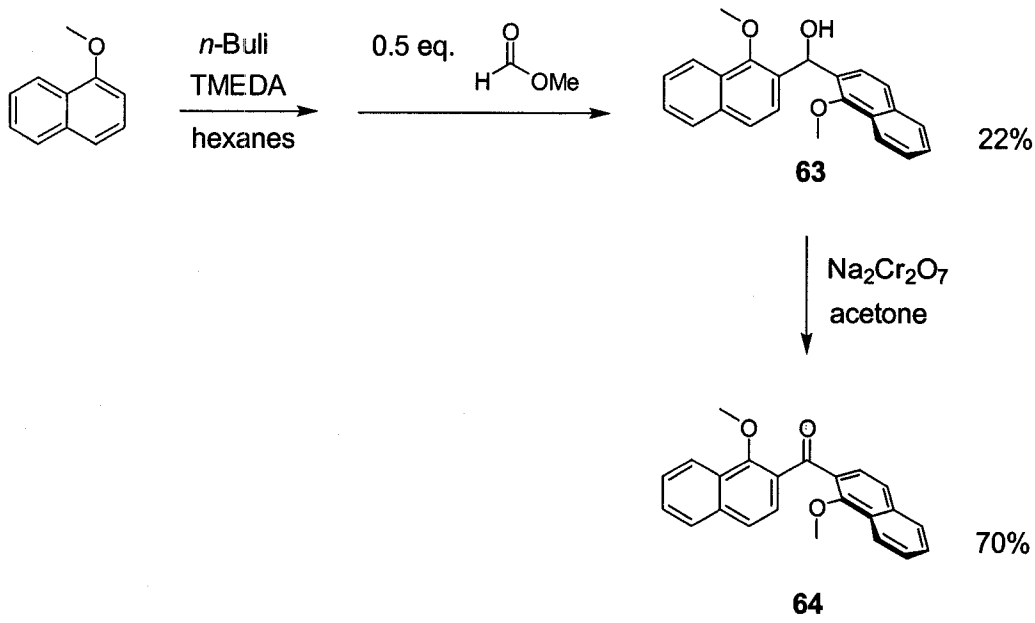
Equation 15. Lithiating 2,4-dibromo-1-methoxynaphthalene **61**



An alternative approach to bromination followed by lithium halide exchange is to directly lithiate the methoxy arene. When *n*-BuLi is used as lithiating agent in

hexanes, 2-lithio-1-methoxynaphthalene **6** and 8-lithio-1-methoxynaphthalene **7** are both produced, with the former obtained as the major product (**Scheme 1**).[14] When this mixture of lithiated compounds is treated with methyl formate, a complex mixture is produced which includes the desired product, bis(1-methoxy-2-naphthyl)methanol, **63** (**Scheme 14**).

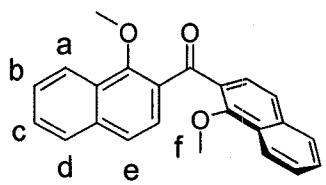
Scheme 14. Synthesis of Bis(1-methoxy-2-naphthyl)methanone **64**



By TLC analysis, there were eight different compounds in the product mixture and although the byproducts were not isolated, two of the expected undesired products are bis(1-methoxy-8-naphthyl)methanol and 1-methoxy-2-naphthyl 1-methoxy-8-naphthyl methanol. Despite the low yield, alcohol **63** was obtained in pure form and oxidized to bis(1-methoxy-2-naphthyl)methanone, **64**, with sodium dichromate (**Scheme 14**).

The ^{1}H NMR of bis(1-methoxy-2-naphthyl)methanol, **63**, has two doublets (8.13 and 7.85 ppm) and a multiplet (7.44-7.66 ppm) in the aromatic region, as well as the expected methoxy (3.94 ppm), methine (6.94 ppm) and hydroxyl resonances (3.22 ppm). The correlated spectrum shows the typical correlations for a 1,2-disubstituted benzene ring (8.13 ↔ 7.46; 7.85 ↔ 7.44; 7.46 ↔ 7.44) and two mutually coupled doublets hidden in the multiplet (7.61 ↔ 7.59), which characterizes a 1,2-disubstituted naphthalene ring. Also, there is the expected correlation between the methine peak and the hydroxyl peak (6.94 ↔ 3.22).

The ^{1}H NMR spectrum of bis(1-methoxy-2-naphthyl)methanone, **64**, is complicated by second order effects. In the aromatic region of the ^{1}H NMR spectrum, however, there are two doublets (8.21 ppm, 2H and 7.89 ppm, 2H), as well as two complex multiplets (7.66 ppm, 4H and 7.57 ppm, 4H). The correlations in the ^{1}H NMR spectrum can be assigned as follows: a,d ↔ 8.21, 7.89 ppm; b,c ↔ 7.52-7.64 ppm; e,f ↔ 7.66 ppm (**Figure 9**). The ^{13}C NMR spectrum displays the expected carbonyl peak at 194.8 ppm.



64

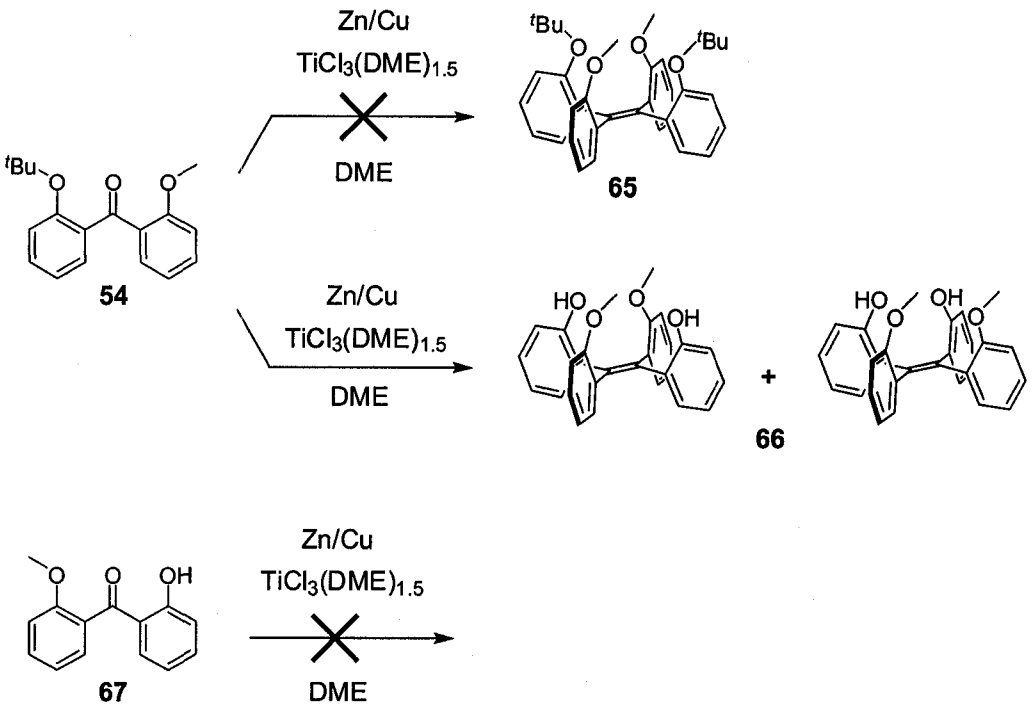
Figure 9. Bis(1-methoxy-2-naphthyl)methanol **64** with labels

Chapter 2.2. McMurry Couplings

Carefully controlled conditions must be employed when the McMurry reaction is used to couple *ortho*-substituted benzophenone compounds. Chung, et al., reported that the best method for running these McMurry reactions is to follow Fürstner's "instant method" modification.[27] The ketone, $TiCl_3(DME)_{1.5}$, and Zn/Cu were all dried on a high vacuum line or on a Schlenk vacuum line with heating (~ 45 °C). Ideally, all reagents should be freshly prepared to ensure purity. Less controlled conditions lead to the formation of the tetraarylethane by-product and very little, if any, of the desired tetraarylethene.

2-*tert*-Butoxy-2'-methoxybenzophenone **54** was coupled using $TiCl_3$ and Zn/Cu in DME, unexpectedly giving a mixture of (*E*)- and (*Z*)-bis(2-hydroxyphenyl)-bis(2-methoxyphenyl)ethenes, **66**, in a ratio of 1:1 (**Scheme 15**).[34]

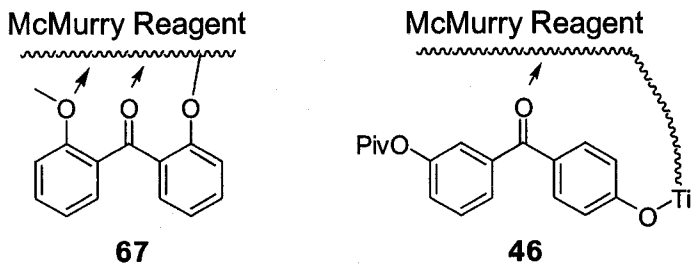
Scheme 15. The McMurry reaction on **54**



Fujita, et al., also synthesized **66**, but in seven steps starting from the ketone in a 7:1 (E:Z) ratio. If the extra time and added expense is acceptable, then Fujita's method is preferable for synthesizing the (*E*)-bis(2-hydroxyphenyl)-bis(2-methoxyphenyl)ethene compound as it is favoured in a 7:1 ratio, while this McMurry reaction is better for synthesizing (*Z*)-bis(2-hydroxyphenyl)-bis(2-methoxyphenyl)ethene because it is in a 1:1 ratio and requires fewer synthetic steps.

The expected product was (*E*)- and (*Z*)-bis(2-*tert*-butoxyphenyl)-bis(2-methoxyphenyl)ethene, **65**, however, the reaction conditions surprisingly induced both carbonyl coupling and *tert*-butoxy deprotection (**Scheme 15**). As a control experiment, the McMurry reaction was attempted on the deprotected 2-hydroxy-2'-methoxybenzophenone, **67**, but gave no conversion of the starting material. This implies that the deprotection of the *tert*-butoxy group must occur after the carbonyl coupling.[34]

It is surprising that 2-hydroxy-2'-methoxybenzophenone failed to react in the McMurry reaction, considering Gauthier's successful McMurry reaction with a benzophenone compound that has an unprotected hydroxy group at the *para* position.[29]

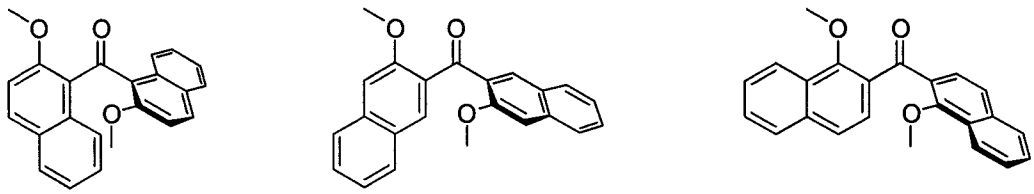


67 **46**

Figure 9. A comparison of **67** and **46**

Apparently, the hydroxy group itself is harmless in the McMurry reaction, unless it is at the *ortho*-position. Perhaps benzophenone derivatives with a hydroxyl group at the *ortho*-position bind irreversibly to the surface of the heterogeneous McMurry reagent until the aqueous workup (**Figure 10**).

It was natural to synthesize the three regioisomers bis(2-methoxy-1-naphthyl)methanone, **57**, bis(3-methoxy-2-naphthyl)methanone, **59**, and bis(1-methoxy-2-naphthyl)methanone, **64**, for the purpose of evaluating these substrates in the McMurry reaction (**Figure 11**).



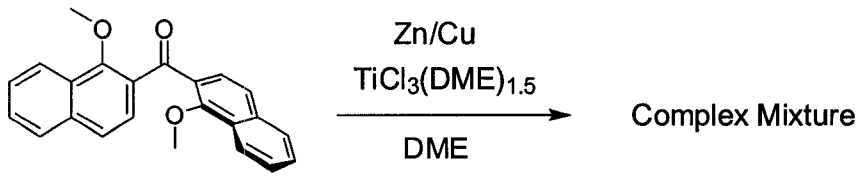
57 **59** **64**

Figure 11. A comparison of isomeric dinaphthyl ketones

The gross difference in solubility and other physical properties among the three compounds was unexpected. The vast majority of naphthalene compounds tend to be very crystalline; however, bis(1-methoxy-2-naphthyl)methanone **64** was found to be a viscous oil with a consistency similar to many carbohydrate derivatives. Bis(3-methoxy-2-naphthyl)methanone, **59**, however, is a solid and is soluble in most typical organic solvents. Bis(2-methoxy-1-naphthyl)methanone, **57**, also a solid, is completely insoluble in ether, acetonitrile, benzene, acetone, 1,2-dimethoxyethane, tetrahydrofuran, and poorly soluble in both CH_2Cl_2 and $CHCl_3$ (**Figure 8**).

Bis(1-methoxy-2-naphthyl)methanone **64** undergoes reaction with $TiCl_3(DME)_{1.5}$ and Zn/Cu using Fürstner's "instant method" to produce a large number of compounds, as observed by TLC analysis, but none of the desired product (**Equation 16**). The ^1H NMR spectrum of the side products do not fit with the expected ^1H NMR spectrum of the expected product. It is interesting to recall the increase in reactivity of 1-methoxynaphthalene over 2-methoxynaphthalene with $AlCl_3$ and EtSH (**Scheme 2**). 1-methoxynaphthalene was converted to naphthalene whereas 2-methoxynaphthalene stopped reacting at the ethyl 2-naphthly sulfide. Perhaps in the McMurry reaction with Bis(1-methoxy-2-naphthyl)methanone, **64**, similarly allows unexpected reactivity of the methoxy group at the 1-position.

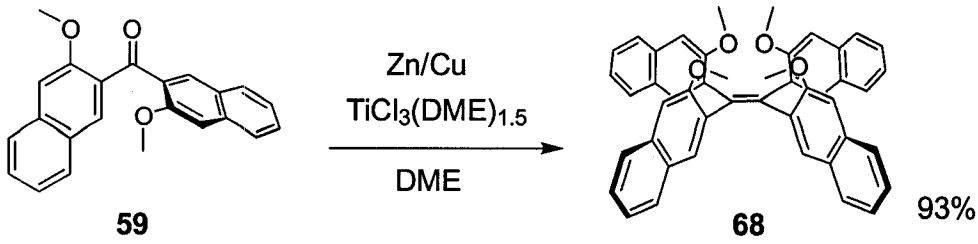
Equation 16. McMurry Reaction on **64**



64

Conversely, bis(3-methoxy-2-naphthyl)methanone, **59**, reacted smoothly with $TiCl_3(DME)_{1.5}$ and Zn/Cu using the "instant method" to produce the desired tetrakis(3-methoxy-2-naphthyl)ethene, **70**, in very high yield, free of significant byproducts (**Equation 17**).

Equation 17. Synthesis of Tetrakis(3-methoxy-2-naphthyl)ethene **68**



59 **68** 93%

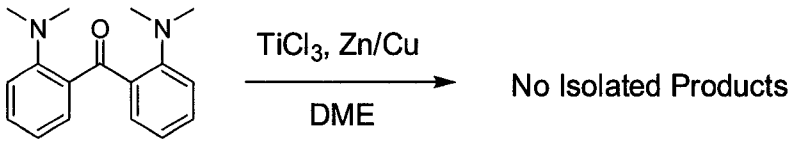
The ^{1}H NMR spectrum of this compound depends significantly on temperature. At room temperature, restricted rotation prevents the four methoxy groups from being equivalent. At 20 °C there are two methoxy resonances (3.56 (s, 9H), and 3.50 (s, br, 3H)) instead of just one resonance and there are two broad aromatic singlet resonances (7.72 (s, 3H), 7.44 (s, br, 1H)) instead of just one aromatic resonance. There is a clear 3:1 ratio between the signal environments for the affected aromatic singlet and methoxy groups. At 60 °C, the barrier for the restricted rotation is overcome and the ^{1}H NMR spectrum for the affected singlet and methoxy peak sharpens and resolves, appearing as follows: δ = 7.71 (s, br, 4H), 3.59 (s, 12H).

The aromatic region of the ^{1}H NMR spectrum at 60 °C shows the expected two singlets (7.71 and 6.88 ppm), two triplets (7.30 and 7.17 ppm) and a multiplet (7.55-7.6 ppm) that can reasonably be interpreted to contain the two expected doublets. The correlations for the ^{1}H NMR spectrum show a pattern typical for a 1,2-disubstituted aromatic.

Bis(2-methoxy-1-naphthyl)methanone, **57**, was found to be completely insoluble in DME, but was nonetheless treated with $TiCl_3(DME)_{1.5}$ and Zn/Cu, without positive results. This is not surprising, because bis(2-methoxy-1-naphthyl)methanone, **57**, and the McMurry reagent are both insoluble and generally, two heterogeneous compounds do not readily react.

Bis(2-*N*,*N*-dimethylamino-1-phenyl)methanone, **55**, was the final substrate evaluated for McMurry olefination. Unfortunately, no products or unreacted starting material could be isolated from the reaction (**Equation 18**).

Equation 18. McMurry on **55**



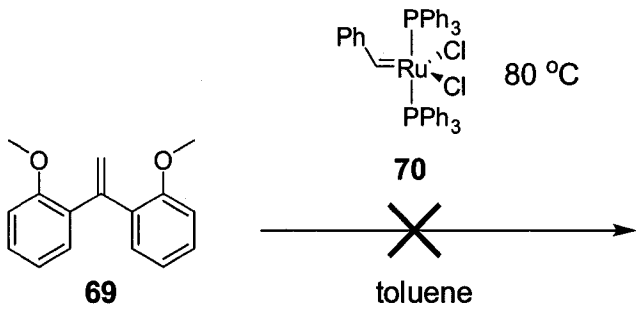
55

The work up for this reaction consisted of filtering the crude mixture over celite and washing with large amounts of CH_2Cl_2. Perhaps the compound bonded to the titanium during the reaction and remained attached during the work up process.

Chapter 2.3 Approaches to *ortho*-substituted tetraphenylethenes

Olefin metathesis reactions were attempted on 1,1-bis(2-methoxyphenyl)ethene **69** by using the Grubbs second generation catalyst[41], **70** and the Hoveya-Grubbs second generation catalyst,[42] but both reactions returned only starting material (**Equation 19**).

Equation 19. Olefin Metathesis Attempt

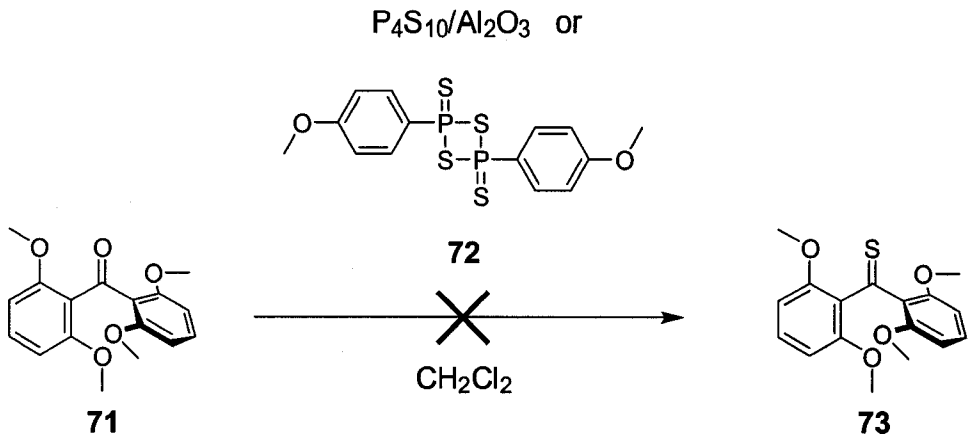


This is not surprising, given that the production of tetra-substituted ethenes via olefin metathesis is extremely rare.[43]

Tetrakis(2,6-dihydroxyphenyl)ethene, **5**, was a desired for its ability to bind to either a silica surface or a metal both above or below the double bond. Because Dr. Chung had prove that the McMurry reaction could not be used to make **5**, we thought that perhaps the Barton Kellogg olefination reaction may work. One version of the Barton olefination methodology requires a thioketone.

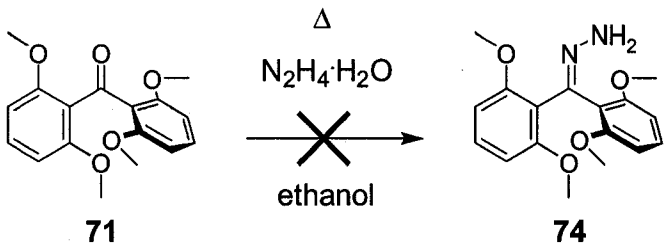
Numerous attempts were made to convert 2,2',6,6'-tetramethoxybenzophenone, **71**, into 2,2',6,6'-tetramethoxythiobenzophenone, **73**, with Lawesson's reagent, **72**, or P_4S_{10} / Al_2O_3 either at room temperature or at reflux, but all attempts produced nothing but starting material (**Equation 20**).[44, 45]

Equation 20. Attempted Synthesis of **73**



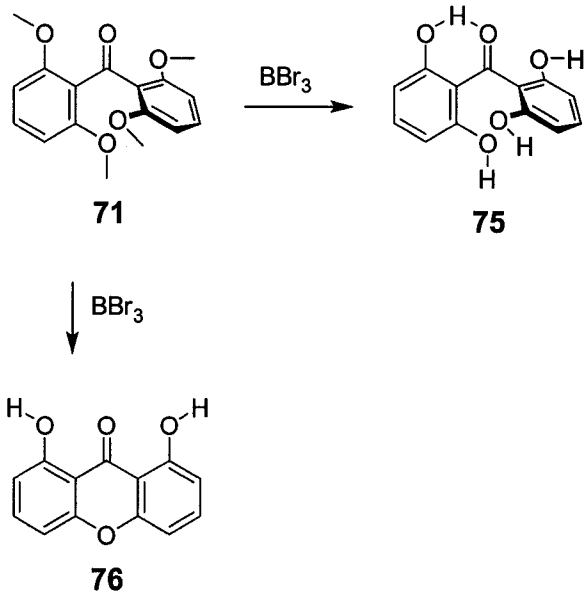
In addition, one attempt was made to form the corresponding hydrazone of 2,2',6,6'-tetramethoxybenzophenone, **71**, with $N_2H_4 \cdot H_2O$ in ethanol at reflux, also without success (**Equation 21**).

Equation 21. Attempted Synthesis of **74**



Finally, an attempt was made to produce 2,2',6,6'-tetrahydroxybenzophenone, **75**, from 2,2',6,6'-tetramethoxybenzophenone, **71**. Because **75** should have less steric bulk than **71**, it is possible that **75** might react with Lawesson's reagent or hydrazine hydrate. The reaction with BBr_3, however, succeeded only once. All further attempts to reproduce the reaction produced the unwanted xanthone **76** as the major product (**Equation 22**).

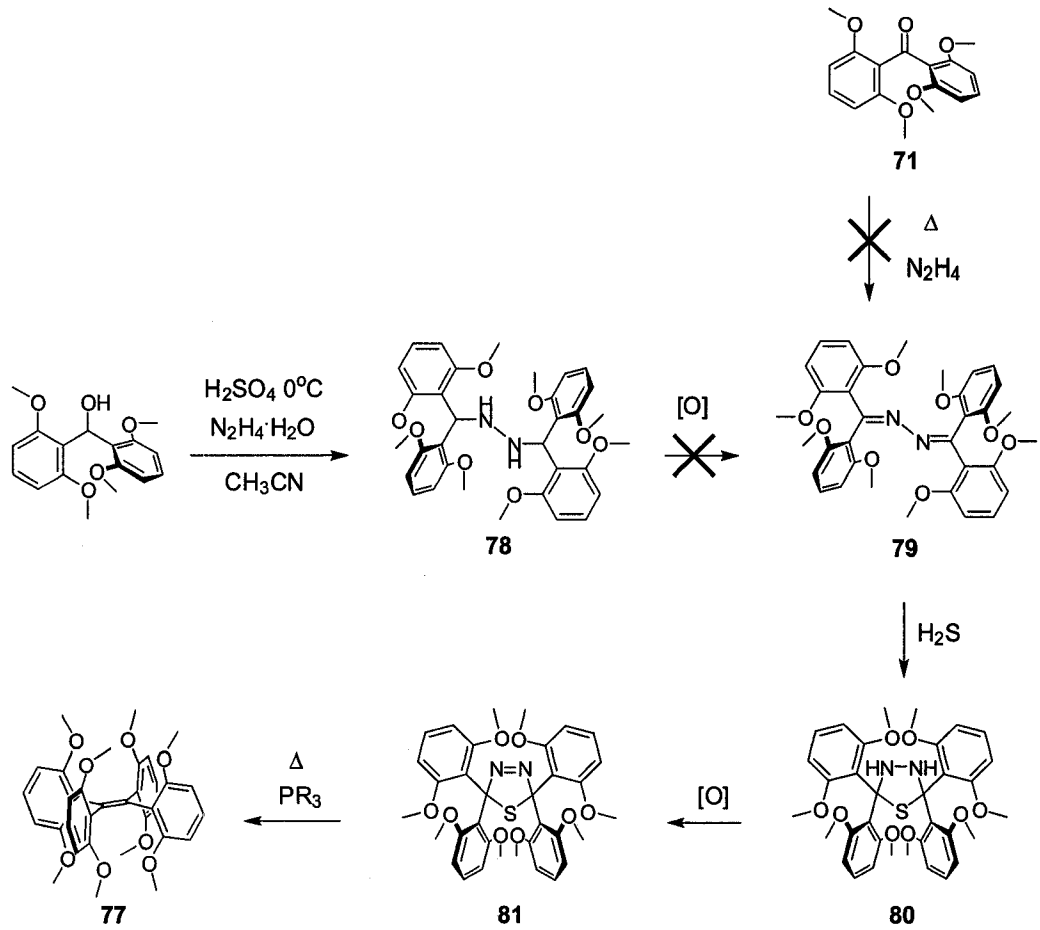
Equation 22. 2,2',6,6'-tetrahydroxybenzophenone **75**



71 **75** **76**

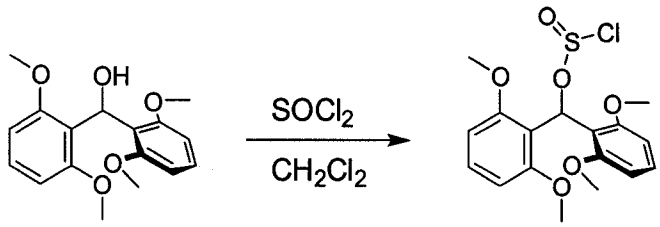
Because 2,2',6,6'-tetramethoxybenzophenone **71** does not react with hydrazine, it was thought that perhaps 2,2',6,6'-tetramethoxybenzophenol might react to form 1,2-bis(di-2,6-dimethoxyphenylmethyl)hydrazine, **78**, which could be subsequently oxidized to bis(imine), **79**, one of the required components for the Barton-Kellogg olefination, as illustrated in (**Scheme 16**).

Scheme 16. Using **78** in the Barton-Kellogg methodology



In an attempt to make hydrazine **78**, 2,2',6,6'-tetramethoxybenzophenol was treated with $SOCl_2$, producing what appeared to be the chlorosulfite intermediate on the pathway to the chloride. Based on ^1H NMR spectroscopy and HRMS, the product has been tentatively assigned to be adduct **82** (**Equation 23**). An attempted reaction of **82** with hydrazine resulted in no reaction. Presumably, chlorosulfite **82** is too sterically hindered to allow a chloride to displace chlorosulfate and produce the desired chloride product.

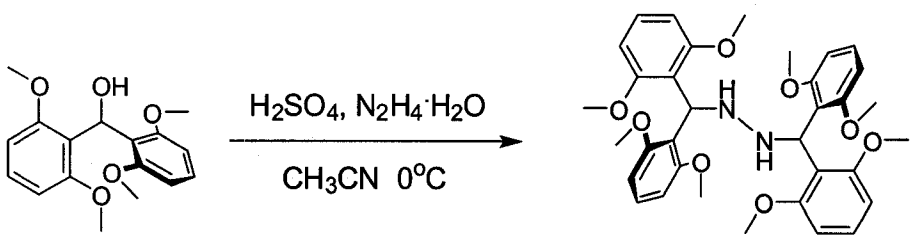
Equation 23. Synthesis of **82**



82

Given that the alcohol does not react to form the chloride, the use of acid to generate the carbocation in the presence of hydrazine was next investigated **(Equation 24)**.[46]

Equation 24. 1,2-bis(di-2,6-dimethoxyphenylmethyl)hydrazine **78**



78

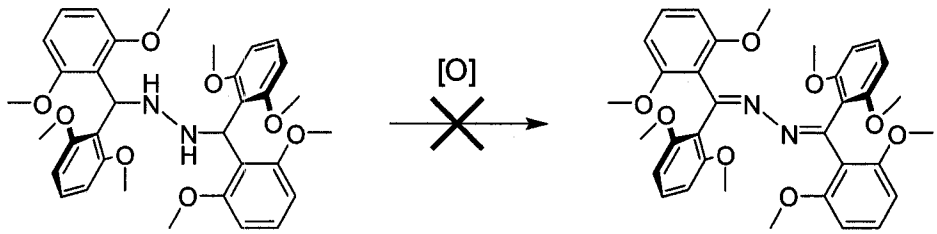
2,2',6,6'-Tetramethoxybenzophenol was dissolved in acetonitrile in the presence of excess insoluble hydrazine hydrate. The addition of H_2SO_4 at 0 °C produced predominantly 1,2-bis(di-(2,6-dimethoxyphenyl)methyl)hydrazine **78** **(Equation 24)** in good yield but the product was impure impure. Hydrazine **78** could not be purified by flash chromatography because it is unstable on both Al_2O_3 and silica supports and all attempts at recrystallization gave powders.

Due to symmetry, the ^1H NMR spectrum of 1,2-bis(di-2,6-(dimethoxyphenyl)methyl)hydrazine **78** has only four signals, an aromatic triplet and doublet as well as methine and methoxy resonances. The ^{13}C NMR spectrum has the expected four aromatic resonances (159.0, 158.5, 128.4, 127.5), a methine peak

(104.9) and the methoxy peak (55.6). The HRMS value of *m/z* = 604.2778 is similar to the expected value of 604.2784.

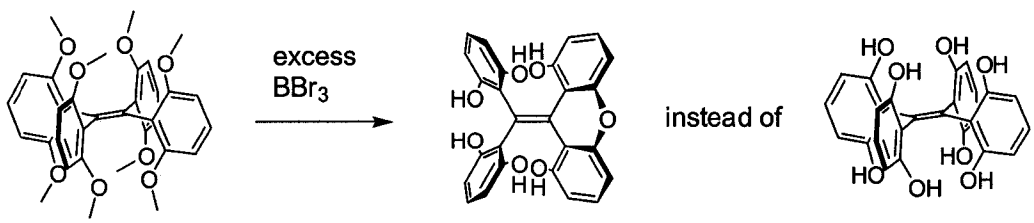
The acid presumably reacts with the soluble 2,2',6,6'-tetramethoxybenzophenol, which then traps the $N_2H_4 \cdot H_2O$ in the insoluble lower layer of the reaction mixture. The oxidation of hydrazine **78** to the diimine **79** was attempted at room temperature with oxidizing agents such as PbO_2, $K_2(S_2O_8)$ with cat. $NiSO_4$,[47] and hydrogen peroxide. Diimine **79** was not produced from any of these reactions (**Equation 25**), however, the use of PbO_2 produced partial oxidation to the azo compound.

Equation 25. Attempted oxidation of **78**



78 **79**

Because it is clear that 2,2',6,6'-tetrahydroxybenzophenone, **75,** is susceptible to unwanted condensation reactions, it should at least be considered that tetrakis(2,6-dimethoxyphenyl)ethene, **77**, may behave similarly under standard demethylation conditions (BBr_3) (**Figure 12**).



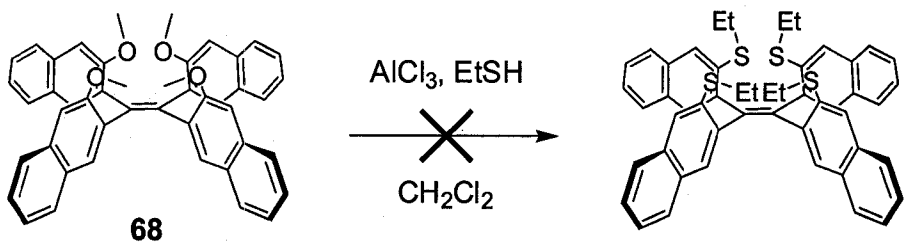
77 **5**

Figure 12. Possible Undesired Condensation

Section 2.4. Sulfide Synthesis

The unusual thiolation reaction of 2-methoxynaphthalene with $AlCl_3$ and EtSH in CH_2Cl_2 to produce ethyl 2-naphthyl sulfide was successfully reproduced.[17] Unfortunately, all attempts to conduct this reaction with tetrakis(3-methoxy-2-naphthyl)ethene, **68**, were unsuccessful - only starting material was recovered (**Equation 26**).

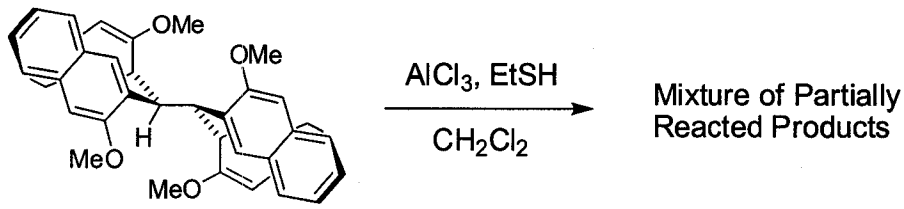
Equation 26. Reaction of **68** with $AlCl_3$ and EtSH



68

On the other hand, the reaction of $AlCl_3$ and EtSH with tetrakis(3-methoxy-2-naphthyl)ethane, **83**, produced a mixture of products in which some of the methoxy groups were replaced by ethylmercapto groups, as identified by ^1H NMR spectroscopy (**Equation 27**).

Equation 27. Reaction of **83** with $AlCl_3$ and EtSH

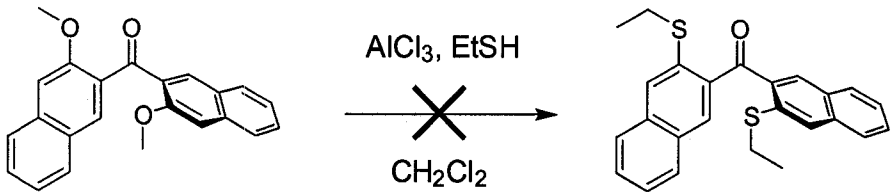


83

Complete conversion, however, could not be obtained. Tetrakis(3-methoxy-2-naphthyl)ethane, **83**, was synthesized from tetrakis(3-methoxy-2-naphthyl)ethene, **68**, in an unsuccessful McMurry reaction.

Since the thiolation of tetrakis(3-methoxy-2-naphthyl)ethene, **68**, was unsuccessful, the same reaction was attempted on the precursor, bis(3-methoxy-2-naphthyl)methanone, **59** (**Equation 28**).

Equation 28. Attempted Synthesis of **84**



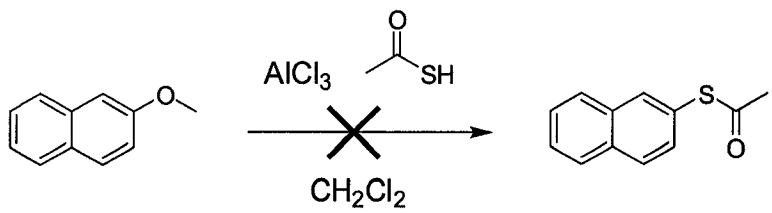
59 **84**

^{1}H NMR spectroscopy showed that there was a reaction between bis(3-methoxy-2-naphthyl)methanone, **59**, and the $AlCl_3$, but ethanethiol was not incorporated into the naphthalene framework (**Equation 28**).

A similar reaction involving 2-methoxynaphthalene, $AlCl_3$ and thioacetic acid was attempted, in an effort to make 2-thioacetylnaphthalene, which would be easier to

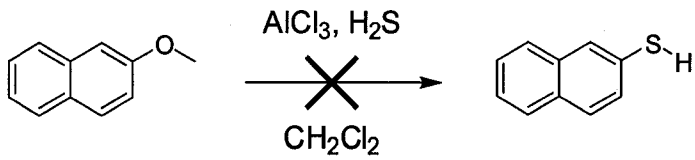
deprotect that the thioether (**Equation 29**). This, too, failed to react, returning only starting material.

Equation 29. Reaction of 2-methoxynaphthalene with $AlCl_3$ and thioacetic acid



The direct reaction of 2-methoxynaphthalene with $AlCl_3$ and H_2S also only produced starting material (**Equation 30**).

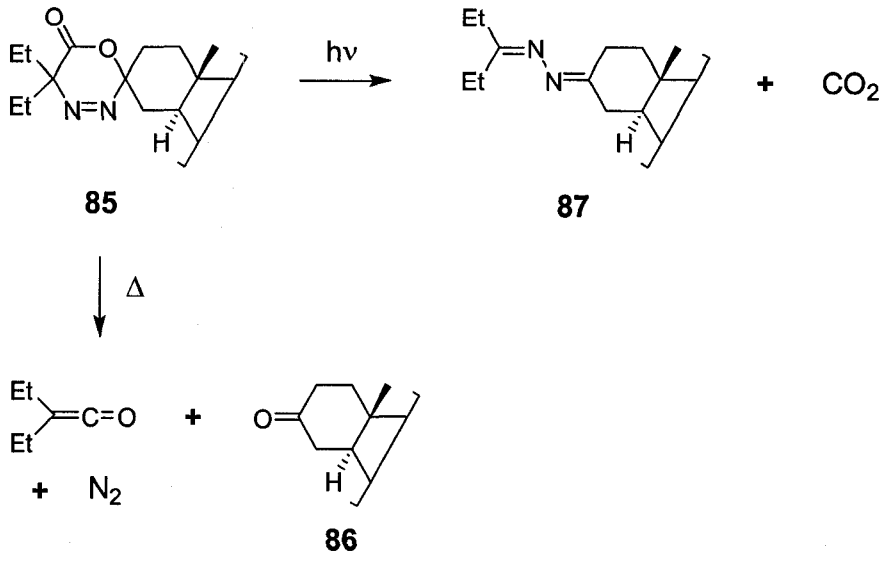
Equation 30. Reaction of 2-methoxynaphthalene with $AlCl_3$ and H_2S



2.5 Future Work

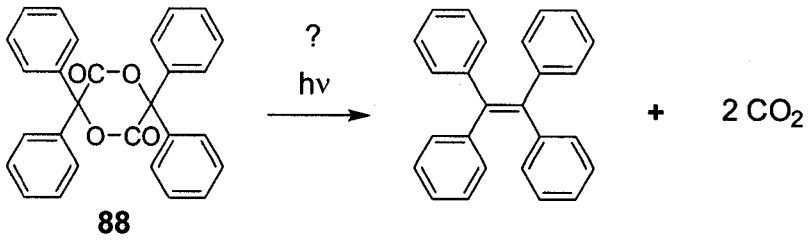
In an interesting report from the early 1970's, a six membered azolactone **85** was used in the two fold extrusion process of the Barton-Kellogg olefination. When this azolactone was heated, nitrogen gas was released, cleanly producing a diethylketene and the ketone **86** (**Scheme 17**). Conversely, carbon dioxide and an azine **87** were cleanly produced when the azolactone was subjected to UV light (**Scheme 17**).[20]

Scheme 17. Azolactone reaction with UV light or heat



The authors did not discuss the preparation and reaction of a 1,4-dioxane-2,5-dione with UV light to determine if two molecules of carbon dioxide could be liberated to produce the desired ethene.

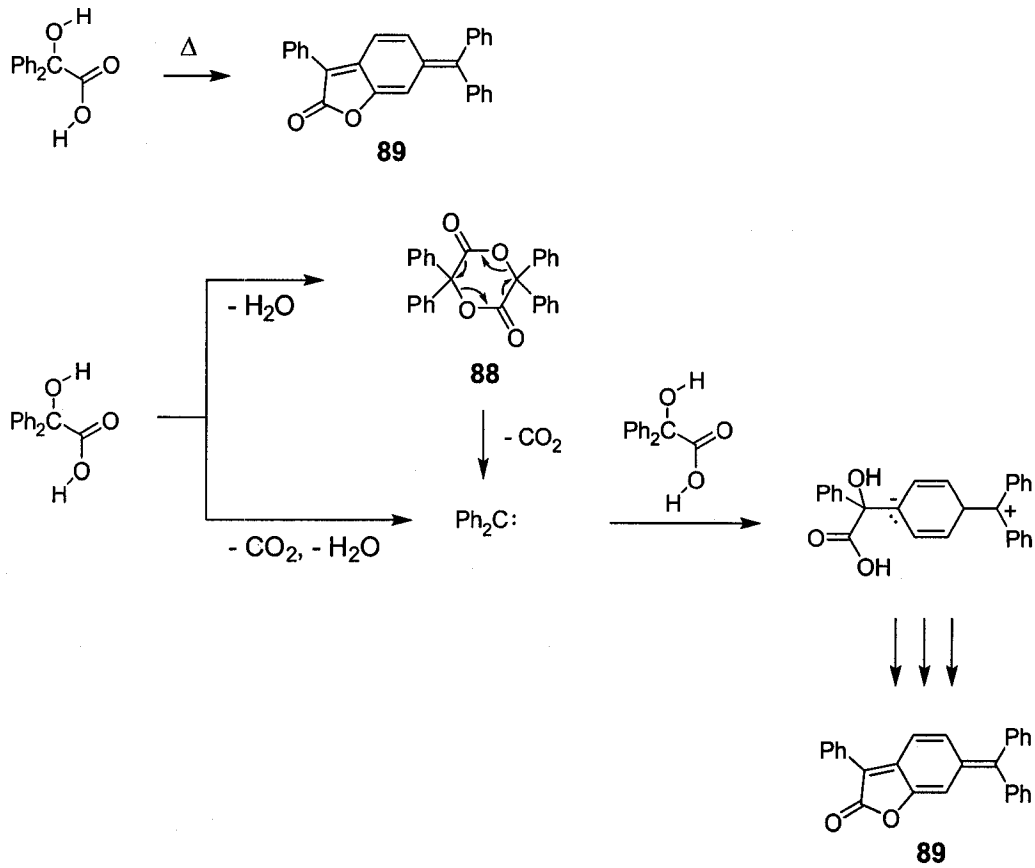
Scheme 18. Will a 1,4-dioxane-2,5-dione emit 2 CO_2 with hν



If the expulsion of two molecules of carbon dioxide works on a simple 1,4-dioxane-2,5-dione (e.g. **88**), the methodology could extended to the bulkier systems (**Scheme 18**).

It is known in the literature that the heating of benzilic acid will produce the *p*-quinodimethane derivative **89** (**Scheme 19**).[51]

Scheme 19. The Reaction of Benzilic Acid Upon Heating

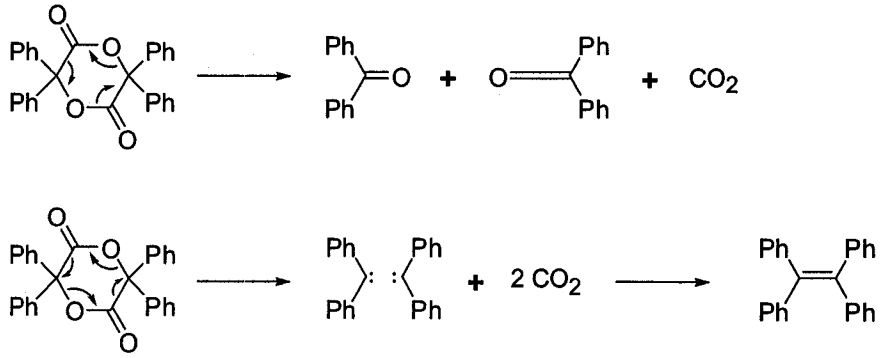


The mechanism proposed by the authors involves the formation of the dilactone **88** and its breakdown into the carbene. In this proposed mechanism, the carbene attacks benzilic acid to produce *p*-quinodemethane derivative **89** (**Scheme 19**).[51] If the authors are correct and an *in situ* dilactone ejects CO_2 to produce carbenes, then the proposed reaction may only create a carbene that unfortunately, would probably react with the methoxy functionality of 2,2',6,6'-tetramethoxybenzophenone **71** (see **Figure 6** page 11).

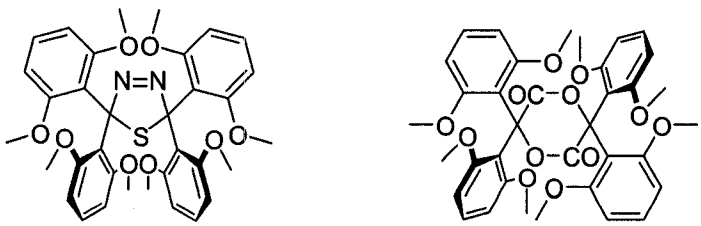
For this reaction to work successfully both molecules of CO_2 should be emitted simultaneously. If only one CO_2 molecule is emitted then a ketene and a ketone could be produced (**Scheme 20**), similar to the loss of nitrogen in **Scheme 17** (page

46). The simultaneous emission of two CO_2 molecules would presumably produce two carbenes. Ideally, the close proximity of the two carbenes would promote coupling. If the two carbenes do not immediately couple to produce the desired ethene, then undesired side reactions would be expected as described in **Figure 6** (page 10).

Scheme 20. Mechanistic Possibilities



One potential advantage of this idea is that the 1,4-dioxane-2,5-dione involves the synthesis of a six membered heterocyclic ring, which would keep the two bulky bis(2,6-dimethoxyphenyl)methyl groups farther away from each other than does the five membered ring of a thiadiazoline (**Figure 12**).



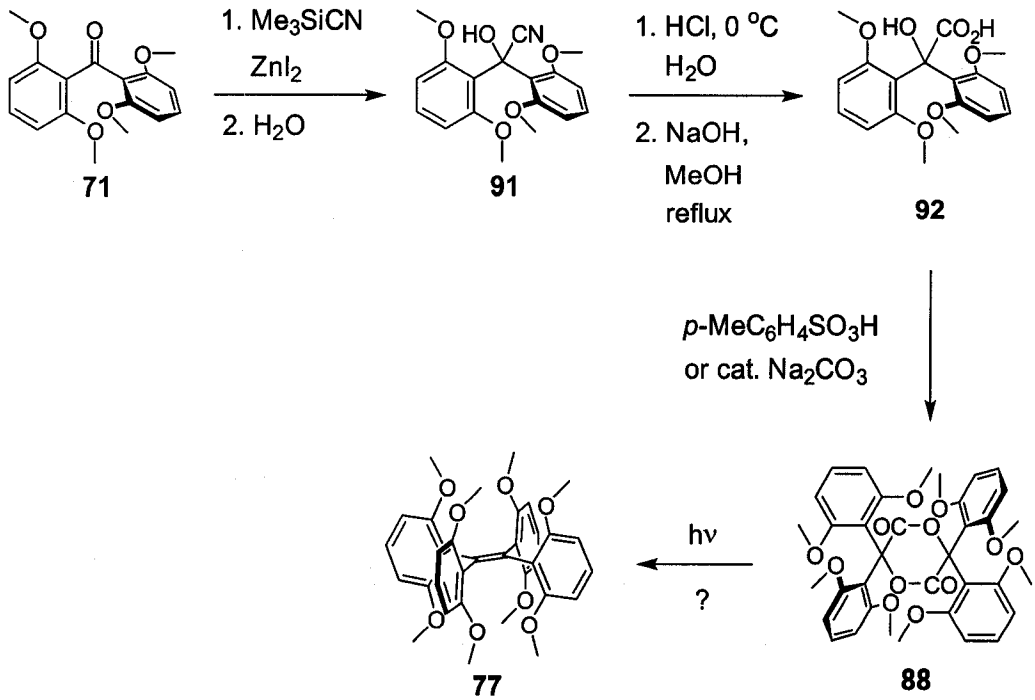
81 thiadiazoline

90 1,4-dioxane-2,5-dione

Figure 12. A comparison of steric bulk in **81** vs. **90**

The synthetic strategy to such dioxane diones could be accomplished by a reaction between 2,2',6,6'-tetramethoxybenzophenone, **71**, Me_3SiCN and cat. ZnI_2 to form cyanohydrin **91** (**Scheme 21**).[48]

Scheme 21. A proposed scheme for synthesizing **77**



Hydrolysis could lead to the α-hydroxyl carboxylic acid, **92**.[49] Dimerization under controlled acidic conditions (p-$MeC_6H_4SO_3H$)[50] or basic conditions (Na_2CO_3)[51] would lead to dione **88**, provided carbocation formation can be avoided and the steric bulk of the α-hydroxyl carboxylic acid is not too great (**Scheme 21**).

2.6 Conclusion

Extensions and new limitations to the McMurry reaction have been found. The McMurry reaction will not work on dinaphthyl ketones more sterically hindered than tetrakis(3-methoxy-2-naphthyl)ethene, **59**, and cannot be used to make the corresponding tetrakis(*N,N*-dimethylaminophenyl)ethene. It can however, be used to couple tetrakis(3-methoxy-2-naphthyl)ethene, **59**, and 2-Methoxy-2'-*tert*-butoxybenzophenone, **54**.

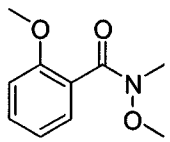
Tetrakis(1-methoxy-2-naphthyl)ethene remains an elusive and difficult compound to synthesize, as is tetrakis(2,6-dihydroxyphenyl)ethene, but a different variation of the Barton-Kellogg olefination methodology could succeed where our previous attempts were unsuccessful.

Chapter 3 Experimental

Results and Methods. CH_2Cl_2 and acetonitrile were dried by distillation over $CaCl_2$. DME, ether, and THF were distilled over Na/benzophenone ketyl. All compounds not synthesized were purchased commercially. ^1H NMR spectra were recorded on a Bruker AM-300 and ^{13}C NMR spectra were recorded on a Bruker AM-400 calibrated to 100 MHz. Elemental Analyses were performed by the University of Alberta Microanalysis Laboratories. IR spectra were taken by with a Nicola Magna 750 FTIR

spectrometer and a Nic-Plan FTIR microscope. High resolution mass spectra were taken by the University of Alberta mass spectra services. The majority of the flash columns were run with 230 – 400 mesh silacycle silica. Compound **68** was purified on a flash column with 230 – 400 EM science silica.

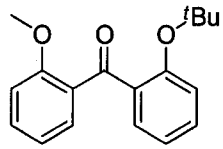
$TiCl_3$ was obtained from the Aldrich company. $TiCl_3 \cdot DME_{1.5}$ was made from Titanium powder and $TiCl_4$.[33] Zn/Cu couple was made from Zn metal and $CuSO_4$ in deoxegenated water following the literature preparation.[52] Both 2-methoxynaphthalene and 1-methoxynaphthalene were purchased from the Aldrich Chemical Company. *N,N*-dimethylaniline was purchased from the Fisher Chemical Company. 2,2',6,6'-tetramethoxybenzophenone and 2,2',6,6'-tetramethoxybenzophenol were prepared following this literature reference.[46]



53

***N*-methyl-2,*N*-dimethoxybenzamide 53.** To a solution of 2-methoxybenzoyl chloride (3.151 g, 18.5 mmol) and methoxymethylamine hydrochloride (1.804 g, 18.5 mmol) in anhydrous CH_2Cl_2 (20 mL) was added pyridine (2.8 mL) slowly in portions, producing a large amount of heat. One hour later a large amount of white precipitate separated. This reaction mixture was dissolved in additional CH_2Cl_2 (100 mL). The resulting solution was washed with 2M NaOH (3 x 20 mL). The aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic phases were dried over

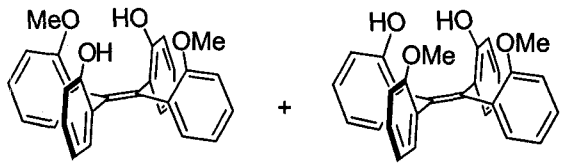
$MgSO_4$, filtered through filter paper, and the solvents were removed under reduced pressure, producing 3.738 g of crude product. This product was recrystallized from hexanes with a minimum amount of CH_2Cl_2 at 0 °C producing 3.166 g of off-white crystals. Yield: 88%. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.36 (td, J = 7.9, 1.8 Hz, 1H), 7.3-7.26 (m, 1H), 6.98 (td, J = 7.47, 0.9 Hz, 1H), 6.93 (d, J = 8.4 Hz, 1H), 3.85 (s, 3H), 3.56 (s, br, 3H), 3.31 (s, br, 3H). This compound is further characterized in the literature.[53]



54

2-*tert*-butoxy-2'-methoxybenzophenone 54. A solution of *tert*-butoxybenzene (0.3649 g, 2.425 mmol) and TMEDA (0.5 mL, 3.3 mmol) in diethyl ether (2 mL) was cooled to -78 °C. 2.5 M *n*-BuLi in hexanes (1.5 mL, 3.75 mmol) was added dropwise to the solution. The flask was allowed to warm to room temperature. A separate flask was prepared containing *N*-methyl-2,*N*-dimethoxybenzamide **53** (0.2465 g, 1.263 mmol) in diethyl ether (2 mL). The *N*-methyl-2,*N*-dimethoxybenzamide **53** solution was transferred into the *tert*-butoxybenzene solution via cannula after the *tert*-butoxybenzene metallation had stirred for four hours. The reaction mixture immediately turned green; however, the colour eventually turned red. After two hours, the reaction was quenched with H_2O (5 mL) and then diethyl ether (10 mL) was added. The aqueous layer was extracted with diethyl ether (3 x 5 mL). The combined organic fractions were washed with H_2O (2 x 5 mL), dried with $MgSO_4$,

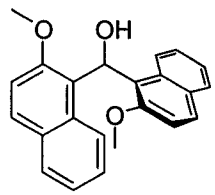
and filtered through filter paper. The solvent was removed under reduced pressure to produce 0.4218 g of a crude product mixture. The mixture was purified by flash chromatography to produce 2-*tert*-butoxy-2'-methoxybenzophenone **54** (0.2452 g, 0.863 mmol). Yield 68%. IR (microscope): 3271, 2923, 1643, 1250, 1159, 1113 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.60 (dd, J = 7.6, 1.9 Hz, 1H), 7.51 (dd, J = 7.6, 1.8 Hz, 1H), 7.40 (m, 2H), 7.11 (dt, J = 7.5, 1.1 Hz, 1H), 7.03-6.95 (m, 2H), 6.91 (d, J = 7.6, 1.8 Hz, 1H), 3.68 (s, 3H), 1.08 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 196.1, 158.1, 154.4, 136.0, 132.6, 131.5, 130.6, 130.2, 130.0, 122.3, 131.8, 120.0, 111.6, 79.5, 55.7, 28.3. HRMS (EI) *m/z* calcd for $C_{18}H_{20}O_3$: 284.1412; found: 284.1410 (7%), 228 (66), 213 (39), 197 (100), 135 (46), 121 (32), 120 (20), 108 (43), 92 (26), 77 (37).



66

(*E*)- and (*Z*)-Bis(2-hydroxyphenyl)-bis(2-methoxyphenyl)ethenes 66. Zn/Cu couple (0.1240 g, 1.897 mmol) and $TiCl_3$ (0.6251 g, 4.053 mmol) were heated to reflux in DME (12 mL) for two hours. The heating source was removed. A solution of 2-*tert*-butoxy-2'-methoxybenzophenone **54** (0.1915 g, 0.6734 mmol) in anhydrous DME (6 mL) was added to the reaction via cannula transfer. Within two minutes the reaction turned dark black with a slight green hue. After 48 hours the reaction mixture was poured through celite and rinsed with CH_2Cl_2 (100 mL). The crude product was purified by flash column chromatography eluted with hexane, then 50%

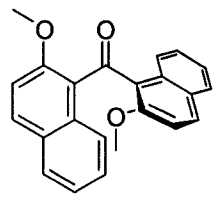
CH_2Cl_2/hexane, and then CH_2Cl_2 to produce (*E*)- and (*Z*)-bis(2-hydroxyphenyl)-bis(2-methoxyphenyl)ethenes **68** (0.0463 g, 0.109 mmol) as a 1:1 mixture by spectroscopic analysis. Yield 32%. ^{1}H NMR (300 MHz, C_6D_6): δ = 7.31 (d, J = 7.63, 2H), 7.22 (d, J = 7.02 Hz, 2H), 7.07 (d, J = 7.26, 2H), 6.75-6.92 (m, 14H), 6.52-6.68 (m, 12H), 6.28 (d, J = 8.2 Hz, 2H), 6.21 (d, J = 8.2 Hz, 2H), 3.22 (s, 6H), 3.13 (s, 6H). These two compounds have been previously characterized.[1]



56

Bis(2-methoxy-1-naphthyl)methanol 56. Under an atmosphere of argon 1-bromo-2-methoxynaphthalene (3.12 mg, 13.2 mmol) was dissolved in THF (12.5 mL). A stir bar and Mg turnings (330 mg, 13.6 mmol) were added to the solution under a flow of argon and the reaction was left stirring. Anthracene (1 mg) and dibromoethane (2 drops) were added to help initiate the formation of the Grignard reagent. The reaction mixture was heated to 55 °C for five hours. The reaction mixture was allowed to cool to room temperature and then methyl formate (0.40 mL, 6.5 mmol) in THF (10 mL) was added slowly. The following day, the reaction mixture was quenched with H_2O (10 mL). The aqueous layer was extracted with ethyl ether (3 x 30 mL). The combined organic fractions were dried with $MgSO_4$, filtered through filter paper, and the solvent was removed under reduced pressure.

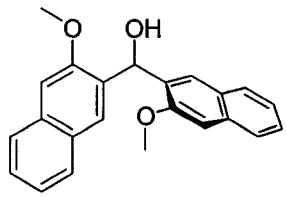
The crude product was purified by flash column chromatography to give bis(2-methoxy-1-naphthyl)methanol **56** (850 mg, 3.79 mmol) as a yellow solid. Yield 58%. IR (film) 3488, 3052, 2936, 2837, 1085 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 8.6 Hz, 2H), 7.80 (d, *J* = 9.0 Hz, 2H), 7.78 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.39 (td, *J* = 6.8 Hz, 1.6 Hz, 2H), 7.33 (td, *J* = 6.8, 1.2 Hz, 2H), 7.28 (d, *J* = 9.0 Hz, 2H), 6.05 (d, *J* = 8.8 Hz, 1H), 3.77 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 197.3, 152.4, 132.7, 132.0, 128.2, 117.5, 116.3, 43.5. HRMS calcd for $C_{23}H_{20}O_3$ *m/z* = 344.14124, found *m/z* = 344.14060.



57

Bis(2-methoxy-1-naphthyl)methanone 57. Bis(2-methoxy-1-naphthyl)methanol **56** (654 mg, 1.90 mmol) was dissolved in CH_2Cl_2 (20 mL). PCC (425 mg, 1.97 mmol) was added to the reaction mixture and allowed to stir overnight. The following day, the reaction mixture was filtered through silica gel. The crude product was purified by flash chromatography to give bis(2-methoxy-1-naphthyl)methanone (289 mg, 0.844 mmol) as a yellow solid. Yield 44%. IR (microscope) 3077, 2944, 2843 1274, 1207 1148 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 8.6 Hz, 2H), 7.89 (d, *J* = 9.0 Hz), 7.82 (d, *J* = 8.1 Hz, 2H), 7.52 (td, *J* = 6.9, 1.4 Hz, 2H), 7.40 (td, *J* = 6.8, 1.1 Hz, 2H), 7.16 (d, *J* = 9.1 Hz, 2H), 3.38 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 199.8, 155.7, 131.9, 131.7, 129.2, 127.9, 127.4, 127.2, 125.1, 124.0,

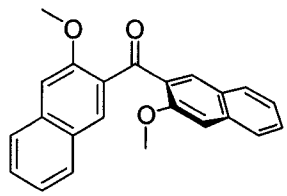
113.9, 56.7. ^{1}H GCOSY (300 MHz, $CDCl_3$): δ = 8.18 ↔ 7.52; 7.89 ↔ 7.16; 7.40 ↔ 7.82, 7.52. HRMS calcd for $C_{23}H_{18}O_3$ *m/z* = 342.12558, found *m/z* = 342.12515.



58

Bis(3-methoxy-2-naphthyl)methanol 58. 2-methoxynaphthalene (2.05 g, 12.9 mmol) and TMEDA (2 mL, 13 mmol) were dissolved in THF (40 mL) under an argon atmosphere. At –10 °C, 2.5 M *n*-Buli in hexanes (5 mL, 12.5) was added to the reaction mixture dropwise via syringe. After two hours, a solution of methyl formate (0.31 mL, 5.0 mmol) in THF (10 mL) was transferred to the reaction flask via cannula at 0 °C. The solution immediately turned green and eventually turned orange. The reaction was allowed to warm overnight. Ten hours later, the reaction was quenched with H_2O (20 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with H_2O (2 x 10 mL), sat. NaCl (1 x 10 mL), dried with anhydrous $MgSO_4$ and filtered through filter paper. The solvent was removed under reduced pressure to give 3.479 g of crude material. This material was purified by flash silica chromatography eluting first with 10% ether/hexane and then 30% ether/hexane to afford bis(3-methoxy-2-naphthyl)methanol **58** (1.35 g, 0.00392 mol) that is almost pure by ^{1}H NMR spectroscopy. An unidentified minor impurity could not be removed, so the material was used as is in the next step. Yield 60% slightly impure. IR (film) 3365, 3054, 3003, 2937, 2835 1095, 1025 cm^{-1}. ^{1}H NMR

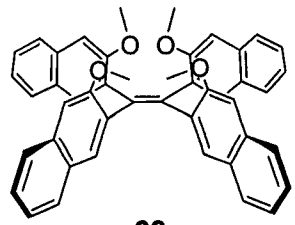
(300MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.3 Hz, 2H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.68 (s, 2H), 7.43 (td, *J* = 6.9, 1.3 Hz, 2H), 7.32 (td, *J* = 6.8, 1.3 Hz, 2H), 7.18 (s, 2H), 6.62 (d, *J* = 4.7 Hz, 1H), 3.94 (s, 6H), 3.47 (d, *J* = 4.7 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 155.7, 134.0, 132.4, 128.7, 128.0, 127.2, 126.3, 126.2, 123.8, 105.4, 67.2, 55.5. ^1H GCOSY (300 MHz, $CDCl_3$): δ = 7.75 ↔ 3.47, 7.70; 7.70 ↔ 7.32; 6.62 ↔ 3.47. HRMS calcd for $C_{23}H_{20}O_3$ *m/z* = 344.14124, found *m/z* = 344.14119.



59

Bis(3-methoxy-2-naphthyl)methanone 59. Bis(3-methoxy-2-naphthyl)methanol **58** (425 mg, 1.24 mmol) was added to a solution of $Na_2Cr_2O_7$ in acetone (15 mL) and H_2O (5 mL). Concentrated H_2SO_4 (1 mL) was added to the reaction mixture. After nineteen hours, H_2O (20 mL) was added to the solution. The aqueous phase was extracted with ethyl ether (3 x 30 mL). The combined organic fractions were washed with distilled H_2O (2 x 10 mL) and sat. NaCl (10 mL). The organic phase was dried with $MgSO_4$, filtered through filter paper and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography to give bis(3-methoxy-2-naphthyl)methanone **59**, (276 mg, 0.806 mmol) as a slightly yellow solid. Yield 65%. IR (film) 3054, 2974, 2947, 2837, 1626, 1199 ^1H NMR (300 MHz, $CDCl_3$): δ = 8.08 (s, 2H), 7.83 (dd, *J* = 8.1, 0.7 Hz, 2H), 7.76 (dd, *J* = 8.2, 0.8 Hz, 2H), 7.52 (td, *J* = 6.9, 1.3 Hz, 2H), 7.38 (td, *J* = 6.9, 1.5 Hz, 2H), 7.16 (s, 2H),

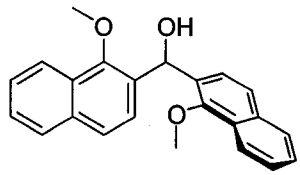
3.77 (s, 6H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 194.8, 155.8, 136.0, 131.9, 131.3, 129.0, 128.1, 128.0, 126.4, 124.2, 105.9, 55.6. ^{1}H GCOSY (300 MHz, $CDCl_3$): δ = 7.38 $\leftrightarrow$ 7.83, 7.52; 7.76 $\leftrightarrow$ 7.52. HRMS calcd for $C_{23}H_{18}O_3$ *m/z* = 342.12558, found *m/z* = 342.125551.



68

tetrakis(3-methoxy-2-naphthyl)ethene 68. In a glove box, Bis(3-methoxy-2-naphthyl)methanone **59** (48.8 mg, 0.142 mmol), Zn/Cu (15.0 mg, 0.229 mmol) and $TiCl_3(DME)_{1.5}$ (119.5 mg, 0.413 mmol) were placed in a small Schlenk flask. A stir bar and DME (6 mL) were then added, the flask was sealed with a greased glass stopper, taken out of the glove box, and allowed to stir magnetically at room temperature for 66 hours. The reaction was quenched with 2M HCl (10 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic fractions were then extracted with H_2O (2 x 10 mL), sat. NaCl (aq), and then dried over $MgSO_4$. The solvent was then removed under reduced pressure to produce 58.4 mg of crude material. That material was then purified by column chromatography using CH_2Cl_2 as an eluent. The desired product tetrakis(3-methoxy-2-naphthyl)ethene **68** (43.2 mg, 0.066 mmol) was produced in 93 % yield as a yellow solid. IR (film) 3053, 2999, 2950, 2830, 1628, 1597, 1257, 1172, 1019 cm^{-1}. ^{1}H NMR (300 MHz, 20 °C, $CDCl_3$): δ = 7.72 (s, 3H), 7.55-7.6 (m, 8H), 7.44 (s, br, 1H), 7.31 (t, *J* = 7.4 Hz, 4H), 7.18 (t, J

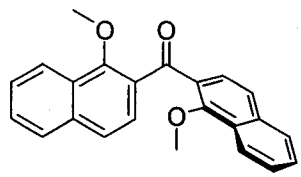
= 7.5 Hz, 4H), 6.88 (s, 4H), 3.56 (s, 9H), 3.50 (s, br, 3H). ^{1}H NMR (300 MHz, 60 °C, $CDCl_3$): δ = 7.71 (s, br, 4H), 7.55-7.6 (m. 8H), 7.30 (t, J = 7.4 Hz, 4H), 7.17 (t, J = 7.5 Hz, 4H), 6.88 (s, 4H), 3.59 (s, 12H). ^{1}H GCOSY (300 MHz, $CDCl_3$): δ = 7.54 ↔ 7.31, 7.18; 7.31 ↔ 7.18. ^{13}C NMR (400 MHz, 20 oC, $CDCl_3$): δ = 156.4, 133.7, 130.7, 128.5, 127.6, 126.0, 125.4, 122.9, 105.2, 55.4. HRMS calcd for $C_{46}H_{36}O_4$ *m/z* = 652.26135, found *m/z* = 652.26246.



63

Bis(1-methoxy-2-naphthyl)methanol 63. 1-Methoxynaphthalene (3 mL, 20 mmol) and TMEDA (3 mL, 20 mmol) were dissolved in dry hexanes (20 mL). 2.5M *n*-BuLi in hexanes (8.4 mL, 21 mmol) was added dropwise via syringe, creating a red solution. Three hours later, the reaction mixture was cooled to -78 °C and a solution of methyl formate (0.49 ml, 8 mmol) in THF (20 mL) was added to the reaction via cannula transfer. The solution turned a green colour. The reaction was allowed to return to room temperature overnight with magnetic stirring. The following day, the reaction was quenched with H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic fractions were washed with H_2O (2 x 10 mL) and sat. NaCl (aq) (10 mL). The organic phase was then dried with anhydrous $MgSO_4$, filtered through filter paper, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (SiO_2:

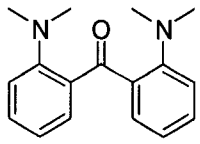
50% CH_2Cl_2/hexanes) to give bis(1-methoxy-2-naphthyl)methanol **63** (0.6104 g, 1.77 mmol) as a yellow oil. Yield 22%. IR (microscope): 3407, 3054. 2938, 2841, 1930, 1597 1081, 1033 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.13 (d, J = 8.0 Hz, 2H), 7.85 (d, J = 7.8 Hz, 2H), 7.44 – 7.66 (m, 8H), 6.94 (s, 1H), 3.94 (2, 6H), 3.22 (s, br, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 134.7, 131.6, 129.0, 128.2, 127.8, 126.1, 125.4, 124.3, 122.3, 66.4, 62.4. ^1H GCOSY (300 MHz, $CDCl_3$): δ = 8.13 ↔ 7.46; 7.85 ↔ 7.44; 7.61 ↔ 7.59; 7.46 ↔ 7.44; 6.94 ↔ 3.22. HRMS calcd for $C_{23}H_{20}O_3$ m/z = 344.14124, found m/z = 344.14060.



64

Bis(1-methoxy-2-naphthyl)methanone 64. A suspension was made of bis(1-methoxy-2-naphthyl)methanol **63** (0.9176 g, 2.66 mmole) and $Na_2Cr_2O_7$ in a mixed solvent system of acetone (30 mL) and H_2O (10 mL). H_2SO_4 (1 mL) was added dropwise. Three hours later, the reaction mixture was extracted with CH_2Cl_2 (3 x 30 mL). This solution was washed with H_2O (3 x 10 mL) and sat. NaCl (aq) (10 mL). The solution was dried over $MgSO_4$, filtered through filter paper, and the solvent was removed under reduced pressure to give bis(1-methoxy-2-naphthyl)methanone **64** (705 mg, 2.06 mmol) as a yellow oil. Yield 77%. IR (microscope): 3055, 2937, 2846, 1933, 1654 1208, 1093 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.21 (d, J = 7.1 Hz, 2H), 7.89 (d, J = 8.07 Hz, 2H), 7.66 (m, 4H), 7.52-7.64 (m, 4H), 3.83 (s, 6H).

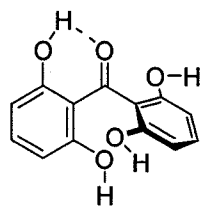
^{13}C NMR (400 MHz, $CDCl_3$): δ = 194.8, 155.9, 136.0, 131.9, 131.2, 129.0, 128.0, 126.4, 124.2, 105.9, 55.6. ^{1}H GCOSY (300 MHz, $CDCl_3$): δ = 8.21 ↔ 7.56; 7.89 ↔ 7.60; 7.60 ↔ 7.56. HRMS calcd for $C_{23}H_{18}O_3$ *m/z* = 342.12558, found *m/z* = 342.12551.



55

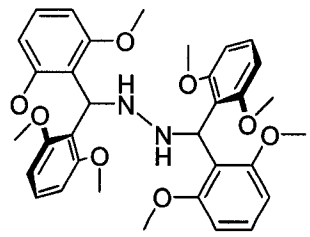
Bis(2-*N*,*N*-dimethylaminophenyl)methanone 55. *N*,*N*-dimethylaniline (7.6 mL, 60 mmoles) and TMEDA (3 mL, 20 mmol) were dissolved in hexanes (12 mL). At room temperature, 2.5 M *n*-BuLi in hexanes (8 mL, 20 mmol) was added via syringe into the reaction. The reaction mixture was heated to 65 °C for 23 h. The resultant solution was then cooled to -78 °C and a solution of *N*,*N*-dimethylcarbamoyl chloride (0.91 mL, 9.9 mmol) in THF (20 mL) was transferred via cannula. After three hours, 2M NaOH (20 mL) was added to quench the reaction. The two layers were separated in a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic fractions were washed with 2M NaOH (2 x 20 mL) and sat. NaCl (aq) (20 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered through filter paper, and then the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2: CH_2Cl_2) giving bis(2-*N*,*N*-dimethylamino-1-phenyl)methanone **55** (640 mg, 2.38 mmol) as an orange solid. Yield 24%. IR (microscope) 3083, 3016, 2954, 2865, 2801, 1946, 1640, 1160, 1052 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 (dd, *J* = 7.7, 1.7 Hz, 2H), 7.35 (td, *J* =

7.1, 1.7 Hz, 2H), 6.97 (dd, J = 8.4, 0.8 Hz, 2H), 6.77 (td, J = 7.4, 1.0 Hz, 2H), 2.82 (s, 12H). ^{13}C NMR (400 MHz, $CDCl_3$): δ = 197.3, 152.4, 132.7, 132.0, 128.2, 117.5, 116.3, 43.5. HRMS Calcd for $C_{17}H_{20}ON_2$ *m/z* = 268.15756, found *m/z* = 268.15730.



75

2,2',6,6'-tetrahydroxybenzophenone 75. To a solution of 2,2',6,6'-tetramethoxybenzophenone **71** (26.5 mg, 0.088 mmoles) in CH_2Cl_2, an unknown excess of BBr_3 was added. After stirring for fifteen hours, the reaction was quenched with H_2O (10 mL). This quenching produced orange solids. Additional CH_2Cl_2 (30 mL) was added which dissolved the solid. The reaction mixture was further extracted with CH_2Cl_2 (2 x 30 mL). The combined organic fractions were washed with H_2O (2 x 10 mL), sat. NaCl (aq) (10 mL) and then dried with $MgSO_4$ and filtered through filter paper. The solvent was removed under reduced pressure to produce 2,2',6,6'-tetrahydroxybenzophenone (**75**) (10.5 mg, 0.043 mmol) as an orange solid. Yield 49 %. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.84 (s, OH, 1H), 7.72 (s, OH, 2H), 7.62 (td, J = 8.38, 0.32 Hz, 1H), 7.31 (t, J = 8.25 Hz, 1H), 6.93 (dd, J = 8.42, 0.93 Hz, 1H), 6.81 (dd, J = 8.28, 0.93 Hz, 1H), 6.49 (d, J = 8.25, 2H), 1.26 (s, 1H). ^{1}H GCOSY (300 MHz, $CDCl_3$): δ = 7.62 ↔ 6.93, 6.81; 7.31 ↔ 6.49. Due to the small amount of product and reproducibility problems, full characterization was not possible.



77

1,2-(bis(2,6-dimethoxyphenyl)methyl)hydrazine 77. A biphasic solution of 2,2',6,6'-tetramethoxybenzophenol (30.3 mg, 1.00 mmol) in CH_3CN (2 mL) over $N_2H_4 \cdot H_2O$ (0.1 mL, 0.02 mol) was cooled with an ice bath. H_2SO_4 was added dropwise to the solution and with each drop the solution turned red momentarily. The H_2SO_4 was added until the reaction mixture turned red permanently. A few drops of hydrazine hydrate were added to the solution until the reaction mixture again became colourless. CH_2Cl_2 (20 mL) was immediately added. The resulting solution was then washed with H_2O (2 x 5 mL), sat. NaCl (aq), dried over $MgSO_4$ and filtered through filter paper. The solvent was removed under reduced pressure to give 28.5 mg of crude material. The major product was 1,2-(bis(2,6-dimethoxyphenyl)methane)hydrazine **77**, identified spectroscopically, accompanied by an unidentified byproduct. The unidentified byproduct is most likely the result of acetonitrile reacting with the intermediate carbocation.[46] IR (microscope): 3092, 2987, 2932, 2830, 1587, 1241, 1106 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.05$ (t, $J = 8.27$ Hz, 4H), 6.43 (d, $J = 8.29$ Hz, 8H), 6.25 (s, 2H), 3.62 (s, 24H). ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 159.0, 158.5, 128.4, 127.5\ 104.9, 55.6$. HRMS (EI) *m/z* calcd for $C_{34}H_{40}O_8N_2$: *m/z* = 604.27844; found: *m/z* = 604.27786(15 %), 287.12844(89%), 151.07579(100%).

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