2,2',6,6'-Tetrasubstituted Diarylethynes: Models to Test Proximity and Position in Catalysis.

Kevin Levon Evans  
Louisiana State University and Agricultural & Mechanical College
INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps. Each original is also photographed in one exposure and is included in reduced form at the back of the book.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.
2,2',6,6'-Tetrasubstituted diarylethynes: Models to test proximity and position in catalysis

Evans, Kevin LeVon, Ph.D.

The Louisiana State University and Agricultural and Mechanical Col., 1993
2,2',6,6'-TETRASUBSTITUTED DIARYLETHYNES: MODELS TO TEST PROXIMITY AND POSITION IN CATALYSIS

A Dissertation

Submitted to the Graduate Faculty of Louisiana State University and Agricultural and Mechanical College in partial fulfillment of the requirements for the degree of Doctor of Philosophy

in

The Department of Chemistry

by
Kevin LeVon Evans
B.A., Glenville State College, 1987
May 1993
ACKNOWLEDGEMENT

I would like to thank Professor Richard D. Gandour who has been much more than just an advisor, he has been a friend. He gave me the independence and encouragement that I required to succeed. He advised me in both my academic and personal life.

I would like to thank my family and friends for their love and support throughout this endeavor. They were always available when I needed a friend and restored my confidence when I doubted my abilities. A special thanks to my friends in Louisiana who made this an enjoyable and educational time.

Many people at LSU have been instrumental to my success. Dr. Frank R. Fronczek solved the X-ray crystal structures. Dr. David Vargas taught me the NMR techniques necessary to assign the proton and carbon spectra of the products. Many undergraduate students have work with me throughout the years and all have been very helpful. In particular, Joe Guitreau and Enoch T. Huang were especially helpful. There are many others who go unmentioned, but I appreciate your support. Thank you all for your friendship and support.
TABLE OF CONTENTS

Acknowledgement ................................................................. ii

List of Figures ........................................................................ vi

List of Schemes ......................................................................... viii

Abstract .................................................................................. xi

CHAPTER 1: INTRODUCTION .................................................. 1

1.1 ORIGINS OF CATALYTIC POWER IN ENZYMES .......... 3
  1.1.1 Orbital Steering .......................................................... 3
  1.1.2 Propinquity ............................................................... 6
  1.1.3 Entropy Trapping ....................................................... 7
  1.1.4 Spatiotemporal Hypothesis ....................................... 7
  1.1.5 Summary ................................................................. 10

1.2 PROJECT GOAL ............................................................. 11
  1.2.1 Proximity Effect ......................................................... 13
  1.2.2 Positioning of Catalytic Groups ................................. 14

1.3 RATIONALE FOR THE DESIGN OF THE MODEL .......... 15
  1.3.1 Rigid Framework ..................................................... 15
  1.3.2 Free Rotation .......................................................... 15
  1.3.3 Appropriate Geometry for Catalysis ......................... 16
  1.3.4 Variability of Tethers ................................................. 17

1.4 SPECIFIC GOAL ............................................................ 18

CHAPTER 2: PROPOSED SYNTHESSES OF DIARYLETHYNE MODELS ........................................... 19

2.1 RETROSYNTHETIC ANALYSIS ...................................... 19
  2.1.1 Pathway 1 ............................................................... 20
  2.1.2 Pathway 2 ............................................................... 22
    2.1.2.1 Route A ............................................................ 24
    2.1.2.2 Route B ............................................................ 24
    2.1.2.3 Route C ............................................................ 24
  2.1.3 Summary ................................................................. 25
2.2 SYNTHESES OF MONO- AND DIARYLETHYNES ......................... 26
  2.2.1 Elimination Reactions .................................................. 26
    2.2.1.1 Halogenation-Dehydrohalogenation of Ketones ............ 27
    2.2.1.2 Dehydrohalogenation of Dihaloalkenes .................... 28
    2.2.1.3 Ring Fragmentation of Preconstructed Heterocycles ...... 28
    2.2.1.4 Opening of Benzofurans ...................................... 29
  2.2.2 Substitution Reactions ................................................ 30
    2.2.2.1 Grignard Reaction ................................................ 30
    2.2.2.2 Copper-mediated Coupling .................................... 31
    2.2.2.3 Palladium-mediated Coupling .................................. 32
    2.2.2.4 Friedel-Crafts Alkylation with Tetrachlorocyclopropene .. 34
  2.3 CONCLUSIONS ..................................................................... 35

CHAPTER 3: RESULTS AND DISCUSSION ........................................... 37

3.1 PROTECTING GROUPS FOR PHENOLS ...................................... 37

3.2 ARYL TRIFLATES ................................................................. 38

3.3 ARYL HALIDES ........................................................................ 39

3.4 SYNTHESES OF ARYLETHYNES ............................................ 40
    3.4.1 Halogenation-Dehydrohalogenation of Ketones ............. 41
      3.4.1.1 Formation of the Vinyl Chloride ......................... 41
      3.4.1.2 Dehydrohalogenation of Vinyl Chlorides ............... 43
      3.4.1.3 Limitations of this Reaction .............................. 43
    3.4.2 Palladium-mediated Coupling ..................................... 45

3.5 SYNTHESES OF DIARYLETHYNES ........................................ 47

3.6 SAPONIFICATION OF THE METHYL ESTER .............................. 49

3.7 DEMETHYLATIONS .................................................................. 51
    3.7.1 Boron Tribromide .................................................... 51
    3.7.2 Boron Trichloride .................................................... 52
    3.7.3 Trimethylsilyl Iodide ............................................... 54
    3.7.4 Acetic Acid/Sulfuric Acid ........................................... 56

3.8 OPENING OF 2-PHENYLBENZOFURAN .................................... 56
3.9 LACTONIZATION TO ISOBENZOFURANONES AND BENZOPYRANONES ........................................... 58
  3.9.1 Bromolactonization ......................................................... 58
  3.9.2 Palladium-mediated Lactonization .................................. 59
  3.9.3 Uncatalyzed Lactonization .............................................. 60

3.10 EXPERIMENTAL ............................................................... 61
  3.10.1 General Methods ......................................................... 61
  3.10.2 Preparative Methods .................................................... 62

CHAPTER 4: CONCLUSION ......................................................... 86

4.1 SUMMARY OF PROGRESS .................................................. 86
  4.1.1 Retrosynthetic Pathway 1 ............................................... 86
  4.1.2 Retrosynthetic Pathway 2 ............................................... 88

4.2 FUTURE SYNTHETIC EFFORTS ............................................ 89
  4.2.1 Retrosynthetic Pathway 3 ............................................... 90
  4.2.2 Retrosynthetic Pathway 4 ............................................... 92

4.3 CONCLUSION ................................................................. 94

Bibliography ................................................................. 100

Appendix A: Crystallographic Data for 2'-Acetoxy-6'-methoxyacetophenone ........................................ 112

Appendix B: Crystallographic Data for 2-(1-Chlorovinyl)-1,3-dimethoxybenzene ................................... 114

Appendix C: Crystallographic Data for 2-[2,6-Dimethoxyphenyl)ethynyl]-3-methoxybenzoic Acid .......... 116

Appendix D: Crystallographic Data for Boracycle ................................................................. 119

Appendix E: Crystallographic Data for 2-(2,6-Dimethoxyphenyl)benzofuran-4-carboxylic acid .......... 122

Appendix F: Crystallographic Data for 5-Methoxy-3-(2,6-dimethoxyphenyl)-1H-benzo-2-pyran-1-one .... 125

Appendix G: Crystallographic Data for (Z)-4-Methoxy-3-[(2,6-dimethoxyphenyl)methylene-1(3H)-isobenzofuranone ................................................................. 128

Vita ................................................................. 131
LIST OF FIGURES

Figure 1.1 Intramolecular Model with Bimolecular Counterpart .................. 3
Figure 1.2 Koshland's Models to Study the Effect of Orientation
on the Relative Rates of Lactonization .............................................. 4
Figure 1.3 Effect of Proximity on the Relative Rates of Anhydride Formation .. 6
Figure 1.4 Effect of Orientation on Relative Rates of Lactonization ............. 8
Figure 1.5 Effect of Freezing One Rotation on Relative Rates .................... 9
Figure 1.6 Hydrocarbon Analogues to Arylpropionic Acids ...................... 10
Figure 1.7 Diarylethylene Models for the Study of Proximity on Catalysis ...... 12
Figure 1.8 Illustration of the Fixed Orbits of Functional Groups
on Diarylenethylenes ......................................................................... 13
Figure 1.9 PCMODEL PI Calculated Transition Structure for
Hydrolysis Reaction ........................................................................... 16
Figure 3.1 Coordination of Alkylithium .................................................. 39
Figure 3.2 Bis-[2-Methoxy-6-(methoxymethoxy)phenyl]ethyne ................. 47
Figure 3.3 Enyne Side-product Formed in the Coupling Reaction ............. 48
Figure 3.4 Proposed Bidentate Boron Complex ....................................... 53
Figure 3.5 Alternate Benzofuran from Demethylation with
Trimethylsilyl Iodide .......................................................................... 55
Figure 3.6 Proposed Transition Structures for Cyclization
to Benzofuran and Isobenzofuranones .............................................. 55
Figure 3.7 Transition Structure for Bromolactonization ........................... 59
Figure 4.1 List of New Arylethynes Synthesized ................................. 94
Figure 4.2  List of Diarylethynes Synthesized .................................................. 96

Figure 4.3  Series of Arylnaphthylethynes to Study Proximity
              and Position in Catalysis ................................................................. 96
**LIST OF SCHEMES**

| Scheme 1.1 | D'Souza and Bender’s Cyclodextrin Model of Chymotrypsin | 2 |
| Scheme 1.2 | Preliminary Model of the Hydrolysis Reaction | 17 |
| Scheme 2.1 | Retrosynthetic Pathway for the Tethered and Untethered Diarylethyynes | 20 |
| Scheme 2.2 | Retrosynthetic Pathway for the Tethered Diarylethyynes | 23 |
| Scheme 2.3 | Classic Synthesis of Diphenylethyne | 27 |
| Scheme 2.4 | Halogenation-Dehydrohalogenation of Ketones | 27 |
| Scheme 2.5 | Dehydrohalogenation of Dihaloalkenes | 28 |
| Scheme 2.6 | Ring Fragmentation of Preconstructed Heterocycles | 29 |
| Scheme 2.7 | Ring Opening of Benzofuran. | 29 |
| Scheme 2.8 | Ring Opening of Furylnaphthalene | 30 |
| Scheme 2.9 | Grignard Reactions for Synthesizing Diarylethyynes | 31 |
| Scheme 2.10 | Castro-Stephens Coupling Reaction | 32 |
| Scheme 2.11 | Friedel-Crafts Alkylation with Tetrachlorocyclopropene | 35 |
| Scheme 3.1 | Protection of Phenol in 2’-Hydroxy-6’-methoxyacetophenone | 37 |
| Scheme 3.2 | Protection of Resorcinol and Resorcinol Monomethyl Ether | 38 |
| Scheme 3.3 | Synthesis of Aryl Triflates | 39 |
| Scheme 3.4 | Synthesis of Aryl Halides | 40 |
| Scheme 3.5 | Synthesis of 1-Chloro-3-ethynyl-2,4-dimethoxybenzene | 41 |
| Scheme 3.6 | Synthesis of Vinyl Chlorides | 42 |
| Scheme 3.7 | Dehydrohalogenation of Vinyl Chloride to Arylethyynes | 43 |
Scheme 3.8 Attempted Dehydrohalogenation of 2-(1-Chlorovinyl)-1-benzyloxy-6-methoxybenzene ............... 44
Scheme 3.9 Dehydrohalogenation of 2-(1-Chlorovinyl)-1-benzyloxy-3-methoxybenzene Using Trimethylsilyl Iodide ......................... 45
Scheme 3.10 Attempted Palladium-mediated Coupling of Aryl Triflate with Trimethylsilylethyne ................................. 46
Scheme 3.11 Palladium-mediated Coupling Forming Arylethynes ................................................................. 46
Scheme 3.12 Palladium-mediated Coupling of an Aryl Triflate with Arylethynes Forming Diarylethynes ................................. 48
Scheme 3.13 Palladium-mediated Coupling of Aryl Iodides with an Arylethyne Forming Diarylethynes ................................................................. 50
Scheme 3.14 Hydrolysis of Methyl Ester ......................................................... 51
Scheme 3.15 Demethylation Using Boron Tribromide .............................................. 51
Scheme 3.16 Mono-demethylation of 2',6'-Dimethoxyacetophenone ......................... 52
Scheme 3.17 Demethylation Using Boron Trichloride ............................................ 53
Scheme 3.18 Cleavage of the Boron Ring ........................................................... 54
Scheme 3.19 Demethylation Using Trimethylsilyl Iodide ........................................... 54
Scheme 3.20 Demethylation by Sulfuric Acid/Acetic Acid ........................................ 56
Scheme 3.21 Opening of 2-Phenylbenzofuran to 1-(2-Acetoxyphenyl)-2-phenylethyne ................................................. 57
Scheme 3.22 Bromolactonization Forming Benzopyranones .................................. 58
Scheme 3.23 Palladium-mediated Lactonization Forming Benzopyranones ......... 60
Scheme 3.24 Uncatalyzed Lactonization Forming Isobenzofuranones ............... 60
Scheme 4.1 Intramolecular General-acid Hydrolysis of an Acetal ....................... 86
Scheme 4.2 Precursor to the Untethered Diarylethyne Model .......................... 87
| Scheme 4.3 | Proposed Synthesis of a Precursor to Untethered Diarylethylene | 87 |
| Scheme 4.4 | Proposed Synthesis of Carboxyl Protected Aryl Iodide Synthon | 89 |
| Scheme 4.5 | Retrosynthetic Pathway for Synthesizing the Tethered Diarylethylene Models by Opening of Lactones | 91 |
| Scheme 4.6 | Synthesis of Alkynes and Alkenes Using Zinc | 91 |
| Scheme 4.7 | Retrosynthetic Pathway for Synthesizing the Tethered Diarylethynes | 93 |
| Scheme 4.8 | Synthesis of Benzofurans, Benzopyranones, and Isobenzofuranones | 97 |
Enzymes exhibit extraordinary efficiency and specificity in catalysis. A source of the catalytic power observed in enzymes has been attributed to the ability of the enzyme-substrate complex to bring the substrate into close proximity to the catalytic groups and properly oriented for reaction. However, the contributions of proximity and of orientation to the origin of catalytic power have not been quantified. How much does proximity and orientation contribute to the rate enhancement? We have proposed a series of tethered and untethered 2,2',6,6'-tetrasubstituted diarylethynes to study the effect of proximity of the catalytic group to the substrate on catalysis.

The syntheses of the diarylethynyl models require efficient procedures for the synthesis of 2,6-disubstituted arylethynes and unsymmetrical 2,2',6,6'-tetrasubstituted diarylethynes. A literature search for the preparation of mono- and diarylethynes has revealed no examples of 2,6-disubstituted arylethynes with oxygen substituents or unsymmetrical 2,2',6,6'-tetrasubstituted diarylethynes. The methodology developed for synthesizing these mono- and diarylethynes serves as a basis for synthesizing the models.

Two procedures have been developed for the synthesis of arylethynes. The first method involves a modification of a classic procedure for synthesizing arylethynes from acetophenones. The second procedure involves a palladium-mediated coupling of aryl iodides with trimethyl[(trimethylsilyl)ethynyl]stannane, followed by cleaving the trimethylsilyl group. The advantages and disadvantages of these procedures are discussed. Six new arylethynes have been synthesized by these methods.
Unsymmetrical diaryl- and arynaphthylethynes have been synthesized by palladium-mediated coupling of arylethynes with aryl triflates or halides. The arynaphthylethynes serve as precursors to another series of models, which have different distances and orientations between the functional groups, to test proximity on catalysis. A close precursor, 2-[2-methoxy-6-(methoxymethoxy)phenylethynyl]-3-methoxybenzoate, to the untethered diarylethynyl was synthesized. One pathway for the synthesis of the tethered models has been eliminated; however, three additional pathways are proposed.

The ortho-substituted functional groups of the 2,2',6,6'-tetrasubstituted diarylethynes react with ethyne to form three heterocycles. The robust chemistry of the demethylation and lactonization of the diarylethynes provides an easy entry to unusual and highly substituted 2-arylbenzofurans, 3-arylbenzopyranones, and 3-benzylideneisobenzofuranones.
CHAPTER 1: INTRODUCTION

Enzymes exhibit extraordinary efficiency and specificity in catalysis. Enzymes promote very fast reactions, frequently between relatively unreactive functional groups at mild conditions of temperature and pH. A source of the catalytic power observed in enzymes has been attributed to the ability of the enzyme-substrate complex to bring the substrate into close proximity to the catalytic groups and properly oriented for reaction. However, the contributions of proximity and of orientation to the origin of catalytic power has not been quantified. How much does proximity and orientation contribute to the rate enhancement? To explore the catalytic efficiency observed in enzymes, two types of chemical models have been developed: host-guest and intramolecular.

Host-guest models have a catalytic group attached to a substrate-binding cavity (host), such as crown ethers\(^1\) and cyclodextrins,\(^2\) or to a substrate-binding cleft.\(^3\) The cavities and cleft bind a substrate (guest) by recognizing either complementary surfaces or functionalities. Once the substrate is bound, transformation of the bound substrate into product occurs.

An example of a host-guest model is the cyclodextrin model of chymotrypsin.\(^2\) (Scheme 1.1) The cavity of the cyclodextrin, a hydrophobic pocket, serves as the binding site, and an imidazole and carboxylate ion as the catalytic group. The \(m\)-\(tert\)-butylphenyl ring binds inside the cavity of cyclodextrin 1.1, orienting the acetate into close proximity of the imidazole, which catalyzes the hydrolysis of the acetate by a general-base mechanism. Deacylation of the acyl-cyclodextrin regenerates 1.1.
Intramolecular models have the catalytic group and substrate attached to the same framework. An example of an intramolecular reaction is the general-base-catalyzed hydrolysis of aspirin. To quantify the effects of the intramolecular reaction (first-order rate constant), the reaction is compared to a bimolecular counterpart (second-order rate constant). This prohibits direct comparison of the rates, and forces a comparison based on effective molarity (EM). Effective molarity is defined as the concentration of the catalytic group required to make the bimolecular reaction proceed at the observed rate of the intramolecular process. Calculating the effective molarity has stringent requirements: (1) the mechanism for both the bimolecular and intramolecular reaction must be the same; (2) the rate constants for both processes must be determined under the same conditions. To accurately calculate the effective molarity, one needs the rate constant for a bimolecular reaction with the same $pK_a$ for the catalytic group as that of the intramolecular reaction. Frequently, one obtains these by interpolation from a series of rate constants of similar reactions.

Scheme 1.1 D'Souza and Bender's Cyclodextrin Model of Chymotrypsin.
Intramolecular reactions commonly show large rate acceleration over bimolecular reactions; frequently approaching the enhancement observed in enzymes. Thus, intramolecular reactions are commonly used as simple models of the enzyme-substrate complex to explain the effects of orientation and proximity of the catalytic group to the substrate in catalysis. The studies of intramolecular reactions have resulted in numerous theories to explain the catalytic efficiency of enzymes. A brief summary of the major theories and ensuing controversies follows.

1.1.1 Orbital Steering

Koshland suggested that the enzymic catalytic power arises from "orbital steering," i.e., the directing of the orientation of the orbitals in the reacting atoms. Storm and Koshland observed that small changes in the orientation of reacting groups in lactonizations and thiolactonizations of structurally related aliphatic molecules lead to large differences in the relative reaction rates. (Figure 1.2) Koshland, using a theoretical argument, stated that holding two molecules or groups in close proximity, as...
in an intramolecular reaction, results only in a maximum 55.5-fold rate enhancement over a bimolecular reaction.

After correcting the relative rates of lactonization and thiolactonization for proximity, torsional strain, and conformational isomers, the rate enhancement should represent contributions from orientational factors. Orbital steering can account for a rate enhancement factor as large as $10^4$ per reacting atom.\(^6\) This large orientational factor requires each atom to have an stringent orientational preference; reacting at only a fraction (reaction window) of its surface.

![Diagram](image)

**Correction factors:**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Uncorrected</th>
<th>Corrected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximity:</td>
<td>1</td>
<td>79</td>
</tr>
<tr>
<td>X = O</td>
<td></td>
<td>6630</td>
</tr>
<tr>
<td>Corrected Relative Rate</td>
<td>1</td>
<td>413</td>
</tr>
<tr>
<td>X = S</td>
<td>1</td>
<td>1590</td>
</tr>
<tr>
<td>Corrected Relative Rate</td>
<td>1</td>
<td>2020</td>
</tr>
</tbody>
</table>

**Figure 1.2** Koshland's Models to Study the Effect of Orientation on the Relative Rates of Lactonization.

Orbital steering has been highly controversial. Capon\(^9\) states that no significance can be placed on correction factors used by Storm and Koshland for increases in

\(^a\)Koshland\(^7\) reported the corrected relative rate as 1660. Based on the correction factors listed, the corrected relative rate is 1590.

\(^b\)Correction factor for torsional strain was not applied.
torsional strain and the losses of rotational freedom. He states the factor for strain is underestimated, and that a factor for loss of internal rotational entropy should be included. The differences in the rate constants for the lactonizations could arise solely from differences in the increase in strain and loss of rotational freedom on going to the transition structure.

Bruice et al.\textsuperscript{10} rejected orbital steering because a rate enhancement of $10^8$ requires a reaction window of 0.1°. However, Bruice's calculation only included a reaction window for one reacting atom. Storm and Koshland\textsuperscript{73} disagreed with 0.1° reaction window, and calculated that an orientation factor of $10^4$ can be achieved by two $10^5$ reaction windows.

The biggest controversy surrounds the magnitude of the proximity correction. Bruice\textsuperscript{11} argued that experimentally observed intramolecular/intermolecular rate ratios exceed 55. Page and Jencks\textsuperscript{12} calculated, based on the loss of entropy in cyclopentadiene dimerization, that the proximity factor is approximately $10^5$. Dafforn and Koshland\textsuperscript{13} disagreed with the interpretation of the experimental rate ratios and calculated the loss of entropy for the formation of dibromine, which corresponds to a factor of 55. Page\textsuperscript{14} stated that the formation of dibromine was not a suitable model to estimate the entropic loss of more complex bimolecular reactions, and that rate enhancements up to $10^8$ can be rationalized by changes in entropy without the introduction of new concepts.
1.1.2 Propinquity

Bruice and Pandit\textsuperscript{15} proposed that the catalytic power observed in enzymatic and intramolecular reactions results from holding the functional groups in close proximity. Bruice et al.\textsuperscript{15,16} measured the rates of anhydride formation of glutarate and succinate monoesters (Figure 1.3) and concluded the following: (1) the increased reaction rates for succinate monoesters, compared with glutarate analogues, are due to closer reacting centers; (2) increasing the $\beta$-substitution of the glutarate monoester increases the population of conformations in which the esters is closer to the nucleophilic carboxylate, which is reflected by an increase in the rate; (3) likewise, increasing the rigidity of molecule results in an increase in the rate. All rate enhancements over the bimolecular reaction were attributed to a decrease in the translational entropy. Page and Jencks\textsuperscript{12} calculated that the loss of translational entropy was on the order of 25-30 eu, corresponding to a factor of $10^5$-$10^6$ in rate acceleration. Bruice\textsuperscript{17} offered that the propinquity effect, holding reactants in close proximity, can account for rate enhancement factor of $10^8$.

![Figure 1.3](image.png)

\textbf{Figure 1.3} Effect of Proximity on the Relative Rates of Anhydride Formation.
1.1.3 Entropy Trapping

Page and Jencks,\textsuperscript{12,18} based on a theoretical study of cyclopentadiene dimerization, attribute the catalytic power of enzymes to entropy trapping. When the enzyme-substrate complex forms, the rotational and translational entropies of the substrate are stopped, resulting in a lower entropy barrier to reaction. The entropy of every molecule is composed of the sum of translational, rotational, and internal entropies. The combining of two molecules to form one leads to the loss of one set of rotational and translational entropies. Because translational and rotational entropies are only slightly effected by molecular size, the transition structure or product will have approximately the same translational and rotational entropy as each of the reactants. The loss is partially compensated by an increase in the internal entropy due to new modes of internal rotation and vibration. Thus, the entropic barrier that must be overcome for a relatively simple reaction at a standard state of $1M$ is approximately $-35$ entropy units. This corresponds to a rate acceleration of $10^8 M$, which should be obtainable by binding to an enzyme active site or by an intramolecular reaction.

1.1.4 Spatiotemporal Hypothesis

Menger\textsuperscript{19} labelled the catalytic power observed in enzymatic and intramolecular reactions as the "spatiotemporal postulate"; i.e., the rate of reaction is proportional to the \textit{time} that the functional groups reside within a critical distance. Menger proposed that the distance was more important than the orientation between the functional groups. To prove this point, he studied the lactonization of substituted norbornyls.\textsuperscript{20} (Figure 1.4)
Figure 1.4 Effect of Orientation on Relative Rates of Lactonization.

Molecules 1.2 and 1.3 have similar O\textsubscript{1}⋯C\textsubscript{2} distances but the O\textsubscript{1}⋯C\textsubscript{2}⋯C\textsubscript{3} angles differ by 10°; and molecules 1.4 and 1.5 have similar O\textsubscript{1}⋯C\textsubscript{2} distances but the O\textsubscript{1}⋯C\textsubscript{2}⋯C\textsubscript{3} angles differ by 9°. According to Koshland’s orbital steering hypothesis, the alignment variation of 10° should result in a difference of 10^4 in the rates. The lactonization of 1.2 and 1.3 are almost identical, as those for 1.4 and 1.5 suggesting that angular displacement of 10° is not significant when the groups are held at a constant distance.

Menger also questioned the explanation offered by Page and Jencks\textsuperscript{12,18} that the catalytic power was a result of changes in entropy. Four points that Menger disagreed with were: (1) If entropy is so important, why are some intramolecular so slow (EM<1)? Menger disagreed with Page and Jencks’ explanation\textsuperscript{12} that effective molarities less than 1 are the result of "loose" transition structures. Menger stated that "loose" transition states should be present in both the intramolecular and intermolecular counterpart, therefore, the effect would be cancelled in the effective molarity comparison. (2) Freezing a single rotation in an intramolecular process can enhance the rate by more than a factor of 5. Menger observed that freezing one bond in the arylpropionic acids 1.6 and 1.7 results in an enhancement of 10^4. (Figure 1.5) (3) Entropies of activation show no relationship to EM values. (4) The severe model
dependency of the entropy calculations question their validity. Dafforn and Koshland\textsuperscript{13} calculated a value of 55 for the formation of dibromine, and Page and Jencks\textsuperscript{12} calculated an enhancement factor of $10^8$ for dimerization of cyclopentadiene.

\begin{center}
\begin{tabular}{c c}
\includegraphics[width=0.2\textwidth]{figure1_6} & \includegraphics[width=0.2\textwidth]{figure1_7} \\
EM = $5 \times 10^8$ M & EM = $4 \times 10^4$ M \\
1.6 & 1.7
\end{tabular}
\end{center}

\textbf{Figure 1.5} Effect of Freezing One Rotation on Relative Rates.

The criticisms by Menger did not go unanswered by Page and Jencks. Their rebuttal\textsuperscript{21} to Menger's four points was as follows: (1) EM values less than 1 can be explained by "loose" transition states. Changes in the motional degrees of freedom which occur in the intermolecular reaction have no corresponding change in the intramolecular process. Therefore, the effects will not be cancelled in the comparison of EM. (2) The value of $10^4$ observed in the cyclization of arylpropionic acids is explained in terms of release of strain energy. Page and Jencks compared the ring closures of arylpropionic acids 1.6 and 1.7 (Figure 1.5) to the corresponding hydrocarbons 1.8-1.11. (Figure 1.6) MM2 calculations indicate that 1,8-disubstituted naphthalene 1.8 is 25.6 kJ mol\textsuperscript{-1} more strained than the 1,2-disubstituted benzene 1.10. The ring closure of the arylpropionic acid 1.6 is accompanied by about 20 kJ mol\textsuperscript{-1} less change in strain energy than is that of 1.7. Together with the extra loss of internal rotation required for the cyclization of 1.7, the predicted difference in EM between 1.6
and 1.7 is $5 \times 10^4$. (3) The large variation in effective molarities is that the intramolecular reaction often involves the introduction or the removal of strain energy upon ring closure. (4) Page and Jencks re-explain their reasoning why the formation of dibromine was not an adequate model for calculating entropy because the reactants, bromine atoms, have no rotational entropy. Consequently, unlike most bimolecular combinations, there is a gain in rotational entropy when dibromine is formed from two bromine atoms.

![Figure 1.6 Hydrocarbon Analogues to Arylpropionic Acids.](image)

1.1.5 Summary

This is not a complete list of the explanations proposed to explain the catalytic power in enzymes. However, this covers some of the most important views, and the other theories are usually related to one of theories discussed. For example, Milstien and Cohen\textsuperscript{22} have proposed stereopopulation control, i.e. narrowing the distribution of conformational isomers, as the source of enzymatic catalytic power. This explanation is similar to Bruice's propinquity hypothesis.\textsuperscript{15} Houk et al.\textsuperscript{23} suggest that the enhancements in rates of enzymatic and intramolecular reactions can be understood in terms of entropy, enthalpy, and transition-state theory.
In addition, numerous similarities exist between the hypotheses. Menger’s spatiotemporal hypothesis is related to Bruice’s propinquity hypothesis. Bruice attributes the rate enhancement observed in enzymatic and intramolecular reactions to holding the groups in proximity, and also states that distance is more important than orientation. Also, the spatiotemporal hypothesis can be related to entropy. The time that functional groups reside within a critical distance is reflected by the entropy of the system. Bruice attributes the rate enhancement of intramolecular over bimolecular reactions to a decreases in translational entropy.

The spatiotemporal hypothesis is a commonly accepted explanation, however, considerable work still needs to be done to understand the catalytic power observed in enzymatic and intramolecular reactions. To date, the models that have been studied have flaws, usually relief of strain. In the absence of strain, how critical to the rate enhancement is the positioning and orientation of a catalytic group to the substrate in catalysis? To answer this question a series of rigid molecules possessing identical intramolecular reactions at gradually changing distances or orientation needs to be synthesized. We have proposed such a series of molecules to study the effect of proximity on catalysis.

1.2 PROJECT GOAL

The objective of the research is the synthesis and kinetic studies of a series of molecules, which avoid the difficulties and biases of previous models, for the study of proximity effects on catalysis. (Figure 1.7) In the tethered
molecules, 1.12t and 1.13t, the interacting functional groups are conformationally constrained into position, whereas, in the untethered molecules, 1.12u and 1.13u, the functional groups must rotate about the ethynediyl spacer, a molecular axle, into juxtaposition. The proximity effect is the enhancement in the rate of the tethered molecule compared with the untethered molecule. General-base-catalyzed hydrolysis of the dichloroacetate ester of both the tethered and untethered molecules react via an intramolecular mechanism allowing direct comparison of the first-order rate constants, thus, avoiding the difficulties of effective molarity. The molecules have identical minimum distances and orientations between the catalyst and substrate. In addition, there are no steric interactions or relief of strain to either accelerate or retard the reactions.

Figure 1.7 Diarylethyne Models for the Study of Proximity on Catalysis.
1.2.1 Proximity Effect

The hydrolysis of the dichloroacetate esters in the untethered and tethered molecules should proceed via identical transition structures, which will be verified by comparing activation parameters and solvent isotope effects. The proximity effect can be quantified for the diarylethynes, 1.12, and the 1,1'-dinaphthylethynes, 1.13, by the ratios $k_{1.12t}/k_{1.12u}$ and $k_{1.13t}/k_{1.13u}$, respectively, where $k_{1.12t}$, $k_{1.12u}$, $k_{1.13t}$, $k_{1.13u}$ are the unimolecular rate constants for the solvolysis of the dichloroacetate esters of 1.12t, 1.12u, 1.13t, and 1.13u, respectively. The expected higher rate constants in the tethered versus the untethered molecules should correspond to a less negative change in the entropy of activation, the magnitude of which depends on the advantage of holding the groups proximate to each other.

![Figure 1.8](image)

**Figure 1.8** Illustration of the Fixed Orbits of Functional Groups on Diarylethynes.

The two frameworks restrict the functional groups into fixed circular orbits about the ethynediyl spacer. (Figure 1.8) The arc length, $a$, in which an intramolecular reaction occurs, is the same for both 1.12 and 1.13, however, the circumference of 1.13 (30 Å) is approximately twice the circumference of 1.12 (15.5 Å). The larger
circumference that the functional groups traverse for 1.13u than in 1.12u lowers the probability that the groups will be within close proximity. Thus, a larger proximity effect should be observed for 1.13 than in 1.12. If the solvation changes are rapid and there is a small or no barrier of rotation about the ethynediyl, then the rate enhancement equals \( x/a \) and \( y/a \) for 1.12 and 1.13, respectively. A larger proximity effect should be observed in 1.13 than in 1.12, because \( y \) is greater than \( x \).

\[
\frac{k^{1.13u}/k^{1.12u}}{k^{1.12u}/k^{1.12u}} = \frac{y/a}{x/a} = \frac{y}{x}
\]

### 1.2.2 Positioning of Catalytic Groups

The minimum distance between the carboxylate and ester occurs when the rings are co-planar. Rotation about the ethynediyl spacer increases this distance to a point (hash marks) where intramolecular catalysis does not occur. (Figure 1.8) These two loci on the circumference define the boundaries of the arc length, \( a \), in which intramolecular catalysis occurs.

Comparing the rate enhancements of hydrolysis between diarylethynes 1.12 and 1,1'-dinaphthylethyne 1.13 will verify that \( a \) is equal in the two frameworks. If the ratio of the ratio of rate constants equals the ratio of the circumferences (see equation above), then the rate enhancement can be attributed to entropy, i.e., increased probability of having the reactants positioned for reaction. If so, then \( a \) defines the precision of positioning a carboxylate for catalysis. If the ratio of ratios does not equal two, then some factors, other than probability, affect the rate constants.
1.3 RATIONALE FOR THE DESIGN OF THE MODEL

1.3.1 Rigid Framework

The diarylethyne backbone offers many advantages. The rigidity of rings defines the geometry, reducing the number of possible conformations. The interacting groups are forced into a circular orbit around the ethynediyl spacer. The tethered and untethered molecules will have identical minimum distances and orientations. The molecules will absorb in the UV-VIS region enabling the measurement of small concentrations of the compounds. The compounds should easily crystallize allowing not only product conformation by single crystal X-ray analysis, but also giving the distances and angles between the functional groups in the solid state.

1.3.2 Free Rotation

The rotation about the ethynediyl spacer regulates the formation of the encounter complex. The internal rotation in diphenylethyne has been repeatedly studied. X-ray crystallography\textsuperscript{24} reveal that diphenylethyne has a planar conformation in the crystal phase. Interpretations of electronic absorption spectra\textsuperscript{25} and vibrational spectra\textsuperscript{26} suggest that the most probable conformation in solution is planar. Quantum mechanical calculations, using CNDO,\textsuperscript{27} INDO,\textsuperscript{27} and CNDO/2,\textsuperscript{24a} calculate the perpendicular conformation to be more stable by 0.4 to 0.7 kcal-mol\textsuperscript{-1}. Molecular orbital calculations,\textsuperscript{28} using RHF/3-21G, RHF/6-31G\textsuperscript{*}, MP2/6-31G\textsuperscript{*}, calculate the co-planar conformation to be more stable, by ca. 0.5 kcal-mol\textsuperscript{-1}, than the perpendicular. The small difference in energy between the co-planar and perpendicular conformations gives an
indication of relatively unhindered rotation. At room temperature the barrier to rotation will be exceeded, allowing free rotation in the untethered molecules.

1.3.3 Appropriate Geometry for Catalysis

The separation of the carboxylate and the dichloroacetoxy on the adjacent ring is appropriate for intramolecular general-base-catalyzed hydrolysis. The constraints of the model prevent nucleophilic acyl transfer to the carboxy. PCMODEL PI\textsuperscript{29} calculations suggest that a molecule of water can easily fit between the syn-oriented carboxy and the acetoxy. (Figure 1.9) The ethynediyl spacer occupies a minimal volume so that it does not interfere with the formation of the bridging water transition structure.

![Figure 1.9](image)

**Figure 1.9** PCMODEL PI Calculated Transition Structure for Hydrolysis Reaction. Hydrogen Bonds are Represented by Dashed Lines.
Oliver\textsuperscript{30} has studied the hydrolysis of diarylethyne 1.14. (Scheme 1.2) He concludes, based on kinetic studies, that hydrolysis occurs via intramolecular general-base catalysis with participation of the syn-oriented lone pair of the carboxy. The nucleophilic acyl transfer mechanism is not involved. In addition, Engberts et al.\textsuperscript{31} have extensively measured rates and thermodynamic parameters for hydrolysis of aryl dichloroacetate esters in various solvent mixtures. These studies will serve as a reference to confirm the mechanism of the hydrolysis of dichloroacetate ester of the tethered and untethered models.

![Scheme 1.2 Preliminary Model of the Hydrolysis Reaction.](image)

1.3.4 Variability of Tethers

The tether forces the groups to lie on the same side, controls the flexibility of the models, and limits the maximum separation between the groups. The ideal tether needs to restrict the distance between the functional groups to be less than or equal the arc length, $a$, where intramolecular catalysis occurs; but still possesses some flexibility because a reaction is a continuum of structures. PCMODEL PI\textsuperscript{29} calculations suggest that the tether needs to contain at least four atoms between the oxygens. Different tethers change the range of possible distances between the carboxylate and the ester, and give insight to the optimal range for hydrolysis by carboxylate.
The polyether tether (shown in 1.12t and 1.13t) appears to be a good choice because the groups should be restricted within the arc length, $a$, the chain is flexible, and macrocyclization is relatively easy. In addition, the polyether tether enhances the solubility in water compared with a hydrocarbon tether. Other tethers that are being considered include longer polyethers, 1,5-pentanediyl, 1,4-butanediyl and $\alpha,\alpha'$-o-xylene. Using a smaller tether or a stiffer tether or both reveals how restricting the groups to a smaller space will affect catalysis.

1.4 SPECIFIC GOAL

The goal of my research is to develop synthetic strategies for the diarylethynes 1.12t and 1.12u. The primary goal will be developing a synthesis for 2,2',6,6'-tetrasubstituted diarylethynes that will serve as a precursor to these targets.
CHAPTER 2: PROPOSED SYNTHESSES OF DIARELETHYNE MODELS

2.1 RETROSYNTHETIC ANALYSIS

Two pathways for the synthesis of the tethered, 1.12t, diarylethynes and one pathway for the synthesis of the untethered, 1.12u, diarylethyne models have been developed. For synthesizing a series of tethered diarylethynes, adding the tether in the last step is ideal. If the tether is added early in the synthesis, then new reaction conditions might have to be developed for each subsequent reaction for each tether. In addition, some tethers may inhibit a reaction, cause a side-reaction(s), or be destroyed in the subsequent reactions. In both proposed retrosynthetic pathways, the tethered is added late in the synthesis.

The following abbreviations are used in the retrosynthetic schemes. Protecting groups for phenols, such as methyl, methoxymethyl (MOM), methoxyethoxymethyl (MEM), and benzyl (Bn) ethers, are represented by P and P'. Halides and triflates are represented by X, and halides and tosylates by Y. Some possible tethers, T, include 3-oxapentane-1,5-diyl, pentane-1,5-diyl, butane-1,4-diyl, and α,α'-o-xylene. The bifunctional reagents needed for O-alkylation are diethylene glycol ditosylate, 1,5-dibromopentane, 1,4-dibromobutane or α,α'-dibromo-o-xylene, respectively. Diethylene glycol ditosylate can be synthesized by the reaction of diethylene glycol and p-toluenesulfonyl chloride in pyridine.32 1,5-Dibromopentane, 1,4-dibromobutane and α,α'-dibromo-o-xylene are commercially available.
2.1.1 Pathway 1

Scheme 2.1 shows a possible retrosynthetic pathway for synthesizing the tethered, \textbf{1.12t}, and untethered, \textbf{1.12u}, diarylethynes. Adding the tether, T, in the final step is ideal for synthesizing a series of tethered diarylethynes. \textit{O}-Alkylation of either the dihydroxy (P=H) or the trihydroxy (P=P'=H) diarylethyne \textbf{2.2} with a bifunctional reagent using the Williamson ether synthesis affords the tethered diarylethynye \textbf{2.1t}. If the tether is added to the trihydroxy molecule, making the correct phenolate is the key step in the \textit{O}-alkylation. Because the phenol on the benzoate ring is the most acidic, it will ionize first. Two equivalents of a weak base will ionize this oxygen and only one of the phenols on the other ring. Ring closure to either oxygen of the bishydroxyaryl ring gives the tethered diarylethynye \textbf{2.1t}.

\begin{center}
\begin{tikzpicture}
  \node (a) at (0,0) {COOH \quad HO};
  \node (b) at (1.5,0) {COOR \quad P'O};
  \node (c) at (0,-1.5) {COOR \quad P'O};
  \node (d) at (1.5,-1.5) {COOR \quad P'O};
  \node (e) at (0,-3) {COOR \quad P'O};
  \node (f) at (1.5,-3) {COOR \quad P'O};

  \draw[-] (a) -- (b);
  \draw[-] (b) -- (c);
  \draw[-] (c) -- (d);
  \draw[-] (d) -- (e);
  \draw[-] (e) -- (f);

  \node (g) at (0,-0.5) {2.1t};
  \node (h) at (1.5,-0.5) {2.2};
  \node (i) at (0,-2) {2.3};
  \node (j) at (1.5,-2) {2.4};

\end{tikzpicture}
\end{center}

\textbf{Scheme 2.1} Retrosynthetic Pathway for the Tethered and Untethered Diarylethynes.
The untethered diarylethyn, 1.12u (2.2: P=CH₃, P'=H), can be synthesized by mono-deprotection of diarylethyn 2.2, followed by saponification of the ester. If the protecting groups are the same (P=P'=CH₃), mono-demethylation of one of the methoxys on the bismethoxyaryl ring yields the untethered molecule, 1.12u. If the protecting groups are different, cleavage of P' (P'=MOM, MEM, or benzyl ether) gives the untethered molecule. Benzyl, MOM, and MEM ethers can be cleaved in the presence of methyl ethers.

Cleavage of the phenolic protecting group(s) yields either the di- or trihydroxy diarylethyn required for the O-alkylation with the tether. The phenols must be protected for the palladium-mediated coupling of the aryl halide or triflate 2.3 with arylalkyne 2.4 to prevent cyclization to 2-arylbenzofurans. Palladium-mediated coupling reactions are most efficient when electron-poor aryl halides or triflates are used; therefore, it is best to have the aryl triflate on the most electron-poor ring, i.e., the benzoate ring.

Aryl triflates are easily formed by the reaction of the corresponding phenols with trifluoromethanesulfonic anhydride in the presence of a base. Aryl triflate 2.3 (P=R=CH₃) can be easily synthesized by esterification and triflation of commercially available 3-methoxysalicylic acid.

Numerous methods are available for synthesizing arylethynes. The synthesis of 2.4 (P=P'=CH₃) can be accomplished by a two-step transformation of arylacetylts to arylethynes. Alternatively, 2.4 can be synthesized by the palladium-mediated coupling of 2,6-disubstitutediodobenzene, formed by ortho-lithiation of 1,3-disubstituted aryls,
with trimethylsilyl ethyne. However, as mentioned above, electron-rich aryl halides and triflates are reluctant to undergo palladium-mediated coupling reactions.\textsuperscript{35} Compound 2.4 was unknown prior to this work.

### 2.1.2 Pathway 2

Scheme 2.2 shows an alternate retrosynthetic pathway for synthesizing the tethered diarylethynes. This scheme has been developed after observing that the phenol on the benzoate ring readily cyclizes with the ethyne to form 2-arylbenzofuran. The tethered diarylethyne would be synthesized by the opening of the benzofuran 2.5 and simultaneously trapping the incipient oxy anion with the tether. Cleavage of the phenolic protecting group and saponification of the ester yield the tethered diarylethyne, 2.1t. Opening of the benzofuran ring to the diarylethyne is the key step in this scheme.

A non-nucleophilic base must be used to open the benzofuran to avoid attack of the base on the carboxylate. Another possible problem is the base could destroy the tether. If true, two equivalents of the base could be added to 2.8 forming a diarylethyne with two oxy anions. Adding a bifunctional reagent, such as diethylene glycol ditosylate, to the two oxy anions forms the tethered diarylethynes, 2.1t.

Three routes are possible for synthesizing benzofuran 2.5. Route C appears preferable because the tether is added later in the synthesis. The only difference in the routes is the sequence of the reactions. In route A, the tether is attached prior to the coupling to form the diarylethyne; in route B, the tether is added after forming the diarylethyne but before cyclization to the benzofuran; and, in route C, the coupling to
form the diarylethyne and cyclization to the benzofuran occurs prior to adding the tether. Only trial and error will show which route is most effective.

Scheme 2.2 Retrosynthetic Pathway for the Tethered Diarylethynes.
2.1.2.1 Route A

Benzofuran 2.5 can be synthesized by cleaving the phenolic protecting group on the benzoate ring of diarylethyne 2.6; followed by cyclization of the incipient phenol with the ethyne. The diarylethyne 2.6 can be synthesized by palladium-mediated coupling of an aryl halide or triflate 2.3 with arylethyne 2.7, using procedures described in Section 2.1.1. If the hydroxy substituent is not protected on the aryl halide, 2.3 (X=I; P=H), the coupling with arylalkyne 2.7 directly yields the benzofuran 2.5.34

The synthesis of the aryl halide or triflate 2.3 is discussed in Section 2.1.1. The arylethyne 2.7 can be synthesized by O-alkylation of arylethyne 2.4 (Scheme 2.1, P'=H), or by using the tether as both a phenolic protecting group and a directing group for ortho-lithiation and iodination reactions. Palladium-mediated coupling reaction of the aryl iodide with trimethylsilyl ethyne will give arylethyne 2.7.

2.1.2.2 Route B

The cyclization reaction of diarylethyne 2.6 to benzofuran 2.5 is identical to route A. O-Alkylation of the untethered diarylethyne 2.2 (P'=H) yields diarylethyne 2.6. A proposed synthesis of diarylethyne 2.2 is discussed in Section 2.1.1.

2.1.2.3 Route C

Benzofuran 2.5 can be synthesized by alkylation of the phenol of benzofuran 2.8 using Williamson ether synthesis. The benzofuran backbone can be synthesized by cleavage of the phenolic protecting group on the benzoate ring of diarylethyne 2.2;
followed by cyclization of the incipient phenol with the ethyne. Cleavage of one of the phenolic protecting groups on the dioxyaryl ring gives benzofuran 2.8. The synthesis of diarylethyne 2.2 is discussed in Section 2.1.1.

2.1.3 Summary

Both retrosynthetic pathways have many common reactions. Effective procedure for synthesizing aryl triflates, aryl halides, arylethyynes and diarylethyynes are needed. The synthesis of aryl triflates is straightforward by the reaction of the corresponding phenol with trifluoromethanesulfonic anhydride in the presence of a base. Aryl iodides can be synthesized by an ortho-lithiation/iodination sequence of 1,3-disubstituted aryls. Snieckus\textsuperscript{37} has summarized the ortho directing ability of numerous functional groups in metalation reactions. Winkle and Ronald\textsuperscript{38} have observed that metalation using the MOM ether, a relatively strong ortho-directing group, in conjunction with a weak ortho-directing group, such as methoxy, yields either the 1,2,3- or 1,2,4-isomer depending on solvent.

The synthesis of 2,2',6,6'-tetrasubstituted diarylethyynes is necessary for both retrosynthetic pathways. Only two diarylethyynes having substituents in the 2,2',6,6'-positions are reported in the literature, specifically bis-(2,4,6-tri-tert-butylphenyl)ethyne\textsuperscript{39} and bis-(2,4,6-trimethylphenyl)ethyne\textsuperscript{40}; and only limited examples of 2,2'-disubstituted diarylethyynes. Most are symmetrically substituted. Developing an effective procedure for synthesizing the crowded diarylethyynes is crucial to the success of this project.
2.2 SYNTHESES OF MONO- AND DIARYLETHYNES

The literature on the synthesis of mono- and diarylethynes can be divided into two categories: elimination and substitution reactions. Elimination reactions involve the transformation of a preformed two-carbon chain into an ethyne. Substitution reactions generally involve a transition-metal-mediated coupling of an aryl halide and ethyne. A review of the current methods available for synthesizing mono- and diarylethynes follows:

2.2.1 Elimination Reactions

Elimination reactions are more useful for synthesizing terminal arylethynes than diarylethynes. The drawback of synthesizing diarylethynes by elimination reactions is that the synthesis of the key intermediates is more laborious than synthesizing the diarylethynes by substitution methods. The classic examples of synthesizing diarylethynes by elimination reactions are the dehydrohalogenation of the vicinal dibromide 2.9 by Limpricht and Schwanert in 1868; and, the dehydrohalogenation followed by Fritsh-Buttenburg-Wiechell rearrangement of the chloroalkene 2.10 in 1894. (Scheme 2.3) The remainder of this section primarily discusses the syntheses of terminal arylethynes.
2.2.1.1 Halogenation-Dehydrohalogenation of Ketones

Phosphorus pentachloride reacts with carbonyl compounds forming gem-dichlorides, vinyl chlorides or mixtures. The vinyl chlorides are formed by elimination of hydrogen chloride from gem-dichlorides that contain an \( \alpha \)-hydrogen. Acetophenones yield primarily vinyl chlorides and only a trace of the gem-dichlorides can be isolated. Dehydrohalogenation of either chloro compounds yield the same arylethyne. (Scheme 2.4) The dehydrohalogenation has generally been done using either alcoholic potassium hydroxide solution or by sodium amide in liquid ammonia. Formation of the vinyl chlorides from acetophenones and subsequent dehydrohalogenations result in moderate yields of the arylethynes.

\[
\text{Ar-} \xrightarrow{\text{PCLI}_5} \text{Ar-} + \text{Cl-Cl} \xrightarrow{\text{KOH}} \text{Ar=H}
\]

Scheme 2.4 Halogenation-Dehydrohalogenation of Ketones.
2.2.1.2 Dehydrohalogenation of Dihaloalkenes

Aryl dihaloalkenes are synthesized by chain extension of benzaldehyde by a Wittig reaction. Corey and Fuchs\textsuperscript{45} have shown that benzaldehyde reacts with carbon tetrabromide-triphenylphosphine to form the bromoalkene \textbf{2.11}. Villieras et al.\textsuperscript{46} find that aldehydes react with LiCl\textsubscript{2}-P(O)(OC\textsubscript{2}H\textsubscript{5})\textsubscript{2} to form dichloroalkenes, \textbf{2.12}. (Scheme 2.5) The dichloroalkenes have been prepared in 80-97 % yield from benzaldehydes containing either electron-withdrawing or electron-donating substituents in either the ortho or para positions. Dehydrohalogenation of the dihaloalkenes with two to three equivalents of butyllithium yields the terminal arylethyynes. The yields for the elimination to arylethyynes range from 73-91\%.\textsuperscript{46}

\[
\begin{align*}
\text{Ar-} & \xrightarrow{\text{BuLi}} \text{H} \\
\text{2.11} \quad X = \text{Br} & \\
\text{2.12} \quad X = \text{Cl}
\end{align*}
\]

\textbf{Scheme 2.5} Dehydrohalogenation of Dihaloalkenes.

2.2.1.3 Ring Fragmentation of Preconstructed Heterocycles

Semicarbazones, \textbf{2.13}, are synthesized from aryl ketones and semicarbazide hydrochloride.\textsuperscript{47} Selenium dioxide oxidations of aryl ketone semicarbazones, \textbf{2.13}, in acetic acid affords 1,2,3-selenadiazoles, \textbf{2.14}.\textsuperscript{48} Pyrolysis of the selenadiazoles yields arylethyynes.\textsuperscript{49} (Scheme 2.6) This method can be used to synthesize both mono- and diarylethyynes. The aryl ring was either unsubstituted or contained a para substituent.
The yield for the selenium dioxide oxidation to the 1,2,3,-selenadiazoles ranged from 50-70\%, and thermolysis to the diarelethyn ranged from 60-84\%. Diphenylethyn was synthesized directly from the selenium dioxide oxidation of deoxybenzoin semicarbazone, 2.13: R = Ph, in 67\% yield.

\[
\begin{align*}
\text{Scheme 2.6 Ring Fragmentation of Preconstructed Heterocycles.}
\end{align*}
\]

### 2.2.1.4 Opening of Benzofurans

Cleavage of the benzofuran ether ring, 2.15, occurs using either sodium-pyridine\textsuperscript{4,5,0} or sodium-DMSO\textsuperscript{51} forming 2-hydroxyphenylethyn, 2.16. (Scheme 2.7) Nabulsi\textsuperscript{52} has recently modified the ring opening in sodium-pyridine by including an \textit{in situ} acetylation to form the acetate. The acetate derivative is more stable and easier to handle than the phenol. Poor yields of 2.16 have been obtained by reacting 3-bromobenzofuran, 2.17, with magnesium-copper alloy. (Scheme 2.7) A better yield, 67\%, has been obtained by using three equivalents of butyllithium\textsuperscript{53}

\[
\begin{align*}
\text{Scheme 2.7 Ring Opening of Benzofuran.}
\end{align*}
\]
Schmidt et al.\textsuperscript{54} have shown that furylnaphthalene, 2.18, opens with butyllithium in tetrahydrofuran. (Scheme 2.8) Quenching the reaction with methanol forms the dinaphthylethyne, 2.19.

![Scheme 2.8 Ring Opening of Furylnaphthalene.](image)

2.2.2 Substitution Reactions

Substitution reactions are relatively new and have the advantages over elimination reactions of requiring readily prepared or commercially available intermediates. The majority of mono- and diarylethynes currently synthesized use one of the following substitution reactions.

2.2.2.1 Grignard Reaction

Collet and Jacques\textsuperscript{40a} prepared symmetrical diarylethynes by either a cobalt(II)- or nickel(II)-catalyzed Grignard reaction of arylmagnesium bromide with either tri- or tetrachloroethene. The yields of diarylethynes was low; accompanied with approximately equal yield of biaryls. (Scheme 2.9) With naphthyl Grignards, reduced Grignard reagent was also formed.
Scheme 2.9 Grignard Reactions for Synthesizing Diarylethynes.

2.2.2.2 Copper-mediated Coupling

Castro and Stephens\textsuperscript{55} have shown that aryl iodides couple with cuprous ethynides in refluxing pyridine to form diarylethynes. (Scheme 2.10) Aryl halides with an ortho nucleophilic substitution, such as hydroxy or carboxylic acid, cyclize to the corresponding heterocycles. Protection of the substituents as either the ether or ester, respectively, prevent cyclization.

The major drawback to the Castro-Stephen coupling is synthesizing the cuprous acetylides. Okuro et al.\textsuperscript{56} have shown that a catalytic amount of copper iodide using potassium carbonate as the base in dimethylformamide couples aryl halides with arylethynes. Sonogashira et al.\textsuperscript{57} have shown that using palladium(0) and copper iodide, as co-catalyst, in diethylamine also couples aryl iodides with arylethynes under milder conditions and without synthesizing the cuprous ethynides.
2.2.2.3 Palladium-mediated Coupling

Palladium-mediated cross-coupling reactions of aryl halides or triflates with alkynes are currently the most frequently used method for synthesizing aryl- and diarylethynes. Numerous variations of the coupling reaction have been developed since Dieck and Heck\textsuperscript{35a} reported the (Ph\textsubscript{3}P\textsubscript{2})\textsubscript{2}Pd(OAc)\textsubscript{2} catalyzed coupling of aryl iodides with alkynes.

Negishi et al.\textsuperscript{35b} have reported a Pd(PPh\textsubscript{3})\textsubscript{4} catalyzed coupling of aryl halides with alkynylzinc reagents yielding either mono- or diarylethynes. Synthesizing terminal arylethynes requires coupling with ethynylzinc chloride, which is easily prepared from commercially available ethynyllithium-ethylenediamine complex. For synthesizing diarylethynes, the alkynylzinc reagent is formed by adding butyllithium to the alkyne followed by anhydrous zinc chloride. This coupling reaction is effective when using either aryl iodides or activated (electron-poor) aryl bromides. Unactivated aryl bromides are inert at room temperature.
Austin et al.\textsuperscript{58} have developed a Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} catalyzed coupling procedure for the synthesis of terminal arylethylenes. Palladium-mediated coupling of an aryl bromide with ethynyltrimethylsilane yields a trimethylsilylethynylated aryl. Cleavage of the trimethylsilyl group with potassium carbonate in methanol at ambient temperature affords the terminal arylethyne.

Chen and Yang\textsuperscript{59} have expanded the Heck reaction\textsuperscript{35a} to include, in addition to aryl halides, the coupling of aryl triflates with alkynes. The conditions are essentially the same except the catalyst is changed to Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} and dimethylformamide is used as the solvent. Chen and He\textsuperscript{60} have expanded the alkynylzinc coupling by Negishi\textsuperscript{35b} to include the coupling of aryl triflates with organozinc reagents. Again, the coupling reaction is essentially the same, except lithium chloride is added and dimethylformamide is used as co-solvent with tetrahydrofuran.

Stille\textsuperscript{61} reports conditions for the palladium-mediated coupling reactions of aryl halides with organostannanes. The coupling of aryl iodides and bromides are generally efficient; whereas, the coupling of aryl chlorides require electron-withdrawing substituents on the ring. Echavarren and Stille\textsuperscript{62} have expanded this reaction to include the coupling of aryl triflates. The cross coupling proceeds rapidly with either Pd(PPh\textsubscript{3})\textsubscript{4} or Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2}. Using the Pd(PPh\textsubscript{3})\textsubscript{4} catalyst, the order of selectivity was I>Br>OTf; whereas, for Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2}, the order changed to I>OTf>Br. Lithium chloride is essential for the coupling of aryl triflates.\textsuperscript{63} In the absence of lithium chloride, decomposition of the catalyst occurs. Presumably, chloride is needed to produce the aryl palladium chloride, thus allowing transmetalation.
Electron-rich aryl halides and triflates are less reactive in palladium-mediated coupling reactions.\textsuperscript{35} Recently, Saa et al.\textsuperscript{35c} have systematically studied palladium-mediated coupling of highly hindered, electron-rich aryl triflates with organostannanes. The optimal conditions are \( \text{Pd(PPh}_3\text{)}_2\text{Cl}_2 \), triphenylphosphine, and lithium chloride in refluxing dimethylformamide. With electron-rich aryl triflates, triphenylphosphine is needed to prevent palladium black from precipitating after a few minutes; whereas added triphenylphosphine slows the rate and decreases the efficiency with electron-poor aryl triflates. Also, 10-15 mol \% of palladium is needed for electron-rich triflates; and electron-poor triflates react efficiently with 3-6 mol \%.

\subsection*{2.2.2.4 Friedel-Crafts Alkylation with Tetrachlorocyclopropene}

Friedel-Crafts alkylations of two equivalents of an aromatic compound with one equivalent of tetrachlorocyclopropene form diarylcyclopropenones.\textsuperscript{64} Elimination of carbon monoxide occurs either thermally\textsuperscript{64a} or photochemically,\textsuperscript{64b,c} yielding diareylethyynes. (Scheme 2.11) Both symmetrical and unsymmetrical diareylethyynes can be synthesized. Unsymmetrical diareylethyynes are synthesized by adding one equivalent of the least electron-rich aryl to tetrachlorocyclopropene, followed by the more electron-rich aryl.\textsuperscript{64a,b}

The coupling of two equivalents of 1,3-dimethoxybenzene with one equivalent of tetrachlorocyclopropene in 1,2-dichloroethane yields cyclopropenone \textsuperscript{2.20}. Elimination of carbon monoxide affords diareylethyne \textsuperscript{2.21}.\textsuperscript{64a} (Scheme 2.11) This is a quick entry into diareylethyynes; unfortunately when 1,3-substituted aryls are used, the
substitution pattern of the diareylethyn is not correct for the models. This method has also been used to synthesize bis-(2,4,6-trimethylphenyl)ethyne.40b

![Scheme 2.11 Friedel-Crafts Alkylation with Tetrachlorocyclopropene.](image)

2.3 CONCLUSIONS

The synthesis of 2,6-disubstituted arylethynes and unsymmetrical 2,2’,6,6’-tetrarsubstituted diareylethynes is necessary for synthesizing the target molecules. Several methods for synthesizing mono- and diareylethynes have been reported in literature. However, prior to this work, no examples of 2,6-disubstituted arylethynes with oxygen substituents, or unsymmetrical 2,2’,6,6’-tetasubstituted diareylethynes were known. Only two symmetrical diareylethynes with substituents in the 2,2’,6,6’-positions are reported. These diareylethynes also have 4,4’-substituents, and the substituents are either methyl or tert-butyl.

Of the four methods for synthesizing these symmetrical diareylethynes, only one is satisfactory. The synthesis of 2,4,6-bis-(tri-tert-butylphenyl)ethyne could possibly be adapted to synthesize the diareylethyne models. The synthesis essentially involves two
successive Castro-Stephens$^{55}$ couplings, Section 2.2.2.2. The synthesis of \textit{bis}-(2,4,6-trimethylphenyl)ethyne has been reported by three methods. None of which are satisfactory. The Grignard reaction$^{40a}$, Section 2.2.2.1, forms only symmetrical diarylethyynes, and the yield of diarylethyne is poor. The Friedel-Crafts coupling, Section 2.2.2.4, of aryls with tetrachlorocyclopropene yields the wrong substitution pattern, i.e., 2,2',4,4'-positions, with 1,3-disubstituted aryls. The third method$^{40c}$ was by dehydrohalogenation of 1,2-dichloro-1,2-(2,4,6-trimethylphenyl)ethane, similar to the method by Limpricht and Schwanert.$^{41}$

The only elimination reaction that can possibly be used in synthesizing the diarylethyne models is the opening of the benzofuran, Section 2.2.1.4. Unfortunately, it cannot be used in the presence of a carboxylate. The carboxylate on the 2-arylbenzofuran intermediates will be destroyed unless a non-nucleophilic base is used. Although, there are no examples of using a non-nucleophilic base to open a benzofuran ether ring, and only one example of opening a 2-arylbenzofuran, the result of other bases suggest that the 2-arylbenzofuran ring can be opened to form diarylethynes.

Two substitution reactions can be used -- the Castro-Stephens coupling and the palladium-mediated coupling. The palladium-mediated coupling reaction offers the advantage that either aryl halides or triflates can be coupled with ethynes. The challenge will be determining which variation works best for the synthesizing the unsymmetric tetrasubstituted diarylethylene models.
This chapter basically consists of two parts. The first half discusses the results of my synthetic efforts, and the second reports the experimental procedures. As mentioned in the previous chapter, many reactions are common to both retrosynthetic pathways. Therefore, the discussion of the results is divided into sections based on the type of reaction. The progress made on the individual retrosynthetic pathways will be briefly summarized in the final chapter.

3.1 PROTECTING GROUPS FOR PHENOLS

The phenol on 2'-hydroxy-6'-methoxyacetophenone, 3.1, was protected as the acetate, 3.2, the benzyl ether, 3.3, and the MEM ether, 3.4 in 74.2%, 85.2% and 91.7% yields, respectively. (Scheme 3.1) All of the products were identified by $^1$H NMR; $^{13}$C NMR and mass spectra were also collected for 3.4.

\[
\begin{align*}
\text{3.1} & \quad \text{3.2} \\
\text{3.3} & \quad \text{3.4}
\end{align*}
\]

\begin{align*}
\text{3.1} & \quad \text{3.2} & \text{R} &= \text{Ac} \\
\text{3.3} & \quad \text{R} &= \text{CH}_2\text{Ph} \\
\text{3.4} & \quad \text{R} &= \text{MEM}
\end{align*}

Scheme 3.1 Protection of Phenol in 2'-Hydroxy-6'-methoxyacetophenone.
Following the procedure by Winkle and Ronald, resorcinol monomethyl ether, 3.5, was slowly added into a suspension of sodium hydride in ethyl ether and dimethylformamide. Slow addition of chloromethyl methyl ether yielded the MOM protected phenol, 3.6, in 87.6%. (Scheme 3.2) This procedure was adapted to protect resorcinol, 3.7; yielding the MOM diprotected resorcinol, 3.8, in 73.0%. The MOM protected phenols 3.6 and 3.7 were identified by comparison of the $^1$H NMR spectra with the literature.

![Chemical Structures](image)

**Scheme 3.2** Protection of Resorcinol and Resorcinol Monomethyl Ether.

### 3.2 ARYL TRIFLATES

Aryl triflates were synthesized by a straightforward transformation from the corresponding phenols. Adding trifluoromethanesulfonic anhydride to the phenols 3.9 and 3.10 in the presence of a triethylamine and methylene chloride at such a rate as to maintain the temperature between -10 to -15 °C, produced the triflates 3.11 and 3.12 in 95.1% and 96.5% yield, respectively. (Scheme 3.3) Aryl triflate 3.11 was identified by comparison of the $^1$H NMR and $^{13}$C NMR with literature values; aryl triflate 3.12 was fully characterized by $^1$H and $^{13}$C NMR, FT-IR, and mass spectroscopy. We
have used this procedure to transform many substituted phenols into aryl triflates with isolated yields greater than 90%.\textsuperscript{71}

![Scheme 3.3 Synthesis of Aryl Triflates.](image)

### 3.3 ARYL HALIDES

Following the basic procedure developed by Winkle and Ronald,\textsuperscript{38} 1-methoxy-3-(methoxymethoxy)benzene, 3.6, and 1,3-\textit{bis}(methoxymethoxy)benzene, 3.8, are lithiated by the reaction with tert-butyllithium in hexane. Metalation using the MOM ether, a relatively strong ortho-directing group, in conjunction with a weak ortho-directing group, such as methoxy, yields the 1,2,3-isomer when weakly coordinating solvents, such as hexanes and benzene, are used.\textsuperscript{38} The 1,2,3-isomer is favored because the meta groups also participates in coordinating to the alkyllithium (Figure 3.1); whereas, with a good coordinating solvent, such as ether, the weak meta substituent ligand is not strongly involved in coordinating, therefore metalation occurs at the least hindered ortho position relative to the MOM ether.

![Figure 3.1 Coordination of Alkyllithium.](image)
Iodine was added to the organo-lithium species forming the aryl iodides. (Scheme 3.4) Bulb-to-bulb distillation in a Kugelrohr apparatus yielded 60.0% and 37.3% of the aryl iodides, 3.13 and 3.14, respectively. The low yield of aryl iodide 3.14 presumably was caused either by water in the solvent, quenching the butyllithium, or insufficient reaction time; ca. 40% of starting material, 3.8, was recovered. Aryl iodide 3.13 was identified by comparison of $^1$H NMR with the literature, and aryl iodide 3.14 was identified by $^1$H NMR spectroscopy.

\[
\begin{align*}
\text{OR} & \quad \text{1. i-BuLi} \quad \text{OMOM} \\
\text{3.6} & \quad \\n\text{R} = \text{CH}_3 \\
\text{3.8} & \quad \\n\text{R} = \text{MOM} \\
\end{align*}
\]

\[
\begin{align*}
\text{OR} & \quad \text{I} \\
\text{3.13} & \quad \\n\text{R} = \text{CH}_3 \\
\text{3.14} & \quad \\n\text{R} = \text{MOM} \\
\end{align*}
\]

**Scheme 3.4** Synthesis of Aryl Halides.

### 3.4 SYNTHESSES OF ARYLETHYNES

Two methods were used in synthesizing arylethyynes: an elimination reaction and a substitution reaction. The elimination reaction was easier; however, only methyl ethers as the phenolic protecting group survived the reaction conditions. The palladium-mediated substitution reaction allowed the formation of symmetrical and unsymmetrical arylethyynes, with protecting groups other than methyl ethers, but the work-up was more difficult.
3.4.1 Halogenation-Dehydrohalogenation of Ketones

3.4.1.1 Formation of the Vinyl Chloride

Following a classic procedure\textsuperscript{43} to convert an acetophenone into the corresponding vinyl chloride resulted in an undesired product when used on 2',6'-dimethoxyacetophenone, 3.15. Two concurrent reactions took place between the electron-rich acetophenone and phosphorus pentachloride -- formation of a vinyl chloride and chlorination of the aromatic ring. (Scheme 3.5) This product was confirmed by dehydrohalogenation to 1-chloro-3-ethynyl-2,4-dimethoxybenzene, 3.16, which was identified by single crystal X-ray analysis.\textsuperscript{73}

![Scheme 3.5 Synthesis of 1-Chloro-3-ethynyl-2,4-dimethoxybenzene.](image)

Phosphorus pentachloride can undergo both an auto-ionization equilibrium (1) and a dissociation equilibrium (2):\textsuperscript{74}

\[
2\text{PCl}_5 \rightleftharpoons \text{PCl}_4^+ + \text{PCl}_6^- \quad (1)
\]
\[
\text{PCl}_5 \rightleftharpoons \text{PCl}_3 + \text{Cl}_2 \quad (2)
\]

Electrophilic chlorination of the electron-rich ring is presumably caused by dichlorine. Whereas, the formation of the vinyl chloride requires the tetraphosphonium ion.\textsuperscript{74} Adding a large excess of phosphorus trichloride decreases the concentration of dichlorine in solution, and thus prevents chlorination of the ring. The phosphorus
trichloride appears to have no effect on the auto-ionization equilibrium (1), and to not hinder the formation of the vinyl chloride.

\[
\begin{align*}
\text{OR} & \quad \text{PCl}_3, \text{PCl}_3, \text{Benzene} & \text{OR} \\
\text{OCH}_3 & \quad \text{Cl} & \text{OCH}_3 \\
3.15 & \quad R = \text{CH}_3 & 3.18 & \quad R = \text{CH}_3 \\
3.3 & \quad R = \text{CH}_2\text{Ph} & 3.19 & \quad R = \text{CH}_2\text{Ph}
\end{align*}
\]

\[
\begin{align*}
\text{OCH}_3 & \quad \text{PCl}_3, \text{PCl}_3, \text{Benzene} & \text{OCH}_3 & \quad \text{Cl} \\
3.17 & & 3.20
\end{align*}
\]

**Scheme 3.6** Synthesis of Vinyl Chlorides.

Adding a five-fold excess of phosphorus trichloride to acetophenones 3.15 and 3.3 prior to the addition of phosphorus pentachloride quantitatively, based on the NMR spectrum, produced the vinyl chloride without chlorinating the ring.\(^6\)\(^8\) (Scheme 3.6) Preventing chlorination of the naphthyl ring in the transformation of 1-acetyl-2,7-dimethoxynaphthalene, 3.17, into the corresponding vinyl chloride required an eleven-fold excess of phosphorus trichloride.\(^7\)\(^5\) Purified yields of vinyl chlorides 3.18, 3.19, 3.20 were 72.3%, 81.4%, and 78.1%, respectively. All vinyl chlorides were characterized by \(^1\)H and \(^13\)C NMR, FT-IR, and mass spectroscopies. Elemental analyses and single crystal X-ray structures of 3.18\(^6\) and 3.20\(^7\) were also obtained.
3.4.1.2 Dehydrohalogenation of Vinyl Chlorides

Dehydrohalogenation by lithium diisopropylamide at room temperature converted quantitatively, based on NMR spectra, the vinyl chlorides 3.18 and 3.20 into the corresponding ethynes, 3.21 and 3.22. Overall isolated yields for the two-step process using crude vinyl chlorides were 79.6% and 85.0% for 2-ethynyl-1,3-dimethoxybenzene, 3.21, and 1-ethynyl-2,7-dimethoxynaphthalene, 3.22, respectively. Both arylethynes were fully characterized by $^1$H and $^{13}$C NMR, FT-IR, mass spectrometry, elemental analysis, and single crystal X-ray analysis.

![Scheme 3.7 Dehydrohalogenation of Vinyl Chloride to Arylethynes.](image)

3.4.1.3 Limitations of this Reaction

This two-step transformation of aryl ketones to aryl ethynes is very effective for synthesizing electron-rich acetophenones containing methoxy groups. The harsh reaction conditions (acidic in step one and a strong base in step two) prevents the use of
common phenolic protecting groups. Common protecting groups, such as MOM, MIP, and THP, would hydrolyze in the acidic conditions of phosphorus pentachloride and phosphorus trichloride reaction. The MEM and benzyl protecting groups are stable in both basic media and acidic media to pH = 1. The MEM-protected acetophenone 3.4 is cleaved in the phosphorus pentachloride reaction. The unidentified product turns into a black tar after sitting overnight on vacuum pump. The benzyl-protected acetophenone 3.3, (Scheme 3.6), does survive the acidic conditions of the phosphorus pentachloride reaction.

Dehydrohalogenation of the benzyl-protected vinyl chloride, 3.19, using lithium diisopropylamide resulted in a mixture of products. The only product isolated (29%) and identified was benzofuran 3.23, which presumably was formed by abstraction of one of the methylene protons on the benzyl protecting group followed by cyclization and isomerization to benzofuran. Attempted dehydrohalogenation using tert-butyllithium as the base yielded 84.7% of 3.24. (Scheme 3.8) Benzofuran 3.23 was identified by $^1$H NMR and FT-IR spectra. The assignment of 3.24 was based on $^1$H and $^{13}$C NMR spectra.

Scheme 3.8 Attempted Dehydrohalogenation of 2-(1-Chlorovinyl)-1-benzyloxy-6-methoxybenzene.
Cleaving the benzyl ether, prior to dehydrohalogenation by lithium diisopropylamide, would eliminate the side-reaction that forms benzofuran 3.23. Trimethylsilyl iodide, which selectively cleaves benzyl ethers in the presence of methyl ethers, appeared promising. The reaction of benzyl-protected vinyl chloride 3.19 gave the expected result, cleavage of benzyl group, and an unexpected result, elimination of the vinyl chloride forming 2-ethynyl-1-hydroxy-6-methoxybenzene, 3.25. (Scheme 3.9) This reaction was run on 1.09 mmol scale in an NMR tube. This product was immediately transformed into the acetate with acetic anhydride in refluxing pyridine forming 1-acetoxy-2-ethynyl-3-methoxybenzene, 3.26. The crude yield for the two-step reaction was 57.8%. This reaction was not optimized or attempted on a larger scale. Arylethyynes 3.25 and 3.26 were identified by $^1$H NMR and FT-IR.

![Scheme 3.9 Dehydrohalogenation of 2-(1-Chlorovinyl)-1-benzyloxy-3-methoxybenzene Using Trimethylsilyl Iodide.](image)

### 3.4.2 Palladium-mediated Coupling

The palladium-mediated coupling of aryl triflate 3.11 with trimethylsilylethyne was unsuccessful; only starting material was recovered. (Scheme 3.10) The same result was observed by Saá et al. in the attempted coupling of 3.11 with phenylethyne using the same conditions. However, by using tributyl(phenylethynyl)stannane they obtained
the coupled product in 50% yield. Leung successfully coupled 2,6-dimethoxyiodo-
benzene with trimethylsilylethylene using palladium(0) and copper iodide, as co-catalyst, 
in 82% yield.

Scheme 3.10 Attempted Palladium-mediated Coupling of Aryl Triflate with 
Trimethylsilylethylene.

The palladium-mediated coupling of aryl iodide 3.13 with trimethyl[tri-
methylsilyl]ethynyl]stannane formed the arylethyne, 3.27 (Scheme 3.11), and 
diarylethyne 3.28, bis-[2-methoxy-6-(methoxymethoxy)phenyl]ethyne. (Figure 3.2) 
Based on NMR integration, the mixture contained approximately 76% of arylethyne and 
24% of diarylethyne. The diarylethyne was presumably formed by traces of hydrogen 
iodide that was not removed in synthesizing the aryl iodide. (The hydrogen iodide 
would cleave the trimethylsilyl protecting group allowing the ethyne to react with two 
molecules of aryl iodide.)

Scheme 3.11 Palladium-mediated Coupling Forming Arylethyynes.
The crude reaction product was stirred overnight with potassium fluoride in methanol to cleave the silyl group. Bulb-to-bulb distillation in a Kugelrohr apparatus yielded 53.8% of 2-ethynyl-1-methoxy-3-(methoxymethoxy)benzene, 3.29. These conditions were not optimized. (Removal of all traces of hydrogen iodide in the aryl iodide should increase the yield of arylethyne and prevent the formation of the diarylethyne.) Arylethyne 3.29 was identified by ^1H NMR.

Using identical conditions, aryl iodide 3.14 was transformed into the arylethyne, 3.30. The arylethyne, 3.30, was identified by ^1H NMR of the crude reaction product as the major product. The crude reaction mixture was then stirred overnight with potassium fluoride in methanol, presumably forming arylethyne 3.31. The product was destroyed while attempting a bulb-to-bulb distillation.

3.5 SYNTHESSES OF DIARYLETHYNES

Adapting the procedure by Chen and Yang, aryl triflate 3.12 was coupled with arylethynes 3.21, 3.29, and 3.22 yielding diarylethynes 3.32, 3.33, and 3.34 in 62%, 45% and 57% isolated yields, respectively. (Scheme 3.12) In the first coupling reaction
bis-1,3-(2,6-dimethoxyphenyl)butenyne, 3.35 (Figure 3.3), was isolated as a side-product (ca. 5%).

Scheme 3.12 Palladium-mediated Coupling of an Aryl Triflate with Arylethynes Forming Diarylethynes.

The enyne is presumably formed in the initial reduction of the palladium(II) catalyst to the catalytic species, palladium(0). This reduction normally produces a diethyne compound. Enynes can be synthesized by the direct coupling of two ethynes by using palladium(II), however, the proposed mechanism involves a palladium(II)-palladium(IV) catalytic cycle.

Figure 3.3 Enyne Side-product Formed in the Coupling Reaction.
Using a palladium(0) catalyst in the coupling reaction prevented the formation of the enyne 3.35, however, the yield of the diarylethylene 3.32 was low. Coupling the triflate and the tin derivative of the alkyne was another possible method to prevent this side-reaction. Difficulty in purifying the tin derivative of 3.21 prevented the investigation of this coupling procedure.

Even though the palladium(II) catalyst forms an enyne, this catalyst remains the best method for synthesizing the desired diarylethynes. The enyne 3.35 is easily separated from the diarylethylene 3.32 by flash chromatography. Also, an excess of the alkyne is used in the coupling reaction, so the formation of a small amount of enyne should not reduce the yield of the diarylethynes.

Huang,85 using a procedure similar to Sonogashira et al.,57 showed that the aryl iodide 3.36 couples with arylethylene 3.21 yielding diarylethylene 3.3788 in 59% yield. (Scheme 3.13) Prince86 showed that the naphthyl iodide 3.38 couples with arylethylene 3.21 using similar conditions, forming arylnaphthylethylene in 48% yield.87 All diarylethynes were fully characterized by $^1$H and $^{13}$C NMR, and FT-IR. Elemental analyses and mass spectra were obtained for diarylethynes 3.32, 3.34, 3.37, and 3.39. Single crystal X-ray structures were solved for 3.32,88 3.37,89 and 3.39.90

3.6 SAPONIFICATION OF THE METHYL ESTER

Castro and Stephens91 showed that a refluxing 1.5 N KOH solution cleanly hydrolyzes the ester of methyl 2-(phenylethynyl)benzoate. Oliver80 attempted this procedure with methyl 2-(2-methoxyphenylethynyl)benzoate, which resulted in a mixture
Scheme 3.13 Palladium-mediated Coupling of Aryl Iodides with an Arylethyne Forming Diarylethylenes.

of products that he proposed were lactones. By stirring the ester at room temperature for two days in a methanol-water mixture, buffered with sodium carbonate, Oliver obtained the carboxylic acid in 88% yield. Using the same conditions, the hydrolysis of the ester of diarylethyne 3.32 showed very little product was formed after stirring for two days. Primarily unreacted starting material was isolated. Stirring at room temperature required 8 days for all of the starting material to be consumed. Alternatively, refluxing the solution for 12 hours hydrolyzed the ester yielding 82.6% of diarylethyne 3.40. (Scheme 3.14) The product was fully characterized by $^1$H and $^{13}$C NMR, FT-IR, mass spectroscopy, elemental analysis, and single crystal X-ray analysis.
3.7 DEMETHYLATIONS

3.7.1 Boron Tribromide

A large excess of boron tribromide at -20 °C will cleave a methoxy faster than a methyl ester. Huang showed that six equivalents of boron tribromide in refluxing methylene chloride completely demethylates diarylethynyl 3.37 forming a mixture of diarylethynyl 3.41 and benzopyranone 3.42. (Scheme 3.15) The yield of diarylethynyl was poor (ca. 1%). (Possibly using milder conditions, stirring at room temperature, the yield of diarylethynyl could be increased.) Both the diarylethynyl 3.41 and benzopyranone 3.42 were identified by single crystal X-ray analysis.

All attempts to cleave the methoxys of methyl 2-[(2,6-dimethoxyphenyl)-ethynyl]-3-methoxybenzoate, 3.32, formed a black tar. Thin layer chromatography
suggested one main product and four minor products. Isolation of the individual compounds was never accomplished. NMR spectra of the crude products were inconclusive, but suggested an absence of the desired demethylation.

### 3.7.2 Boron Trichloride

Boron trichloride demethylates less vigorously and more selectively than boron tribromide. Boron trichloride readily demethylates methoxys ortho to a carbonyl group presumably by bidentate coordination of the boron with two oxygen atoms, but only slowly demethylates other methoxys. This selectivity allows mono-demethylation of polymethoxylated compounds. Mono-demethylation of 3.15 with boron trichloride yields 2'-hydroxy-6'-methoxyacetophenone, 3.1, in 80 % yield. (Scheme 3.16)

We hoped boron trichloride would selectively demethylate only one methoxy on the dimethoxyphenyl ring of diarylethyne 3.32 by bridging the two rings in a bidentate complex to the carbonyl oxygen and one of the methoxys on the dimethoxyphenyl ring. (Figure 3.4) Saponification of this product would yield the untethered molecule.
Contrary to the prediction, boron trichloride demethylated the methoxy on the benzoate ring, which cyclized to benzofuran 3.43. Excess boron trichloride demethylated two methoxys, one on each ring, to give the boracycle, 3.44, a novel 18 π-electron aromatic. (Scheme 3.17) The benzofuran and boracycle were characterized by $^1$H and $^{13}$C NMR, FT-IR, mass spectroscopy and single crystal X-ray analysis. Elemental analysis was obtained for the benzofuran 3.43; the presence of boron in 3.44 was confirmed by $^{11}$B NMR.

Refluxing the boracycle 3.44 in acetic acid cleaves the boron ring yielding methyl 2-(2-hydroxy-6-methoxyphenyl)benzofuran-4-carboxylate, 3.45. (Scheme 3.18) Benzofuran 3.45 was fully characterized by $^1$H and $^{13}$C NMR, FT-IR, mass spectroscopy, and elemental analysis.
3.7.3 Trimethylsilyl Iodide

Complete demethylation of diarylethyne 3.32 was accomplished using an excess of trimethylsilyl iodide. The $^1$H NMR spectrum showed that after 7 days at 50 °C all of the methyls were cleaved and the tetrasyloxydiarylethyne had formed. When methanol was added to cleave the trimethylsilyl groups, cyclization to benzofuran 3.46 occurred immediately. (Scheme 3.19) Benzofuran 3.46 was fully characterized by $^1$H and $^{13}$C NMR, FT-IR, and mass spectroscopy.

The carboxyl substituent appears to promote the cyclization of the hydroxy, on the same ring, with the ethyne to form 2-arylbenzofurans. When the trimethylsilyl groups are cleaved, three hydroxys are formed allowing the possibility of forming two...
2-arylbenzofurans, 3.46 and 3.47. (Figure 3.5) We see no evidence of forming benzofuran 3.47. Additional evidence of the assistance from the carboxyl is that only diarylethyne 3.41 and benzopyranone 3.42 were isolated from the complete demethylation of diarylethyne 3.37 with boron tribromide, Section 3.7.1.

![Image of benzofuran 3.47]

**Figure 3.5** Alternate Benzofuran from Demethylation with Trimethylsilyl Iodide.

The transition structure for cyclization to benzofuran 3.46 probably involves a concerted attack at the ethynyl carbons. The hydroxy attacks the distal carbon atom and a proton, donated by intramolecular general acid catalysis by the carboxy, adds to the other carbon. (Figure 3.6) A similar transition structure has been proposed by Letsinger et al.\(^\text{98}\) to explain the facile lactonization of 2,2'-(1,2-ethylenediyl)bis-benzoic acid. In this reaction, the carboxylate adds to one carbon and a proton, donated by the carboxy on the neighboring ring, adds to the other carbon. (Figure 3.6)

![Image of proposed transition structures]

**Figure 3.6** Proposed Transition Structures for Cyclization to Benzofuran and Isobenzofuranones.
3.7.4 Acetic Acid/Sulfuric Acid

Stirring arylethynylbenzoic acid in a solution of acetic acid that contains a drop of sulfuric acid typically promotes lactonization, yielding either 3-arylbenzopyranones or 3-benzylideneisobenzofuranones. Using these conditions with diareylethynes 3.32 and 3.40, results in demethylation of the methoxy on the carboxyphenyl ring and cyclization to 2-arylbenzofuran 3.43 and 3.48, respectively. (Scheme 3.20)

Benzofuran 3.48 was fully characterized by $^1$H and $^{13}$C NMR, FT-IR, mass spectroscopy, elemental analysis, and single crystal X-ray analysis. Benzofuran 3.43 was also synthesized by demethylation using boron trichloride, Section 3.7.2. This reaction proved a better method for synthesizing the benzofuran 3.43, because no side products are formed, and the reaction conditions and purification of the product is easier.

3.8 OPENING OF 2-PHENYLBENZOFURAN

Before attempting to open the furan ring of the 2-arylbenzofurans 3.43, 3.46, and 3.48, generalized reaction conditions needed to be developed. The simplest model
compound, 2-phenylbenzofuran, was synthesized by a Castro-Stephens coupling.\textsuperscript{55} Chapter 2, Section 2.2.2.2 (Scheme 2.10).

Stirring 2-phenylbenzofuran, 3.49, with two equivalent of lithium diisopropylamide, a strong, non-nucleophilic base, at room temperature, followed by quenching with acetyl chloride yielded, based on GC integration, <20\% of 1-(2-acetoxyphenyl)-2-phenylethyne, 3.50. (Scheme 3.21) The major compound was unreacted starting material. Side reactions occurred when the reaction was refluxed. In addition to forming 3.50, two other products were formed. One of the side products had a retention time that was the same as the starting material, making it impossible to know by GC/MS if all the starting material had been consumed.

\textbf{Scheme 3.21} Opening of 2-Phenylbenzofuran to 1-(2-Acetoxyphenyl)-2-phenylethyne.

Stirring 2-phenylbenzofuran, 3.49, with two equivalents of butyllithium in tetrahydrofuran for four hours, followed by quenching with acetyl chloride yields exclusively 1-(2-acetoxyphenyl)-2-phenylethyne, 3.50. With benzofurans, 3.43, 3.46, and 3.48, butyllithium cannot be used. Because butyllithium appears to be excellent reagent for opening the furan, it may be best to protect the carboxylate against nucleophilic attack.
3.9 LACTONIZATION TO ISOBENZOFURANONES AND BENZOPYRANONES

3.9.1 Bromolactonization

4-Bromo-3-arylbenzopyranones are synthesized by bromolactonization of either alkyl 2-(arylethynyl)benzoates or 2-(arylethynyl)benzoic acids. In the presence of bromine in acetic acid, alkyl 2-(arylethynyl)benzoates undergo bromolactonization to yield bromobenzopyranones.\textsuperscript{100} Alternatively, the two-step reaction of alkyl 2-(arylethynyl)benzoates with mercuric acetate in acetic acid, followed by bromine in chloroform yields bromobenzopyranones.\textsuperscript{101} In the presence of \(N\)-bromosuccinimide, sodium bicarbonate and \(N\)-benzyltrimethylammonium hydroxide in methylene chloride, 2-(arylethynyl)benzoic acids bromolactonize to yield bromobenzopyranones.\textsuperscript{102}

Diarylethyne 3.32 rapidly reacts with bromine to yield 68.5\% of benzopyranone 3.51. (Scheme 3.22) Bromination of the electron-rich dimethoxyphenyl ring occurs in the presence of any excess bromine. Benzopyranone 3.51 was fully characterized by \(^1\)H and \(^{13}\)C NMR, FT-IR, mass spectroscopy, and elemental analysis.

\[ \text{COOCH}_3 \quad \text{OCH}_3 \]
\[ \text{Br}_2 \rightarrow \text{HOAc} \]
\[ \text{H}_3\text{CO} \quad \text{OCH}_3 \]

**Scheme 3.22** Bromolactonization Forming Benzopyranones.

Stabilization of the bromonium ion intermediate controls the regioselectivity for forming the 6-membered lactone.\textsuperscript{100} (Figure 3.7) The dimethoxyphenyl group provides
greater stabilization to the brominium ion because it is a more electron-donating group than the other aryl ring. The dimethoxyphenyl ring can freely rotate to allow maximum overlap with the $\pi$ orbitals involved in complexing the bromonium ion. The cyclic transition structure constrains the $\pi$ system of the (methoxycarbonyl)aryl group to be orthogonal to the $\pi$ orbitals of the brominium complex.

![Figure 3.7 Transition Structure for Bromolactonization.](image)

3.9.2 Palladium-mediated Lactonization

Presumably, the palladium catalyst complexes with the alkyne making it more electronegative and, therefore, more susceptible to nucleophilic attack from the carboxyl(ate). The palladium-mediated lactonization of diarylethyne 3.40 yielded primarily benzopyranone 3.52. (Scheme 3.23) Proton NMR and IR spectra showed only a trace of the alternate lactonization product, isobenzofuranone 3.53. Benzopyranone 3.52 was fully characterized by $^1$H and $^{13}$C NMR, FT-IR, mass spectroscopy, elemental analysis and single crystal X-ray analysis.103
3.40  

\[ \text{OCH}_2 \text{H}, \text{CH}_3 \text{CO} \]

Scheme 3.23  Palladium-mediated Lactonization Forming Benzopyranones.

3.9.3 Uncatalyzed Lactonization

Oliver showed that uncatalyzed lactonizations of 2-(arylethynyl)benzoic acids having a single methoxy or acetoxy substituent in the 2' or 4' position yield exclusively isobenzofuranones, whereas unsubstituted 2-(arylethynyl)benzoic acid formed a mixture of isobenzofuranone and benzopyranone. Diarylethynle 3.40, which contains a methoxy at the 2' and 6' positions and also 3 position, yielded primarily isobenzofuranone 3.53. (Scheme 3.24) A small amount of 3-arylbenzopyranone 3.52 was formed. Isobenzofuranone 3.53 was fully characterized by $^1$H and $^{13}$C NMR, FT-IR, mass spectroscopy, elemental analysis, and single crystal X-ray analysis.

Scheme 3.24  Uncatalyzed Lactonization Forming Isobenzofuranones.
3.10 EXPERIMENTAL

3.10.1 General Methods

$^1$H NMR spectra were recorded with either a Bruker AM 400 FT-NMR or Bruker AM 200 FT-NMR spectrometer at 400 and 200 Mhz, respectively. Unless noted otherwise, $^{13}$C NMR spectra were recorded with a Bruker AM 400 FT-NMR spectrometer at 100 MHz. Unless noted otherwise, all NMR spectra were recorded in CDCl$_3$. Proton chemical shifts are expressed in parts per million (ppm) downfield from internal tetramethylsilane (TMS); coupling constants which were verified using PANIC (Parameter Adjustment in NMR by Iteration Calculation) are listed as $J$; observed coupling constants not verified are listed as $J_{\text{app}}$; all coupling constants are reported in Hz. $^{13}$C chemical shifts are also expressed in ppm relative to the solvent chemical shift. Assignments of the $^1$H and $^{13}$C NMR signals were made using COSY,$^{105}$ NOESY,$^{106}$ INAPT,$^{107}$ and direct$^{108}$ and inverse long-range$^{109}$ (two- and three-bond) $^1$H-$^{13}$C correlation experiments. Infrared spectra were recorded on a Perkin Elmer 1760X FT-IR spectrophotometer as a thin film and reported in cm$^{-1}$. Mass spectra were obtained with a Hewlett-Packard 5985 and 5971A mass spectrometers. Elemental analyses were performed by Onieda Research Services of Whitesboro, New York.

Unless otherwise noted, materials were obtained from commercial sources and used without further purification. Tetrahydrofuran (THF) was distilled from potassium. Dichloromethane and $N,N$-dimethylformamide (DMF) were distilled from CaH$_2$ and stored over 4Å sieves under N$_2$. Triethylamine was first distilled from phenyl isocyanate, then distilled from KOH and stored over KOH pellets under N$_2$. Pyridine
and diisopropylamine were distilled from NaOH and stored over NaOH pellets under N₂. 2',6'-Dimethoxyacetophenone and 3-methoxysalicylic acid were purified by bulb-to-bulb distillation in a Kugelrohr apparatus. The silica gel used for flash column chromatography was 40-63 μm (230-400 mesh) silica gel 60 (E. Merck).

3.10.2 Preparative Methods

2'-Hydroxy-6'-methoxyacetophenone, 3.1: A 1M-BCl₃ solution in CH₂Cl₂ (37.5 mL, 37.5 mmol) was added dropwise over 15 min to a solution of 2',6'-dimethoxyacetophenone (4.51 g, 25 mmol) in CH₂Cl₂ (80 mL) at -78 °C under N₂. The flask was removed from the cold bath and stirred for 30 min at rt, then poured over ice (75 g). The organic layer was extracted with 3N NaOH (4 × 50 mL). Rotary evaporation of the organic layer yielded 2',6'-dimethoxyacetophenone (0.87 g, 19.1%). The combined alkaline extracts were acidified with concd H₂SO₄ and extracted with CH₂Cl₂ (2 × 100 mL). The CH₂Cl₂ extracts were dried (MgSO₄) and concentrated by rotary evaporation to yield a light yellow solid (3.23 g, 78.1%). Mp 59-60 °C (Lit.¹⁰ mp 60 °C).

2'-Acetoxy-6'-methoxyacetophenone, 3.2: A solution of 3.1 (4.98 g, 30.0 mmol) and Ac₂O (5.84 mL, 60.0 mmol) in pyridine (30 mL) was refluxed for 30 min. The reaction was poured over ice (=50 g), acidified with concd HCl to pH=4, and extracted with benzene (3 × 25 mL). The benzene extracts were washed with H₂O (2 × 25 mL), satd NaHCO₃ (1 × 25 mL), and dried (MgSO₄). Rotary evaporation of the solvent yielded a white solid and a yellow liquid. The white solid was washed with hexane yielding 3.2 (4.64 g, 74.2%). ¹H NMR (200 MHz): δ 7.35 (dd, 1H, J_app = 7.6 and 8.4, C4'), 6.82
(d, 1H, \( J_{app} = 8.4 \)), 6.71 (d, 1H, \( J_{app} = 7.6 \)), 3.85 (s, 3H, OCH\(_3\)), 2.49 (s, 3H, Ar-C(O)CH\(_3\)), 2.23 (s, 3H, -OC(O)CH\(_3\)). MS, \( m/e \) (relative intensity): 209 (M\(^+\)+1, 1.0), 208 (M\(^+\), 9.0), 167 (7.1), 166 (68.6), 152 (13.8), 151 (100), 148 (16.1), 136 (6.8), 107 (7.9), 43 (40.4). IR: 3088 and 3015 (aromatic C-H stretch), 2962 and 2851 (methyl C-H stretch), 1755 (acetoxy C=O stretch), 1687 (acetyl C=O stretch), 1604 (C\(^\equiv\) ring stretch). Mp 81.5-83.0 °C (Lit.\(^{6b}\) mp 80 °C).

2'-Benzyloxy-6'-methoxyacetophenone, 3.3: To a solution of 3.1 (0.83 g, 5.0 mmol) dissolved in acetone (40 mL) was added KI (0.91 g, 5.5 mmol), K\(_2\)CO\(_3\) (2.42 g, 17.5 mmol) and benzyl chloride (0.63 mL, 5.5 mmol). The solution was refluxed for 48 h. The solvent was removed by rotary evaporation; bulb-to-bulb distillation in a Kugelrohr apparatus (140-150 °C, 0.03 mm; Lit.\(^{6a}\) bp 150-152 °C, 0.05 mm) yielded a colorless oil (1.09 g, 85.2%). \(^1\)H NMR (200 MHz): \( \delta \) 7.18-7.38 (m, 6H), 6.54-6.61 (m, 2H), 5.08 (s, 2H, CH\(_2\)), 3.80 (s, 3H, OCH\(_3\)), 2.49 (s, 3H, CH\(_3\)).

2'-Methoxy-6'-(2-methoxyethoxy)methoxyacetophenone, 3.4: A solution of 3.1 (1.68 g, 10.0 mmol) dissolved in THF (10 mL) was added to a suspension of NaOH (0.48 g, 12.0 mmol) in HMPA (5 mL) under N\(_2\). The mixture was refluxed for 1.5 h, cooled to rt, followed by slow addition (10 min) of MEMCl (1.37 mL, 12.0 mmol) dissolved in THF (10 mL), and stirred at rt for 8 h. The reaction was diluted with 10% KOH (20 mL), and extracted with Et\(_2\)O (5 × 25 mL). The combined extracts were washed with 10% KOH (2 × 25 mL), satd brine (3 × 25 mL), and dried (Na\(_2\)SO\(_4\)). Rotary evaporation of the solvent yielded a yellow oil (2.33 g, 91.7%). \(^1\)H NMR (200 MHz): \( \delta \) 7.24 (dd, 1H, \( J_{app} = 8.3 \) and 8.3, C4'), 6.80 (d, 1H, \( J_{app} = 8.3 \)), 6.59 (d, 1H, \( J_{app} = \))
8.3), 5.25 (s, 2H, OCH₂O), 3.77-3.82 (m, 2H), 3.80 (s, 3H, Ar-OCH₃), 3.52-3.56 (m, 2H), 3.36 (s, 3H, OCH₃), 2.48 (s, 3H, CH₃).

^1^C NMR (50 MHz): 202.3 (C=O), 156.4, 153.9, 130.4 (C₄'), 121.5 (C¹'), 107.3, 104.7, 93.4 (OCH₂O), 71.3, 67.7, 58.8 (–CH₂OCH₂), 55.7 (Ar-OCH₃), 32.2 (C(O)CH₃).

MS, m/e (relative intensity): 255 (M*:1, 1.8), 254 (M⁺, 13.9), 179 (68.6), 178 (15.4), 166 (31.0), 151 (89.3), 136 (26.7), 107 (17.9), 91 (15.8), 89 (100), 59 (99.7), 43 (23.1), 29 (14.7).

1-Methoxy-3-(methoxymethoxy)benzene, 3.6: Following the procedure by Winkle and Ronald, a solution of 3-methoxyphenol (6.21 g, 50 mmol) in Et₂O (25 mL) was added dropwise to a suspension of NaH (2.4 g, 100 mmol) in Et₂O (250 mL) and DMF (50 mL) under N₂ taking 15 min. The reaction was stirred for 30 min at rt, followed by dropwise addition (15 min) of MOMCl (7.97 mL, 105 mmol) dissolved in Et₂O (25 mL). Stirring was continued for 15 min, and then the reaction was carefully quenched with H₂O (100 mL). The phases were separated and the aqueous phase extracted with Et₂O (2 × 50 mL). The combined organic layers were washed with 10% NaOH (3 × 100 mL), H₂O (1 × 100 mL), satd NaHCO₃ (1 × 100 mL), and dried (MgSO₄). The solvent was removed by rotary evaporation; bulb-to-bulb distillation in a Kugelrohr apparatus (40-50 °C, 0.05 mm; Lit.: bp 123-123.5 °C, 17 mm) yielded a colorless oil (7.37 g, 87.6%). ^1^H NMR (200 MHz; Lit.): δ 7.13-7.21 (m, 1H), 6.52-6.66 (m, 3H), 5.14 (s, 2H, OCH₂O), 3.76 (s, 3H, Ar-OCH₃), 3.46 (s, 3H, OCH₃).

1,3-Bis(methoxymethoxy)benzene, 3.8: Adapting the procedure by Winkle and Ronald, a solution of resorcinol (5.50 g, 0.05 mol) in Et₂O (25 mL) was added dropwise to a mechanically stirred suspension of NaH (4.8 g, 0.2 mmol) in Et₂O (250 mL) under N₂ taking 15 min. The reaction was stirred for 30 min at rt, followed by dropwise addition (15 min) of MOMCl (7.97 mL, 105 mmol) dissolved in Et₂O (25 mL). Stirring was continued for 15 min, and then the reaction was carefully quenched with H₂O (100 mL). The phases were separated and the aqueous phase extracted with Et₂O (2 × 50 mL). The combined organic layers were washed with 10% NaOH (3 × 100 mL), H₂O (1 × 100 mL), satd NaHCO₃ (1 × 100 mL), and dried (MgSO₄). The solvent was removed by rotary evaporation; bulb-to-bulb distillation in a Kugelrohr apparatus (40-50 °C, 0.05 mm; Lit.): bp 123-123.5 °C, 17 mm) yielded a colorless oil (7.37 g, 87.6%). ^1^H NMR (200 MHz; Lit.): δ 7.13-7.21 (m, 1H), 6.52-6.66 (m, 3H), 5.14 (s, 2H, OCH₂O), 3.76 (s, 3H, Ar-OCH₃), 3.46 (s, 3H, OCH₃).
mL) and DMF (50 mL) under N₂ taking 30 min. The reaction was stirred for 1 h, followed by dropwise addition (1 h) of MOMCl (16.0 mL, 0.21 mol) dissolved in Et₂O (25 mL). Stirring was continued for 15 min, and then the reaction was carefully quenched with H₂O (100 mL). The phases were separated and the aqueous phase extracted with Et₂O (2 x 50 mL). The combined organic layers were washed with 10% NaOH (4 x 100 mL), H₂O (1 x 100 mL), satd NaHCO₃ (1 x 100 mL), and dried (MgSO₄). The solvent was removed by rotary evaporation; bulb-to-bulb distillation in a Kugelrohr apparatus (78-81 °C, 0.05 mm, Lit.¹ 137 °C, 7 mm) yielded a colorless oil (7.23, 73.0%). ¹H NMR (200 MHz; Lit.²): δ 7.19 (t, 1H, J₂₃ = 8.0, C5), 6.68-6.75 (m, 3H), 5.16 (s, 4H, OCH₂ O), 3.48 (s, 6H, OCH₃).

Methyl 2-Hydroxy-3-methoxybenzoate, 3.10: A solution of 3-methoxysalicylic acid (25.78 g, 0.153 mol), MeOH (18.6 mL), 1,2-dichloroethane (46.0 mL), and concd H₂SO₄ (2.3 mL) was refluxed for 87 h. The organic layer was washed with H₂O (1 x 20 mL), satd NaHCO₃ (2 x 20 mL) and dried (MgSO₄). The solvent was removed by rotary evaporation; bulb-to-bulb distillation in Kugelrohr apparatus yielded a white powder (24.98 g, 89.6%). Mp 61.5-62.1 °C. (Lit.¹¹ mp 61-62 °C).

2,6-Dimethoxyphenyl trifluoromethanesulfonate, 3.11: To a solution 2,6-dimethoxyphenol (5.48 g 35.5 mmol) in CH₂Cl₂ (20 mL) and NEt₃ (5.2 mL) at -15 °C under N₂ was added triflic anhydride (11.20 g, 39.7 mmol) at such a rate as to maintain the temperature between -15 to -10 °C. The solution was placed in a refrigerator (1 °C) overnight. The solvent was removed by rotary evaporation; bulb-to-bulb distillation in a Kugelrohr apparatus (92-94°C, 0.25 mm) yielded a colorless oil (9.64 g, 94.9%). ¹H
NMR (200 MHz; Lit.69,70): δ 7.19 (t, 1H, J<sub>app</sub> = 8.5, C4), 6.59 (d, 2H, J<sub>app</sub> = 8.5, C3 and C5), 3.82 (s, 6H, OCH<sub>3</sub>). 13C NMR (50 MHz; Lit.70): δ 152.4 (C2 and C6), 128.6 (C4), 128.0 (C1), 118.7 (CF<sub>3</sub>, J<sub>C,F</sub> = 320 Hz), 104.6 (C3 and C5), 55.6 (OCH<sub>3</sub>).

2-Methoxy-6-(methoxycarbonyl)phenyl trifluoromethanesulfonate, 3.12: To a solution of 3.10 (6.46 g, 35.44 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) and NEt<sub>3</sub> (5.7 mL) at -15 °C under N<sub>2</sub> was added triflic anhydride (11.23 g, 39.80 mmol) at such a rate as to maintain the temperature between -15 to -10 °C. The solution was placed in a refrigerator (1 °C) overnight. The solvent was removed by rotary evaporation; bulb-to-bulb distillation in a Kugelrohr apparatus (125-130°C, 0.10 mm) yielded a colorless oil (10.27 g, 96.5%). 

1H NMR (400 MHz): δ 7.56 (dd, 1H, J = 7.98 and 1.32, C5), 7.37 (dd, 1H, J = 8.34 and 7.98, C4), 7.21 (dd, 1H, J = 7.98 and 1.32, C3), 3.94 (s, 3H, C(0)OCH<sub>3</sub>), 3.91 (s, 3H, OCH<sub>3</sub>). 13C NMR: 164.4 (>C=O), 151.7 (C2), 137.5 (C1), 128.4 (C4), 125.6 (C6), 123.1 (C5), 118.6 (CF<sub>3</sub>, J<sub>C,F</sub> = 320 Hz), 116.8 (C3), 56.3 (OCH<sub>3</sub>), 52.5 (C(O)OCH<sub>3</sub>).

IR: 3093 (aromatic C-H stretch), 2957 and 2848 (methyl C-H stretch), 1734 (C=O stretch), 1423 (asymmetric S(=O)<sub>2</sub> stretch), 1582 (C=C ring stretch), 1316, 1206, 1138.

MS, m/e (relative intensity): 314 (M<sup>+</sup>, 7), 79 (65), 69 (96), 53 (43), 51 (62), 45 (100).

2-Iodo-1-methoxy-3-(methoxymethoxy)benzene, 3.13: Following the basic procedure by Winkle and Ronald,38 a 1.7-M t-BuLi solution in pentane was added to a solution of 3.6 (6.73 g, 40 mmol) dissolved in hexane (200 mL) at 0 °C under N<sub>2</sub>. The reaction was stirred for 30 min at 0 °C, followed by the dropwise addition of I<sub>2</sub> (13.20, 52 mmol) dissolved in THF (50 mL). The reaction was stirred at rt for 30 min. The organic layer was washed with 10% Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (2 × 100 mL), H<sub>2</sub>O (1 × 100 mL), satd
NaHCO₃ (1 × 100 mL), and dried (MgSO₄). The solvent was removed by rotary evaporation; bulb-to-bulb distillation in a Kugelrohr apparatus (95-105°C, 0.05 mm; Lit.³⁸ bp 80-83 °C, 0.10 mm) yielded a reddish oil (7.06 g, 60.0%). ¹H NMR (200 MHz; Lit.³⁸): δ 7.23 (dd, 1H, J_app = 8.7 and 7.9, C5), 6.72 (d, 1H, J_app = 8.7), 6.53 (d, 1H, J_app = 7.9), 5.25 (s, 2H, OCH₂), 3.88 (s, 3H, Ar-OCH₃), 3.51 (s, 3H, OCH₃). MS, m/e (relative intensity): 295 (M⁺+1, 7.0), 294 (M⁺, 66.2), 264 (22.0), 167 (14.2), 137 (13.4), 107 (15.9), 45 (100).

2-Iodo-1,3-bis(methoxymethoxy)benzene, 3.14: Adapting the procedure by Winkle and Ronald,³⁸ a 1.5-M t-BuLi solution in pentane (28 mL, 42 mmol) was added to a solution of 3.8 (6.94 g, 35 mmol) dissolved in hexane (175 mL) at 0 °C under N₂. The reaction was stirred for 1 h at 0 °C, followed by the dropwise addition of I₂ (11.55, 45.5 mmol) dissolved in THF (50 mL), and stirred at rt for 1 h. The organic layer was washed with 10% Na₂S₂O₃ (2 × 100 mL), H₂O (3 × 100 mL), satd NaHCO₃ (1 × 100 mL), and dried (MgSO₄). The solvent was removed by rotary evaporation; bulb-to-bulb distillation in a Kugelrohr apparatus (90-105°C, 0.05 mm) yielded a dark brown oil, which was dissolved in EtOAc and passed through a short column of silica gel (eluant: hexane/EtOAc 1:1) yielding a pale yellow oil (4.23 g, 37.3%). This product contained a trace (< 5%) of 3.8. (Note: The low yield of aryl iodide 3.14 presumably was caused either by water in the solvent, quenching the butyllithium, or insufficient reaction time; ~40% of starting material, 3.8, was recovered.) ¹H NMR (200 MHz): δ 7.21 (t, 1H, J_app = 8.3, C5), 6.75 (d, 2H, J_app = 8.3.), 5.25 (s, 4H, CH₂), 3.52 (s, 6H, OCH₃).
2-(1-Chlorovinyl)-1,3-dimethoxybenzene, 3.18: To a solution of 2',6'-dimethoxyacetophenone (21.62 g, 0.12 mol) and PCl₃ (57.6 ml, 0.66 mol) in benzene (180 mL) was added PCl₅ (27.49 g, 0.13 mol). The flask was flushed with N₂ and stirred overnight at rt. The reaction mixture was poured over ice (=300 g). The layers were separated and the organic layer was washed with H₂O (3 x 100 mL), satd NaHCO₃ solution (1 x 100 mL), and dried (MgSO₄). The solvent was removed by rotary evaporation leaving a pale yellow oil (23.12 g, 96.7%) that solidified upon standing. For analytical purposes, a small sample was purified by flash chromatography (6/1 hexane/EtOAc) yielding white crystals. ¹H NMR (400 MHz): δ 7.25 (t, 1H, J = 8.35, C5), 6.55 (d, 2H, J = 8.35, C4 and C6), 5.73 (d, 1H, J = 1.00, =CH₂), 5.33 (d, 1H, J = 1.00, =CH₂), 3.83 (s, 6H, OCH₃). ¹³C NMR: 157.6 (Cl and C3), 132.0 (>C=), 130.3 (C5), 118.4 (CH₂), 116.9 (C2), 103.9 (C4 and C6), 56.0 (OCH₃). IR: 3103 (=C-H stretch), 3005 (aromatic C-H stretch), 2938 and 2839 (methyl C-H stretch), 1645 (C=C stretch), 1591 (C=C ring stretch), 892 (out of plane =C-H bending). MS, m/e (relative intensity): 198 (M⁺, 1.4), 135 (100), 105 (83), 89 (48), 79 (65), 77 (71), 63 (67), 62 (35), 51 (27). Anal. Calcd for C₁₀H₁₁O₂Cl: C, 60.46; H, 5.58. Found: C, 60.19; H, 5.42.

1-Benzylxyo-2-(1-chlorovinyl)-3-methoxybenzene, 3.19: To a solution of 3.3 (7.23 g, 28.21 mmol) and PCl₃ (14.0 ml, 160.46 mmol) in benzene (60 mL) was added PCl₅ (7.05 g, 33.85 mmol). The flask was flushed with N₂ and stirred overnight at rt. The solution was poured over ice (=200 g) and diluted with Et₂O (200 mL). The organic layer was washed with H₂O (2 x 100 mL), 10% NaOH (3 x 100 mL), satd NaHCO₃ (1
× 100 mL), and dried (MgSO₄). The solvent was removed by rotary evaporation to form a yellow oil, which was dissolved in hexane and passed through a short silica gel column (eluant: hexane) yielding a off-white oil (6.31 g, 81.4%). ¹¹H NMR (400 MHz): δ 7.43 (d, 2H, J₁₀ = 7.3, C₂' and C₆'), 7.35 (dd, 2H, J₁₀ = 7.3 and 7.2, C₃' and C₅'), 7.29 (t, 1H, J₁₀ = 7.2, C₄'), 7.21 (dd, 1H, J₁₀ = 8.3 and 8.1, C₅), 6.57 (d, 1H, J₁₀ = 8.1, C₄ or C₆), 6.55 (d, 1H, J₁₀ = 8.3, C₄ or C₆), 5.76 (d, 1H, J₁₀ = 0.8, =CH₂), 5.37 (d, 1H, J₁₀ = 0.8, =CH₂), 5.12 (s, 2H, OCH₂), 3.83 (s, 3H, OCH₃). ¹³C NMR: 157.7 (C₃), 156.6 (Cl), 137.0 (C₁'), 132.0 (C₅), 130.2 (C₅), 128.4 (C₃'), 127.6 (C₄'), 126.7 (C₂'), 118.6 (=CH₂), 117.5 (C₂), 105.5 and 104.1 (C₄ and C₆), 70.3 (OCH₂), 56.0 (OCH₃). IR: 3091 (=C-H stretch), 3065 and 3031 (aromatic C-H stretch), 2938 and 2839 (methyl C-H stretch), 1645 (C=C stretch), 1592 (C=C ring stretch), 893 (out of plane =C-H bending). MS, m/e (relative intensity): 275 (M⁺+1, 0.6), 274 (M⁺, 4.0), 239 (53.1), 183 (18.4), 92 (18.6), 91 (100), 65 (21.8).

2-Ethynyl-1,3-dimethoxybenzene, 3.21: A 2-M BuLi solution in hexanes (150 mL, 0.3 mol) was added slowly under N₂ to a solution of HN(i-Pr)₂ (50.45 mL, 0.36 mol) in THF (120 mL) at -78 °C. The temperature was raised to 0 °C for 20 min, and then cooled to -78 °C. Crude 3.18 (23.12 g, 0.116 mol) dissolved in THF (120 mL) was added slowly to the LDA solution. The cold bath was removed and the solution was stirred for 5 h. The reaction was quenched with H₂O (100 mL), and the organic layer was washed with H₂O (2 × 100 mL), 2N HCl (3 × 100 mL), H₂O (1 × 100 mL), and dried (MgSO₄). The solvent was removed by rotary evaporation leaving a tan solid. Sublimation yielded white crystals (15.53 g, 82.5%). ¹¹H NMR (400 MHz): 7.25 (t, 1H,
$J = 8.50, \text{ C5})$, 6.54 (d, 2H, $J = 8.50, \text{ C4 and C6})$, 3.89 (s, 6H, OCH$_3$), 3.57 (s, 1H, \equiv\text{CH}). \quad ^{13}\text{C NMR (CDCl$_3$): 162.1 (C1 and C3), 130.2 (C5), 103.4 (C4 and C6), 100.2 (C2), 85.3 (\equiv\text{C}), 76.2 (\equiv\text{CH}), 56.0 (\text{OCH}_3)$. IR: 3276 ($\equiv\text{C-H stretch}$), 2979 and 2845 (methyl C-H stretch), 2111 (C≡C stretch), 1590 (C=C ring stretch). MS, $m/e$ (relative intensity): 162 ($M^+$, 37), 91 (24), 89 (25), 76 (46), 65 (100), 63 (36), 50 (54). Anal. Calcd for C$_{10}$H$_{10}$O$_2$: C, 74.06; H, 6.21. Found: C, 74.33; H, 6.28.

**Attempted Dehydrohalogenation of 1-Benzylxy-2-(1-chlorovinyl)-3-methoxybenzene, 3.19:**

*Method A: Using LDA.* A 2.02-$M$ BuLi solution in hexanes (3.3 mL, 6.7 mmol) was added slowly under N$_2$ to a solution of HN(i-Pr)$_2$ (1.22 mL, 8.7 mmol) in THF (5 mL) at -78 °C. The temperature was raised to 0 °C for 20 min, and then cooled to -78 °C. A solution of 3.19 (0.80 g, 2.9 mmol) dissolved in THF (5 mL) was added to the LDA solution. The cold bath was removed and the solution was stirred at rt for 20 h. The reaction was quenched with H$_2$O (15 mL), and extracted with hexane (3 x 15 mL). The combined organic layers were washed with H$_2$O (3 x 15 mL), satd NaHCO$_3$ (1 x 15 mL), and dried (MgSO$_4$). The solvent was removed by rotary evaporation leaving a brown oil. Flash column chromatography (eluant: hexane/EtOAc 2:1) yielded a greenish oil (0.20 g, 29%). Based on $^1$H NMR and IR spectra, the product was identified as 4-methoxy-3-methyl-2-phenylbenzofuran,\textsuperscript{79} 3.23. $^1$H NMR (200 MHz): $\delta$ 7.71-7.81 (m, 2H), 7.11-7.54 (m, 5H), 6.56-6.65 (m, 1H), 3.90 (s, 3H, OCH$_3$), 2.62 (s, 3H, CH$_3$). IR: 3054 (aromatic C-H stretch), 2958 and 2837 (methyl C-H stretch), 1601 (C=C ring stretch).
**Method B: Using tert-butyllithium.** To a solution of 3.19 (0.55 g, 2.0 mmol) dissolved in benzene was added 1.68-M t-BuLi solution in pentane (1.31 mL, 2.2 mmol) under N₂. The reaction was stirred for 15 min at rt, then quenched with H₂O (20 mL), and diluted with Et₂O (20 mL). The organic layer was washed with satd NaHCO₃ (2 × 20 mL), and dried (MgSO₄). The solution was concentrated by rotary evaporation, and then dried on the vacuum pump for 1 h yielding a pale yellow oil (0.50 g, 84.7%). Based on ¹H, ¹³C, and IR spectra, the product was identified as 1-benzyloxy-2-(2-tert-butylvinyl)-3-methoxybenzene, 3.24. ¹H NMR (200 MHz): δ 7.33-7.52 (m, 5H, benzyl H), 7.07-7.16 (m, 1H, C5), 6.57-6.71 (m, 4H), 5.11 (s, 2H, OCH₂Ph), 3.86 (s, OCH₃), 1.13 (s, 9H, t-Bu). ¹³C NMR (50 MHz): δ 158.2, 157.3, 146.3 (=C(H)-t-Bu), 137.3 (C1'), 128.3, 127.6, 127.2, 127.0 (C5), 115.9 (C2), 114.7 (=C(H)Ar), 105.8, 104.4, 70.6 (–OCH₃), 55.8 (OCH₃), 34.0 (C(CH₃)₃), 29.6 (C(CH₃)₃). IR: 3032 (aromatic C-H stretch), 2956 and 2864 (methyl C-H stretch), 1585 (C=C ring stretch). MS, m/e (relative intensity): 297 (M⁺+1, 7.4), 296 (M⁺, 33.2), 225 (34.1), 205 (32.1), 163 (26.2), 149 (60.9), 137 (17.3), 91 (100), 57 (55.7)

**2-Ethynyl-1-hydroxy-6-methoxybenzene, 3.25:** To a solution of 3.19 (300 mg, 1.09 mmol) dissolved in CDCl₃ (0.5 mL) in an NMR tube was added TMSI (0.62 mL, 4.36 mmol) under N₂. The reaction was monitored by ¹H NMR; after 70 min the benzyl ether had been cleaved. The reaction was quenched with MeOH (5 mL), and diluted with Et₂O (20 mL). The organic layer was washed with H₂O (3 × 10 mL), satd NaHCO₃ (1 × 10 mL), and dried (MgSO₄). Rotary evaporation of the solvent yielded a greenish-brown oil, which contained a mixture of products (3.25 and benzyl iodide).
Re-dissolved the oil in Et$_2$O (20 mL) and extracted with 10% NaOH (3 × 10 mL). The combined aqueous extracts were acidified with concd HCl, and extracted with Et$_2$O (3 × 10 mL). The Et$_2$O layer was washed with H$_2$O (1 × 10 mL), and dried (MgSO$_4$). Rotary evaporation yielded a brown oil (0.12 g, crude yield 75%). $^1$H NMR (200 MHz): δ 7.19 (dd, 1H, $J_{app}$ = 8.4 and 8.3, C$_5$), 6.59 (d, 1H, $J_{app}$ = 8.3), 6.44 (d, 1H, $J_{app}$ = 8.4), 6.03 (bs, 1H, OH), 3.88 (s, 3H, OCH$_3$), 3.69 (s, 1H, =CH). IR: 3482 (O-H stretch), 3276 (=C-H stretch), 2941 and 2840 (methyl C-H stretch), 2106 (C=C stretch).

2-Ethynyl-1-acetoxy-3-methoxybenzene, 3.26: A solution of crude 3.25 (120 mg, 0.81 mmol) and Ac$_2$O (0.15 mL, 1.62 mmol) in pyridine (5 mL) was refluxed for 90 min. The reaction was poured over ice (=10 g). The layer was extracted with Et$_2$O (2 × 15 mL). The combined Et$_2$O extracts were washed with 10% KOH (3 × 10 mL), satd NaHCO$_3$ (1 × 25 mL), and dried (MgSO$_4$). Rotary evaporation of the solvent yielded a golden oil (120 mg, crude yield 77.7%). $^1$H NMR (200 MHz): δ 7.24-7.30 (m, 1H), 6.70-6.80 (m, 2H), 3.89 (s, 3H, OCH$_3$), 3.48 (s, 1H, =CH), 2.32 (C(O)OCH$_3$). IR: 3276 (≡C-H stretch), 2109 (C≡C stretch), 1770 (C=O stretch).

1-methoxy-3-(methoxymethoxy)-2-[(trimethylsilyl)ethynyl]benzene, 3.27: A solution of crude 3.13 (4.41 g, 15.0 mmol), trimethyl[(trimethylsilyl)ethynyl]stannane (4.31 g, 16.5 mmol) and Pd(PPh$_3$)$_4$ (0.69 g, 0.6 mmol) in benzene (150 mL) was refluxed for 24 h under N$_2$. The solution was diluted with Et$_2$O (100 mL), then H$_2$O (50 mL) was added, which produced a black solid. After filtration of the two layers, the organic layer was washed with H$_2$O (2 × 50 mL), 10% NH$_4$OH (4 × 50 mL), satd NaHCO$_3$ (1 × 50 mL), and dried (MgSO$_4$). The solvent was removed by rotary evaporation yielding a
dark brown oil (4.00 g). $^1$H NMR and GC/MS indicated the brown oil consisted of
$\approx$76% of 3.27 and $\approx$24% of 3.28, bis-[(2-methoxy-6-(methoxymethoxy)phenyl]-
acetylene. $^8$2 (Note: The diarylethyne was presumably formed by trace of HI that was
not removed in synthesizing aryl iodide, 3.13.) The crude product was used in the next
step.

2-Ethynyl-1-methoxy-3-(methoxymethoxy)benzene, 3.29: The crude product from the
previous step (4.00 g) was dissolved in MeOH (75 mL) and stirred with KF (2.61 g,
45.0 mmol) overnight. H$_2$O (75 mL) was added. The solution was extracted with Et$_2$O
(4 × 50 mL). The combined organic layers were washed with H$_2$O (3 × 50 mL), satd
NaHCO$_3$ (1 × 50 mL), and dried (MgSO$_4$). The solvent was removed by rotary
evaporation; bulb-to-bulb distillation in a Kugelrohr apparatus (70-80 °C, 0.05 mm)
yielded a colorless oil (1.55 g, 53.8% for the two steps). $^1$H NMR (200 MHz): $\delta$ 7.23
(dd, 1H, $J_{app}$ = 8.5 and 8.4, C5), 6.76 (d, 1H, $J_{app}$ = 8.4, C4), 6.57 (d, 1H, $J_{app}$ = 8.5,
C6), 5.26 (s, 2H, OCH$_2$O), 3.89 (s, 3H, Ar-OCH$_3$), 3.54 (s, 1H, =CH), 3.51 (s, 3H,
OCH$_3$).

1,3-Bis(methoxymethoxy)-2-[(trimethylsilyl)ethynyl]benzene, 3.30: A solution of
crude 3.14 (2.92 g, 9.0 mmol), trimethyl[(trimethylsilyl)ethynyl]stannane (2.58 g, 9.9
mmol) and Pd(PPh$_3$)$_4$ (0.42 g, 0.36 mmol) in benzene (90 mL) was refluxed for 16 h
under N$_2$. The solution was diluted with Et$_2$O (100 mL), H$_2$O (50 mL) was added, and
filtered. The organic layer was washed with H$_2$O (1 × 50 mL), 10% NH$_4$OH (4 × 50
mL), satd NaHCO$_3$ (2 × 50 mL), and dried (MgSO$_4$). The solvent was removed by
rotary evaporation yielding a black oil (2.90 g). $^1$H NMR indicated that 3.30 was the
major product; however, traces of two other products were also present. $^1$H NMR (200 MHz): $\delta$ 7.18 (t, 1H, $J_{app} = 8.4$, C5), 6.75 (d, 2H, $J_{app} = 8.4$, C4 and C6), 5.23 (s, 4H, OCH$_2$O), 3.53 (s, 6H, OCH$_3$), 0.26 (s, 9H, Si(CH$_3$)$_3$). The crude product was used in the next step.

**Attempted synthesis of 2-Ethynyl-1,3-bis(methoxymethoxy)benzene, 3.31:** The crude product from the previous step (2.90 g) was dissolved in MeOH (100 mL) and stirred with KF (1.57 g, 27.0 mmol) overnight. H$_2$O (150 mL) was added. The solution was extracted with Et$_2$O (4 x 50 mL). The combined organic layer was washed with H$_2$O (3 x 50 mL), satd NaHCO$_3$ (1 x 50 mL), and dried (MgSO$_4$). The solvent was removed by rotary evaporation yielding a black oil. Attempted bulb-to-bulb distillation up to 160° in a Kugelrohr apparatus (0.05 mm), yielded nothing. The compound in the distilling flask was a black tar and insoluble in CDCl$_3$. It was presumed, but not known, that 3.31 was formed, but destroyed in the Kugelrohr distillation.

**Methyl 2-[(2,6-dimethoxyphenyl)ethynyl]-3-methoxybenzoate, 3.32:** A solution of 3.12 (2.21 g, 7.0 mmol), 3.21 (1.70 g, 10.5 mmol), Pd(PPh$_3$)$_2$Cl$_2$ (0.10 g, 0.14 mmol), NEt$_3$ (5.00 mL) and DMF (40 mL) was stirred between 61-85 °C for 40 h under N$_2$. The reaction was diluted with H$_2$O (45 mL), then extracted with 1:1 pet. ether:Et$_2$O (5 x 50 mL). The combined organic extracts were washed with 1% HCl (2 x 50 mL), H$_2$O (3 x 50 mL), and dried (MgSO$_4$). Rotary evaporation of the solvent yielded a yellow solid (1.42 g, 62%). For analytical purposes, a small amount was recrystallized from EtOAc to give colorless crystals. $^1$H NMR (400 MHz): 7.49 (dd, 1H, $J = 7.89$ and 0.87, C6), 7.28 (dd, 1H, $J = 7.89$ and 8.27, C5), 7.22 (t, 1H, $J = 8.41$, C4'), 7.03 (dd,
1H, J = 8.27 and 0.87, C4), 6.54 (d, 2H, J = 8.41, C3' and C5'), 3.95 (s, 3H, C3-OCH3), 3.94 (s, 3H, C(O)OCH3), 3.93 (s, 6H, C2',C6'-OCH3). 13C NMR: 167.3 (>C=O), 161.6 (C2' and C6'), 160.7 (C3), 133.7 (C1), 129.8 (C4'), 128.2 (C5), 122.0 (C6), 113.9 (C4), 113.7 (C2), 103.6 (C3' and C5'), 102.4 (C1'), 92.0 and 91.8 (C=C), 56.5 (C3-OCH3), 56.2 (C2',C6'-OCH3), 52.0 (C(O)OCH3). IR: 2947 and 2839 (methyl C-H stretch), 2212 (C=C stretch), 1729 (C=O stretch), 1581 (C=C ring stretch). MS, m/e (relative intensity): 326 (M+, 61), 163 (77), 151 (58), 138 (100), 91 (73), 76 (99), 75 (79), 63 (76), 59 (72). Anal. Calcd for C19H18O5: C, 69.93; H, 5.56. Found C, 69.95; H, 5.76.

Methyl 2-[(2-methoxy-6-(methoxymethoxy)phenyl)ethynyl]-3-methoxybenzoate, 3.33:
A solution of 3.12 (1.89 g, 6.0 mmol), 3.29 (1.50 g, 7.8 mmol), Pd(PPh3)Cl2 (0.17 g, 0.24 mmol), NEt3 (4 mL) and DMF (30 mL) was stirred between 70-72 °C for 30 h under N2. The reaction was diluted with H2O (30 mL), then extracted with EtjO (4 x 25 mL). The combined organic extracts were washed with 1 N HCl (2 x 25 mL), H2O (1 x 25 mL), satd NaHCO3 (1 x 25 mL), and dried (MgSO4). Rotary evaporation of the solvent yielded a orange solid. Attempted flash column chromatography using 1:3 hexane/CH2Cl2 as eluant but the product stuck to silica gel. After collecting 600 mL, only a small amount of product had been recovered. Flushing column with 2 L CH2Cl2 yielded a golden solid (0.97 g, 45.3%). 1H NMR (400 MHz): δ 7.48 (dd, 1H, J = 7.90 and 0.87, C6), 7.30 (dd, 1H, J = 8.22 and 7.90, C5), 7.21 (dd, 1H, J = 8.41 and 8.34, C4'), 7.04 (dd, 1H, J = 8.22 and 0.87, C4), 6.76 (dd, 1H, J = 8.41 and 0.54, C5'), 6.60 (dd, 1H, J = 8.34 and 0.54, C3'), 5.30 (s, 2H, -OCH2O-), 3.94 (s, 3H, C3-OCH3), 3.93 (s, 3H, C(O)OCH3), 3.92 (s, 3H, C2'-OCH3), 3.54 (s, 3H, -OCH2OCH3). 13C NMR:
Methyl 2-[(2,7-dimethoxynaphthyl)ethynyl]-3-methoxybenzoate, 3.34: A solution of 3.12 (0.63 g, 2.0 mmol), 3.22 (0.64 g, 3.0 mmol), Pd(PPh₃)Cl₂ (0.03 g, 0.04 mmol), NEt₃ (1.4 mL), and DMF (20 mL) was stirred at 80-90 °C for 70 h. The reaction was diluted with H₂O (15 mL) precipitating 3.34 as a brown solid. The precipitate was filtered and flash column chromatography (eluant: hexane/EtOAc 4:1) yielded a yellow solid (0.59 g, 78.7%). \(^1\)H NMR (400 MHz): \(\delta 8.11 \text{ (d, } 1H, J = 2.48, C8')\), 7.74 (d, 1H, \(J = 8.98, C4')\), 7.66 (d, 1H, \(J = 8.75, C5')\), 7.58 (dd, 1H, \(J = 7.74 \text{ and } 0.99, C6\)), 7.32 (dd, 1H, \(J = 8.74 \text{ and } 7.74, C5\)), 7.11 (dd, 1H, \(J = 7.87 \text{ and } 0.99, C4\)), 7.10 (d, 1H, \(J = 8.98, C3'\)), 7.05 (dd, 1H, \(J = 7.85 \text{ and } 2.48\)), 4.09 (s, 3H, C2'-OCH₃ or C7'-OCH₃), 4.08 (s, 3H, C2'-OCH₃ or C7'-OCH₃), 4.02 (s, 3H, C3-OCH₃), 3.93 (s, 3H, C(O)OCH₃).

\(^{13}\)C NMR: \(\delta 166.5 \text{ (C=O)}, 160.7 \text{ (C3)}, 159.8 \text{ (C2')}, 159.3 \text{ (C7')}, 136.6 \text{ (C8a')}, 132.7 \text{ (C1)}, 130.1 \text{ (C4')}, 129.3 \text{ (C5')}, 128.1 \text{ (C5)}, 123.9 \text{ (C4a')}, 122.1 \text{ (C6)}, 116.9 \text{ (C6')}, 114.03 \text{ (C2)}, 113.96 \text{ (C3')}, 110.0 \text{ (C4)}, 106.0 \text{ (C1')}, 104.6 \text{ (C8')}, 94.7 \text{ and } 93.0 \text{ (C= C)}, 56.6 \text{ (OCH₃)}, 56.4 \text{ (OCH₃)}, 55.6 \text{ (OCH₃)}, 51.9 \text{ (C(O)OCH₃)}. IR: 2950 and 2842 (methyl C-H stretch), 2199 (C=C stretch), 1724 (C=O stretch), 1623 (C=C ring stretch). MS, \(m/e\) (relative intensity): 376 (M⁺, 100), 377 (M⁺+1, 41), 343 (35), 329 (42), 315 (42), 313 (38), 287 (49), 285 (52), 202 (41), 189 (38), 94(37), 88 (36). Anal. Calcd for C₂₃H₂₆O₅: C, 73.39; H, 5.36. Found: C, 73.74; H, 5.47.
Methyl 2-[(2,6-dimethoxyphenyl)ethynyl]benzoate, 3.37: A solution of 3.21 (4.05 g, 25 mmol), methyl 2-iodobenzoate (6.57 g, 25 mmol), CuI (0.08 g, 0.42 mmol), and Pd(PPh₃)₄ (0.32 g, 0.28 mmol) in HNEt₂ (150 mL) was stirred overnight at rt under N₂. The solution was filtered through a fritted glass (vf) funnel. The solvent was removed by rotary evaporation. The resulting orange solid was dissolved in benzene (50 mL) and washed with water (2 × 50 mL). The organic layer was passed through a short column of alumina, and the solvent removed by rotary evaporation. Successive recrystallization from Et₂O yielded white crystals (4.37 g, 59.0%). ¹H NMR (400 MHz): δ 7.93 (dd, 1H, J = 7.86 and 1.14, C2), 7.70 (dd, 1H, J = 7.66 and 1.03, C5), 7.43 (ddd, 1H, J = 7.66, 7.52, and 1.14, C4), 7.31 (ddd, 1H, J = 7.86, 7.52, and 1.03, C3), 7.19 (t, 1H, J = 8.35, C4'), 6.51 (d, 2H, J = 8.35, C3' and C5'), 3.86 (s, 6H, C2',C6'-OCH₃), 3.93 (s, 3H, C(O)OCH₃). ¹³C NMR: δ 166.7 (C=O), 161.3 (C2' and C6'), 133.9 (C3), 131.2 (C1), 131.1 (C4), 129.9 (C6), 129.8 (C4'), 127.2 (C5), 124.1 (C2), 103.2 (C3' and C5'), 101.4 (C1'), 96.3 (C7), 87.0 (C7'), 55.7 (OCH₃), 51.6 (C(O)OCH₃). IR: 3066 (aromatic C-H stretch), 2949 and 2839 (methyl C-H stretch), 2213 (C≡C stretch), 1732 (C=O stretch). MS, m/e (relative intensity): 297 (M⁺+1, 6.2), 296 (M⁺, 31.0), 235 (31.1), 233 (34.6), 221 (48.8), 133 (100), 104 (37.9), 91 (33.5), 89 (32.7), 82 (40.6), 77 (37.5), 76 (54.9), 75 (50.5). Anal. Calcd for C₁₈H₁₆O₄: C, 72.89; H, 5.44. Found: C, 72.88; H, 5.39.

2-[(2,6-Dimethoxyphenyl)ethynyl]-3-methoxybenzoic acid, 3.40: A mixture of 3.32 (2.28 g, 7.0 mmol) and NaHCO₃ (1.18 g, 14.0 mmol) was placed in MeOH (50 mL) and H₂O (25 mL). The pH was adjusted to 11 with 10% NaOH and the reaction was
refluxed for 12 h. The reaction mixture was acidified and the precipitate filtered, washed with H2O, and dried to give a white solid (1.81 g, 82.6%). 1H NMR (400 MHz): δ 7.92 (dd, 1H, J = 8.02 and 0.88, C6), 7.39 (dd, 1H, J = 8.44 and 8.02, C5), 7.29 (t, 1H, J = 8.33, C4'), 7.13 (dd, 1H, J = 8.44 and 0.88, C4), 6.55 (d, 2H, J = 8.33, C3', C5'), 4.01 (s, 3H, C3-OCH3), 3.95 (s, 6H, C2', C6'-OCH3).

13C NMR: 167.1 (C=O), 161.4 (C2', C6'), 160.4 (C3), 131.4 (C1), 131.1 (C4'), 129.0 (C5), 124.3 (C6), 114.6 (C4), 112.2 (C2), 103.4 (C3', C5'), 100.5 (C1'), 96.3 (-C=), 91.0 (-C=), 56.7 (C3-OCH3), 56.1 (C2', C6'-OCH3).

IR: 2966 (O-H stretch), 2204 (C=O stretch), 1694 (C=O stretch).

MS, m/e (relative intensity): 313 (M+1, 22.3), 312 (M+, 100), 254 (17.0), 253 (70.1), 237 (15.8), 226 (15.8), 151 (21.1), 150 (13.9), 147 (15.4), 106 (25.6), 105 (14.6), 91 (19.8). Anal. Calcd for C18H16O5: C, 69.22; H, 5.16. Found: C, 69.17; H, 5.22.

**Methyl 2-(2,6-dimethoxyphenyl)benzofuran-4-carboxylate, 3.43:**

**Method A.** A solution of 3.32 (326 mg, 1.0 mmol) in concd HOAc (20 mL) and 9 M H2SO4 (3 mL) was stirred overnight at rt. The reaction mixture was diluted with H2O (20 mL) and extracted with Et2O (4 x 25 mL). The combined Et2O extracts were washed with 10% KOH (4 x 25 mL), satd NaHCO3 (1 x 25 mL) and dried (MgSO4). Rotary evaporation of the solvent yielded a white solid (260 mg, 83.3%). 1H NMR (400 MHz): δ 7.97 (dd, 1H, J = 7.75 and 0.78, C5), 7.70 (ddd, 1H, J = 8.11, 0.81 and 0.78, C7), 7.44 (d, 1H, J = 0.81, C3), 7.36 (t, 1H, J = 8.43, C4'), 7.30 (dd, 1H, J = 8.11 and 7.75, C6), 6.65 (d, 2H, J = 8.43, C3', C5'), 3.97 (s, 3H, C(O)OCH3), 3.81 (s, 6H, C2', C6'-OCH3). 13C NMR: 167.2 (C=O), 159.1 (C2', C6'), 155.2 (C7a), 152.0 (C2), 131.2 (C4'), 129.5 (C3a), 125.0 (C5), 122.8 (C6), 122.1 (C4), 115.6 (C7), 108.7 (C3),
108.7 (C1'), 104.1 (C3', C5'), 56.0 (C2', C6'-OCH₃), 51.8 (C(O)OCH₃). IR: 2950 and 2840 (methyl C-H stretch), 1717 (C=O stretch), 1589 (C=C ring stretch). MS, m/e (relative intensity): 313 (M+1, 18.4), 312 (M+, 100), 281 (14.0), 265 (18.5), 251 (24.1), 237 (17.0), 223 (13.5), 148 (14.1). Anal. Calcd for C₁₈H₁₆O₅: C, 69.22; H, 5.16. Found: C, 69.09; H, 5.11.

Method B. A solution of 3.32 (979 mg, 3.0 mmol) in CH₂Cl₂ (60 mL) was cooled to -78 °C under N₂. A 1-M BCl₃ solution in CH₂Cl₂ (4.5 mL, 4.5 mmol) was added dropwise, and the flask was allowed to warm to rt. After stirring for 2.5 h, the reaction was quenched with water (50 mL). The organic layer was washed with H₂O (2 x 25 mL), satd NaHCO₃ (3 x 25 mL), and dried (MgSO₄). The CH₂Cl₂ was removed by rotary evaporation yielding an orange solid. Cold CH₃CN (10 mL) was added to the orange solid, and the mixture filtered. The remaining yellow solid (226 mg) was identified as boracycle 3.44 (see below). Slow evaporation of the acetonitrile yielded colorless crystals of 3.43 (491 mg, 52.4%).

Characterization of Boracycle, 3.44: ¹H NMR: δ 10.01 (s, 1H, OH), 8.14 (dd, 1H, J = 7.87 & 1.06, C5), 7.92 (dd, 1H, J = 8.07 & 1.06, C7), 7.41 (dd, 1H, J = 8.31 & 8.29, C4'), 7.40 (dd, 1H, J = 8.07 & 7.87, C6), 7.08 (dd, 1H, J = 8.29 & 0.74, C3'), 6.77 (dd, 1H, J = 8.31 & 0.74, C5'), 4.05 (s, 3H, C6'-OCH₃), 4.03 (s, 3H, C(O)OCH₃). ¹³C NMR: 169.3 (C=O), 165.7 (C2), 156.8 (C6'), 156.5 (C8), 154.6 (C2'), 130.9 (C4'), 128.4 (C9), 127.6 (C5), 123.8 (C6), 122.9 (C4), 117.2 (C7), 111.9 (C3'), 106.2 (C1'), 104.4 (C5'), 56.3 (C6'-OCH₃), 53.2 (C(O)OCH₃). ¹¹B NMR (128 MHz; External standard: BF₃·Et₂O): δ 28.1 ppm. IR: 3323 (O-H stretch), 1699 (C=O stretch).
Methyl 2-(2-hydroxy-6-methoxyphenyl)benzofuran-4-carboxylate, 3.45: A solution of 3.44 (100 mg, 0.31 mmol) in HOAc (10 mL) was refluxed overnight. The reaction was diluted with H₂O (15 mL) and extracted with CH₂Cl₂ (4 × 20 mL). The combined extracts were washed with H₂O (1 × 20 mL), satd NaHCO₃ (2 × 20 mL), and dried (MgSO₄). The solvent was removed by rotary evaporation yielding a tan solid. ¹H NMR (400 MHz): δ 7.99 (bs, 1H, OH), 7.97 (d, 1H, J = 7.82, C5), 7.84 (s, 1H, C3), 7.66 (d, 1H, J = 7.93, C7), 7.32 (dd, 1H, J = 7.93 and 7.82, C6), 7.24 (dd, 1H, J = 8.34 and 8.21, C4'), 6.69 (d, 1H, J = 8.21, C3'), 6.56 (d, 1H, J = 8.34, C5'), 3.99 (s, 3H, OCH₃), 3.94 (s, 3H, C6'-OCH₃). ¹³C NMR: 166.8 (C=O), 158.1 (C6'), 155.7 (C20), 153.2 (C7a), 152.9 (C2), 130.9 (C4'), 129.1 (C3a), 125.9 (C5), 123.5 (C6), 122.4 (C4), 115.0 (C7), 110.2 (C3'), 108.4 (C3), 105.4 (C1'), 102.8 (C5'), 55.9 (C6'-OCH₃), 51.9 (C(O)OCH₃). IR: 3448 (O-H stretch), 2966 and 2840 (methyl C-H stretch), 1716 (C=O stretch). MS, m/e (relative intensity): 299 (M⁺+1, 36.4), 298 (M⁺, 100), 267 (37.1), 266 (53.5), 238 (41.4), 237 (32.6), 223 (26.0), 139 (24.0).

2-(2,6-Dihydroxyphenyl)benzofuran-4-carboxylic acid, 3.46: In a NMR tube, 3.32 (326 mg, 1.0 mmol) was dissolved in CDCl₃ (0.75 mL) under N₂. The tube was placed in a H₂O bath at 50 °C. Iodotrimethylsilane (0.78 mL, 5.5 mmol) was added. After 6 d, ¹H NMR indicated that all methyls had been cleaved. The reaction was quenched with MeOH (5 mL), and diluted with Et₂O (30 mL). The organic layer was washed with H₂O (2 × 10 mL), satd brine (3 × 10 mL), and dried (MgSO₄). The solvent was removed by rotary evaporation yielding a tan solid (174 mg, 64.4%). ¹H NMR (400 MHz; acetone-d₆): 8.74 (bs, OH), 7.98 (dd, 1H, J = 7.70 and 0.83, C5), 7.82 (ddd, 1H,
$J = 8.14, 0.97$ and $0.83, C7$), $7.79$ (d, $1H, J = 0.97, C3$), $^{13}C$ NMR (acetone-d$_6$): $167.8$ (C=O), $157.5$ (C$_2$, C$_6$), $155.2$ (C$_7a$), $153.9$ (C$_2$), $131.7$ (C$_4$), $130.5$ (C$_3a$), $126.4$ (C$_5$), $124.0$ (C$_6$), $123.4$ (C$_4$), $116.2$ (C$_7$), $109.1$ (C$_3$), $108.5$ (C$_3$, C$_5$), $106.1$ (C$_1$). IR: $3462$ (phenol O-H stretch), $3079$ (carboxylic acid O-H stretch), $1683$ (C=O stretch).

2-(2,6-Dimethoxyphenyl)benzofuran-4-carboxylic acid, 3.48: A solution of 3.40 (312 mg, 1.0 mmol) in concd HOAc (20 mL) and $9 M$ H$_2$SO$_4$ (3 mL) was stirred for 2 h at rt. The reaction mixture was diluted with H$_2$O (20 mL) and extracted with Et$_2$O (3 × 20 mL). The combined Et$_2$O extracts were washed with satd NaHCO$_3$ (6 × 15 mL), until the aqueous layer was neutral. The Et$_2$O layer was dried (MgSO$_4$) and rotary evaporation yielded a yellowish solid (283 mg, 94.9%). $^1H$ NMR (400 MHz): δ $8.06$ (dd, $1H, J = 7.74$ and $0.78, C5$), $7.76$ (ddd, $1H, J = 8.14, 0.78$ and $0.77, C7$), $7.52$ (d, $1H, J = 0.77, C3$), $^{13}C$ NMR: $171.9$ (C=O), $159.2$ (C$_2$, C$_6$), $155.3$ (C$_7a$), $152.5$ (C$_2$), $131.3$ (C$_4$), $130.3$ (C$_3a$), $125.9$ (C$_5$), $122.9$ (C$_6$), $121.2$ (C$_4$), $116.4$ (C$_7$), $108.9$ (C$_3$), $108.7$ (C$_1$), $104.1$ (C$_3$, C$_5$), $56.2$ (C$_2$, C$_6'$-OCH$_3$). IR: $2944$ (O-H stretch), $1683$ (C=O stretch). MS, m/e (relative intensity): $299$ (M$^+$+1, 20.3), $298$ (M$^+$, 100), $265$ (16.2), $251$ (23.1), $240$ (24.3), $237$ (19.9), $186$ (16.2), $148$ (16.5), $147$ (55.0), $133$ (16.9), $77$ (13.2), $76$ (16.3). Anal. Calcd for C$_{17}$H$_{14}$O$_5$: C, 68.45; H, 4.73. Found: C, 68.16; H, 4.80.
2-Phenylbenzofuran, 3.49: Following the basic procedure by Castro and Stephens, a solution of 2-bromophenol (3.46 g, 20 mmol) and cuprous phenylacetylide (3.29 g, 20 mmol) in pyridine (100 mL) was refluxed for 8 h. The reaction was diluted with H₂O (200 mL) and 2N HCl (200 mL), and extracted with Et₂O (4 × 100 mL). The combined Et₂O extracts were washed with 2N HCl (3 × 100 mL), H₂O (1 × 100 mL), and dried (MgSO₄). The solvent was removed by rotary evaporation yielding a brown solid. The solid was decolorized with activated charcoal in MeOH (150 mL) yielding a tan solid. Recrystallization from pet. ether yielded white crystals (2.64 g, 68.0%). "H NMR (200 MHz; Lit.¹⁴): "8 7.84-7.89 (m, 2H), 7.21-7.59 (m, 7H), 7.01 (s, 1H). MS, m/e (relative intensity): 195 (M⁺+1, 39.3), 194 (M⁺, 100), 166 (13.7), 165 (88.8), 164 (12.9), 139 (12.0), 97 (19.2), 82 (15.6).

Attempted Ring Opening of 2-Phenylbenzofuran, 3.49, with LDA: A 2.5-M BuLi solution in hexanes (3.0 mL, 7.5 mmol) was added under N₂ to a solution of HN(i-Pr)₂ (1.4 mL, 10.0 mmol) in benzene (5 mL) at 0 °C and stirred for 25 min. A solution of 3.49 (0.97 g, 5.0 mmol) dissolved in benzene (10 mL) was added to the LDA solution, and continued stirring for 20 h. The reaction was quenched with AcCl (3.56 mL, 50 mmol). H₂O (20 mL) and Et₂O (50 mL) were added. The organic layer was washed with 2N HCl (1 × 15 mL), H₂O (3 × 15 mL), satd NaHCO₃ (1 × 15 mL), and dried (MgSO₄). The solvent was removed by rotary evaporation yielding a brown solid (1.25 g). GC/MS indicated the brown solid was a mixture of: 17% N,N-diisopropylacetamide, 63% benzofuran 3.49, and 20% 1-(2-acetoxyphenyl)-2-phenylethyne, 3.50. Note: This reaction was also attempted by refluxing the solution.
In addition to 3.50, two side-products (unidentified) were formed. By GC integration, 3.50 was the minor product.)

1-(2-Acetoxyphenyl)-2-phenylethyne, 3.50: To a solution of 3.49 (0.22 g, 1.13 mmol) in THF (10 mL) was added 2.44 M BuLi solution in hexane (0.82 mL, 2.0 mmol). The solution was stirred at rt for 4.5 h, and then quenched with AcCl (0.71 mL, 10 mmol). H₂O (5 mL) and Et₂O (40 mL) were added. The organic layer was washed with H₂O (3 × 15 mL), satd NaHCO₃ (1 × 15 mL), and dried (MgSO₄). The solvent was removed by rotary evaporation yielding a yellow oil (0.25 g, 92.6%). ¹H NMR (200 MHz): δ 7.09-7.58 (m, 9H, Ar), 2.34 (s, 3H, -OC(0)CH₃). MS, m/e (relative intensity): 237 (M⁺+1, 5.2), 236 (M⁺, 29.0), 195 (35.4), 194 (100), 166 (11.1), 165 (77.1), 164 (12.3), 163 (11.1), 139 (9.0), 43 (23.2).

4-Bromo-3-(2,6-dimethoxyphenyl)-1H-benzo-2-pyran-1-one, 3.51: A solution of Br₂ (0.052 mL, 1.0 mmol) in HOAc (5 mL) was added dropwise into a mixture of 3.32 (326 mg, 1.0 mmol) and LiBr (130 mg, 1.5 mmol) in HOAc (10 mL) taking 25 min. The reaction was stirred for an additional 30 min. The reaction was diluted with H₂O (20 mL) and extracted with Et₂O (3 × 20 mL). The Et₂O extracts were washed with 10% Na₂S₂O₃ (2 × 20 mL), 10% KOH (4 × 20 mL), satd NaHCO₃ (1 × 20 mL), and dried (MgSO₄). The solvent was removed by rotary evaporation yielding a white, foamy solid. Chromatography (flash column, hexane/EtOAc 2:1) followed by recrystallization from hexane/EtOAc (3:1) yielded white crystals (268 mg, 68.5%). ¹H NMR (400 MHz): 7.69 (dd, 1H, J = 7.70 and 0.89, C8), 7.65 (dd, 1H, J = 8.19 and 0.89, C6), 7.42 (t, 1H, J = 8.46, C4'), 7.33 (dd, 1H, J = 8.19 and 7.70, C7), 6.64 (d, 2H, J = 8.46, C3', C5').
84

3.99 (s, 3H, C5-OCH3), 3.78 (s, 6H, C2', C6'-OCH3). 13C NMR: 167.3 (C1), 159.6 (C2', C6'), 154.8 (C5), 150.8 (C3), 132.4 (C4'), 125.6 (C4a), 124.9 (C8a), 124.7 (C8), 123.7 (C7), 115.0 (C6), 106.8 (C1'), 103.9 (C3', C5'), 97.5 (C4), 56.0 (C2', C6'-OCH3), 51.9 (C5-OCH3). IR: 3004 (aromatic C-H stretch), 2947 and 2840 (methyl C-H stretch), 1726 (C=O stretch). MS, m/e (relative intensity): 393 (M+ +2, 20.1), 392 (M+ +1, 92.1), 391 (M+, 19.9), 390 (100), 361 (19.0), 358 (19.1), 296 (16.4), 295 (9.7), 281 (27.0), 279 (30.6), 265 (10.6), 251 (12.1), 237 (9.4), 189 (14.1), 147 (28.7), 45 (23.2). Anal. Calcd for C18H15O5Br: C, 55.26; H, 3.86. Found: C, 55.02; H, 3.92.

5-Methoxy-3-(2,6-dimethoxyphenyl)-1H-benzo-2-pyran-1-one, 3.52: A solution of 3.40 (937 mg, 3.0 mmol) and Pd(PPh3)2Cl2 (105 mg, 0.15 mmol) in CH3CN (60 mL) was refluxed overnight. The acetonitrile was removed by rotary evaporation yielding an orange tar. Chromatography (flash column, CHCl3/EtOAc 2:1) followed by recrystallization from acetone yielded white crystals (763 mg, 81.4%). 1H NMR (400 MHz): δ 7.90 (ddd, 1H, J = 7.98, 0.81 and 0.80, C8), 7.42 (dd, 1H, J = 8.13 and 7.98, C7), 7.33 (t, 1H, J = 8.43, C4'), 7.14 (dd, 1H, J = 8.13 and 0.81, C6), 6.92 (dd, 1H, J = 0.80, C4), 6.59 (d, 2H, J = 8.43, C3', C5'), 3.91 (s, 3H, C5-OCH3), 3.78 (s, 6H, C2', C6'-OCH3). 13C NMR: 163.5 (C=O), 159.0 (C2', C6'), 154.1 (C5), 148.4 (C3), 131.3 (C4'), 128.4 (C4a), 128.1 (C7), 121.5 (C8a), 120.8 (C8), 114.1 (C6), 112.0 (C1'), 103.8 (C3', C5'), 102.9 (C4), 56.0 (C2',C6'-OCH3), 55.8 (C5-OCH3). IR: 2952 and 2839 (methyl C-H stretch), 1725 (C=O stretch). MS, m/e (relative intensity): 313 (M+ +2, 20.6), 312 (M+, 100), 254 (12.5), 253 (69.9), 237 (13.3), 151 (14.0), 150 (13.3), 149 (12.6), 108 (10.9), 105 (13.5), 91 (21.4), 77 (10.6). Anal. Calcd for C18H16O3: C, 69.22; H, 5.16. Found: C, 69.40; H, 5.25
(Z)-4-Methoxy-3-[(2,6-dimethoxyphenyl)methylene]-1\( (3H) \)-isobenzofuranone, 3.53:

A solution of 3.40 (312 mg, 1.0 mmol) in 0.05 \( M \) phosphate buffer (pH = 7.0, 100 mL) was refluxed overnight. After the mixture was cooled, the white solid (194 mg, 62.2%) was filtered, washed with \( \text{H}_2\text{O} \) (3 \( \times \) 20 mL) and dried. \( ^1\text{H} \) NMR (400 MHz): \( \delta \) 7.48 (dd, 1H, \( J = 7.64 \) and 0.60, C7), 7.45 (dd, 1H, \( J = 8.02 \) and 7.64, C6), 7.26 (t, 1H, \( J = 8.38 \), C4'), 7.14 (dd, 1H, \( J = 8.02 \) and 0.60, C5), 6.87 (s, 1H, =CH(Ar)), 6.60 (d, 2H, \( J = 8.38 \), C3', C5'), 4.01 (s, 3H, C4-OCH\(_3\)), 3.85 (s, 6H, C2', C6'-OCH\(_3\)). \( ^{13}\text{C} \) NMR: 167.2 (C=O), 158.1 (C2', C6'), 155.0 (C4), 144.4 (C3), 130.7 (C6), 129.5 (C4'), 127.7 (C3a), 126.5 (C7a), 116.8 (C7), 115.2 (C5), 111.4 (C1'), 103.9 (=CH(Ar)), 103.8 (C3', C5'), 55.9 (C2', C6'-OCH\(_3\)), 55.7 (C4-OCH\(_3\)). IR: 2996 (aromatic C-H stretch), 2943 and 2842 (methyl C-H stretch), 1763 (C=O stretch). MS, \( m/e \) (relative intensity): 313 (M\(^+1\), 18.2), 312 (M\(^+\), 100), 156 (10.1), 136 (81.2), 108 (8.4), 106 (31.7), 76 (8.7).

CHAPTER 4: CONCLUSION

4.1 SUMMARY OF PROGRESS

4.1.1 Retrosynthetic Pathway 1

The retrosynthetic pathway 1, proposed in Chapter 2, Section 2.1.1, appears useful for the synthesis of the untethered diarylethyne model. A close precursor, diarylethyne 3.33, to the untethered target molecule has been synthesized. Saponification of the ester of diarylethyne 3.33, using a procedure similar to the method developed by Oliver\textsuperscript{30} and also used on 3.32, should yield diarylethyne 4.1 The general-acid catalyzed hydrolysis of the acetal, MOM ether, of diarylethyne 4.1 could be measured. (Scheme 4.1)

![Scheme 4.1 Intramolecular General-acid Hydrolysis of an Acetal.](image)

Alternatively, the MOM phenolic protecting group of diarylethyne 4.2 could be cleaved in an acidic methanol solution at room temperature yielding diarylethyne 4.2. (Scheme 4.2) Transformation of the resulting phenol into the dichloroacetate ester affords the untethered diarylethyne, 1.12u, which allows the measurement of general-base catalyzed hydrolysis of the dichloroacetate.
Another possible synthesis of diarelethylene, 4.2, would involve the hydrolysis of the methyl ester and the acetoxy of diarelethylene 4.3. Diarelethylene 4.3 could be synthesized by the palladium-mediated coupling of arelethylene, 3.26, with aryl triflate, 3.12. (Scheme 4.3) If the synthesis of arelethylene 3.26 can be performed on a larger scale, then this method would be the best route for forming the diarelethylene, 4.2. (The synthesis of arelethylene 3.26 (Chapter 3, Section 3.4.1.3) is easier than the synthesis of the MOM-protected arelethylene 3.29).

**Scheme 4.3** Proposed Synthesis of a Precursor to Untethered Diarelethylene.

Retrosynthetic pathway 1 was not effective for the synthesis of the tethered diarelethenes. In all attempts to cleave the methyl ethers of diarelethylene 3.32, the resulting phenol on the carboxyphenyl ring immediately cyclized with the ethyne to
form 2-arylbenzofurans. (Chapter 3, Section 3.7) Although, other phenolic protecting
groups are cleaved under milder conditions, it appears unlikely that the phenol on the
carboxyphenyl ring will be stable.

4.1.2 Retrosynthetic Pathway 2

Retrosynthetic pathway 2, Chapter 2, Section 2.1.2, was developed after
observing that all attempts to demethylate diarylethyne 3.32 yielded 2-arylbenzofurans.
Limited progress was made on this pathway. Attempting to open 2-phenylbenzofuran,
3.49, with lithium diisopropylamide was unsuccessful. However, 3.49 was easily opened
with butyllithium.

To continue along this pathway requires either screening non-nucleophilic bases
in an attempt to find a base which opens the benzofuran ether ring, or protect the
carboxylate against nucleophilic attack. Carboxylic acids can be protected against
nucleophilic attack by forming an oxazoline. Oxazolines are stable in the presence
butyllithium and direct the attack of butyllithium to the ortho position.\textsuperscript{115} Meyers et
al.\textsuperscript{116} have synthesized aryl oxazoline 4.4. (Scheme 4.4) Protecting the phenol of 4.4
as the MOM ether should direct the ortho-lithiation/iodination sequence to the ortho
position between the two groups to give aryl iodide, 4.5.
4.2 FUTURE SYNTHETIC EFFORTS

The proposed synthesis of the untethered target molecule, 1.12u, from diarylethyne 3.33 is discussed in Section 4.1.1. The synthesis of the tethered target molecule, 1.12t, requires more work. Currently, the best approach to synthesize the tethered diarylethynes is to protect the carboxyl as the oxazoline prior to forming the benzofurans. Oxazolines, which are stable against nucleophilic bases, allow the use of butyllithium to open the benzofuran ether ring.

An advantage of our models is that many pathways are possible for synthesizing the tethered and untethered molecules. Two additional retrosynthetic pathways have been developed for synthesizing the tethered diarylethynes. Based on the previous results, it appears best to avoid using methyl ethers as a phenolic protecting group, and to protect the carboxyl from nucleophilic attack. In the following retrosynthetic schemes, carboxyl protecting groups are represented by CPG.

Scheme 4.4 Proposed Synthesis of Carboxyl Protected Aryl Iodide Synthon.
4.2.1 Retrosynthetic Pathway 3

An alternate retrosynthetic pathway for synthesizing the tethered diarylethynes, 2.1t, involves the ring opening of either the tethered benzopyranones, 4.6 and 4.7, or tethered isobenzofuranone, 4.8. (Scheme 4.5) The lactone serves as a protecting group for both the carboxyl and the ethyne. Formation of the lactone prevents cyclization of the phenol with the ethyne to form benzofurans.

The tethered diarylethyne, 2.1t, would be synthesized by the ring opening of the lactones, 4.6-4.8, which form the ethyne and the carboxylic acid. Although a literature search for preparation of diarylethynes has not revealed any examples in which lactones are opened to form diarylethynes, the method seems valid. The benzopyranones 4.6 and the isobenzofuranones 4.8 could possibly be opened with a strong, non-nucleophilic base. The bromobenzopyranones 4.7 could possibly be opened by zinc. Zinc has been used to synthesize alkyynes by dehalogenation of vicinal haloalkenes, and alkenes from β-halo ester. (Scheme 4.6)

O-Alkylation of either the dihydroxy (P=H) or the trihydroxy (P=P'=H) lactones, 4.9-4.11, with a bifunctional reagent using the Williamson ether synthesis affords the tethered lactones, 4.6-4.8, respectively. Benzopyranones 4.9 are synthesized by palladium-mediated lactonization of 2-(arylethynyl)benzoic acids. Bromobenzopyranones 4.10 are synthesized by bromolactonization of alkyl 2-(arylethynyl)benzoates or 2-(arylethynyl)benzoic acids. Isobenzofuranones 4.11 are synthesized by the uncatalyzed lactonization of 2-(arylethynyl)benzoic acids.
Scheme 4.5  Retrosynthetic Pathway for Synthesizing the Tethered Diarylethyne Models by Opening of Lactones.

Scheme 4.6  Synthesis of Alkynes and Alkenes Using Zinc.
Lactones 4.9-4.11 (P=P'=CH₃) have been synthesized in 81% (3.52), 68% (3.51), and 62% (3.53) yields, respectively. (Chapter 3, Section 3.9) Other phenolic protecting group, such as MOM, MEM, and benzyl ethers, should survive the palladium-mediated and the uncatalyzed lactonizations to form benzopyranones 4.9 and isobenzofuranones 4.11, respectively. Bromolactonization of alkyl 2-(arylethynyl)benzoates are run in acetic acid,¹⁰⁰,¹⁰¹ which limits the phenolic protecting groups to alkyl ethers. The MOM, MEM and benzyl ethers are cleaved under the acidic conditions.³³ The MOM, MEM and benzyl ethers should survive the conditions of bromolactonization of 2-(arylethynyl)-benzoic acids.

### 4.2.2 Retrosynthetic Pathway 4

A fourth retrosynthetic pathway is shown in Scheme 4.7. This pathway is the least desirable for synthesizing a series of tethered diarylethynes, because the tether is added early in the synthesis. New reaction conditions might have to be developed for the palladium-mediated coupling reaction for each tether. Some tethers may prevent the coupling, cause side-reactions, or be destroyed in the subsequent reactions. However, this pathway does avoid the deprotection of the phenols on the diarylethynes. Such a strategy eliminates the possibility of the phenol on the carboxyphenyl ring to cyclize with the ethyne to form benzofurans.

In Scheme 4.7, the tethered diarylethynes 2.1t would be formed by an intramolecular palladium-mediated coupling of the aryl halide or triflate with the arylethyne of the tethered molecule, 4.12. The tethered molecule 4.12 can be
synthesized by O-alkylation of the aryl halide \textbf{4.13} (P=H) with the tether. Once alkylated, arylethyne \textbf{2.4} (P=H) would be added forming \textbf{4.12}. No advantage is apparent in the order of attaching the tether. The tether could first be attached to arylethyne \textbf{2.4} and then to the aryl halide or triflate \textbf{4.13}.

A proposed synthesis of aryl iodide \textbf{4.13} (P=MOM) using oxazoline as the carboxyl protecting group is shown in Scheme 4.3. Other carboxyl protecting groups that can be used in this retro-synthetic pathway include methyl ester and acetics. If the carboxyl protecting group is an acetal, then, after acetal cleavage, the aldehyde must be oxidized to a carboxylic acid. Two procedures have been developed for the synthesis of arylethyynes. (Chapter 3, Section 3.4) Of particular relevance is the synthesis of arylethyne \textbf{3.25} (2.4: P=H, P'=CH₃). (Chapter 3, Section 3.4.1.3)
4.3 CONCLUSION

Numerous precursors to the tethered, \textbf{1.12t}, and the untethered, \textbf{1.12u}, diarylethyynes models have been made and characterized. The new mono- and diarylethyynes listed below are a source of intermediates for synthesizing the target molecules. In addition to the specific compounds synthesized, the methodology developed allows the synthesis of related compounds.

Two procedures for synthesizing arylethyynes (Figure 4.1) have been developed. Arylethyynes \textbf{3.21} and \textbf{3.25} have been synthesized in two steps from 2',6'-dimethoxyacetophenone and 2'-benzyloxy-6'-methoxyacetophenone, respectively, by a modification of a classic procedure for synthesizing arylethyynes from acetophenones.

The acidic conditions of the phosphorus pentachloride and phosphorus trichloride reaction limit the phenolic protecting group to either alkyl or benzyl ethers in the synthesis of the vinyl chlorides. When methyl ethers are used, dehydrohalogenation of the vinyl chloride using lithium diisopropylamide forms arylethyne \textbf{3.21}. Trimethylsilyl iodide cleaves the benzyl ether and dehydrohalogenates the vinyl chloride to form arylethyne \textbf{3.25}, which was immediately transformed into the acetate \textbf{3.26}.

\begin{center}
\begin{tabular}{l}
\textbf{3.21} \, R = R^1 = CH_3 \\
\textbf{3.25} \, R = H; R^1 = CH_3 \\
\textbf{3.26} \, R = Ac; R^1 = CH_3 \\
\textbf{3.29} \, R = MOM; R^1 = CH_3 \\
\textbf{3.31} \, R = R^1 = MOM \\
\end{tabular}
\end{center}

\textbf{Figure 4.1} List of New Arylethyynes Synthesized.
Arylethyne 3.29 has been synthesized by a palladium-mediated coupling of aryl iodide 3.13 with trimethyl[(trimethylsilyl)ethynyl]stannane, followed by cleaving the silyl group with potassium fluoride. Arylethyne 3.31 is presumably formed using the same conditions, but was destroyed during bulb-to-bulb distillation. The precursor, trimethylsilyl arylethylene 3.30 has been formed and identified. The work-up and purification of the arylethylenes synthesized by the palladium-mediated coupling reactions are more difficult, however, methyl and MOM ethers and the acetate ester are stable phenolic protecting groups under the reaction conditions. Benzyl and MEM ethers should also survive the conditions.

The synthesis of unsymmetrical 2,2',6,6'-tetrasubstituted diarylethylenes has also been accomplished. (Figure 4.2) Diarylethylenes 3.32 and 3.33 were synthesized by palladium-mediated coupling of aryl triflate 3.12 with arylethylenes 3.21 and 3.29, respectively. Aqueous base hydrolyzes the methyl ester of diarylethylene 3.32 to yield diarylethylene 3.40. Diarylethylene 3.33 is a very close precursor to the untethered diarylethylene model, 1.12u. Saponification of the methyl ester, cleavage of the MOM protecting group, and transformation of the resulting phenol into the dichloroacetate ester yields the untethered diarylethylene 1.12u. Huang85 has synthesized a 2,2',6'-trisubstituted diarylethylene 3.37 by the palladium-mediated coupling reaction of aryl iodide 3.36 with arylethylene 3.21.

Two arylnaphthylethylenes have also been synthesized. (Figure 4.2) Palladium-mediated coupling of aryl triflate 3.12 with naphthylethylene 3.22 yields the phenyl-naphthylethylene 3.34. Prince86 has shown that the opposite coupling reaction also works.
Figure 4.2 List of Diarylethynes Synthesized.

Arylethyne 3.21 couples with naphthyl iodide 3.38 to form phenylnaphthylethyne 3.39. These mixed systems are precursors to another series of diarylethylene models, which have different distances and orientations between the reacting groups, to test proximity and position on catalysis. (Figure 4.3)

Figure 4.3 Series of Arylnaphthylethyynes to Study Proximity and Position in Catalysis.

The ortho-substituted functional groups of 2,2',6,6'-tetrasubstituted diarylethynes 3.32 and 3.40 react with the ethyne to form three heterocycles. (Scheme 4.8) This strategy provides a robust synthesis of three highly functionalized heterocycles.
Scheme 4.8 Synthesis of Benzofurans, Benzopyranones, and Isobenzofuranones.

In diarylethynes 3.32 and 3.40, demethylation of the methoxy on the aryl ring that bears the carboxyl or methoxycarbonyl substituent yields 2-arylbenzofurans. Boron trichloride mono-demethylates 3.32, which cyclizes to benzofuran 3.43. Complete demethylation of 3.32 is accomplished using an excess of trimethylsilyl iodide yielding benzofuran 3.46. Stirring 3.32 or 3.40 in acetic acid/sulfuric acid promotes mono-demethylation of the diarylethynes, which subsequently cyclize to yield benzofurans 3.43 and 3.48, respectively.
Bromobenzopyranones are synthesized by bromolactonization of alkyl 2-(arylethynyl)benzoates\textsuperscript{100,101} or 2-(arylethynyl)benzoic acids.\textsuperscript{102} Bromolactonization of 3.32 yields bromobenzopyranone 3.51. Palladium-mediated lactonization of 2-(arylethynyl)-benzoic acids yield benzopyranones; the uncatalyzed lactonization yield benzopyranones or isobenzofuranones or mixtures depending on the substituents on the aromatic rings.\textsuperscript{30,98} Palladium-mediated lactonization of 3.40 yields primarily benzopyranone, 3.52. Uncatalyzed lactonization 3.40 yields primarily isobenzofuranone 3.53.

In summary, the synthesis of the tethered, 1.12t, and the untethered, 1.12u, diarylethynes has been initiated. Two retrosynthetic pathways were originally developed for the synthesis of the target molecules. Retrosynthetic pathway 1 (Chapter 3, Section 2.1.1) appears promising for the synthesis of the untethered diarylethyne; a close precursor was synthesized. However, this method is eliminated as a possible route for the synthesis of the tethered diarylethynes. All attempts to demethylate diarylethyne 3.32 yielded 2-arylbenzofurans. (Chapter 3, Section 3.7)

By protecting the carboxyl against nucleophilic attack, retrosynthetic pathway 2, (Chapter 3, Section 2.1.2), remains a plausible route for the synthesis of the tethered molecules. A synthesis of an aryl iodide synthon, in which the carboxyl is protect as the oxazoline, is proposed in section 4.1.2. If the carboxyl is not protected against nucleophilic attack, a search for a non-nucleophilic base which will open the benzofuran ether ring is required. Protecting the carboxyl against nucleophilic attack is the easier route.
Two additional retrosynthetic pathways have been developed. Retrosynthetic Pathway 3 forms the tethered diarylethynes by opening tethered lactones. The lactones serve as a protecting group for both the carboxyl and ethyne. Pathway 4 connects an aryl halide and an arylethyne to a tether prior to the palladium-mediated coupling. The pros and cons of these pathways have been discussed in section 4.2.1 and 4.2.2, respectively.

In summary, five new arylethynes have been synthesized and characterized. Three unsymmetrical 2,2',6,6'-tetrasubstituted diarylethynes were synthesized and fully characterized. We have reported the synthesis of the first unsymmetrical tetrasubstituted diarylethyne. Prince and I have synthesized two new 2,2',6,7'-tetrasubstituted arylnaphthylethynes, which serve as a basis for a new series of models to test proximity and position in catalysis. The robust chemistry of the demethylation and lactonization of diarylethynes 3.32 and 3.40 yielded three benzofurans, two benzofuranones and one isobenzofuranone. All of the heterocycles are new compounds and have been fully characterized.
BIBLIOGRAPHY


100


28. Mr. Joey W. Storer, UCLA, unpublished results.

29. PCMODEL 3.2; Serena Software, Bloomington, IN; Gajewski, J. J.; Gilbert, K. E., Indiana University


65. The synthesis of 2'-acetoxy-6'-methoxyacetophenone has been reported twice: (a) Adam, W.; Hadjiarapoglou, L.; Mosandl, T; Saha-Moller, C. R.; Wild, D. "Chemical Model Studies on the Mutagenesis of Benzofuran Dioxetanes in the Ames Test: Evidence for the Benzofuran Epoxide as Ultimate Mutagen." *J. Am. Chem. Soc.* 1991, 113, 8005-8011. (b) Naik, R. M.; Thakor, V. M. "Chromones. III. Kostanecki-Robinson Acylation of some o-Hydroxyacetophenones." *Proc. Indian Acad. Sci.* 1953, 37A, 774-783 (CA 48:10019h). The data obtained by these authors are not the same. The characterization reported by Adam et al. is not correct. The ¹H NMR, IR, and melting point that I recorded do not agree with the values reported by Adam et al. The structure of my product was confirmed by single crystal X-ray analysis (see Appendix A). My melting point does agree with value listed by Naik and Thakor.

66. The synthesis of 2'-benzyloxy-6'-methoxyacetophenone has been reported twice: (a) Kametani, T.; Kano, S. "Syntheses of Heterocyclic Compounds. LXXX. Synthesis of Papaverine Derivatives. 10. Synthesis of 1-(2,3-Dihydroxyphenyl)- and 1-(2,6-Dihydroxyphenyl)-3-methyl-6,7-methylenedioxyisoquinoline and its related compounds." *Yakugaku Zasshi* 1963, 83, 356-360 (CA 59:7573c). (b) Baker, W.; Simmonds, W. H. C. "Derivatives of 5:6:4' and 5:8:4'-Trihydroxyflavones, and a Note on the Structure of Ginkgetin." *J. Chem. Soc.* 1940, 1370-1374. The data obtained by these authors are not the same. Kametani and Kano report obtaining an oil, bp 150-152°C, 0.05 mm. Bakers and Simmonds report obtaining a solid, mp 74°C. I collected a colorless oil, bp 140-150°C 0.05 mm, in a bulb-to-bulb distillation in a Kugelrohr apparatus.


71. These reaction were run by Joe Guitreau, an undergraduate student who worked in these laboratories.

72. 2-Iodo-1,3-bis(methoxymethoxy)benzene has been previously synthesized, but was immediately transformed into 2-iodo-1-hydroxy-3-(methoxymethoxy)benzene: Sloan, C. P.; Cuevas, J. C.; Quesnelle, C.; Snieckus, V. "Aryl Radical-Induced Cyclization Routes to Furo[2,3-b]benzofuran. Abbreviated Formal Syntheses of Aflatoxins B₁ and B₂." *Tetrahedron Lett.* 1988, 29, 4685-4686. No procedure, spectral data, or yield are reported.


75. Keisha R. Boss, a Project SEED participant for summer 1989, first performed this reaction. Philippe Prince, a graduate student in these laboratories, later optimized the conditions.

76. ORTEP drawing and crystallographic coordinates are reported in Appendix B.


79. The synthesis of 4-methoxy-3-methyl-2-phenylbenzofuran has been reported: Banerji, A.; Nayak, S. K. "Synthesis of O-Heterocycles via Intramolecular Reductive Deoxygenation of o-Aroyloxyacetophenones: One-step Synthesis of Benzofurans." *J. Chem. Soc., Chem. Commun.* 1990, 150-151. The $^1$H NMR and IR spectra I obtained are in general agreement with the values reported. However, Banerji and Nayak obtained a white solid, mp 50-51°C, whereas, I isolated a greenish oil. Clearly, my product was not pure. I also cannot state absolutely that I obtained the 4-methoxy-3-methyl-2-phenylbenzofuran due to the discrepancy of physical property and the poor resolution of both my $^1$H NMR spectrum and the reported $^1$H NMR spectrum.


81. Dr. On-tai Lueng was a postdoctoral fellow in these laboratories.

82. $^1$H NMR (400 MHz): $\delta$ 7.18 (dd, 2H, $J = 8.39$ and 8.37, C4), 6.75 (d, 2H, $J = 8.37$, C5), 6.59 (d, 2H, $J = 8.39$, C3), 5.31 (s, 4H, -OCH$_2$Q-), 3.91 (s, 6H, Ar-OCH$_3$), 3.54 (s, 6H, -OCH$_3$). Mass spec., m/e (relative intensity): 359 (M$^+$+1, 4.4), 358 (M$^+$, 20.3), 313 (10.6), 283 (7.1), 282 (40.0), 281 (100), 267 (18.0), 266 (9.1), 252 (7.7), 45 (53.1).


85. Enoch T. Huang was a Princeton undergraduate student who worked in these laboratories during the summer of 1990 and 1992.

86. Philippe Prince is a graduate student in these laboratories.


92. ORTEP drawing and crystallographic coordinates are reported in Appendix C.


97. ORTEP Drawing and crystallographic coordinates are reported in Appendix D.


99. ORTEP drawing and crystallographic coordinates are reported in Appendix E.


103. ORTEP drawing and crystallographic coordinates are reported in Appendix F.

104. ORTEP drawing and crystallographic coordinates are reported in Appendix G.


112. The coupling between H3 and H7 in benzofurans have been previously observed: Elvidge, J. A.; Foster, R. G. "The Long-Range Proton-Proton Couplings in Indene and Benzofuran." *J. Chem. Soc.* **1963**, *590-592.

113. C3, which is bonded to boron, does not show up because of quadrupolar relaxation.


APPENDIX A: CRYSTALLOGRAPHIC DATA FOR
2'-ACETOXY-6'-METHOXYACETOPHENONE

2'-Acetoxy-6'-methoxyacetophenone, 3.2: C_{11}H_{12}O_{4}, M_r = 208.2, monoclinic, P2_1/n,
a = 12.5221(6), b = 7.2458(4), \( c = 12.8955(7) \text{ Å} \), \( \beta = 114.456(4) ^\circ \), \( V = 1065.1(2) \text{ Å}^3 \),
\( Z = 4, D_x = 1.299 \text{ g cm}^{-3} \) at 296 K, \( \lambda(\text{Cu K}\alpha) = 1.54184 \text{ Å} \), \( \mu = 0.79 \text{ mm}^{-1} \), \( F(000) = 440 \), 2191 unique data measured, final \( R = 0.040 \) for 1972 reflections with \( I > 3.0\sigma(I) \).

Figure A.1 ORTEP drawing of 2'-Acetoxy-6'-methoxyacetophenone.
Table A.1 Coordinates and Isotropic Thermal Parameters.

\[ B_{eq} = \frac{8\pi^2}{3} \sum \sum U_{ij} \hat{a}_i \cdot \hat{a}_j \cdot a_j \]

<table>
<thead>
<tr>
<th></th>
<th>(x)</th>
<th>(y)</th>
<th>(z)</th>
<th>(B_{eq}) ((\text{Å}^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>O1</td>
<td>0.59514(6)</td>
<td>0.2682(1)</td>
<td>0.25805(6)</td>
<td>3.91(2)</td>
</tr>
<tr>
<td>O2</td>
<td>0.57962(7)</td>
<td>0.7604(1)</td>
<td>0.49597(6)</td>
<td>4.37(2)</td>
</tr>
<tr>
<td>O3</td>
<td>0.41622(7)</td>
<td>0.5482(2)</td>
<td>0.21017(8)</td>
<td>5.10(2)</td>
</tr>
<tr>
<td>O4</td>
<td>0.68463(8)</td>
<td>0.4807(2)</td>
<td>0.19715(7)</td>
<td>6.25(2)</td>
</tr>
<tr>
<td>C1</td>
<td>0.63419(9)</td>
<td>0.3534(2)</td>
<td>0.36530(8)</td>
<td>3.38(2)</td>
</tr>
<tr>
<td>C2</td>
<td>0.58980(7)</td>
<td>0.5236(2)</td>
<td>0.37736(7)</td>
<td>3.06(2)</td>
</tr>
<tr>
<td>C3</td>
<td>0.62114(8)</td>
<td>0.5959(2)</td>
<td>0.48822(8)</td>
<td>3.35(2)</td>
</tr>
<tr>
<td>C4</td>
<td>0.7077(1)</td>
<td>0.4993(2)</td>
<td>0.58074(9)</td>
<td>4.22(3)</td>
</tr>
<tr>
<td>C5</td>
<td>0.7503(1)</td>
<td>0.3311(2)</td>
<td>0.5637(1)</td>
<td>4.88(3)</td>
</tr>
<tr>
<td>C6</td>
<td>0.7144(1)</td>
<td>0.2560(2)</td>
<td>0.4558(1)</td>
<td>4.40(3)</td>
</tr>
<tr>
<td>C7</td>
<td>0.50400(8)</td>
<td>0.6254(2)</td>
<td>0.27539(8)</td>
<td>3.46(2)</td>
</tr>
<tr>
<td>C8</td>
<td>0.5326(1)</td>
<td>0.8175(2)</td>
<td>0.2543(1)</td>
<td>4.79(3)</td>
</tr>
<tr>
<td>C9</td>
<td>0.6283(1)</td>
<td>0.3430(2)</td>
<td>0.17989(9)</td>
<td>4.09(2)</td>
</tr>
<tr>
<td>C10</td>
<td>0.5859(1)</td>
<td>0.2300(3)</td>
<td>0.0744(1)</td>
<td>6.08(4)</td>
</tr>
<tr>
<td>C11</td>
<td>0.6202(1)</td>
<td>0.8467(2)</td>
<td>0.60482(9)</td>
<td>4.68(3)</td>
</tr>
</tbody>
</table>

Table A.2 Coordinates and Isotropic Thermal Parameters for Hydrogen Atoms.

<table>
<thead>
<tr>
<th></th>
<th>(x)</th>
<th>(y)</th>
<th>(z)</th>
<th>(B_{iso}) ((\text{Å}^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>H4</td>
<td>0.727(1)</td>
<td>0.548(2)</td>
<td>0.655(1)</td>
<td>5.4(3)</td>
</tr>
<tr>
<td>H5</td>
<td>0.813(1)</td>
<td>0.256(3)</td>
<td>0.631(1)</td>
<td>8.1(5)</td>
</tr>
<tr>
<td>H6</td>
<td>0.748(1)</td>
<td>0.150(2)</td>
<td>0.445(1)</td>
<td>6.6(4)</td>
</tr>
<tr>
<td>H8a</td>
<td>0.466(1)</td>
<td>0.860(3)</td>
<td>0.189(2)</td>
<td>10.5(6)</td>
</tr>
<tr>
<td>H8b</td>
<td>0.595(1)</td>
<td>0.809(3)</td>
<td>0.228(1)</td>
<td>8.5(5)</td>
</tr>
<tr>
<td>H8c</td>
<td>0.584(2)</td>
<td>0.892(3)</td>
<td>0.328(2)</td>
<td>10.3(6)</td>
</tr>
<tr>
<td>H10a</td>
<td>0.511(2)</td>
<td>0.192(3)</td>
<td>0.053(1)</td>
<td>9.3(5)</td>
</tr>
<tr>
<td>H10b</td>
<td>0.629(2)</td>
<td>0.127(4)</td>
<td>0.080(2)</td>
<td>15.6(8)</td>
</tr>
<tr>
<td>H10c</td>
<td>0.593(2)</td>
<td>0.294(3)</td>
<td>0.019(1)</td>
<td>8.7(5)</td>
</tr>
<tr>
<td>H11a</td>
<td>0.705(1)</td>
<td>0.867(2)</td>
<td>0.637(1)</td>
<td>5.3(3)</td>
</tr>
<tr>
<td>H11b</td>
<td>0.604(1)</td>
<td>0.763(2)</td>
<td>0.661(1)</td>
<td>6.4(4)</td>
</tr>
<tr>
<td>H11c</td>
<td>0.581(1)</td>
<td>0.971(3)</td>
<td>0.588(1)</td>
<td>7.5(4)</td>
</tr>
</tbody>
</table>
APPENDIX B: CRYSTALLOGRAPHIC DATA FOR 2-(1-CHLOROVINYL)-1,3-DIMETHOXYBENZENE

2-(1-Chlorovinyl)-1,3-dimethoxybenzene, 3.18: $C_{10}H_{11}ClO_2$, $M_r = 198.7$, monoclinic, $P2_1/c$, $a = 11.2844(7)$, $b = 7.0024(13)$, $c = 13.0774(9)$ Å, $\beta = 93.713(6)^\circ$, $V = 1031.2(3)$ Å³, $Z = 4$, $D_x = 1.279$ g cm⁻³ at 295 K, $\lambda$(Cu $K\alpha$) = 1.54184 Å, $\mu = 30.50$ cm⁻¹, $F(000) = 416$, 2124 unique data measured, final $R = 0.084$ for 1437 reflections with $I > 3.0\sigma(I)$.

Figure B.1 ORTEP drawing of 2-(1-chlorovinyl)-1,3-dimethoxybenzene.
Table B.1  Coordinates and Isotropic Thermal Parameters.

\[ B_{eq} = \frac{8\pi^2}{3} \sum \sum U_{ij} a_i^* a_j a_i a_j \]

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>x</td>
<td>y</td>
<td>z</td>
<td>(B_{eq}) (Å²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cl1</td>
<td>0.7800(2)</td>
<td>0.1438(3)</td>
<td>0.6146(2)</td>
<td>8.45(5)</td>
<td></td>
</tr>
<tr>
<td>O1</td>
<td>0.5880(3)</td>
<td>0.3925(5)</td>
<td>0.7674(2)</td>
<td>7.94(8)</td>
<td></td>
</tr>
<tr>
<td>O2</td>
<td>0.9265(2)</td>
<td>0.5915(4)</td>
<td>0.6103(2)</td>
<td>5.57(6)</td>
<td></td>
</tr>
<tr>
<td>C1</td>
<td>0.6860(4)</td>
<td>0.5061(7)</td>
<td>0.7754(3)</td>
<td>5.35(9)</td>
<td></td>
</tr>
<tr>
<td>C2</td>
<td>0.7599(3)</td>
<td>0.4948(6)</td>
<td>0.6930(3)</td>
<td>4.83(9)</td>
<td></td>
</tr>
<tr>
<td>C3</td>
<td>0.8599(3)</td>
<td>0.6093(6)</td>
<td>0.6937(3)</td>
<td>4.68(9)</td>
<td></td>
</tr>
<tr>
<td>C4</td>
<td>0.8908(4)</td>
<td>0.7308(7)</td>
<td>0.7751(3)</td>
<td>5.6(1)</td>
<td></td>
</tr>
<tr>
<td>C5</td>
<td>0.8153(5)</td>
<td>0.7347(8)</td>
<td>0.8560(4)</td>
<td>6.8(1)</td>
<td></td>
</tr>
<tr>
<td>C6</td>
<td>0.7136(4)</td>
<td>0.6256(8)</td>
<td>0.8549(3)</td>
<td>6.4(1)</td>
<td></td>
</tr>
<tr>
<td>C7</td>
<td>0.7286(3)</td>
<td>0.3673(7)</td>
<td>0.6060(3)</td>
<td>5.8(1)</td>
<td></td>
</tr>
<tr>
<td>C8</td>
<td>0.6694(5)</td>
<td>0.4138(9)</td>
<td>0.5057(4)</td>
<td>4.6(1)*</td>
<td></td>
</tr>
<tr>
<td>C9</td>
<td>0.4936(4)</td>
<td>0.4326(9)</td>
<td>0.8313(4)</td>
<td>7.8(1)</td>
<td></td>
</tr>
<tr>
<td>C10</td>
<td>1.0241(4)</td>
<td>0.7162(8)</td>
<td>0.6015(4)</td>
<td>6.6(1)</td>
<td></td>
</tr>
<tr>
<td>Cl1'</td>
<td>0.6374(4)</td>
<td>0.4491(7)</td>
<td>0.5200(3)</td>
<td>6.98(9)*</td>
<td></td>
</tr>
<tr>
<td>C8'</td>
<td>0.7671</td>
<td>0.1937</td>
<td>0.6011</td>
<td>6.*</td>
<td></td>
</tr>
</tbody>
</table>

Table B.2  Coordinates and Isotropic Thermal Parameters for Hydrogen Atoms.

|    |    |    |    |    |
|----|----|----|----|
| x  | y  | z  | \(B_{iso}\) (Å²) |
| H4 | 0.9601 | 0.8079 | 0.7759 | 7 |
| H5 | 0.8347 | 0.8149 | 0.9131 | 8 |
| H6 | 0.6629 | 0.6341 | 0.9099 | 8 |
| H91 | 0.5125 | 0.3913 | 0.8993 | 10 |
| H92 | 0.4240 | 0.3682 | 0.8050 | 10 |
| H93 | 0.4795 | 0.5663 | 0.8314 | 10 |
| H101 | 0.9972 | 0.8481 | 0.5936 | 8 |
| H102 | 1.0653 | 0.6807 | 0.5433 | 8 |
| H103 | 1.0759 | 0.7061 | 0.6614 | 8 |
APPENDIX C: CRYSTALLOGRAPHIC DATA FOR 
2-[2,6-DIMETHOXYPHENYL)ETHYNYL]-3-METHOXYBENZOIC ACID

2-[2,6-Dimethoxyphenyl)ethynyl]-3-methoxybenzoic acid, 3.40: C_{18}H_{16}O_{5}, M_r = 312.3, 
monoclinic, P2_1/c, a = 7.9263(7), b = 8.0539(9), c = 24.315(2) Å, β = 97.859(7)°, V = 
1537.6(5) Å³, Z = 4, D_x = 1.349 g cm⁻³ at 298 K, λ(Mo Kα) = 0.71073 Å, μ = 0.92 
cm⁻¹, F(000) = 656, 4455 unique data measured, final R = 0.043 for 3095 reflections 
with I > 3.0σ(I).

Figure C.1 ORTEP drawing of 2-[(2,6-dimethoxyphenyl)ethynyl]-
3-methoxy-benzoic acid.
Table C.1 Coordinates and Isotropic Thermal Parameters.

\[ B_{eq} = \frac{8\pi^2}{3} \sum \sum U_{ij} \alpha_i^\star \alpha_j^\star \alpha_i \alpha_j \]

<table>
<thead>
<tr>
<th></th>
<th>( x )</th>
<th>( y )</th>
<th>( z )</th>
<th>( B_{eq} ) (Å²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O1</td>
<td>0.4693(1)</td>
<td>0.2656(2)</td>
<td>0.74183(4)</td>
<td>4.44(2)</td>
</tr>
<tr>
<td>O2</td>
<td>-0.0810(1)</td>
<td>0.1414(1)</td>
<td>0.65684(3)</td>
<td>3.65(2)</td>
</tr>
<tr>
<td>O3</td>
<td>0.1339(1)</td>
<td>0.6514(1)</td>
<td>0.60418(4)</td>
<td>4.24(2)</td>
</tr>
<tr>
<td>O4</td>
<td>0.4139(1)</td>
<td>0.1160(2)</td>
<td>0.54671(4)</td>
<td>5.44(3)</td>
</tr>
<tr>
<td>O5</td>
<td>0.4186(2)</td>
<td>0.1644(2)</td>
<td>0.45752(4)</td>
<td>6.23(3)</td>
</tr>
<tr>
<td>C1</td>
<td>0.3189(2)</td>
<td>0.1913(2)</td>
<td>0.74752(5)</td>
<td>3.17(3)</td>
</tr>
<tr>
<td>C2</td>
<td>0.2837(2)</td>
<td>0.1151(2)</td>
<td>0.79601(5)</td>
<td>3.81(3)</td>
</tr>
<tr>
<td>C3</td>
<td>0.1252(2)</td>
<td>0.0479(2)</td>
<td>0.79757(5)</td>
<td>4.07(3)</td>
</tr>
<tr>
<td>C4</td>
<td>-0.0007(2)</td>
<td>0.0537(2)</td>
<td>0.75240(6)</td>
<td>3.76(3)</td>
</tr>
<tr>
<td>C5</td>
<td>0.0342(2)</td>
<td>0.1289(2)</td>
<td>0.70384(5)</td>
<td>2.94(3)</td>
</tr>
<tr>
<td>C6</td>
<td>0.1947(2)</td>
<td>0.1978(2)</td>
<td>0.70038(4)</td>
<td>2.71(2)</td>
</tr>
<tr>
<td>C7</td>
<td>0.2279(2)</td>
<td>0.2778(2)</td>
<td>0.65010(4)</td>
<td>2.85(2)</td>
</tr>
<tr>
<td>C8</td>
<td>0.2468(2)</td>
<td>0.3417(2)</td>
<td>0.60721(4)</td>
<td>2.88(2)</td>
</tr>
<tr>
<td>C9</td>
<td>0.2471(1)</td>
<td>0.4351(2)</td>
<td>0.55676(4)</td>
<td>2.81(2)</td>
</tr>
<tr>
<td>C10</td>
<td>0.1800(2)</td>
<td>0.5962(2)</td>
<td>0.55539(5)</td>
<td>3.32(3)</td>
</tr>
<tr>
<td>C11</td>
<td>0.1599(2)</td>
<td>0.6883(2)</td>
<td>0.50673(6)</td>
<td>4.24(3)</td>
</tr>
<tr>
<td>C12</td>
<td>0.2087(2)</td>
<td>0.6225(2)</td>
<td>0.45924(5)</td>
<td>4.71(4)</td>
</tr>
<tr>
<td>C13</td>
<td>0.2808(2)</td>
<td>0.4684(2)</td>
<td>0.45978(5)</td>
<td>4.21(3)</td>
</tr>
<tr>
<td>C14</td>
<td>0.3011(2)</td>
<td>0.3721(2)</td>
<td>0.50786(5)</td>
<td>3.19(3)</td>
</tr>
<tr>
<td>C15</td>
<td>0.3809(2)</td>
<td>0.2070(2)</td>
<td>0.50573(5)</td>
<td>3.67(3)</td>
</tr>
<tr>
<td>C16</td>
<td>0.5988(2)</td>
<td>0.2649(3)</td>
<td>0.78918(6)</td>
<td>5.09(4)</td>
</tr>
<tr>
<td>C17</td>
<td>-0.2504(2)</td>
<td>0.0829(3)</td>
<td>0.65945(6)</td>
<td>5.28(4)</td>
</tr>
<tr>
<td>C18</td>
<td>0.0673(2)</td>
<td>0.8155(3)</td>
<td>0.60619(7)</td>
<td>5.25(4)</td>
</tr>
</tbody>
</table>
Table C.2 Coordinates and Isotropic Thermal Parameters for Hydrogen Atoms.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Biso (Å²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H5O</td>
<td>0.487(3)</td>
<td>0.055(3)</td>
<td>0.4603(9)</td>
<td>12.1(7)</td>
</tr>
<tr>
<td>H2</td>
<td>0.369(2)</td>
<td>0.112(2)</td>
<td>0.8275(5)</td>
<td>4.1(3)</td>
</tr>
<tr>
<td>H3</td>
<td>0.103(2)</td>
<td>-0.005(2)</td>
<td>0.8317(5)</td>
<td>5.0(3)</td>
</tr>
<tr>
<td>H4</td>
<td>-0.111(2)</td>
<td>0.009(2)</td>
<td>0.7546(5)</td>
<td>4.1(3)</td>
</tr>
<tr>
<td>H11</td>
<td>0.111(2)</td>
<td>0.797(2)</td>
<td>0.5062(6)</td>
<td>5.3(4)</td>
</tr>
<tr>
<td>H12</td>
<td>0.189(2)</td>
<td>0.684(2)</td>
<td>0.4249(7)</td>
<td>7.3(5)</td>
</tr>
<tr>
<td>H13</td>
<td>0.320(2)</td>
<td>0.422(2)</td>
<td>0.4265(6)</td>
<td>5.3(4)</td>
</tr>
<tr>
<td>H16b</td>
<td>0.696(2)</td>
<td>0.322(2)</td>
<td>0.7772(6)</td>
<td>6.3(4)</td>
</tr>
<tr>
<td>H16c</td>
<td>0.623(2)</td>
<td>0.149(2)</td>
<td>0.7999(6)</td>
<td>5.7(4)</td>
</tr>
<tr>
<td>H16a</td>
<td>0.557(2)</td>
<td>0.325(2)</td>
<td>0.8204(7)</td>
<td>6.9(4)</td>
</tr>
<tr>
<td>H17b</td>
<td>-0.304(2)</td>
<td>0.144(3)</td>
<td>0.6880(8)</td>
<td>8.9(5)</td>
</tr>
<tr>
<td>H17c</td>
<td>-0.246(2)</td>
<td>-0.042(3)</td>
<td>0.6665(7)</td>
<td>8.3(5)</td>
</tr>
<tr>
<td>H17a</td>
<td>-0.309(2)</td>
<td>0.103(2)</td>
<td>0.6235(7)</td>
<td>6.6(4)</td>
</tr>
<tr>
<td>H18b</td>
<td>0.041(2)</td>
<td>0.829(2)</td>
<td>0.6441(6)</td>
<td>6.5(4)</td>
</tr>
<tr>
<td>H18c</td>
<td>-0.028(2)</td>
<td>0.828(2)</td>
<td>0.5780(6)</td>
<td>6.4(4)</td>
</tr>
<tr>
<td>H18a</td>
<td>0.156(2)</td>
<td>0.901(2)</td>
<td>0.5964(6)</td>
<td>7.3(5)</td>
</tr>
</tbody>
</table>
APPENDIX D: CRYSTALLOGRAPHIC DATA FOR BORACYCLE

Boracycle, 3.44: \( \text{C}_{17}\text{H}_{13}\text{BO}_6 \), \( M_r = 324.1 \), orthorhombic, \( P2_12_12_1 \), \( a = 5.0855(2) \), \( b = 16.9133(11) \), \( c = 17.1693 \) Å, \( V = 1476.8(3) \) Å\(^3\), \( Z = 4 \), \( D_x = 1.458 \text{ g cm}^{-3} \) at 296 K, \( \lambda(\text{Mo K}\alpha) = 0.71073 \) Å, \( \mu = 1.03 \text{ cm}^{-1} \), \( F(000) = 672 \), 1537 unique data measured, final \( R = 0.043 \) for 1136 reflections with \( I > 3.0\sigma(I) \).

Figure D.1 ORTEP drawing of the boracycle 3.44.
Table D.1 Coordinates and Isotropic Thermal Parameters.

\[ B_{eq} = \left( \frac{8\pi^2}{3} \right) \sum_i \sum_j U_{ij} A_i A_j \]

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>( B_{eq} ) (\text{Å}^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O1</td>
<td>0.6997(5)</td>
<td>0.5649(1)</td>
<td>0.5178(1)</td>
<td>5.17(6)</td>
</tr>
<tr>
<td>O2</td>
<td>0.4733(5)</td>
<td>0.4798(1)</td>
<td>0.7731(1)</td>
<td>4.96(6)</td>
</tr>
<tr>
<td>O3</td>
<td>0.3370(5)</td>
<td>0.6388(1)</td>
<td>0.5970(1)</td>
<td>3.91(5)</td>
</tr>
<tr>
<td>O4</td>
<td>-0.1807(7)</td>
<td>0.6424(2)</td>
<td>0.8564(2)</td>
<td>9.33(8)</td>
</tr>
<tr>
<td>O5</td>
<td>-0.4280(6)</td>
<td>0.7447(1)</td>
<td>0.8348(1)</td>
<td>6.15(6)</td>
</tr>
<tr>
<td>O6</td>
<td>0.1660(6)</td>
<td>0.5302(2)</td>
<td>0.8557(1)</td>
<td>6.38(7)</td>
</tr>
<tr>
<td>C1</td>
<td>0.7444(8)</td>
<td>0.5139(2)</td>
<td>0.5780(2)</td>
<td>4.13(8)</td>
</tr>
<tr>
<td>C2</td>
<td>0.9346(8)</td>
<td>0.4557(2)</td>
<td>0.5772(2)</td>
<td>4.89(9)</td>
</tr>
<tr>
<td>C3</td>
<td>0.9647(8)</td>
<td>0.4079(2)</td>
<td>0.6417(2)</td>
<td>5.42(9)</td>
</tr>
<tr>
<td>C4</td>
<td>0.8127(8)</td>
<td>0.4160(2)</td>
<td>0.7064(2)</td>
<td>5.06(9)</td>
</tr>
<tr>
<td>C5</td>
<td>0.6219(8)</td>
<td>0.4739(2)</td>
<td>0.7073(2)</td>
<td>4.26(8)</td>
</tr>
<tr>
<td>C6</td>
<td>0.5842(7)</td>
<td>0.5253(2)</td>
<td>0.6445(2)</td>
<td>3.61(7)</td>
</tr>
<tr>
<td>C7</td>
<td>0.3842(7)</td>
<td>0.5848(2)</td>
<td>0.6549(2)</td>
<td>3.61(7)</td>
</tr>
<tr>
<td>C8</td>
<td>0.2302(7)</td>
<td>0.5960(2)</td>
<td>0.7193(2)</td>
<td>3.46(7)</td>
</tr>
<tr>
<td>C9</td>
<td>0.0687(7)</td>
<td>0.6639(2)</td>
<td>0.7003(2)</td>
<td>3.54(7)</td>
</tr>
<tr>
<td>C10</td>
<td>0.1413(7)</td>
<td>0.6879(2)</td>
<td>0.6258(2)</td>
<td>3.65(7)</td>
</tr>
<tr>
<td>C11</td>
<td>0.0470(8)</td>
<td>0.7504(2)</td>
<td>0.5844(2)</td>
<td>4.85(8)</td>
</tr>
<tr>
<td>C12</td>
<td>-0.1463(9)</td>
<td>0.7941(2)</td>
<td>0.6204(2)</td>
<td>5.35(9)</td>
</tr>
<tr>
<td>C13</td>
<td>-0.2360(8)</td>
<td>0.7744(2)</td>
<td>0.6937(2)</td>
<td>4.92(9)</td>
</tr>
<tr>
<td>C14</td>
<td>-0.1359(7)</td>
<td>0.7095(2)</td>
<td>0.7349(2)</td>
<td>3.87(8)</td>
</tr>
<tr>
<td>C15</td>
<td>-0.2427(8)</td>
<td>0.6949(2)</td>
<td>0.8132(2)</td>
<td>4.81(9)</td>
</tr>
<tr>
<td>C16</td>
<td>0.857(1)</td>
<td>0.5537(2)</td>
<td>0.4493(2)</td>
<td>5.9(1)</td>
</tr>
<tr>
<td>C17</td>
<td>-0.542(1)</td>
<td>0.7344(3)</td>
<td>0.9102(2)</td>
<td>7.6(1)</td>
</tr>
<tr>
<td>B</td>
<td>0.278(1)</td>
<td>0.5363(2)</td>
<td>0.7853(2)</td>
<td>4.4(1)</td>
</tr>
</tbody>
</table>
Table D.2  Coordinates and Isotropic Thermal Parameters for Hydrogen Atoms.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>$B_{iso}$ (Å$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H06</td>
<td>0.0074</td>
<td>0.5706</td>
<td>0.8615</td>
<td>10</td>
</tr>
<tr>
<td>H2</td>
<td>1.0434</td>
<td>0.4486</td>
<td>0.5327</td>
<td>6</td>
</tr>
<tr>
<td>H3</td>
<td>1.0960</td>
<td>0.3679</td>
<td>0.6408</td>
<td>7</td>
</tr>
<tr>
<td>H4</td>
<td>0.8375</td>
<td>0.3823</td>
<td>0.7501</td>
<td>6</td>
</tr>
<tr>
<td>H11</td>
<td>0.1104</td>
<td>0.7630</td>
<td>0.5338</td>
<td>6</td>
</tr>
<tr>
<td>H12</td>
<td>-0.2191</td>
<td>0.8385</td>
<td>0.5943</td>
<td>6</td>
</tr>
<tr>
<td>H13</td>
<td>-0.3695</td>
<td>0.8057</td>
<td>0.7169</td>
<td>6</td>
</tr>
<tr>
<td>H16a</td>
<td>1.0324</td>
<td>0.5422</td>
<td>0.4640</td>
<td>7</td>
</tr>
<tr>
<td>H16b</td>
<td>0.8538</td>
<td>0.6005</td>
<td>0.4188</td>
<td>7</td>
</tr>
<tr>
<td>H16c</td>
<td>0.7882</td>
<td>0.5110</td>
<td>0.4197</td>
<td>7</td>
</tr>
<tr>
<td>H17a</td>
<td>-0.4061</td>
<td>0.7320</td>
<td>0.9481</td>
<td>9</td>
</tr>
<tr>
<td>H17b</td>
<td>-0.6404</td>
<td>0.6866</td>
<td>0.9111</td>
<td>9</td>
</tr>
<tr>
<td>H17c</td>
<td>-0.6549</td>
<td>0.7776</td>
<td>0.9213</td>
<td>9</td>
</tr>
</tbody>
</table>
APPENDIX E: CRYSTALLOGRAPHIC DATA FOR 2-(2,6-DIMETHOXYPHENYL)BENZOFURAN-4-CARBOXYLIC ACID

2-(2,6-Dimethoxyphenyl)benzofuran-4-carboxylic acid, 3.48: C$_{17}$H$_{14}$O$_{5}$, $M_r$ = 298.3, monoclinic, $P2_1/c$, $a = 16.315(2)$, $b = 4.1755(2)$, $c = 22.299(2)$ Å, $\beta = 111.413(8)^\circ$, $V = 1414.2(5)$ Å$^3$, $Z = 4$, $D_x = 1.401$ g cm$^{-3}$ at 298 K, $\lambda$(Cu $K\alpha$) = 1.54184 Å, $\mu = 8.22$ cm$^{-1}$, $F(000) = 624$, 2905 unique data measured, final $R = 0.040$ for 2209 reflections with $I > 2.0\sigma(I)$.

Figure E.1 ORTEP drawing of 2-(2,6-dimethoxyphenyl)benzofuran-4-carboxylic acid.
Table E.1 Coordinates and Isotropic Thermal Parameters.

\[ B_{eq} = (8\pi^2/3)\sum_j U_{ij} \hat{a}_i \cdot \hat{a}_j \cdot \hat{a}_j \]

<table>
<thead>
<tr>
<th></th>
<th>( x )</th>
<th>( y )</th>
<th>( z )</th>
<th>( B_{eq} ) (\text{Å}^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O1</td>
<td>0.89179(6)</td>
<td>0.5242(4)</td>
<td>0.69087(5)</td>
<td>4.70(3)</td>
</tr>
<tr>
<td>O2</td>
<td>0.58941(7)</td>
<td>0.6904(3)</td>
<td>0.64130(6)</td>
<td>5.05(3)</td>
</tr>
<tr>
<td>O3</td>
<td>0.67775(6)</td>
<td>0.2675(3)</td>
<td>0.72565(5)</td>
<td>3.69(2)</td>
</tr>
<tr>
<td>O4</td>
<td>0.91262(8)</td>
<td>0.2596(4)</td>
<td>0.99844(5)</td>
<td>5.65(3)</td>
</tr>
<tr>
<td>O5</td>
<td>0.94310(7)</td>
<td>0.4919(4)</td>
<td>0.91946(5)</td>
<td>4.87(3)</td>
</tr>
<tr>
<td>C1</td>
<td>0.8151(1)</td>
<td>0.6454(5)</td>
<td>0.64851(7)</td>
<td>3.91(4)</td>
</tr>
<tr>
<td>C2</td>
<td>0.8093(1)</td>
<td>0.8000(5)</td>
<td>0.59198(7)</td>
<td>5.03(4)</td>
</tr>
<tr>
<td>C3</td>
<td>0.7292(1)</td>
<td>0.9169(6)</td>
<td>0.55219(8)</td>
<td>5.67(5)</td>
</tr>
<tr>
<td>C4</td>
<td>0.6549(1)</td>
<td>0.8823(5)</td>
<td>0.56637(8)</td>
<td>5.35(5)</td>
</tr>
<tr>
<td>C5</td>
<td>0.6601(1)</td>
<td>0.7279(5)</td>
<td>0.62285(7)</td>
<td>4.13(4)</td>
</tr>
<tr>
<td>C6</td>
<td>0.7405(1)</td>
<td>0.6049(4)</td>
<td>0.66507(6)</td>
<td>3.45(3)</td>
</tr>
<tr>
<td>C7</td>
<td>0.74831(9)</td>
<td>0.4528(4)</td>
<td>0.72601(6)</td>
<td>3.27(3)</td>
</tr>
<tr>
<td>C8</td>
<td>0.81104(9)</td>
<td>0.4641(4)</td>
<td>0.78561(6)</td>
<td>3.32(3)</td>
</tr>
<tr>
<td>C9</td>
<td>0.77988(9)</td>
<td>0.2823(4)</td>
<td>0.82696(6)</td>
<td>3.15(3)</td>
</tr>
<tr>
<td>C10</td>
<td>0.69775(9)</td>
<td>0.1657(4)</td>
<td>0.78771(7)</td>
<td>3.36(3)</td>
</tr>
<tr>
<td>C11</td>
<td>0.6443(1)</td>
<td>-0.0238(5)</td>
<td>0.80845(8)</td>
<td>4.21(4)</td>
</tr>
<tr>
<td>C12</td>
<td>0.6755(1)</td>
<td>-0.0950(5)</td>
<td>0.87352(8)</td>
<td>4.48(4)</td>
</tr>
<tr>
<td>C13</td>
<td>0.7559(1)</td>
<td>0.0165(5)</td>
<td>0.91467(7)</td>
<td>3.96(4)</td>
</tr>
<tr>
<td>C14</td>
<td>0.80970(9)</td>
<td>0.2048(4)</td>
<td>0.89307(6)</td>
<td>3.36(3)</td>
</tr>
<tr>
<td>C15</td>
<td>0.89350(9)</td>
<td>0.3277(5)</td>
<td>0.93866(6)</td>
<td>3.81(4)</td>
</tr>
<tr>
<td>C16</td>
<td>0.9689(1)</td>
<td>0.5456(6)</td>
<td>0.67524(9)</td>
<td>5.95(5)</td>
</tr>
<tr>
<td>C17</td>
<td>0.5125(1)</td>
<td>0.8680(7)</td>
<td>0.6086(1)</td>
<td>7.68(7)</td>
</tr>
</tbody>
</table>
Table E.2 Coordinates and Isotropic Thermal Parameters for Hydrogen Atoms.

<table>
<thead>
<tr>
<th>Atom</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>(B_{iso} (\text{Å}^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>H4O</td>
<td>0.981(2)</td>
<td>0.374(8)</td>
<td>1.033(1)</td>
<td>13.7(9)</td>
</tr>
<tr>
<td>H2</td>
<td>0.860(1)</td>
<td>0.821(5)</td>
<td>0.5824(8)</td>
<td>5.9(5)</td>
</tr>
<tr>
<td>H3</td>
<td>0.726(1)</td>
<td>1.026(5)</td>
<td>0.5142(8)</td>
<td>6.6(5)</td>
</tr>
<tr>
<td>H4</td>
<td>0.597(1)</td>
<td>0.973(5)</td>
<td>0.5396(8)</td>
<td>6.9(5)</td>
</tr>
<tr>
<td>H8</td>
<td>0.8632(9)</td>
<td>0.586(4)</td>
<td>0.7978(6)</td>
<td>4.1(4)</td>
</tr>
<tr>
<td>H11</td>
<td>0.5878(9)</td>
<td>-0.100(4)</td>
<td>0.7777(7)</td>
<td>4.8(4)</td>
</tr>
<tr>
<td>H12</td>
<td>0.641(1)</td>
<td>-0.227(5)</td>
<td>0.8897(7)</td>
<td>6.0(5)</td>
</tr>
<tr>
<td>H13</td>
<td>0.777(1)</td>
<td>-0.041(5)</td>
<td>0.9601(7)</td>
<td>5.2(4)</td>
</tr>
<tr>
<td>H16a</td>
<td>1.020(1)</td>
<td>0.436(6)</td>
<td>0.7129(9)</td>
<td>9.4(6)</td>
</tr>
<tr>
<td>H16b</td>
<td>0.980(1)</td>
<td>0.774(6)</td>
<td>0.6691(9)</td>
<td>8.6(6)</td>
</tr>
<tr>
<td>H16c</td>
<td>0.957(1)</td>
<td>0.434(6)</td>
<td>0.6336(8)</td>
<td>7.6(6)</td>
</tr>
<tr>
<td>H17a</td>
<td>0.524(1)</td>
<td>1.105(6)</td>
<td>0.6048(9)</td>
<td>9.6(7)</td>
</tr>
<tr>
<td>H17b</td>
<td>0.476(1)</td>
<td>0.819(6)</td>
<td>0.631(1)</td>
<td>9.9(7)</td>
</tr>
<tr>
<td>H17c</td>
<td>0.483(1)</td>
<td>0.783(6)</td>
<td>0.565(1)</td>
<td>11.5(8)</td>
</tr>
</tbody>
</table>
APPENDIX F: CRYSTALLOGRAPHIC DATA FOR 5-METHOXY-3-(2,6-DIMETHOXYPHENYL)-1H-BENZO-2-PYRAN-1-ONE

5-Methoxy-3-(2,6-dimethoxyphenyl)-1H-benzo-2-pyran-1-one, 3.52: C_{18}H_{16}O_5, M_r = 312.3, triclinic, \( P\overline{1} \), \( a = 7.7197(6) \) Å, \( b = 9.6126(8) \) Å, \( c = 11.9115(10) \) Å, \( \alpha = 110.548(6)^\circ \), \( \beta = 101.151(7)^\circ \), \( \gamma = 103.454(7)^\circ \), \( V = 767.4(4) \) Å\(^3\), \( Z = 2 \), \( D_x = 1.352 \) g cm\(^{-3}\) at 296 K, \( \lambda(Cu K\alpha) = 1.54184 \) Å, \( \mu = 7.79 \) cm\(^{-1}\), \( F(000) = 328 \), 3155 unique data measured, final \( R = 0.045 \) for 2703 reflections with \( I > 3.0\sigma(I) \).

![Figure F.1 ORTEP drawing of 5-methoxy-3-(2,6-dimethoxyphenyl)-1H-benzo-2-pyran-1-one.](image-url)
Table F.1 Coordinates and Isotropic Thermal Parameters.

\[ B_{eq} = \frac{8\pi^2/3}{\Sigma \Sigma} \Sigma \Sigma \Sigma U_{ij} \mathbf{a}_i \cdot \mathbf{a}_j \mathbf{a}_j \]

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(x)</td>
<td>(y)</td>
<td>(z)</td>
</tr>
<tr>
<td>O1</td>
<td>0.3538(2)</td>
<td>0.7764(1)</td>
<td>0.3672(1)</td>
</tr>
<tr>
<td>O2</td>
<td>0.8688(2)</td>
<td>0.6586(1)</td>
<td>0.54049(9)</td>
</tr>
<tr>
<td>O3</td>
<td>0.7599(2)</td>
<td>0.9564(1)</td>
<td>0.1990(1)</td>
</tr>
<tr>
<td>O4</td>
<td>0.6989(2)</td>
<td>0.8305(1)</td>
<td>0.31651(9)</td>
</tr>
<tr>
<td>O5</td>
<td>0.7031(2)</td>
<td>0.2945(1)</td>
<td>0.09225(9)</td>
</tr>
<tr>
<td>C1</td>
<td>0.4573(2)</td>
<td>0.7721(2)</td>
<td>0.4716(1)</td>
</tr>
<tr>
<td>C2</td>
<td>0.4153(2)</td>
<td>0.8111(2)</td>
<td>0.5846(1)</td>
</tr>
<tr>
<td>C3</td>
<td>0.5260(2)</td>
<td>0.7971(2)</td>
<td>0.6827(1)</td>
</tr>
<tr>
<td>C4</td>
<td>0.6771(3)</td>
<td>0.7459(2)</td>
<td>0.6725(1)</td>
</tr>
<tr>
<td>C5</td>
<td>0.7212(2)</td>
<td>0.7085(2)</td>
<td>0.5598(1)</td>
</tr>
<tr>
<td>C6</td>
<td>0.6125(2)</td>
<td>0.7233(2)</td>
<td>0.4584(1)</td>
</tr>
<tr>
<td>C7</td>
<td>0.6636(2)</td>
<td>0.6964(2)</td>
<td>0.3404(1)</td>
</tr>
<tr>
<td>C8</td>
<td>0.6759(2)</td>
<td>0.5643(2)</td>
<td>0.2618(1)</td>
</tr>
<tr>
<td>C9</td>
<td>0.7168(2)</td>
<td>0.5567(2)</td>
<td>0.1466(1)</td>
</tr>
<tr>
<td>C10</td>
<td>0.7247(2)</td>
<td>0.4175(2)</td>
<td>0.0581(1)</td>
</tr>
<tr>
<td>C11</td>
<td>0.7516(2)</td>
<td>0.4123(2)</td>
<td>-0.0542(1)</td>
</tr>
<tr>
<td>C12</td>
<td>0.7755(2)</td>
<td>0.5440(2)</td>
<td>-0.0800(1)</td>
</tr>
<tr>
<td>C13</td>
<td>0.7728(2)</td>
<td>0.6824(2)</td>
<td>0.0055(1)</td>
</tr>
<tr>
<td>C14</td>
<td>0.7428(2)</td>
<td>0.6877(2)</td>
<td>0.1190(1)</td>
</tr>
<tr>
<td>C15</td>
<td>0.7364(2)</td>
<td>0.8340(2)</td>
<td>0.2099(1)</td>
</tr>
<tr>
<td>C16</td>
<td>0.1980(2)</td>
<td>0.8306(2)</td>
<td>0.3757(2)</td>
</tr>
<tr>
<td>C17</td>
<td>0.9791(3)</td>
<td>0.6389(2)</td>
<td>0.6405(2)</td>
</tr>
<tr>
<td>C18</td>
<td>0.7136(3)</td>
<td>0.1516(2)</td>
<td>0.0066(2)</td>
</tr>
</tbody>
</table>
Table F.2 Coordinates and Isotropic Thermal Parameters for Hydrogen Atoms.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>B&lt;sub&gt;iso&lt;/sub&gt; (Å&lt;sup&gt;2&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H2</td>
<td>0.302(3)</td>
<td>0.850(2)</td>
<td>0.591(2)</td>
<td>7.1(5)</td>
</tr>
<tr>
<td>H3</td>
<td>0.496(3)</td>
<td>0.823(2)</td>
<td>0.758(2)</td>
<td>7.2(5)</td>
</tr>
<tr>
<td>H4</td>
<td>0.761(2)</td>
<td>0.741(2)</td>
<td>0.746(2)</td>
<td>6.3(4)</td>
</tr>
<tr>
<td>H8</td>
<td>0.653(2)</td>
<td>0.478(2)</td>
<td>0.289(1)</td>
<td>4.9(4)</td>
</tr>
<tr>
<td>H11</td>
<td>0.754(2)</td>
<td>0.316(2)</td>
<td>-0.111(1)</td>
<td>4.8(4)</td>
</tr>
<tr>
<td>H12</td>
<td>0.787(2)</td>
<td>0.541(2)</td>
<td>-0.161(1)</td>
<td>5.7(4)</td>
</tr>
<tr>
<td>H13</td>
<td>0.793(2)</td>
<td>0.777(2)</td>
<td>-0.011(1)</td>
<td>6.6(5)</td>
</tr>
<tr>
<td>H16a</td>
<td>0.160(3)</td>
<td>0.833(2)</td>
<td>0.292(2)</td>
<td>8.8(6)</td>
</tr>
<tr>
<td>H16b</td>
<td>0.111(3)</td>
<td>0.758(2)</td>
<td>0.394(2)</td>
<td>9.1(6)</td>
</tr>
<tr>
<td>H16c</td>
<td>0.247(3)</td>
<td>0.938(2)</td>
<td>0.450(2)</td>
<td>8.1(5)</td>
</tr>
<tr>
<td>H17a</td>
<td>1.070(3)</td>
<td>0.603(2)</td>
<td>0.610(2)</td>
<td>7.4(5)</td>
</tr>
<tr>
<td>H17b</td>
<td>1.033(2)</td>
<td>0.733(2)</td>
<td>0.712(1)</td>
<td>6.5(5)</td>
</tr>
<tr>
<td>H17c</td>
<td>0.897(2)</td>
<td>0.559(2)</td>
<td>0.659(1)</td>
<td>5.9(4)</td>
</tr>
<tr>
<td>H18a</td>
<td>0.698(2)</td>
<td>0.078(2)</td>
<td>0.052(2)</td>
<td>6.4(5)</td>
</tr>
<tr>
<td>H18b</td>
<td>0.618(2)</td>
<td>0.113(2)</td>
<td>-0.075(2)</td>
<td>6.9(5)</td>
</tr>
<tr>
<td>H18c</td>
<td>0.846(3)</td>
<td>0.178(2)</td>
<td>-0.007(2)</td>
<td>8.4(6)</td>
</tr>
</tbody>
</table>
APPENDIX G: CRYSTALLOGRAPHIC DATA FOR (Z)-4-METHOXY-3-[(2,6-DIMETHOXYPHENYL)METHYLENE-1(3H)-ISOBENZOFURANONE

(Z)-4-Methoxy-3-[(2,6-dimethoxyphenyl)methylene]-1(3H)-isobenzofuranone, 3.53: $\text{C}_{18}\text{H}_{16}\text{O}_5$, $M_r = 312.3$, triclinic, $P\bar{1}$, $a = 6.8297(4)$, $b = 10.4824(10)$, $c = 12.2123(7)$ Å, $\alpha = 69.510(7)^\circ$, $\beta = 76.924(5)^\circ$, $\gamma = 76.058(7)^\circ$, $V = 785.12(7)$ Å$^3$, $Z = 2$, $D_x = 1.321$ g cm$^{-3}$ at 297 K, $\lambda(\text{Cu K}\alpha) = 1.54184$ Å, $\mu = 7.62$ cm$^{-1}$, $F(000) = 328$, 3109 unique data measured, final $R = 0.041$ for 2816 reflections with $I > 3.0\sigma(I)$.

Figure G.1 ORTEP drawing of (Z)-4-methoxy-3-[(2,6-dimethoxyphenyl)methylene]-1-(3H)-isobenzofuranone.
Table G.1 Coordinates and Isotropic Thermal Parameters.

\[ B_{eq} = \frac{8\pi^2}{3} \sum \sum U_{ij} a_i^* a_j^* a_i a_j \]

<table>
<thead>
<tr>
<th></th>
<th>( x )</th>
<th>( y )</th>
<th>( z )</th>
<th>( B_{eq} (\text{\AA}^2) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>O1</td>
<td>0.6333(2)</td>
<td>0.3494(1)</td>
<td>0.15240(9)</td>
<td>6.42(3)</td>
</tr>
<tr>
<td>O2</td>
<td>0.0941(2)</td>
<td>0.1098(1)</td>
<td>0.34304(9)</td>
<td>5.88(3)</td>
</tr>
<tr>
<td>O3</td>
<td>0.2102(2)</td>
<td>0.7376(1)</td>
<td>0.23357(9)</td>
<td>5.80(3)</td>
</tr>
<tr>
<td>O4</td>
<td>0.2898(1)</td>
<td>0.50844(8)</td>
<td>0.26571(7)</td>
<td>4.24(2)</td>
</tr>
<tr>
<td>O5</td>
<td>0.3269(2)</td>
<td>0.21957(9)</td>
<td>0.61740(7)</td>
<td>4.72(2)</td>
</tr>
<tr>
<td>C1</td>
<td>0.5047(2)</td>
<td>0.2742(2)</td>
<td>0.14261(1)</td>
<td>5.29(3)</td>
</tr>
<tr>
<td>C2</td>
<td>0.5140(3)</td>
<td>0.2369(2)</td>
<td>0.0423(1)</td>
<td>7.38(5)</td>
</tr>
<tr>
<td>C3</td>
<td>0.3803(4)</td>
<td>0.1561(2)</td>
<td>0.0446(1)</td>
<td>8.42(5)</td>
</tr>
<tr>
<td>C4</td>
<td>0.2365(3)</td>
<td>0.1113(2)</td>
<td>0.14111(1)</td>
<td>6.96(4)</td>
</tr>
<tr>
<td>C5</td>
<td>0.2269(2)</td>
<td>0.1494(1)</td>
<td>0.2410(1)</td>
<td>5.06(3)</td>
</tr>
<tr>
<td>C6</td>
<td>0.3593(2)</td>
<td>0.2315(1)</td>
<td>0.2428(1)</td>
<td>4.38(3)</td>
</tr>
<tr>
<td>C7</td>
<td>0.3449(2)</td>
<td>0.2642(1)</td>
<td>0.3530(1)</td>
<td>3.94(2)</td>
</tr>
<tr>
<td>C8</td>
<td>0.3126(2)</td>
<td>0.3891(1)</td>
<td>0.36387(9)</td>
<td>3.60(2)</td>
</tr>
<tr>
<td>C9</td>
<td>0.2798(2)</td>
<td>0.4331(1)</td>
<td>0.46809(9)</td>
<td>3.51(2)</td>
</tr>
<tr>
<td>C10</td>
<td>0.2831(2)</td>
<td>0.3593(1)</td>
<td>0.5876(1)</td>
<td>3.73(2)</td>
</tr>
<tr>
<td>C11</td>
<td>0.2413(2)</td>
<td>0.4350(1)</td>
<td>0.6663(1)</td>
<td>4.28(3)</td>
</tr>
<tr>
<td>C12</td>
<td>0.1970(2)</td>
<td>0.5791(1)</td>
<td>0.6266(1)</td>
<td>4.56(3)</td>
</tr>
<tr>
<td>C13</td>
<td>0.1936(2)</td>
<td>0.6526(1)</td>
<td>0.5093(1)</td>
<td>4.46(3)</td>
</tr>
<tr>
<td>C14</td>
<td>0.2355(2)</td>
<td>0.5762(1)</td>
<td>0.4313(1)</td>
<td>3.82(2)</td>
</tr>
<tr>
<td>C15</td>
<td>0.2407(2)</td>
<td>0.6232(1)</td>
<td>0.3032(1)</td>
<td>4.31(3)</td>
</tr>
<tr>
<td>C16</td>
<td>0.7833(3)</td>
<td>0.4001(2)</td>
<td>0.0542(2)</td>
<td>8.65(6)</td>
</tr>
<tr>
<td>C17</td>
<td>0.0634(3)</td>
<td>0.0418(2)</td>
<td>0.3437(2)</td>
<td>7.56(5)</td>
</tr>
<tr>
<td>C18</td>
<td>0.3429(3)</td>
<td>0.1429(2)</td>
<td>0.7384(1)</td>
<td>5.45(4)</td>
</tr>
</tbody>
</table>
Table G.2 Coordinates and Isotropic Thermal Parameters for Hydrogen Atoms.

<table>
<thead>
<tr>
<th></th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>$B_{iso}$ ($\text{Å}^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H2</td>
<td>0.610(3)</td>
<td>0.267(2)</td>
<td>-0.025(2)</td>
<td>9.3(5)</td>
</tr>
<tr>
<td>H3</td>
<td>0.380(3)</td>
<td>0.131(2)</td>
<td>-0.022(2)</td>
<td>9.3(5)</td>
</tr>
<tr>
<td>H4</td>
<td>0.143(3)</td>
<td>0.043(2)</td>
<td>0.143(2)</td>
<td>10.2(6)</td>
</tr>
<tr>
<td>H7</td>
<td>0.354(2)</td>
<td>0.186(1)</td>
<td>0.426(1)</td>
<td>4.9(3)</td>
</tr>
<tr>
<td>H11</td>
<td>0.245(2)</td>
<td>0.385(1)</td>
<td>0.747(1)</td>
<td>5.3(3)</td>
</tr>
<tr>
<td>H12</td>
<td>0.166(2)</td>
<td>0.625(1)</td>
<td>0.689(1)</td>
<td>6.1(4)</td>
</tr>
<tr>
<td>H13</td>
<td>0.164(2)</td>
<td>0.752(2)</td>
<td>0.481(1)</td>
<td>5.5(3)</td>
</tr>
<tr>
<td>H16a</td>
<td>0.867(4)</td>
<td>0.448(3)</td>
<td>0.075(2)</td>
<td>15.2(9)</td>
</tr>
<tr>
<td>H16b</td>
<td>0.711(3)</td>
<td>0.449(2)</td>
<td>-0.010(2)</td>
<td>10.8(6)</td>
</tr>
<tr>
<td>H16c</td>
<td>0.862(3)</td>
<td>0.316(2)</td>
<td>0.033(2)</td>
<td>8.9(5)</td>
</tr>
<tr>
<td>H17a</td>
<td>-0.137(5)</td>
<td>0.013(3)</td>
<td>0.431(3)</td>
<td>15.6(9)</td>
</tr>
<tr>
<td>H17b</td>
<td>-0.006(3)</td>
<td>-0.042(2)</td>
<td>0.324(2)</td>
<td>9.4(6)</td>
</tr>
<tr>
<td>H17c</td>
<td>-0.139(3)</td>
<td>0.099(2)</td>
<td>0.282(2)</td>
<td>10.5(6)</td>
</tr>
<tr>
<td>H18a</td>
<td>0.377(3)</td>
<td>0.045(2)</td>
<td>0.741(2)</td>
<td>7.6(5)</td>
</tr>
<tr>
<td>H18b</td>
<td>0.203(3)</td>
<td>0.161(2)</td>
<td>0.786(2)</td>
<td>7.3(4)</td>
</tr>
<tr>
<td>H18c</td>
<td>0.445(3)</td>
<td>0.174(2)</td>
<td>0.767(2)</td>
<td>8.4(5)</td>
</tr>
</tbody>
</table>
VITA

Kevin LeVon Evans was born in Weston, West Virginia on August 15, 1966. He graduated from Gilmer County High School in Glenville, West Virginia in May of 1984. He attended Glenville State College where he received a Bachelors of Arts Degree in Chemistry in August of 1987. In September, he attended Louisiana State University in Baton Rouge, where he is currently a candidate for the degree of Doctor of Philosophy in the Department of Chemistry.
DOCTORAL EXAMINATION AND DISSERTATION REPORT

Candidate: Kevin LeVon Evans

Major Field: Chemistry

Title of Dissertation: 2,2',6,6'-Tetrasubstituted Diarylethynes: Models to Test Proximity and Position in Catalysis

Approved:

Richard D. Jancour
Major Professor and Chairman

Dean of the Graduate School

EXAMINING COMMITTEE:

Amy M. Sundberg
Kalle T. Valsberg
Steven F. Williams

Mark J. McLaughlin

Date of Examination:

April 6, 1993