

Quinone Formation via Ceric Ammonium Nitrate Oxidations of 2-Alkyl-1,4-dialkoxybenzenes

by

Alexander Linwood Simmons

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Director of Thesis: Brian E. Love, PhD

Major Department: Chemistry

Quinones are cyclohexadiendiones that have a variety of uses ranging from medical applications to synthetic building blocks.¹ Medicinal applications stem from the potent biological activity (*e.g.* antitumor and antibiotic) these compounds and some derivatives possess.^{2, 3}

The most common preparation method to access these compounds is oxidative demethylation of hydroquinone dimethyl ethers (**1**, R₁=R₃: Me) typically using ceric ammonium nitrate (CAN) as seen in Figure 1. Oxidation using CAN can yield a product mixture of the (mono)quinone (**2**) and the symmetric dimeric quinone (**3**).

Previous work^{4, 5} in our group has resulted in the development of several protocols for altering the monoquinone to diquinone ratio by altering reaction conditions (*e.g.* substrate concentration, mode of addition, *etc.*). The current focus further explores manipulation of this ratio and reaction efficacy through substrate solubility and cerium coordination. We will discuss how ether linkages of various hydrophobicities and coordination modes change product outcome and if altering a single ether linkage (R₁) or both linkages (both R₁ and R₃) affect the product ratio.

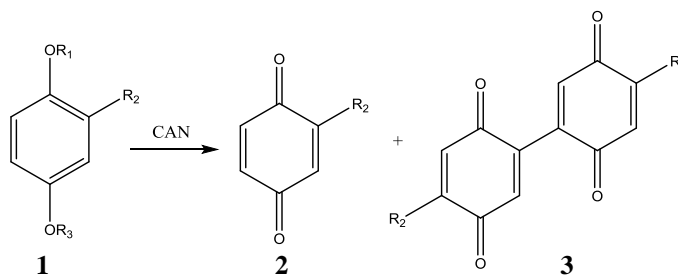


Figure 1 – General Substrate Reaction

Quinone Formation via Ceric Ammonium Nitrate Oxidations of 2-Alkyl-1,4-dialkoxybenzenes

A Thesis

Presented To the Faculty of the Department of Chemistry

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In Partial Fulfillment of the Requirements for the Degree

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by

Alexander Linwood Simmons

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by

Alexander Linwood Simmons

Approved by:

Director of Thesis: _____
Brian E. Love, PhD

Committee Member: _____
Shouquan Huo, PhD

Committee Member: _____
Colin S. Burns, PhD

Committee Member: _____
Mary A. Farwell, PhD

Chair of the Department
of Chemistry & Committee
Member: _____
Andrew T. Morehead, PhD

Dean of the Graduate School: _____
Paul J. Gemperline, PhD

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Table of Contents

List of Tables	vii
List of Graphs	viii
List of Figures	ix
List of Abbreviations	xiii
Chapter 1: Introduction to Quinones.....	1
1.1 Synthesis of Quinones.....	3
Chapter 2: Alkoxy Group Effects on Dimer Formation	8
2.1 CAN Oxidation Methods	8
2.1.1 Rate and Concentration Effects	10
2.2 Solubility Effects	13
2.2.1 Substrate Synthesis	15
2.3 Oxidation of Substrates.....	29
Chapter 3: Chelation and Stabilization Effects on Dimer Formation	35
3.1 Experiment Design.....	36
3.1.1 Substrate Synthesis	38
3.2 CAN Studies	42
Chapter 4: Micelle Effects on Dimer Formation	48
4.1 Experiment Design.....	48
4.1.1 Substrate Synthesis	50
4.2 CAN Results and Discussion	53
4.2.1 CAN SDS Studies	54

Chapter 5: Substituent Size Effects on Dimer Formation	56
5.1 Experiment Design.....	56
5.1.1 Substrate Synthesis	57
5.2 Results and Discussion	58
Chapter 6: Substrate Electronic Effects on Dimer Formation	61
6.1 Hammett Value Comparison to Dimer Yield	61
6.2 Experimental Design and Future Work	65
Chapter 7: Conclusions	66
Chapter 8: Experimental	69
8.1 “Mono-substituted” Arenes	78
8.2 “Di-substituted” Arenes	95
Chapter 9: References	105

List of Tables

Table 1: Synthesis of 13a	12
Table 2: Results of Dilution Studies	13
Table 3: Planned Substrates (1 , when R ₂ : <i>t</i> -butyl, R ₃ : Me)	17
Table 4: Synthesized Substrates (1 , when R ₂ & R ₃ : Me) using Standard Microwave Method	27
Table 5: Synthesized Substrates (1a) using Standard Microwave Method	28
Table 6: Synthesized Substrates (1b) using Standard Microwave Method	29
Table 7: Substrates Tested under Standard CAN Conditions (1a)	30
Table 8: Substrates Tested under Standard CAN Conditions (1b)	31
Table 9: Substrates Tested under MQ or DQ CAN Conditions.....	34
Table 10: Substrates Tested for Chelation or Stabilization Effects (1a)	43
Table 11: Substrates Tested for Chelation or Stabilization Effects (1b)	44
Table 12: Substrates Tested for Chelation	46
Table 13: Synthesized Surfactant-like Substrates using Standard Microwave Method	52
Table 14: Surfactant-like Substrates under Standard CAN Conditions.....	53
Table 15: Results of SDS Studies	55
Table 16: Substrates Tested under Standard CAN Conditions (Figure 50 Substrates)	59

List of Graphs

Graph 1: σ Values vs. Diquinone Yields	62
Graph 2: σ^+ Values vs. Diquinone Yields.....	62
Graph 3: σ^- Values vs. Diquinone Yields	63
Graph 4: σ_I Values vs. Diquinone Yields	63
Graph 5: σ_R Values vs. Diquinone Yields	63

List of Figures

Abstract

Figure 1: General Substrate Reaction

Chapter 1

Figure 2: Synthesis of Aflatoxin B ₂	1
Figure 3: Quinones of Relevance.....	1
Figure 4: Quinone Types	2
Figure 5: Bond Lengths	2
Figure 6: CAN Oxidation.....	3
Figure 7: Hypervalent Iodine Oxidation Mechanism	4
Figure 8: CAN Oxidation Mechanism – Monoquinone from Hydroquinone Dimethyl Ethers	4
Figure 9: CAN Oxidation Mechanism – Monoquinone from Hydroquinone.....	5
Figure 10: Dibenzofuran Formation	5
Figure 11: Diquinones Found in Nature	5
Figure 12: CAN Oxidation Mechanism – Diquinone	6

Chapter 2

Figure 13: Synthesis of Herbertenones A and B.....	8
Figure 14: Synthesis of Blattellaquinone.....	9
Figure 15: Oxidation of 13a	11
Figure 16: Synthesis of 13a	12
Figure 1: General Substrate Reaction	15, 29
Figure 17: General Substrate Synthesis for Table 3 Compounds.....	16

Figure 18: Dimerization of 3- <i>t</i> -butyl-4-hydroxyanisole	19
Figure 19: Synthesis of 17a	19
Figure 20: Alkylation of BHA using Phase Transfer Catalyst	20
Figure 21: Alkylation of BHA using Microwave Reaction	21
Figure 22: Microwave Synthesis of 15a	22
Figure 23: Microwave Synthesis of 19a	23
Figure 24: Microwave Synthesis of 18a	23
Figure 25: Microwave Synthesis of 20a	23
Figure 26: Microwave Synthesis of 22a	23
Figure 27: Microwave Synthesis of 23a	24
Figure 28: Microwave Synthesis of 24a	24
Figure 29: Traditional Synthesis of 24a	24
Figure 30: Microwave Synthesis of 26a	25
Figure 31: Microwave Synthesis of 27a	25
Figure 32: Synthesis of 4-methoxy-2-methylphenol	26
 <u>Chapter 3</u>	
Figure 33: Six-Membered Amide Stabilized CAN Reaction	35
Figure 34: Variations of Amine and Amide Containing Substrates	37
Figure 35: Substrates to Chelate CAN.....	38
Figure 36: Synthesis of 43	39
Figure 37: Synthesis of 44	39
Figure 38: Synthesis of 46	40
Figure 39: Synthesis of 38	40

Figure 40: Microwave Synthesis of 36	40
Figure 41: Microwave Synthesis of 39	41
Figure 42: Synthesis of 40	41
Figure 43: Synthesis of 41	42
Figure 44: Synthesis of 42	42
Figure 1: General Substrate Reaction	43

Chapter 4

Figure 1: General Substrate Reaction	48, 53
Figure 45: Surfactant-like Substrates.....	49
Figure 46: SDS Micelle Structure.....	50
Figure 32: Synthesis of 4-methoxy-2-methylphenol	51
Figure 47: Synthesis of 49	51
Figure 48: Synthesis of 50	51
Figure 15: Oxidation of 13a	54

Chapter 5

Figure 49: Cyclohexane Conformation Equilibrium and A-Value Calculation	56
Figure 50: Substrates with Different Alkyl Group Size.....	57
Figure 51: Synthesis of 54	57
Figure 52: Synthesis of 58 with Dimethyl Sulfate.....	58
Figure 53: Synthesis of 58 with Methyl Iodide	58
Figure 54: Diquinone Formation Transition State	60

Chapter 6

Figure 55: Intermediates of Diquinone Formation	62
---	----

Figure 56: Nitration of 60 with CAN.....	64
---	----

Chapter 7

Figure 1: General Substrate Reaction	66
--	----

Figure 33: Six-Membered Amide Stabilized CAN Reaction	67
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Figure 57: Substrates with Different Alkyl Group Size.....	68
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List of Symbols and Abbreviations

Å: angstrom(s)	Ph: phenyl
Ac: acetyl	q: quartet
BHA: butylated hydroxyanisole	s: singlet
<i>t</i> -Bu or <i>t</i> -butyl: tertiary butyl group	Sat. NaCl: saturated aqueous sodium chloride
¹³ C NMR: carbon nuclear magnetic resonance spectroscopy	SDS: sodium dodecyl sulfate
CAN: ceric ammonium nitrate	t: triplet
δ: chemical shift in parts per million	TBAB: tetrabutylammonium bromide
d: doublet	TES: triethylsilane
dd: doublet of doublets	TFA: trifluoroacetic acid
4-DMAP: 4-dimethylaminopyridine	THF: tetrahydrofuran
DMF: dimethyl formamide	Ts: <i>para</i> -toluenesulfonyl (tosyl)
DMSO: dimethyl sulfoxide	
DQ: diquinone	
dt: doublet of triplets	
Et: ethyl	
g: gram	
¹ H NMR: proton nuclear magnetic resonance spectroscopy	
hr: hour(s)	
Hz: Hertz	
<i>J</i> : coupling constant in Hertz	
LAH: lithium aluminum hydride	
m: multiplet	
Me: methyl group	
min: minute(s)	
MQ: monoquinone	
Ms: methanesulfonyl (mesyl)	

Chapter 1: Introduction to Quinones

Cyclohexadiendiones, better known as quinones, are a vital class of compounds that possess interesting reactivity as well as a unique structure. They have been used as synthetic spring-boards to allow for interesting reactions including use of pericyclic chemistry to form natural product backbones. For example, Corey, *et al.*⁶ used 2-methoxy-1,4-benzoquinone as a synthetic building block to synthesize Aflatoxin B₂ as seen in Figure 2. In particular, the first step used a chiral oxazaborolidinium triflimide (**6**), to efficiently form the cycloadduct (**7**) via 1,3 dipolar cycloaddition, between 2-methoxy-1,4-benzoquinone (**4**) and 2,3-dihydrofuran (**5**) in a 65% yield and an enantiomeric purity of 99%.

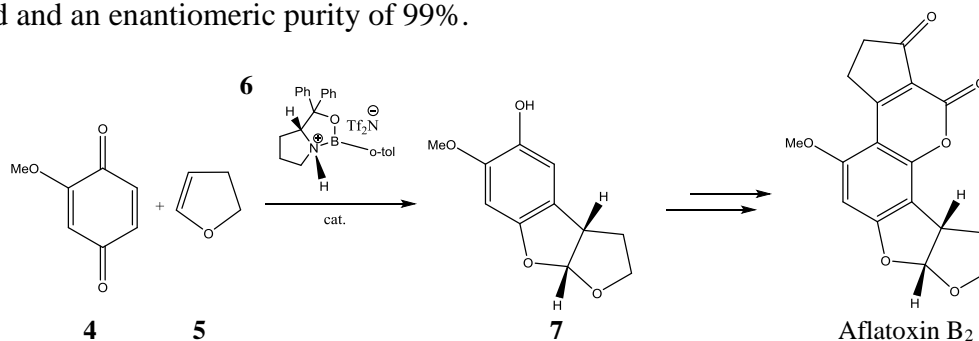


Figure 2 – Synthesis of Aflatoxin B₂

Quinones are also abundant in biological systems¹ an example being the electron mediator, ubiquinone (see Figure 3). Medicinally, quinone structures are found in several natural products, for example Vitamin K₂, and in anticancer agents like popolohuanonone E.⁷

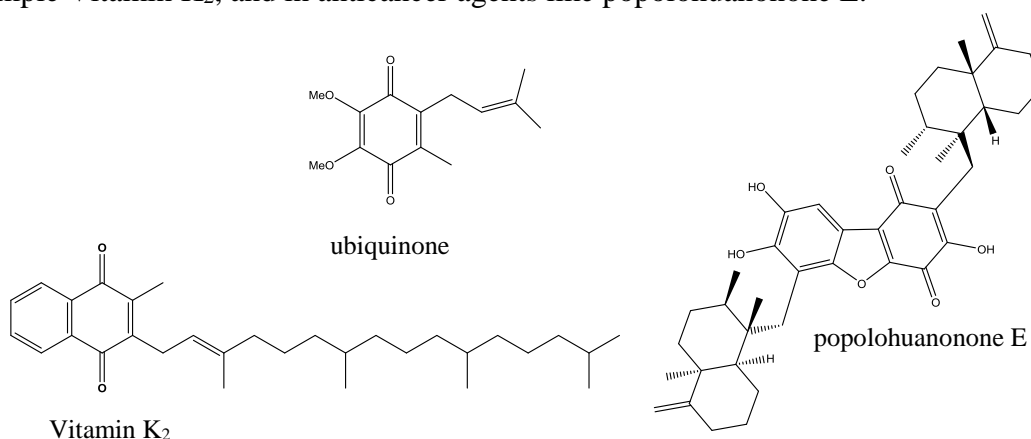


Figure 3 – Quinones of Relevance

Quinones have a general structure as seen in Figure 4, where the carbonyl groups can be present in either the ortho or para position in the cyclohexadiene ring system.

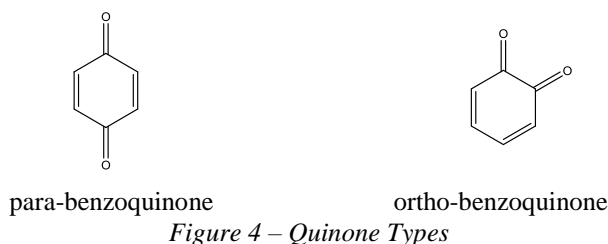


Figure 4 – Quinone Types

Ortho-quinones differ from para-quinones in both reactivity and in thermal stability. Possibly due to the close proximity of the carbonyl carbons with partial positive charges, ortho-benzoquinone is more thermodynamically unstable than para-benzoquinone. Ortho-benzoquinone also has a smaller calculated HOMO-LUMO gap showing increased reactivity.⁸ As might be expected, para-benzoquinone reactivity is similar to that of α,β -unsaturated carbonyl compounds.^{9, 10} Previous studies^{11, 12} have found that para-benzoquinone has bond lengths that correspond with a nonaromatic system, showing much more localized electron density on the oxygens in the respective carbonyls (as seen in Figure 5). In the case of the dianion of para-hydroxyphenol, the structure still appears to be closer to the bond lengths of benzene¹³ (1.40 Å), rather than the benzoquinone structure.

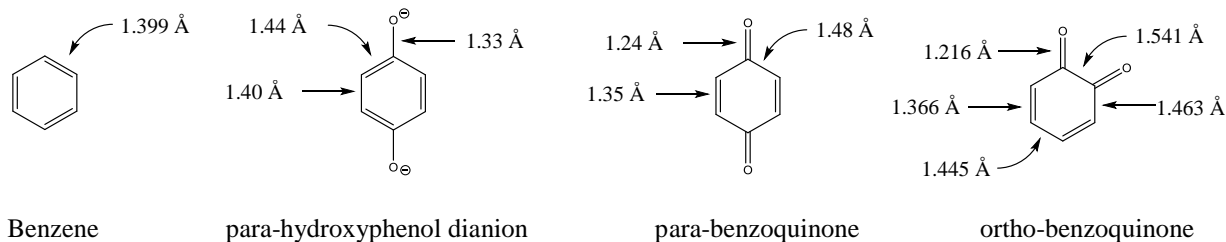


Figure 5 – Bond Lengths

Chapter 1.1 Synthesis of Quinones

There are several synthetic routes available to form quinones. Starting materials such as phenols, hydroquinones (diphenols), and hydroquinone dimethyl ethers (dimethoxybenzenes) can each be used with different oxidizing reagents to successfully form quinones. The most useful of these methods is oxidative demethylation of hydroquinone dimethyl ethers (Figure 6) due to the ether stability, especially when designing a synthesis.¹⁴

There has been success using hypervalent iodine¹⁴ to synthesize quinones from hydroquinone dimethyl ethers where the oxidant is easily regenerated by hydrogen peroxide. Other oxidants such as silver nitrate¹⁵ and nitric acid¹⁶ have also been employed. The problem associated with using silver nitrate is reagent cost, and the corrosive nature of nitric acid can also be a problem. Ceric ammonium nitrate (CAN) is a mild oxidant that has typically short reaction times (less than one hour), especially when compared to hypervalent iodine that has reaction times greater than one hour.¹⁴ When comparing oxidants, hypervalent iodine is very attractive since it is able to be regenerated and can be polymer supported. CAN is unique since it is a single electron oxidant, in comparison with hypervalent iodine that is a two electron oxidant. Both of these oxidants will form (mono)quinones, but CAN will actually form the quinone dimer (diquinone) as well as the monoquinone (as seen in Figure 6).

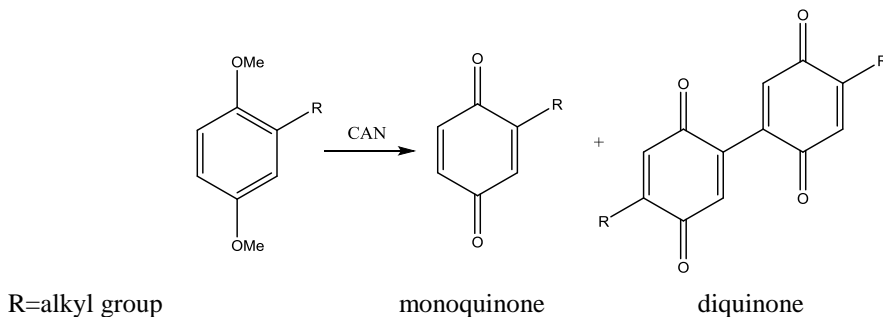


Figure 6 - CAN Oxidation

CAN reactions can yield a mixture of both products and are believed to proceed through radical cationic intermediates. Reagents other than CAN require conditions that are strongly acidic, have poor solubility in reaction solvents (such as acetonitrile), or are not single electron oxidants, and therefore don't lead to dimer formation.

When comparing the mechanism of monoquinone formation using hypervalent iodine¹⁴ (Figure 7) to the mechanism of CAN oxidations¹⁷ (Figure 8) it is clear how these oxidants react differently. Proton transfer steps in these mechanisms are not explicitly shown.

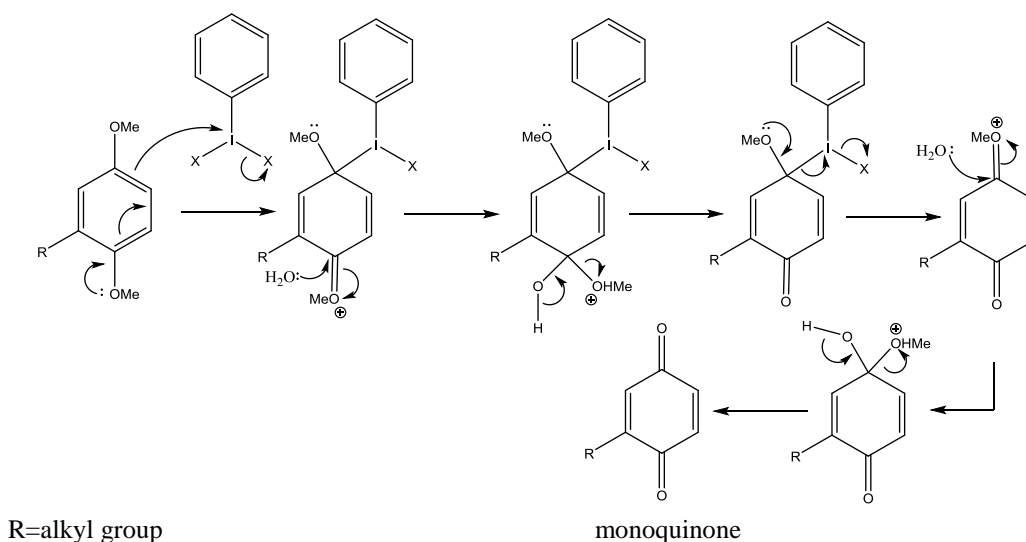


Figure 7 – Hypervalent Iodine Oxidation Mechanism

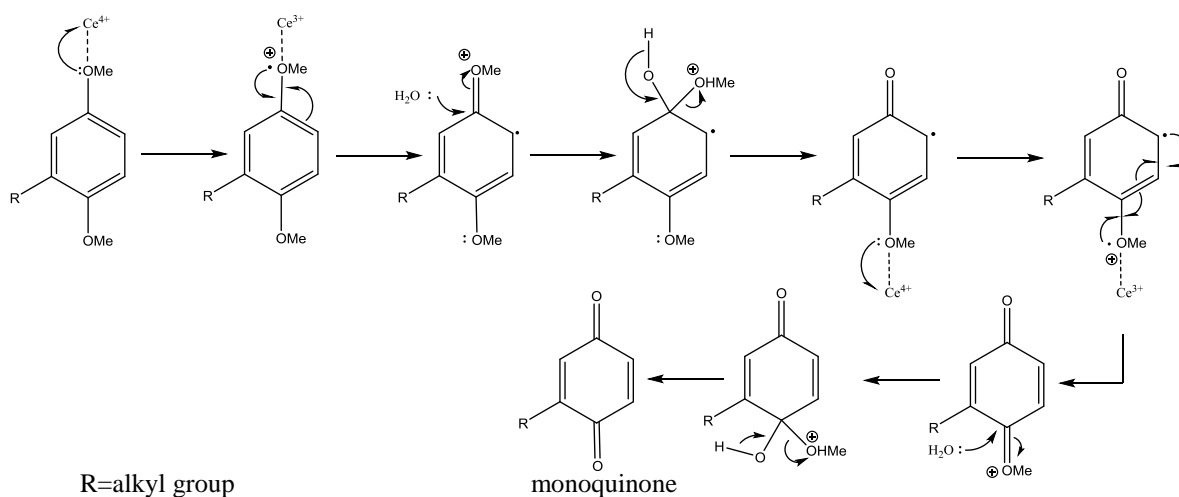


Figure 8 – CAN Oxidation Mechanism – Monoquinone from Hydroquinone Dimethyl Ethers

Isotopic labeling studies¹⁷ have shown the oxygen in the final oxidized quinone product is from the aqueous reaction solution in the CAN oxidation. Similarly, it is believed the oxygen in the final product of the hypervalent iodine oxidation is also from the reaction media.¹⁴

The mechanism for oxidation of hydroquinones via CAN is believed to be similar, differing in that nucleophilic attack of water is less probable than simple deprotonation of the formed carbonyl (as depicted in Figure 9).

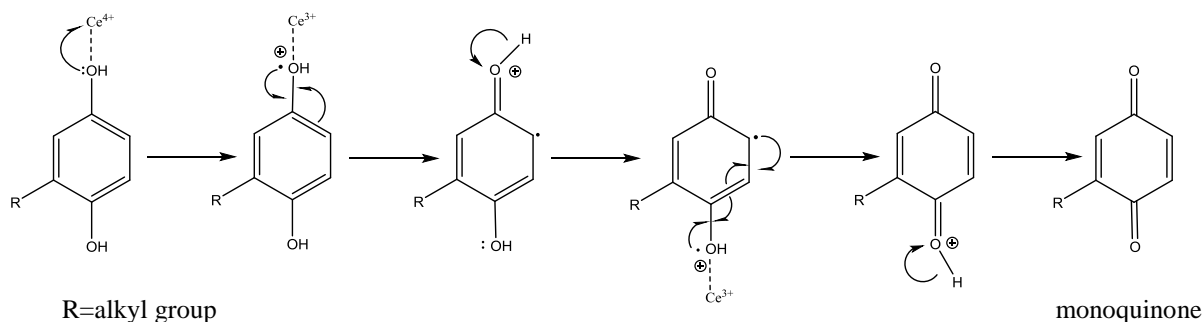


Figure 9 – CAN Oxidation Mechanism – Monoquinone from Hydroquinone

Dimeric quinones (diquinones) are also useful compounds that have applications similar to their monoquinone counterparts. These compounds can be used as potential precursors to dibenzofurans (as seen in Figure 10) and also have been found in nature (Figure 11).^{4, 7}

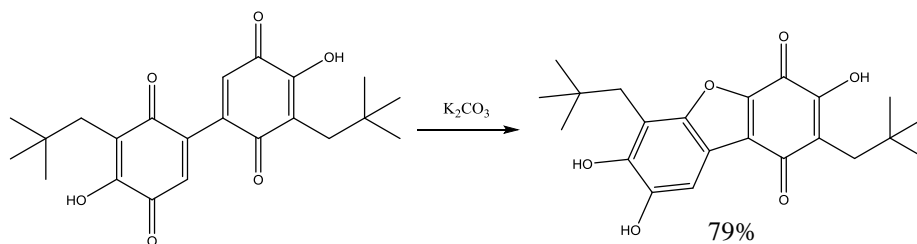


Figure 10 – Dibenzofuran Formation

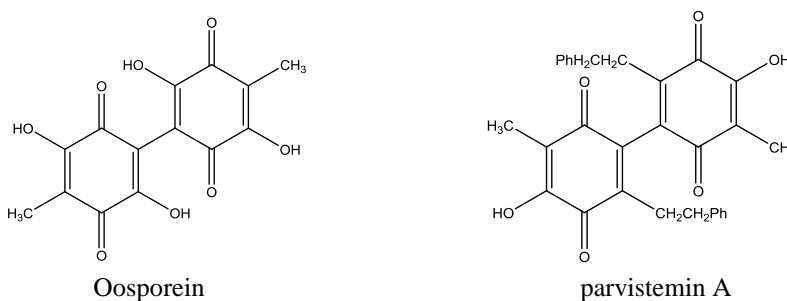


Figure 11 – Diquinones Found in Nature

It is hypothesized that the electron rich aromatic system can attack the radical cationic intermediate formed during the CAN oxidation reaction, and undergo electrophilic aromatic substitution, forming the biaryl product (Figure 12).

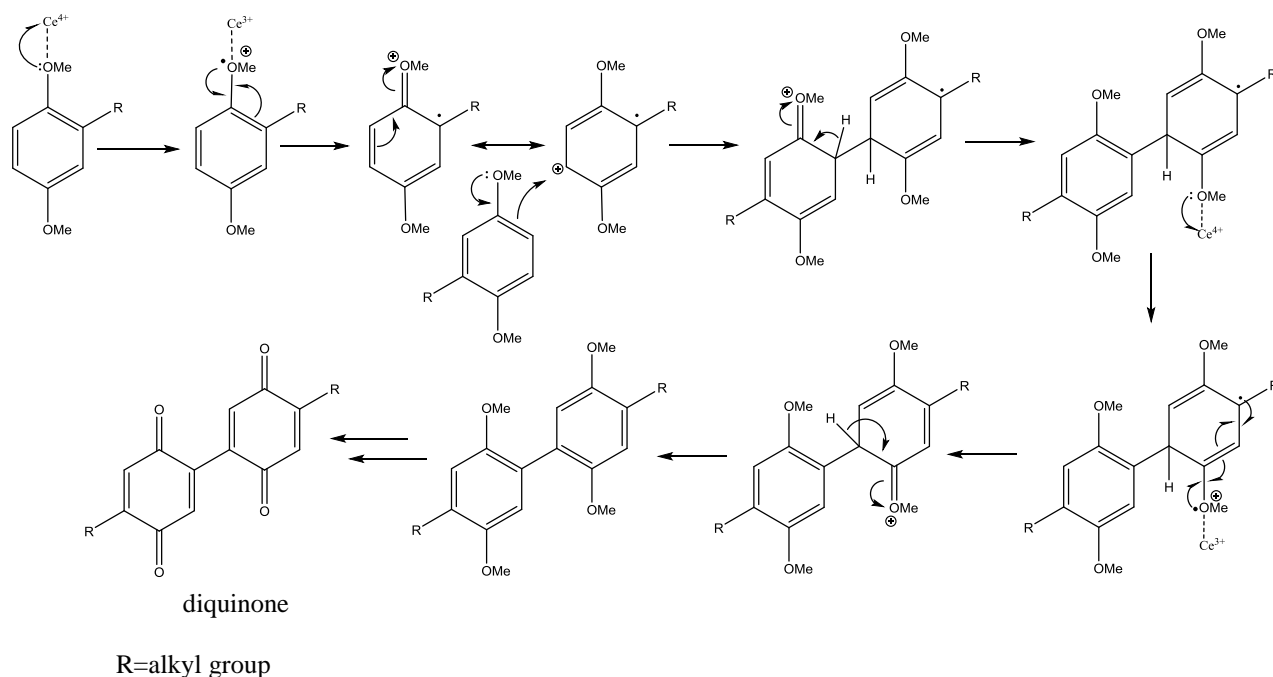


Figure 12 – CAN Oxidation Mechanism - Diquinone

Due to the mild reaction conditions, CAN is an ideal choice for oxidative coupling of two aryl systems. Previous reports^{5, 18} have shown that diquinone formation does not occur from the oxidation of monoquinone, but only occurs when the hydroquinone dimethyl ether is present. In other words, it has been shown the oxidative coupling does not occur after monoquinone has been formed. This supports the hypothesis that diquinones are formed through an intermediate in the oxidation reaction. When comparing the mechanisms of monoquinone and diquinone formation, monoquinone formation requires that two electrons are removed by CAN during oxidation, totaling two equivalents of oxidant. For the corresponding diquinone, two electrons are removed per arene (four total) plus two electrons for the dimer formation, equating to six electrons removed from the dimer starting material (or three equivalents of CAN per starting

arene). Previous work has shown that the use of less than three equivalents of CAN yield a partially oxidized dimer⁴ as one of the products, further supporting that dimer formation happens prior to the complete oxidation of the arenes (as seen in Figure 12).

There are several factors that have been previously reported to affect the product ratio of monoquinone to diquinone.^{4, 5} Several of these factors include reaction solvent, mode of addition, substrate solubility, concentration of CAN solution, and electron density within the arene. The goal of this work was to examine how several of these factors change the product ratio of monoquinone and diquinone, and how to improve current methodology.

Chapter 2: Alkoxy Group Effects on Dimer Formation

The use of CAN as an oxidant to form quinone products or intermediates has been used in several syntheses of natural products. Sometimes, though, the desired product is not obtained. For example, in the total synthesis of herbertenones A and B treatment of **8** with CAN failed to produce the desired monoquinone intermediate (**9**) and instead produced only the corresponding diquinone (**10**) in a 53 % yield (as seen in Figure 13).¹⁹ The reaction did not selectively form the monoquinone over the corresponding dimer. This provides an example of a case where being able to control monoquinone and diquinone product ratios would be helpful. Much of this project is focused on the investigation of factors which affect such ratios.

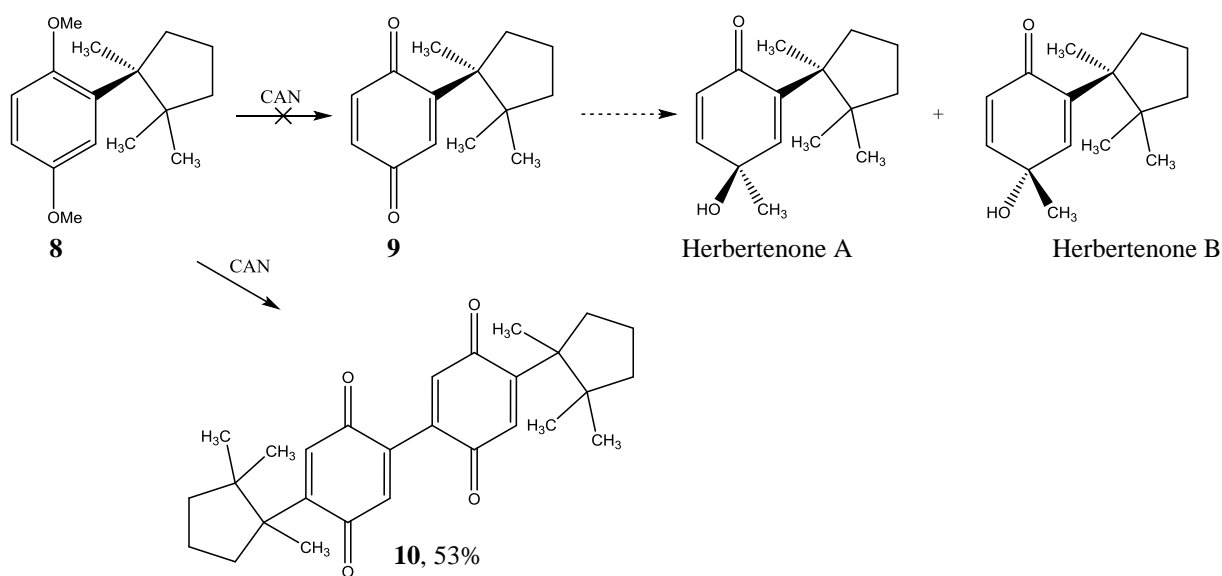


Figure 13 – Synthesis of Herbertenones A and B

Chapter 2.1 CAN Oxidation Methods

In order to develop methods to selectively produce either the monoquinone or diquinone, variations on traditional CAN methods were explored previously in our group. In traditional CAN oxidation reactions, the arene is dissolved in acetonitrile and the CAN is dissolved in water. The aqueous CAN solution is then added to the stirred arene solution, known colloquially

as “traditional addition”. This method typically favors monoquinone formation.^{4,5} Protocols were developed based on the order of addition and changing the reaction solvent. It was determined that more polar solvents such as DMSO rather than acetonitrile, typically encouraged monoquinone formation when coupled with the traditional mode of addition. The inverse of this method (inverse addition, adding the arene to the CAN solution) was discovered to produce a higher yield of diquinone, especially when coupled with solvents less polar than acetonitrile.⁵

Later work²⁰ applied these protocols to the synthesis of blattellaquinone (**11**), improving the mole ratio of the monoquinone (**11**) to diquinone (**12**) from 7.4:1 to 23:1 (Figure 14) as compared to the previous report.²¹ Although the methodology has been improved to be selective in the cases of quinone synthesis, there were several interesting trends observed in the previous work.^{4,5} It was interesting that DMSO helped favor the monoquinone formation and THF encouraged dimer formation. It was also shown that longer alkyl chains (more hydrophobic) in the 2-alkyl-1,4-dimethoxybenzenes did not necessarily increase the yield of diquinone, although the less polar solvent did improve the diquinone yield. The focus of this project was to understand what factors impact the product ratio (monoquinone to diquinone) centered on these interesting findings.

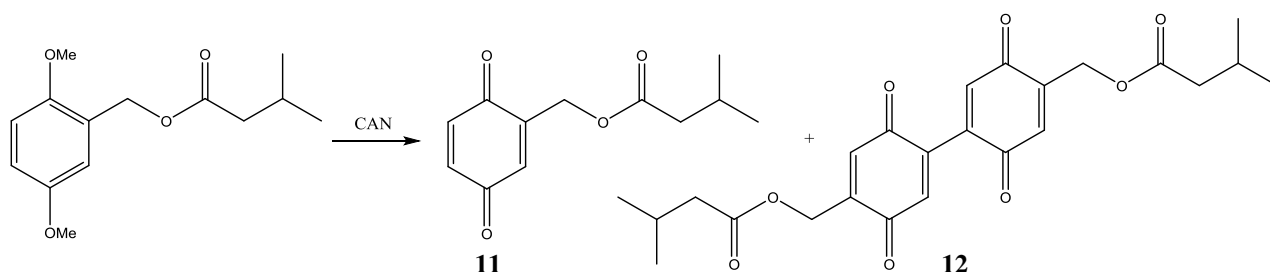


Figure 14 – Synthesis of Blattellaquinone

Chapter 2.1.1 Rate and Concentration Effects

When examining the oxidation reaction in terms of the rate law, diquinone formation is second order with respect to the amount of arene present, whereas the monoquinone is first order with respect to the arene. A set of reactions was designed to test whether the amount of monoquinone versus diquinone formed was controlled primarily by kinetics or if something more complex was taking place.

In order to accurately determine if the product ratios were changed significantly, two sets of reactions were devised. One set of reactions varied concentrations of the reagents and another set of reactions utilized varied addition times over which the aqueous CAN was added to the reaction vessel. Using this methodology, changing the concentrations or the addition times would change the concentration of arene, ultimately changing the rate which product was formed. If this reaction was under traditional kinetic control, the decrease in concentration would lead to a higher amount of monoquinone formed and a lower percent yield of diquinone. Diluting the arene solution to half the original concentration was expected to decrease the rate of monoquinone formation by half, too. However, diluting concentration of the arene solution to half the original concentration would be expected to slow the rate of diquinone formation to one fourth of the original rate. Since the rate of diquinone formation is more adversely affected by the dilution, it was expected that the more dilute the solutions would lead to a higher percentage of monoquinone if kinetic effects were significant. By testing the varied concentrations, this allowed for a simple determination if concentration alters diquinone formation.

A substrate that produced both monoquinone **2a** and diquinone **3a** was selected (2-*t*-butyl-1,4-dimethoxybenzene, **13a**) to determine if concentration or addition time alters diquinone formation. This substrate (**13a**), tested with a previously reported procedure,⁵ produced an

approximate 15% yield of monoquinone **2a** and an approximate 50% yield of diquinone (**3a**).

The method which gave these results used inverse addition with three and a half equivalents of 1 M aqueous CAN, and an equal volume of acetonitrile to dissolve the arene. Two reactions in this study changed the time of addition extending the time two and four times the standard addition time of 10-15 minutes. Longer addition times were expected to reduce the effective concentration of the arene in the reaction mixture.

Another two reactions were used to study the impact of dilution of the reaction media on the product ratio by using a 0.5 M aqueous CAN solution and a 0.25 M aqueous CAN solution, both reactions using equal volume amounts of acetonitrile as the solvent for the arene. The addition rate was also modified to ensure approximately the same rate of acetonitrile/arene solution was added to the CAN solution.

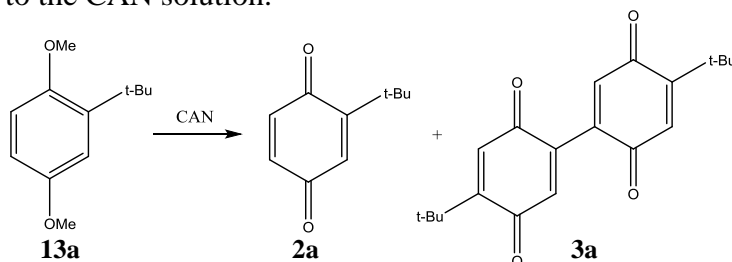


Figure 15 – Oxidation of **13a**

The starting material **13a** was synthesized from commercially available BHA, as depicted in Figure 16. Several methods (as indicated by Table 1) were devised including using different methylating agents such as dimethyl sulfate and methyl iodide paired with different bases. Methyl iodide was found not to alkylate BHA to **13a** under several different conditions. When using the dimethyl sulfate in THF and heating at reflux overnight while gently stoppered, the product **13a** was isolated in 88% yield. However, to force the reaction to completion two and a half equivalents of dimethyl sulfate were necessary. Another method²² proved to be useful using lithium hydroxide monohydrate with only one and a half equivalents of dimethyl sulfate,

producing **13a** in 75% yield. The authors believe the lithium counter-ion helps direct the methylation allowing dimethyl sulfate to be used in smaller amounts. In their study they found they could use half an equivalent of dimethyl sulfate, utilizing both methyls as alkylating agents, however we were unable to reproduce this using our substrate.

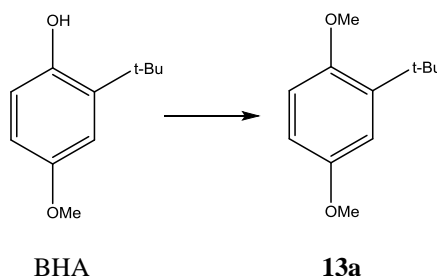


Figure 16 – Synthesis of **13a**

Table 1 – Synthesis of **13a**

<i>Trial</i>	<i>Base (mol equiv.)</i>	<i>Methylating Agent (mol equiv.)</i>	<i>Solvent</i>	<i>Temperature (°C)</i>	<i>Yield of 13a (%)</i>
1	potassium <i>t</i> -butoxide (1.1)	Methyl iodide (1.3)	THF	RT	0%
2	potassium <i>t</i> -butoxide (3.1)	Dimethyl sulfate (3.5)	DMSO	150 °C	14%
3	potassium <i>t</i> -butoxide (2.0)	Dimethyl sulfate (3.0)	THF	reflux	88%
4	Lithium hydroxide monohydrate (1.1)	Dimethyl sulfate (1.5)	THF	RT	75%

RT=room temperature

With usable quantities of **13a** in hand, we began to investigate its oxidation with CAN under various conditions. Interestingly, as indicated by the data in Table 2, there is little change in the amount of diquinone formed in each set of reactions (tested in duplicate). This data suggests that this reaction is not controlled by kinetics, otherwise a noticeable increase in monoquinone yield would have been observed in the reaction run under the most dilute conditions, or in the reaction with the largest addition time.

Table 2 – Results of Dilution Studies

<i>Trial</i>	<i>Solvent Volume (mL)</i>	<i>Addition Time (min)</i>	<i>Monoquinone (2a) Yield (%)</i>	<i>Diquinone (3a) Yield (%)</i>
<i>Standard Method⁵</i>	water (7.0 mL) acetonitrile (7.0 mL)	10-15 min	12%	46%
1	water (7.0 mL) acetonitrile (7.0 mL)	23 min	39%	46%
2	water (7.0 mL) acetonitrile (7.0 mL)	24 min	33%	40%
1	water (7.0 mL) acetonitrile (7.0 mL)	42 min	39%	33%
2	water (7.0 mL) acetonitrile (7.0 mL)	37 min	39%	46%
1	water (14.0 mL) acetonitrile (14.0 mL)	20 min	49%	31%
2	water (14.0 mL) acetonitrile (14.0 mL)	16 min	39%	46%
1	water (28.0 mL) acetonitrile (28.0 mL)	38 min	45%	21%
2	water (28.0 mL) acetonitrile (28.0 mL)	43 min	39%	40%

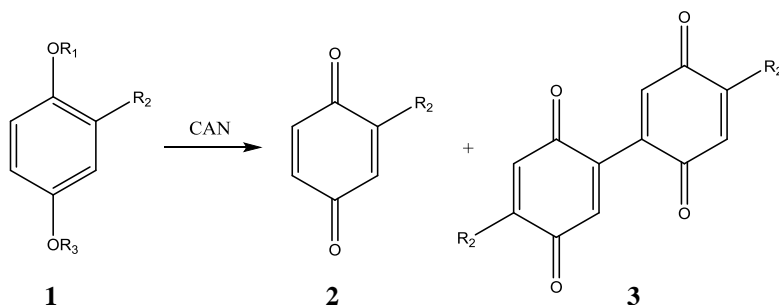
Chapter 2.2 Solubility Effects

Since simple kinetics could not explain the differences in monoquinone to diquinone ratios, other facts had to be considered. As mentioned earlier, according to the presumed mechanism, the arene and the radical cationic intermediate would need to be in close proximity to allow for dimer formation. One hypothesis is that aggregation of arene allows both of these species to be in close proximity to one another. In traditional addition, the arene is evenly dispersed throughout the acetonitrile reaction medium at the point where CAN is introduced. Thus, when a dimethoxybenzene derivative is first oxidized to the corresponding radical cation, it is more likely to be surrounded by solvent (acetonitrile and water) than other arene molecules. Such a situation should favor monoquinone formation. With inverse addition on the other hand, since the substrates are not very water soluble, it is thought that as these compounds are added to an aqueous system, they aggregate together, allowing for the formation of the radical cationic

intermediate in close proximity to the arene, encouraging dimer formation. Although the dilution study data presented in Table 2 shows dilution or addition time does not alter dimer formation, it does not refute this hypothesis. The acetonitrile/arene solution is added to the more polar aqueous CAN solution and can potentially cause the aggregation of the arene. If the arene is dilute within the acetonitrile solution, introduction of the more polar aqueous CAN would still allow for the arene to aggregate, in the presence of excess of CAN, to form the desired dimer.

To test if the aggregation of these compounds is indeed influencing the product ratio in the reaction, a new study was devised. Aggregation of these compounds should correlate to the solubility of the compounds in the aqueous CAN solution. It was hypothesized that more water soluble compounds should produce more monoquinone and conversely, the less water soluble the compound, the more diquinone should be formed. Also, the more polar substrates would be expected to have a larger solvation sphere of water surrounding them, inhibiting the interactions between the arene and radical cationic intermediate, reducing dimer formation. In the more nonpolar substrates, the polar solvent network within the aqueous CAN will force the nonpolar substrates to aggregate together. It was proposed that this aggregation would increase dimer formation due to the close proximity of the arene and intermediate.

Previous work⁴ has shown there is a possible correlation between the electron density in the arene and the diquinone yield. In this study it was critical to only change the solubility of the substrate without substantially changing the electron density in the arene. To minimize the differences in substrate electron densities, substrates were modified at the R₁ and R₃ ether linkage positions rather than the R₂ position (seen in Figure 1) with different hydrophilic and hydrophobic side chains.



R₂: a: *t*-butyl, b: methyl

Figure 1 – General Substrate Reaction

In this study, the substrates tested had an R₂ group of either methyl or *t*-butyl. Previous studies⁵ have shown that the *t*-butyl substrate (**13a**) produced both monoquinone (**2a**, ~15% yield by mass) and diquinone (**3a**, ~50% yield by mass) in a one to two mole ratio, respectively (Figure 1). The study also showed that methyl substrate (**1b**, R₁, & R₃: Me) produced mostly diquinone (**3b**, 90% yield).

The protocol⁵ that produced the diquinone from the *t*-butyl substrate (**13a**) in an ~50% yield was used for this study. This method allowed for a quick determination if the yield increased or decreased from the “standard” substrate yield of 50%. The methyl substrate was also of interest to determine if the amount of monoquinone for this substrate could be increased. The method used inverse addition with three and a half equivalents of 2 M aqueous CAN, and an equal volume of acetonitrile to dissolve the arene. To carry out these experiments different ether linkages (**1**, R₁ & R₃) were chosen based on availability and ease of access.

Chapter 2.2.1 Substrate Synthesis

Table 3 illustrates several substrates that possess different ether linkages at the R₁ position of **1**. It was planned that each of these substrates would be synthesized through a standard displacement reaction as seen in Figure 17. 3-*t*-butyl-4-hydroxyanisole (BHA) was used

as the starting material since it was commercially available. The starting material had a small amount (<5%) of an isomer (2-*t*-butyl-4-hydroxyanisole) present and was not further purified.

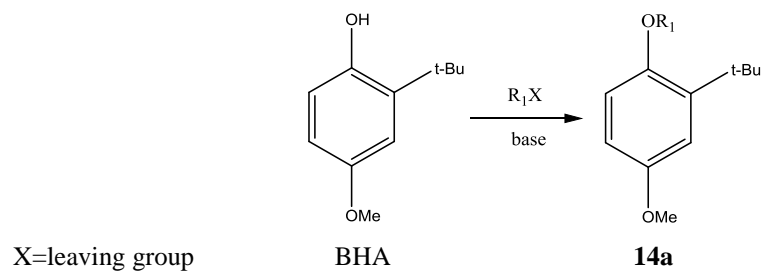
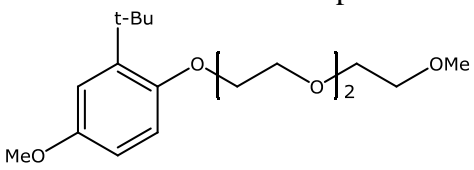
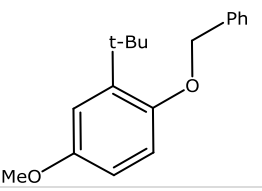
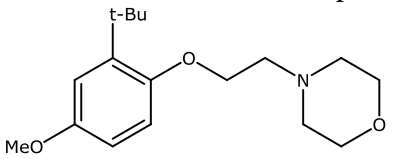
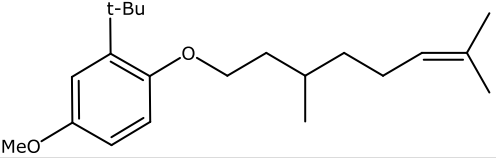
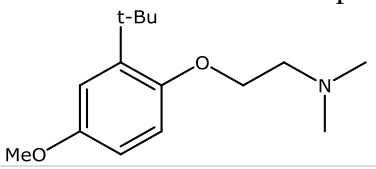
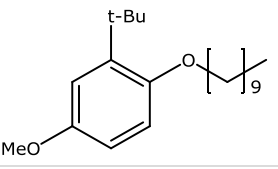
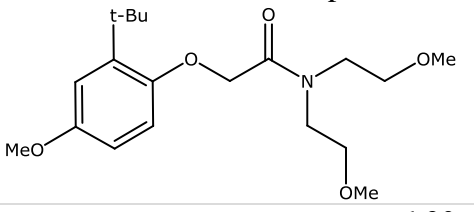
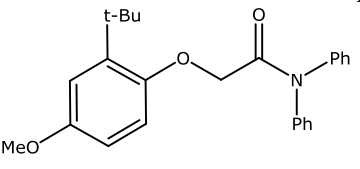
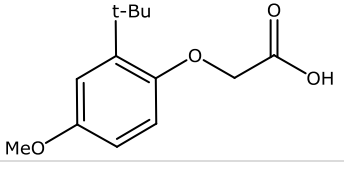
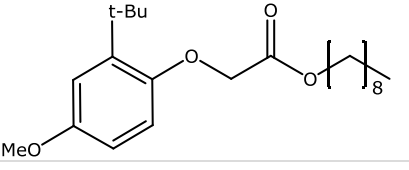
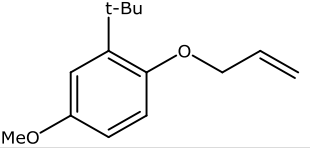


Figure 17 – General Substrate Synthesis for Table 3 Compounds

Table 3 – Planned Substrates (**1**, when R₂: *t*-butyl, R₃: Me)

Entry	Hydrophilic Substrate	Entry	Hydrophobic Substrate
1	<p>compound 19a</p> 	6	<p>compound 15a</p> 
2	<p>compound 18a</p> 	7	<p>compound 27a</p> 
3	<p>compound 22a</p> 	8	<p>compound 23a</p> 
4	<p>compound 26a</p> 	9	<p>compound 24a</p> 
5	<p>compound 20a</p> 	10	<p>compound 21a</p> 
		11	<p>compound 17a</p> 

We sought to find a widely applicable method to synthesize these substrates, with initial investigations centered on the synthesis of compound **15a**. Treatment of BHA with benzyl chloride in THF using potassium *t*-butoxide as the base produced only unreacted starting material and a product impurity after heating at reflux overnight. We hypothesized that the benzyl chloride may not have been reactive enough to undergo this conversion or that there was not complete deprotonation with potassium *t*-butoxide due to the steric hindrance of both *t*-butyl groups in the arene and the base. To allow for complete deprotonation, sodium hydride was tested under dry reaction conditions, but only unreacted starting materials and a trace of the product was isolated. Similarly, we tried the reaction using potassium carbonate in DMF at 50 °C, but the reaction yielded only starting material. We also attempted using benzyl chloride in toluene with a slight excess potassium *t*-butoxide as the base. The solution was heated at reflux overnight and the reaction yielded a complex mixture of products.

In an effort to identify the impurity of the original THF/potassium *t*-butoxide reaction and what other compounds were in the complex mixture of the toluene/potassium *t*-butoxide reaction, a trial study was devised. We were unsure if there were other reactions competing with the alkylation of the phenol, and wanted to further optimize our synthesis to minimize impurity formation.

Two trials allowed the BHA stir while at reflux overnight in the presence of potassium *t*-butoxide, one using toluene as the solvent and the other using THF, both in the absence of any alkylating agent. The flask was open to the air for the duration of the stirring time. The reaction in toluene yielded only dimerized product in ~100% yield, while in THF, there was unreacted starting material and some dimer. Figure 18 show the dimerization of the compounds. We

hypothesized the dimerization is competing with alkylation and a dry nitrogen atmosphere would prevent air oxidation, which would prevent dimerization.

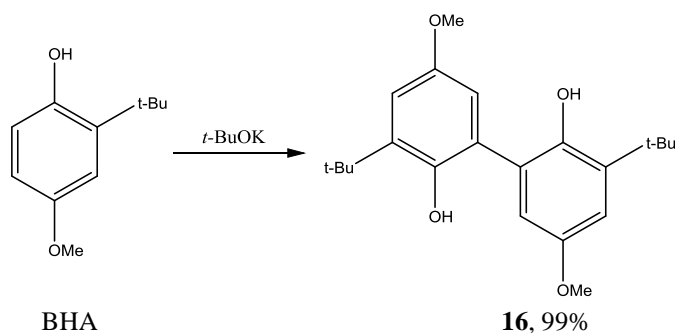


Figure 18 – Dimerization of 3-*t*-butyl-4-hydroxyanisole

We then attempted alkylating BHA using benzyl bromide, in freshly distilled THF. The reaction mixture was allowed to stir at room temperature overnight under with a dry nitrogen atmosphere. The product isolated was the desired alkylated product **15a** in a 99% yield (if pure) with a trace amount of unreacted starting material. When compared with the above reactions where dimer was observed, the absence of oxygen allowed for the alkylation to proceed with no dimer produced. We are not aware of an exact mechanism of how this oxidation/dimerization occurs.

The introduction of other alkyl groups was then explored after a “standard” method was determined. Commercially available alkylating agents, such as 4-(2-chloroethyl)morpholine hydrochloride and allyl bromide were explored first. Using the previous method (Figure 19), **17a** was synthesized in an 88% yield.

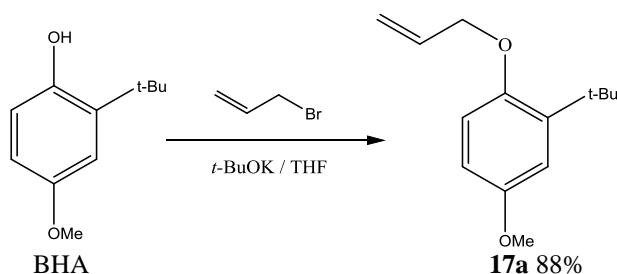


Figure 19 – Synthesis of **17a**

This method was also tested with 4-(2-chloroethyl)morpholine hydrochloride, but failed to yield the desired product **18a**. This was surprising due to the reactive nature of the alkylating agent. In this case, there was still a significant amount of unreacted starting material. Another method was explored using dichloromethane, a phase transfer catalyst (tetrabutylammonium bromide), and concentrated sodium hydroxide (seen in Figure 20). Using BHA with this method (Figure 20) and 4-(2-chloroethyl)morpholine hydrochloride, the product (**18a**) was believed to be isolated in a 87% yield (although this product seemed to degrade quickly). The method was expanded to include benzyl bromide to see if this method was applicable to more nonpolar substrates. **15a** was isolated in a ~100% yield.

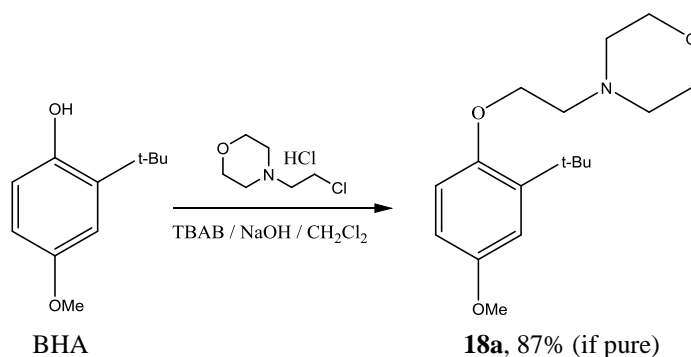


Figure 20 – Alkylation of BHA using Phase Transfer Catalyst

Other alkyl groups were modified with groups that could be easily displaced, such as tosylates or mesylates. Triethylene glycol monomethyl ether tosylate was prepared by allowing tosyl chloride to react with triethylene glycol monomethyl ether in dichloromethane. The tosylate was isolated in an 87% yield. The triethylene glycol monomethyl ether tosylate was then allowed to react with BHA in an attempt to form the alkylated product (**19a**) using the newly developed phase transfer method, however the reaction did not proceed to completion after several days with gentle heating.

Other authors²³ reported success when using a microwave based reaction for the synthesis of aryl ethers. This methodology was adapted for our transformation. The method was initially screened using triethylene glycol monomethyl ether tosylate (seen in Figure 21) and benzyl bromide. BHA was dissolved in DMSO and was deprotonated with potassium *t*-butoxide. The tosylate was then added to the solution and the combined mixture was heated in a microwave reactor for 20 minutes at 70 °C with a maximum power of 150 W. The desired product **19a** was isolated in an 88% yield. Alkylation using benzyl bromide was also tested under similar conditions, allowing this mixture to be heated to 150 °C for 10 minutes, yielding the desired product (**15a**) in an 88% yield.

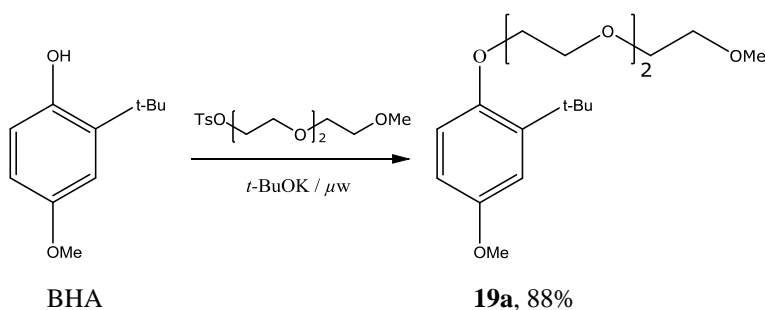


Figure 21 – Alkylation of BHA using Microwave Reaction

Due to the success of the reaction, the method was further optimized using the previously tested alkylating agents (benzyl bromide, Figure 22; and triethylene glycol monomethyl ether tosylate, Figure 23) along with sodium chloroacetate (forming **20a**). Allyl bromide was not tested with this method due to the low boiling point (below 150 °C), which reduced the potential benefit of the microwave synthesis. The optimized method that became our “general method” was to combine one and a half equivalents of potassium *t*-butoxide with one equivalent of BHA and 1.2 equivalents of the alkylating agent in the presence of catalytic amounts of sodium iodide and 4-dimethylaminopyridine. The combined mixture was then heated in a microwave reactor for 20 minutes at 150 °C with a maximum power of 150 W. This method offers clear advantages

over traditional thermally heated reactions, especially decreasing reaction times from overnight to less than half an hour. When the improved method (seen in Figure 24) was applied to the previously tested 4-(2-chloroethyl)morpholine hydrochloride to form **18a**, we discovered the previous product we believed to be **18a**, was actually an unknown product that degraded in the presence of air over several days. We confirmed the identity of **18a** using both ^1H NMR and ^{13}C NMR spectroscopy. The NMR spectra of this product matched the morpholine structure more closely than previous results. The product **18a** was formed with minimal impurities in a 97% yield using the microwave method. Similarly, the sodium chloroacetate derivative (**20a**) was produced in a 55% yield after purification. In all variations of the microwave reaction (Figure 25), there was a small amount of unreacted starting material that contaminated the product. When attempting to make the methyl ester derivative of **20a**, the ester was hydrolyzed and only **20a** was isolated. Since the carboxylic acid would need to be transformed into the corresponding acyl chloride to allow for the formation of the desired ester coupled with the low yield of the carboxylic acid, the product was not further pursued. Treatment of BHA with 1-bromodecane and 2-chloro-*N,N*-dimethylethylamine hydrochloride gave good yields of the desired ethers. Figures 22 through Figure 27 show the substrate syntheses using this method.

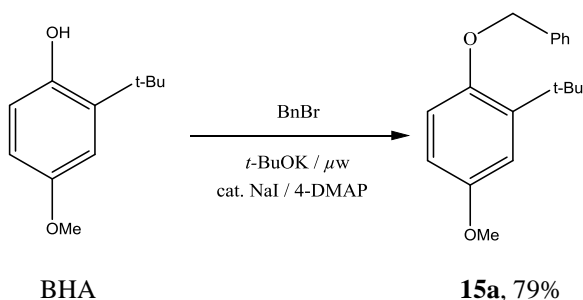


Figure 22 – Microwave Synthesis of 15a

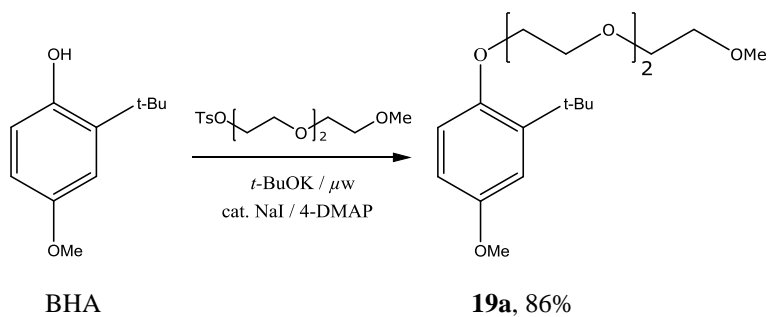


Figure 23 – Microwave Synthesis of 19a

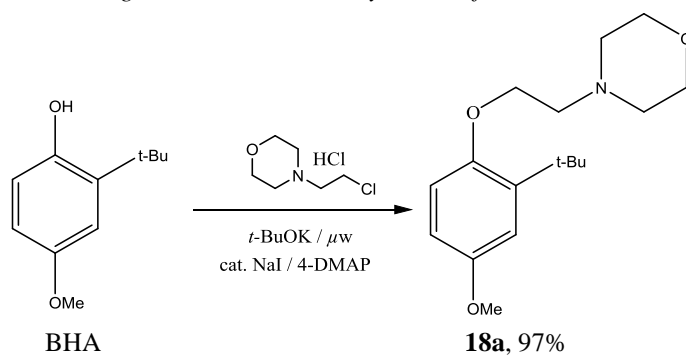


Figure 24 – Microwave Synthesis of 18a

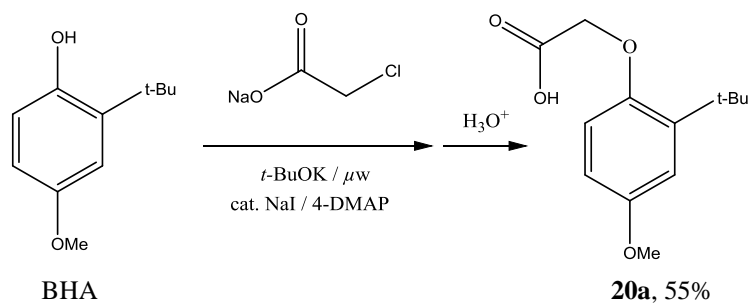


Figure 25 – Microwave Synthesis of 20a

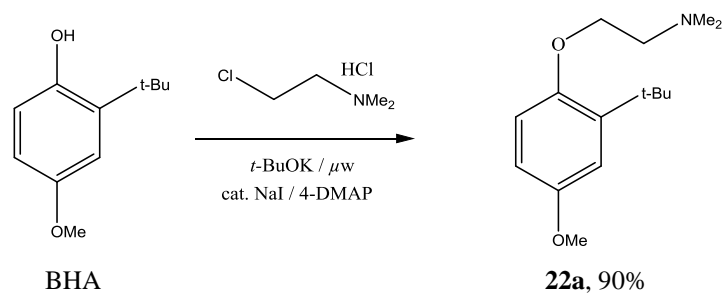


Figure 26 – Microwave Synthesis of 22a

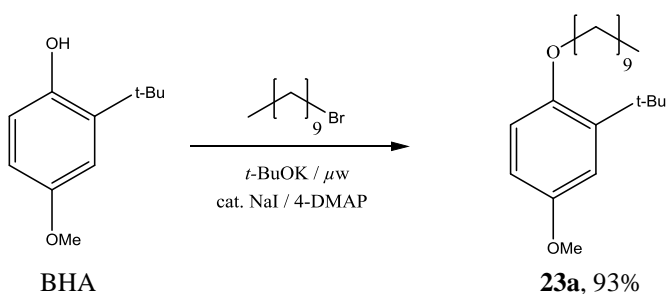


Figure 27 – Microwave Synthesis of 23a

After successfully synthesizing the arenes from commercially available starting materials, we turned our focus to interesting alkylating agents that could be easily synthesized. Three alkylating agents were required to synthesize the remaining substrates planned in Table 3. The diphenyl amide was previously prepared by allowing chloroacetyl chloride to react with diphenylamine. The product was used to form **24a** using the previously described microwave method. However, due to the low yield (35%), the reaction was tested under more traditional conditions (Figure 29). Following the THF/potassium *t*-butoxide method previously described increased the yield to 66%.

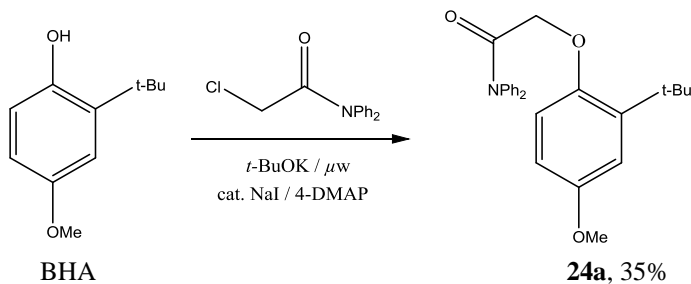


Figure 28 – Microwave Synthesis of 24a

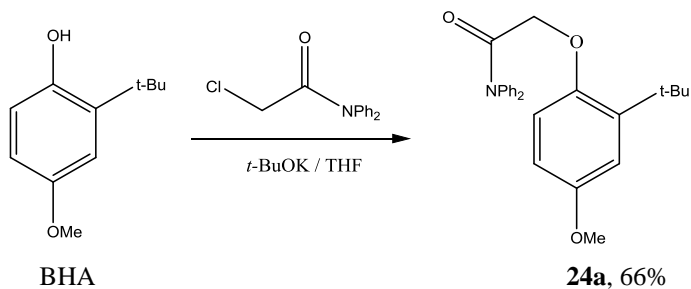


Figure 29 – Traditional Synthesis of 24a

Following the previous amide formation method, chloroacetyl chloride was combined with bis-(2-methoxyethyl)amine to form the corresponding amide (**25**). The microwave reaction method allowed for formation of **26a** in 77% yield (Figure 30). To synthesize the β -citronellol derivative (**27a**), β -citronellol was treated with tosyl chloride anticipating the tosylated β -citronellol to be formed similar to the tosylation of the triethylene glycol monomethyl ether. However, under several different conditions, there was limited formation of the tosylate. Attempts were then made to prepare the iodide by first converting the alcohol to the mesylate (prepared by reaction with mesyl chloride) and then treating with sodium iodide. This reaction produced a mixture of the iodide and the mesylate. It was then determined the mesylate was stable and the iodide was not necessary. The BHA was treated with β -citronellol mesylate under the standard microwave conditions forming **27a** in an 84% yield.

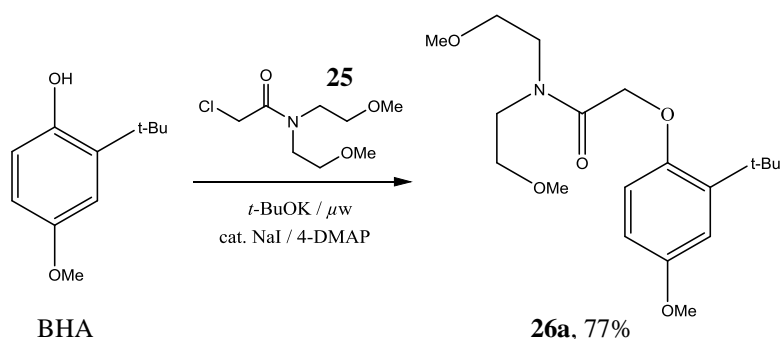


Figure 30 – Microwave Synthesis of **26a**

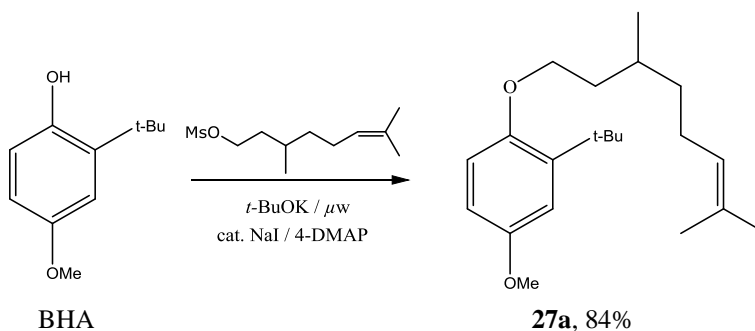


Figure 31 – Microwave Synthesis of **27a**

The next objective was to form **29** as seen in Figure 32. It was of particular interest to be able to compare substrates derived from **29** with those derived from BHA, as it was already known that under conditions where **13a** produced an almost equal mixture of monoquinone and diquinone, that **1b** (R₁, & R₃: Me) produced mostly diquinone. Literature²⁴ suggested **29** could be produced through selective monomethylation of methyl hydroquinone (**28b**) using concentrated sulfuric acid, catalytic sodium nitrite, and methanol. This was an attractive avenue to synthesize the starting anisole (**29**) due to the commercial availability of the starting material (**28b**). Gambarotti *et al.*²⁴ suggested a radical based reaction that allows for the selective monomethylation, however, were not aware of a proven mechanism for this reaction. When using this reaction, we were able to generate the methylated hydroquinone (**29**) in a 91% yield with less than 10% of the other isomer (as determined by ¹H NMR).

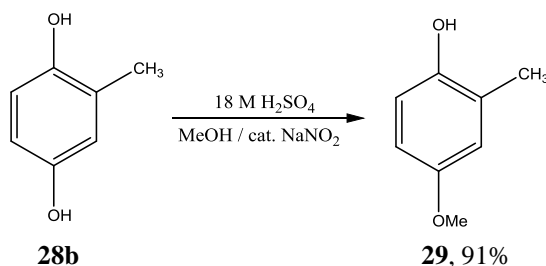
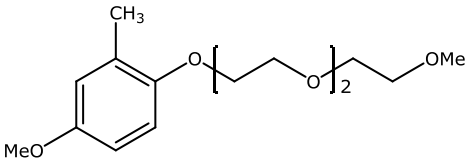
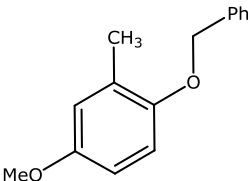
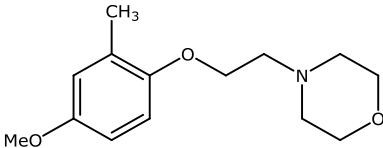
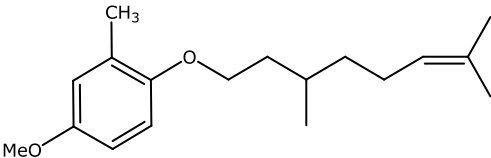
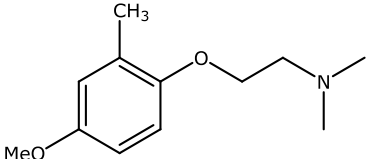
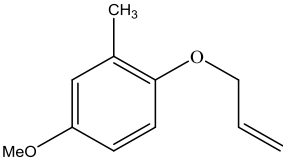
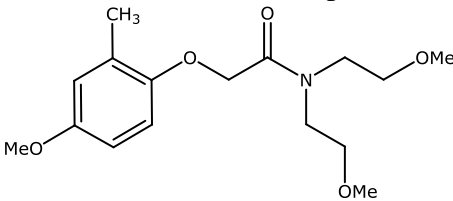
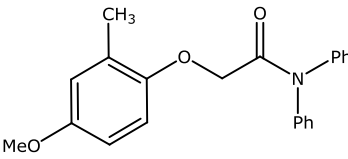
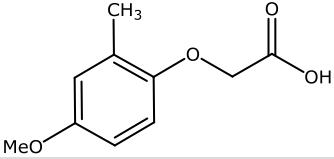


Figure 32 – Synthesis of 4-methoxy-2-methylphenol

The methodology developed using the microwave reactor was used to synthesize derivatives of **29** (product yields of such reactions are given in Table 4).

Table 4 – Synthesized Substrates (**1**, when R₂ & R₃: Me) using Standard Microwave Method

Hydrophilic Substrate	Yield (%)	Hydrophobic Substrate	Yield (%)
<p>compound 19b</p> 	90% if pure	<p>compound 15b</p> 	69%
<p>compound 18b</p> 	64%	<p>compound 27b</p> 	36%
<p>compound 22b</p> 	69%	<p>compound 17b</p> 	81%*
<p>compound 26b</p> 	58%	<p>compound 24b</p> 	35%*
<p>compound 20b</p> 	55% if pure	*made using standard THF method	

Not only was this method applicable to alkylate phenols, we extended the work to alkylate hydroquinones. We were interested in learning how changing both ether linkages could affect the monoquinone to diquinone ratio upon CAN oxidation as well as only modifying one alkoxy group. The synthesized hydroquinone derivatives are shown in Tables 5 and 6.

Table 5 – Synthesized Substrates (**1a**) using Standard Microwave Method

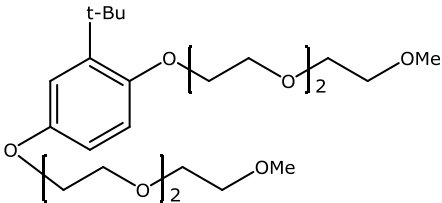
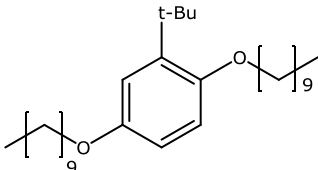
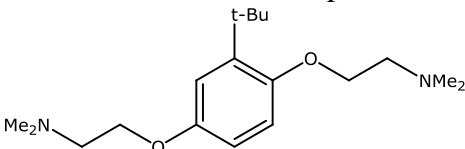
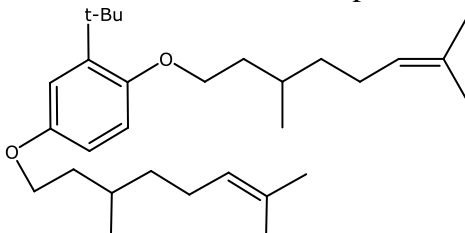
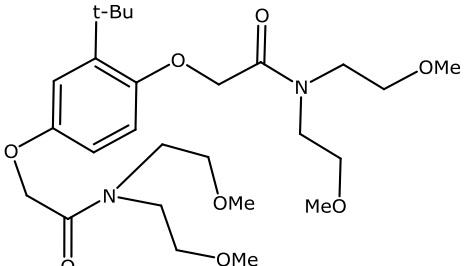
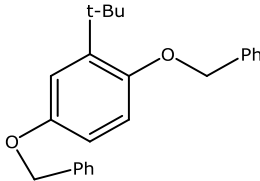
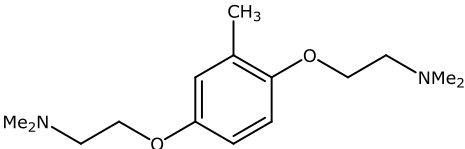
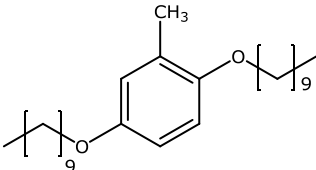
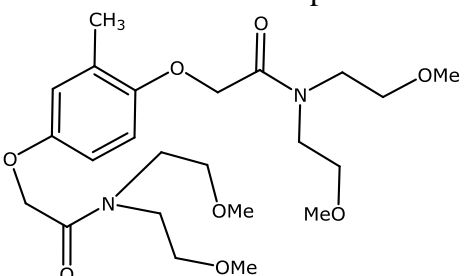
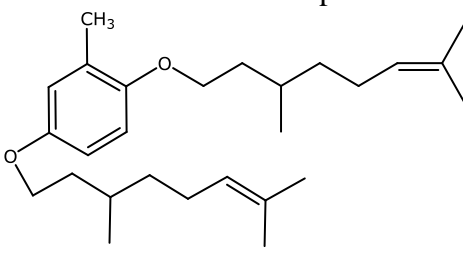
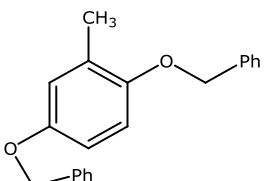
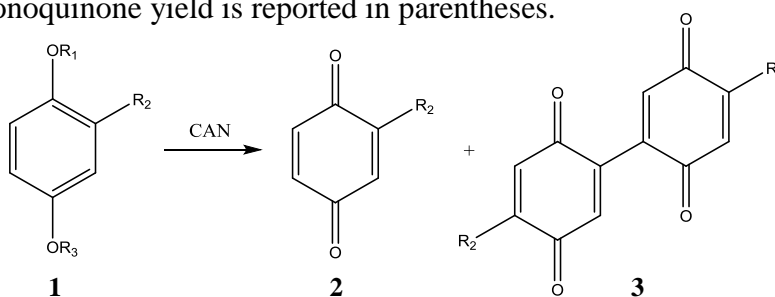
Hydrophilic Substrate	Yield (%)	Hydrophobic Substrate	Yield (%)
<p>compound 30a</p> 	50	<p>compound 31a</p> 	85%
<p>compound 32a</p> 	75%	<p>compound 33a</p> 	73%
<p>compound 34a</p> 	78%	<p>compound 35a</p> 	88%

Table 6 – Synthesized Substrates (**1b**) using Standard Microwave Method

Hydrophilic Substrate	Yield (%)	Hydrophobic Substrate	Yield (%)
<p>compound 32b</p> 	75%	<p>compound 31b</p> 	73%
<p>compound 34a</p> 	20%	<p>compound 33b</p> 	51%
		<p>compound 35b</p> 	80%

Chapter 2.3 Oxidation of Substrates

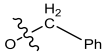
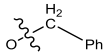
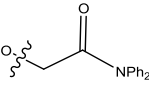
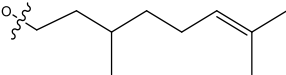
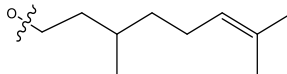
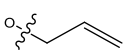
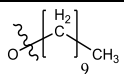
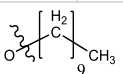
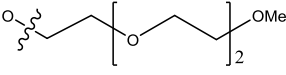
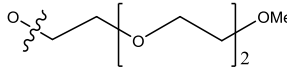
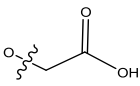
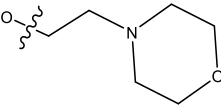
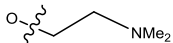
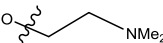
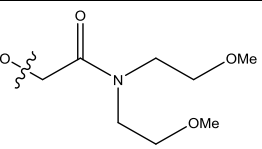
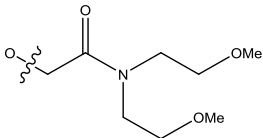
As previously described, the hydroquinone dialkyl ether substrates were then oxidized using the standard CAN method. Table 7 depicts the product outcomes. Diquinones were typically isolated in relatively pure form. If the monoquinone was likewise isolated in relatively pure form, the monoquinone yield is reported in parentheses.



R₂: a: *t*-butyl, b: methyl

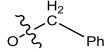
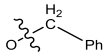
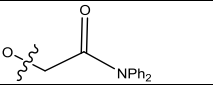
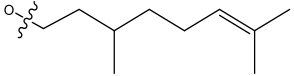
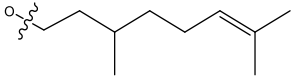
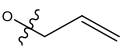
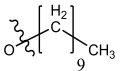
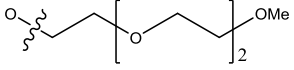
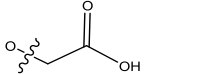
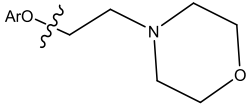
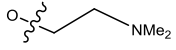
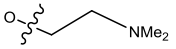
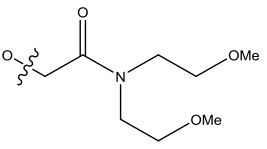
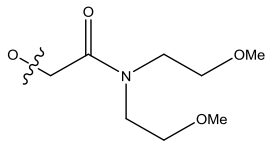
Figure 1 – General Substrate Reaction

Table 7 –Substrates Tested under Standard CAN Conditions (**1a**)

Entry (Compound)	R_1 Group	R_3 Group	R_2 : Me or <i>t</i> -Butyl	DQ Yield %, (MQ Yield, %)
Standard ⁵	Me	Me	<i>t</i> -butyl	46% (12%)
1 (15a)		Me	<i>t</i> -butyl	43%
2 (35a)			<i>t</i> -butyl	18%
3 (24a)		Me	<i>t</i> -butyl	0% (70%)*
4 (27a)		Me	<i>t</i> -butyl	67% (79%) impure
5 (33a)			<i>t</i> -butyl	Complex* mixture
6 (17a)		Me	<i>t</i> -butyl	37% (43% MQ)
7 (23a)		Me	<i>t</i> -butyl	49% *
8 (31a)			<i>t</i> -butyl	12% *
9 (19a)		Me	<i>t</i> -butyl	46% (52%)
10 (30a)			<i>t</i> -butyl	16%
11 (20a)		Me	<i>t</i> -butyl	49% (43%)
12 (18a)		Me	<i>t</i> -butyl	37% (6%)
13 (22a)		Me	<i>t</i> -butyl	61% (0%)
14 (32a)			<i>t</i> -butyl	0% (30%)
15 (26a)		Me	<i>t</i> -butyl	0% (79%)
16 (34a)			<i>t</i> -butyl	0% (55%)

*=THF was added in equal volume as acetonitrile to aid dissolution

Table 8 –Substrates Tested under Standard CAN Conditions (**1b**)

Entry (Compound)	R_1 Group	R_3 Group	R_2 : Me or <i>t</i> -Butyl	DQ Yield %, (MQ Yield, %)
Standard ⁵	Me	Me	Me	91%
1 (15b)		Me	Me	57%
2 (35b)			Me	33%
3 (24b)		Me	Me	~53% (impure)
4 (27b)		Me	Me	Complex mixture
5 (33b)			Me	Complex mixture
6 (17b)		Me	Me	74% (8% MQ)
7 (31b)			Me	66% *
8 (30b)		Me	Me	25%
9 (20b)		Me	Me	49%
10 (18b)		Me	Me	66%
11 (22b)		Me	Me	74% (0%)
12 (32b)			Me	29% (41%)
13 (26b)		Me	Me	25% (0%)
14 (34b)			Me	0% (58%)

*=THF was added in equal volume as acetonitrile to aid dissolution

Based on our hypothesis, the polar substrates (Table 7, entries 9-16) should yield primarily monoquinone and the nonpolar substrates (Table 7, entries 1-8) should form mostly diquinone. Similarly, we hypothesized there would be similar trends with the substrates shown in Table 8. However, this was not the case. The substrate with two benzyl groups, (**35a**, Table 7, entry 2) showed a sharp decrease in diquinone formation from the “standard”. In the monobenzyl substrate (**15a**, Table 7, entry 1), there was slight decrease from the “standard” as well. We were curious if there was a partial oxidation of the resulting benzyl alcohol produced from oxidative dealkylation. However, the yield of diquinone did not change when using eight equivalents of CAN, so we concluded this oxidation was not competing with quinone formation.

Also, interestingly the nonpolar diphenyl amide (**24a**, Table 7, entry 3) only formed monoquinone. The more polar substrates also did not follow the hypothesis, with the polyoxygenated chain (**19a**, Table 7, entry 9) showing no decrease in diquinone formation. The other polar substrates were similar, forming moderate yields of diquinone. The substrates in Table 8 also did not follow the hypothesis, generally decreasing diquinone yields with all substrates. Typically, in each of these tests, when the R₂ group was methyl, there was a higher percentage of diquinone formed. It is also noteworthy that all of the dialkylated substrates produced lower yields of diquinone than the “standard” whether the substrate was more or less polar.

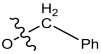
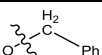
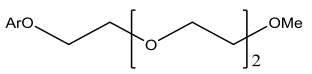
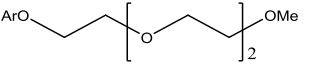
Although we did not see a direct trend as our hypothesis predicted, there were several interesting results. Most of the substrates we chose to explore contained various functional groups that we assumed would not be reactive in the oxidation reaction. The results were very interesting that groups of similar predicted polarity could change the amount of diquinone formed drastically. We saw no formation of diquinone with the amide substrate (**26a**, Table 7,

entry 15) with increased monoquinone formation, which followed our prediction. What was interesting was an increased formation of diquinone with the amine substrate (**22a**, Table 7, entry 13). We saw a similar correlation with the substrates in Table 8. Both of these substrates (amides and amines) based on our hypothesis should have formed primarily monoquinone since they are both polar substrates. However, there is a distinct difference between these substrates where the amines form diquinone and the amides form monoquinone. We hypothesized that the amide could be stabilizing the radical intermediate and making the compound less reactive towards electrophilic aromatic substitution, which will be discussed in more detail in the following chapter.

We were also interested to see if directing/chelating the CAN with other substituents would be possible and if it would increase dimerization. With each of the above substrates there are a large number of groups that could coordinate with the cerium(IV) center. Recent literature²⁵ has suggested that CAN has a self-assembled dimeric cerium core when in acidic solution. This dimeric structure could be of interest since it would allow for two electron oxidation of the arene species. We wondered if somehow preservation of this dimeric cerium(IV) species was significant in diquinone formation, and if a group that could coordinate with cerium(IV) might disrupt the CAN dimer and then lead to greater monoquinone formation.

Previously developed⁵ methods were used in an attempt to increase the yield of monoquinone and diquinone respectively in two select substrates that had moderate success in controlling monoquinone or diquinone formation. The monoquinone method used DMSO as the solvent rather than acetonitrile and the diquinone protocol decreased the aqueous CAN concentration to 1 M. The yields for these trials are shown in Table 9.

Table 9 –Substrates Tested under MQ or DQ CAN Conditions

Entry (Compound)	Method: MQ or DQ Favoring	R ₁ Group	R ₃ Group	R ₂ :Me or <i>t</i> - Butyl	DQ Yield %, (MQ Yield, %)
1 (15a)	DQ		Me	<i>t</i> -butyl	37% (43% MQ)
2 (35a)	DQ			<i>t</i> -butyl	24%
3 (19a)	MQ		Me	<i>t</i> -butyl	0% (84%)
4 (30a)	MQ			<i>t</i> -butyl	0% (trace MQ)

The results of substrate with the single polyoxygenated chain (**19a**, Table 9, entry 3) was of interest due to the diquinone yield dropped to zero percent and monoquinone formation drastically increased. When two polyoxygentated chains were present however, the reaction produced a complex mixture where partially oxidized species were present. In the case of the benzyl substrates (**15a** & **35a**, Table 9, entries 1 & 2), the monobenzylated substrate actually gave a slightly lower yield of diquinone under these conditions compared to the standard conditions (37% versus 43%), whereas the dibenzylated substrate gave a slightly higher yield of diquinone (24% versus 18%).

Based on the data there seems to be little evidence to support the idea that solubility is a major influencing factor in controlling the monoquinone to diquinone product ratio. This lead us to believe there were other factors that could be impacting the amount of diquinone formed more directly.

Chapter 3: Chelation and Stabilization Effects on Dimer Formation

When comparing amide substrates with amine substrates (**22** versus **26**, Table 7, entry 13 versus 15 & Table 8, entry 11 versus 13) we noticed substrates with amide substituents tended to form much more monoquinone and that those with amines produced primarily diquinone. Diquinone yield went to almost zero percent in the amides and monoquinone formation increased to 61-74% yield. One possible explanation for this was that the amide could be stabilizing the radical cationic intermediate and making the compound less reactive towards electrophilic aromatic substitution.

Due to large partial negative charge on the oxygen in the amide, we believe there could be an intramolecular intermediate stabilization as seen in Figure 33. We hypothesize this intermediate helps stabilize the radical cation, especially when the arene is hindered, causing less diquinone to be formed. The stabilization of the intermediate would make it less electrophilic and less prone to electrophilic aromatic substitution, allowing for more monoquinone to be formed. In the case of the diphenyl amide, (**24**, Table 7, entry 3 and Table 8, entry 3) it was observed the larger alkyl group (*t*-butyl versus methyl) produced more monoquinone, suggesting there may be still be additional factors that influence the monoquinone to diquinone product ratio.

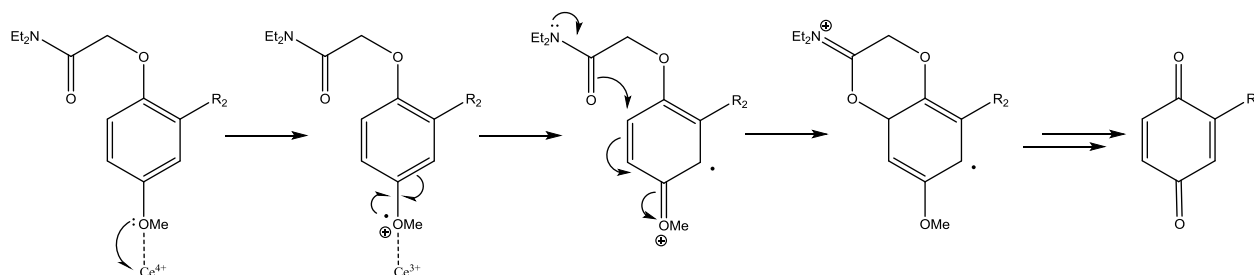


Figure 33 – Six-Membered Amide Stabilized CAN Reaction

Another possible explanation for the greater monoquinone formation using amide-containing alkoxy groups was that these groups could be interacting with the cerium(IV) center of CAN. We were interested if chelating the CAN with other substituents (e.g. with alcohols) would increase or decrease dimerization.

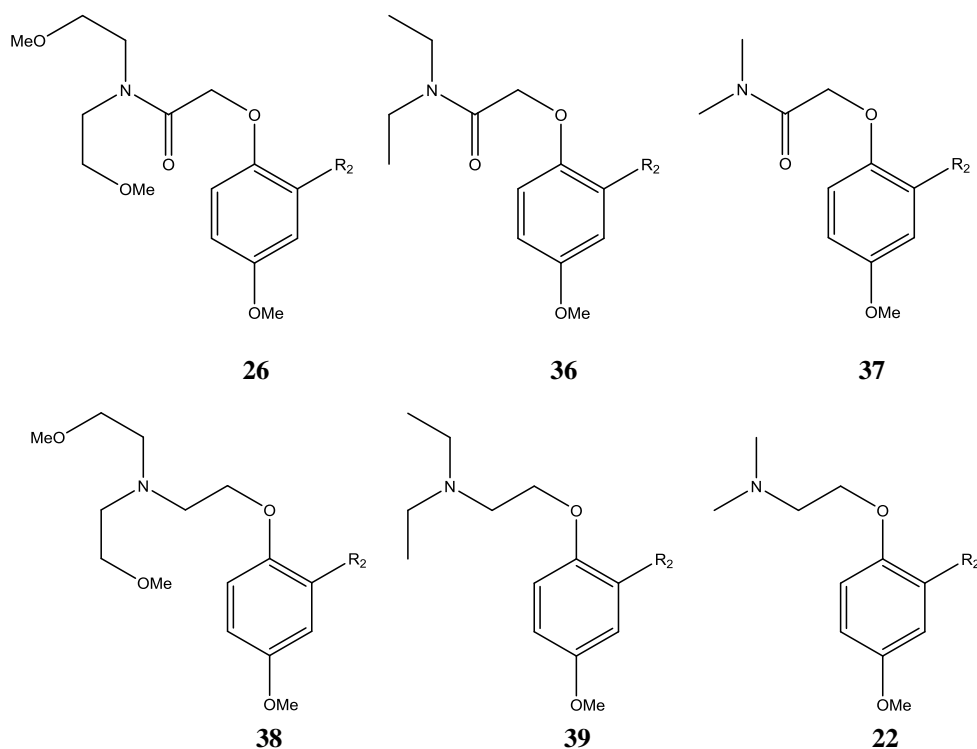
Recent literature²⁵ has suggested that CAN has a self-assembled dimeric cerium core when in acidic solution. It is plausible that this dimeric structure could be interacting with the arene in a different way than previously understood. This dimeric structure could be of interest since it would allow for two electron oxidation of the arene species. If there is a group that can coordinate with the dimeric cerium or the single cerium by chelation, it was of interest to determine if this coordination was altering diquinone formation.

Chapter 3.1 Experimental Design

As previously noted, amine substrates (**22**; Table 7, entry 13 & Table 8, entry 11) produce mostly diquinone upon treatment with CAN, whereas amide substrates (**26**; Table 7, entry 15 & Table 8, entry 13) produce either entirely monoquinone, (in the case of the **26a**) or greatly reduced yields of diquinone (in the case **26b**). There were two key differences though, in the structures of the alkoxy groups of these two pairs of compounds (**26** versus **22**). **26** not only contains an amide functional group in comparison to **22**, but also contains methoxy groups which might increase the amount of interaction between the substrate and the cerium (IV) center.

We were curious if there was a single functional difference between **26** and **22** that caused the large change in diquinone formation. We decided a systematic study of a set of substrates that changed only a single functional group at a time, would help determine if the functionality caused the increased monoquinone yields of **26**. To test if the methoxy groups on **26** were in fact altering the product yield, we designed substrate **36** to have the amide

functionality, without the methoxy groups. We also wanted to determine if the amide functionality was the major influencing factor rather than the methoxy groups, so we designed compound **38**. Further testing our theory, we designed **39** and **37** to compare with previously tested **22** to give a direct comparison between the alkyl groups. This allowed a full panel of substrates that ranged in amine to amide functionality, along with substrates that contained or did not contain methoxy groups (as seen in Figure 34).



R₂: a: *t*-butyl, b: methyl

Figure 34 – Variations on Amine and Amide Containing Substrates

Another set of experiments was also designed to determine if a good chelating group would alter the amount of diquinone produced. These substrates (**40** and **41**, in Figure 35) were designed to have lone pairs of electrons that would allow for direct coordination with CAN. Additionally, we were interested in using commercially available reagents to introduce such groups. **42** was used as a substrate that was highly polar, but could not chelate with CAN in the

inner coordination sphere, since it has no available lone pairs on the nitrogen. Preparation of **42** would also allow us to investigate another possible explanation for the noticeable difference in the reactivity of amine-bearing substrates and amide-bearing substrates. As CAN oxidation proceeds, the reaction mixture becomes increasingly acidic. Under such conditions, the amine sidechains are likely to be protonated, whereas the less basic amides are not. We thought that the presence or absence of these cationic sidechains might be influencing the monoquinone to diquinone product ratio.

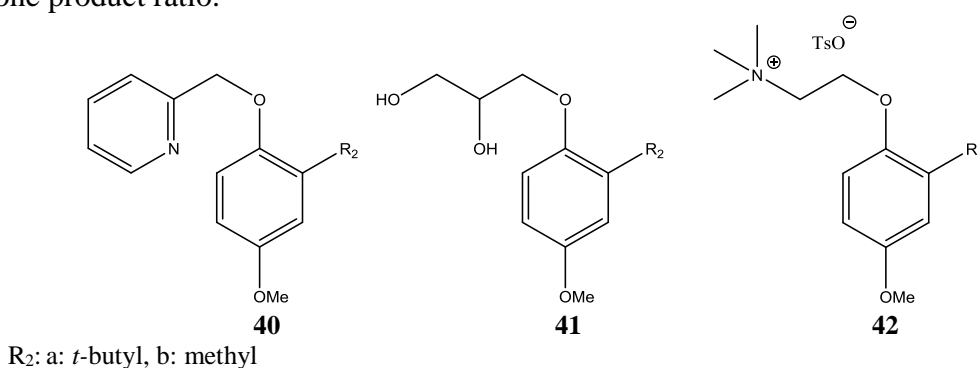


Figure 35 – Substrates to Chelate CAN

Chapter 3.1.1 Substrate Synthesis

The synthesis of substrates **26** and **22** was discussed previously in chapter two. The alkylating agent necessary for the preparation of **39** was commercially available, however, those needed for the preparation of **36** and **37** were not commercially available.

Synthesis of the desired dimethylamide **43** began with 40% aqueous dimethylamine combined with chloroacetyl chloride (as seen in Figure 36). The reaction of these compounds produced the desired amide as well as an unknown compound. The product mixture was washed with 1 M sodium hydroxide and yielded the product **43** in a 14% yield with a trace amount of the impurity. We believed there was a large portion of the product lost during the workup/purification step of the reaction.

In a separate attempt to synthesize the product **43**, we attempted to continuously extract the product from the reaction mixture. A mixture of dichloromethane and aqueous sodium hydroxide was added to the reaction mixture. The continuous extraction of the reaction mixture yielded a complex mixture and no desired product was isolated. We further attempted this transformation by using 2 M dimethylamine in THF rather than using aqueous dimethylamine. Only hydrolyzed starting material was isolated from the reaction.

Interestingly, when using diethyl amine rather than dimethyl amine, the amide **44** was formed in 81% yield. We believe the aqueous solution of the dimethylamine allows for competing side reactions that produce the unknown impurity in the reaction whereas in the reaction with diethylamine, no impurity was found. **43** was not used as an alkylating agent due to the low yield and impure form of the product obtained.

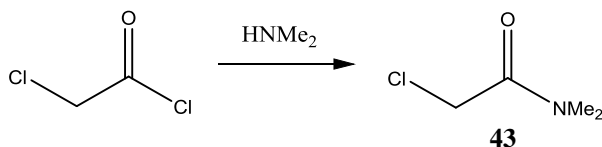


Figure 36 – Synthesis of **43**

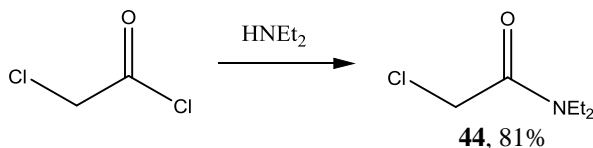


Figure 37 – Synthesis of **44**

With the successful preparation of the diethylamide **44**, we planned to prepare the amine starting materials that were not commercially available. We first attempted to reduce amide **45** to the amine **46** through an *in situ* borane reduction²⁶ using iodine and sodium borohydride. The reduction resulted in a complex mixture. Rather than try to find other methods to reduce **45** to **46**, we used previously synthesized **26** to synthesize **38** using LAH. The reduction unfortunately yielded a mixture of unknown compound and unreacted starting material. We applied the

previous *in situ* borane reduction method to the synthesis of **38** and found after purification **38a** was produced in 53% yield and **38b** was produced in 44% yield.

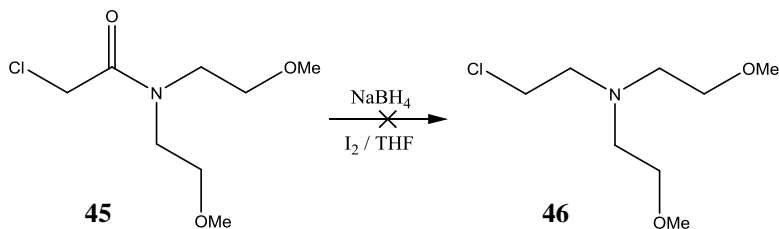
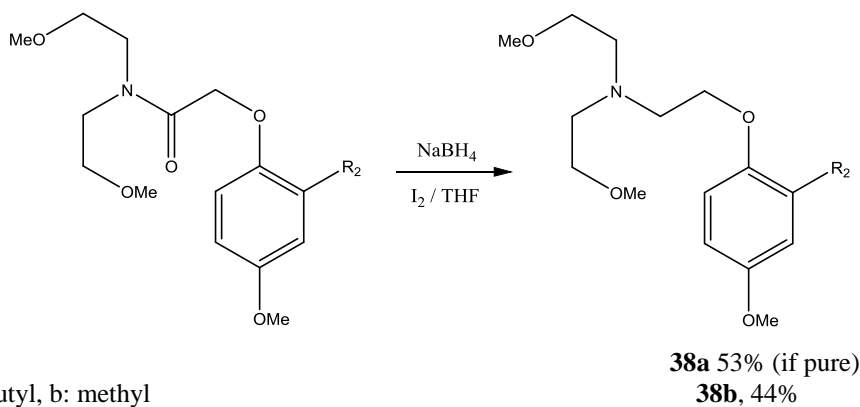


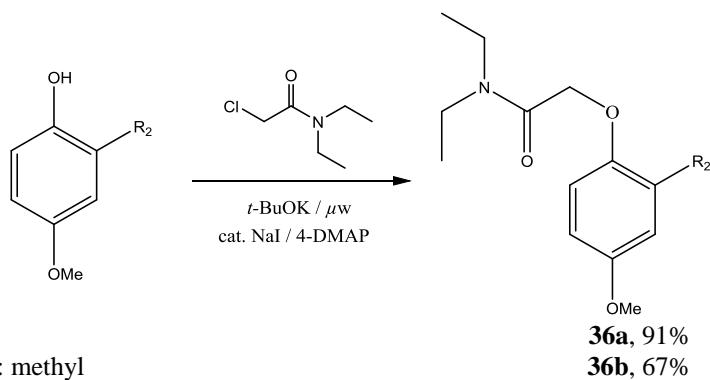
Figure 38 – Synthesis of **46**



R₂: a: *t*-butyl, b: methyl

Figure 39 – Synthesis of **38**

Using previously developed methodology,²³ **36** and **39** were synthesized using potassium *t*-butoxide with catalytic amounts of sodium iodide and 4-dimethylaminopyridine in a microwave reactor as seen in Figures 40 and 41.



R₂: a: *t*-butyl, b: methyl

Figure 40 – Microwave Synthesis of **36**

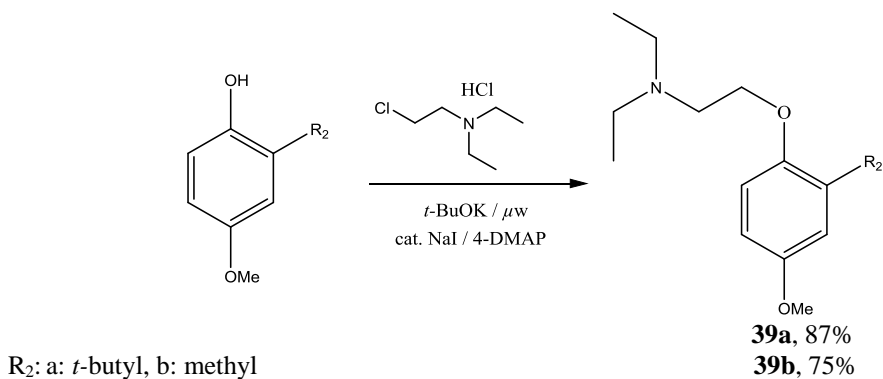


Figure 41 – Microwave Synthesis of **39**

With the successful completion of the amine/amide derivatives, our focus shifted to the preparation of chelating substrates. **40** was synthesized using the previously described microwave method²³ using 2-picolyl chloride hydrochloride as the alkylating agent as seen in Figure 42.

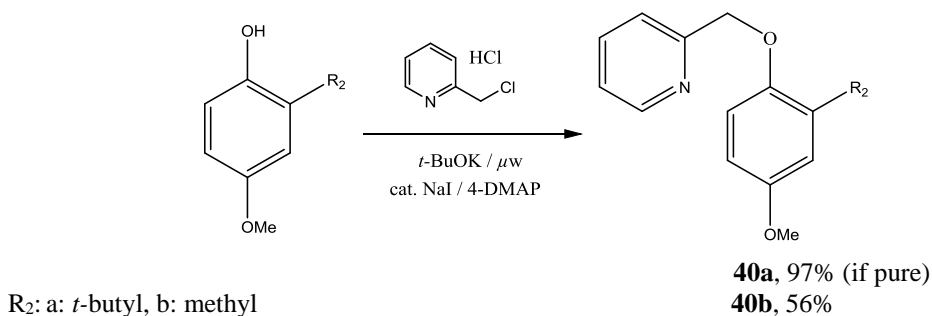


Figure 42 – Synthesis of **40**

Due to the low boiling point of epichlorohydrin (below 150 °C) the standard microwave synthesis was not used for the synthesis of **41**, similar to the previous synthesis using allyl bromide. Instead, a more traditional THF protocol as previously described was used to form **41** (seen in Figure 43). Due to the reactivity, we discovered the epoxide from the epichlorohydrin was converted to the diol **41** under standard workup conditions.

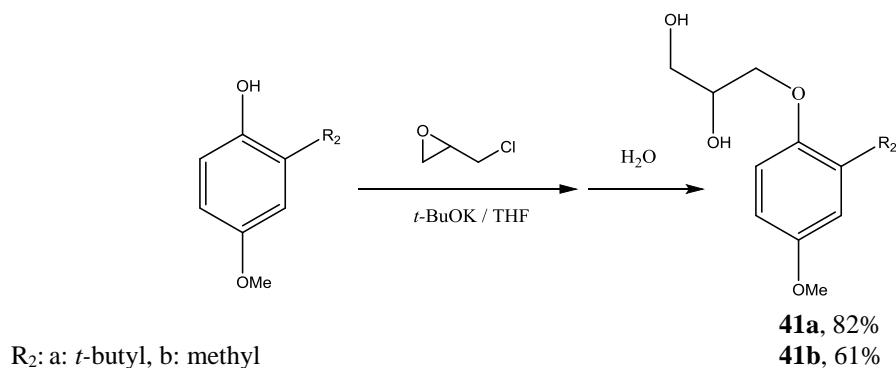


Figure 43 – Synthesis of **41**

The substrate **42** was synthesized by methylating previously prepared **22** with methyl tosylate (seen in Figure 44). Methyl tosylate was chosen over other methylating agents since the counter ion would not be oxidized when tested in CAN studies.

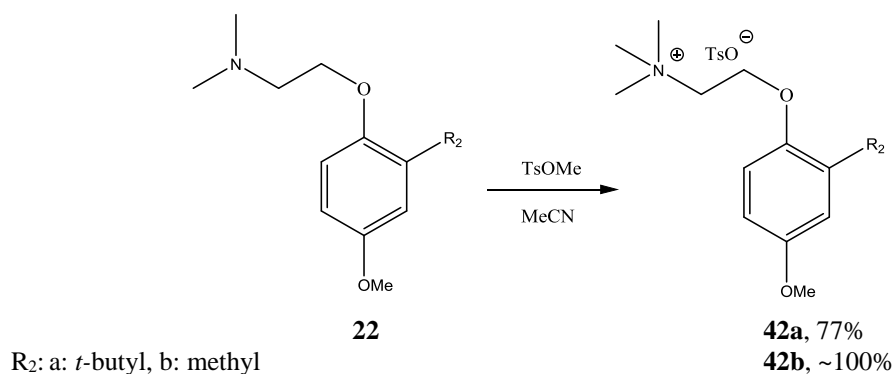
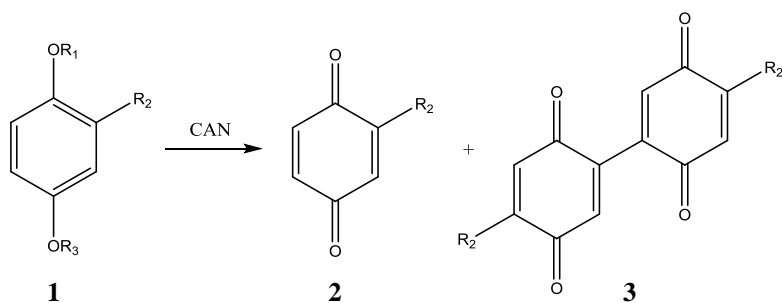


Figure 44 – Synthesis of **42**

Chapter 3.2 CAN Studies

The substrate testing began with the standard protocol described in chapter two. Tables 10 & 11 show the results for the amide/amine trials. Based on our hypothesis that amides were stabilizing the radical cationic intermediate of the oxidation reaction, these substrates should give primarily monoquinone, and the amine substrates should give primarily diquinone.



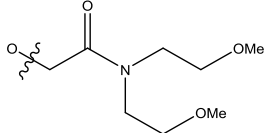
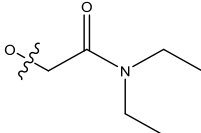
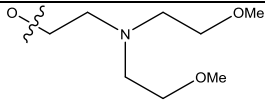
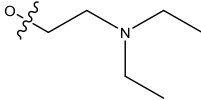
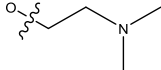
R_2 : a: *t*-butyl, b: methyl

Figure 1 – General Substrate Reaction

Table 10 –Substrates Tested for Chelation or Stabilization Effects (**1a**)

Entry (Compound)	R_1 Group	R_3 Group	R_2 : Me or <i>t</i> -Butyl	DQ Yield %, (MQ Yield, %)
Standard ⁵	Me	Me	<i>t</i> -butyl	46% (12%)
1 (26a)		Me	<i>t</i> -butyl	0% (79% MQ)
2 (36a)		Me	<i>t</i> -butyl	0% (74% MQ)
3 (38a)		Me	<i>t</i> -butyl	37%
4 (39a)		Me	<i>t</i> -butyl	37%
5 (22a)		Me	<i>t</i> -butyl	61% (0% MQ)

Table 11 –Substrates Tested for Chelation or Stabilization Effects (**1b**)

Entry	<i>R</i> ₁ Group	<i>R</i> ₃ Group	<i>R</i> ₂ :Me or <i>t</i> -Butyl	DQ Yield %, (MQ Yield, %)
Standard ⁵	Me	Me	Me	91%
1 (26b)		Me	Me	25% (0% MQ)
2 (36b)		Me	Me	4% (53% MQ)
3 (38b)		Me	Me	74%
4 (39b)		Me	Me	65%
5 (22b)		Me	Me	74% (0% MQ)

The results from these trials were very interesting, showing a decline in diquinone formation in the amide trials, but diquinone formation remained high for the amines. When comparing the amides with methoxy groups (**26**, Tables 10 & 11, entry 1) to the amides without methoxy groups (**36**, Tables 10 & 11, entry 2), there was some change in diquinone yield. There was little difference in diquinone yield from the amines with methoxy groups (**38**, Tables 10 & 11, entry 3), to amines without methoxy groups (**39**, Tables 10 & 11, entry 4). Based on these results, the methoxy groups did not appear to have a large effect on the amount of diquinone formed.

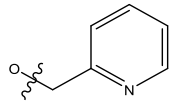
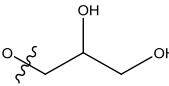
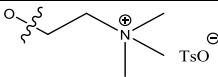
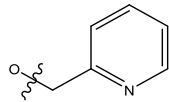
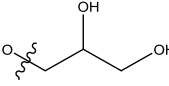
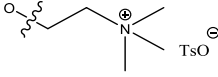
The largest difference in diquinone yield was between the amides (**26** & **36**, Tables 10 & 11, entries 1 & 2) and their respective amines (**38** & **39**, Tables 10 & 11, entries 3 & 4). It is clear the amide functionality is a major influencing factor in formation of monoquinone in this reaction set. Interestingly, there was a difference between the diethylamine substrate (**39**, Tables

10 & 11, entry 4) and the dimethylamine substrate (**22**, Tables 10 & 11, entry 5). We are unsure why these amine substrates have a noticeable difference in diquinone yield, and believe further investigations are necessary.

The results argue against chelation of the methoxy groups with the cerium(IV) center of CAN being a significant effect. However, the data is consistent with the stabilization of the radical cationic intermediate by the carbonyl group, since there is a large effect on the amount of monoquinone and diquinone produced when comparing amine versus amide substrates. Further studies are needed to support this hypothesis and are planned for the future.

To further rule out that chelation was significantly impacting the amount of diquinone formed, we tested substrates **40**, **41**, and **42**, under standard conditions. The first two compounds possessed lone pairs that could chelate with the CAN. Table 12 shows the data collected from these studies.

Table 12 –Substrates Tested for Chelation

Entry (Compound)	R_1 Group	R_3 Group	R_2 : Me or <i>t</i> -Butyl	DQ Yield %, (MQ Yield, %)
Standard ⁵	Me	Me	<i>t</i> -butyl	46% (12%)
1 (40a)		Me	<i>t</i> -butyl	Unknown solid
2 (41a)		Me	<i>t</i> -butyl	52% (39% MQ)
3 (42a)		Me	<i>t</i> -butyl	54% *
Standard ⁵	Me	Me	Me	91%
4 (40b)		Me	Me	Unknown solid
5 (41b)		Me	Me	87% (15% MQ)
6 (42b)		Me	Me	65% *

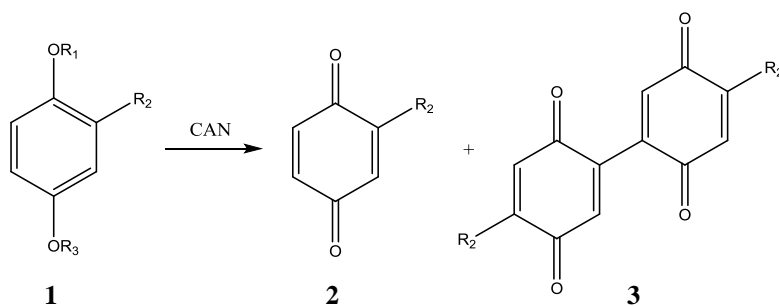
*=Water was used to dissolve the arene rather than acetonitrile

The results from the chelation studies show little to no chelation effect on the amount of dimerization occurring. In both of the pyridine substrates (**40**, Table 12, entries 1 & 4), the product isolated was a solid insoluble in organic solvents with no diquinone or monoquinone detected (by ¹H NMR). Further characterization of these products is necessary to determine how the product was oxidized. Results for the diol-bearing substrates (**41**, Table 12, entries 2 & 5) were similar to those obtained for the corresponding dimethoxybenzene (Table 12, “standards”). No remarkable effects were observed for the quaternary ammonium salts (**42**, Table 12, entries 3 & 6), except that the diquinone yield for the methyl substrate was lower than the standard (Table 12, standard versus entry 6).

Based on the data, if chelation is occurring, this interaction does not change the amount of diquinone formed. It is more likely that stabilizing the intermediate (Figure 33) is occurring in these reactions, which is supported by the interesting shift towards monoquinone in the amide substrates. Further work with amide stabilization and the correlation to higher monoquinone yields would be of interest.

Chapter 4: Micelle Effects on Dimer Formation

Previously, we tested substrate solubility (Figure 1) by modifying (from a methoxy group) a single alkyl group (R_1) or by changing both alkyl groups symmetrically ($R_1=R_3$). We were curious if there was a significantly polar alkyl group and a nonpolar arene system ($R_1 \neq R_3$), if self-aggregation (similar to micelle formation) would increase dimer formation. We were interested in studying how the product ratios would change in these surfactant-like compounds. We were also curious if simply adding a surfactant, like sodium dodecyl sulfate (SDS), would promote aggregation and allow for increased dimer formation. Similar to previous studies, we believed the aggregation of these compounds would allow for more dimer formation due to the close proximity of the electron dense arene and the radical cationic intermediate.



R_2 : a: *t*-butyl, b: methyl

Figure 1 – General Substrate Reaction

Chapter 4.1 Experimental Design

To test this method, substrates that could potentially form micellar aggregates were designed. Testing these substrates under the standard conditions was important to be able to compare this micellar aggregation to solubility effects investigated with the other previously tested substrates. The desired substrates (**47** and **48**) have both polar and nonpolar chains, and can aggregate as seen in Figure 45. Surfactants such as SDS have a low critical micelle concentration (CMC, the concentration threshold where micelles begin to form in solution) and

are similar in structure to the desired substrates **47** and **48**. This low CMC of SDS (8.2 mM in water²⁷) lead us to believe that our substrate should form micelles at the much higher 0.5 M concentration, under standard CAN oxidation conditions.

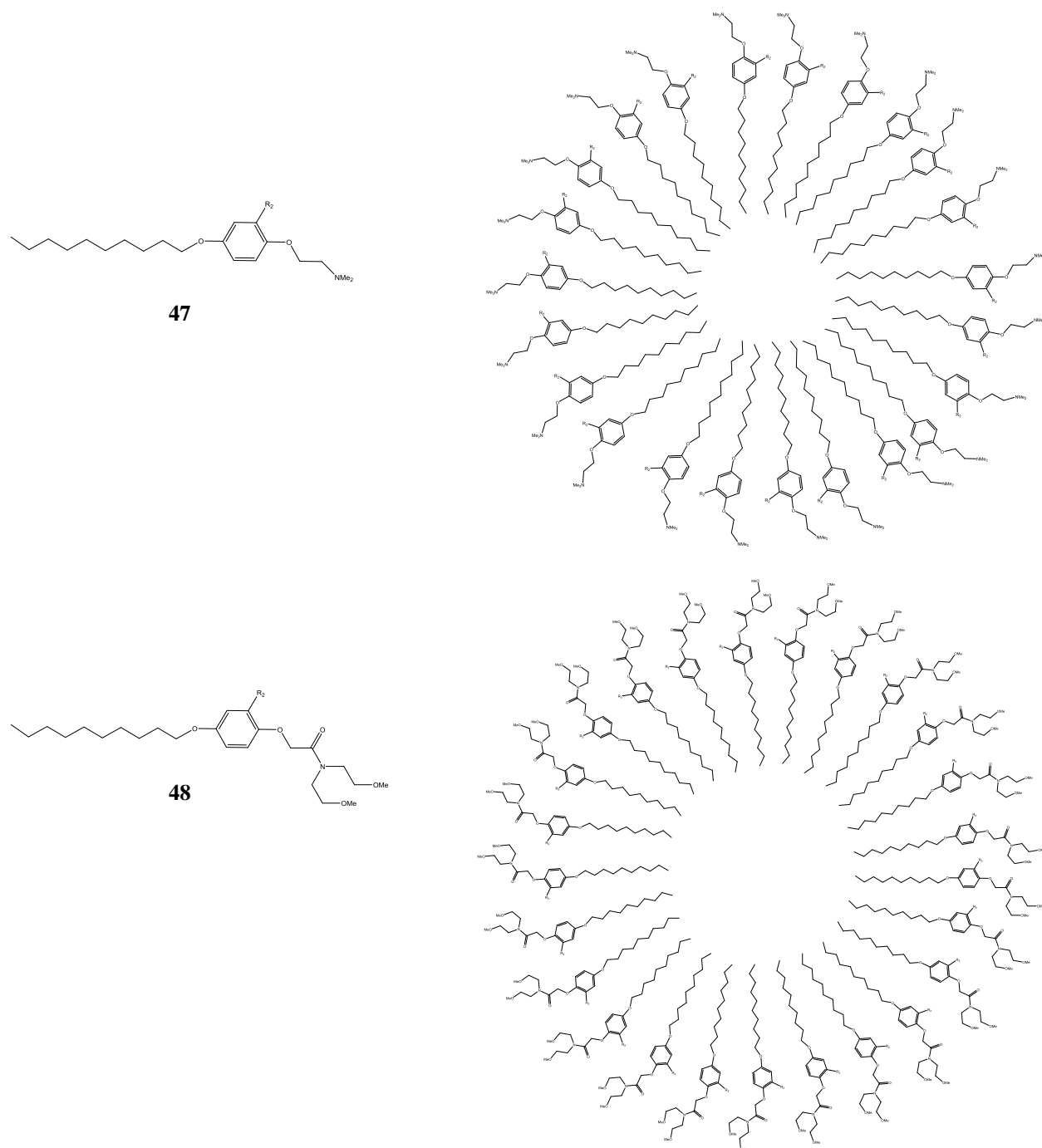


Figure 45 – Surfactant-like Substrates

The use of a surfactant was also of interest to determine if aggregation of previous substrate **13a** inside the micelle would increase dimer formation. We were curious if an all aqueous solvent system in the presence of different concentrations of SDS would allow for more dimerization. Figure 46 illustrates the aggregation of **13a** in the SDS micelle. This method would allow for the arene and radical cationic intermediate to be in close proximity similarly to the previously discussed surfactant-like substrates.

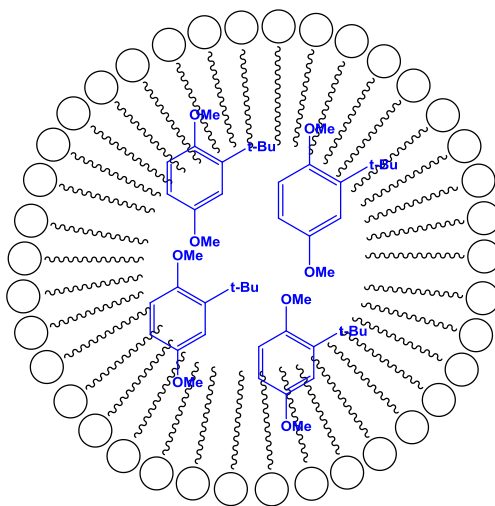


Figure 46 – SDS Micelle Structure

Chapter 4.1.1 Substrate Synthesis

Using a previously discussed literature method²⁴ we were able to mono-methylate methyl hydroquinone (**28b**) to form **29** (as seen in Figure 32). This method was modified to add a longer alkyl chain to methyl hydroquinone. A nonyl chain was able to be added to the arene by using one equivalent of the methyl hydroquinone in a diethyl ether solution combined with two equivalents of 1-nonanol, one equivalent of 18 M sulfuric acid, and a catalytic amount of sodium nitrite (as seen in Figure 47). As seen in the literature precedent, the alkoxy group was introduced preferentially at the less sterically hindered phenolic site. This method was moderately successful on a small scale with *t*-butyl hydroquinone forming only **50** in a 62%

yield. A mixture of monoalkylated isomers (alkylation at either hydroxyl) was isolated when scaling up the reaction (greater than 10 mmol) as seen in Figure 48 (isolated in a 55% yield if pure isomer mixture). We were surprised that a mixture of isomers was isolated, since the size of the *t*-butyl group should have provided a significant amount of steric hindrance and not allowed for the isomer **51** to form.

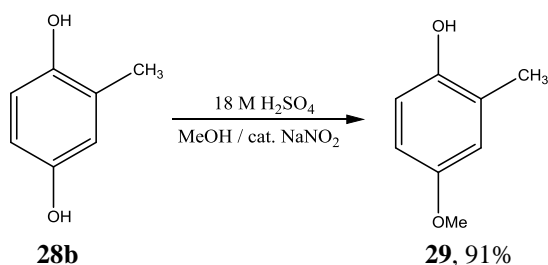


Figure 32 – Synthesis of 4-methoxy-2-methylphenol

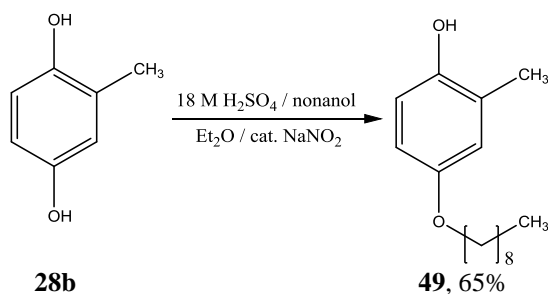


Figure 47 – Synthesis of 2-*t*-butyl-1-hydroxy-4-nonyloxybenzene

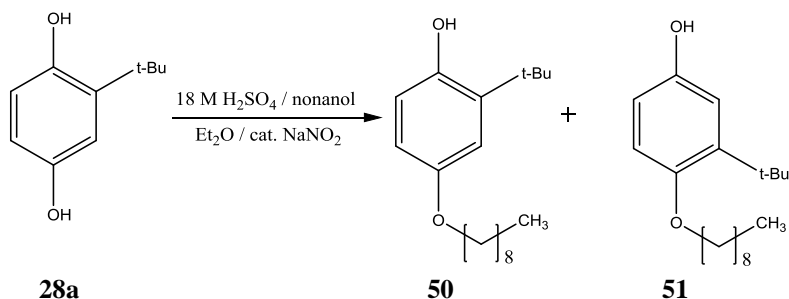
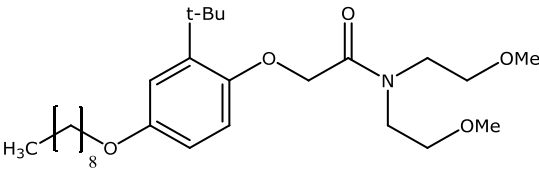
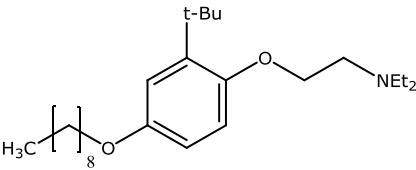
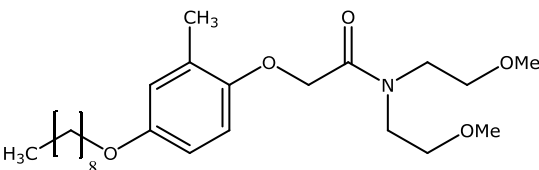
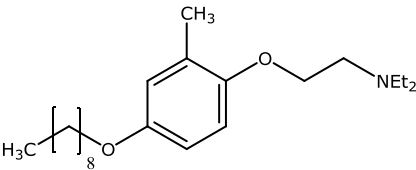
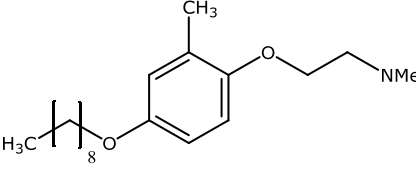


Figure 48 – Synthesis of **50**

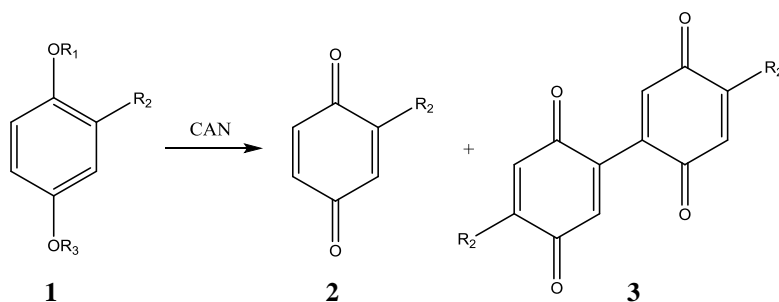
After successful synthesis of **49** and **50**, these compounds were further modified using the previously developed microwave protocol to form the substrates in Table 13 from previously made or commercially available alkylating agents.

Table 13 – Synthesized Surfactant-like Substrates using Standard Microwave Method

<i>Amide Substrates</i>	<i>Yield (%)</i>	<i>Amine Substrates</i>	<i>Yield (%)</i>
<p>compound 48a</p> 	66%	<p>compound 52a</p> 	77%
<p>compound 48b</p> 	60%	<p>compound 52b</p> 	62%
		<p>compound 47b</p> 	65% if pure

Chapter 4.2 CAN Results and Discussion

The synthesized substrates were tested under standard CAN conditions (2 M aqueous CAN with an equal-volume amount of acetonitrile to dissolve the arene). The results of the CAN reactions are shown in Table 14.



R₂: a: *t*-butyl, b: methyl

Figure 1 – General Substrate Reaction

Table 14 – Surfactant-like Substrates Tested under Standard CAN Conditions

Entry (Compound)	R ₁ Group	R ₂ : Me or <i>t</i> -Butyl	DQ Yield %, (MQ Yield, %)
1 (48a)		<i>t</i> -Butyl	0% (71%)
2 (52a)		<i>t</i> -Butyl	6% (37%)
3 (48b)		Me	26% (90%)
4 (52b)		Me	17% (16%)
5 (47b)		Me	Complex mixture

Based on the above data in Table 14 the self-aggregation of these compounds does not increase diquinone formation. It appears the previously discussed amide stabilization is prevalent

in several of these compounds (**48**, Table 14, entries 1 & 3) and results in lower diquinone yield than the hydroquinone dimethyl ether **13a**.

Chapter 4.2.1 CAN SDS Studies

In addition to allowing these compounds to aggregate prior to treatment with CAN, we were interested in investigation of the aggregation of the compounds inside of a micelle prior to treatment with CAN. We used the standard substrate, **13a**, for these trials similar to the previous studies. These trials used 1.0 mmol of the arene in comparison to the literature standard method⁵ that used a 2.0 mmol scale. The volumes of the solvent system were adjusted accordingly and are reflected in Table 15. We chose SDS as the surfactant due to the low CMC (8.2 mM) in water²⁷ and since it could not be further oxidized using CAN. Several variations of the oxidation protocol were tested. “Method A” used 3.5 equivalents of a 2 M aqueous CAN solution and an equal volume amount of 1 equivalent of arene, mixed with SDS in acetonitrile, added to the CAN solution over several minutes (the “standard” method). “Method B” was similar to “Method A”, but instead of using acetonitrile to suspend the arene/SDS mixture, an equal volume of water was used. “Method C” used the aqueous solvent system described in “Method B”, but changed the mode of addition, adding the aqueous CAN solution to the aqueous arene/SDS suspension. In each of the methods, the SDS/arene mixture formed a milky suspension in both water and acetonitrile trials. Table 15 shows the quinone yields for the different methods.

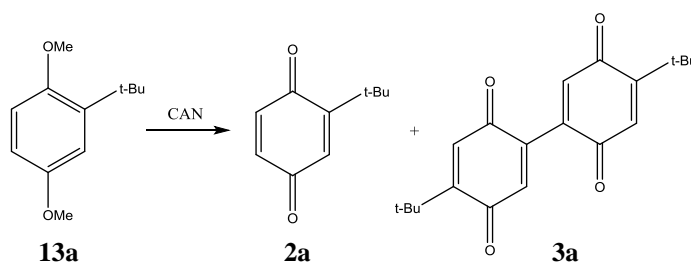


Figure 15 – Oxidation of **13a**

Table 15 – Results of SDS Studies

<i>Trial</i>	<i>Method A, B, or C</i>	<i>SDS Added (mol %)</i>	<i>DQ Yield % 15, (MQ Yield % 14)</i>
<i>Standard Method⁵</i>	water (3.5 mL) acetonitrile (3.5 mL)	0%	46% (12%)
1	A	3%	36% (35% MQ)
2	A	6%	50% (27% MQ)
3	B	1.5% (½ CMC)	49% (34% MQ)
4	B	3% (CMC)	43% (58% MQ)
5	B	6%	42% (41% MQ)
6	B	12%	41% (48% MQ)
7	B	30%	60% (106% MQ)*
8	C	3%	36% (38% MQ)
9	C	6%	42% (41% MQ)

*= not completely dry sample

Based on the above data in Table 15, there is little evidence that having the arene in a micelle promotes dimer formation. There could be several reasons for these interesting results. The arene should be encapsulated by the SDS, but perhaps the CAN is only interacting with arene that is released from the micelle. This release could occur upon addition of the micelles into the rapidly stirring CAN solution, either by the micelles being broken apart by the rapid stirring or the local decrease in concentration of the SDS. The local decrease in concentration would allow for SDS concentration to fall below the CMC, releasing the arene.

Chapter 5: Substituent Size Effects on Dimer Formation

When comparing all previous data sets, the methyl substrates (**1b**) typically favored diquinone formation when compared to the *t*-butyl substrates (**1a**). We were interested in determining if alkyl group size impacted diquinone formation. There could be a potential steric interaction during the dimerization that inhibits the amount of diquinone formed. We postulated that the more hindered the arene is, the less dimer formed.

Chapter 5.1 Experimental Design

To test whether size of these alkyl groups plays a large role in diquinone formation, we sought to investigate substrates that would be an intermediate size between the methyl substrate (**1b**) and *t*-butyl substrate (**1a**). One way of comparing group size is through the use of A-values. A-values are calculated values (Figure 49) that are dependent on the equilibrium constant between the axial and equatorial conformation of the group (R in Figure 49) in a cyclohexane ring system. The larger the group, the more 1,3-diaxial interactions and gauche interactions with the ring carbon-carbon bonds occur, favoring the equatorial position over the axial position. This change in the equilibrium constant changes the A-value, therefore the A-value correlates with the size of the group. A-values for different size substituents (with similar electronic nature as **1**) found in the literature²⁸ were screened and the compounds in Figure 50 were of interest.

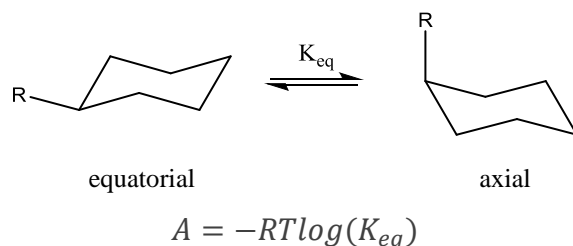


Figure 49 – Cyclohexane Conformation Equilibrium and A-Value Calculation

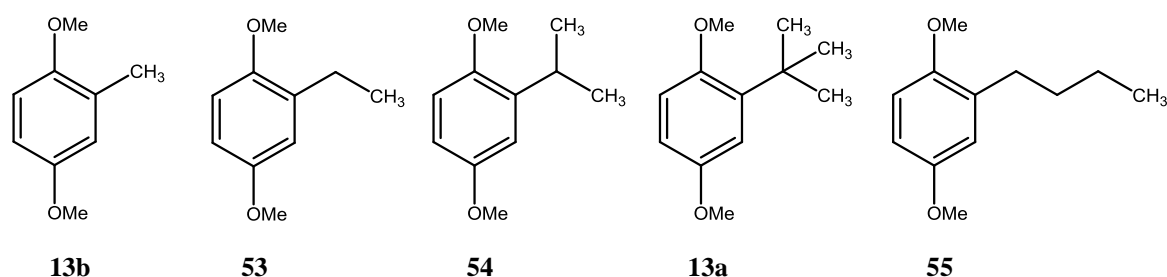


Figure 50 – Substrates with Different Alkyl Group Size

Chapter 5.1.1 Substrate Synthesis

Substrates **13b**, **53**, and **55** were previously synthesized^{4, 5} in our group and **13a** was prepared as previously discussed in chapter 2. **54** was prepared from commercially available 2,5-dimethoxyacetophenone (**56**) as shown in Figure 51. **56** was treated with MeMgCl in THF under a dry nitrogen atmosphere and the corresponding alcohol (**57**) was isolated in a 93% yield. The alcohol was reduced with triethylsilane (TES) and trifluoroacetic acid (TFA) forming **54** in a 95% yield after isolation.

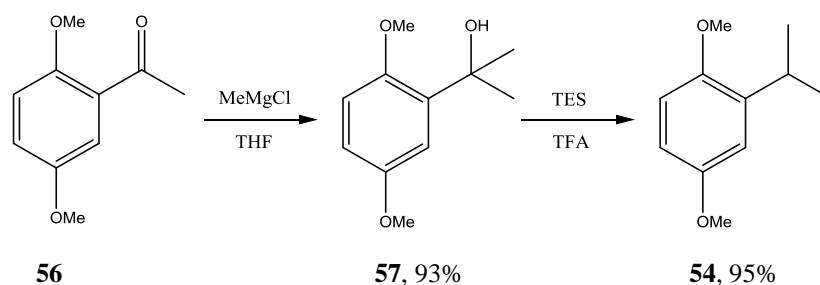


Figure 51 – Synthesis of 54

We were also interested in forming the methylated form of **57** to determine how the methoxy or hydroxyl groups altered the yield of diquinone. The alcohol (**57**) was initially treated with sodium hydride and dimethyl sulfate (shown in Figure 52) and was heated at reflux overnight in THF. However, the reaction yielded a mixture of the methylated product (**58**) and the elimination product (**59**).

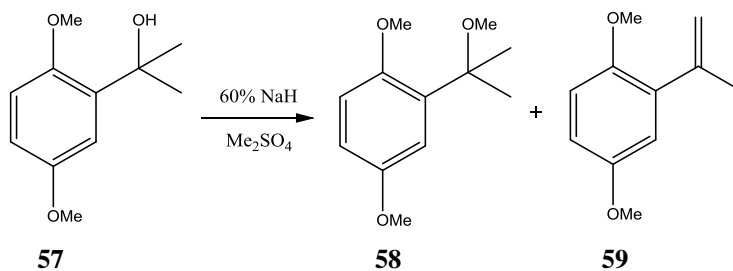


Figure 52 – Synthesis of **58** with Dimethyl Sulfate

The conversion of the alcohol (**57**) into **58** was attempted using methyl iodide and sodium hydride (shown in Figure 54), and was stirred at ambient temperature overnight in THF. The isolated product was **58** in an approximate 99% yield.

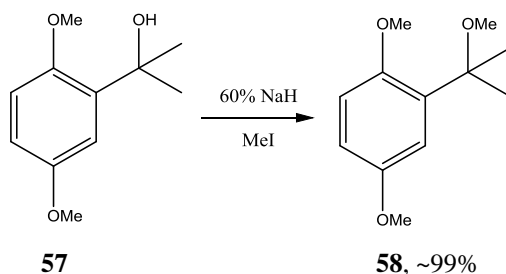
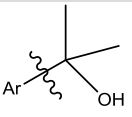
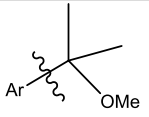


Figure 53 – Synthesis of **58** with Methyl Iodide

Chapter 5.2 Results and Discussion

For comparing these substrates, the standard method (1 M aqueous CAN with equivolume acetonitrile) was used. Table 16 shows the yield of monoquinone and diquinone as compared to the A-value of the substituent.

Table 16 –Substrates Tested under Standard CAN Conditions (Figure 50 Substrates)

Entry (Compound)	R Group	A-Value ²⁸ (kcal/mol)	MQ Yield (%)	DQ Yield (%)
1 (13b)	Methyl	1.74	2%	93%
2 (53)	Ethyl	1.79	2%	75%
3 (55)	<i>n</i> -Butyl	N/A	6%	78%
4 (54)	Isopropyl	2.21	10%	60%
5 (13a)	<i>t</i> -Butyl	4.7	12%	46%
6 (57)		N/A	35%	36%
7 (58)		N/A	33%	11%

The results of the study clearly show that the larger group the lower the amount of diquinone formed. Although A-values were not previously well defined in literature for the *n*-butyl substituent, the steric size is hypothesized to be similar to ethyl since there is little increase in size at the α -carbon. We also tested **57** and **58**. Although the side chains in these two substrates are different electronically than a *t*-butyl group, we believe in solution these groups are sterically larger than a *t*-butyl group. This can be explained by solvation and the larger amount of hydrogen bonding that can occur in the aqueous reaction media.

This interesting result may be due to how the arene and radical cationic intermediate are combining. One can imagine two different orientations of the two reactants leading to the dimer (shown in Figure 54). The first is an “end to end” configuration, where the compounds overlap with limited R₂ group interaction. The size of the R₂ group would not be expected to have a significant impact on the monoquinone/diquinone selectivity if this were the preferred transition state. However, if the transition state involved pi stacking as shown in Figure 54 there would be

a significant interaction between the sidechains. In this case, the larger the R_2 group, the more the pi stacking system is disrupted. If steric hindrance were to raise the energy of the transition state of the “pi stacked” transition state, it might lead to less formation of diquinone. On the other hand, when the R_2 group is small, there are not significant steric interactions between the R_2 groups, allowing for tighter pi stacking and more formation of diquinone. Previous literature^{29, 30} has shown pi stacking of an electron deficient arene and an electron rich arene is a favorable interaction. Due to the cationic nature of the intermediate and the electron rich character of the dimethyl hydroquinone ether, this interaction should be favorable, and supports that the “stacked” transition state is preferred over the “end to end” transition state. The data shown in Table 16 supports this hypothesis, and we wish to further study this correlation.

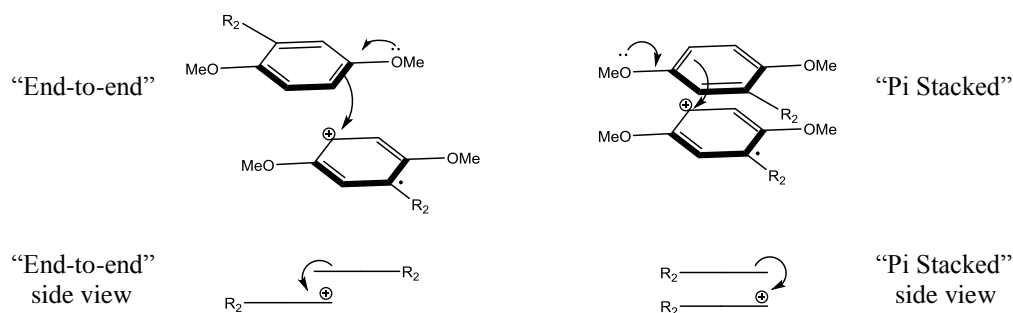


Figure 54 – Diquinone Formation Transition State

Chapter 6: Substrate Electronic Effects on Dimer Formation

In previous group studies⁴ there has been evidence that suggests substrates with groups that are good electron withdrawing groups or groups that are good electron donating groups have low yields of diquinone formation. It appears only some substrates produce large yields of diquinone and it would be of interest to determine if there is quantitative evidence that supports this correlation.

Chapter 6.1 Hammett Value Comparison to Dimer Yield

There are several methods to determine the amount of electron density in an arene system and how different groups add to or withdraw from the arene pi electron system. One of the most widely used quantitative methods for determining the electron donating or withdrawing ability of different groups is the use of Hammett values for the linear free-energy relationships of substituents.³¹ We were interested if there was correlation between Hammett values³¹ and the observed differences in diquinone yield. To determine this correlation, we plotted each of the sigma values against previously recorded⁴ diquinone yields (shown in Graph 1-Graph 5). Based on the proposed mechanism, if the cationic intermediate is stabilized, it may not be sufficiently reactive (electrophilic) in order for dimer formation to compete effectively with other reactions. Similarly, we believe if a strong electron withdrawing group is present, the decrease in electron density decreases the nucleophilicity of the arene preventing dimer formation (depicted in Figure 55). With this hypothesis, we believe there should be a “window” where substituents of intermediate electron donating capability should produce higher amounts of diquinone.

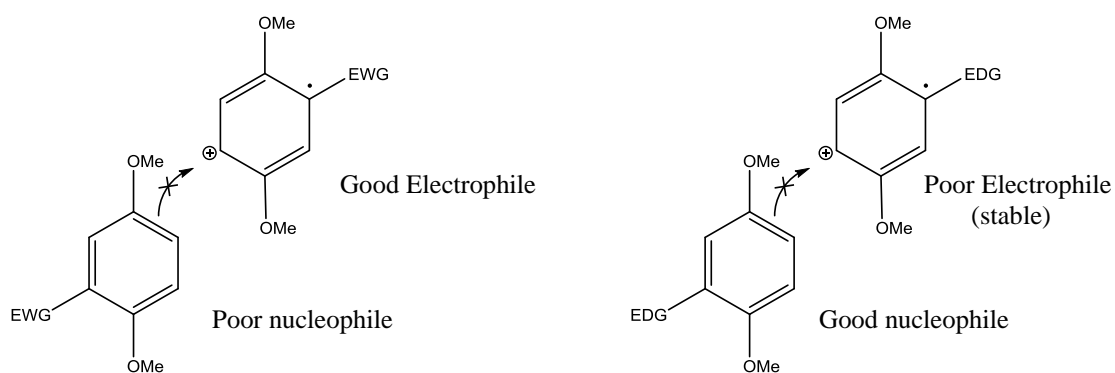
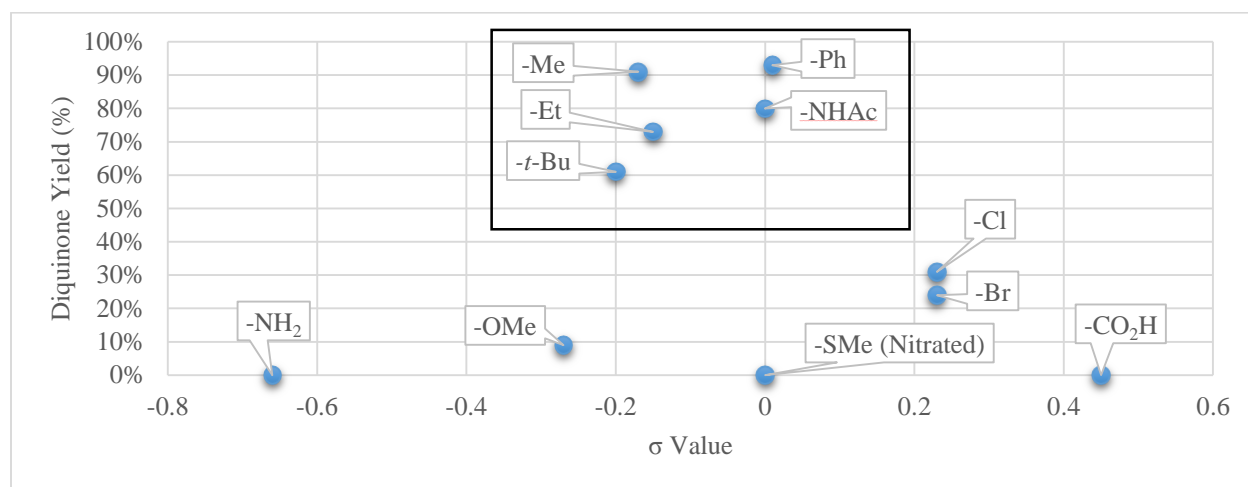
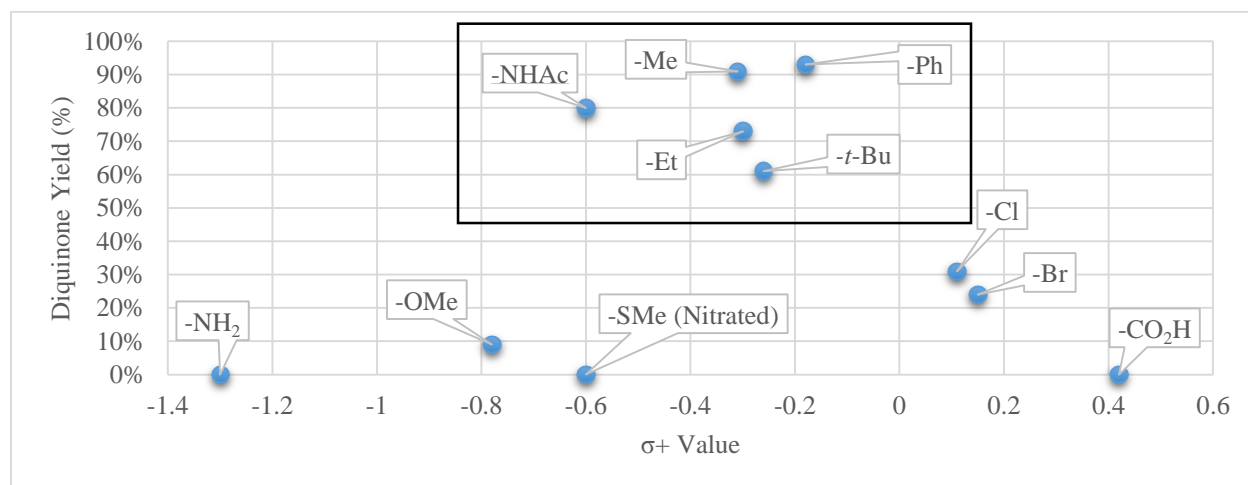


Figure 55 – Intermediates of Diquinone Formation

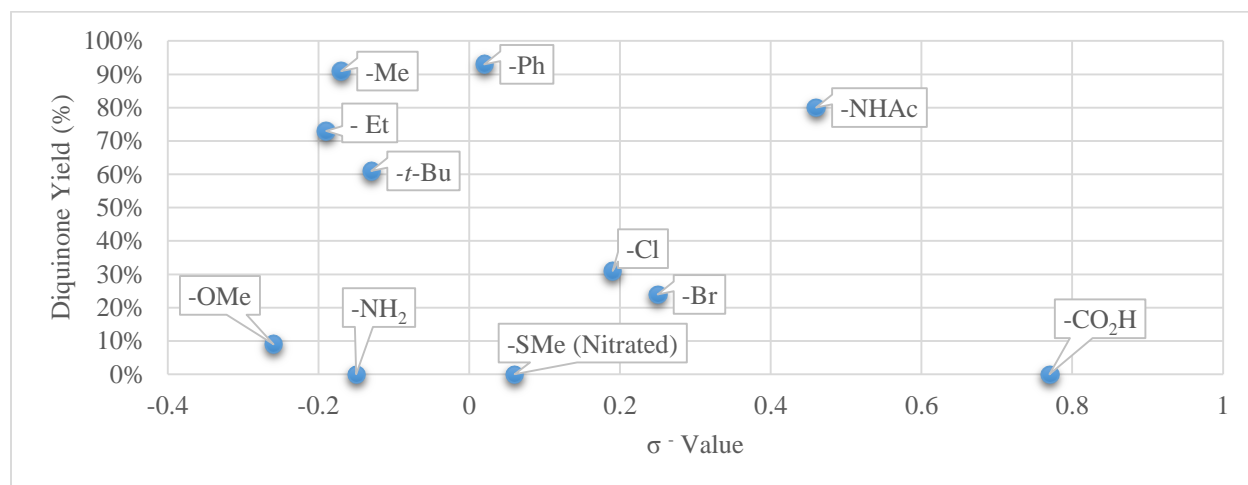
Graph 1 – σ Values vs. Diquinone Yields



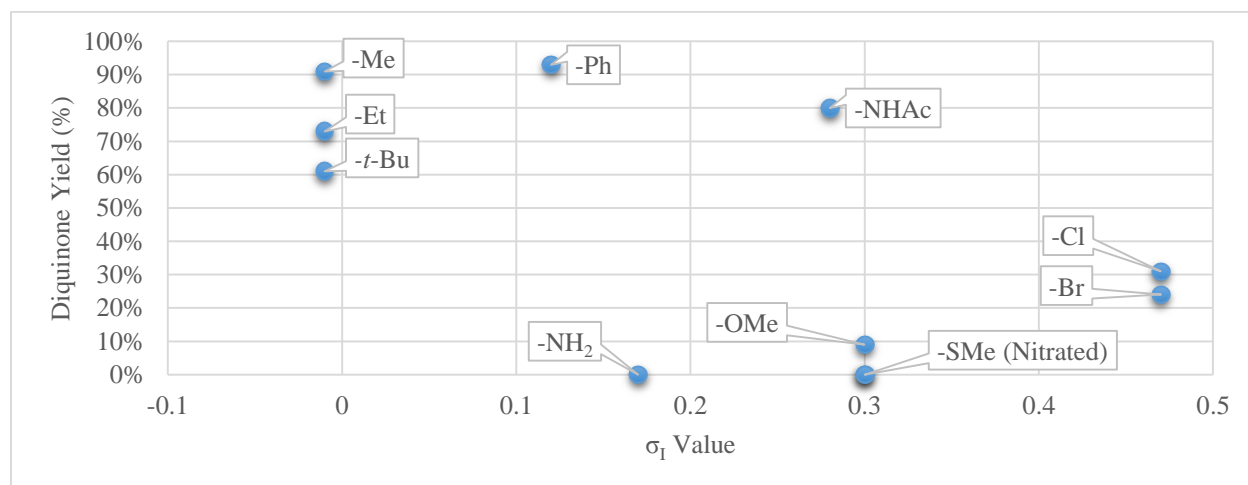
Graph 2 – σ^+ Values vs. Diquinone Yields



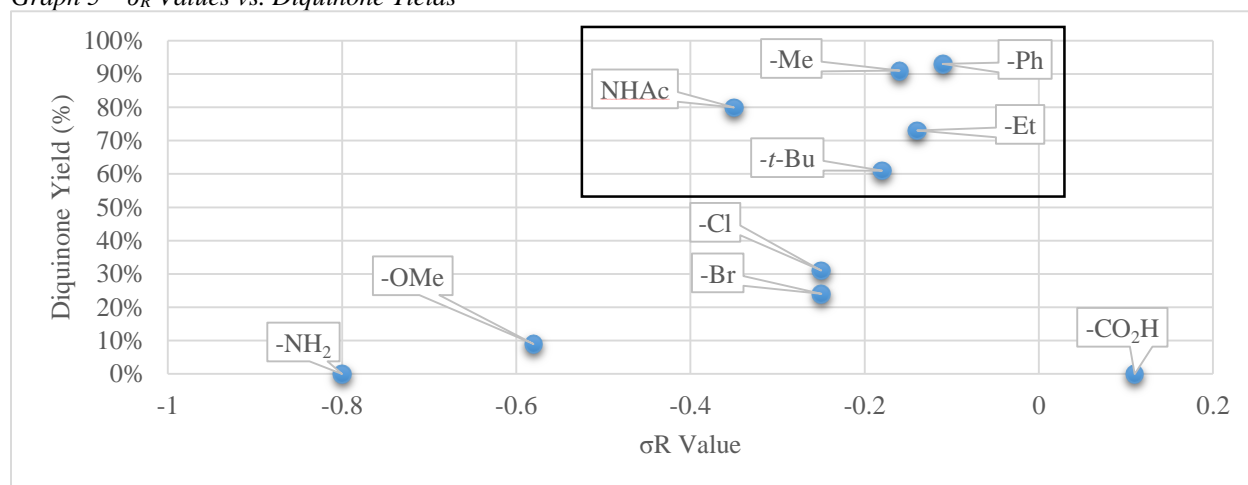
Graph 3 – σ^- Values vs. Diquinone Yields



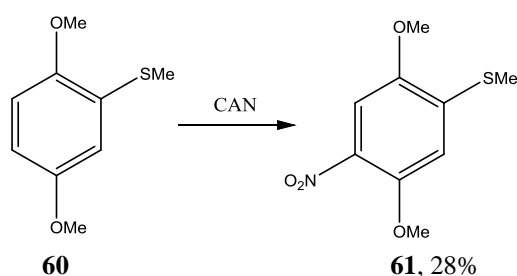
Graph 4 – σ_I Values vs. Diquinone Yields



Graph 5 – σ_R Values vs. Diquinone Yields



Based on the data shown in Graph 4, there is not a significant trend that shows inductive effects (σ_I) of substituents correlate with diquinone yield. Not surprisingly based on the mechanism, there is also not a correlation with anion stabilizing (σ^-) groups (Graph 3). As predicted, there seems to be a moderate correlation with electron donation (σ , Graph 1), cation stabilization (σ^+ , Graph 2), and resonance contribution (σ_R , Graph 5). In Graphs 1, 2, and 5, there is a cluster of high diquinone forming substrates within an intermediate electron donating/stabilization range, with the exception of the methylthio substrate. This substrate only produced the nitrated product, and no quinone formation occurred with this substrate (as depicted in Figure 56).^{4, 32}



*Figure 56 – Nitration of **60** with CAN*

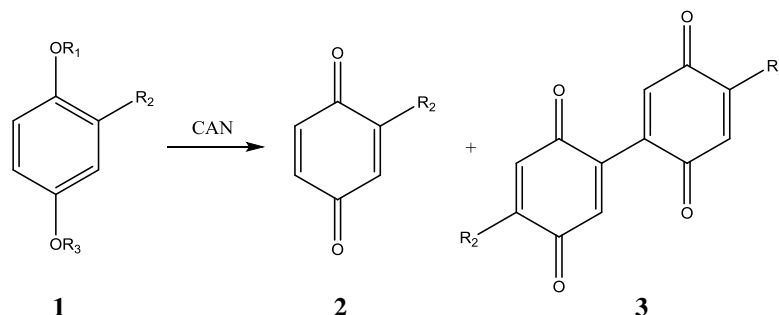
There also was a cluster of high diquinone forming substrates when comparing the resonance stabilization ability of each substituent (σ_R) with the exception of the two halogenated substrates. These substrates both have inductive withdrawal capabilities as well as stabilization through resonance. Since the σ_R does not account for the inductive withdrawal of these groups, that could cause these groups to not follow similar trends as the other substrates. Another noteworthy point is that electronic differences in substrates is only one of the factors that contributes to diquinone formation. As discussed in previous chapters, alkyl group size can also change the amount of diquinone formed.

Chapter 6.2 Experimental Design and Future Work

The group hopes to further investigate this correlation of arene electron density and diquinone formation. We hope to use previously developed methods^{33, 34} to both calculate and experimentally determine the reduction potentials of these substrates. The reduction potential correlates directly to how easily an electron can be removed (or gained) in the aromatic system and reflects the amount of electron density within the pi system. Based on the correlation of the Hammett values, we hope to determine if there is a correlation between the reduction potential of these substrates and diquinone yield. If such a correlation exists, we hope to be able to use computational methods to further design substrates with an “ideal” reduction potential for diquinone formation.

Chapter 7: Conclusions

The oxidations of 2-alkyl-1,4-dialkoxybenzenes to their respective monoquinones and diquinones has shown interesting results and a large array of factors that influence the product selectivity of the reaction (Figure 1). As was previously noted, it is important to have a selective and widely applicable method to form both monoquinones and diquinones.



R₂: a: *t*-butyl, b: methyl

Figure 1 – General Substrate Reaction

Through each of these studies we have found several important factors that correlate with an increase or decrease in diquinone formation. We determined that both amount of solvent used and the addition time do not significantly influence the amount of diquinone formed. This leads to the conclusion that this oxidation is not primarily controlled by traditional kinetics.

Further investigation of different hydrophobic and hydrophilic substrates allowed testing of how solvation or aggregation of these substrates influences diquinone formation. By testing a wide array of substrates, we determined simple hydrophobicity or hydrophilicity does not control the product outcome. We also investigated this theory by forming single compounds with both hydrophilic and hydrophobic groups resulting in limited change in diquinone formation. Similarly, using SDS as a surfactant to assist aggregation failed to produce an increase in diquinone formation. This limited formation could be due to several factors, including that the

CAN may only be interacting with the arene that is released from the micelle rather than the aggregated arene within the micelle.

When comparing how substrate alkyl groups alter diquinone and monoquinone formation, we found there was not a significant change in diquinone formation when using groups that potentially chelate CAN. We discovered there is a clear difference when using a substrate that has amide functionality versus amine functionality. We believe the amide functionality allows for an intermediate stabilization as shown in Figure 33, therefore encouraging monoquinone formation. We believe this stabilization of the radical cationic intermediate decreases the electrophilicity the intermediate, which decreases the rate at which it is able to combine with the neutral substrate, resulting in limited diquinone formation.

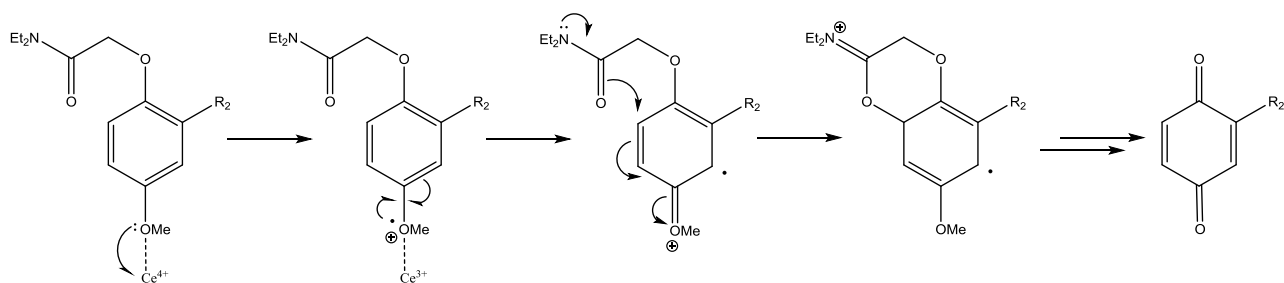


Figure 33 – Six-Membered Amide Stabilized CAN Reaction

Another influencing factor associated with limited diquinone yield was the size of the R_2 group in Figure 1. We determined by comparing the A-values of different substituents, there was a correlation between the amount of diquinone formed and group size. The larger groups correlated with a lower amount of diquinone formed. The illustration of the predicted transition state (Figure 57) of the reaction shows how larger steric requirements of the R_2 group could change the amount of pi stacking in the system. In this case, the larger the R_2 group, the more the pi stacking system is disrupted. If steric hindrance were to raise the energy of the transition state of the “pi stacked” transition state, it might lead to less formation of diquinone. On the other

hand, when the R₂ group is small, there are not significant steric interactions between the R groups, allowing for tighter pi stacking and more formation of diquinone.



Figure 57 – Pi Stacked Transition State

We wish to further test the electronic nature of each substrate by comparing the reduction potentials of substrates that form high versus low yields of diquinone. As previously discussed, there is a correlation between the amount of electron density in the arene, and how much diquinone is formed. We hope to use reduction potentials as a way to further study the electron density within the arene structure and if these potentials follow a similar trend, allowing prediction of product outcome.

We hope these contributions will be able to be used to design better syntheses of both monoquinones and diquinones, as well as contribute to the understanding of major factors that influence CAN oxidations of 2-alkyl-1,4-dialkoxybenzenes.

Chapter 8: Experimental

Each of the substrates and products described below was characterized by ^1H NMR and/or ^{13}C NMR using a Bruker Avance 400 NMR instrument. Solvents and reagents were ACS reagent grade materials and were not further purified before use unless specified. Microwave reactions were carried out in a CEM Discovery microwave reactor.

Standard THF Alkylation Method: The phenol (1 eq.) was dissolved in freshly distilled THF (20 mL) in an oven dried 50 mL round bottom flask equipped with magnetic stir bar and water condenser. Potassium *t*-butoxide (1.2 eq.) was added to the flask all at once (there was an immediate color change to a dark red solution). The alkylating agent (1.2 eq.) was added to an oven dried 10 mL Erlenmeyer flask and was dissolved with freshly distilled THF (5 mL). The solution was added all at once to the round bottom flask via pipette. The combined mixture was allowed to stir while heating at reflux overnight while under a dry nitrogen atmosphere. The resulting solution was diluted with water (25 mL), basified with aqueous (1 M to 6 M) NaOH to pH 14, and was extracted with diethyl ether (2 x 25 mL). The combined organic layers were washed with water (1 x 50 mL), sat. NaCl (1 x 5 mL), and dried (MgSO_4). The solvent was removed under reduced pressure.

Standard Microwave Alkylation Method: The phenol (1 eq.) was dissolved in DMSO (10 mL) in a 25 mL round bottom flask equipped with magnetic stir bar, air condenser, and distillation apparatus. Potassium *t*-butoxide (1.5 eq.) was added to the flask all at once (there was an immediate color change to a dark red solution). Catalytic amounts of both sodium iodide and 4-dimethylaminopyridine were added to the solution. The alkylating agent (1.1 eq.) was added to a 10 mL Erlenmeyer flask and was dissolved with DMSO (5 mL). The solution was added all at once to the round bottom flask via pipette. The combined mixture was heated in a microwave

reactor at 150 °C with a max power of 150 W for 20 min, while stirring. The resulting solution was diluted with water (25 mL), basified with aqueous (1 M to 6 M) NaOH to pH 14, and was extracted with diethyl ether (2 x 25 mL). The combined organic layers were washed with water (1 x 50 mL), sat. NaCl (1 x 5 mL), and dried (MgSO₄). The solvent was removed under reduced pressure.

Standard CAN Oxidation Method: A 1.0 mmol sample of the arene was dissolved in 1.8 mL of acetonitrile and was added slowly over several minutes to a rapidly stirred solution of CAN (1.92 g, 3.5 mmol) which had been dissolved in 1.8 mL of distilled water in a 10 mL round-bottom flask. After the addition was complete, the mixture was stirred for an additional 1 hour at room temperature open to the air. The mixture was diluted with 25 mL of water, and the resulting precipitate collected by suction filtration. The precipitate was washed with several 10 mL portions of water and then finally with approximately 5 mL of ice cold ethanol. The resulting yellow solid (diquinone) was dried at room temperature under vacuum.

The filtrate from the filtration described above was extracted with ether (2 x 25 mL). The combined organic layers were washed with water (1 x 50 mL), sat. NaCl (1 x 5 mL), and dried (MgSO₄). The solvent was removed under reduced pressure.

Diquinone Favoring CAN Oxidation Method⁵: A 1.0 mmol sample of the arene was dissolved in 3.5 mL of acetonitrile and was added slowly over several minutes to a rapidly stirred solution of CAN (1.92 g, 3.5 mmol) which had been dissolved in 3.5 mL of distilled water in a 10 mL round-bottom flask. After the addition was complete, the mixture was stirred for an additional 1 hour at room temperature open to the air. The mixture was diluted with 25 mL of water, and the resulting precipitate collected by suction filtration. The precipitate was washed

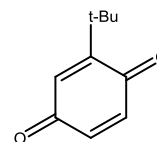
with several 10 mL portions of water and then finally with approximately 5 mL of ice cold ethanol. The resulting yellow solid (diquinone) was dried at room temperature under vacuum.

The filtrate from the filtration described above was extracted with ether (2 x 25 mL). The combined organic layers were washed with water (1 x 50 mL), sat. NaCl (1 x 5 mL), and dried (MgSO₄). The solvent was removed under reduced pressure.

Monoquinone Favoring CAN Oxidation Method⁵: A sample of CAN (1.92 g, 3.5 mmol) was added portion-wise over 5 minutes to a rapidly stirred solution of 1.0 mmol of arene dissolved in 5.0 mL of DMSO in a 10 mL round-bottom flask. After the addition was complete, the mixture was stirred for an additional 1 hour at room temperature open to the air. The mixture was diluted with 25 mL of water and was extracted with ether (2 x 25 mL). The combined organic layers were washed with water (1 x 50 mL), sat. NaCl (1 x 5 mL), and dried (MgSO₄). The solvent was removed under reduced pressure.

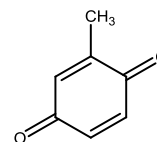
2-*t*-Butyl-*p*-benzoquinone, **2a**

¹H NMR (CDCl₃): δ 1.27 (s, 9H), 6.58 (s, 1H), 6.671 (d, *J* = 2.5 Hz, 1H), 6.673 (d, *J* = 2.5 Hz, 1H).



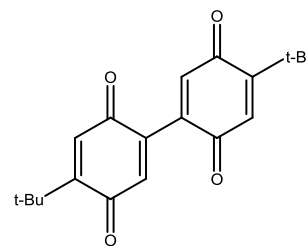
2-Methyl-*p*-benzoquinone, **2b**

¹H NMR (CDCl₃): δ 2.06 (s, 3H), 6.62 (m, 1H), 6.71 (dd, *J* = 10.1 Hz, 2.4 Hz, 1H), 6.76 (d, *J* = 10.1 Hz, 1H).



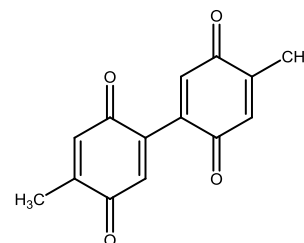
5,5'-Di-*t*-butyl-2,2'-bis-*p*-benzoquinone, **3a**

^1H NMR (CDCl_3): δ 1.30 (s, 18H), 6.68 (s, 2H), 6.75 (s, 2H).



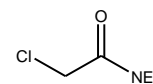
5,5'-Dimethyl-2,2'-bis-*p*-benzoquinone, **3b**

^1H NMR (CDCl_3): δ 2.09 (d, $J = 1.1$ Hz, 6H), 6.69 (q, $J = 1.1$ Hz, 2H), 6.80 (s, 2H).

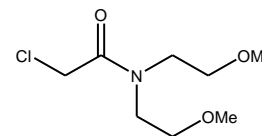


2-chloro-*N,N*-diethylacetamide, **44**

Chloroacetyl chloride (2.78 g, 24.6 mmol) was dissolved with 25 mL of dichloromethane in a 100 mL round bottom flask, equipped with a magnetic stir bar, and chilled in an ice bath. Diethylamine (3.64 g, 49.9 mmol) was dissolved with 25 mL of dichloromethane in a 25 mL Erlenmeyer flask. The diethylamine solution was added to the chilled round bottom flask via addition funnel over 12 min, while gently stoppered. The combined solution was stirred and allowed to warm to ambient temperature as the ice bath melted over 2.75 hrs, while gently stoppered. The solution was diluted with dichloromethane (50 mL) and was washed with 1 M HCl (2 x 25 mL), water (1 x 25 mL), sat. NaCl (1 x 10 mL), and dried (MgSO_4). The solvent was removed under reduced pressure yielding the product as a clear yellow oil in 81% yield (2.98 g). ^1H NMR (CDCl_3): δ 1.14 (t, $J=0.0$ Hz, 3H), 1.24 (t, $J=7.2$ Hz, 3H), 3.37 (q, $J=7.2$ Hz, 2H), 3.41 (q, $J=7.2$ Hz, 2H), 4.09 (s, 2H); ^{13}C NMR (CDCl_3): δ 12.6, 14.3, 40.5, 41.3, 42.4, 165.6.

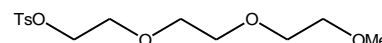


2-chloro-*N,N*-bis-(2-methoxyethyl)acetamide, 25



Chloroacetyl chloride (1.41 g, 12.5 mmol) was dissolved with 15 mL of dichloromethane in a 50 mL round bottom flask, equipped with a magnetic stir bar, and chilled in an ice bath. Bis(2-methoxyethyl)amine (3.344 g, 25.14 mmol) was dissolved with 10 mL of dichloromethane in a 25 mL Erlenmeyer flask. The amine solution was added to the chilled round bottom flask via pipette over several min, forming white smoke. The combined solution was stirred and allowed to warm to ambient temperature as the ice bath melted over 22.25 hrs, while gently stoppered. The solution was diluted with dichloromethane (25 mL) and was washed with 1 M HCl (2 x 10 mL), water (1 x 25 mL), sat. NaCl (1 x 15 mL), and dried (MgSO₄). The solvent was removed under reduced pressure yielding the product as a clear light yellow oil in 86% yield (2.25 g). ¹H NMR (CDCl₃): δ 3.33 (s, 3H), 3.34 (s, 3H), 3.51-3.63 (m, 8H), 4.25 (s, 2H); ¹³C NMR (CDCl₃): δ 41.7, 46.7, 49.4, 58.8, 59.0, 70.3, 70.7, 167.4.

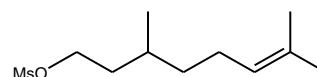
Triethylene glycol monomethyl ether tosylate



Triethylene glycol monomethyl ether (9.05 g, 55.2 mmol) was dissolved with 30 mL of dichloromethane in a 250 mL round bottom flask, equipped with a magnetic stir bar. Triethylamine (8.53 g, 84.6 mmol) was dissolved with 10 mL of dichloromethane in a 25 mL Erlenmeyer flask. The amine solution was added all at once to the round bottom flask and the combined mixture was chilled in an ice bath. Tosyl chloride (12.78 g, 66.11 mmol) was dissolved with 40 mL of dichloromethane in a 50 mL beaker. The tosyl chloride solution was added to the chilled round bottom flask via pipette over several min. The combined solution was further diluted with 40 mL of dichloromethane, the ice bath was removed, and the solution was allowed to stir for 6.75 hrs, while gently stoppered at ambient temperature. The solution was

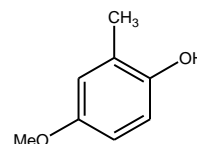
washed with 3 M HCl (3 x 15 mL), water (1 x 50 mL), sat. NaCl (1 x 10 mL), and dried (MgSO₄). The solvent was removed under reduced pressure yielding the product as a clear light yellow oil in ~100% yield (17.54 g). ¹H NMR (CDCl₃): δ 2.45 (s, 3H), 3.37 (s, 3H), 3.53 (m, 2H), 3.59 (m, 6H), 3.60 (dd, *J*=4.8 Hz, *J*=4.8 Hz, 2H), 4.16 (dd, *J*=4.8 Hz, *J*=4.8 Hz, 2H), 7.35 (d, *J*=8.1 Hz, 2H), 7.79 (d, *J*=8.1 Hz, 2H); ¹³C NMR (CDCl₃): δ 21.6, 59.0, 68.6, 69.2, 70.5 (2C), 70.7, 71.8, 128.0, 129.6, 133.0, 144.8.

β-citronellol mesylate



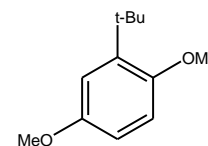
β-citronellol (10.26 g, 65.77 mmol) was dissolved with 25 mL of dichloromethane in a 250 mL round bottom flask, equipped with a magnetic stir bar. Triethylamine (13.49 g, 133.6 mmol) was dissolved with 10 mL of dichloromethane in a 25 mL Erlenmeyer flask. The amine solution was added all at once to the round bottom flask, diluted with 100 mL of dichloromethane, and the solution was chilled in an ice bath. Mesyl chloride (9.09 g, 79.0 mmol) was dissolved with 10 mL of dichloromethane in a 10 mL Erlenmeyer flask. The mesyl chloride solution was added to the chilled round bottom flask via pipette over several min, minimizing heat release. The ice bath was removed and the solution was allowed to stir for 6 hrs, while gently stoppered at ambient temperature. The solution was washed with 3 M HCl (3 x 15 mL), water (1 x 50 mL), sat. NaCl (1 x 10 mL), and dried (MgSO₄). The solvent was removed under reduced pressure yielding the product as a clear yellow oil in 83% yield (12.81 g). ¹H NMR (CDCl₃): δ 0.93 (d, *J*=6.5 Hz, 3H), 1.22 (m, 1H), 1.35 (m, 1H), 1.60 (m, 2H), 1.61 (s, 3H), 1.68 (s, 3H), 1.78 (m, 1H), 1.99 (m, 1H), 3.00 (s, 3H), 4.26 (m, 2H), 5.08 (dt, *J*=1.4 Hz, *J*=7.1 Hz, 1H).

4-methoxy-2-methylphenol, **29**



Methylhydroquinone (1.698 g, 13.69 mmol) was dissolved with 15 mL of anhydrous methanol in a 50 mL round bottom flask, equipped with magnetic stir bar. 18 M H₂SO₄ (1.0 mL, 18 mmol) was added to the round bottom flask dropwise to minimize heat release. Sodium nitrite (0.062 g, 0.90 mmol) was added all at once to the flask, forming a dark brown solution. The combined solution was allowed to stir at ambient temperature for 5 hrs, while stoppered. The resulting solution was diluted with water (25 mL) and was extracted with diethyl ether (3 x 30 mL). The combined ether layers were washed with sat. NaCl (1x 10 mL) and dried (MgSO₄). The solvent was removed under reduced pressure yielding the product as a brown solid in 97% yield (1.84 g). ¹H NMR (CDCl₃): δ 2.17 (s, 3H), 3.74 (s, 3H), 6.60 (dd, *J*=3.1 Hz, *J*=8.6 Hz, 1H), 6.68 (d, *J*=3.1Hz, 1H), 6.69 (d, *J*=8.6 Hz, 1H); ¹³C NMR (CDCl₃): δ 16.1, 55.8, 111.9, 115.6, 116.7, 125.1, 147.9, 153.5.

2-*t*-butyl-1,4-dimethoxybenzene, **13a**

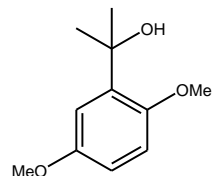


Butylated hydroxyanisole (5.80 g, 32.2 mmol) was dissolved with 30 mL of THF in a 100 mL round bottom flask, equipped with a magnetic stir bar. Lithium hydroxide monohydrate (1.50 g, 35.7 mmol) was added all at once to the round bottom flask. Dimethyl sulfate (6.09 g, 48.3 mmol) was dissolved with 30 mL of THF in a 50 mL Erlenmeyer flask. The solution was added via pipette to the round bottom flask. The resulting cloudy mixture was allowed to stir for 17.5 hrs at ambient temperature, while gently stoppered. The resulting pink solution was diluted with 6 M NaOH (15 mL, 90 mmol), transferred to a 250 mL Erlenmeyer flask, and was allowed to stir open to the air for 2.25 hours at ambient temperature. The solution was diluted with water (50 mL) and was extracted with diethyl ether (2 x 50 mL). The combined

ether layers were washed with water (1x 75 mL), sat. NaCl (1 x 5 mL), and dried (MgSO₄). The solvent was removed under reduced pressure and the resulting yellow oil was a mixture of the arene and dimethyl sulfate as determined by ¹H NMR. The oil was dissolved in diethyl ether (10 mL) and was combined with 3 M NaOH (15 mL, 45 mmol). The mixture stirred for 5.5 hrs at ambient temperature open to the air. The solution was diluted with water (50 mL) and was extracted with diethyl ether (2 x 50 mL). The combined ether layers were washed with water (1x 75 mL), sat. NaCl (1 x 5 mL), and dried (MgSO₄). The solvent was removed under reduced pressure yielding the product as a yellow oil in 75% yield (4.69 g). ¹H NMR (CDCl₃): δ 1.36 (s, 9H), 3.75 (s, 3H), 3.77 (s, 3H), 6.66 (dd, *J*=3.1 Hz, *J*=8.8 Hz, 1H), 6.78 (d, *J*=8.8 Hz, 1H), 6.89 (d, *J*=3.1 Hz, 1H); ¹³C NMR (CDCl₃): δ 29.7 (3C), 34.9, 55.6, 55.7, 109.8, 112.4, 114.3, 139.9, 153.0, 153.3.

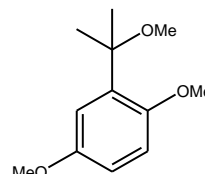
2-(1-hydroxy-1-methylethyl)-1,4-dimethoxybenzene, 57

2,5-Dimethoxyacetophenone (1.52 g, 8.44 mmol) was dissolved with 25 mL of freshly distilled THF in an oven dried 50 mL round bottom flask. The solution was chilled in an ice bath, and 2 M methylmagnesium chloride (6.4 mL, 13 mmol) in THF was slowly added to the solution via syringe over 3 min. The combined solution warmed to ambient temperature as the ice bath melted while stirring for 5.75 hrs under a dry nitrogen atmosphere. The resulting solution was slowly quenched with sat. ammonium chloride (15 mL) and was combined with diethyl ether (75 mL). The organic layer was washed with water (2 x 50 mL), sat. NaCl (1 x 5 mL), and dried (MgSO₄). The solvent was removed under reduced pressure yielding the product as a tan oil in 93% yield (1.54 g). ¹H NMR (CDCl₃): δ 1.58 (s, 6H), 3.76 (s,



3H), 3.85 (s, 3H), 6.72 (dd, $J=3.1$ Hz, $J=8.8$ Hz, 1H), 6.83 (d, $J=8.8$ Hz, 1H), 6.92 (d, $J=3.1$ Hz, 1H); ^{13}C NMR (CDCl_3): δ 29.6 (2C), 55.7, 55.8, 72.5, 111.3, 112.0, 113.1, 137.2, 151.1, 153.7.

1,4-Dimethoxy-2-(1-methoxy-1-methylethyl)-benzene, **58**



2-(1-hydroxy-1-methylethyl)-1,4-dimethoxybenzene (0.60 g, 3.1 mmol) was dissolved with 15 mL of freshly distilled THF, in an oven dried 50 mL round bottom flask equipped with a magnetic stir bar. The solution was chilled in an ice bath and a 60% sodium hydride paraffin dispersion (0.50 g, 12.5 mmol) was added to the round bottom flask portion-wise over several minutes. Methyl iodide (1.10 g, 7.75 mmol) was dissolved with 5 mL of freshly distilled THF in an oven dried 10 mL Erlenmeyer flask. The iodide solution was slowly added to the round bottom flask via pipette over several minutes. The combined mixture was allowed to stir for 20 hrs at ambient temperature while under a dry nitrogen atmosphere. The resulting solution was diluted with water (25 mL), basified to pH 14 with 3 M NaOH, and was extracted with diethyl ether (2 x 25 mL). The combined ether layers were washed with water (1 x 50mL), sat. NaCl (1 x 5 mL), and dried (MgSO_4). The solvent was removed under reduced pressure yielding the product as a clear colorless oil in ~100% yield (0.65 g). ^1H NMR (CDCl_3): δ 1.58 (s, 6H), 3.22 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 6.74 (dd, $J=3.1$ Hz, $J=8.8$ Hz, 1H), 6.82 (d, $J=8.8$ Hz, 1H), 7.04 (d, $J=3.1$ Hz, 1H); ^{13}C NMR (CDCl_3): δ 26.5 (2C), 50.6, 55.6, 55.9, 76.6, 111.9, 112.8, 114.0, 135.1, 151.5, 153.5.

2,5-dimethoxy-1-(1-methylethyl)-benzene, **54**

2-(1-hydroxy-1-methylethyl)-1,4-dimethoxybenzene (1.15 g, 5.88 mmol)

was dispersed with triethylsilane (1.71 g, 6.12 mmol) in a 25 mL round

bottom flask, equipped with a magnetic stir bar. The silane mixture was chilled in an ice bath.

Trifluoroacetic acid (6.0 mL) was added dropwise over 8 min to the chilled round bottom flask.

The resulting solution stirred for 85 min while open to the air, at ambient temperature. The flask

was equipped with a water condenser, and solution was then heated to reflux and stirred for 60

min while open to the air. The mixture was slowly diluted with 1 M NaOH, then 6 M NaOH

adjusting the pH of the solution to pH 14. The solution was then extracted with diethyl ether (2 x

50 mL). The combined ether layers were washed with 1 M NaOH (1 x 40 mL), water (1 x 50

mL), sat. NaCl (1 x 5 mL), and dried (MgSO₄). The solvent was removed under reduced pressure

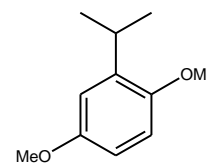
and the oil was separated by vacuum distillation at 100 °C. The desired product was the residue

isolated as a tan liquid in 95% yield (1.00 g), with a trace of triethylsilane. ¹H NMR (CDCl₃): δ

1.19 (d, 6H), 3.29 (quin, *J*=6.9 Hz, 1H), 3.75 (s, 3H), 3.77 (s, 3H), 6.66 (dd, *J*=3.1 Hz, *J*=8.8

Hz, 1H), 6.75 (d, *J*=8.8 Hz, 1H), 6.80 (d, *J*=3.1 Hz, 1H); ¹³C NMR (CDCl₃): δ 22.7 (2C), 26.8,

55.6, 56.0, 110.0, 111.4, 113.1, 138.5, 151.2, 153.7.



Chapter 8.1 “Monosubstituted” Arenes

1-allyloxy-2-*t*-butyl-4-methoxybenzene, **17a**

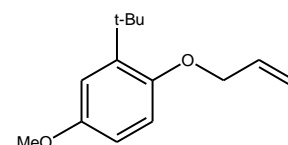
This compound was synthesized using butylated hydroxyanisole (0.76 g,

4.2 mmol) as the starting phenol and allyl bromide (0.62 g, 5.1 mmol) as

the alkylating agent, following the standard THF method. During workup, the solution was not

basified. The product was isolated as a light yellow oil in 88% yield (0.82 g). ¹H NMR (CDCl₃):

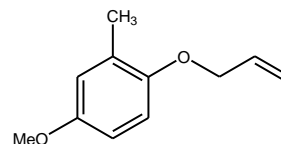
δ 1.39 (s, 9H), 3.75 (s, 3H), 4.49-4.51 (m, 2H), 5.24-5.46 (m, 2H), 6.03-6.12 (m, 1H), 6.65 (dd,



$J=3.1$ Hz, $J=8.8$ Hz, 1H), 6.78 (d, $J=8.8$ Hz, 1H), 6.88 (d, $J=3.1$ Hz, 1H); ^{13}C NMR (CDCl_3): δ 29.7 (3C), 35.0, 69.5, 109.8, 113.3, 114.3, 116.7, 133.9, 140.0, 151.8, 153.4.

2-allyloxy-5-methoxytoluene, **17b**

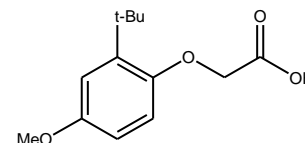
This compound was synthesized using 4-methoxy-2-methylphenol (0.42 g, 3.0 mmol) as the starting phenol and allyl bromide (0.50 g, 4.1



mmol) as the alkylating agent, following the standard THF method. During workup, the solution was not basified. The product was isolated as a brown oil in 81% yield (0.44 g). ^1H NMR (CDCl_3): δ 2.23 (s, 3H), 3.73 (s, 3H), 4.44-4.47 (m, 2H), 5.22-5.42 (m, 2H), 6.00-6.09 (m, 1H), 6.65 (dd, $J=3.0$ Hz, $J=8.8$ Hz, 1H), 6.72 (m, 2H); ^{13}C NMR (CDCl_3): δ 16.5, 55.6, 69.6, 110.8, 112.8, 116.8, 128.4, 134.0, 151.1, 153.6.

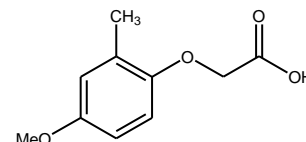
2-(2-*t*-butyl-4-methoxyphenoxy) acetic acid, **20a**

This compound was synthesized using butylated hydroxyanisole (0.345 g, 1.92 mmol) as the starting phenol and 2.5 eq. of sodium chloroacetate



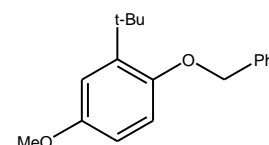
(0.566 g, 4.84 mmol) as the alkylating agent, following the standard microwave method. The method was modified by not using catalytic sodium iodide. The workup did not include basifying the solution, and instead the solution was acidified to pH 1 with 6 M HCl. Standard workup for the microwave method followed. An acid-base extraction was used to purify the product. After the removal of solvent, the product was isolated as a tan solid in a 37% yield (0.17 g), with a trace amount of starting material. ^1H NMR (CDCl_3): δ 1.40 (s, 9H), 3.77 (s, 3H), 4.64 (s, 2H), 6.65 (dd, $J=2.9$ Hz, $J=8.8$ Hz, 1H), 6.70 (d, $J=8.8$ Hz, 1H), 6.90 (d, $J=2.9$ Hz, 1H).

2-(4-methoxy-2-methylphenoxy) acetic acid, **20b**



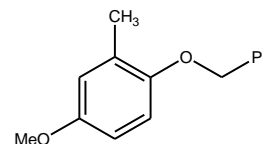
This compound was synthesized using 4-methoxy-2-methylphenol (0.305 g, 1.69 mmol) as the starting phenol and 1.3 eq. of sodium chloroacetate (0.599 g, 5.12 mmol) as the alkylating agent, following the standard microwave method. The method was modified by dissolving the phenol in 15 mL of DMSO and solid alkylating agent was added directly to the phenol solution. During workup, the solution was acidified with aqueous HCl rather than basified. Following a trituration of the impure solid with petroleum ether (5 mL) the product was isolated as a tan solid in 55% yield (0.28 g). ¹H NMR (CDCl₃): δ 2.27 (s, 3H), 3.75 (s, 3H), 4.63 (s, 2H), 6.65 (dd, *J*=2.8 Hz, *J*=8.8 Hz, 1H), 6.70 (d, *J*=8.8 Hz, 1H), 6.74 (d, *J*=2.9 Hz, 1H).

1-benzyloxy-2-*t*-butyl-4-methoxybenzene, **15a**



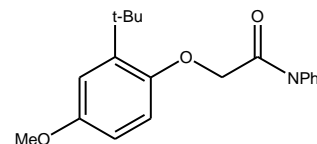
This compound was synthesized using butylated hydroxyanisole (0.290 g, 1.61 mmol) as the starting phenol and benzyl bromide (0.30 g, 1.8 mmol) as the alkylating agent, following the standard microwave method. The method was modified by using only 1.2 eq. of potassium *t*-butoxide, no catalysts, 5 mL total of DMSO as the solvent, and shortening the reaction time to 10 min. The workup was also modified: the solution was not basified and two water washes, 20 mL each, purified the product. The product was isolated as a clear yellow oil in 88% yield (0.37 g). ¹H NMR (CDCl₃): δ 1.40 (s, 9H), 3.76 (s, 3H), 5.06 (s, 2H), 6.66 (dd, *J*=3.1 Hz, *J*=8.8 Hz, 1H), 6.85 (d, *J*=8.8 Hz, 1H), 6.92 (d, *J*=3.1 Hz, 1H), 7.30-7.46 (m, 6H); ¹³C NMR (CDCl₃): δ 29.8 (3C), 35.0, 55.6, 70.7, 109.8, 113.2, 114.5, 127.2 (2C), 127.6, 128.5 (2C), 137.7, 140.0, 151.9, 153.4.

2-benzyloxy-5-methoxytoluene, 15b



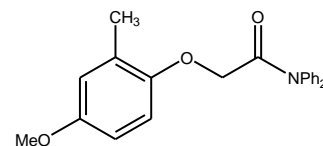
This compound was synthesized using 4-methoxy-2-methylphenol (0.36 g, 3.0 mmol) as the starting phenol and 1.1 eq. of benzyl bromide (0.51 g, 3.0 mmol) as the alkylating agent, following the standard microwave method. The method was modified by using only 1.2 eq. of potassium t-butoxide. The product was isolated as a brown oil in 69% yield (0.41 g). ^1H NMR (CDCl_3): δ 2.26 (s, 3H), 3.72 (s, 3H), 4.99 (s, 2H), 6.64 (dd, $J=3.1$ Hz, $J=8.8$ Hz, 1H), 6.74 (d, $J=8.8$ Hz, 1H), 6.78 (d, $J=3.1$ Hz, 1H), 7.28-7.42 (m, 6H); ^{13}C NMR (CDCl_3): δ 16.7, 27.8, 55.7, 70.6, 110.9, 112.9, 117.1, 127.2, 127.5, 127.8, 128.53, 128.57, 128.59, 137.8, 151.2, 153.7.

2-(2-*t*-butyl-4-methoxyphenoxy)-*N,N*-diphenyl acetamide, 24a



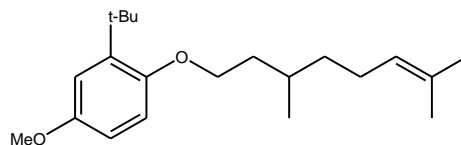
This compound was synthesized using butylated hydroxyanisole (0.315 g, 1.75 mmol) as the starting phenol and 1 eq. of 2-chloro-*N,N*-diphenylacetamide (0.432 g, 1.76 mmol) as the alkylating agent, following the standard THF method. The method was modified by using only 1.1 eq. of potassium t-butoxide and addition of a catalytic amount of 4-dimethylaminopyridine. The impure product was recrystallized from ethanol (10 mL) and yielded the product as a white powder in 66% yield (0.34 g). ^1H NMR (CDCl_3): δ 1.38 (s, 9H), 3.74 (s, 3H), 4.51 (s, 2H), 6.56 (d, $J=8.8$ Hz, 1H), 6.60 (dd, $J=2.8$ Hz, $J=8.8$ Hz, 1H), 6.87 (d, $J=2.8$ Hz, 1H), 7.36 (m, 10H).

2-(4-methoxy-2-methylphenoxy)-*N,N*-diphenyl acetamide, **24b**



This compound was synthesized using 4-methoxy-2-methylphenol (0.34 g, 2.5 mmol) as the starting phenol and 1.1 eq. of 2-chloro-*N,N*-diphenylacetamide (0.68 g, 2.8 mmol) as the alkylating agent, following the standard THF method. The method was modified by addition of a catalytic amount of both sodium iodide and 4-dimethylaminopyridine. The impure product was recrystallized from ethanol (5 mL) and yielded the product as a white powder in 35% yield (0.30 g). ¹H NMR (CDCl₃): δ 2.13 (s, 3H), 3.73 (s, 3H), 4.55 (s, 2H), 6.61 (dd, *J*=2.8 Hz, *J*=8.8 Hz, 1H), 6.63 (d, *J*=8.8 Hz, 1H), 6.90 (d, *J*=2.8 Hz, 1H), 7.25-7.36 (m, 10H).

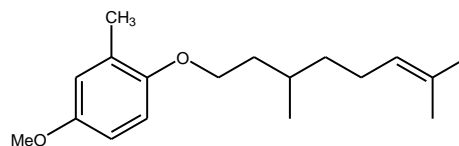
2-*t*-Butyl-1-(3,7-dimethyl-oct-6-enyloxy)-4-methoxybenzene, **27a**



This compound was synthesized using butylated hydroxyanisole (0.935 g, 5.19 mmol) as the starting phenol and β-citronellol mesylate (1.376 g, 5.880 mmol) as the alkylating agent, following the standard microwave method. The workup was modified: the solution was not basified and three extractions with diethyl ether, 25 mL each, were used to isolate the compound. The product was isolated as a brown oil in 84% yield (1.39 g). ¹H NMR (CDCl₃): δ 0.95 (d, *J*=6.6 Hz, 3H), 1.22 (m, 1H), 1.38 (s, 9H), 1.60 (m, 2H), 1.60 (s, 3H), 1.68 (s, 3H), 1.78 (m, 1H), 1.87 (m, 1H), 2.02 (m, 2H), 3.75 (s, 3H), 3.95 (m, 2H), 5.11 (m, 1H), 6.66 (dd, *J*=3.1 Hz, *J*=8.8 Hz, 1H), 6.77 (d, *J*=8.8 Hz, 1H), 6.88 (d, *J*=3.1 Hz, 1H); ¹³C NMR (CDCl₃): δ 17.7, 19.6, 25.5, 25.8, 29.5, 29.7 (3C), 35.0, 36.6, 37.2, 55.6, 66.4, 109.7, 112.3, 114.4, 124.7, 131.3, 139.6, 152.3, 153.0.

2-(3,7-dimethyl-oct-6-enyloxy)-5-methoxytoluene, 27b

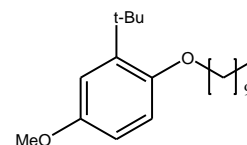
This compound was synthesized using 4-methoxy-2-methylphenol (0.42 g, 3.0 mmol) as the starting phenol and



β -citronellol mesylate (0.72 g, 3.1 mmol) as the alkylating agent, following the standard microwave method. The product was isolated as a brown oil in 64% yield (0.54 g). ^1H NMR (CDCl_3): δ 0.95 (d, $J=6.6$ Hz, 3H), 1.21 (m, 1H), 1.40 (m, 2H), 1.60 (s, 3H), 1.68 (s, 3H), 1.78 (m, 1H), 1.87 (m, 1H), 2.01 (m, 2H), 2.20 (s, 3H), 3.74 (s, 3H), 3.94 (m, 2H), 5.10 (m, 1H), 6.63 (dd, $J=3.1$ Hz, $J=8.6$ Hz, 1H), 6.70-6.74 (m, 2H); ^{13}C NMR (CDCl_3): δ 16.4, 17.7, 19.6, 25.5, 25.7, 29.6, 36.4, 37.2, 55.7, 67.0, 110.8, 112.2, 128.2, 131.2, 151.6, 153.3.

2-*t*-butyl-1-decyloxy-4-methoxybenzene, 23a

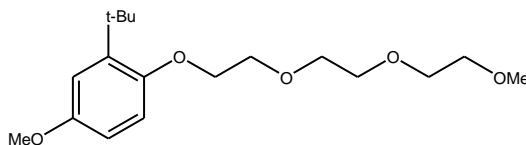
This compound was synthesized using butylated hydroxyanisole



(0.818 g, 4.54 mmol) as the starting phenol (dissolved in 5 mL of DMSO) and 1.2 eq. of 1-bromodecane (1.285 g, 5.86 mmol) as the alkylating agent, following the standard microwave method. The workup was modified: the solution was not basified and three extractions with diethyl ether, 25 mL each, were used to isolate the compound. The product was isolated as a clear colorless oil in 93% yield (1.36 g). ^1H NMR (CDCl_3): δ 0.88 (t, $J=7.1$ Hz, 3H), 1.28 (m, 12H), 1.38 (s, 9H), 1.49 (m, 2H), 1.81 (m, 2H), 3.75 (s, 3H), 3.91 (t, $J=6.5$ Hz, 2H), 6.65 (dd, $J=3.1$ Hz, $J=8.8$ Hz, 1H), 6.76 (d, $J=8.8$ Hz, 1H), 6.88 (d, $J=3.1$ Hz, 1H); ^{13}C NMR (CDCl_3): δ 14.1, 22.7, 26.4, 29.37, 29.42, 29.60, 29.64, 29.7 (3C), 29.8, 32.0, 35.0, 55.6, 68.3, 109.9, 112.3, 114.4, 139.6, 152.3, 153.0.

2-*t*-butyl-4-methoxy-1-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}benzene, 19a

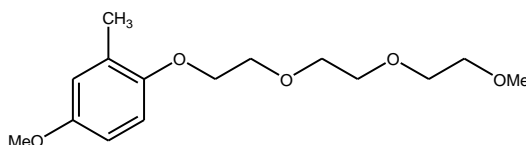
This compound was synthesized using butylated hydroxyanisole (0.91 g, 5.1 mmol) as the starting



phenol and triethylene glycol monomethyl ether tosylate (1.933 g, 6.142 mmol) as the alkylating agent, following the standard microwave method. The workup was modified: the solution was not basified and three extractions with diethyl ether, 25 mL each, were used to isolate the compound. The product was isolated as a brown oil in 86% yield (1.42 g). ¹H NMR (CDCl₃): δ 1.37 (s, 9H), 3.38 (s, 3H), 3.53 (m, 2H), 3.66 (m, 4H), 3.69 (m, 2H), 3.76 (s, 3H), 3.88 (dd, *J*=4.8 Hz, *J*=4.8 Hz, 2H), 4.08 (dd, *J*=4.8 Hz, *J*=4.8 Hz, 2H), 6.65 (dd, *J*=3.1 Hz, *J*=8.8 Hz, 1H), 6.78 (d, *J*=8.8 Hz, 1H), 6.87 (d, *J*=3.1 Hz, 1H); ¹³C NMR (CDCl₃): δ 29.7 (3C), 35.0, 55.6, 59.0, 67.7, 70.0, 70.6, 70.7, 72.0, 109.7, 112.8, 114.3, 139.9, 151.9, 153.3.

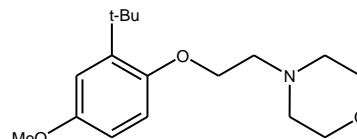
4-methoxy-1-{2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy}-2-methylbenzene, 19b

This compound was synthesized using 4-methoxy-2-methylphenol (0.41 g, 3.0 mmol) as the starting



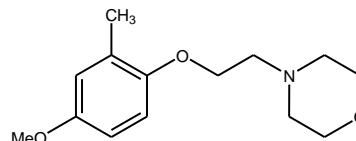
phenol and triethylene glycol monomethyl ether tosylate (1.13 g, 3.6 mmol) as the alkylating agent, following the standard microwave method. The workup was modified: the solution was not basified and three extractions with diethyl ether, 30 mL each, were used to isolate the compound. The product was isolated as a brown oil in 90% yield (0.66 g), with trace impurities. ¹H NMR (CDCl₃): δ 2.20 (s, 3H), 3.37 (s, 3H), 3.53 (m, 2H), 3.66 (m, 4H), 3.66 (m, 2H), 3.73 (s, 3H), 3.83 (dd, *J*=4.8 Hz, *J*=4.8 Hz, 2H), 4.04 (dd, *J*=4.8 Hz, *J*=4.8 Hz, 2H), 6.64 (dd, *J*=3.1 Hz, *J*=8.8 Hz, 1H), 6.67 (d, *J*=8.8 Hz, 1H), 6.71 (d, *J*=3.1 Hz, 1H).

4-[2-(2-*t*-butyl-4-methoxyphenoxy)ethyl] morpholine, **18a**



This compound was synthesized using butylated hydroxyanisole (0.838 g, 4.66 mmol) as the starting phenol and 1.5 eq. of 4-(2-chloroethyl)morpholine hydrochloride (1.310 g, 7.043 mmol) as the alkylating agent, following the standard microwave method using 3 eq. of potassium *t*-butoxide. The method was modified by dissolving the phenol in 15 mL of DMSO and solid alkylating agent was added directly to the phenol solution. The work up was modified by using three extractions with diethyl ether, 30 mL each, to isolate the compound. The product was isolated as a brown oil in 97% yield (1.32 g). ¹H NMR (CDCl₃): δ 1.38 (s, 9H), 2.57 (dd, *J*=4.6 Hz, *J*=4.6 Hz, 4H), 2.83 (t, *J*=6.0 Hz, 2H), 3.72 (dd, *J*=4.6 Hz, *J*=4.6 Hz, 4H), 3.76 (s, 3H), 4.06 (t, *J*=6.0 Hz, 2H), 6.66 (dd, *J*=3.1 Hz, *J*=8.8 Hz, 1H), 6.79 (d, *J*=8.8 Hz, 1H), 6.89 (d, *J*=3.1 Hz, 1H); ¹³C NMR (CDCl₃): δ 29.8 (3C), 35.0, 54.1 (2C), 55.6, 58.0, 67.0 (2C), 109.8, 112.8, 114.4, 139.8, 151.9, 153.3.

4-[2-(2-methyl-4-methoxyphenoxy)ethyl] morpholine, **18b**

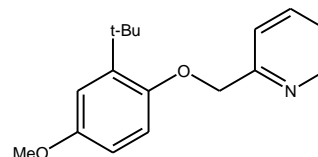


This compound was synthesized using 4-methoxy-2-methylphenol (0.38 g, 2.6 mmol) as the starting phenol and 1.2 eq. of 4-(2-chloroethyl)morpholine hydrochloride (0.58 g, 3.1 mmol) as the alkylating agent, following the standard microwave method using 3 eq. of potassium *t*-butoxide. The method was modified by dissolving the phenol in 15 mL of DMSO and solid alkylating agent was added directly to the phenol solution. The product was isolated as a brown oil in 64% yield (0.42 g). ¹H NMR (CDCl₃): δ 2.20 (s, 3H), 2.59 (dd, *J*=4.6 Hz, *J*=4.6 Hz, 4H), 2.83 (t, *J*=5.7 Hz, 2H), 3.72 (dd, *J*=4.6 Hz, *J*=4.6 Hz, 4H), 3.77 (s, 3H), 4.06 (t, *J*=5.7 Hz, 2H), 6.64 (dd, *J*=3.0 Hz, *J*=8.9 Hz,

1H), 6.75 (m, 2H); ¹³C NMR (CDCl₃): δ 16.5, 54.1 (2C), 55.6, 57.9, 67.0 (2C), 110.8, 112.5, 117.0, 128.3, 151.2, 153.6.

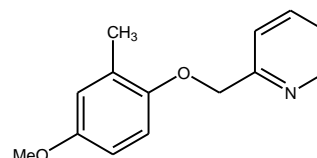
2-(2-*t*-butyl-4-methoxyphenoxy)methyl)pyridine, **40a**

This compound was synthesized using butylated hydroxyanisole (0.55 g, 3.1 mmol) as the starting phenol and 2-picolyl chloride hydrochloride (0.58 g, 3.5 mmol) as the alkylating agent, following the standard microwave method using 2.2 eq. of potassium *t*-butoxide. The method was modified by dissolving the phenol in 15 mL of DMSO and solid alkylating agent was added directly to the phenol solution. The product was isolated as a brown oil in 97% yield (0.80 g), with trace impurities. ¹H NMR (CDCl₃): δ 1.43 (s, 9H), 3.73 (s, 3H), 5.22 (s, 2H), 6.64 (dd, *J*=3.1 Hz, *J*=8.8 Hz, 1H), 6.81 (d, *J*=8.8 Hz, 1H), 6.93 (d, *J*=3.1 Hz, 1H), 7.18 (m, 1H), 7.58 (d, *J*=7.8 Hz 1H), 7.70 (m, 1H), 8.58 (m, 1H); ¹³C NMR (CDCl₃): δ 29.8 (3C), 35.0, 55.5, 71.4, 109.8, 113.4, 114.6, 121.2, 122.5, 137.0, 139.8, 149.0, 151.4, 153.6, 158.0.



2-(4-methoxy-2-methylphenoxy)methyl)pyridine, **40b**

This compound was synthesized using 4-methoxy-2-methylphenol (0.42 g, 3.0 mmol) as the starting phenol and 2-picolyl chloride hydrochloride (0.55 g, 3.4 mmol) as the alkylating agent, following the standard microwave method using 2.2 eq. of potassium *t*-butoxide. The method was modified by dissolving the phenol in 15 mL of DMSO and solid alkylating agent was added directly to the phenol solution. The product was isolated as a brown oil in 56% yield (0.39 g). ¹H NMR (CDCl₃): δ 2.31 (s, 3H), 3.73 (s, 3H), 5.15 (s, 2H), 6.63 (dd, *J*=3.1 Hz, *J*=8.8 Hz, 1H), 6.77 (m,



2H), 7.19 (m, 1H), 7.54 (d, $J=7.9$ Hz, 1H), 7.68 (m, 1H), 8.56 (d, $J=4.8$ Hz, 1H); ^{13}C NMR (CDCl_3): δ 16.6, 55.6, 71.2, 110.8, 112.5, 117.2, 121.0, 122.4, 128.2, 136.8, 149.1, 150.7, 153.7, 158.0.

2-*t*-butyl-1-(2-dimethylaminoethoxy)-4-methoxybenzene, 22a

This compound was synthesized using butylated hydroxyanisole

(0.881 g, 4.89 mmol) as the starting phenol and 2-chloro-*N,N*-

dimethylethylamine hydrochloride (0.779 g, 5.41 mmol) as the alkylating agent, following the

standard microwave method using 2.5 eq. of potassium *t*-butoxide. The workup was modified:

the solution was not basified and three extractions with diethyl ether, 30 mL each, were used to

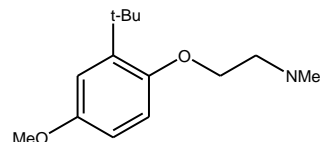
isolate the compound. The product was isolated as a brown oil in 90% yield (1.10 g). ^1H NMR

(CDCl_3): δ 1.37 (s, 9H), 2.34 (s, 6H), 2.78 (t, $J=6.4$ Hz, 2H), 3.75 (s, 3H), 4.05 (t, $J=6.4$ Hz,

2H), 6.66 (dd, $J=3.1$ Hz, $J=8.8$ Hz, 1H), 6.79 (d, $J=8.8$ Hz, 1H), 6.89 (d, $J=3.1$ Hz, 1H); ^{13}C

NMR (CDCl_3): δ 29.8 (3C), 34.9, 45.9, 46.2, 55.6, 58.6, 67.2, 109.8, 113.0, 114.3, 139.9, 152.0,

153.3.



2-(2-dimethylaminoethoxy)-5-methoxytoluene, 22b

This compound was synthesized using 4-methoxy-2-methylphenol

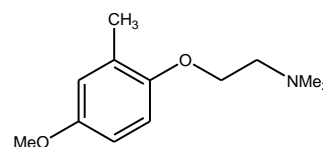
(0.40 g, 2.9 mmol) as the starting phenol and 2-chloro-*N,N*-

dimethylethylamine hydrochloride (0.46 g, 3.2 mmol) as the alkylating agent, following the

standard microwave method using 2.5 eq. of potassium *t*-butoxide. The method was modified by

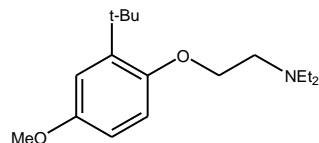
dissolving the phenol in 15 mL of DMSO and solid alkylating agent was added directly to the

phenol solution. The solution was not basified during workup. The product was isolated as a



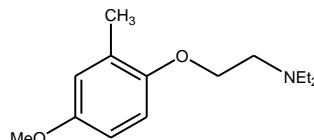
brown oil in 69% yield (0.42 g). ^1H NMR (CDCl_3): δ 2.20 (s, 3H), 2.34 (s, 6H), 2.73 (t, $J=5.8$ Hz, 2H), 3.74 (s, 3H), 4.00 (t, $J=5.8$ Hz, 2H), 6.64 (dd, $J=2.9$ Hz, $J=8.8$ Hz, 1H), 6.71 (d, $J=2.9$ Hz, 1H), 6.74 (d, $J=8.8$ Hz, 1H); ^{13}C NMR (CDCl_3): δ 16.5, 46.1 (2C), 55.6, 58.6, 67.5, 110.8, 112.5, 116.9, 128.3, 151.3, 153.5.

2-*t*-butyl-1-(2-diethylaminoethoxy)-4-methoxybenzene, 39a



This compound was synthesized using butylated hydroxyanisole (0.52 g, 2.9 mmol) as the starting phenol and 2-chloro-*N,N*-diethylethylamine hydrochloride (0.56 g, 3.3 mmol) as the alkylating agent, following the standard microwave method using 2.5 eq. of potassium *t*-butoxide. The method was modified by dissolving the phenol in 15 mL of DMSO and solid alkylating agent was added directly to the phenol solution. The product was isolated as a clear light yellow oil in 87% yield (0.70 g). ^1H NMR (CDCl_3): δ 1.06 (t, $J=7.2$ Hz, 3H), 1.37 (s, 9H), 2.62 (q, $J=7.2$ Hz, 2H), 2.89 (t, $J=6.7$ Hz, 2H), 3.75 (s, 3H), 4.01 (t, $J=6.7$ Hz, 2H), 6.66 (dd, $J=3.1$ Hz, $J=8.8$ Hz, 1H), 6.80 (d, $J=8.8$ Hz, 1H), 6.88 (d, $J=3.1$ Hz, 1H); ^{13}C NMR (CDCl_3): δ 11.9, 12.1, 29.7 (3C), 35.0, 47.8, 47.9, 52.4, 55.6, 67.4, 109.8, 112.9, 114.3, 139.8, 152.1, 153.2.

2-(2-diethylaminoethoxy)-5-methoxytoluene, 39b



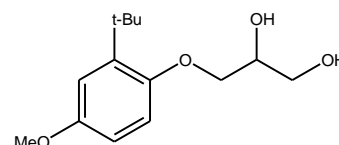
This compound was synthesized using 4-methoxy-2-methylphenol (0.44 g, 3.2 mmol) as the starting phenol and 2-chloro-*N,N*-diethylethylamine hydrochloride (0.61 g, 3.5 mmol) as the alkylating agent, following the standard microwave method using 2.5 eq. of potassium *t*-butoxide. The method was modified by dissolving the phenol in 15 mL of DMSO and solid alkylating agent was added directly to the phenol solution. The product was isolated as a brown oil in 75% yield (0.57 g). ^1H NMR

(CDCl₃): δ 1.07 (t, $J=7.2$ Hz, 3H), 2.20 (s, 3H), 2.63 (q, $J=7.2$ Hz, 2H), 2.87 (t, $J=6.2$ Hz, 2H), 3.73 (s, 3H), 3.98 (t, $J=6.2$ Hz, 2H), 6.64 (dd, $J=3.1$ Hz, $J=8.7$ Hz, 1H), 6.68-6.71 (m, 2H); ¹³C NMR (CDCl₃): δ 12.01 (2C), 16.5, 47.9 (2C), 51.9, 55.6, 67.6, 110.7, 112.0, 117.0, 128.1, 151.4, 153.4.

3-(2-*t*-butyl-4-methoxyphenoxy)-propane-1,2-diol, **41a**

This compound was synthesized using butylated hydroxyanisole

(0.44 g, 2.4 mmol) as the starting phenol and epichlorohydrin (0.34

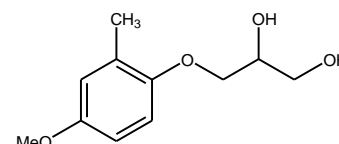


g, 3.6 mmol) as the alkylating agent, following the standard THF method. The solution was not basified during workup. The product was isolated as a clear yellow oil in 82% yield (0.51 g). ¹H NMR (CDCl₃): δ 1.39 (s, 9H), 2.76 (dd, $J=2.7$ Hz, $J=5.0$ Hz, 1H), 2.85 (dd, $J=4.2$ Hz, $J=5.0$ Hz, 1H), 3.36 (m, 1H), 3.75 (s, 3H), 3.93 (dd, $J=5.5$ Hz, $J=10.9$ Hz, 1H), 4.19 (dd, $J=3.1$ Hz, $J=10.9$ Hz, 1H), 6.66 (dd, $J=3.1$ Hz, $J=8.8$ Hz, 1H), 6.76 (d, $J=8.8$ Hz, 1H), 6.88 (d, $J=3.1$ Hz, 1H); ¹³C NMR (CDCl₃): δ 29.8 (3C), 35.0, 44.8, 50.4, 55.6, 69.4, 109.8, 113.2, 114.4, 140.0, 151.6, 153.6.

3-(4-methoxy-2-methylphenoxy)-propane-1,2-diol, **41b**

This compound was synthesized using 4-methoxy-2-methylphenol

(0.34 g, 2.5 mmol) as the starting phenol and epichlorohydrin (0.37



g, 4.0 mmol) as the alkylating agent, following the standard THF method. The solution was not basified during workup. The product was isolated as a clear yellow oil in 61% yield (0.32 g). ¹H NMR (CDCl₃): δ 2.22 (s, 3H), 2.73 (dd, $J=2.7$ Hz, $J=5.0$ Hz, 1H), 2.89 (dd, $J=4.2$ Hz, $J=5.0$ Hz, 1H), 3.31 (m, 1H), 3.75 (s, 3H), 3.93 (dd, $J=5.5$ Hz, $J=11.1$ Hz, 1H), 4.14 (dd, $J=3.0$ Hz,

$J=11.1$ Hz, 1H), 6.64 (dd, $J=3.3$ Hz, $J=8.9$ Hz, 1H), 6.71-6.75 (m, 2H); ^{13}C NMR (CDCl_3): δ 16.4, 44.6, 50.4, 55.6, 69.7, 110.9, 113.0, 117.0, 128.5, 151.0, 153.9.

2-(2-*t*-butyl-4-methoxyphenoxy)-*N,N*-bis-(2-methoxyethyl) acetamide, **26a**

This compound was synthesized using butylated

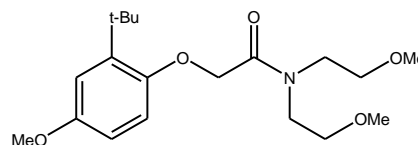
hydroxyanisole (0.789 g, 4.38 mmol) as the starting phenol

and 2-chloro-*N,N*-bis-(2-methoxyethyl)acetamide (1.008 g, 4.800 mmol) as the alkylating agent,

following the standard microwave method. The workup was modified: the solution was not

basified and three extractions with diethyl ether, 30 mL each, were used to isolate the compound.

The product was isolated as a brown oil in 77% yield (1.24 g), with trace impurities. ^1H NMR (CDCl_3): δ 1.40 (s, 9H), 3.33 (s, 3H), 3.34 (s, 3H), 3.51-3.63 (m, 8H), 3.75 (s, 3H), 4.76 (s, 2H), 6.65 (dd, $J=3.1$ Hz, $J=8.8$ Hz, 1H), 6.77 (d, $J=8.8$ Hz, 1H), 6.88 (d, $J=3.1$ Hz, 1H); ^{13}C NMR (CDCl_3): δ 29.8 (3C), 35.0, 46.1, 48.4, 55.6, 58.9, 59.1, 67.8, 70.4, 71.1, 109.9, 113.3, 114.4, 140.0, 151.6, 153.7, 169.0.



2-(2-methyl-4-methoxyphenoxy)-*N,N*-bis-(2-methoxyethyl) acetamide, **26b**

This compound was synthesized using 4-methoxy-2-

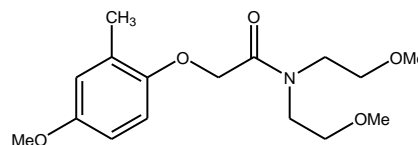
methylphenol (0.41 g, 3.0 mmol) as the starting phenol and 2-

chloro-*N,N*-bis-(2-methoxyethyl)acetamide (0.70 g, 3.3 mmol) as the alkylating agent, following

the standard microwave method using 1.2 eq. of potassium *t*-butoxide. The solution was not

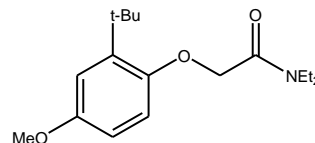
basified during workup. The product was isolated as a brown oil in 58% yield (0.54 g). ^1H NMR

(CDCl_3): δ 2.26 (s, 3H), 3.30 (s, 3H), 3.34 (s, 3H), 3.51-3.63 (m, 8H), 3.74 (s, 3H), 4.76 (s, 2H), 6.62 (dd, $J=3.1$ Hz, $J=8.8$ Hz, 1H), 6.72 (d, $J=3.1$ Hz, 1H), 6.75 (d, $J=8.8$ Hz, 1H); ^{13}C NMR



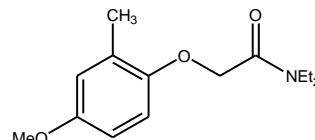
(CDCl₃): δ 16.5, 46.3, 48.3, 55.6, 58.8, 59.0, 68.0, 70.6, 71.0, 110.8, 112.7, 112.7, 117.0, 128.2, 150.7, 153.9, 169.1.

2-(2-*t*-butyl-4-methoxyphenoxy)-*N,N*-diethyl acetamide, **36a**



This compound was synthesized using butylated hydroxyanisole (0.43 g, 2.4 mmol) as the starting phenol and 1.1 eq. of 2-chloro-*N,N*-diethylacetamide (0.40 g, 2.7 mmol) as the alkylating agent, following the standard THF method using 1.2 eq. of potassium *t*-butoxide. The method was modified by addition of a catalytic amount of both sodium iodide and 4-dimethylaminopyridine. The product was isolated as a brown oil in 91% yield (0.64 g). ¹H NMR (CDCl₃): δ 1.17-1.20 (m, 6H), 1.39 (s, 9H), 3.41-3.45 (m, 4H), 3.75 (s, 3H), 4.62 (s, 2H), 6.66 (dd, *J*=3.1 Hz, *J*=8.8 Hz, 1H), 6.79 (d, *J*=8.8 Hz, 1H), 6.89 (d, *J*=3.1 Hz, 1H); ¹³C NMR (CDCl₃): δ 12.8, 14.4, 29.6 (3C), 35.0, 40.0, 41.3, 55.6, 68.5, 109.9, 113.6, 114.4, 140.1, 151.7, 153.8, 167.4.

2-(4-methoxy-2-methylphenoxy)-*N,N*-diethyl acetamide, **36b**

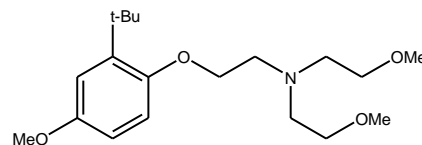


This compound was synthesized using 4-methoxy-2-methylphenol (0.32 g, 2.3 mmol) as the starting phenol and 1.1 eq. of 2-chloro-*N,N*-diethylacetamide (0.40 g, 2.7 mmol) as the alkylating agent, following the standard THF method using 1.2 eq. of potassium *t*-butoxide. The method was modified by addition of a catalytic amount of both sodium iodide and 4-dimethylaminopyridine. The product was isolated as a brown oil in 67% yield (0.39 g). ¹H NMR (CDCl₃): δ 1.12-1.20 (m, 6H), 2.24 (s, 3H), 3.37-3.43 (m, 4H), 3.73 (s, 3H), 4.62 (s, 2H), 6.64 (dd, *J*=3.0 Hz, *J*=8.8 Hz, 1H), 6.72 (d, *J*=3.0 Hz, 1H), 6.77 (d, *J*=8.8 Hz,

^1H); ^{13}C NMR (CDCl_3): δ 12.8, 14.3, 16.5, 40.2, 41.4, 55.6, 68.7, 110.8, 112.6, 117.1, 128.1, 150.7, 153.9, 167.5.

[2-(2-*t*-butyl-4-methoxyphenoxy)-ethyl]-bis-(2-methoxyethyl)-amine, **38a**

2-(2-*t*-butyl-4-methoxyphenoxy)-*N,N*-bis-(2-methoxyethyl)



acetamide (0.40 g, 1.1 mmol) was dissolved with freshly

distilled THF in an oven dried 25 mL round bottom flask, equipped with a magnetic stir bar.

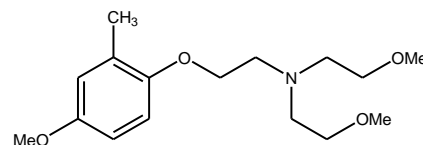
Sodium borohydride (0.138 g, 3.63 mmol) was added all at once to the solution, and the slurry was cooled in an ice bath. Iodine (0.298 g, 1.17 mmol) was added portion-wise over several minutes minimizing effervescence, and forming a yellow solution. The resulting solution stirred while chilled in an ice bath for 30 min under dry nitrogen atmosphere, and the yellow color disappeared. The flask was equipped with a water condenser, and the clear colorless solution was heated to reflux and stirred for 7 hrs while under a dry nitrogen atmosphere. The resulting solution was cooled in an ice bath and was slowly quenched with 1 M HCl (5 mL, 5 mmol). The mixture stirred while in the ice bath for an additional 30 min. The solution was then basified to pH 14 with 3 M NaOH and was extracted with diethyl ether (2 x 25 mL). The combined ether layers were washed with sat. NaCl (1 x 10 mL) and dried (MgSO_4). The solvent was removed under reduced pressure yielding the product as a yellow oil in 47% yield (0.18 g). ^1H NMR (CDCl_3): δ 1.35 (s, 9H), 3.16-3.20 (m, 4H), 3.34 (s, 6H), 3.37-3.38 (m, 2H), 3.76-3.82 (m, 7H), 4.36 (t, J = 6.2 Hz, 2H), 6.67 (dd, J =3.1 Hz, J =8.8 Hz, 1H), 6.85-6.87 (m, 2H); ^{13}C NMR (CDCl_3): δ 29.8 (3C), 34.9, 55.6, 58.8 (2C), 60.2, 60.5 (2C), 63.9, 67.8 (2C), 109.9, 113.7, 114.4, 139.9, 151.4, 153.6.

Bis-(2-methoxy-ethyl)-[2-(4-methoxy-2-methyl-phenoxy)-ethyl]-amine, **38b**

2-(2-methyl-4-methoxyphenoxy)-*N,N*-bis-(2-methoxyethyl)

acetamide (0.89 g, 2.9 mmol) was dissolved with freshly

distilled THF in an oven dried 50 mL round bottom flask, equipped with a magnetic stir bar.



Sodium borohydride (0.28 g, 7.4 mmol) was added all at once to the solution, and the slurry was

cooled in an ice bath. Iodine (1.05 g, 4.13 mmol) was added portion-wise over several minutes

minimizing effervescence, and forming a yellow solution. The resulting solution was diluted

with THF (7.5 mL) and the flask was equipped with a water condenser. The solution was heated

to reflux and stirred for 16.5 hrs while under a dry nitrogen atmosphere. The resulting solution

was slowly quenched with 1 M HCl (10 mL, 10 mmol). The solution was then basified to pH 14

with 3 M NaOH and was extracted with diethyl ether (3 x 25 mL). The combined ether layers

were washed with water (1 x 25 mL), sat. NaCl (1 x 10 mL), and dried (MgSO₄). The solvent

was removed under reduced pressure yielding a mixture of product and starting material as

determined by ¹H NMR. The mixture was purified with an acid-base extraction and the solvent

was removed under reduced pressure yielding the product as a clear colorless oil in 44% yield

(0.37 g). ¹H NMR (CDCl₃): δ 2.20 (s, 3H), 2.85 (t, *J*=6.0 Hz, 4H), 3.02 (t, *J*=6.0 Hz, 2H), 3.34

(s, 6H), 3.50 (t, *J*=6.0 Hz, 4H), 3.75 (s, 3H), 4.00 (t, *J*=6.0 Hz, 2H), 6.65 (dd, *J*=3.1 Hz, *J*=8.7

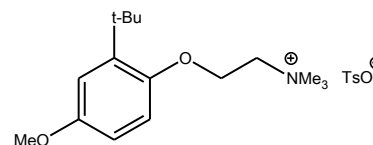
Hz, 1H), 6.71-6.75 (m, 2H); ¹³C NMR (CDCl₃) 16.5, 54.2, 54.7 (2C), 55.6, 58.8 (2C), 67.3, 71.3

(2C), 110.7, 112.0, 117.0, 128.0, 151.3, 153.4.

[2-(2-*t*-butyl-4-methoxyphenoxy)-ethyl]-trimethylammonium tosylate, **42a**

2-*t*-butyl-1-(2-dimethylaminoethoxy)-4-methoxybenzene (0.35

g, 1.4 mmol) was dissolved in 10 mL acetonitrile in a 25 mL

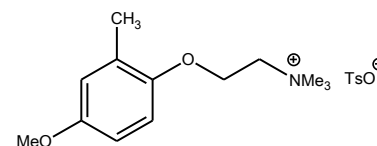


round bottom flask, equipped with a magnetic stir bar. Methyl tosylate (0.29 g, 1.6 mmol) was dissolved with 5 mL acetonitrile in a 10 mL Erlenmeyer flask. The solution was added all at once to the round bottom flask. The combined solution stirred at ambient temperature for 18.5 hrs, while stoppered. The solvent was removed under reduced pressure yielding the product as a white solid in 77% yield (0.47 g). ¹H NMR (D₂O): δ 1.35 (s, 9H), 2.38 (s, 3H), 3.29 (s, 9H), 3.80 (s, 3H), 3.88-3.90 (m, 2H), 4.45-4.47 (m, 2H), 6.88 (dd, *J*=3.1 Hz, *J*=8.9 Hz, 1H), 7.00 (d, *J*=3.1 Hz, 1H), 7.06 (d, *J*=8.9 Hz, 1H), 7.34 (d, *J*=8.1 Hz, 2H), 7.68 (d, *J*=8.1 Hz, 2H).

[2-(4-methoxy-2-methylphenoxy)-ethyl]-trimethylammonium tosylate, **42b**

2-(2-dimethylaminoethoxy)-5-methoxytoluene (0.31 g, 1.5 mmol)

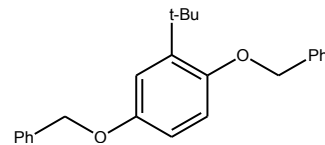
was dissolved in 10 mL acetonitrile in a 25 mL round bottom



flask, equipped with a magnetic stir bar. Methyl tosylate (0.30 g, 1.6 mmol) was dissolved with 5 mL acetonitrile in a 10 mL Erlenmeyer flask. The solution was added all at once to the round bottom flask. The combined solution stirred at ambient temperature for 18.5 hrs, while stoppered. The solvent was removed under reduced pressure yielding the product as a tan solid in ~100% yield (0.63 g). ¹H NMR (D₂O): δ 2.20 (s, 3H), 2.35 (s, 3H), 3.24 (s, 9H), 3.80 (s, 3H), 3.77-3.79 (m, 2H), 4.35-4.37 (m, 2H), 6.80 (dd, *J*=3.0 Hz, *J*=9.0 Hz, 1H), 6.85-6.92 (m, 2H), 7.30 (d, *J*=8.1 Hz, 2H), 7.67 (d, *J*=8.1 Hz, 2H).

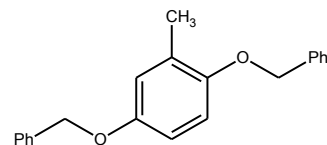
Chapter 8.2 “Disubstituted” Arenes

1,4-Bis-benzyloxy-2-*t*-butylbenzene, **35a**



This compound was synthesized using *t*-butylhydroquinone (0.773 g, 4.83 mmol) as the starting phenol and 2 eq. of benzyl bromide (1.658 g, 9.696 mmol) as the alkylating agent, following the standard microwave method using 2.2 eq. of potassium *t*-butoxide. The workup was modified: the solution was not basified and three extractions with diethyl ether, 25 mL each, were used to isolate the compound. The product was isolated as a tan solid in 88% yield (1.42 g). ¹H NMR (CDCl₃): δ 1.39 (s, 9H), 5.00 (s, 2H), 5.06 (s, 2H), 6.73 (dd, *J*=3.0 Hz, *J*=8.8 Hz, 1H), 6.84 (d, *J*=8.8 Hz, 1H), 6.99 (d, *J*=3.0 Hz, 1H), 7.32-7.44 (m, 10H); ¹³C NMR (CDCl₃): δ 29.8 (3C), 35.0, 70.60, 70.63, 111.0, 113.1, 115.4, 127.3 (2C), 127.6 (2C), 128.5 (2C), 137.4, 137.7, 140.0, 152.1, 152.7.

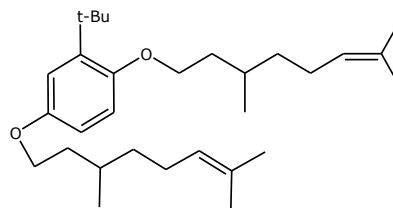
2,5-bis-benzyloxytoluene, **35b**



This compound was synthesized using methylhydroquinone (0.57 g, 4.6 mmol) as the starting phenol and 2 eq. of benzyl bromide (1.59 g, 9.30 mmol) as the alkylating agent, following the standard microwave method using 2.2 eq. of potassium *t*-butoxide. The workup was modified using three extractions with diethyl ether, 25 mL each, to isolate the compound. The product was isolated as a brown oil in 80% yield (1.12 g). ¹H NMR (CDCl₃): δ 2.40 (s, 3H), 5.09 (s, 2H), 5.10 (s, 2H), 6.73 (dd, *J*=2.9 Hz, *J*=8.8 Hz, 1H), 6.89 (d, *J*=8.8 Hz, 1H), 6.97 (d, *J*=2.9 Hz, 1H), 7.41-7.53 (m, 10H); ¹³C NMR (CDCl₃): δ 16.7, 70.6, 70.8, 112.1, 112.8, 118.2, 127.3 (2C), 127.6 (2C), 128.0, 128.7 (2C), 137.6 137.8, 151.5, 153.0.

1,4-Bis-(3,7-dimethyl-oct-6-enyloxy)-2-*t*-butylbenzene, **33a**

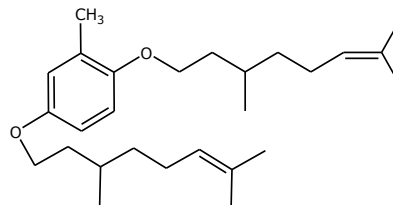
This compound was synthesized using *t*-butylhydroquinone (0.42 g, 2.6 mmol) as the starting phenol and 2 eq. of β -citronellol mesylate (1.22 g, 5.20 mmol) as the alkylating agent,



following the standard microwave method using 2.2 eq. of potassium *t*-butoxide. The product was isolated as a brown oil in 73% yield (0.85 g). ^1H NMR (CDCl_3): δ 0.94 (d, $J=6.6$ Hz, 3H), 0.95 (d, $J=6.6$ Hz, 3H), 1.20-1.35 (m, 4H), 1.37 (s, 9H), 1.60 (m, 4H), 1.61 (s, 6H), 1.68 (s, 6H), 1.78-1.85 (m, 4H), 2.00 (m, 4H), 3.91 (m, 4H), 5.10 (m, 2H), 6.65 (dd, $J=3.0$ Hz, $J=8.8$ Hz, 1H), 6.76 (d, $J=8.8$ Hz, 1H), 6.87 (d, $J=3.0$ Hz, 1H); ^{13}C NMR (CDCl_3): δ 17.7 (2C), 19.55, 19.62, 25.5 (2C), 25.7 (2C), 29.5, 29.6, 29.8 (3C), 35.0, 36.4, 36.6, 37.17, 37.21, 66.4, 66.7, 110.5, 112.3, 115.0, 124.7, 124.8, 131.2, 131.3, 139.5, 152.1, 152.5.

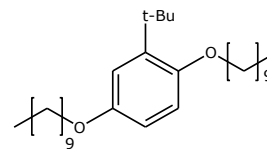
2,5-Bis-(3,7-dimethyl-oct-6-enyloxy)-toluene, **33b**

This compound was synthesized using methylhydroquinone (0.32 g, 2.6 mmol) as the starting phenol and 2 eq. of β -citronellol mesylate (1.22 g, 5.20 mmol) as the alkylating agent,



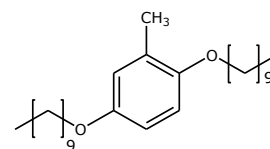
following the standard microwave method using 2.2 eq. of potassium *t*-butoxide. The product was isolated as a brown oil in 51% yield (0.88 g). ^1H NMR (CDCl_3): δ 0.93 (d, $J=6.6$ Hz, 3H), 0.94 (d, $J=6.5$ Hz, 3H), 1.18-1.30 (m, 4H), 1.36-1.39 (m, 4H), 1.61 (s, 6H), 1.68 (s, 6H), 1.78-1.85 (m, 4H), 2.00 (m, 4H), 3.92 (m, 4H), 5.10 (m, 2H), 6.64 (dd, $J=3.0$ Hz, $J=8.8$ Hz, 1H), 6.71-6.73 (m, 2H); ^{13}C NMR (CDCl_3): δ 16.4, 17.7 (2C), 19.59, 19.64, 25.50, 25.51, 25.7 (2C), 27.6, 29.57, 36.4, 36.5, 37.16, 37.20, 66.8, 67.0, 111.6, 112.2, 117.7, 127.8, 128.1, 131.2, 151.5, 152.8.

2-*t*-butyl-1,4-didecyloxybenzene, 31a



This compound was synthesized using *t*-butylhydroquinone (0.527 g, 3.29 mmol) as the starting phenol and 2.5 eq. of 1-bromodecane (1.604 g, 7.26 mmol) as the alkylating agent, following the standard microwave method using 2.5 eq. of potassium *t*-butoxide. The product was isolated as a brown oil in 85% yield (1.21 g). The solution was not basified during workup. ¹H NMR (CDCl₃): δ 0.88 (t, *J*=6.9 Hz, 6H), 1.27-1.28 (m, 24H), 1.38 (s, 9H), 1.43 (m, 4H), 1.73-1.81 (m, 4H), 3.87-3.92 (m, 4H), 6.64 (dd, *J*=3.0 Hz, *J*=8.8 Hz, 1H), 6.74 (d, *J*=8.8 Hz, 1H), 6.88 (d, *J*=3.0 Hz, 1H); ¹³C NMR (CDCl₃): δ 14.1 (2C), 22.7 (2C), 26.1, 26.4, 29.2 (2C), 29.35 (2C), 29.4, 29.48, 29.50, 29.53, 29.60, 29.63, 29.8 (3C), 31.9 (2C), 35.0, 68.3, 68.5, 110.5, 112.3, 114.1, 114.9, 139.3, 139.5, 152.1, 152.5.

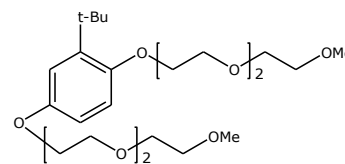
2,5-didecyloxytoluene, 31b



This compound was synthesized using methylhydroquinone (0.422 g, 3.40 mmol) as the starting phenol and 2.5 eq. of 1-bromodecane (1.651 g, 7.470 mmol) as the alkylating agent, following the standard microwave method using 2.5 eq. of potassium *t*-butoxide. The solution was not basified during workup. The product was isolated as a tan solid in 73% yield (1.00 g). ¹H NMR (CDCl₃): δ 0.88 (t, *J*=6.9 Hz, 6H), 1.27-1.28 (m, 24H), 1.38 (s, 9H), 1.43 (m, 4H), 1.73-1.81 (m, 4H), 2.20 (s, 3H), 3.87-3.92 (m, 4H), 6.64 (dd, *J*=3.0 Hz, *J*=9.0 Hz, 1H), 6.74 (m, 2H); ¹³C NMR (CDCl₃): δ 14.1 (2C), 16.4, 22.7 (2C), 26.1, 26.2, 29.3 (2C), 29.4 (2C), 29.5 (2C), 29.58 (2C), 29.60, 29.63, 31.9 (2C), 68.6, 68.9, 111.6, 112.3, 117.6, 128.1, 151.5, 152.8.

2-*t*-Butyl-1,4-bis-[2-[2-(2-methoxy-ethoxy)-ethoxy]-ethoxy]benzene, **30a**

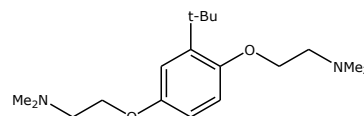
This compound was synthesized using *t*-butylhydroquinone (0.744 g, 4.65 mmol) as the starting phenol and 3 eq. of triethylene glycol



monomethyl ether tosylate (4.429 g, 13.93 mmol) as the alkylating agent, following the standard microwave method using 3 eq. of potassium *t*-butoxide. The method was modified by heating the combined solution in a microwave reactor to 180 °C with a max power of 150 W for 30 min. The solution was not basified during workup. The reaction produced a mixture of fully and partially alkylated products. The mixture was treated under identical conditions and the desired product was isolated as a brown goo in 72% yield (1.54 g). ¹H NMR (CDCl₃): δ 1.37 (s, 9H), 3.38 (s, 6H), 3.55 (m, 4H), 3.65 (m, 8H), 3.72 (m, 4H), 3.83-3.87 (m, 4H), 4.07 (m, 4H), 6.64 (dd, *J*=3.0 Hz, *J*=8.8 Hz, 1H), 6.75 (d, *J*=8.8 Hz, 1H), 6.90 (d, *J*=3.0 Hz, 1H); ¹³C NMR (CDCl₃): δ 29.7 (3C), 34.9, 59.0 (2C), 67.6, 67.8, 69.9, 10.0, 70.5, 70.56, 7.64 (2C), 70.7, 70.8, 71.9 (2C), 110.7, 112.7, 115.1, 127.0, 129.6, 152.0, 152.5.

1,4-bis(2-dimethylaminoethoxy)-2-*t*-butylbenzene, **32a**

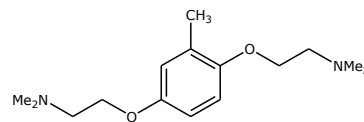
This compound was synthesized using *t*-butylhydroquinone (0.314 g, 1.96 mmol) as the starting phenol and 2.2 eq of 2-chloro-*N,N*-dimethylethylamine



hydrochloride (0.627 g, 4.35 mmol) as the alkylating agent, following the standard microwave method using 5 eq. of potassium *t*-butoxide. The method was modified by dissolving the phenol in 15 mL of DMSO and solid alkylating agent was added directly to the phenol solution. The product was isolated as a brown oil in 75% yield (0.44 g). ¹H NMR (CDCl₃): δ 1.36 (s, 9H), 2.36 (s, 6H), 2.34 (s, 6H), 2.70 (t, *J*=5.8 Hz, 2H), 2.77 (t, *J*=6.4 Hz, 2H), 4.00 (t, *J*=5.8 Hz, 2H), 4.05 (t, *J*=6.4 Hz, 2H), 6.67 (dd, *J*=3.0 Hz, *J*=8.8 Hz, 1H), 6.78 (d, *J*=8.8 Hz, 1H), 6.90 (d, *J*=3.0 Hz,

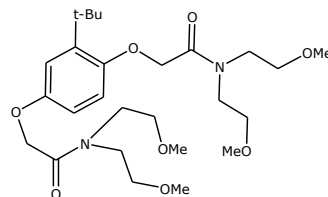
^1H); ^{13}C NMR (CDCl_3): δ 29.8 (3C), 34.9, 45.8 (2C), 46.1 (2C), 58.5, 58.6, 66.2, 67.1, 110.5, 112.9, 115.1, 139.7, 152.0, 152.5.

2,5-bis(2-dimethylaminoethoxy)toluene, **32b**



This compound was synthesized using methylhydroquinone (0.412 g, 3.32 mmol) as the starting phenol and 2.2 eq of 2-chloro-*N,N*-dimethylethylamine hydrochloride (1.054 g, 7.319 mmol) as the alkylating agent, following the standard microwave method using 5 eq. of potassium *t*-butoxide. The method was modified by dissolving the phenol in 15 mL of DMSO and solid alkylating agent was added directly to the phenol solution. The workup was modified using three extractions with diethyl ether, 25 mL each, to isolate the compound. The product was isolated as a brown oil in 58% yield (0.51 g). ^1H NMR (CDCl_3): δ 2.20 (s, 3H), 2.32 (s, 6H), 2.34 (s, 6H), 2.68 (t, $J=5.8$ Hz, 2H), 2.73 (t, $J=5.8$ Hz, 2H), 3.98-4.02 (m, 4H), 6.66 (dd, $J=2.9$ Hz, $J=8.8$ Hz, 1H), 6.71-6.74 (m, 2H); ^{13}C NMR (CDCl_3): δ 16.4, 45.9 (2C), 46.1 (2C), 58.4, 58.5, 66.5, 67.4, 111.6, 112.3, 117.8, 128.1, 151.3, 152.7.

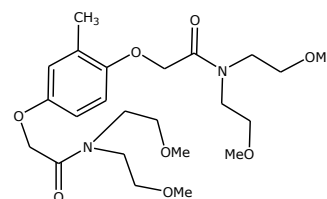
2-(4-{[Bis-(2-methoxy-ethyl)-carbamoyl]-methoxy}-2-*t*-butylphenoxy)-*N,N*-bis-(2-methoxy-ethyl)-acetamide, **34a**



This compound was synthesized using *t*-butylhydroquinone (0.491 g, 3.07 mmol) as the starting phenol and 2.2 eq. of 2-chloro-*N,N*-bis-(2-methoxyethyl)acetamide (1.410 g, 6.71 mmol) as the alkylating agent, following the standard microwave method using 2.5 eq. of potassium *t*-butoxide. The workup was modified: the solution was not basified and three extractions with diethyl ether, 25 mL each, were used to isolate the compound. The product was isolated as a red oil in 78% yield (1.23 g). ^1H NMR

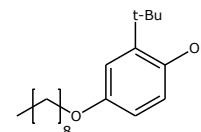
(CDCl₃): δ 1.39 (s, 9H), 3.30-3.34 (m, 12H), 3.51-3.63 (m, 16H), 4.74 (m, 4H), 6.67 (dd, $J=3.0$ Hz, $J=8.8$ Hz, 1H), 6.73 (d, $J=8.8$ Hz, 1H), 6.96 (d, $J=3.0$ Hz, 1H); ¹³C NMR (CDCl₃): δ 29.8 (3C), 35.0, 46.1, 46.4, 48.3, 48.4, 58.80, 58.84, 59.0 (2C), 67.5, 67.7, 70.4, 70.6, 71.0, 110.9, 113.2, 115.3, 140.0, 152.0, 152.3, 169.9, 169.0.

2-(4-{[Bis-(2-methoxy-ethyl)-carbamoyl]-methoxy}-2-methyl-phenoxy)-*N,N*-bis-(2-methoxy-ethyl)-acetamide, **34b**



This compound was synthesized using methylhydroquinone (0.380 g, 3.06 mmol) as the starting phenol and 2.2 eq. of 2-chloro-*N,N*-bis-(2-methoxyethyl)acetamide (1.410 g, 6.71 mmol) as the alkylating agent, following the standard microwave method using 2.5 eq. of potassium *t*-butoxide. The workup was modified: the solution was not basified and three extractions with diethyl ether, 25 mL each, were used to isolate the compound. The product was isolated as a red oil in 20% yield (0.29 g). ¹H NMR (CDCl₃): δ 2.25 (s, 3H), 3.30-3.34 (m, 12H), 3.52-3.60 (m, 16H), 4.74 (s, 2H), 4.75 (s, 2H), 6.67 (dd, $J=3.0$ Hz, $J=8.8$ Hz, 1H), 6.73 (d, $J=8.8$ Hz, 1H), 6.76 (d, $J=2.9$ Hz, 1H); ¹³C NMR (CDCl₃): δ 16.5, 27.4, 31.2, 46.28, 46.33, 48.3, 58.8, 59.01, 59.03, 67.5, 67.9, 70.56, 70.60, 70.9, 112.0, 112.6, 117.8, 128.2, 151.2, 152.5, 168.9, 169.0.

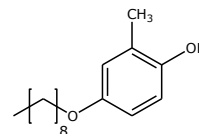
2-*t*-butyl-4-nonyloxyphenol, **50**



t-Butylhydroquinone (0.57 g, 3.4 mmol) was dissolved with 5 mL of diethyl ether in a 15 mL round bottom flask, equipped with magnetic stir bar. 1-Nonanol (0.99 g, 6.9 mmol) was added to the round bottom flask all at once, followed by 18 M H₂SO₄ (0.3 mL, 5.4 mmol) dropwise to minimize heat release. Sodium nitrite (0.03 g, 0.4 mmol) was added all at

once to the flask, forming a brown solution. The combined solution was allowed to stir at ambient temperature for 3.25 hrs, while stoppered. The resulting solution was diluted with water (30 mL) and was extracted with diethyl ether (2 x 30 mL). The combined ether layers were washed with water (1 x 50 mL), sat. NaCl (1x 5 mL) and dried (MgSO₄). The solvent was removed under reduced pressure yielding a mixture of product and 1-nonanol as determined by ¹H NMR. The mixture was purified via Kugelrohr distillation and the residue yielded the product as a brown oil in 62% yield (0.62 g). ¹H NMR (CDCl₃): δ 0.88 (t, *J*=7.1 Hz, 3H), 1.27-1.30 (m, 10H), 1.39 (s, 9H), 1.40-1.42 (m, 2H), 1.71-1.79 (m, 2H), 3.87 (t, *J*=6.6 Hz, 3H), 6.57 (m, 2H), 6.86 (m, 1H); ¹³C NMR (CDCl₃): δ 14.1, 22.7, 26.11, 29.3, 29.46, 29.49, 29.52, 29.57 (3C), 31.9, 34.7, 68.7, 111.3, 114.9, 116.8, 137.6, 147.2, 152.9.

2-methyl-4-nonyloxyphenol, 49

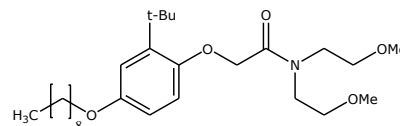


Methylhydroquinone (0.42 g, 3.4 mmol) was dissolved with 5 mL of diethyl ether in a 15 mL round bottom flask, equipped with magnetic stir bar. 1-Nonanol (0.99 g, 6.9 mmol) was added to the round bottom flask all at once, followed by 18 M H₂SO₄ (0.3 mL, 5.4 mmol) dropwise to minimize heat release. Sodium nitrite (0.03 g, 0.4 mmol) was added all at once to the flask, forming a brown solution. The combined solution was allowed to stir at ambient temperature for 3 hrs, while stoppered. The resulting solution was diluted with water (20 mL) and was extracted with diethyl ether (2 x 25 mL). The combined ether layers were washed with water (1 x 25 mL), sat. NaCl (1x 5 mL) and dried (MgSO₄). The solvent was removed under reduced pressure yielding a mixture of product and 1-nonanol as determined by ¹H NMR. The mixture was purified via Kugelrohr distillation and the residue yielded the product as a brown oil in 65% yield (0.55 g), with a trace amount of 1-nonanol. ¹H NMR (CDCl₃): δ 0.88 (t,

$J=7.1$ Hz, 3H), 1.27-1.30 (m, 10H), 1.34-1.42 (m, 2H), 1.69-1.77 (m, 2H), 2.20 (s, 3H), 3.87 (t, $J=6.6$ Hz, 3H), 6.60 (dd, $J=2.9$ Hz, $J=8.6$ Hz, 1H), 6.66 (d, $J=8.6$ Hz, 1H), 6.69 (d, $J=2.9$ Hz, 1H); ^{13}C NMR (CDCl_3): δ 14.1, 16.1, 22.7, 26.1, 29.3, 29.42, 29.44, 29.6, 31.9, 68.8, 112.7, 115.5, 117.5, 125.0, 147.8, 153.1.

2-(2-*t*-butyl-4-nonyloxyphenoxy)-*N,N*-bis-(2-methoxyethyl) acetamide, **48a**

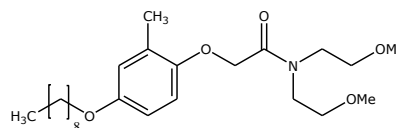
This compound was synthesized using 2-*t*-butyl-4-nonyloxyphenol (0.39 g, 1.3 mmol) as the starting phenol



and 2-chloro-*N,N*-bis-(2-methoxyethyl)acetamide (0.30 g, 1.4 mmol) as the alkylating agent, following the standard microwave method using 1.2 eq. of potassium *t*-butoxide. The product was isolated as a red oil in 66% yield (0.41 g). ^1H NMR (CDCl_3): δ 0.88 (t, $J=6.3$ Hz, 3H), 1.27-1.30 (m, 10H), 1.34-1.42 (m, 2H), 1.40 (s, 9H), 1.73-1.77 (m, 2H), 3.33 (s, 3H), 3.34 (s, 3H), 3.50-3.64 (m, 8H), 3.89 (t, $J=6.4$ Hz, 2H), 4.74 (s, 2H), 6.63 (m, 1H), 6.75 (m, 1H), 6.88 (s, 1H); ^{13}C NMR (CDCl_3): δ 14.1, 22.7, 26.1, 29.3, 29.5 (2C), 29.6, 29.9 (3C), 31.9, 35.0, 46.1, 48.4, 58.9, 59.1, 67.8, 68.4, 70.5, 71.1, 110.6, 113.3, 114.9, 140.0, 151.5, 153.2, 168.9.

2-(4-nonyloxy-2-methylphenoxy)-*N,N*-bis-(2-methoxyethyl) acetamide, **48b**

This compound was synthesized using 2-methyl-4-nonyloxyphenol (0.41 g, 1.6 mmol) as the starting phenol and

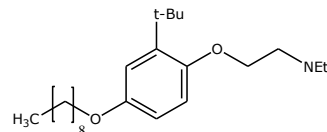


2-chloro-*N,N*-bis-(2-methoxyethyl)acetamide (0.37 g, 1.8 mmol) as the alkylating agent, following the standard microwave method using 1.2 eq. of potassium *t*-butoxide. The product was isolated as a brown oil in 60% yield (0.42 g). ^1H NMR (CDCl_3): δ 0.88 (t, $J=7.1$ Hz, 3H), 1.27-1.30 (m, 10H), 1.34-1.42 (m, 2H), 1.73-1.77 (m, 2H), 2.25 (s, 3H), 3.30 (s, 3H), 3.33 (s, 3H), 3.50-3.64 (m, 8H), 3.87 (t, $J=6.6$ Hz, 2H), 4.75 (s, 2H), 6.61 (dd, $J=3.0$ Hz, $J=8.8$ Hz, 1H),

6.70-6.72 (m, 2H); ^{13}C NMR (CDCl_3): δ 14.1, 16.5, 22.7, 26.1, 29.3, 29.4, 29.5, 29.6, 31.9, 46.3, 48.3, 58.8, 59.0, 68.0, 68.4, 70.6, 71.0, 111.6, 112.7, 117.7, 128.1, 150.6, 153.4, 169.1.

[2-(2-*t*-butyl-4-nonyloxyphenoxy)-ethyl]-diethylamine, **52a**

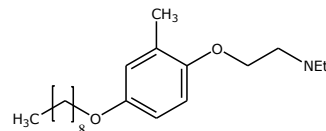
This compound was synthesized using 2-*t*-butyl-4-nonyloxyphenol (0.58 g, 2.0 mmol) as the starting phenol and 1.2 eq. of 2-chloro-



N,N-diethylethylamine hydrochloride (0.41 g, 2.4 mmol) as the alkylating agent, following the standard microwave method using 2.5 eq. of potassium *t*-butoxide. The method was modified by dissolving the phenol in 15 mL of DMSO and solid alkylating agent was added directly to the phenol solution. The product was isolated as a brown oil in 77% yield (0.60 g), as a mixture of isomers. ^1H NMR (CDCl_3): δ 0.88 (t, $J=6.4$ Hz, 3H), 1.07 (t, $J=7.0$ Hz, 6H), 1.27-1.39 (m, 19H), 1.55 (m, 2H), 1.73-1.77 (m, 2H), 2.61-2.65 (m, 4H), 2.86-2.93 (m, 2H), 3.85-3.90 (m, 2H), 3.99-4.02 (m, 2H), 6.65-6.87 (m, 3H).

[2-(4-nonyloxy-2-methylphenoxy)-ethyl]-diethylamine, **52b**

This compound was synthesized using 2-methyl-4-nonyloxyphenol (0.51 g, 2.0 mmol) as the starting phenol and 1.2 eq. of 2-chloro-



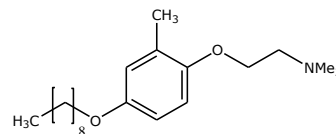
N,N-diethylethylamine hydrochloride (0.41 g, 2.4 mmol) as the alkylating agent, following the standard microwave method using 2.5 eq. of potassium *t*-butoxide. The method was modified by dissolving the phenol in 15 mL of DMSO and solid alkylating agent was added directly to the phenol solution. The product was isolated as a brown oil in 62% yield (0.44 g). ^1H NMR (CDCl_3): δ 0.88 (m, 3H), 1.07 (m, 3H), 1.27-1.39 (m, 10H), 1.43 (m, 2H), 1.73-1.77 (m, 2H),

2.20 (s, 3H), 2.61-2.65 (m, 4H), 2.86-2.93 (m, 2H), 3.84-3.90 (m, 2H), 3.97-4.00 (m, 2H), 6.65-6.87 (m, 3H).

[2-(4-nonyloxy-2-methylphenoxy)-ethyl]-dimethylamine, **47b**

This compound was synthesized using 2-methyl-4-nonyloxyphenol

(0.50 g, 2.0 mmol) as the starting phenol and 2-chloro-*N,N*-



dimethylethylamine hydrochloride (0.33 g, 2.3 mmol) as the alkylating agent, following the

standard microwave method using 2.5 eq. of potassium *t*-butoxide. The method was modified by

dissolving the phenol in 15 mL of DMSO and solid alkylating agent was added directly to the

phenol solution. The product was isolated as a brown oil in 65% yield (0.42 g), with trace

impurities. ¹H NMR (CDCl₃): δ 0.88 (m, 3H), 1.27-1.39 (m, 10H), 1.43 (m, 2H), 1.73-1.77 (m,

2H), 2.20 (s, 3H), 2.34 (s, 6H), 2.73 (t, *J*=5.9 Hz, 2H), 3.86-3.89 (m, 2H), 4.00 (t, *J*=5.9 Hz,

2H), 6.65-6.87 (m, 3H).

Chapter 9: References

- (1) Abraham, I.; Joshi, R.; Pardasani, P.; Pardasani, R. T. *J. Braz. Chem. Soc.* **2011**, 22, 385-421.
- (2) Garuti, L.; Roberti, M.; Pizzirani, D. *Mini-Rev. Med. Chem.* **2007**, 7, 481-489.
- (3) Sperry, J.; Bachu, P.; Brimble, M. A. *Nat. Prod. Rep.* **2008**, 25, 376-400.
- (4) Love, B. E.; Bonner-Stewart, J.; Forrest, L. A. *Synlett* **2009**, 813-817.
- (5) Love, B. E.; Duffy, B. C.; Simmons, A. L. *Tetrahedron Lett.* **2014**, 55, 1994-1997.
- (6) Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, 127, 11958-11959.
- (7) Anderson, J. C.; Denton, R. M.; Wilson, C. *Org. Lett.* **2005**, 7, 123-125.
- (8) Scott, L. T.; Rozeboom, M. D.; Houk, K. N.; Fukunaga, T.; Lindner, H. J.; Hafner, K. *J. Am. Chem. Soc.* **1980**, 102, 5169-5176.
- (9) Katritzky, A. R.; Fedoseyenko, D.; Mohapatra, P. P.; Steel, P. J. *Synthesis* **2008**, 777-787.
- (10) Kutyshev, A. A. *Tetrahedron* **1991**, 47, 8043-8065.
- (11) O'Malley, P. J. *Antioxid. Redox Signal.* **2001**, 3, 825-838.
- (12) Wheeler, D. E.; Rodriguez, J. H.; McCusker, J. K. *J. Phys. Chem. A* **1999**, 103, 4101-4112.
- (13) Tamagawa, K.; Iijima, T.; Kimura, M. *J. Mol. Struct.* **1976**, 30, 243-253.
- (14) Tohma, H.; Morioka, H.; Harayama, Y.; Hashizume, M.; Kita, Y. *Tetrahedron Lett.* **2001**, 42, 6899-6902.
- (15) Snyder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, 94, 227-231.
- (16) Musgrave, O. C. *Chem. Rev.* **1969**, 69, 499-531.
- (17) Jacob, P.; Callery, P. S.; Shulgin, A. T.; Castagnoli, N. *J. Org. Chem.* **1976**, 41, 3627-3629.
- (18) Maruyama, K.; Sohmiya, H.; Tsukube, H. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2069-2074.
- (19) Srikrishna, A.; Ravikumar, P. C.; Krishnan, H. S. *Synthesis* **2008**, 1527-1534.
- (20) Love, B. E.; Duffy, B. C. *Chem. Educator* **2014**, 19, 287-288.
- (21) Feist, P. L. *J. Chem. Educ.* **2008**, 85, 1548.

- (22) Basak (née Nandi), A.; Nayak, M. K.; Chakraborti, A. K. *Tetrahedron Lett.* **1998**, 39, 4883-4886.
- (23) Xu, B.; Xue, J.; Zhu, J.; Li, Y. *Chem. Lett.* **2008**, 37, 202-203.
- (24) Gambarotti, C.; Melone, L.; Punta, C.; Shisodia, S. U. *Curr. Org. Chem.* **2013**, 17, 1108-1113.
- (25) Demars, T. J.; Bera, M. K.; Seifert, S.; Antonio, M. R.; Ellis, R. J. *Angew. Chem. Int. Ed. Engl.* **2015**, 54, 7534-7538.
- (26) Prasad, A. S. B.; Kanth, J. V. B.; Periasamy, M. *Tetrahedron* **1992**, 48, 4623-4628.
- (27) Aguiar, J.; Carpena, P.; Molina-Bolívar, J. A.; Carnero Ruiz, C. J. *Colloid Interface Sci.* **2003**, 258, 116-122.
- (28) Eliel, E. L.; Wilen, S. H.; Doyle, M. P. In *Basic Organic Stereochemistry*; Wiley-Interscience: New York, 2001; pg. 443-445.
- (29) Yamada, S.; Tokugawa, Y. *J. Am. Chem. Soc.* **2009**, 131, 2098-2099.
- (30) Cockroft, S. L.; Perkins, J.; Zonta, C.; Adams, H.; Spey, S. E.; Low, C. M. R.; Vinter, J. G.; Lawson, K. R.; Urch, C. J.; Hunter, C. A. *Org. Biomol. Chem.* **2007**, 5, 1062-1080.
- (31) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, 91, 165-195.
- (32) Love, B. E. *Unpublished Data*.
- (33) Namazian, M.; Coote, M. L. *J. Phys. Chem. A* **2007**, 111, 7227-7232.
- (34) Ajloo, D.; Yoonesi, B.; Soleymanpour, A. *Int. J. Electrochem. Sci.* **2010**, 5, 459-477.

