Synthesis of Dibenzofurans via a Palladium Catalyzed Oxidative Ring Closure Reaction

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Synthesis of Dibenzofurans via a Palladium Catalyzed Oxidative Ring Closure Reaction

An Honors Thesis

Presented to

the Department of Chemistry

of the University of New Orleans

In Partial Fulfillment

of the Requirements for the Degree of

Bachelor of Science, with Honors in Chemistry

by

Sadia Akram

May 2013
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Abstract

The cannabinoid partial agonist BAY 59-3704 has been identified as an attractive target to explore structure-activity relationships at cannabinoid receptors for the development of a therapeutic agent for psychostimulant addiction. This thesis will describe the studies associated with the optimization of a palladium-catalyzed oxidative ring closure reaction for the synthesis of dibenzofuran analogues from substituted diaryl ethers. These dibenzofurans are viewed as rigid analogues of BAY 59-3704 and will provide useful information about molecular interactions at cannabinoid receptors. The scope and limitations of the palladium-catalyzed oxidative ring closure reaction as it relates to the synthesis of the target dibenzofuran analogues will be presented.

Key Words: cannabinoid, dibenzofuran, diaryl either, palladium, oxidative ring closure.


Introduction

Problems of Drug Addiction

In 2009, approximately 21.8 million people aged 12 or older were identified as illicit drug users according to the National Household Survey on Drug Use and Health.1 Of those surveyed, the abuse of psychostimulants, including methamphetamine and cocaine, contributed significantly (39%) to the overall national profile of illicit drug use. Today, there has been little deviation from this level of psychostimulant abuse. Unfortunately, there currently are no effective pharmacotherapies for the treatment of either cocaine or methamphetamine addiction. In lieu of the lack of any clinically available medications for these widely abused illicit drugs, the proposed study to develop new medications is highly significant.

The development of new medications for the treatment of illicit drug abuse is extremely important to the welfare of the United States and the health of its citizens. There is substantial evidence indicating that the cannabinoid system can modulate dopaminergic transmission indirectly and thus mediate the effects of psychostimulants on the reward and pleasure circuitry of the brain.2-5 Studies have shown that the cannabinoid agonist WIN55,212-2 (Figure 1) attenuates the rewarding actions of cocaine and decreased the reinforcing actions of cocaine.6,7 In addition, the cannabinoid antagonist SR141716A has been shown to modulate the rewarding effects of drugs like opiates, cocaine and nicotine.8 More recently, the cannabinoid antagonist AM251 has been reported to reduce methamphetamine self-administration in rodents and primates.9 However, current antagonists act as inverse agonists at the cannabinoid receptor and therefore produce side effects that have limited their clinical usefulness. Thus, the development and investigation of novel cannabinoid based medications (low efficacy agonists) is highly significant since the availability of these compounds will aid in identifying new treatment
strategies for psychostimulant abuse and dependence. Compounds identified in this study will be made available to the NIDA Addiction Treatment Discovery Program as well as to other researchers to evaluate the therapeutic potential for the treatment of drug addiction.

![Chemical structures](image)

**Figure 1.** Cannabinoids that have been shown to effect psychostimulant activity

**Cannabinoid Receptors**

![Diagram of cannabinoid receptors](image)

**Figure 2.** Cannabinoid Receptors

The principal psychoactive component of marijuana is Δ⁹-tetrahydrocannabinol (Δ⁹-THC). The effects of Δ⁹-THC are mediated by occupation of receptors located throughout the body. Currently two subtypes of transmembrane G-protein coupled receptors have been reported (CB1 and CB2). The CB1 receptors are found in the CNS with high density in the
In addition, CB1 receptors exist in a variety of other organs that include the heart, small intestine, vas deferens, testis and uterus. CB2 receptors are primarily in organs associated with the immune system (tonsils, spleen and immune cells). However, a recent report has described CB2 receptors present in the CNS, although at a much smaller concentration than CB1 receptors. While both CB1 and CB2 receptors have been cloned and the amino acid sequences known, the three-dimensional structures of the receptors and structures of the binding sites have yet to be established. To date, characterization of these receptor subtypes has relied upon ligand–receptor interactions.

**CB1 Receptor Ligands**

![Figure 3. CB1 Receptor Agonists](image-url)
The CB1 receptor is pharmacologically activated upon small molecule occupation of the binding site. Four classes of ligands typify CB1 receptor agonists (Figure 2).9 These include the classical cannabinoids typified by Δ⁹-THC and HU-210; the non-classical cannabinoids [e.g. CP55,940, BAY38-727122] the aminoidoles [e.g. WIN55,212-2]; and the endogenous cannabinoids [e.g. anandamide].19 These ligands typically exhibit nanomolar affinity for CB1 receptors and are generally non-selective for CB1 over CB2 receptor subtypes. Of these, anandamide has been reported to exhibit a significant differential in binding affinities between the two subtypes \(K_i = 61\) nM (CB1) and \(K_i = 1930\) nM (CB2).23 CB1 receptor agonists inhibit cAMP production through inhibition of adenylyl cyclase,24 inhibit Ca\(^{2+}\) influx25, activate K\(^+\) channels26 and activate MAP kinase pathways.27 CB1 receptor agonists have been shown to increase intracellular dopamine levels in brain (striatum) similar to cocaine.28-30 It is believed that CB1 agonist modulation of dopamine levels in the CNS is responsible in part for the abuse liability observed for cannabinoid agonists.3,4,31

Among known CB agonists, several compounds have been reported to exhibit low efficacy agonist profiles in vitro and in vivo. These partial agonists include Δ⁹-THC32, BAY59-3704,33-35 CB-25 and CB-52 (Figure 3)36,37 All of these CB ligands exhibited modest binding affinity at CB1 and CB2 receptor subtypes \(K_i\) values 30-50 nM). Only CB-25 exhibited CB1 selective low nanomolar affinity \(K_i = 5\) nM) at CB1 receptors. These compounds stimulated \[^{35}S\]GTPgS binding, but were significantly less efficacious than the full agonists CP-55,940, BAY 38-7271 or WIN 55,212-2 and hence have been designated as partial agonists. It is noteworthy that BAY 59-3074 exhibited no abuse potential and did not produce withdrawal behavioral effects when daily doses were stopped after two weeks.34 The phenols CB-25 and
CB-52 were characterized as partial agonists at CB1 receptor subtypes and neutral antagonists at CB2 receptor subtypes.\textsuperscript{36,37}

![Chemical structures of BAY 59-3074, CB-25, and CB-52]

**Figure 4.** Low Efficacy Cannabinoid Agonists

**Novel CB1 Receptor Low Efficacy Cannabinoid Agonists**

The development of new CB1 selective, low efficacy agonists as a pharmacotherapy for cocaine and/or methamphetamine addiction to our knowledge has not been explored. Cannabinoid full agonists and antagonists clearly have limitations as therapeutics due to deleterious side effects. However a CB1 selective low efficacy agonist would likely have diminished side effects relative to a full agonist or antagonist, while effectively modulating psychostimulant mediated dopaminergic activity. The development of a low efficacy CB1 agonist for use as a substitution therapy for cocaine and/or methamphetamine is highly innovative. This approach has been successfully used for decades for opioid addiction. The low efficacy opioid agonist methadone remains one of the leading treatment strategies for heroin addiction.

Recent studies have suggested that in a controlled environment with compliant patients, agonist-based approaches may be more successful for maintenance and withdrawal symptoms than antagonist based approaches, which are plagued with potential side effects.\textsuperscript{56} Therefore, it is attractive to develop new psychostimulant medications from low efficacy cannabinoid agonists.
rather than from known cannabinoid antagonist/inverse agonists. It is envisaged that such an approach would minimize the potential for adverse side effects and provide compounds with better safety profiles.

**Novel CB1 Receptor Ligands.**

The BAY59-3704 diaryl ether scaffold is ideally suited to explore this hypothesis in that it already has been established that specific structural modification of BAY59-3704 can lead to a full agonist profile [BAY 38-7271]. Therefore it is reasonable to believe that an alternative modification of the biaryl ether system would lead to diminished efficacy and a CB1 selective low efficacy agonist profile. This complete spectrum of pharmacological activity within a single class of molecular scaffolds is well established among opioid receptor ligands but has not been fully realized in a cannabinoid system. Clearly the development of such a class of full spectrum CB ligands would not only be highly innovative but also highly desirable by providing tools to study the fundamentals of receptor activation.

While BAY59-3704 has been known for several years, it has received limited attention and has not been studied as a treatment for drug abuse. Presumably this is due to low CB1 selectivity and limited availability of the drug. A systematic investigation of the structure-activity relationships of the target diaryl ethers and related derivatives will provide significant insight into important structural features associated with high potency and low efficacy. Although, some structure-activity studies have been reported in the patent literature, there remains a significant amount of SAR to investigate. This will aid in the development of a CB1 pharmacophore that can be used to design novel compounds targeted as low efficacy agonists. In addition, hybrid structures of known low efficacy CB1 ligands have not been explored
previously. As such, additional innovation can be gleaned from the novel hybrid structures that will be developed during this investigation from BAY59-3704 and CB-25.

**Previous Research**

An efficient, safe, and scalable method for the preparation of phloroglucinol monoaryl ethers has been developed by the Trudell Group to prepare novel diaryl ether molecular scaffolds similar to that of BAY59-3704. A variety of novel functionalized phloroglucinol monoaryl ethers were synthesized using a two-step procedure (Scheme 1). Target ethers were synthesized by coupling electron-deficient aryl fluorides with 3,5-dimethoxyphenol via nucleophilic aromatic substitution (S\(_{\text{N}}\)Ar) in N-methylpyrrolidone (NMP) and KOH. The uncatalyzed aryl coupling reaction was chemoselective and furnished the diaryl ethers cleanly with few side reactions. Subsequent boron tribromide-mediated demethylation gave a series of phloroglucinol monoaryl ethers in good overall yields. Monoalkylation of the phenol group then furnished a series of alkyl phloroglucinol monoaryl ethers for biological study at cannabinoid receptors.

**Scheme 1.** Synthesis of phloroglucinol monoaryl ethers and alkyl phloroglucinol monoaryl ethers
From these studies, the phloroglucinol derivative AMS-167 (Figure 4) exhibited exceptionally high affinity for CB1 receptors ($K_i = 1.2 \text{ nM}$). The improved binding affinity of the diaryl ether AMS-167 over BAY 59-3704 prompted us to use AMS-167 as our lead compound the development of new cannabinoid receptor ligands. Since it had already been shown that specific structural modification of the BAY59-3704 diaryl ether scaffold could lead to a full agonist profile [BAY 38-7271], it was reasonable to believe that an alternative modification of the biaryl ether system would lead to diminished efficacy and a CB1 selective low efficacy agonist profile. While BAY59-3704 has been known for several years, it has received limited attention and has not been studied as a treatment for drug abuse. Presumably this is due to low CB1 selectivity and limited availability of the drug. The design of novel CB1 receptor ligands will be guided by the structures of lead compound AMS-167. The diaryl ether derivative AMS-167 will serves as the template for the investigation of the SAR of these potentially potent ligands.

![Figure 5. AMS-167 and BAY-3074](image)

**Rigid Analogues of AMS-167**

As part of a study aimed at evaluating the structure-activity relationships of AMS-167 it was of interest to prepare a rigid analogue of AMS-167. A rigid analogue would provide important conformational information about how AMS-167 interacts with the cannabinoid receptor. To this end, the dibenzofuran analogue of AMS-167 was identified as a synthetic target (Figure 5). By
forming a covalent carbon-carbon bond between the two aryl rings of AMS-167, the dibenzofuran derivative would have much less conformational freedom. Hence the dibenzofuran system would provide important information regarding the relative positions of the functional groups and the importance for binding at cannabinoid receptors.

**Synthetic Approach: Palladium Catalyzed Oxidative Ring Closure:**

In a recent article\(^{82}\) published in the *Journal of Organic Chemistry*, a new reaction for intramolecular palladium(II)-catalyzed oxidative carbon-carbon bond formation was described. In this paper, diaryl ethers and diaryl amines were readily converted into dibenzofuran and carbazole derivative via intramolecular palladium(II)-catalyzed oxidative ring closure (Figure 6). In this study the authors showed that the use of pivalic acid as the reaction solvent, instead of acetic acid, afforded greater reproducibility, higher yields, and broader scope of substrates.\(^{82}\) Based upon this study, the intramolecular palladium(II)-catalyzed oxidative ring closing reaction seemed like an ideal method for the preparation of the dibenzofuran molecular scaffold that would be needed for the synthesis of a rigid analogue of AMS-167 (Figure 6).

\[
\begin{align*}
\text{X} & \quad \text{Y} \quad \text{Pd(OAc)}_2 \quad \text{PivOH, air} \\
\text{X} & \quad \text{Y} \\
\text{X} = \text{O, NH} & \quad \text{X} = \text{O, NH} \\
\text{up to 95\% yield}
\end{align*}
\]

**Figure 6.** Intramolecular palladium (II)-catalyzed oxidative ring closing reaction

As illustrated by retrosynthetic analysis in Scheme 2, the intramolecular palladium(II)-catalyzed oxidative ring closing reaction could be used to generate the appropriately substituted
dibenzofuran from the corresponding diaryl ether. To this end, the focus of this research was to explore the potential of the intramolecular palladium(II)-catalyzed oxidative ring closing reaction for the construction of the dibenzofuran. This Honors Thesis describes the studies associated with the optimization of the palladium-catalyzed oxidative ring closure reaction for the synthesis of dibenzofuran. In addition the thesis describes the scope and limitations of the palladium-catalyzed oxidative ring closure reaction as it relates to the synthesis of dibenzofuran analogues.

**Scheme 2.** Retrosynthetic analysis of rigid analogue of AMS-167.
Results and Discussion

Synthesis of 2-(3,5-Dimethoxyphenoxy)-6-(trifluoromethyl)-benzonitrile

Prior to beginning of the study on the palladium-catalyzed oxidative ring closure reaction it was necessary to synthesize the diaryl ether precursor, 2-(3,5-dimethoxyphenoxy)-6-(trifluoromethyl)-benzonitrile (1). As illustrated in Scheme 3, the diaryl ether 1, was prepared from 3,5-dimethoxyphenol and 2-fluoro-6-(trifluoromethyl)-benzonitrile using reaction conditions previously developed in our laboratories. This furnished the diaryl ether 1 in 99% yield and in high purity.

Scheme 3. 2-(3,5-dimethoxyphenoxy)-6-(trifluoromethyl)-benzonitrile (1)

With the diaryl ether 1 in hand, it was essential to characterize the compound by $^1$H NMR in order to use NMR to evaluate the success of the palladium-catalyzed oxidative ring closure reaction. As illustrated in Figure 7, the protons $H5$ and $H2'$ of 1, will be absent in the dibenzofuran 2. Therefore it should be possible to monitor these signals to determine the progress of the reaction.
Figure 7. Comparison of diphenyl ether 1 with benzofuran 2.

The $^1$H NMR spectrum of 1, is shown in Figure 8. Based upon the shielding effects of the substituents and the spin-spin splitting, the signal for $H5$ was assigned to the doublet at 7.15 ppm. Alternatively, the signal for $H2'$ was assigned as the singlet at 6.26 ppm.

Figure 8. $^1$H NMR Spectrum of 2-(3,5-dimethoxyphenoxy)-6-(trifluoromethyl)-benzonitrile (1)
As illustrated in Scheme 4, optimization of the palladium-catalyzed oxidative ring closure involves the identification of the optimum reagent concentrations, reaction temperature and reaction time. The chemical reagents involved in the transformation includes: diaryl ether 1, palladium(II)-acetate [Pd(OAc)$_2$], pivalic acid [(CH$_3$)$_3$CO$_2$H], an oxygen source (air or O$_2$) and potassium carbonate (K$_2$CO$_3$). In an effort to optimize the conditions for the palladium-catalyzed oxidative ring closure reaction of 1, a series of experiments were performed using varied reaction conditions.

**Figure 9.** $^{13}$C NMR Spectrum of 2-(3,5-dimethoxyphenoxy)-6-(trifluoromethyl)benzonitrile (1)
Scheme 4. Palladium-catalyzed oxidative ring closure reaction of 1.

As summarized in Table 1, the first study examined the effect of catalyst loading on the efficiency of the reaction. In this study the amount of palladium acetate was varied relative to the amount of the diaryl ether 1. All other reagents and conditions were maintained at similar levels.

Table 1. Effect of Catalyst Loading

<table>
<thead>
<tr>
<th>Entry</th>
<th>1 (mmol)</th>
<th>Catalyst (mol %)</th>
<th>K₂CO₃ mol%</th>
<th>Oxygen Source</th>
<th>Pivalic Acid (gm)</th>
<th>Temp (°C)</th>
<th>Time (hrs)</th>
<th>Conv. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA-99</td>
<td>0.5</td>
<td>Pd(OAc)₂ (5%)</td>
<td>10</td>
<td>air</td>
<td>0.45</td>
<td>120</td>
<td>72</td>
<td>31</td>
</tr>
<tr>
<td>SA-98</td>
<td>0.5</td>
<td>Pd(OAc)₂ (10%)</td>
<td>10</td>
<td>air</td>
<td>0.45</td>
<td>120</td>
<td>72</td>
<td>&lt;1</td>
</tr>
<tr>
<td>SA-102</td>
<td>0.5</td>
<td>Pd(OAc)₂ (20%)</td>
<td>10</td>
<td>air</td>
<td>0.9</td>
<td>120</td>
<td>72</td>
<td>72</td>
</tr>
<tr>
<td>SA-104</td>
<td>0.5</td>
<td>Pd(OAc)₂ (25%)</td>
<td>10</td>
<td>air</td>
<td>1.1</td>
<td>120</td>
<td>72</td>
<td>81</td>
</tr>
<tr>
<td>SA-107</td>
<td>0.5</td>
<td>PdCl₂ (20%)</td>
<td>20</td>
<td>air</td>
<td>1.0</td>
<td>120</td>
<td>72</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

From this study it was clear that catalyst loading had a significant effect on the ring closure reaction. As a catalyst, Pd(OAc)₂ was most effective for ring closure when present in 20 mol% to 25 mol%. This afforded good conversion of the diaryl ether 1 into the dibenzofuran 2. Clearly high catalyst loading was necessary to obtain high conversion of 1 into 2. Low catalyst loading (5 -10 mol %) gave low conversion of 1 into 2. It is noteworthy, that the palladium chloride
(entry SA-107) gave poor conversion at high catalyst loading despite the efficiency observed for palladium acetate. In summary the results of this catalyst loading study demonstrate that Pd(OAc)$_2$ is an effective catalyst for the ring closure reaction at high loading concentrations. However, Pd(OAc)$_2$ was inefficient at low loading and PdCl$_2$ was unreactive in this system.

**NMR Analysis of Dibenzofuran 2**

![NMR Spectrum](image)

**Figure 10:** $^1$H NMR Spectrum of 7,9-dimethoxy-2-(trifluoromethyl)dibenzofuran-carbonitrile(2)

The $^1$H NMR spectrum of 2, is shown in Figure 10. Based upon the shielding effects of the substituent and the spin-spin splitting, the addition of carbon-carbon bond results in electron deficient ring system and the activating O-methyl groups are now asymmetrical, shows two peaks at 4.08 and 3.93 ppm. Peaks are shifted down field and we see two doublets at 7.68 ppm and 8.22 ppm.
Effect of Surface Area

Table 2 summarizes the effect that reaction media surface area can play in product formation. Since the reaction progress is dependent upon the reactants exposure to air it was of interest to see if a larger reaction surface area would effect the conversion of 1 into 2. In this study a broad diameter 20 ml reaction vial was employed instead of a narrow 10 ml reaction tube. Using the optimized catalyst loading of 25 mol% it was found that increasing the surface area of the reaction media led to increased reaction times and lower conversion (39%) into product (entry SA-106). The addition of Pd(OAc)$_2$ over the course of 12 days did lead to better conversion (66%) but did not improve the overall conversion relative to the reaction tube.

Table 2. Use of a Reaction Vial

<table>
<thead>
<tr>
<th>Entry</th>
<th>1 (mmol)</th>
<th>Pd(OAc)$_2$ (mol %)</th>
<th>K$_2$CO$_3$ mol%</th>
<th>Oxygen Source</th>
<th>Pivalic Acid (gm)</th>
<th>Temp (°C)</th>
<th>Time (hrs)</th>
<th>Conv. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA-106 (V)*</td>
<td>0.5</td>
<td>25</td>
<td>25</td>
<td>air</td>
<td>2</td>
<td>120</td>
<td>72</td>
<td>39</td>
</tr>
<tr>
<td>SA-111 (V)*</td>
<td>2.1</td>
<td>3 × 25</td>
<td>3 × 25</td>
<td>air</td>
<td>3 × 1</td>
<td>120</td>
<td>12 (days)</td>
<td>66</td>
</tr>
</tbody>
</table>

*V = vial

While the difference in reaction efficiency between the small volume and large volume reaction vessels is not fully understood at this time, it seems that the effect may be related to cooling efficiency of the glass vessels. The narrow reaction tube seemed to keep the solvent from evaporating away from the reaction mixture. The broader diameter reaction vial seemed to allow the solvent to vaporize into the air. This would lead to a significant reduction in volume, which in turn may have led to thermal decomposition of the catalyst. This would be consistent with the
fact that addition of second and third portion of Pd(OAc)$_2$ was necessary to move the reaction forward.

**Effects of Microwave Heating**

Table 3 shows the effects of microwave heating. Attempts to decrease the reaction time and to make the reaction more environmentally friendly (Green Chemistry) were unsuccessful. The results from these experiments indicate that microwave heating is not applicable for this reaction. The high localized heat results in decomposition of catalyst. The low conversion to product is presumably due to failure to regenerate the catalyst, which is essential for this reaction.

**Table 3. Effects of Microwave Heating**

<table>
<thead>
<tr>
<th>Entry</th>
<th>1 (mmol)</th>
<th>Pd(OAc)$_2$ (mol %)</th>
<th>K$_2$CO$_3$ (mol %)</th>
<th>Oxygen Source</th>
<th>Pivalic Acid (gm)</th>
<th>Temp (°C)</th>
<th>Time (hrs)</th>
<th>Conv. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA-117</td>
<td>0.5</td>
<td>2 × 25</td>
<td>25</td>
<td>air</td>
<td>3 × 1</td>
<td>110</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>SA-123</td>
<td>0.5</td>
<td>10</td>
<td>25</td>
<td>O$_2$</td>
<td>4</td>
<td>150</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>SA-124</td>
<td>0.5</td>
<td>25</td>
<td>25</td>
<td>air</td>
<td>2.5</td>
<td>110</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>

**Effect of Oxygen Source**

As summarized in Table 4, it was determined that air was most effective source of oxygen for the palladium catalyzed reaction. The addition of alternative oxygen sources had a negative effect on product formation.
Table 4. Alternative Oxygen Sources

<table>
<thead>
<tr>
<th>Entry</th>
<th>1 (mmol)</th>
<th>Pd(OAc)$_2$ (mol%)</th>
<th>K$_2$CO$_3$ (mol%)</th>
<th>Oxygen Source</th>
<th>Pivalic Acid (gm)</th>
<th>Temp (°C)</th>
<th>Time (hrs)</th>
<th>Conv. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA-101</td>
<td>0.5</td>
<td>10</td>
<td>10</td>
<td>EtOH</td>
<td>0.45</td>
<td>120</td>
<td>72</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.2 ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SA-115</td>
<td>0.5</td>
<td>3 × 25</td>
<td>25</td>
<td>H$_2$O$_2$</td>
<td>3 × 1.0</td>
<td>120</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>(MW)*</td>
<td></td>
<td></td>
<td></td>
<td>(0.2 mmol)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SA-117</td>
<td>0.5</td>
<td>20</td>
<td>3 × 20</td>
<td>Benzoic Acid</td>
<td>3 × 1.0</td>
<td>120</td>
<td>2</td>
<td>&lt; 20</td>
</tr>
<tr>
<td>(MW)*</td>
<td></td>
<td></td>
<td></td>
<td>(0.75mmol)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*MW = microwave

Reaction Monitored via Gas Chromatography

Although $^1$H NMR was effective at monitoring the progress of the reaction it was not very efficient for the high-throughput screening of reactions. A more time efficient technique was needed to monitor the reaction thus allow for faster analysis. To this end, an analysis method was developed using gas chromatography. GC parameters are optimized initially by using starting material and product mixture. The initial temperature set at 230 °C for 2 mins and 270 °C for 8 mins. The ramp time set at 15 °C/min. Total operation time is set to be at 12 mins and 67 sec. The retention times for first optimized reaction for 2-(3,5-dimethoxyphenoxy)-6-(trifluoromethyl)benzonitrile and 7,9-dimethoxy-2-(trifluoromethyl)dibenzoferan-4-carbonitrile are 4.57 and 5.96 respectively. Retention time vs. conversion data for respective dibenzofuran is plotted in Figure 11.

Table 5 summarizes reaction conditions that were explored using gas chromatographic analysis for monitoring the conversion of diaryl ether 1 into dibenzofuran 2. In addition to time
efficiency, gas chromatography offered the advantage that the reaction could be continuously monitored. As illustrated in Figure 8, product formation could be followed in real time. This afforded a better sense of how the reaction progressed as well as an indication of when the reaction was complete.

**Table 5. Reactions Monitored GC Analysis**

<table>
<thead>
<tr>
<th>Entry</th>
<th>1 (mmol)</th>
<th>Catalyst (mol %)</th>
<th>K₂CO₃ mol%</th>
<th>Oxygen Source</th>
<th>Pivalic Acid (gm)</th>
<th>Temp (°C)</th>
<th>Time (hrs)</th>
<th>Conv. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA-126</td>
<td>0.5</td>
<td>Pd(OAc)₂ (25)</td>
<td>25</td>
<td>air</td>
<td>1.1</td>
<td>120</td>
<td>144</td>
<td>82</td>
</tr>
<tr>
<td>SA-127</td>
<td>0.5</td>
<td>Pd(OAc)₂ (25)</td>
<td>25</td>
<td>air</td>
<td>1.1</td>
<td>120</td>
<td>144</td>
<td>63</td>
</tr>
<tr>
<td>(RBF reflux)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SA-128</td>
<td>0.5</td>
<td>Pd(OAc)₂ (25)</td>
<td>25</td>
<td>air</td>
<td>1.1</td>
<td>160</td>
<td>44</td>
<td>0</td>
</tr>
<tr>
<td>SA-129</td>
<td>0.5</td>
<td>Pd(OAc)₂ (25)</td>
<td>25</td>
<td>air</td>
<td>2</td>
<td>120</td>
<td>49</td>
<td>7</td>
</tr>
<tr>
<td>(IMes 50 mol%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SA-131</td>
<td>0.5</td>
<td>Rh₂(OAc)₄ (25)</td>
<td>25</td>
<td>air</td>
<td>1.1</td>
<td>120</td>
<td>24</td>
<td>3</td>
</tr>
</tbody>
</table>

As shown in Table 5, gas chromatography analysis was consistent with NMR analysis for product formation. Using optimized reaction conditions (entry SA-126), GC analysis gave similar results to NMR analysis obtained previously for the same set of conditions (Table 1, entry SA-104). Using gas chromatography to evaluate reaction progress, several additional experiments were performed. First, the reaction was performed in a 25 ml round bottom flask fitted with a condenser to see if minimization of solvent loss accompanied a larger reaction
surface area would have an effect (entry SA-127). This experiment demonstrated that maintaining solvent levels was critical to the success of the reaction while the importance of surface area was less significant. In a second experiment the effect of increased temperature was explored. (entry SA-128). In this experiment the temperature was increased to 160 °C. As expected, the increase in temperature resulted in decomposition of catalyst and led to low conversion of 1 into product. In a third experiment (entry SA-129) the N-heterocyclic carbene precusor (IMes•HCl) was added to the reaction mixture. A previous report had suggested that this ligand promoted the reaction of palladium catalysts in oxidative ring closure reactions. However, under these reaction conditions, the addition of IMes•HCl did not improve the conversion and in fact completely shut down the catalytic reaction. Finally, rhodium (II) acetate [Rh$_2$(OAc)$_4$] (entry SA-13) was explored as a catalyst for the ring closure reaction. However, under the optimized conditions established for palladium acetate, rhodium acetate was unreactive.

![Conversion Monitored by Gas Chromatography](image)

**Figure 11.** Conversion Monitored by Gas Chromatography shows the respective increase in product with time for reaction SA-126 and SA-132.
Synthesis of Analogues

After optimizing reaction condition for the formation of 2 (Table 6, SA-126), attempts were made to synthesize dibenzofuran analogues. In case of SA-132 maximum conversion was observed. Strong electron withdrawing NO₂ has a positive effect on product formation by making the ring system electron deficient along with activating effect of methoxy (OCH₃) on the neighboring ring. SA-135 shows low conversion and some peaks of side reaction are also observed through GC. Pd insertion in halogenated ring structure could be a possible result of observed side reaction peaks. The product was undetermined in case of SA-138 and SA-140 as multiple side reaction peaks are observed along with product peaks. As reaction is performed in open air, formation of benzoic acid and other related products have been formed.

Scheme 5. Synthesis of Dibenzofurans

Table 6: Synthesis data of dibenzofuran Analogues

<table>
<thead>
<tr>
<th>Entry (diaryl ether)</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>% Conv. (Dibenzofuran)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA-126 (1)</td>
<td>CN</td>
<td>CF₃</td>
<td>H</td>
<td>83 (2)</td>
</tr>
<tr>
<td>SA-132 (3)</td>
<td>H</td>
<td>H</td>
<td>NO₂</td>
<td>97 (7)</td>
</tr>
<tr>
<td>SA-135 (4)</td>
<td>Cl</td>
<td>H</td>
<td>Cl</td>
<td>40 (8)</td>
</tr>
<tr>
<td>SA-138 (5)</td>
<td>CN</td>
<td>H</td>
<td>CHO</td>
<td>IM*</td>
</tr>
<tr>
<td>SA-140 (6)</td>
<td>H</td>
<td>H</td>
<td>CHO</td>
<td>IM*</td>
</tr>
</tbody>
</table>

*IM = Intractable mixture
Conclusion

Various attempts have been made to optimize the synthesis of dibenzofuran via palladium catalyzed ring closure reaction. This has been achieved by altering the catalyst and its amount, changing oxygen source, changing reaction vial surface area, and using microwave techniques. The results of this study show that the synthesis of dibenzofuran via palladium catalyzed oxidative ring closure reaction is a very slow reaction. Catalyst loading of 25 mol% of Pd(OAc)$_2$, 25 mol% K$_2$CO$_3$, pivalic acid as a solvent and air as oxygen source are essential conditions to get a dibenzofuran in good yield. In addition, electron-withdrawing groups had a positive effect on ring closure and product yield.
Future research efforts will focus on the synthesis of other dibenzofuran analogues in good yields and the development of an efficient method for purification of the product. The application of this research toward the synthesis of rigid analogues cannabinoid receptor ligands will also be pursued.

**Scheme 6. Synthesis of Potential Cannabinoid Agonists**
Experimental

2-(3,5-Dimethoxyphenoxy)-6-(trifluoromethyl)-benzonitrile; General Procedure A

To a solution of 3,5-dimethoxyphenol (3.4 g, 22 mmol), dissolved in NMP (15 mL) was added Cs₂CO₃ (9.8 g, 30 mmol). The mixture was heated under nitrogen at 50°C oil bath for 30 minutes to furnish a dark brown phenoxide solution. The aryl fluoride (9.8 g, 30 mmol) in NMP (15 mL) was syringed into the solution and the mixture was to stirred at 65 °C for 4 h. The reaction was monitored by TLC until the aryl fluoride could no longer be observed. The reaction mixture was allowed to cool to room temperature and then added to H₂O (20 mL). The resulting suspension was extracted with toluene (3 x 15 mL). The combined organic extracts were washed with H₂O (15mL), brine (15 mL) then dried over MgSO₄ and filtered. The solvent was removed under reduced pressure and the residue was triturated with H₂O (10 mL), filtered, washed with water and then dried under vacuum to afford a shiny white solid; yield: 6.36 g (99 %); mp 95-97 °C.

¹H NMR (CDCl₃) δ: 7.57 (t, J = 8.0 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 6.36 (s, 1H), 6.25 (s, 2H), 3.78 (s, 6H).

¹³C NMR (CDCl₃) δ: 162.2, 161.5, 156.1, 134.4, 134.1, 123.8, 121.1, 120.4, 112.6, 100.8, 98.9, 97.9, 55.7.

1,3-Dimethoxy-5-(4-nitrophenoxo)benzene

Prepared according to the general procedure ‘A’ using 3,5-dimethoxyphenol (1.13 g, 7.3mmol) Cs₂CO₃ (3.3 g, 10 mmol), and 1-fluoro-4-nitrobenzene (0.95 g, 6.7 mmol) in NMP (10 mL) at 65 °C for 2 h. Purification by tituration and filtration afforded a light yellow solid; yield 1.75 g

¹H NMR (CDCl₃): δ = 8.20 (d, J = 8.0 Hz, 2 H), 7.05 (d, J = 8.0 Hz, 2 H), 6.34 (t, J = 2.0 Hz, 1
H), 6.24 (d, J = 2.0 Hz, 2 H), 3.78 (s, 6H).

\(^{13}\)C NMR (CDCl\(_3\)): \(\delta = 163.3, 162.2, 156.7, 126.1, 117.5, 115.6, 99.6, 97.7, 55.8\)

**2,4-Dichloro-1-(3,5-dimethoxyphenoxy)benzene**

Prepared according to general procedure A using 3,5-dimethoxyphenol (3.4 g, 22 mmol), Cs\(_2\)CO\(_3\) (9.8 g, 30 mmol), and 2,4-dichloro-1-fluorobenzene (3.3 g, 20 mmol) in NMP (15 mL) at 120 °C for 2 h. Purification by flash chromatography (10% EtOAc–hexane) afforded a white solid; yield: 5.0 g (84%); mp 44–45 °C.

\(^1\)H NMR (CDCl\(_3\)): \(\delta = 7.48 \) (d, \(J = 2.0 \) Hz, 1 H), \(7.19 \) (dd, \(J = 8.0, 2.0 \) Hz, 1 H), \(6.96 \) (d, \(J = 8.0 \) Hz, 1 H), \(6.22 \) (dd, \(J = 2.0, 2.0 \) Hz, 1H), \(6.10 \) (t, \(J = 2.0 \) Hz, 2 H), \(3.74 \) (s, 6 H).

\(^{13}\)C NMR (CDCl\(_3\)): \(\delta = 161.9, 158.7, 151.2, 130.7, 129.7, 128.3, 127.0, 122.1, 96.7, 96.0, 55.7\).

**2-(3,5-dimethoxyphenoxy)-5-formylbenzonitrile**

Prepared according to the general Procedure A using 3,5-dimethoxyphenol (1.13, 7.3mmol), Cs\(_2\)CO\(_3\) (3.26g, 10mmol), and 3-fluoro-5-formylbenzonitrile (1g, 6.7mmol) in NMP (10 mL) at 50 °C for 1 h and then 35 °C for 21 h. General procedure A was followed for purification, afforded a tangerine solid; yield: 1.72g (91%).

\(^1\)H NMR (CDCl\(_3\)): \(\delta = 9.98 \) (s, 1H), \(8.30 \) (s, 1H), \(8.23 \) (d, 2H), \(7.51 \) (d, 2H), \(6.29 \) (s, 2H), \(6.09 \) (s, 1H), \(3.83 \) (s, 6H).

\(^{13}\)C NMR (CDCl\(_3\)): \(\delta = 191.0, 165.4, 160.2, 160.1, 132.8, 135.3, 130.7, 118.7, 115.8, 104.9, 95.9, 93.5, 55.8\).

**4-(3,5-Dimethoxyphenoxy)benzaldehyde**

Prepared according to the general procedure A using 3,5-dimethoxyphenol (1.13, 7.3 mmol), Cs\(_2\)CO\(_3\) (3.26g, 10mmol), 4-fluorobenzaldehyde (0.83g, 6.7 mmol), in 10 mL of NMP at
60 °C for 3 h. General purification procedure A is followed and by column chromatography (20% EtOAc/Hexane) afforded a white solid; yield: 1.1g (64%).

$^1$H NMR (CDCl$_3$): $\delta$: 9.98 (s, 1H), 7.95 (d, 2H), 7.33(d, 2H), 6.29 (s, 2H), 6.09 (s, 1H), 3.83 (s, 6H).

$^{13}$C NMR (CDCl$_3$): $\delta$ = 191.0, 162.8, 160.2, 160.1, 131.0, 130.0, 118.0, 95.9, 93.5, 55.8

**General Procedure B for intramolecular Pd(II)-catalyzed oxidative ring closure reaction.**

In a typical reaction the diaryl compound (0.5 mmol), Pd(OAc)$_2$ (25 mol%), K$_2$CO$_3$ (25 mol%) and pivalic acid (1100 mg) was added to a 10 ml reaction tube. The uncapped tube was placed in an oil bath and the mixture was stirred at a set temperature over a specified time. The reaction was monitored by NMR or gas chromatography. The solution was then cooled to room temperature, diluted with dichloromethane (10 ml), washed with saturated aqueous solution of Na$_2$CO$_3$, dried over Na$_2$SO$_4$, filtered and evaporated under reduced pressure. The crude product was purified by silica gel chromatography or Prep TLC to afford the corresponding dibenzofuran.

**7,9-Dimethoxy-2-(trifluoromethyl)dibenzofuran-4-carbonitrile**

Prepared according to general procedure B using 2-(3,5-Dimethoxyphenoxy)-6-(trifluoromethyl)-benzonitrile (0.16g, 0.5 mmol), Pd(OAc)$_2$ (0.028g, 0.125 mmol), K$_2$CO$_3$ (0.017, 0.125 mmol) in 1.2 g of pivalic acid. The product is purified via column chromatography, to afford a white solid; yield (82%).

$^1$H NMR (CDCl$_3$): $\delta$: 8.22 (d, 2H), 7.68 (d, 2H), 6.82 (d, 1H), 6.48 (s, 1H), 3.93 (s, 3H), 3.78 (s, 3H).

$^{13}$C NMR (CDCl$_3$): $\delta$ = 159.7, 158.5, 150.9, 145.0, 126.4, 124.9, 123.9, 120.6, 115.8, 113.4, 106.4, 96.1, 88.6, 87.8, 56.1, 55.8.
1,3-Dimethoxy-8-nitrodibenzofuran

Prepared according to general procedure B using 2-(3,5-Dimethoxyphenoxy)-6-(trifluoromethyl)-benzonitrile (0.14g, 0.5 mmol), Pd(OAc)₂ (0.028g, 0.125 mmol), K₂CO₃ (0.017, 0.125 mmol) in 1.2 g of Pivalic Acid. The product was purified via prep plate thin layer chromatography to afford a yellowish solid; yield (97%).

¹H NMR (CDCl₃): δ: 8.86 (d, 1H), 8.27 (q, 2H), 7.54 (d, 2H), 6.74 (d, 1H), 6.47 (d, 1H), 4.05 (s, 3H), 3.85 (s, 1H).

¹³C NMR (CDCl₃): δ = 162.6, 159.7, 150.9, 146.0, 145.9, 128.3, 120.2, 116.7, 114.5, 112.4, 88.6, 87.8, 56.1, 55.8.

6,8-Dichloro-1, 3-dimethoxydibenzofuran

Prepared according to general procedure B using 2-(3,5-Dimethoxyphenoxy)-6-(trifluoromethyl)-benzonitrile (0.15g, 0.5 mmol), Pd(OAc)₂ (0.028g, 0.125 mmol), K₂CO₃ (0.017, 0.125 mmol) in 1.2 g of pivalic acid. The product was purified via column chromatography to afford a white solid; yield (40%).

¹H NMR (CDCl₃): δ : 7.39 (d, 1H), 7.21 (d, 1H), 6.78 (s, 1H), 6.15 (d, 1H), 3.83 (s, 3H), 3.83 (s, 3H).

¹³C NMR (CDCl₃): δ = 159.7, 158.5, 150.9, 145.0, 130.1, 118.5, 113.4, 111.1, 106.4, 88.6, 87.8, 56.1, 55.8.
2-Formyl-7, 9-dimethoxydibenzofuran-4-carbonitrile

Prepared according to general procedure B using 2-(3,5-Dimethoxyphenoxy)-6-(trifluoromethyl)-benzonitrile (0.14g, 0.5 mmol), Pd(OAc)$_2$ (0.028g, 0.125 mmol), K$_2$CO$_3$ (0.017, 0.125 mmol) in 1.2 g of pivalic acid. TLC and NMR data showed an intractable mixture of products.

7,9-Dimethoxydibenzofuran-2-carbaldehyde

Prepared according to general procedure B using 2-(3,5-dimethoxyphenoxy)-6-(trifluoromethyl)-benzonitrile (0.13g, 0.5 mmol), Pd(OAc)$_2$ (0.028g, 0.125 mmol), K$_2$CO$_3$ (0.017, 0.125 mmol) in 1.2 g of pivalic acid. TLC and NMR data show intractable mixture of products.
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This is to certify that Sadia Akram has successfully completed her Senior Honors Thesis, entitled:

Synthesis of Dibenzo furans via a Palladium Catalyzed Oxidative Ring Closure Reaction

Mark L. Trudell
Director of Thesis

John B. Wiley
for the Department

Abu Kabir Mostofa Sarwar
for the University

Abu Kabir Mostofa Sarwar
Honors Program

April 29, 2013
Date