Palladium-Catalyzed Carbocyclizations of Substituted Benzoic Acids and Tandem One-Pot Acyl Heck/Heck Coupling of Indanones

THESIS

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By

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Abstract

Indanones and indenones are common structural motifs found in pharmaceuticals and biologically active natural products. Transition metal-catalyzed annulation processes represent the most current methods of synthesizing these attractive targets. However, the known methods to synthesize indanones and indenones generally suffer from poor regioselectivity, excess waste production, the use of high pressures of carbon monoxide, and/or poor functional group tolerance. The preparation of exo-methylene indanones and indenones from a novel palladium-catalyzed acyl-Heck cyclization of substituted benzoic acids is described herein. Formation of either the exo-methylene indanones or indenones can be controlled by simply changing the ligand. Low palladium loadings of 1 mol % provides moderate to excellent yields with broad functional group tolerance. Moreover, acetic acid is the only stoichiometric byproduct produced in this process.

The degradation of the Pd(OAc)$_2$/P(o-tol)$_3$ used to form exo-methylene indanones into the well-known Herrmann-Beller palladacycle was observed and utilized in a tandem one-pot coupling process. This palladacycle is a robust Heck coupling catalyst, and because it is in the presence of a newly formed alkene, simply adding an arylbromide and a base provided access to a variety of aryl substituted exo-methylene indanones. Markedly, the synthesis of Indanorine, an antiproliferative agent, was achieved in good yield. Further application of this method toward the synthesis of donepezil which is
marketed by Pfizer as Aricept® (donepezil HCl) for the treatment of mild, moderate, and severe Alzheimer’s disease is also reported.
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Chapter 1: Palladium-Catalyzed Synthesis of Indanones and Indenones from Substituted Benzoic Acids

1.1 Introduction

The formation of carbon-carbon bonds by acylmetallation of olefins is a powerful synthetic transformation.\(^1\) The palladium-catalyzed carbonylative coupling reaction of aryl or vinyl halides with olefins is the most common type of this transformation. Although the high toxicity of carbon monoxide requires the use of specific equipment and safety protocols, it is commonly employed in industrial settings. Despite the rapid development in recent years of more efficient and benign reaction conditions (i.e. ambient temperature and low pressures <5 bar), the use of carbon monoxide in complex molecule synthesis is not common compared to industrial use. The high toxicity of carbon monoxide requires the use of specific equipment and safety protocols which is most likely the reason for synthetic chemists’ reluctance. Methods utilizing CO sources such as Mo(CO)\(_6\)\(^2\) and aldehydes\(^3\) have been reported but the additional waste production and expense make these methods unattractive. Formation of acylmetal complexes from activated carboxylic acid derivatives such as acylchlorides\(^4\), thioesters\(^5\), and anhydrides\(^6\) is also well known. However, their use as acylderivatives is limited due to the preparation of the starting substrates as well as the ability of these complexes to undergo decarbonylation.\(^7\) Because of our group’s interest in utilizing the carboxylic acid
functional group in metal-mediated processes, we focused our attention on forming metal acyl species from carboxylic acids.

The formation of cyclic ketones like indanones and indenones is especially important. These structural motifs are commonly found in pharmaceuticals and natural products including Aricept® (1.1), a potent acetylcholinesterase inhibitor marketed for the treatment of Alzheimer Disease,⁸ the anti-cancer drug indanocine (1.2),⁹ as well as the natural occurring biologically active class of pterosins (1.3) (Figure 1).¹⁰

![Chemical structures of biologically important compounds](image-url)

Figure 1. Biologically important compounds with an indanone core

Due to the biological importance of these molecules, the development of efficient and green variants to the current methods is necessary. Although there are many processes available to form the indanone and indenone scaffolds, issues with waste production and regioselectivity of annulation processes are still problematic. The most common method of forming indanones involve Friedel-Crafts type cyclizations.¹¹ Although many improvements have been reported, harsh reaction conditions (>140 °C) and large amounts of acidic waste from the use of excess lewis or protic acids render these reactions unfavorable.¹² Furthermore, mixtures of regioisomers are usually
obtained unless these positions are blocked by substitution. Carbonylative Heck coupling represents a very powerful method by introducing the carbonyl of the indanone using carbon monoxide. An obvious drawback to this chemistry is the need for specialized equipment due to the high toxicity and high pressures required. Furthermore, the use of aryl halides and other coupling partners such as boronic acids requires the use of excess base producing large amounts of waste.

More recently, the coupling of ortho haloaryl aldehydes with alkynes to indenones has been reported. However, this method requires the use of excess base and only symmetrical alkynes are used to avoid producing regioisomers. The synthesis of indenones from aryne precursors has also been reported, but excess cesium fluoride is needed to generate the aryne in situ and poor regioselectivity is obtained. A single example of the cyclization of a phosphoric anhydride to yield an indanone has also been reported, but required the synthesis and isolation of the starting phosphoric anhydride.

The method reported herein offers an efficient and practical synthesis of indanones and indenones from readily accessible benzoic acid derivatives. High selectivity of either the exo-methylene indanones or indenones can be obtained by simply changing the ligand. Moreover, acetic acid is produced as the only stoichiometric byproduct and no carbon monoxide is required. This reaction has broad functional group tolerance and produces moderate to excellent yields with the use of only 1 mol % palladium.

We proposed that activation of the benzoic acid in situ as its anhydride would be necessary for this acyl Heck reaction. The proposed mechanism of this carbocyclization
with acetic anhydride is depicted in Scheme 1. The activation of the benzoic acid as its anhydride followed by selective oxidative addition of the palladium would yield the acylpalladium species 2.1. Carbocyclization to form the alkylpalladium compound 2.2 followed by β-hydride elimination would furnish the 2-exo-methylene indanone which could then undergo isomerization to yield the 2-methylindenone. The resulting hydridopalladium complex 2.3 would then eliminate acetic acid to regenerate the Pd(0) species and turnover the catalytic cycle.

Figure 2. Proposed mechanism for the carbocyclization of 2-allylbenzoic acid
One potential drawback to this method was the selectivity of the initial oxidative addition. Previous work by Gooßen and coworkers showed that the insertion of an anhydride could be controlled by placing a bulky t-butyl group at one end of the anhydride.\textsuperscript{18} However, due to the expense of pivalic anhydride and the more harsh conditions required to remove the pivalic acid waste, we chose to use acetic anhydride. We envisioned that this insertion could be controlled by coordination of the appended alkene (Figure 2). Another potential limiting factor in this reaction is the ability of the formed acyl metal species to undergo decarbonylation. We hypothesized that mild reaction conditions would limit the amount of this probable side reaction.

1.2 Results and Discussion

1.2.1 Synthesis of 2-Allybenzoic Acid Derivatives

The 2-allylbenzoic acid derivatives were prepared from the anthranilic acids as depicted in Figure 3. The anthranilic acid is converted to the corresponding 2-iodobenzoic acids by a Sandmeyer type reaction with Sodium nitrite and Potassium iodide. Next using modified Knochel conditions to perform a magnesium-iodine exchange coupling reaction with allylbromide provides the 2-allylbenzoic acids in good to excellent yields.

![Figure 3. Synthesis of 2-allybenzoic acid derivatives](image-url)
We initially tested our hypothesis by treating 2-allylbenzoic acid with acetic anhydride in the presence of 1 mol % Pd(OAc)$_2$ and 1.2 mol % P(o-tol)$_3$ (Table 1) in THF at ambient temperature. We were pleased to find the cyclization proceeded smoothly to afford the $\text{exo}$-methylene indanone in moderate yield (entry 1). Heating the reaction and using 2 mol % phosphine increased the yield to 89%. Although switching the ancillary ligand to AsPh$_3$ and PPh$_3$ did not improve the yield, the use of PCy$_3$ furnished 2-methyl indenone as the major product (entries 3-5). Using a Pd(0) source with P(o-tol)$_3$ resulted in diminished yields of the indanone (entry 6), while no cyclization was observed with PdCl$_2$ (entry 7). Quantitative conversion to the corresponding anhydride was observed in the absence of palladium (entry 8). Acetic anhydride was found to be necessary for cyclization and removal of the phosphine resulted in low yields (Entry 9 and 10). Furthermore, tetrahydrofuran was found to be the best solvent as lower yields and a mixture of indanone and indenone products were obtained with acetonitrile and benzene (entry 11 and 12).
1.2.2 Substrate Scope for Indanone and Indenone Formation

With the optimized conditions in hand, a variety of 2-allylbenzoic acids were cyclized to the corresponding exo-methylene indanones (Table 2). Methyl substitution on the ring was well tolerated giving yields of 91% - 92% (2b, 2c, 2d). Electron donating groups had little effect on the cyclization providing the corresponding indanones in yields.
of 82% - 86% (2e, 2f, 2g). Notably, 2-allyl-5-hydroxybenzoic acid underwent cyclization with concomitant protection of the hydroxy group as an acetate in an 52% yield (2g). Increasing the amount of acetic anhydride to 3 equivalents provided an 82% yield of the acetate protected product. Arylbromides were left unaffected during the cyclization, but required the use of the less basic ligand, triphenylarsine, to provide a 60% yield (2h). Electron deficient aryl chlorides, aryl fluorides, and naphthoic derivatives proceeded to cyclize in high yields, but the corresponding indenone was observed as a minor side product for the aryl chloride (2i) and naphthoic (2j) derivatives requiring an increase in Pd loading to 2 mol %. The reaction scope was also extended to heteroaromatics with an indole substrate providing 50% of the desired cyclized product.
Table 2. Acyl-Heck reactions of benzoic acids to form exo-methylene indanones

Our initial screening showed that the PCy₃ ligand selectively provided the indenone as the major product. We hypothesized that the exo-methylene indanone
product formed in the reaction is subsequently isomerized in the presence of this catalyst system. To test this indanone (1b) was subjected to the Pd/PCy₃ conditions and nearly complete conversion to the corresponding indenone was observed (Scheme 2). It is likely the isomerization occurs faster than the NMR timescale. Acetic acid, which is produced from the initial anhydride formation (Scheme 1), was found to be necessary for isomerization. However, additional acetic acid did not increase the amount of isomerization in either the P(o-tol)₃ or PCy₃ catalyst systems.

![Chemical reaction diagram]

Figure 4. Isomerization of indanone to indenone

The scope of the indenone cyclization proved to be tolerant to a variety of functional groups and heterocycles (Figure 5). Methyl substituted 2-allylbenzoic acid cyclized to indenone (3b) in a 75% yield. The electron-rich 2-allyl-5-hydroxybenzoic acid substrate worked well with simultaneous protection as the acetate to provide indenone (3c) in a 60% yield. Electron-deficient aryl chlorides, aryl fluorides, and naphthoic derivatives smoothly cyclized in 60% - 80% yields (3d, 3e, 3f, 3g). The Heck coupling also worked with a disubstituted olefin and gave a moderate yield of the fluorenone. Markedly, an N-allyl indole substrate formed an alkaloid type structural motif in a moderate yield (3i). Cyclization of the substituted indole surprisingly yielded
carbazole (3j) in a 50% yield. The reaction also tolerated sulfur containing heterocycles and the substituted thiophene derivative formed 73% of the cyclized product. Increasing the palladium loading did not improve the yield of the reaction (3a, 3d).

![Chemical Structures and Reaction Scheme](image)

Table 3. Acyl-Heck reactions of benzoic acids to indenones

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield</th>
</tr>
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<tbody>
<tr>
<td>3a</td>
<td>73%</td>
</tr>
<tr>
<td>3b</td>
<td>75%</td>
</tr>
<tr>
<td>3c</td>
<td>60%</td>
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<tr>
<td>3d</td>
<td>65%</td>
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<tr>
<td>3e</td>
<td>68%</td>
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<td>3h</td>
<td>57%</td>
</tr>
<tr>
<td>3i</td>
<td>48%</td>
</tr>
<tr>
<td>3j</td>
<td>51%</td>
</tr>
<tr>
<td>3k</td>
<td>73%</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yields. \(^b\) 2 mol % Pd(OAc)\(_2\), 4 mol % P(Cy)\(_3\) used. \(^c\) 3 mol % Pd(OAc)\(_2\), 6 mol % P(Cy)\(_3\), dioxane, 100°C. \(^d\) 5 mol % Pd(OAc)\(_2\), 10 mol % P(Cy)\(_3\) in dioxane at 100°C.
We hypothesized that isomerization with the Pd/ P(o-tol)$_3$ system does not occur due to the formation of the Hermann-Beller palladacycle.\textsuperscript{19} Monitoring the reaction of 2-allylbenzoic acid and acetic anhydride in the presence of 1 equivalent of Pd(OAc)$_2$ and two equivalents of P(o-tol)$_3$ at ambient temperature by $^{31}$P NMR spectroscopy revealed the formation of a new complex after only 30 min (Figure 5). This broad signal at around 35 ppm is indicative of the Herrmann-Beller Palladacycle.

![Figure 5. $^{31}$P NMR spectra of Pd(OAc)$_2$/P(o-tol)$_3$ cyclization](image)

To test if this palladacycle was the active catalyst for the cyclization, the complex was synthesized separately and reacted with 2-allylbenzoic acid and acetic anhydride (Figure 6). Only a small amount of indanone product was observed confirming it is not
the active catalyst in the acyl-heck coupling reaction, and this product formation is most likely due to residual Pd(OAc)$_2$(P(o-tol)$_3$)$_2$.

![Molecular structure](image)

Figure 6. Reaction of 2-allylbenzoic acid with Herrman-Beller palladacycle

### 1.2.3 Efforts to Cyclize Homoallylic Benzoic Acid Substrate

The cyclization of 2-allylbenzoic acid to form 5-membered rings proceeds smoothly. We were interested in extending the scope of this reaction to form 6-membered rings using a homoallylic system. We first synthesized 2-(but-3-en-1-yl)benzoic acid which can be accessed from 2-methylbenzoic acid as depicted in Figure 7.\(^20\) Using \(^n\)BuLi to deprotonate the benzylic hydrogen followed by addition of allyl bromide provided the product in a 60% yield.
Cyclization to the corresponding \textit{exo}-methylene 6-membered ring was not observed under the optimized conditions found for the formation of the \textit{exo}-methylene indanone. A variety of phosphines were tested including PEt$_3$, PiPr$_2$H, P(2-furyl)$_3$, PPh$_3$, PPh$_2$H, PPh$_2$Cl, P(O/Pr)$_3$, P(OPh)$_3$, DPPE, and 2,2-bipyridine, but no desirable product formation was observed. Increasing the reaction temperature to 100 °C in DMF did not provide any of the desired product.

It is not surprising that more harsh reaction conditions would be required for this cyclization, but an increase in temperature would likely result in decarbonylation of the starting material. We hypothesized that forcing the appended olefin to be in close proximity to the carboxylic acid would increase the rate of cyclization and compete with the decarbonylative pathway. Substitution at the benzylic position could help to preorganize the olefin toward the carboxylic acid. To test this we synthesized 2-(1-phenylbut-3-en-1-yl)benzoic acid from 2-benzylbenzoic acid (Figure 7). However, only the decarbonylated products were observed when reacting the phenyl substituted 2-
homoallylic benzoic acid with Pd(OAc)$_2$, PCy$_3$, and Ac$_2$O, in DMF at 100 °C (detected by GC/MS).

1.3 Future Work

We plan to further explore the cyclization of homoallylic benzoic acid derivatives to the corresponding 6-membered ring. The decarbonylation of the acylpalladium complex could be avoided if the rate of cyclization was faster. It is likely adjusting the catalyst system by switching the ancillary ligand may increase the rate of cyclization. In addition, including a heteroatom in the alkene chain would provide access to biologically important scaffolds. N-allyl anthranilic acids could lead to quinolinones while N-vinyl anthranilic acids could lead to indolinones. Oxygen substitution would also lead to interesting compounds like benzofuranones, chromanones, and chromenones.

1.4 Conclusion

We present a highly efficient and selective method to form \textit{exo}-methylene indanones and indenones from readily accessible substituted benzoic acids. The reaction avoids the use of toxic carbon monoxide and produces acetic acid as the only stoichiometric byproduct. Furthermore this reaction uses only 1 mol % palladium to provide moderate to excellent yields of the products with broad functional group tolerance. A simple change in ligand selectively controls the formation of the indanone or indenone. The biological importance of these structural motifs renders this efficient method as useful.
Chapter 2: One-Pot Tandem Acyl Heck/Heck Coupling Reaction

2.1 Introduction

The Herrmann-Beller palladacycle was first reported in 1995 and is a robust catalyst system used in Heck coupling reactions (Figure 8).\textsuperscript{19,21} When comparing this system with other catalysts used for the Heck reaction, the palladacycle has many advantages including but not limited to: thermal stability (decomposes >250 °C), the requirement of only 1 equivalent of phosphine instead of the usual 2 to 6 equivalents, and high turnover numbers. The use of inexpensive chlorarenes in Heck reactions is favorable but requires much harsher conditions. Due to the thermal stability and reactivity of this complex, chlorarenes can be activated with this palladacycle with the addition of alkali metal salts or tetrabutylammonium bromide.

![Figure 8. Herrmann-Beller palladacycle](image)

Generally, Heck reaction mechanisms begin with a Pd(0) catalyst and upon oxidative addition with the arylhalide or aryltriflate, form a Pd(II) intermediate. It is still
unclear as to whether the Hermann-Beller catalyst goes through a Pd(II) to Pd(IV) mechanism or is reduced \textit{in situ} to a Pd(0) species to undergo a Pd(0) to Pd (II) mechanism. Initially, a Pd(II)/Pd(IV) mechanism was believed to be the most reasonable mechanism by Beller, Hermman and co-workers. However, a report by Louie and Hartwig$^{22}$ showed that palladacycles can be easily transformed into a Pd(0) species making the Pd(0)/Pd(II) mechanism likely.

2.2 Results and Discussion

While screening conditions for the indanone formation with the Pd(OAc)$_2$/P(0-tol)$_3$ system we attempted to isolate the Pd-acyl species by reacting acetic benzoic anhydride with Pd(OAc)$_2$ and P(o-tol)$_3$. Diffusion of pentane into a solution of the complex in toluene gave light yellow platelets which were analyzed by x-ray diffraction. Based on our earlier $^{31}$P NMR experiments we were not surprised to find a palladacycle formed. In fact, the palladacycle was very similar to the Hermann-Beller catalyst with benzoates replacing the typical acetate ligands (Figure 9).

We next sought to explore the use of this catalyst with the newly formed alkene of the indanone. To the best of our knowledge, no Heck coupling with \textit{exo}-methylene indanones have been reported. Furthermore, following the cyclization with another Heck coupling would allow for a tandem one-pot reaction forming two new sp$^2$- sp$^2$ carbon-carbon bonds and require no additional catalyst.
We envisaged that simply adding an arylbromide and base to the crude reaction mixture would furnish the desired products. To our delight, the expected coupled products were obtained albeit in low yields. Optimization of the reaction revealed that removal of the acetic acid and THF under reduced pressure before the addition of 1 equivalent of NBu$_3$, 1.5 equivalents of the aryl bromide, and DMF was necessary. The catalyst is known to be active at elevated temperatures only, and the reaction was found to be optimal at a temperature of 120 °C. The use of NBu$_3$ as a base provided the highest yields compared to NaOAc or NCy$_2$Me. The initial scope for this process is shown in Table 3. All of the reactions formed (E)-alkenes as the major products with a small amount of isomerization to the corresponding indenones. As expected, electron deficient aryl bromides gave higher yields (10a, 10b, 10d) than electron rich aryl bromides (10c).
Notably, Indanorine, an antiproliferative agent,\textsuperscript{23} was synthesized in a 64% yield. The coupling was also performed using a bromo-substituted indole and produced the coupled product in a moderate yield.

![Chemical reaction](image)

Figure 10. One-pot double Heck reaction to form two sp2-sp2 carbon-carbon bonds\textsuperscript{a}

\textbf{2.2.1 Efforts Toward the Synthesis of Donepezil}

The one-pot tandem Heck reaction was utilized in the synthesis of Donepezil, which is marketed by Pfizer as Aricept\textsuperscript{®} (donepezil·HCl) for the treatment of mild, moderate, and severe Alzheimer’s disease. Current synthetic methods involve the use of 4,5-dimethoxyindanone as a starting material. However, this indanone is synthesized...
using a Friedel-Crafts cyclization and a Wittig reaction which produces regioisomers and excess waste making this method less desirable.

Due to the availability of benzoic acid derivatives in nature and the efficient Heck cyclization method reported herein, we present a complimentary synthesis of this drug. Subjecting 4,5-dimethoxy-2-allylbenzoic acid and 4-bromopyridine to optimized one-pot tandem Heck coupling reaction conditions yielded the coupled product (11a). Reaction of 11a with benzyl bromide provided the quaternary pyridinium bromide 11b. Hydrogenation of the pyridine and alkene with Pt2O and ambient hydrogen yielded donepezil (11c).

Due to the typically difficult coupling reaction with a pyridine reagent, the palladium loading for the tandem one-pot Heck coupling was increased to 5 mol%. However, some of the indenone product was observed under these conditions, so the temperature of the cyclization step was lowered to ambient temperature. This also

Figure 11. Currently used synthesis of donepezil
required the lowering of the phosphine loading from 10 mol % to 7 mol %. The coupling reaction proceeds cleanly to the desired product under these conditions.

Figure 12. Synthesis of donepezil utilizing the tandem one-pot Heck reaction

2.3 Future Work

The extension of this tandem one-pot Heck coupling method to arylchlorides is probable and may require some additional optimization (i.e. increased reaction temperatures, addition of salts). Also, the ability to perform the reaction without the necessity of removing the acetic acid formed in the cyclization step would make this method even more efficient. Further optimization of the synthesis donepezil is also underway.

2.4 Conclusion
The degradation of the active Heck catalyst system used to form \textit{exo}-methylene indanones into the well-known Hermann-Beller Palladacycle provides access to a one-pot acyl Heck/Heck coupling to form two sp\textsuperscript{2}-sp\textsuperscript{2} carbon-carbon bonds. Simply adding an arylhalide and amine base to the crude reaction mixture provides access to a variety of coupled indanone products. This tandem Heck coupling reaction was utilized in the synthesis of donepezil, a drug used for the treatment of Alzheimer disease and provides a complimentary method to the currently used synthesis of this drug.
Chapter 3: Experimental Data

3.1 General Methods

Cyclizations were conducted in borosilicate glass vials in an Ar atmosphere. Palladium acetate was obtained from Pressure Chemical Co. and was used without further purification. Acetic anhydride was fractionally distilled from K$_2$CO$_3$. All other commercially obtained reagents were used as received. Thin-layer chromatography (TLC) was conducted with Sorbent Technologies silica gel UV254 precoated plates (0.25 mm), and visualized using UV lamps or KMnO$_4$ staining. $^1$H NMR spectra and $^{13}$C NMR spectra were recorded on a Bruker 400 MHz Avance III or a Bruker 500 MHz DRX and are reported relative to residual solvent CDCl$_3$ ($^1$H, 7.26 ppm, $^{13}$C, 77.0ppm), (CD$_3$)$_2$CO ($^1$H, 2.05 ppm, $^{13}$C, 206.26ppm). IR spectra were recorded on a Perkin Elmer 1600 FT-IR spectrometer. High resolution mass spectral analysis was performed on a Bruker MicOTOF (ESI) at the mass spectrometry facility at The Ohio State University.

3.2 Chapter 1 Experimental Details

Sandmeyer-type reaction with anthranilic acids$^{24}$

To a solution of anthranilic acid (1 equiv) in water (1M) was added concentrated sulfuric acid (2.5 equiv) at 5 °C and an aqueous solution of sodium nitrite (1.1 equiv) slowly.
The resulting solution was stirred for 30 minutes before potassium iodide (1.5 equiv) in sulfuric acid (1M) was added. The solution was then heated at 100 °C for 1 hour. The reaction was cooled to ambient temperature and the precipitate was filtered and washed with water. Further purification with column chromatography on silica gel or recrystallization provided the 2-iodobenzoic acid.

Mg-iodine exchange coupling reaction with substituted benzoic acids:²⁵

The 2-allylbenzoic acids were prepared with a slight modification to a known literature procedure.²⁵ To a stirred solution of 2-iodobenzoic acid and THF (0.33M) at -30 °C in an oven-dried flask under argon was added MeMgBr (1 equiv) and stirred for 5 minutes. Isopropyl Magnesiumchloride (1.2 equiv) was added slowly and the reaction was stirred at -30 °C for 1 hour or until the reaction was complete by GC/MS (an aliquot was quenching with water before analysis). The reaction was then cooled to -40 °C and a solution of CuCN·2LiCl in THF (5 mol %, 0.34M) was added slowly and stirred for about 10 min while warming to -30 °C. Allyl bromide (3 equiv) was added at once and the reaction was allowed to warm to ambient temperature overnight. The reaction was diluted with EtOAc, acidified with 1M HCl to a pH of 3, and extracted with EtOAc (4x). The combined organic layers were washed with brine and dried over Na₂SO₄. The crude mixture was concentrated and purified by column chromatography on silica gel to yield 2-allylbenzoic acid.

Mg-iodine exchange and saponification with substituted alkylbenzoates:
The 2-allylbenzoic acids were prepared with a slight modification to a known literature procedure.\textsuperscript{25} To a stirred solution of the alkyl-2-iodobenzoate in THF (0.33M) at -30 °C in an oven-dried flask under argon was added isopropylmagnesiumchloride (1.2 equiv) slowly and the reaction was stirred at -30 °C for 1 hour or until the reaction was complete by GC/MS (an aliquot was quenching with water before analysis) The reaction was then cooled to -40 °C and a solution of CuCN·2LiCl in THF (5mol%, 0.34M,) was added slowly and stirred for about 10 min while warming to -30 °C. Allyl bromide (3 equiv) was added at once and the reaction was allowed to warm to ambient temperature overnight. The reaction was diluted with EtOAc, quenched with NH$_4$Cl, and extracted with EtOAc (4x). The combined organic layers were washed with brine and dried over Na$_2$SO$_4$. The organic layers were concentrated and dissolved in the corresponding alchol (MeOH or EtOH, 0.25M). The stirred solution of the ester was added an aqueous solution of NaOH (10 equiv, 2.5M) and the reaction was stirred for 6h. The alcohol was distilled off and the crude mixture was washed with Et$_2$O. The aqueous layer was acidified with 1M HCl to a pH of 3 and extracted with CH$_2$Cl$_2$ (3x). The combined CH$_2$Cl$_2$ layers were washed with brine and dried with Na$_2$SO$_4$. The crude mixture was concentrated and purified by column chromatography on silica gel to yield 2-allylbenzoicacid.
**2-allylbenzoic acid:** The general procedure for the Mg-Iodine exchange was followed using 2-iodobenzoic acid (250 mg, 1 mmol). The crude mixture was purified by column chromatography on silica gel (CH$_2$Cl$_2$) to give 90% of the product as a white solid (147 mg, 0.90 mmol). FTIR (CCl$_4$, cm$^{-1}$): 3076, 2976, 1693, 1409, 1300, 1271; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$, ppm 8.06 (dd, $J$ = 1.4, 8.1 Hz, 1H), 7.51 (dt, $J$ = 1.5, 7.6 Hz, 1H), 7.33 - 7.30 (m, 1H), 7.32 (d, $J$ = 15.4 Hz, 1H), 6.10 - 6.00 (m, 1H), 5.08 - 5.01 (m, 2H), 3.84 (d, $J$ = 6.5 Hz, 2H), $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 173.6, 142.8, 137.3, 133.1, 131.7, 131.1, 128.2, 126.3, 115.7, 38.5.

![Chemical Structure](image)

**2-iodo-3-methylbenzoic acid:** The general procedure for the Sandmeyer-type reaction was followed using 3-methylanthranilic acid (3.78 g, 25 mmol). The crude mixture was purified by column chromatography on silica gel (CH$_2$Cl$_2$) to give 29% of the product as a white solid (1.9 g, 7.25 mmol). FTIR (CCl$_4$, cm$^{-1}$): 2974, 2545, 1704, 1567, 1414, 1291, 1261; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$, ppm 7.63 (d, $J$ = 7.2 Hz, 1H), 7.40 (d, $J$ = 7.9 Hz, 1H), 7.31 (t, $J$ = 7.7 Hz, 1H), 2.56 (s, 3H).

Spectroscopic data are in accordance with those described in the literature.$^{26}$
2-allyl-3-methylbenzoic acid: To a stirring solution of 2-iodo-3-methylbenzoic acid (1.85 g, 7.06 mmol) in EtOH (16.5 mL) was added thionyl chloride (650 µL, 8.9 mmol) dropwise. The reaction was heated to reflux for 4.5h. The crude mixture was quenched with NaHCO₃ and extracted with EtOAc (3x20mL). The combined organic layers were washed with brine, dried with Na₂SO₄, and concentrated to give 83% of ethyl-3-methyl-2-iodobenzoate as a colorless oil (1.7 g, 7.1 mmol). ¹H NMR (400 MHz, CDCl₃): δ, ppm 7.38 - 7.32 (m, 2H), 4.42 (q, J=7.2 Hz, 2H), 1.43 (t, J=7.2 Hz, 3H). Spectroscopic data are in accordance with those described in the literature. The general procedure for the Mg-Iodine exchange and saponification was followed using ethyl-3-methyl-2-iodobenzoate (168 g, 5.8 mmol). The crude mixture was purified by column chromatography on silica gel (CH₂Cl₂) to give 72% of the product as a white solid (738 mg, 4.19 mmol). FTIR (CCl₄, cm⁻¹): 3077, 2978, 2661, 1691, 1278; ¹H NMR (400 MHz, CDCl₃): δ, ppm 7.86 (J = 7.7 Hz, d, 1H), 7.36 (J = 7.3 Hz, d, 1H), 6.05 - 5.94 (m, 1H), 5.05 - 4.89 (m, 2H), 3.81 (d, J = 5.9 Hz, 2H), 2.38 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 173.6, 139.8, 138.5, 134.8, 129.4, 129.2, 126.0, 115.1, 34.1, 19.9; HRMS (ESI) calcd for C₁₁H₁₁O₂ [M+H]⁺: 199.073, found 199.0721.
2-iodo-6-methylbenzoic acid: The general procedure for the Sandmeyer-type reaction was followed using 6-methylantranilic acid (3.0 g, 19.8 mmol). The crude mixture was purified by column chromatography on silica gel (CH$_2$Cl$_2$) to give 60% of the product as a white solid (3.12 g, 11.9 mmol). FTIR (CCl$_4$, cm$^{-1}$): 2916, 2649, 2544, 1705, 1586, 1556, 1285; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$, ppm 7.70 (d, $J$ = 7.8 Hz, 1H), 7.22 (d, $J$ = 8.1 Hz, 1H), 7.03 (t, $J$ = 7.8 Hz, 1H), 2.45 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 175.0, 138.8, 136.6, 136.4, 131.0, 129.8, 91.4, 20.2. Spectroscopic data are in accordance with those described in the literature.$^{28}$

2-allyl-6-methylbenzoic acid: The general procedure for the Mg-Iodine exchange was followed using 2-iodo-6-methylbenzoic acid (781 mg, 2.98 mmol). The crude mixture was purified by column chromatography on silica gel (CH$_2$Cl$_2$) to give 81% of the product as a white solid (424 mg, 2.4 mmol). FTIR (CCl$_4$, cm$^{-1}$): 3068, 2925, 1654, 1698, 1549, 1289; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$, ppm 7.28 (t, $J$ = 7.7 Hz, 1H), 7.11 (dd, $J$ = 2.6, 7.6 Hz, 1H), 6.02 - 5.91 (m, 1H), 5.12 - 5.06 (m, 2H), 3.54 (d, $J$ = 7.2 Hz, 2H), 2.45 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 175.3, 137.5, 136.7, 135.7, 132.3,
132.0, 130.1, 128.4, 127.3, 125.9, 116.3, 38.2, 29.7, 22.1, 20.1; HRMS (ESI) calcd for C_{11}H_{12}O_{2} [M+Na]^+: 199.0730, found 199.0721.

Spectroscopic data are in accordance with those described in the literature.\(^{29}\)

2-iodo-5-methylbenzoic acid: The general procedure for the Sandmeyer-type reaction was followed using 6-methylantranilic acid (3.79 g, 25 mmol). The crude mixture was purified by column chromatography on silica gel (CH\(_2\)Cl\(_2\)) to give 72% of the product as an off-white solid (4.72 g, 18 mmol). FTIR (neat, cm\(^{-1}\)): 3155, 3021, 2984, 2925, 1702, 1563, 1470, 1410, 1294, 1259, 1216, 1094, 1016; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\), ppm 10.65 (s, 1H), 7.82 (d, \(J=8.1\) Hz, 1H), 7.76 (d, \(J=2.0\) Hz, 1H), 2.27 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 171.7, 141.7, 138.2, 134.6, 132.8, 90.6, 20.8.

Spectroscopic data are in accordance with those described in the literature.\(^{28}\)
2-allyl-5-methylbenzoic acid: To a stirring solution of 2-iodo-5-methylbenzoic acid (2.9 g, 11.1 mmol) in EtOH (20mL) was added thionyl chloride (1.92 mL, 26.6 mmol) dropwise. The reaction was heated to reflux for 18h. The crude mixture was quenched with NaHCO₃ and extracted with EtOAc (3x20mL). The combined organic layers were washed with brine, dried with Na₂SO₄, and concentrated. The crude reaction mixture was purified by column chromatography on silica gel (Hexanes/EtOAc, 97.5/2.5) to give 90% of ethyl-5-methyl-2-iodobenzoate as a colorless oil (2.87 g, 9.9 mmol). FTIR (neat, cm⁻¹): 2979, 2924, 2869, 1727, 1465, 1296, 1250, 1104, 1021, 817; ¹H NMR (400 MHz, CDCl₃): δ, ppm 7.83 (1H, d, J = 8.1 Hz), 7.59 (1H, d, J = 1.9 Hz), 6.96 (1H, dq, J = 0.6, 3.4 Hz), 4.39 (2H, q, J = 7.2 Hz), 2.33 (3H, s), 1.41 (3H, t, J = 7.2 Hz); ¹³C NMR (CDCl₃, 100 MHz): δ 166.8, 141.0, 138.1, 135.4, 133.5, 131.5, 89.9, 61.6, 20.9, 14.3; HRMS (ESI) calcd for C₁₀H₁₁IO₂ [M+Na]+: 312.9696, found 312.9683. The general procedure for the Mg-Iodine exchange and saponification was followed using ethyl-3-methyl-2-iodobenzoate (2.86g, 9.86 mmol). The crude mixture was purified by column chromatography on silica gel (CH₂Cl₂) to give 87% of the product as a white solid (1.52g, 8.6 mmol). FTIR (CCl₄, cm⁻¹): 3077, 2979, 2922, 1699, 1637, 1570, 1411, 1298, 1272, 1217; ¹H NMR (400 MHz, CDCl₃): δ, ppm 7.86 (1H, s), 7.31 (1H, dd, J = 1.8, 8.0 Hz), 7.20 (1H, d, J = 7.8 Hz), 6.08 - 5.97 (1H, m), 5.05 - 4.99 (2H, m), 3.78 (2H, d, J = 6.6 Hz), 2.37 (3H, s); ¹³C NMR (CDCl₃, 100 MHz): δ 173.7, 139.7, 137.6, 135.9, 133.8, 132.1, 131.1, 128.0, 38.2, 20.7. Spectroscopic data are in accordance with those described in the literature.²⁹
Methyl-2-iodo-4,5-dimethoxybenzoate: A slight modification of the known literature procedure\textsuperscript{30} was used with methyl 2-amino-4,5-dimethoxybenzoate (6.8g, 29.7 mmol) in MeOH. The crude mixture was recrystallized from MeOH to give 73% of methyl-2-iodo-4,5-dimethoxybenzoate as off-white needles (6.98g, 21.7 mmol). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\), ppm 7.44 (s, 1H), 7.39 (s, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.90 (s, 3H). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz): \(\delta\) 165.9, 151.9, 148.6, 126.1, 123.7, 113.8, 84.6, 56.2, 56.0, 52.2; HRMS (ESI) calcd for C\textsubscript{10}H\textsubscript{12}IO\textsubscript{4} [M+Na]\textsuperscript{+}: 344.9582, found 344.9594. Spectroscopic data are in accordance with those described in the literature.\textsuperscript{31}

2-allyl-4,5-dimethoxybenzoic acid: A slight modification to the general procedure for the Mg-Iodine exchange and saponification was followed using methyl-2-iodo-4,5-dimethoxybenzoate (523 mg, 1.62 mmol) dissolved in a LiCl THF solution (1.62 mmol, 0.34M). The reaction was allowed to stir for 2h at -30\textdegree{}C after the addition of iPrMgCl. The crude mixture was purified by column chromatography on silica gel (CH\textsubscript{2}Cl\textsubscript{2}) to give the product (274mg, 1.23 mmol, 76% yield) as a white solid. FTIR (CCl\textsubscript{4}, cm\textsuperscript{-1}): 3078,
3004, 2958, 2934, 2848, 1520, 1464, 1409, 1356, 1264, 1220; \( ^1 \)H NMR (400 MHz, CDCl3): \( \delta, \text{ppm} \ 7.61 \ (s,1H), 6.75 \ (s,1H), 6.11 - 5.98 \ (m,1H), 5.08 - 5.00 \ (m,1H), 3.92 \ (d, J=6.5 \ Hz,3H), 3.81 \ (d, J=6.5 \ Hz,2H); \(^{13}\)C NMR (CDCl3, 100 MHz): \( \delta \ 172.7,152.8,146.8,137.9,137.5,119.5,115.4,114.1,113.4,55.9,55.9,38.4; \) HRMS (ESI) calcd for C\(_{12}\)H\(_{14}\)O\(_4\) [M+H]\(^+\): 223.0965, found 223.0963.

![Image of molecular structure]

**2-iodo-5-hydroxybenzoic acid:** The general procedure for the Sandmeyer reaction was followed using 5-hydroxyanthranilic acid (4.59 g, 30 mmol). The crude mixture was purified by column chromatography on silica gel (Hexanes/EtOAc/MeOH; 80/19/1) to give the product (5.37 g, 20.3 mmol, 67% yield) as a white solid. FTIR (CCl\(_4\), cm\(^{-1}\)): 3261, 1686, 1588, 1438, 1281, 1227, 1142; \(^1\)H NMR (DMSO-d\(_6\), 400 MHz): \( \delta \ 13.18 \ (s,1H), 9.97 \ (s,1H), 7.69 \ (d, J=8.6 \ Hz,1H), 7.12 \ (d, J=2.9 \ Hz,1H), 6.67 \ (dd, J=8.6, 3.0 \ Hz, 1H).

Spectroscopic data are in accordance with those described in the literature.\(^{32}\)

![Image of molecular structure]
**2-allyl-5-methoxybenzoic acid**: To a stirring solution of 2-iodo-5-hydroxybenzoic acid (2.64 g, 10.0 mmol) and potassium carbonate (4.15 g, 30.0 mmol) in anhydrous acetone was added dimethyl sulfate (3.78 mL, 40.0 mmol). The reaction mixture was heated to reflux for 24 hours. After being cooled to ambient temperature, the crude reaction mixture was filtered over a pad of celite, concentrated, and purified by column chromatography on silica gel (hexanes/EtOAc, 20:1) to give methyl-2-iodo-methoxybenzoate (2.63 g, 9.0 mmol, 90% yield) as a white solid. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 8.72 (d, \(J = 8.7\) Hz, 1H), 7.35 (d, \(J = 3.1\) Hz, 1H), 6.75 (d, \(J = 8.7, 3.1\) Hz, 1H), 3.93 (s, 3H), 3.82 (s, 3H). Spectroscopic data are in accordance with those described in the literature.\(^2^4\) The general procedure for the Mg-Iodine exchange and saponification was followed using methyl-2-iodo-methoxybenzoate (500.0 mg, 1.71 mmol). The crude mixture was purified by column chromatography on silica gel (CH\(_2\)Cl\(_2\)/MeOH, 20:1) to give 2-allyl-5-methoxybenoicacid (1.52 g, 8.6 mmol, 80% over two steps) as a white solid. FTIR (film, cm\(^{-1}\)): 3004, 1693, 1609.1, 1571, 1501, 1464, 1420, 1326, 1284, 1243, 1075, 1042, 995; \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.58 (d, \(J = 2.8\) Hz, 1H), 7.21 (d, \(J = 8.5\) Hz, 1H), 7.06 (dd, \(J = 8.5, 2.8\) Hz, 1H), 6.08 – 5.98 (m, 1H), 5.04 – 4.99 (m, 2H), 3.84 (s, 3H), 3.76 (d, \(J = 6.4\) Hz, 2H); \(^1^3\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 172.9, 157.8, 137.7, 134.9, 132.3, 128.9, 119.7, 115.8, 115.4, 55.5, 37.8; HRMS (ESI) calcd for C\(_{11}\)H\(_{12}\)O\(_3\) [M+Na]\(^+\): 215.0679, found 215.0683.
**2-allyl-5-hydroxybenzoic acid:** A modification to the general procedure for the Mg-Iodine exchange was followed using 2-iodo-5-hydroxybenzoic acid (524 mg, 1.98 mmol) dissolved in a LiCl THF solution (2.0 mmol, 0.25M). To the cooled solution was added MeMgBr (930 µL, 2.15M, 2 mmol) and the solution was stirred for 5 minutes. Trimethylsilyl chloride (172 µL, 2 mmol) was added followed by MeMgBr (930 µL, 2.15M, 2 mmol). Another equivalent of trimethylsilylchloride (172 µL, 2 mmol) was added. Isopropyl magnesiumchloride (1.2 equiv) was added slowly and the cloudy reaction mixture was stirred at -30°C for 1 hour. The reaction was then cooled to -40°C and a solution of CuCN·2LiCl in THF (300 µL, 0.05 mmol, 0.34M,) was added slowly and stirred for about 10 min while warming to -30°C. Allyl bromide (520 µL, 6 mmol) was added at once and the reaction was allowed to warm to ambient temperature overnight. The reaction was diluted with EtOAc, acidified with 1M HCl to a pH of 3, and extracted with EtOAc (4x20 mL). The combined organic layers were washed with brine and dried over Na₂SO₄. The crude mixture was concentrated and purified by column chromatography on silica gel (Hexanes/EtOAc, 80/20) to yield 2-allyl-5-hydroxybenzoicacid (307 mg, 1.72 mmol, 87% yield) as a white solid. FTIR (KBr, cm⁻¹): 3289, 3073, 1701, 1611, 1543, 1499, 1455, 1258, 1145, 1099; ¹H NMR (400 MHz, CDCl₃): δ, ppm 12.74 (s, 1H), 9.54 (s, 1H), 7.20 (d, J=2.8 Hz, 1H), 7.07 (d, J=8.3 Hz, 1H), 6.87 (dd, J=2.8, 8.3 Hz, 1H), 5.97 - 5.86 (m, 1H), 4.94 (q, J=6.5 Hz, 1H), 3.58 (td, J=1.5, 6.6 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ 168.7, 155.5, 138.4, 132.0, 131.3, 130.9, 119.0,
116.7, 114.9, 37.0; HRMS (ESI) calcd for C₁₀H₁₀O₃ [M+Na]⁺: 201.0522, found 201.0531.

2-iodo-5-bromobenzoic acid: The general procedure for the Sandmeyer reaction was followed using 5-bromoanthranilic acid (5.03 g, 23 mmol). The crude mixture was filtered to give the product (7.1 g, 21.7 mmol) as a light brown solid and was used without further purification. ¹H NMR (CDCl₃, 250 MHz): δ 8.12 (d, J = 2.5 Hz, 1H), 7.89 (d, J = 8.5 Hz, 1H), 7.32 (dd, J = 8.5, 2.5 Hz, 1H).

Spectroscopic data are in accordance with those described in the literature.³³

2-allyl-5-bromobenzoic acid: To a stirring solution of 2-iodo-5-bromobenzoic acid (7.5 g, 23 mmol) and potassium carbonate (10.4 g, 138 mmol) in anhydrous acetone (78 mL) was added dimethyl sulfate (9.4 mL, 126 mmol). The reaction mixture was heated to reflux for 16 hours. After being cooled to ambient temperature, the crude reaction mixture was filtered over a pad of celite, concentrated, and purified by column chromatography on silica gel (hexanes/EtOAc, 20:1) to give methyl-2-iodo-5-
bromobenzoate (5.06 g, 14.8 mmol, 64% yield) as a light yellow oil. \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 7.91 (d, \(J=2.5\) Hz, 1H), 7.80 (d, \(J=8.4\) Hz, 1H), 7.25 (dd, \(J=8.4\), 2.5 Hz, 1H), 3.93 (s, 3H). Spectroscopic data is in accordance with those described in the literature.\(^{33}\) A slight modification of the general procedure for the Mg-Iodine exchange and saponification was followed using methyl-2-iodo-5-bromobenzoate (1.7 g, 5.0 mmol) and cooling to -40°C throughout the entire reaction before warming to ambient temperature. The crude mixture was purified by column chromatography on silica gel (CH\(_2\)Cl\(_2\)) to give 2-allyl-5-bromobenzoic acid (696 mg, 2.9 mmol, 58% over two steps) as a white solid. FTIR (CCl\(_4\), cm\(^{-1}\)): 3081, 2981, 2644, 2538, 1698, 1639, 1590, 1561, 1483, 1410, 1384, 1297, 1255, 1099, 1076; \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\), ppm 8.19 (s, 1H), 7.61 (d, \(J=8.3\) Hz, 1H), 7.20 (d, \(J=8.3\) Hz, 1H), 6.06 - 5.93 (m, 1H), 5.09 - 5.00 (m, 1H), 3.78 (d, \(J=6.0\) Hz, 2H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 171.7, 141.7, 136.5, 136.0, 134.3, 129.8, 119.9, 116.2, 37.9; HRMS (ESI) calcd for C\(_{10}\)H\(_9\)BrO\(_2\) [M+Na]\(^+\): 262.9678, found 262.9680.

![2-allylbenzoic acid](image)

**2-allylbenzoic acid:** The general procedure for the Mg-Iodine exchange was followed using 2-bromo-5-chlorobenzoic acid (520 mg, 2.21 mmol). The crude mixture was purified by column chromatography on silica gel (Hexanes/EtOAC, 85/15) to give the product (343 mg, 1.74 mmol, 79% yield) as a white solid. FTIR (CCl\(_4\), cm\(^{-1}\)): 3077,
3017, 2926, 2854, 2646, 2542, 1694, 1591, 1562, 1412, 1290, 1264, 1184, 1141, 1111;

^1^H NMR (400 MHz, CDCl3): δ, ppm 8.00 (d, J=8.2 Hz, 1H), 7.33 - 7.28 (m, 2H), 6.06 - 5.95 (m, 1H), 5.12 - 5.04 (m, 1H), 3.81 (d, J=6.6 Hz, 2H), ^13^C NMR (CDCl3, 100 MHz): δ 172.5, 145.0, 139.5, 136.3, 133.2, 131.1, 126.6, 126.4, 116.6, 38.3; HRMS (ESI) calcd for C_{10}H_9ClO_2 [M+Na]^+: 219.0183, found 219.0188.

3-iodo-2-naphthoic acid: The general procedure for the Sandmeyer reaction was followed using 3-amino-2-naphthoic acid (1.24 g, 6.6 mmol). The crude mixture was purified by column chromatography on silica gel (Hexane/EtOAc, 9:1) to give the product (1.26 g, 4.2 mmol, 64% yield) as a light brown solid. FTIR (CCl4, cm\(^{-1}\)): 3045, 2882, 1690, 1560, 1448, 1400, 1288, 1230, 1201, 1135; ^1^H NMR (CDCl3, 400 MHz): δ 8.12 (d, J=2.5Hz, 1H), 7.89 (d, J=8.5 Hz, 1H), 7.32 (dd, J = 8.5, 2.5 Hz, 1H).

2-allylnaphthoic acid: The general procedure for the Mg-Iodine exchange was followed using 2-iodo-5-naphthoic acid (595 mg, 2.0 mmol). The crude mixture was purified by column chromatography on silica gel (Hexanes/EtOAC, 8/1) to give the product (315 mg, 37
1.5 mmol, 75% yield) as a white solid. FTIR (CCl₄, cm⁻¹): 3056, 2971, 2925, 2809, 1688, 1572, 1464, 1410, 1277, 1209, 1139, 1048; ¹H NMR (400 MHz, CDCl₃): δ, 8.66 (s, 1H), 7.93 (d, J=8.1 Hz, 1H), 7.82 (d, J=8.3 Hz, 1H), 7.74 (s, 1H), 7.59 (ddd, J=1.3, 6.9, 8.2 Hz, 1H), 7.51 (ddd, J=1.2, 6.9, 8.1 Hz, 1H), 6.20 - 6.10 (m, 1H), 5.13 - 5.05 (m, 2H), 3.98 (d, J=6.3 Hz, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ 171.8, 137.7, 137.6, 135.5, 133.5, 131.1, 129.5, 128.9, 128.7, 127.2, 126.5, 126.3, 115.9, 38.6; HRMS (ESI) calcd for C₁₄H₁₂O₂ [M+H]⁺: 213.0910, found 213.0899.

2-ido-4-fluorobenzoic acid: The general procedure for the Sandmeyer reaction was followed using 4-fluoroanthranilic acid (3.10 g, 20.0 mmol). After cooling, the crude mixture was filtered to give the product (4.50 g, 16.9 mmol, 85% yield) as a light brown solid and was used without further purification. FTIR (CCl₄, cm⁻¹): 2857, 2648, 2547, 1703, 1586, 1573, 1476, 1412, 1301, 1259, 1203; ¹H NMR (CDCl₃, 400 MHz): δ 8.09 (dd, J=8.8, 5.9 Hz, 1H), 7.79 (dd, J=8.1, 2.5 Hz, 1H), 7.17 (ddd, J=2.5, 7.6, 8.8 Hz, 1H) ¹³C NMR (CDCl₃, 100 MHz): δ δ 169.7, 164.0 (d, J=259.8 Hz), 133.9 (d, J=9.4 Hz), 129.4 (d, J=24.0 Hz), 128.9 (d, J=3.1 Hz), 115.4 (d, J=21.3 Hz), 95.5 (d, J=8.5 Hz); ¹⁹F NMR (CDCl₃, 100 MHz): δ -104.7; HRMS (ESI): calcd for C₇H₄FIO₂ [M+Na]⁺: 288.9132, found 288.9136.
2-allyl-4-fluorobenzoic acid: To a stirring solution of 2-iodo-4-fluorobenzoic acid (3.5 g, 13.1 mmol) and potassium carbonate (5.5 g, 39.6 mmol) in anhydrous acetone (25 mL) was added dimethyl sulfate (5 mL, 52.8 mmol). The reaction mixture was heated to reflux for 24 hours. After being cooled to ambient temperature, the crude reaction mixture was filtered over a pad of celite, concentrated, and purified by column chromatography on silica gel (hexanes/EtOAc, 19:1) to give methyl-2-iodo-4-fluorobenzoate (3.52 g, 9.0 mmol, 95% yield) as a light yellow oil. FTIR (CCl₄, cm⁻¹): 3073, 2999, 2951, 2841, 1731, 1590, 1578, 1481, 1433, 1377, 1293, 1253, 1206, 1190, 1110; ¹H NMR (CDCl₃, 250 MHz): δ 7.87 (dd, J=5.9, 8.8 Hz, 1H), 7.72 (dd, J=2.6, 8.2 Hz, 1H), 7.11 (ddd, J=2.6, 7.7, 8.7 Hz, 1H), 3.91 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 165.7, 163.4 (d, J= 258.0 Hz), 132.7 (d, J = 8.9 Hz), 130.7 (d, J = 3.2 Hz), 128.7 (d, J = 23.9 Hz), 115.1 (d, J = 21.2 Hz), 94.6 (d, J = 8.4 Hz), 52.5; ¹⁹F NMR (CDCl₃, 100 MHz): δ -106.4; HRMS (ESI): calcd for C₈H₆FIO₂ [M+Na]⁺: 302.9289, found 302.9297.

The general procedure for the Mg-Iodine exchange and saponification was followed using methyl-2-iodo-4-fluorobenzoate (478 mg, 1.71 mmol). The crude mixture was purified by column chromatography on silica gel (CH₂Cl₂/MeOH, 20:1) to give 2-allyl-4-fluorobenzoicacid (241 mg, 1.33 mmol, 78% over two steps) as an off-white solid. FTIR (film, cm⁻¹): 3080, 2981, 2656, 2544, 1693, 1639, 1607, 1585, 1496, 1410, 1282, 1236, 1156, 1139, 1072; ¹H NMR (CDCl₃, 400 MHz): δ 8.12 – 8.09 (m, 1H), 7.03 – 6.96 (m, 1H), 6.99 (d, J = 8.2 Hz, 1H), 5.91 (s, 1H), 4.64 (t, J = 2.6 Hz, 1H), 3.95 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 164.4, 163.4 (d, J= 258.0 Hz), 132.7 (d, J = 8.9 Hz), 130.7 (d, J = 3.2 Hz), 128.7 (d, J = 23.9 Hz), 115.1 (d, J = 21.2 Hz), 94.6 (d, J = 8.4 Hz), 52.5; ¹⁹F NMR (CDCl₃, 100 MHz): δ -106.4; HRMS (ESI): calcd for C₈H₆FIO₂ [M+Na]⁺: 302.9289, found 302.9297.
2H), 6.06 – 5.96 (m, 1H), 5.11 – 5.05 (m, 2H), 3.84 (d, J = 6.5 Hz, 2H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 172.2, 165.5 (d, J = 254.7 Hz), 146.7 (d, J = 8.6 Hz), 136.31, 134.5 (d, J = 9.5 Hz), 124.1, 117.9 (d, J = 21.7 Hz), 116.6, 113.5 (d, J = 21.5 Hz), 38.5; $^{19}$F NMR (CDCl$_3$, 100 MHz): δ -105.3; HRMS (ESI): calcd for C$_{10}$H$_9$FO$_2$ [M+Na]$^+$: 203.0479, found 203.0479.

2-iodo-4-fluorobenzoic acid: The general procedure for the Sandmeyer-type reaction was followed using methyl 2-amino-4-fluoroanthrinilic acid (5.0 g, 32.2 mmol). The crude mixture was recrystallized from EtOH/H$_2$O to give 2-iodo-4-fluorobenzoic acid as off-white needles (4.96 g, 18.7 mmol, 58% yield). FTIR (film, cm$^{-1}$): 3050, 2958, 1701, 1560, 1466, 1298, 1258, 1214, 1019, 823, 765; $^1$H NMR (400 MHz, CDCl$_3$): δ 10.17 (s, 1H), 8.01 (dd, J = 5.4, 8.6 Hz, 1H), 7.76 (dd, J = 3.3, 9.2 Hz, 1H), 6.99 (ddd, J = 3.1, 7.6, 8.8 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 170.1 (d, J = 2.2Hz), 162.4 (d, J = 249.2Hz), 143.4 (d, J = 7.3Hz), 134.6 (d, J = 7.0Hz), 121.3 (d, J = 21.8Hz), 119.5 (d, J = 24.3Hz), 87.8 (d, J = 3.7Hz); $^{19}$F NMR (CDCl$_3$, 100 MHz): δ -112.9; HRMS (ESI) calcd for C$_7$H$_4$FIO$_2$ [M+Na]$^+$: 288.9132, found 288.9140.
2-allyl-5-fluorobenzoic acid: To a stirring solution of 2-iodo-5-fluorobenzoic acid (4.01 g, 15.3 mmol) in EtOH (40mL) was added thionyl chloride (2.5 mL, 26.6 mmol) dropwise. The reaction was heated to reflux for 18h. The crude mixture was quenched with NaHCO₃ and extracted with EtOAc (3x20mL). The combined organic layers were washed with brine, dried with Na₂SO₄, and concentrated. The crude reaction mixture was purified by column chromatography on silica gel (CH₂Cl₂) to give ethyl-5-fluoro-2-iodobenzoate as a tan oil (4.5 g, 15.3 mmol, quantitative yield). ¹H NMR (400 MHz, CDCl₃): δ, 7.93 (dd, J=5.3, 8.9 Hz, 1H), 7.53 (q, J=4.0 Hz, 1H), 6.92 (ddd, J=3.1, 7.8, 8.7 Hz, 1H), 4.40 (q, J=7.2 Hz, 2H), 1.41 (t, J=7.1 Hz,3H); ¹³C NMR (CDCl₃, 100 MHz): δ 165.3 (d, J=2.2Hz), 162.4 (d, J=249.2Hz), 142.6 (d, J=7.4Hz), 136.9 (d, J=6.8Hz), 120.1 (d, J=21.8Hz ), 118.3 (d, J=24.3Hz), 87.0 (d, J=3.7Hz), 62.1, 14.2; ¹⁹F NMR (CDCl₃, 100 MHz): δ -113.4. The general procedure for the Mg-Iodine exchange and saponification was followed using ethyl-5-fluoro-2-iodobenzoate (4.0 g, 15.04 mmol). The crude mixture was purified by column chromatography on silica gel (Hexanes:EtOAc, 9:1) to give the product as a white solid (2.16 g, 12.0 mmol, 80% over two steps). FTIR (CCl₄, cm⁻¹): 3081, 3010, 2981, 2906, 2660, 1698, 1639, 1610, 1583, 1496, 1436, 1419, 1396, 1288, 1266, 1223; ¹H NMR (400 MHz, CDCl₃): δ, 7.86 (1H, s), 7.31 (1H, dd, J = 1.8, 8.0 Hz), 7.20 (1H, d, J = 7.8 Hz), 6.08 - 5.97 (1H, m), 5.05 - 4.99 (2H, m), 3.78 (2H, d, J = 6.6 Hz), 2.37 (3H, s).¹³C NMR (CDCl₃, 100 MHz): δ δ 172.4 (d, J=2.2Hz), 160.8 (d, J=245.7Hz), 138.6 (d, J=3.5Hz), 137.0, 132.8 (d, J=7.3Hz ), 129.7 (d, J=7.2Hz), 120.1 (d, J=20.9Hz), 118.1 (d, J=23.2Hz), 115.9, 37.7.; ¹⁹F NMR
(CDCl₃, 100 MHz): δ -115.9; HRMS (ESI): calcd for C₁₀H₉FO₂ [M+Na]⁺: 203.0479, found 203.0473.

1H NMR (DMSO-d₆, 400 MHz): δ 11.9 (s, 1H), 11.8 (s, 1H), 8.01–8.00 (m, 1H), 7.99–7.98 (m, 1H), 7.47–7.44 (m, 1H), 7.19 – 7.12 (m, 2H).

Spectroscopic data are in accordance with those described in the literature.³⁴

**1H-indole-3-carboxylic acid:** Methyl 1H-indole-3-carboxylate (7.0 g, 40 mmol) and an aqueous solution of NaOH (1.5M, 50.0 mL) was heated to reflux for 3h with stirring. The solution was cooled to 0 °C and acidified with HCl to a pH of about 1. The formed precipitate was collected by filtration and washed with cold water. The product was obtained as a white solid and used without further purification. ¹H NMR (DMSO-d₆, 400 MHz): δ 11.9 (s, 1H), 11.8 (s, 1H), 8.01–8.00 (m, 1H), 7.99–7.98 (m, 1H), 7.47–7.44 (m, 1H), 7.19 – 7.12 (m, 2H).

Spectroscopic data are in accordance with those described in the literature.³⁴
1-tosyl-1H-indole-3-carboxylic acid: To a cooled solution (-78 °C) of 1H-indole-3-carboxylic acid (1.5 g, 9.3 mmol) in THF was added nBuLi (a.5M in hexanes, 14.0 mL, 22 mmol, 2.3 equiv) dropwise. The reaction mixture was stirred at -78 °C for 3h and then a solution of tosyl chloride (4.20 g, 22 mmol, 2.3 equiv) in THF was added dropwise. The reaction mixture was allowed to warm to ambient temperature overnight. The reaction was quenched with aqueous NaHSO₄ (5%) and extracted with EtOAc. The combined organic layers were washed with brine, dried with Na₂SO₄, and concentrated. The crude mixture was filtered and washed with cold EtOAc (2x5 mL) to give the product as a white solid (600 mg, 20% yield). FTIR (CCl₄, cm⁻¹): 3145, 2545, 1676, 1594, 1581, 1559, 1488, 1437, 1399, 1372, 1334, 1286, 1250, 1203, 1186, 1164, 1139, 1107, 1089, 1057, 1016, 957; 'H NMR (400 MHz, CDCl₃): δ 8.10 (s, 1H), 8.18–8.16 (m, 1H), 7.99–7.97 (m, 1H), 7.85 (dt, J=5.0, 1.7 Hz, 2H), 7.41–7.34 (m, 2H), 7.28 (d, J=8.0 Hz, 2H), 2.37 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 169.0, 145.9, 134.9, 134.5, 133.5, 130.2, 127.7, 127.2, 125.5, 124.6, 122.2, 113.4, 112.7, 21.6; HRMS (ESI): calcd for C₁₆H₁₃NO₄S [M+Na⁺]: 338.0457, found 338.0464.

2-allyl-1-tosyl-1H-indole-3-carboxylic acid: To a cooled solution (-40 °C) of 1-tosylindole-3-carboxylic acid (315 mg, 1 mmol) in a LiCl solution (0.5 M in THF, 1
mmol) and was added MeMgBr (2.8 M in Et₂O, 0.39 mL, 1.1 mmol) dropwise. The reaction was stirred for 10 min and then a solution of 2,2,6,6-
TetramethylpiperidineMgCl·LiCl (1.0 M in THF/toluene, 1.1 mL, 1.1 mmol) was added dropwise. The reaction was warmed to -30 °C and stirred for 2h. The reaction was cooled to -40 °C and a CuCN·2LiCl solution (0.34 M in THF, 2.95 mL, 1 mmol) was added. The reaction was stirred for 15 min and allylbromide (0.26 mL, 3 mmol) was added at once and the reaction was allowed to warm to ambient temperature overnight.

The reaction mixture was diluted with EtOAc, acidified with HCl to a pH of about 1, and extracted with EtOAc. The combined organic layers were washed with brine, dried with Na₂SO₄, and concentrated. The crude product was purified by column chromatography with silica gel (Hexanes/EtOAc, 9/1) to give the product as a white solid (264 mg, 0.74 mmol, 74% yield). FTIR (CCl₄, cm⁻¹): 2577, 1676, 1554, 1481, 1451, 1424, 1373, 1294, 1249, 1193, 1174, 1152, 1101; ¹H NMR (400 MHz, CDCl₃): δ 12.6 (bs, 1H), 8.21 – 8.19 (m, 2H), 7.73 (d, J = 8.4 Hz, 2H), 7.35 – 7.33 (m, 2H), 7.23 (d, J = 8.0 Hz, 2H), 6.10 – 6.00 (m, 1H), 5.18 – 5.08 (m, 2H), 4.38 (d, J = 6.0 Hz, 2H), 2.35 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 170.3, 148.3, 145.6, 135.9, 135.8, 134.4, 130.0, 127.4, 126.7, 125.1, 124.6, 122.1, 117.1, 114.6, 111.0, 30.6, 21.6; HRMS (ESI): calcd for C₁₉H₁₇NO₄S [M+Na]⁺: 378.0770, found 378.0788.
**1-allylindole-2-carboxylic acid:** Following a reported procedure,\(^3\) To a cooled solution (0 °C) of ethyl indole-2-carboxylate (2.26 g, 12.0 mmol) in DMF was added NaH (suspension in mineral oil, 60% wt, 526.0 mg, 13.2 mmol, 1.1 equiv) in small portions over 15 minutes. The mixture was allowed to warm up to 23 °C and stirred for 1 hour. Allylbromide (1.40 mL, 16.8 mmol, 1.4 equiv) was added in one portion and the mixture was heated to 100 °C for 2 hours. After cooling to ambient temperature, the reaction mixture was quenched with water and extracted with Et\(_2\)O (3 x 40 mL). The combined organic layers were washed with brine, dried with Na\(_2\)SO\(_4\), and concentrated to yield ethyl 1-allylindole-2-carboxylate as a yellow oil which was used without further purification. To a solution of ethyl 1-allylindole-2-carboxylate in EtOH (40 mL) was added and aqueous solution of NaOH (1.5 M, 30 mL) and the reaction mixture was refluxed for 3h. After cooling to ambient temperature, the EtOH was remove under reduced pressure. The crude mixture was acidified to a pH of 1 with HCl (6M) and extracted with EtOAc (3x40 mL). The combined organic layers were dried with Na\(_2\)SO\(_4\) and concentrated. The crude mixture was purified by column chromatography with silica gel (2% MeOH/DCM) to give the product as a white solid (1.62 g, 8.00 mmol, 67% yield over two steps). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.72 (dt, \(J=4.0, 0.9\) Hz, 1H), 7.51 (s, 1H), 7.38 – 7.37 (m, 2H), 7.20–7.16 (m, 1H), 6.07–5.97 (m, 1H), 5.24 (dt, \(J=4.9, 1.6\) Hz, 2H), 5.12 (dd, \(J=10.3, 1.2\) Hz, 1H), 4.92 (dd, \(J=17.1, 1.2\) Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\), 100 MHz): \(\delta\) 166.3, 139.8, 133.7, 126.1, 125.9, 125.8, 122.9, 120.9, 116.2, 112.9, 110.8, 46.8.
Spectroscopic data are in accordance with those described in the literature.\textsuperscript{35}

**2-(3-cyclohex-1-ene)benzoic acid:** A slight modification of the general procedure for the Mg-Iodine exchange was followed using 2-iodobenzoic acid (1.24 g, 5 mmol) and replacing allyl bromide with 3-bromo-cyclohex-1-ene (1.73 mL, 15 mmol). The crude mixture was purified by column chromatography on silica gel (CH\textsubscript{2}Cl\textsubscript{2}) to give the product as a white solid (770 mg, 3.81 mmol, 76% yield). FTIR (CCl\textsubscript{4}, cm\textsuperscript{-1}): 3566, 3066, 3020, 2929, 1690, 1576, 1559, 1458, 1405, 1301, 1272, 1144, 1078; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \textsuperscript{δ} 8.00 (dd, \textit{J}=1.4, 7.9 Hz, 1H), 7.51 (ddd, \textit{J}=7.5, 7.5, 1.5 Hz, 1H), 7.43 (dd, \textit{J}=1.3, 8.0 Hz, 1H), 7.29 (ddd, \textit{J}=7.5, 7.5, 1.4 Hz, 1H), 5.98 - 5.91 (m, 1H), 5.70 - 5.64 (m, 1H), 4.49 - 4.41 (m, 1H), 2.23 - 2.15 (m, 1H), 2.15 - 2.08 (m, 2H), 1.79 - 1.63 (m, 2H), 1.56 - 1.45 (m, 1H); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz): \textsuperscript{δ} 173.4, 148.8, 132.7, 131.2, 130.3, 129.3, 128.5, 128.2, 125.8, 37.8, 32.3, 25.0, 21.2; HRMS (ESI): calcd for C\textsubscript{13}H\textsubscript{14}NaO\textsubscript{2} [M+Na]\textsuperscript{+}: 225.0886, found 225.0886.
**3,4-dibromo-2,5-diethylthiophene:** An oven dried round bottom flask was charged with 3,4-dibromothiophene (2.4 g, 10.0 mmol) and THF (20 mL). The flask was purged with Argon and cooled to -78 °C. LDA (32.4 mL, 0.34M, 11.0 mmol) was added slowly and the reaction was stirred for 30 min. Iodoethane (885 µL, 11.0 mmol) was added at once and the reaction was allowed to warm to ambient temperature overnight. The reaction mixture was quenched with NH₄Cl and extracted with Hexanes (5x20 mL). The combined organic layers were washed with brine and dried over Na₂SO₄, concentrated, and resubjected to the same reaction conditions. The reaction was again quenched with NH₄Cl and extracted with Hexanes (5x20 mL). The combined organic layers were washed with brine and dried over Na₂SO₄ and concentrated to give the product as a light yellow oil (2.34 g, 8.4 mmol, 84% yield over two steps). FTIR (CCl₄, cm⁻¹): 2972, 2932, 2874, 1718, 1662, 1559, 1528, 1457, 1376, 1320, 1254, 1189, 1077, 851; ¹H NMR (400 MHz, CDCl₃): δ 2.81 (q, J=7.5Hz, 4H), 1.25 (t, J=7.5Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz): δ 138.6, 110.5, 23.9, 14.6; HRMS (ESI): calcd for C₈H₁₀Br₂S [M+H]⁺: 296.8943, found 296.8936.
**3,4-dibromo-2,5-diethylthiophene:** An oven dried round bottom flask was charged with 2,5-diethyl-3,4-dibromothiophene (1.49 g, 5.0 mmol), diethyl ether (5 mL) and pentane (5 mL). The flask was purged with Argon and cooled to -78 °C. nBuLi (3.19 mL, 1.43M, 4.56 mmol) was added slowly and the reaction was stirred for 35 min. Carbon dioxide generated from dry ice was bubbled into the solution for 5 min and a white solid formed. The reaction was quenched with water and then NaOH (2.5M, 5mL). The crude reaction mixture was washed with hexanes (2x10 mL) and then acidified with HCl (6M) to a pH of 1-3. The crude reaction mixture is cooled, filtered and washed several times with hexanes. The product was obtained as a white solid (920 mg, 3.5 mmol, 70%) and used without further purification. FTIR (CCl₄, cm⁻¹): 3413, 2972, 2932, 2872, 1686, 1544, 1526, 1420, 1249, 1218; ¹H NMR (400 MHz, CDCl₃): δ 3.14 (q, J=7.5Hz, 2H), 2.80 (q, J=7.5Hz, 2H), 1.31 (t, J=7.5Hz, 6H), 1.27 (t, J=7.5Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz): δ 168.1, 154.9, 139.1, 125.7, 107.9, 24.1, 23.1, 15.5, 14.6; HRMS (ESI): calcd for C₉H₁₁BrO₂S [M+H]⁺: 262.9736, found 262.9744.

![Chemical structure](image)

**4-allyl-2,5-diethylthiophene-3-carboxylic acid:** A slight modification of the general procedure for the Mg-Iodine exchange was followed using 4-bromo-2,5-diethylthiophene-3-carboxylic acid (789 mg, 3 mmol) and cooling the reaction to only 0 °C for 2h after the addition of isopropylmagnesium chloride. The crude mixture was purified by column chromatography on silica gel (Hexanes/EtOAc, 9/1) to give the
product as a white solid (356 mg, 1.6 mmol, 53% yield). FTIR (CCl₄, cm⁻¹): 3079, 2969, 2932, 2874, 2621, 1675, 1546, 1478, 1457, 1427, 1276, 1190, 1091, 993, 910; ¹H NMR (400 MHz, CDCl₃): δ 6.04 - 5.92 (m, 1H), 4.99 - 4.92 (m, 2H), 3.59 (d, J=6.2 Hz, 2H), 3.17 (q, J=7.4 Hz, 2H), 2.74 (q, J=7.7 Hz, 2H), 1.33 (t, J=7.5 Hz, 3H), 1.27 (t, J=7.5 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 170.1, 155.3, 138.7, 137.2, 135.1, 126.0, 114.3, 31.8, 23.9, 21.0, 15.8, 15.7; HRMS (ESI): calcd for C₁₂H₁₆O₂S [M+H]⁺: 225.0944, found 225.0948.

**General procedure for the preparation of exo-methylene indanones and indenones:**

To a 4 mL borosilicate glass vial under argon containing 2-allylbenzoic acid (1.0 mmol) and acetic anhydride (190 µL, 2 mmol, 2 equiv) was added a solution of Pd(OAc)₂ and P(o-tol)₃ in THF (1 mL, 1M). The reaction was capped and heated to 65 °C for 18h. After cooling the reaction to ambient temperature, the product was purified by column chromatography on silica gel.

![Methyldene-2,3-dihydro-1H-inden-1-one (2a)](image)

**Methyldene-2,3-dihydro-1H-inden-1-one (2a):** This reaction was preformed according to the general procedure for the cyclization of substituted benzoic acids using 2-allylbenzoic acid (162 mg, 1.0 mmol). The crude product was purified by column chromatography on silica gel (Hexanes/EtOAc 95/5) to give 88% of the product (127 mg,
0.88 mmol) as a pale yellow oil. FTIR (CCl₄, cm⁻¹): 3074, 2919, 1711, 1656, 1611, 984; ¹H NMR (400 MHz, CDCl3): δ 7.88 (d, J=8.0 Hz, 1H), 7.61 (t, J=7.5 Hz, 1H), 7.50 (d, J=7.1 Hz, 1H), 7.41 (t, J=7.5 Hz, 1H), 6.38 (s, 1H), 5.65 (s, 1H); HRMS (ESI) calcld for C₁₀H₈O [M+Na]⁺: 167.0467, found 167.0461.

7-methyl-2-methylene-2,3-dihydro-1H-inden-1-one (2b): This reaction was preformed according to the general procedure for the cyclization of substituted benzoic acids using 6-methyl-2-allylbenzoic acid (78 mg, 0.44 mmol). The crude product was purified by column chromatography on silica gel (Hexanes/EtOAc 95/5) to give 92% of the product (65 mg, 0.41 mmol) as an off-white solid. FTIR (CCl₄, cm⁻¹): 3066, 3031, 2925, 2849, 1702, 1595, 1474, 1289, 1259, 1200, 1114, 1068, 1007; ¹H NMR (400 MHz, CDCl3): δ ppm 7.45 (t, J=7.5 Hz, 1H), 7.29 (d, J=7.4 Hz, 1H), 7.14 (d, J=7.4 Hz, 1H), 6.32 - 6.29 (m, 1H), 5.59 - 5.57 (m, 1H), 3.72 (s, 2H), 2.71 (s,3H).¹³C NMR (CDCl₃, 100 MHz): δ 194.4, 150.5, 143.7, 139.8, 135.7, 134.2, 129.4, 123.6, 118.3, 31.5, 18.4; HRMS (ESI) calcld for C₁₁H₁₁O₁ [M+H]⁺: 159.0804, found 159.0800.
4-methyl-2-methylene-2,3-dihydro-1H-inden-1-one (2c): This reaction was performed according to the general procedure for the cyclization of substituted benzoic acids using 3-methyl-2-allylbenzoic acid (177 mg, 1.0 mmol). The crude product was purified by column chromatography on silica gel (Hexanes/EtOAc 95/5) to give 92% of the product (145 mg, 0.91 mmol) as an off-white solid. FTIR (CCl₄, cm⁻¹): 3027, 2990, 2820, 1710, 1643, 1491, 1286; ¹H NMR (400 MHz, CDCl₃): δ ppm 7.71 (d, J=7.9 Hz, 1H), 7.42 (d, J=7.0 Hz, 1H), 7.33 (t, J=7.5 Hz, 1H), 6.38 - 6.36 (m, 1H), 5.66 - 5.65 (m, 1H), 3.64 (s, 2H), 2.36 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 193.7, 148.9, 143.4, 138.0, 135.5, 135.3, 127.8, 122.0, 119.1, 30.7, 17.8; HRMS (ESI) calcd for C₁₁H₁₀O₁ [M+Na]⁺: 181.0624, found 181.0623.

6-methyl-2-methylene-2,3-dihydro-1H-inden-1-one (2d): This reaction was performed according to the general procedure for the cyclization of substituted benzoic acids using 5-methyl-2-allylbenzoic acid (177 mg, 1.0 mmol). The crude product was purified by column chromatography on silica gel (Hexanes/EtOAc 95/5) to give 92% of the product (146 mg, 0.92 mmol) as an off-white solid. FTIR (CCl₄, cm⁻¹): 3028, 2990, 2922, 1710, 1644, 1492, 1286; ¹H NMR (400 MHz, CDCl₃): δ ppm 7.67 (s, 1H), 7.44 - 7.36 (m, 2H), 6.35 - 6.33 (m, 1H), 5.62 - 5.61 (m, 1H), 3.70 (s, 2H), 2.42 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 193.5, 147.2, 143.8, 138.4, 137.5, 136.1, 126.0, 124.6, 118.9, 31.4, 21.1; HRMS (ESI) calcd for C₁₁H₁₁O₁ [M+H]⁺: 159.0804, found 159.0810.
5,6-dimethoxy-2-methylene-2,3-dihydro-1H-inden-1-one (2e): This reaction was preformed according to the general procedure for the cyclization of substituted benzoic acids using 4,5-dimethoxy-2-allylbenzoic acid (222 mg, 1.0 mmol). The crude product was purified by column chromatography on silica gel (gradient, Hexanes/EtOAc 95/5 to 80/20) to give 85% of the product (173 mg, 0.85 mmol) as an off-white solid. FTIR (CCl₄, cm⁻¹): 2956, 2934, 2358, 2339, 1700, 1587, 1551, 1499, 1385, 1250, 1233, 1118;¹H NMR (CDCl₃, 400 MHz): δ 7.30 (s, 1H), 6.30 - 6.27 (m, 1H), 5.57 - 5.55 (m, 1H), 3.98 (s, 3H), 3.93 (s, 3H), 3.67 - 3.65 (m, 2H);¹³C NMR (CDCl₃, 100 MHz): δ 192.2, 155.7, 149.7, 145.3, 143.9, 131.4, 117.7, 107.2, 105.2, 56.3, 56.1, 31.5; HRMS (ESI) calcd for C₁₂H₁₃O₃ [M+H]⁺: 205.0859, found 205.0857.

6-dimethoxy-2-methylene-2,3-dihydro-1H-inden-1-one (2f): This reaction was preformed according to the general procedure for the cyclization of substituted benzoic acids using 5-methoxy-2-allylbenzoic acid (192 mg, 1.0 mmol). The crude product was purified by column chromatography on silica gel (5:95 EtOAc/hexanes) to give 86% of
the product (149 mg, 0.86 mmol) as an off-white solid. FTIR (CCl₄, cm⁻¹): 3004, 2958, 2909, 2835, 2358, 1707, 1646, 1490, 1285;¹H NMR (CDCl₃, 400 MHz): δ 7.38 (d, J=8.5 Hz, 1H), 7.31 (d, J=2.5 Hz, 1H), 7.20 (dd, J=2.6, 8.4 Hz, 1H), 3.85 (s, 3H), 3.68 (s, 2H);¹³C NMR (CDCl₃, 100 MHz): δ 193.4, 159.5, 144.1, 139.4, 127.1, 119.1, 105.9, 55.6, 31.1; HRMS (ESI) calcd for C₁₁H₁₁O₂ [M+H]⁺: 175.0754, found 175.0762.

2-methylene-3-oxo-2,3-dihydro-1H-inden-5-yl acetate (2g): This reaction was performed according to the general procedure for the cyclization of substituted benzoic acids using 5-hydroxy-2-allylbenzoic acid (89 mg, 0.5 mmol) and 3 equivalents of acetic anhydride (143 µL, 1.5 mmol). The crude product was purified by column chromatography on silica gel (Hexanes/EtOAc 90/10) to give 82% of the product (83 mg, 0.41 mmol) as a white solid. FTIR (CCl₄, cm⁻¹): 3060, 2924, 2855, 2360, 1770, 1710, 1646, 1614, 1550, 1482, 1369, 1271, 1202, 1177, 1005;¹H NMR (CDCl₃, 400 MHz): δ 7.57 (d, J=2.2 Hz, 1H), 7.50 (d, J=8.0 Hz, 1H), 7.33 (dd, J=2.4, 8.3 Hz, 1H), 6.37 (dt, J=0.7, 2.2 Hz, 1H), 5.66 (dt, J=0.7, 1.8 Hz, 1H), 3.74 (s, 2H), 2.33 (s, 3H);¹³C NMR (CDCl₃, 100 MHz): δ 192.4, 169.2, 150.2, 147.0, 143.4, 139.4, 128.5, 127.2, 119.7, 117.2, 31.2, 20.9; HRMS (ESI) calcd for C₁₂H₁₀NaO₃ [M+Na]⁺: 255.0522, found 225.0520.
6-bromo-2-methylene-2,3-dihydro-1H-inden-1-one (2h): This reaction was preformed according to the general procedure for the cyclization of substituted benzoic acids using 5-bromo-2-allylbenzoic acid (84 mg, 0.5 mmol) and Triphenylarsine (2.1 mg, 0.007 mmol). The crude product was purified by column chromatography on silica gel (gradient; Hexanes/EtOAc 95/5 to 90/10) to give 60% of the product (47 mg, 0.21 mmol) as an off-white solid. FTIR (CCl₄, cm⁻¹): 3058, 2990, 2954, 2925, 2851, 1713, 1642, 1599, 1464, 1423, 1395, 1262, 1200, 1187, 1800, 1111, 1057;¹H NMR (CDCl₃, 400 MHz): δ 7.98 (d, J=1.9 Hz, 1H), 7.70 (dd, J=2.0, 8.1 Hz, 1H), 7.38 (d, J=8.3 Hz, 1H), 6.38 (dt, J=0.6, 2.2 Hz, 1H), 5.67 (dt, J=0.7, 1.8 Hz, 1H), 3.70 (s, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ 191.9, 148.3, 142.9, 140.0, 137.6, 12736, 121.8, 120.2, 31.4; HRMS (ESI) calcd for C₁₀H₇BrO₁ [M+Na]⁺: 244.9572, found 244.9575.

5-chloro-2-methylene-2,3-dihydro-1H-inden-1-one (2i): This reaction was preformed according to the general procedure for the cyclization of substituted benzoic acids using 4-chloro-2-allylbenzoic acid (194 mg, 1.0 mmol). The crude product was purified by column chromatography on silica gel (Hexanes/EtOAc 95/5) to give 81% of the product.
(143 mg, 0.81 mmol) as a white solid. FTIR (CCl₄, cm⁻¹): 3074, 2990, 2922, 2284, 1712, 1648, 1601, 1549, 1422, 1313, 1258, 1211; ¹H NMR (CDCl₃, 400 MHz): δ 7.79 (d, J=8.1 Hz, 1H), 7.48 (s, 1H), 7.40 - 7.36 (m, 1H), 6.37 (dt, J=0.6, 2.2 Hz, 1H), 5.67 - 5.64 (m, 1H), 3.74 (s, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ 192.0, 151.3, 142.8, 141.2, 136.7, 128.4, 126.6, 125.8, 119.9, 31.6; HRMS (ESI) calcd for C₁₀H₇ClO₁ [M+Na]^+: 201.0078, found 201.0087.

2-methylene-2,3-dihydro-1H-cyclopenta[b]naphthalen-1-one (2j): This reaction was preformed according to the general procedure for the cyclization of substituted benzoic acids using 2-allylnaphthoic acid (104 mg, 0.49 mmol). The crude product was purified by column chromatography on silica gel (Hexanes/EtOAc 95/5) to give 70% of the product (66 mg, 0.34 mmol) as a light yellow solid. FTIR (CCl₄, cm⁻¹): 3058, 2988, 2923, 2852, 2300, 1710, 1645, 1629, 1608, 1549, 1395, 1341, 1257; ¹H NMR (CDCl₃, 400 MHz): δ 8.44 (s, 1H), 8.00 (d, J=8.1 Hz, 1H), 7.90 - 7.85 (m, 2H), 7.61 - 7.56 (m, 1H), 7.53 - 7.48 (m, 1H), 6.43 (dt, J=0.8, 2.5 Hz, 1H), 5.69 (dt, J=0.8, 2.0 Hz, 1H), 3.96 - 3.93 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ 193.8, 144.0, 142., 137.3, 135.8, 32.5, 130.3, 128.6, 127.8, 126.2, 125.5, 124.6, 119.5, 31.6; HRMS (ESI) calcd for C₁₄H₁₀O₁ [M+Na]^+: 217.0624, found 217.0626.
5-fluoro-2-methylene-2,3-dihydro-1H-inden-1-one (2k): This reaction was preformed according to the general procedure for the cyclization of substituted benzoic acids using 4-fluoro-2-allylbenzoic acid (180 mg, 1.0 mmol). The crude product was purified by column chromatography on silica gel (gradient, Hexanes/EtOAc 95/5 to 9/1) to give 82% of the product (131 mg, 0.81 mmol) as a light yellow solid. FTIR (CCl₄, cm⁻¹): 3060, 2926, 2854, 1713, 1615, 1593, 1482, 1329, 1255, 1086; ¹H NMR (CDCl₃, 400 MHz): δ 7.86 (dd, J=5.4, 8.5 Hz, 1H), 7.17 - 7.07 (m, 2H), 6.35 (dt, J=0.7, 2.2 Hz, 1H), 5.64 (td, J=0.9, 1.8 Hz, 1H), 3.75 (s, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ 191.6, 167.1 (d, J¹³C-¹⁹F=256.4 Hz), 152.6 (d, J¹³C-¹⁹F=10.2 Hz), 142.9, 134.6 (d, J¹³C-¹⁹F=2.1 Hz), 127.0 (d, J¹³C-¹⁹F=10.3 Hz), 119.4, 115.9 (d, J¹³C-¹⁹F=23.5 Hz), 113.0 (d, J¹³C-¹⁹F=22.7 Hz), 31.8 (d, J¹³C-¹⁹F=2.2 Hz); ¹⁹F NMR (CDCl₃, 400 MHz): δ -101.9; HRMS (ESI) calcd for C₁₀H₇FO [M+H]⁺: 163.0554, found 163.0558.

6-fluoro-2-methylene-2,3-dihydro-1H-inden-1-one (2l): This reaction was preformed according to the general procedure for the cyclization of substituted benzoic acids using 5-fluoro-2-allylbenzoic acid (180 mg, 1.0 mmol). The crude product was purified by
column chromatography on silica gel (gradient, Hexanes/EtOAc 95/5 to 9/1) to give 82% of the product (133 mg, 0.82 mmol) as a light yellow solid. FTIR (CCl₄, cm⁻¹): 3061, 2916, 1715, 1541, 1486, 1274, 1004; ¹H NMR (CDCl₃, 400 MHz): δ 7.51 - 7.44 (m, 2H), 7.31 (dt, J=2.6, 8.6 Hz, 1H), 6.37 (dt, J=0.7, 2.2 Hz, 1H), 5.65 (dt, J=0.7, 1.8 Hz, 1H), 3.71 (s, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ 192.46 (d, J¹³C-¹⁹F=2.9 Hz), 162.4, (d, J¹³C-¹⁹F=248.4 Hz), 145.2 (d, J¹³C-¹⁹F=2.1 Hz), 143.5, 139.9 (d, J¹³C-¹⁹F=7.4 Hz), 127.8 (d, J¹³C-¹⁹F=7.9 Hz), 122.5 (d, J¹³C-¹⁹F=23.6 Hz), 119.9, 110.4 (d, J¹³C-¹⁹F=22.0 Hz), 31.2; ¹⁹F NMR (CDCl₃, 400 MHz): δ -113.8 HRMS (ESI) calcd for C₁₀H₇FO [M+H]⁺: 163.0554, found 163.0548.

![Chemical Structure](image-url)

**2-methylene-4-tosyl-2,3-dihydrocyclopenta[b]indol-1(4H)-one (2m):** This reaction was performed according to the general procedure for the cyclization of substituted benzoic acids using 2-allyl-1-tosyl-1H-indole-3-carboxylic acid (177.5mg, 0.5 mmol) in dioxane with 5 mol% Pd(OAc)₂ and 10 mol% P(o-tolyl)₃ at 100 °C. The crude product was purified by column chromatography on silica gel (Hexanes/EtOAc 9/1) to give 50% of the product (83mg, 0.25 mmol) as an off-white solid. FTIR (CCl₄, cm⁻¹): 3057, 2959, 2926, 2854, 1702, 1648, 1552, 1448, 1406, 1386, 1365, 1232, 1179, 1118, 1089, 1034, 1015, 932; ¹H NMR (CDCl₃, 400 MHz): δ 8.04 - 8.01 (m, 1H), 7.94 - 7.91 (m, 1H), 7.84
(td, J=2.0, 8.4 Hz, 1H), 7.42 - 7.29 (m, 4H), 6.28 (t, J=1.8 Hz, 1H), 5.58 (t, J=1.3 Hz, 1H), 4.03 (t, J=1.6 Hz, 2H), 2.39 (s, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 184.4, 162.1, 146.2, 145.7, 139.9, 134.8, 130.4, 127.0, 126.9, 125.8, 124.9, 121.5, 117.7, 114.0, 30.1, 21.6; HRMS (ESI) calcd for C$_{19}$H$_{15}$NO$_3$S [M+Na]$^+$: 360.0665, found 360.0659.

2-methyl-1H-inden-1-one (3a): This reaction was performed according to the general procedure for the cyclization of substituted benzoic acids with PCy$_3$ using 2-allylbenzoic acid (162 mg, 1.0 mmol). The crude product was purified by column chromatography on silica gel (Hexanes/EtOAc 95/5) to give 73% of the product (105 mg, 0.73 mmol) as a yellow solid. FTIR (CCl$_4$, cm$^{-1}$): 2957, 2927, 2856, 1716, 1552, 1462, 1372, 1259, 1214, 1069, 1009; $^1$H NMR (400 MHz, CDCl$_3$): δ ppm 7.34 (d, J=6.8 Hz, 1H), 7.25 (t, J=7.5 Hz, 1H), 7.15 - 7.04 (m, 2H), 6.90 (d, J=7.0 Hz, 1H), 1.85 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 198.5, 144.8, 143.2, 136.0, 133.6, 130.6, 127.7, 122.4, 121.0, 9.8; HRMS (ESI) calcd for C$_{10}$H$_9$O [M+H]$^+$: 145.0648, found 145.0653.
2,4-dimethyl-1H-inden-1-one (3b): This reaction was performed according to the general procedure for the cyclization of substituted benzoic acids with PCy₃ using 3-methyl-2-allylbenzoic acid (175 mg, 1.0 mmol). The crude product was purified by column chromatography on silica gel (Hexanes/EtOAc 95/5) to give 73% of the product (105 mg, 0.73 mmol) as a yellow solid. FTIR (CDCl₃, cm⁻¹): 3058, 2982, 2919, 2858, 1707, 1606, 1474, 1445, 1382, 1308, 1258, 1237, 1176, 1095; ¹H NMR (CDCl₃, 400 MHz): δ 7.26 - 7.24 (m, 1H), 7.21 (d, J=7.1 Hz, 1H), 7.08 (d, J=7.6 Hz, 1H), 7.03 - 6.99 (m, 1H), 2.25 (s, 3H), 1.87 (d, J=1.8 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 199.1, 142.7, 141.6, 135.6, 135.4, 130.6, 130.2, 127.7, 120.3, 16.9, 10.0; HRMS (ESI) calcd for C₁₁H₁₀O [M+Na]⁺: 181.0624, found 181.0618.

![Chemical Structure of 2,4-dimethyl-1H-inden-1-one (3b)](image)

2-methyl-1-oxo-1H-inden-6-yl acetate (3c): This reaction was performed according to the general procedure for the cyclization of substituted benzoic acids with PCy₃ using 2-allylbenzoic acid (133 mg, 1.0 mmol) and 3 equivalents of acetic anhydride (285 µL, 3 mmol). The crude product was purified by column chromatography on silica gel (Hexanes/EtOAc 9/1) to give 60% of the product (90.5 mg, 0.73 mmol) as a yellow solid. FTIR (CCl₄, cm⁻¹): 3005, 2965, 2923, 1751, 1702, 1420, 1364, 1226, 1092, 918; ¹H NMR (400 MHz, CDCl₃): δ ppm 7.13 - 7.09 (m, 2H), 6.98 - 6.95 (m, 1H), 6.93 - 6.90 (m, 1H), 2.27 (s, 3H), 1.86 (d, J=1.8 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 197.3, 169.2, 150.6,
5-chloro-2-methyl-1H-inden-1-one (3d): This reaction was performed according to the general procedure for the cyclization of substituted benzoic acids with PCy$_3$ using 4-chloro-2-allylbenzoic acid (89 mg, 0.5 mmol). The crude product was purified by column chromatography on silica gel (Hexanes/EtOAc 95/5) to give 65% of the product (58 mg, 0.65 mmol) as a yellow solid. FTIR (CCl$_4$, cm$^{-1}$): 3064, 2919, 2853, 1718, 1604, 1583, 1456, 1336, 1172, 1065; $^1$H NMR (CDCl$_3$, 400 MHz): δ 7.31 - 7.28 (m, 1H), 7.12 - 7.09 (m, 1H), 6.94 (d, $J$=1.7 Hz, 1H), 1.89 (d, $J$=1.8 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ; 197.0, 1.8, 141.8, 139.9, 137.8, 128.9, 127.4, 123.4, 121.8, 10.1; HRMS (ESI) calcd for C$_{10}$H$_7$O$_2$ClO [M+H]$^+$: 179.0258, found 179.0257.

5-fluoro-2-methyl-1H-inden-1-one (3e): This reaction was performed according to the general procedure for the cyclization of substituted benzoic acids with PCy$_3$ using 4-fluoro-2-allylbenzoic acid (89 mg, 0.49 mmol). The crude product was purified by
column chromatography on silica gel (Hexanes/EtOAc 95/5) to give 68% of the product (55 mg, 0.34 mmol) as a yellow solid. FTIR (CCl₄, cm⁻¹): 3067, 2928, 2852 1718, 1613, 1550, 1482, 1268, 1252, 1088, 1007; ¹H NMR (CDCl₃, 400 MHz): δ 7.35 (dd, J=5.2, 7.9 Hz, 1H), 7.06 - 7.03 (m, 1H), 6.75 (ddd, J=1.9, 7.8, 9.5 Hz, 1H), 6.66 (dd, J=2.3, 8.1 Hz, 1H), 1.88 (d, J=1.8 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 197.2, 163.0 (d, J¹³C⁻¹⁹F=248.5 Hz), 143.1 (d, J¹³C⁻¹⁹F=1.6 Hz), 140.2 (d, J¹³C⁻¹⁹F=3.8 Hz), 136.6 (d, J¹³C⁻¹⁹F=5.2 Hz), 132.9 (d, J¹³C⁻¹⁹F=6.6 Hz), 121.8 (d, J¹³C⁻¹⁹F=7.7 Hz), 118.7 (d, J¹³C⁻¹⁹F=22.9 Hz), 111.4 (d, J¹³C⁻¹⁹F=24.9 Hz), 10.0; HRMS (ESI) calcd for C₁₀H₇FO [M+Na]⁺: 185.0373, found 185.0380.

![Image](image-url)

**6-fluoro-2-methyl-1H-inden-1-one (3f):** This reaction was performed according to the general procedure for the cyclization of substituted benzoic acids with PCy₃ using 5-fluoro-2-allylbenzoic acid (180 mg, 1.0 mmol). The crude product was purified by column chromatography on silica gel (Hexanes/EtOAc 95/5) to give 65% of the product (105 mg, 0.65 mmol) as a yellow solid. FTIR (CCl₄, cm⁻¹): 3068, 2925, 2853, 1718, 1611, 1484, 1437, 1374, 1267, 1233, 1162, 1069, 997; ¹H NMR (CDCl₃, 400 MHz): δ 7.14 - 7.11 (m, 2H), 7.09 (dd, J=2.7, 7.1 Hz, 2H), 6.96 - 6.91 (m, 1H), 6.90 - 6.86 (m, 1H), 1.86 (dd, J=0.6, 1.8 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz): δ 192.1, 163.0, (d, J¹³C⁻¹⁹F=249.2 Hz), 143.1 (d, J¹³C⁻¹⁹F=2.0 Hz), 140.2 (d, J¹³C⁻¹⁹F=2.3 Hz), 136.5 (d, J¹³C⁻¹⁹F=24.9 Hz), 10.0; HRMS (ESI) calcd for C₁₀H₇FO [M+Na]⁺: 185.0373, found 185.0380.
$^{19}$F=5.0 Hz), 132.9 (d, $J^{13}$C-$^{19}$F=6.7 Hz), 121.8 (d, $J^{13}$C-$^{19}$F= 7.3 Hz), 118.7 (d, $J^{13}$C-$^{19}$F=22.8 Hz), 111.4 (d, $J^{13}$C-$^{19}$F=24.8 Hz), 10.0; $^{19}$F NMR (CDCl$_3$, 400 MHz): $\delta$ -113.5; HRMS (ESI) calcd for C$_{10}$H$_8$FO [M+H]$^+$: 163.0554, found 163.0555.

2-methylene-2,3-dihydro-1H-cyclopenta[b]naphthalen-1-one (3g): This reaction was preformed according to the general procedure for the cyclization of substituted benzoic acids with PCy$_3$ using 3-allyl-2-naphthoic acid (104 mg, 0.49 mmol). The crude product was purified by column chromatography on silica gel (Hexanes/EtOAc 85/15) to give 80% of the product (76 mg, 0.39 mmol) as a yellow solid. FTIR (CCl$_4$, cm$^{-1}$): 3060, 2918, 2848, 1697, 1636, 1592, 1556, 1255, 1218, $^{1}$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.84 (s, 1H), 7.80 (d, $J$=7.9 Hz, 1H), 7.70 (d, $J$=8.2 Hz, 1H), 7.49 (ddd, $J$=1.3, 7.0, 8.1 Hz, 1H), 7.41 (ddd, $J$=1.3, 7.0, 8.1 Hz, 1H), 7.36 - 7.33 (m, 1H), 7.24 (s, 1H), 1.96 (d, $J$=1.5 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 197.1, 144.6, 140.6, 139.5, 136.5, 133.2, 130.8, 130.4, 128.8, 128.7, 126.7, 124.0, 10.5; HRMS (ESI) calcd for C$_{14}$H$_9$O [M+H]$^+$: 217.0624, found 217.0621.
3,4-dihydro-1H-fluoren-9(2H)-one (3h): This reaction was preformed according to the general procedure for the cyclization of substituted benzoic acids with PCy₃ using 2-cyclohexenebenzoic acid (150 mg, 0.74 mmol). The crude product was purified by column chromatography on silica gel (Hexanes/EtOAc 95/5) to give 57% of the product (79 mg, 0.43 mmol) as a light yellow solid. ¹H NMR (CDCl₃, 400 MHz): δ 7.35 (d, J=6.9 Hz, 1H), 7.29 (ddd, J=1.0, 7.1, 7.9 Hz, 1H), 7.14 (t, J=7.4 Hz, 1H), 6.93 (d, J=7.2 Hz, 1H), 2.43 (ddd, J=2.9, 5.9, 8.8 Hz, 2H), 2.23 (ddd, J=2.8, 5.9, 8.9 Hz, 2H), 1.85 - 1.78 (m, 2H), 1.76 - 1.68 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz): δ; 197.5, 158.1, 144.9, 133.7, 133.0, 131.6, 128.1, 121.6, 118.1, 22.8, 21.9, 21.9, 19.6; HRMS (ESI) calcd for C₁₃H₁₂O [M+H]⁺: 207.0780, found 207.0782.

2-methyl-1H-pyrrolo[1,2-a]indol-1-one (3i): This reaction was preformed according to the general procedure for the cyclization of substituted benzoic acids with PCy₃ using 1-allyl-1H-indole-2-carboxylic acid (48 mg, 0.238 mmol). The crude product was purified by column chromatography on silica gel (Hexanes/CH₂Cl₂ 9/1) to give 48% of the product (21.2 mg, 0.115 mmol) as an orange solid. FTIR (CCl₄, cm⁻¹): 3062, 2925, 2855, 1689, 1618, 1544, 1442, 1404, 1367, 1331, 1274, 1240, 1162, 1115, 1009; ¹H NMR (CDCl₃, 400 MHz): δ 7.84 (s, 1H), 7.80 (d, J=7.9 Hz, 1H), 7.70 (d, J=8.2 Hz, 1H), 7.49 (ddd, J=1.3, 7.0, 8.1 Hz, 1H), 7.41 (ddd, J=1.3, 7.0, 8.1 Hz, 1H), 7.36 - 7.33 (m, 1H),
7.24 (s, 1H), 1.96 (d, J=1.5 Hz, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 197.1, 144.6, 140.6, 139.5, 136.5, 133.2, 130.8, 130.4, 128.8, 128.7, 126.7, 124.0, 10.5; HRMS (ESI) calcd for C$_{12}$H$_9$NO [M+H]$^+$: 184.0757, found 184.0758.

9-tosyl-9H-carbazol-4-yl acetate (3j): This reaction was preformed according to the general procedure for the cyclization of substituted benzoic acids with PCy$_3$ using 2-allyl-1-tosyl-1H-indole-3-carboxylic acid (172 mg, 0.238 mmol). The crude product was purified by column chromatography on silica gel (Hexanes/CH$_2$Cl$_2$ 9/1) to give 51% of the product (97 mg, 0.25 mmol) as a yellow solid. FTIR (CCl$_4$, cm$^{-1}$): 3057, 2977, 2919, 1771, 1598, 1448, 1430, 1371, 1204, 1177, 1168, 1092, 1066, 1029; $^1$H NMR (CDCl$_3$, 400 MHz): δ 8.35 (td, J=0.8, 8.5 Hz, 1H), 8.23 (dd, J=0.7, 8.4 Hz, 1H), 7.93 - 7.90 (m, 1H), 7.71 (d, J=8.6 Hz, 2H), 7.53 - 7.45 (m, 2H), 7.36 (dt, J=0.8, 7.6 Hz, 1H), 7.18 (dd, J=0.8, 8.0 Hz, 1H), 7.12 (d, J=8.1 Hz, 2H), 2.48 (s, 3H), 2.28 (s, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz): δ 168.6, 145.4, 145.1, 139.8, 138.3, 134.9, 129.8, 127.5, 126.5, 124.2, 124.1, 122.2, 118.6, 117.3, 114.9, 112.5, 21.5, 21.3; HRMS (ESI) calcd for C$_{21}$H$_{17}$NNaO$_4$S [M+H]$^+$: 402.0770, found 402.0776.
1,3-diethyl-5-methyl-4H-cyclopenta[c]thiophen-4-one (3k): This reaction was preformed according to the general procedure for the cyclization of substituted benzoic acids with PCy$_3$ using 4-allyl-2,5-diethylthiophene-3-carboxylic acid (168 mg, 0.75 mmol). The crude product was purified by column chromatography on silica gel (Hexanes/EtOAc 95/5) to give 73% of the product (112 mg, 0.544 mmol) as a yellow oil. FTIR (CCl$_4$, cm$^{-1}$): 3155, 2969, 2924, 2865, 1685, 1653, 1456, 1374, 1091; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.00 (q, $J=1.6$ Hz, 1H), 2.90 (q, $J=7.5$ Hz, 2H), 2.64 (q, $J=7.5$ Hz, 2H), 1.82 (d, $J=1.7$ Hz, 3H), 1.29 - 1.22 (m, 6H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 190.9, 150.3, 143.8, 140.4, 137.8, 134.9, 133.7, 21.9, 21.5, 15.6, 14.9, 10.9; HRMS (ESI) for C$_{12}$H$_{14}$OS [M+Na]$^+$: 229.0658, found 229.0667.

3.3 Chapter 2 Experimental Details

General procedure for the tandem cyclization and Heck coupling reaction: To a 4 mL borosilicate glass vial under argon containing 2-allylbenzoic acid (1.0 mmol) and acetic anhydride (190 µL, 2 mmol, 2 equiv) was added a solution of Pd(OAc)$_2$ and P(o-tol)$_3$ in THF (1 mL, 1M). The reaction was capped and heated to 65 °C for 18h. After cooling the reaction to ambient temperature, the THF and acetic acid were removed under
reduced pressure. To the crude reaction mixture was added arylbromide (1.5 equiv), NBu$_3$ (1.05 equiv), and DMF (1M) under argon. The reaction was capped and heated to 120 °C until the reaction was complete (GC analysis, typically 4-8h). After cooling to ambient temperature, the crude reaction mixture was diluted with EtOAc and washed with water (3x) and then brine (1x). The organic layer was dried with Na$_2$SO$_4$, concentrated, and purified by column chromatography on silica gel to yield the pure product.

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\text{(E)-4-((1-oxo-1H-inden-2(3H)-ylidene)methyl)benzonitrile (10a)}: \\
\text{This reaction was preformed according to the general procedure for the tandem cyclization and heck coupling of substituted benzoic acids using 2-allylbenzoic acid (162 mg, 1 mmol) and 4-bromobenzonitrile (274 mg, 1.5 mmol). The crude product was purified by column chromatography on silica gel (75% CH$_2$Cl$_2$/hexanes) to give 77\% of the product (189 mg, 0.77 mmol) as a light yellow solid. FTIR (KBr, cm$^{-1}$): 3036, 2962, 2924, 2222, 1703, 1628, 1604, 1466, 1268; }^{1}\text{H NMR (400 MHz, CDCl$_3$): } \delta \text{ ppm 7.87 (d, } J = 7.8 \text{ Hz, 1H), 7.77 (s, 2H), 7.76 (s, 2H), 7.66 (dt, } J = 1.2, 7.4 \text{ Hz, 1H), 7.62 - 7.58 (m, 2H), 7.48 - 7.42 (m, 1H), 7.45 (t, } J = 7.5 \text{ Hz, 1H), 4.06 (s, 2H).}^{13}\text{C NMR (CDCl$_3$, 100 MHz): } \delta \text{ 193.7,}
\]
149.3, 139.7, 137.9, 137.5, 135.2, 131.3, 130.7, 128.0, 126.2, 124.7, 118.4, 112.6, 32.3; HRMS (ESI) calcd for C\textsubscript{17}H\textsubscript{12}NNaO [M+Na]\textsuperscript{+}: 246.0913, found 246.0914.

\[(E)-4-((1\text{-}oxo\text{-}1\text{-}H\text{-}inden\text{-}2(3H)\text{-}ylidene)methyl)benzaldehyde (10b): \] This reaction was performed according to the general procedure for the tandem cyclization and heck coupling of substituted benzoic acids using 2-allylbenzoic acid (162mg, 1 mmol) and 4-bromobenzaldehyde (278 mg, 1.5 mmol). The crude product was purified by column chromatography on silica gel (75% CH\textsubscript{2}Cl\textsubscript{2}/hexanes) to give 73% of the product (181 mg, 0.73 mmol) as a light yellow solid. FTIR (KBr, cm\textsuperscript{-1}): 3029, 2930, 2842, 1698, 1686, 1561, 1459, 1271, 1214, 1167, 1094, 954, 824; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 7.74 (d, \(J = 7.8\) Hz, 1H), 7.48 (t, \(J = 7.4\) Hz, 1H), 7.36 (d, \(J = 7.5\) Hz, 1H), 7.28 (t, \(J = 7.7\) Hz, 1H). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100 MHz): \(\delta\) 193.4, 149.9, 143.3, 138.3, 134.9, 127.6, 126.4, 124.7, 119.2, 31.8; HRMS (ESI) calcd for C\textsubscript{17}H\textsubscript{12}NO\textsubscript{2} [M+Na]\textsuperscript{+}: 271.0730, found 271.0727.
(E)-2-(4-methoxybenzylidene)-2,3-dihydro-1H-inden-1-one (10c): This reaction was performed according to the general procedure for the tandem cyclization and Heck coupling of substituted benzoic acids using 2-allylbenzoic acid and 4-bromoanisole (280 mg, 1.5 mmol). The crude product was purified by column chromatography on silica gel (75% CH$_2$Cl$_2$/hexanes) to give 77% of the product (189 mg, 0.77 mmol) as a light yellow solid. FTIR (KBr, cm$^{-1}$): 3034, 2923, 1696, 1624, 1601, 1560, 1508, 1466, 1258, 1185, 1100, 1024, 958; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.74 (d, $J = 7.8$ Hz, 1H), 7.48 (t, $J = 7.4$ Hz, 1H), 7.36 (d, $J = 7.5$ Hz, 1H), 7.28 (t, $J = 7.7$ Hz, 1H); $^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 193.4, 149.9, 143.3, 138.3, 134.9, 127.6, 126.4, 124.7, 119.2, 31.8; HRMS (ESI) calcd for C$_{17}$H$_{14}$NaO$_2$ [M+Na]$^+$: 273.0886, found 273.0899.

![Chemical Structure](image)

(E)-2-(naphthalen-2-ylmethylene)-2,3-dihydro-1H-inden-1-one (10d): This reaction was performed according to the general procedure for the tandem cyclization and Heck coupling of substituted benzoic acids using 2-allylbenzoic acid and 2-bromonapthalene (310 mg, 1.5 mmol). The crude product was purified by column chromatography on silica gel (gradient 40% CH$_2$Cl$_2$/hexanes to 40% CH$_2$Cl$_2$/hexanes) to give 66% of the product (178 mg, 0.66 mmol) as a light yellow solid. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$
8.14 (s, 1H), 7.97 - 7.88 (m, 3H), 7.88 - 7.82 (m, 2H), 7.79 (dd, J=1.6, 8.5 Hz, 1H), 7.67 - 7.58 (m, 2H), 7.56 - 7.52 (m, 2H), 7.44 (t, J=7.4 Hz, 1H), 4.15 (s, 2H); 

$^{13}$C NMR (CDCl$_3$, 100 MHz): $\delta$ 194.3, 149.6, 138.1, 134.9, 133.6, 133.3, 133.0, 131.6, 128.6, 128.6, 127.7, 127.4, 126.9, 126.7, 126.2, 124.4, 32.5.

(E)-2-(4-hydroxy-3,5-dimethylbenzylidene)-5,6-dimethoxy-2,3-dihydro-1H-inden-1-one (Indanorine) (10e): This reaction was preformed according to the general procedure for the tandem cyclization and heck coupling of substituted benzoic acids using 4,5-dimethoxy-2-allylbenzoic acid (110 mg, 0.5 mmol) and 4-bromo-2,6-dimethylphenol (151 mg, 0.75 mmol). The crude product was purified by column chromatography on silica gel (75% CH$_2$Cl$_2$/hexanes) to give 64% of the product (104 mg, 0.32 mmol) as a light yellow solid. FTIR (KBr, cm$^{-1}$): 3546, 3178, 2928, 1673, 1654, 1578, 1500, 1291, 1129; $^1$H NMR (Acetone-d$_6$, 500 MHz): $\delta$ 7.39 (s, 2H), 7.36 (t, J = 1.9 Hz, 1H), 7.22 (s, 1H), 7.21 (s, 1H), 3.97 (d, J = 1.6 Hz, 2H), 3.96 (s, 3H), 3.90 (s, 3H), 2.36 (s, 6H); $^{13}$C NMR (Acetone-d$_6$, 125 MHz): $\delta$ 192.9, 156.6, 156.1, 151.0, 145.7, 134.0, 132.7, 132.4, 128.3, 125.5, 108.9, 105.7, 56.6, 56.4, 32.9, 16.8; HRMS (ESI) calcd for C$_{20}$H$_{20}$NaO$_4$ [M+Na$^+$]: 347.1254, found 347.1261.
(E)-2-((1-tosyl-1H-indol-5-yl)methylene)-2,3-dihydro-1H-inden-1-one (10f): This reaction was performed according to the general procedure for the tandem cyclization and Heck coupling of substituted benzoic acids using 2-allylbenzoic acid (154 mg, 0.95 mmol) and 5-bromo-1-tosyl-1H-indole (490 mg, 1.4 mmol). The crude product was purified by column chromatography on silica gel (75% CH₂Cl₂/hexanes) to give 44% of the product (174 mg, 0.42 mmol) as a light yellow solid. FTIR (KBr, cm⁻¹): 3133, 3111, 3051, 2924, 1692, 1630, 1602, 1460, 1370, 1294, 1249, 1173, 1129, 1093, 994; ¹H NMR (400 MHz, CDCl₃): δ, ppm 8.06 (1H, d, J = 8.7 Hz), 7.91 (1H, d, J = 7.7 Hz), 7.85 (1H, s), 7.79 (2H, d, J = 8.4 Hz), 7.76 - 7.72 (1H, m), 7.67 - 7.55 (4H, m), 7.42 (1H, t, J = 7.5 Hz), 7.24 (2H, d, J = 8.0 Hz), 6.72 (1H, d, J = 3.6 Hz), 4.07 (2H, s), 2.35 (3H, s); ¹³C NMR (CDCl₃, 100 MHz): δ 194.2, 149.5, 145.3, 138.1, 135.1, 134.2, 133.8, 131.2, 130.7, 130.0, 127.6, 127.4, 127.2, 126.8, 126.1, 124.4, 124.1, 113.9, 109.1, 32.5, 21.6; HRMS (ESI) calcd for C₂₀H₂₀NaO₄ [M+Na]⁺: 347.1254, found 347.1261.

X-ray crystallographic analysis of Palladacycle.

The crystal used for data collection was a yellow platelet. Examination of the diffraction pattern on a Nonius Kappa CCD diffractometer indicated a triclinic crystal system. All
work was done at 150 K using an Oxford Cryosystems Cryostream Cooler. The structure was solved by the direct methods procedure in SHELXS-97(2). Full-matrix least-squares refinements based on F2 were performed in SHELXL-97(3), as incorporated in the WinGX package(4). Any additional information regarding the crystallographic data can be obtained by contacting the author at kelseycmiles@gmail.com.
References


10. Syrchina, A. I.; Semenov, A. A. *Chemistry of Natural Compounds* 1982, 18, 1.


Appendix A: $^1$H NMR and $^{13}$C NMR Spectra for Selected Compounds