Stereoselective Bond Formation in the Total Synthesis of Rubriflordilactone B

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ABSTRACT

Rubriflordilactone B, an isolate from the Eastern Asian vine *Schisandra rubriflora*, is a bisnortriterpene possessing both inhibitory effects against HIV-infected cells and low levels of cytotoxicity. Synthetic quantities of this molecule would provide the opportunity to study its mechanism of action; however, the synthesis poses several challenges, including the installation of several fused rings and five contiguous stereocenters. We report progress on the synthesis of this natural product from two simple synthons - a butenolide and a substituted indene - by employing several stereoselective bond-forming reactions. The butenolide is formed from a diastereoselective, vinylogous Mukaiyama aldol addition, which then undergoes a photoredox-catalyzed, polar radical crossover cycloaddition with the indene to set all five stereocenters in two steps. These reactions allow for the concise union of the synthons with a high degree of stereoselectivity, paving the way for the completion of the synthesis.
Plants belonging to the genus *Schisandra* have been used extensively in Chinese herbal medicine for many years\(^1\). In 2006, the isolation of two bisnortriterpenoids, rubriflordilactone A and B (1 and 2), from the *Schisandra rubriflora* was reported, the latter being noteworthy for its inhibitory effects against HIV-1\textsubscript{IIIb}-infected T cells\(^1\).

**Figure 1.** Rubriflordilactone A (1) and rubriflordilactone B (2).

From a synthetic viewpoint, the synthesis of these two natural products pose many challenges arising from integration of the seven-membered ring, substitution on the arene ring, and placement of multiple contiguous stereocenters.

In 2014, Li et al. reported the first synthesis of rubriflordilactone A (1) using a 6π-electrocyclization/aromatization step to form the central multisubstituted arene ring. However, this step requires substantial heating of the reactants in DMSO, and the subsequent attachment of the butenolide moiety to complete the synthesis requires the use of a toxic siloxyfuran stannane species with BF\(_3\)•Et\(_2\)O activation\(^2\).

For the synthesis of rubriflordilactone B, we postulated that ring systems can be appended onto the central arene ring system through the use of an acridinium photoredox-catalyzed polar radical crossover cycloaddition (PRCC). In the past, we
have applied the PRCC reaction to the synthesis of tetrasubstituted furan rings from alkenes and alkenols with a high degree of diastereoselectivity, all conducted at room temperature and with a benchtop-stable photocatalyst\(^3\). Herein, we report progress on the synthesis of rubriflordilactone B (2) using a strategy involving the PRCC reaction.

Shown below in Scheme 1 is the retrosynthesis developed for 2.

**Scheme 1. Retrosynthetic Analysis of 2.**

First, the γ-butyrolactone is opened at the C-O single bond, forming a β,γ-unsaturated carboxylic acid 3. We envisioned that an intramolecular PRCC could install this lactone enantioselectively in a forward manner\(^4\). The seven-membered
ring is then disassembled by first cleaving the C9–C10 bond, forming the brominated intermediate 4 that can either be cyclized via a radical cyclization or a reductive Heck coupling. Further cleavage of the C7–C8 bond in 4 yields the tricyclic intermediate 5 and the tetrasubstituted lactone 6, which can be appended onto 5 via Sonogashira coupling between the triflate and the terminal alkyne in the forward direction. Furthermore, 5 can be disconnected into the substituted indene 15 and the butenolide 8, and we envisioned that an intermolecular PRCC between 15 and the allylic alcohol moiety of 8 would yield 5 stereoselectively.

The synthesis began by preparing the indene synthon 15 (Scheme 2). Starting from dihydrocoumarin 9, an intramolecular Friedel-Crafts acylation in neat aluminum chloride and sodium chloride at 200 °C yielded the desired 4-hydroxyindanone 10. However, due to the harsh reaction conditions and intolerable quench, a more user-friendly protocol was desired. Furthermore, low isolated yields were common, ranging from 0 – 33%, due to the presence of coordinated inorganic byproducts leftover from the reaction that were difficult to completely remove, even after column chromatography. These impurities often caused subsequent steps in the synthesis to fail, since the number of moles of 10 actually present was difficult to calculate without using a hexamethyldisiloxane NMR standard. This led to adopting the procedure developed by Pollini et al.5,6: After hydrolysis of the ester bond of 9, the resulting phenol was protected by a benzoyl group, yielding 2-benzoyloxyphenyl-1-propionic acid 11. Formation of the acid chloride through the use of thionyl chloride and catalytic dimethyl formamide, followed by the immediate transfer into a suspension of aluminum chloride in refluxing dichloromethane.
yielded the desired Friedel-Crafts product 12, which, after hydrolysis of the benzoyl ester bond, yielded the desired hydroxyindanone 10 with good yield. Subsequent treatment of 10 with diisopropylamine and slow addition of N-bromosuccinimide yielded 13 with complete regiocontrol. Following the formation of 13 through the hydrolysis of triflic anhydride to yield the triflate 14, the desired substituted indene 15 was formed through a straightforward reduction and strong acid elimination.

**Scheme 2.** Synthesis of the Indene Synthon 15\(^a\).
Reagents and conditions: (a) AlCl₃ (5.6 equiv), NaCl (excess), neat, 200 °C, 2 h, 33%; (b) NaOH, BzCl (1 equiv), 90%; (c) SOCl₂ (1.2 equiv), DMF (2-3 drops), DCM, 50 °C, 4 h, transferred immediately via cannula to (d); (d) AlCl₃ (5.4 equiv), DCM, 40 °C, 12 h, 78% (2 steps); (e) NaOH (30% by weight) 60 °C, 1 h, 93% (f) DIPA (1.0 equiv), DCM, room temp, 1 h; then NBS (0.9 equiv) slow addition via Soxhlet extractor, DCM, reflux, overnight, ortho:para >20:1, 66%; (g) pyridine (2.0 equiv), DCM, cooled to 0 °C; then, Tf₂O (1.2 equiv) added dropwise, DCM, 0 °C – room temp, 30 min (h) NaBH₄ (1.1 equiv), MeOH, 15 h; (i) TsOH•H₂O (0.1 equiv), toluene, reflux under Dean-Stark condenser, 3 h.

Multiple bromination protocols were attempted before deciding on the procedure used in Scheme 2 (Table 1). Beginning with N-bromosuccinimide in acetonitrile at room temperature (entry 1), the resulting product contained virtually only the para regioisomer as determined by ¹H-NMR, and the para configuration was confirmed by HQSC and HMBC 2-dimensional NMR. The dominance of para substitution pattern under these conditions could be due to the large lone pair orbitals on the hydroxyl oxygen hindering the approach of NBS to the ortho position.

Table 1. Bromination Optimization Study.

<table>
<thead>
<tr>
<th>entry</th>
<th>Br source</th>
<th>solvent</th>
<th>additive</th>
<th>temp. (°C)</th>
<th>time</th>
<th>ortho:para</th>
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<tr>
<td>1</td>
<td>NBS</td>
<td>MeCN</td>
<td>-</td>
<td>rt</td>
<td>24 hr</td>
<td>&lt;1:20</td>
</tr>
<tr>
<td>2</td>
<td>elemental Br</td>
<td>AcOH</td>
<td>NaOAc</td>
<td>rt</td>
<td>0.5 hr</td>
<td>2:1</td>
</tr>
<tr>
<td>3</td>
<td>NBS</td>
<td>TFA</td>
<td>-</td>
<td>rt</td>
<td>0.5 hr</td>
<td>3:1</td>
</tr>
<tr>
<td>4</td>
<td>NBS</td>
<td>DCM</td>
<td>DIPA</td>
<td>reflux</td>
<td>18 hr</td>
<td>&gt;20:1</td>
</tr>
<tr>
<td>5</td>
<td>DBTCE</td>
<td>ether</td>
<td>s-BuLi</td>
<td>-94</td>
<td>0.25 hr</td>
<td>&gt;20:1</td>
</tr>
</tbody>
</table>
A switch to polar solvents, acetic acid and trifluoroacetic acid (entries 2, 3) first produced notable ortho:para ratio results. However, if the hydroxyl proton was first removed by a weak base, like diisopropylamine, before adding the brominating agent, complete conversion to the ortho regioisomer was seen. In this case, the phenoxide anion directs the addition of bromine exclusively to the ortho position.

Scheme 3. Bromination of 4-hydroxyindanone 10a.

\[ \text{Reagents and conditions: (a) See Table 1; (b) Me}_2\text{NSO}_2\text{Cl (1.2 equiv), K}_2\text{CO}_3 (1.0 equiv), acetone, reflux, 4 h, 93%; (c) NaBH}_4 (1.1 equiv), MeOH, 15 h, quantitative; (d) TsOH (0.1 equiv), toluene, reflux, 3 h, 83%; (e) sec-BuLi (1.15 M in cyclohexane,} \]
1.0 equiv), THF, -94 °C, 45 min; then dibromotetrachloroethane (1.0 M in THF, 1.0 equiv), -94 °C to room temp, 15 min, 0%.

An extension of utilizing phenoxide as a directing agent for bromination is also illustrated in Scheme 3. Directed ortho metalation (DOM) is a demonstrated procedure for creating single regioisomers through selective deprotonation by a lithium base directed by a chosen directing group. The phenol was protected with a group that can simultaneously direct lithiation to the ortho position as well as serve as a partner for subsequent coupling to the lactone. N,N-dimethylsulfamate was chosen as a protecting group for its demonstrated use in a variety of cross-coupling reactions and for the Lewis-basicty of its carbonyl oxygens that could coordinate with a lithium base to selectively lithiate the ortho position.

Scheme 4. Directed Ortho Lithiation of an Aryl Ring.

\[
\begin{array}{c}
\text{R} \\
\text{R}
\end{array} \xrightarrow{1) \text{s-BuLi, -94 °C, THF, 45 min}} \xrightarrow{2) \text{DBTCE, -94 °C - r.t., 15 min}} \text{Br}
\]

\( ^a \text{R: OMe (33% conversion, >20:1 ortho:para), OSO}_2\text{NMe}_2 (50\% \text{ conversion, >20:1 ortho:para}) \)

As a test of the utility of the DOM procedure, both anisole and phenyl dimethylsulfamate were selectively brominated at the ortho position (Table 1, entry 5, and Scheme 4). The use of dimethylsulfamate saw conversion to the ortho product in only 15 minutes, demonstrating its strength as a directing group. However, when the indyl dimethylsulfamate 16 was subjected to the same
conditions outlined in Scheme 4, no ortho-brominated product was observed. This was rationalized as the benzylic position outcompeting the ortho position for lithiation – the \( pK_a \) of the benzylic proton in indene is anywhere from 20 to 40 units lower than the \( pK_a \) of the ortho aryl proton, so lithiation almost certainly occurred exclusively at this benzylic position.

In Scheme 5 is shown the construction of the butenolide synthon 24. To citraconic anhydride in methanol was added dicyclohexylamine, yielding 18. The slow addition of isobutyl chloroformate forms the carbonate intermediate 19, which is reduced immediately with sodium borohydride and water to the butenolide 20. Deprotonation at the \( \gamma \)-carbon, followed by silylation of the resulting enolate by trimethylsilyl triflate, formed the siloxyfuran 21. The vinylogous Mukaiyama aldol reaction (VMAR) of 21 and 3-(triisopropylsilyl)propionaldehyde 22, catalyzed by the chiral titanium(IV) Carreira catalyst 23\textsuperscript{11,12}, yielded 24 with desired diastereoselectivity greater than 90\% d.e. by GCMS.

The VMAR between 21 and 22 was optimized by considering the effect of catalyst loading and temperature on both the d.e. of the desired adduct and the percent conversion of reactants to products. Before conducting any screens, we hypothesized that both increasing the catalyst loading and increasing the temperature would increase the percent conversion while decreasing the d.e. of the product. Shown in Table 2 are the results from the VMAR optimization reactions.
Scheme 5. Synthesis of Butenolide Synthon 24\textsuperscript{a}.

\[ \text{Reagents and Conditions: (a) Cy}_2\text{NH (1.1 equiv), MeOH, -20 °C – room temp, 2 h; (b) isobutyl chloroformate (1.1 equiv), DCM, 0 °C – room temp, 3 h, immediately taken into freezer overnight; then used immediately in (c); (c) NaBH}_4 (2.0 equiv, 13 M in} \]
H₂O, H₂O, 0 °C – room temp, 2 h; (d) TMSOTf (1.0 equiv), triethylamine (1.2 equiv), DCM, 0 °C for 60 min and room temp for 30 min, 50%; (e) 22 (1.2 equiv), 23 (0.01 equiv), Et₂O, 0 °C, 24 h

As hypothesized, increasing the catalyst loading increased the percent conversion of the reaction by GCMS while it decreased the d.e. of the adduct (entries 1 – 3). The same was found to be true for increasing the reaction temperature (entry 2 and entry 4) as well as increasing the time the reaction was allowed to stir at the given temperature (entries 4 – 5). After considering the results, it was decided that the conditions of entry 1 provided the best compromise between diastereoselectivity and percent conversion.

**Table 2. VMAR Optimization Study.**

<table>
<thead>
<tr>
<th>entry</th>
<th>mol % cat.</th>
<th>temp. (°C)</th>
<th>time (hr)</th>
<th>d.e.</th>
<th>conversion</th>
</tr>
</thead>
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<tr>
<td>1</td>
<td>1</td>
<td>0</td>
<td>24</td>
<td>74%</td>
<td>43%</td>
</tr>
<tr>
<td>2</td>
<td>1.5</td>
<td>0</td>
<td>24</td>
<td>60%</td>
<td>90%</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>0</td>
<td>24</td>
<td>50%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>-20</td>
<td>24</td>
<td>&gt;90%</td>
<td>~10%</td>
</tr>
<tr>
<td>5</td>
<td>1.5</td>
<td>-20</td>
<td>72</td>
<td>52%</td>
<td>&gt;95%</td>
</tr>
</tbody>
</table>
Shorter reaction times and higher temperatures likely result in greater diastereoselectivity because they minimize the opportunity for the product to epimerize. If the aldol adduct is left in the reaction vial with the catalyst, the catalyst can recoordinate to the compound, this time at the butenolide carbonyl (Scheme 6).

**Scheme 6.** Epimerization of 24.

Deprotonation at the γ-carbon of the butenolide reforms the furan ring, which can then be reprotonated with either the same or opposite stereochemistry. Less exposure to the catalyst lowers the risk for epimerization, though it also lowers the conversion to the desired product. Similarly, lower temperatures lower the rate at which epimerization proceeds while also lowering the rate of the aldol addition. Thus, a balance had to be struck between high conversion and high diastereoselectivity.

Shown below in Scheme 6 is the current plan for appending the three synthons – the substituted indene 15, the butenolide 24, and the substituted lactone 6 – together. An intermolecular PRCC reaction catalyzed by the N-phenyl dimethylacridinium photocatalyst 25 and the 2,6-dimethylthiophenol 26 cocatalyst under blue lights we hoped would afford 27 with complete stereocontrol. Treatment of 27 with tetra-n-butylammonium fluoride removed the (triisopropyl)silyl protecting group, yielding the terminal alkene 28, and catalytic
hydrogenation yielded the tricyclic compound 5. Finally, palladium(0) tetrakis(triphenylphosphine)-catalyzed Sonogashira coupling between the aryl triflate 5 and terminal alkyne 6 would yield 4.

Scheme 6. Connection of the Three Synthons.

Reagents and Conditions: (a) 15 (1.5 equiv), 24 (1.0 equiv), 25 (0.05 equiv), 26 (0.20 equiv), DCE, irradiated with 450 nm blue LEDs, 48 h; (b) TBAF (5.0 equiv),
AcOH (6.0 equiv), THF, 0 °C – room temp; (c) Rh(PPh$_3$)$_3$Cl (0.10 equiv), H$_2$, acetone/toluene, room temp; (d) Pd(PPh$_3$)$_4$ (0.05 equiv), Cul (0.05 equiv), diisopropylethylamine (1.5 equiv)

In order to investigate the feasibility of the PRCC in fusing the indene and butenolide synthon, screens of both acridinium catalysts and thiol cocatalysts were carried out (Table 3). Beginning with the N-phenylidemethylacridinium photocatalyst 25 and 2,6-dimethylthiophenol 26, we were pleased to see a 47% crude yield with largely one diastereomer (entry 2).

Table 3. PRCC Reaction of Indene with 24.

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>thiol</th>
<th>eq. indene</th>
<th>eq. aldol</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NONE</td>
<td>26</td>
<td>1.5</td>
<td>1</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>26</td>
<td>1.5</td>
<td>1</td>
<td>47%</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>26</td>
<td>1.5</td>
<td>1</td>
<td>4%</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>26</td>
<td>1</td>
<td>5</td>
<td>23%</td>
</tr>
<tr>
<td>5</td>
<td>25</td>
<td>30</td>
<td>1.5</td>
<td>1</td>
<td>0%</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>31</td>
<td>1.5</td>
<td>1</td>
<td>0%</td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>NONE</td>
<td>1.5</td>
<td>1</td>
<td>0%</td>
</tr>
</tbody>
</table>
However, once we switched to the di-tert-butyl catalyst 29, the yield dropped substantially (entry 3). Also notable is that the yield dropped when switching which reagent was in excess (entry 4). The effect of alkyl substitution on the thiophenol's performance as a cocatalyst was also studied. Increasing the number of alkyl groups on the aryl ring act to weaken the sulfur-hydrogen bond by stabilizing the thiy radical that forms, increasing the rate of H-atom transfer. However, increasing bulk around the thiol could simultaneously impede H-atom transfer by making the hydrogen atom less accessible to the vinyl radical on the cyclized product. Neither of the more highly substituted thiophenols 30 or 31 yielded any product (entries 5 and 6). Lastly, either not subjecting the reaction vial to radiation or leaving out the thiophenol cocatalyst produced none of the expected PRCC reaction product (entries 1 and 7); however, the ¹H-NMR spectra of these two entries did not contain just starting material, so it’s possible that there is some background reactivity that is lowering the yield of this reaction. Another possible reason for the low yields is decomposition of either the butenolide 24 or the product 27 in the extended
presence of the catalyst. From previous PRCC reactions, alkenes with vinyl substituents have an oxidation potential well within the range of the photocatalyst\textsuperscript{14}. The starting butenolide possesses one of these types of double bonds, while the product has two – one with a vinyl methyl group and one with a vinyl triisopropylsilyl group. It is possible that these double bonds could be oxidized by the catalyst, leading to decomposition either before or after the product forms.

The anti-Markovnikov addition of the alcohol to the indene is essential for the correct regiochemistry of the product, and this selectivity is available through single electron chemistry made possible by the photocatalyst\textsuperscript{3}. Irradiation of the reaction excites the acridinium photocatalyst 25, which undergoes single electron transfer to the indene. Single electron oxidation of the indene double bond by the excited state acridinium catalyst forms the indenylium cation-radical intermediate. The alcohol moiety of 24 then adds in an anti-Markovnikov manner to the cation-radical, which is followed by a radical cyclization to close the five-membered ring, leaving a vinyl radical. Hydrogen-atom transfer from the thiophenol 26 to the radical forms the product 27 and a thiylium radical, and reduction of this radical is coupled to the oxidation of the acridinium, completing the catalytic cycle.
Scheme 7. Proposed Mechanism for the PRCC Reaction Between Indene and the Butenolide 24. HAT = H-atom transfer, SET = single electron transfer, Oxidation of the photocatalyst 25 and reduction of the thiophenol cocatalyst 26 are coupled.
The key addition-cyclization step of the PRCC reaction is shown in more detail in Scheme 8. Anti-Markovnikov selectivity comes from the stability of the radical at the benzylic position\(^{14}\). Because the radical cation is delocalized over both alkenyl carbons, the addition of the alcohol can occur in either a Markovnikov or an anti-Markovnikov fashion, with this addition step being reversible. In Markovnikov addition, the radical is localized on a secondary carbon, while in anti-Markovnikov addition, the radical is located on the benzylic carbon. The stability of the benzylic radical in comparison to the secondary carbon radical drives the reaction towards anti-Markovnikov addition. Following the alcohol addition step, radical addition into the alkyne closes the ring in a 5-\textit{exo} manner. This 5-\textit{exo} cyclization is favored over 6-\textit{endo} cyclization because, in the Beckwith transition state, the orbital containing the radical has better overlap at the 5 position over the 6 position.

\textbf{Scheme 8.} Anti-Markovnikov Addition and Radical Cyclization Steps in the PRCC Reaction.
In summary, progress has been made towards the total synthesis of rubriflordilactone B. The substituted indene was prepared through a completely regioselective bromination, and the butenolide was synthesized through a diastereoselective vinylogous Mukaiyama aldol addition. The fusion of these two synthons was accomplished through a photoredox-catalyzed, polar radical crossover cycloaddition, leading to the formation of this key intermediate with high enantiopurity. This work paves the way for the completion of the synthesis of the natural product, which could lead to studies on the pharmacological activity of this compound, as well as other terpenoids of the Schisandraceae family.

REFERENCES


SUPPORTING INFORMATION

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<td>NMR Spectra of Compounds</td>
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I. Methods

General Procedures. All reactions were carried out under a nitrogen atmosphere with dry solvents, unless otherwise noted. Dry solvents were either distilled and stored under nitrogen before use, or stored in a nitrogen-flushed, SureSeal bottle. Triethylamine and diisopropylamine were distilled from potassium hydroxide immediately before use in reactions. Reactions were monitored by thin layer chromatography carried out on silica gel plates using either UV light as a visualizing agent or by using an aqueous cerium ammonium molybdate (CAM) developing agent. Silica gel was used for flash column chromatography. NMR spectra were recorded using either a Bruker 400WB or Bruker B600 instrument and were calibrated using by using residual undeuterated chloroform (δ_H = 7.26 ppm) and deuterated chloroform (δ_C = 77.16 ppm) or residual undeuterated dimethylsulfoxide (δ_H = 2.50 ppm). Gas chromatographs and mass spectra were recorded on an Agilent 6850 Series II gas chromatograph.

Purification of Reagents. Unless otherwise noted, reagents were used without further purification, with the exception of N-bromosuccinimide (NBS) and sec-butyllithium. Crude NBS (10 g) was recrystallized from water (100 mL) heated to 90 °C before use in the o-bromination reaction (6.7 g recovered, 67%). The mother liquor of the recrystallization was a light yellow color, indicating the presence of bromine.

Impure 1.4 M sec-butyllithium solution in cyclohexane was doubly titrated in the following manner to determine its actual concentration before use in ortho-lithiation reactions. Into a sealed, flame-dried, nitrogen flushed round bottom flask
containing a stirred solution of 22.2 mg of 2,2'-bipyridine in 20 mL dry benzene was added 100 μL of the sec-butyllithium solution, turning the bipyridine solution a dark red as the lithium bipyridinyl charge transfer complex formed (see Figure S1). Then, a 1 M sec-butanol solution in dry xylenes was added dropwise to the flask until the dark red color became a bright yellow. This process was then repeated three times, and, with each addition, the volume of sec-butyllithium and sec-butanol added was noted. The actual concentration of the sec-butyllithium solution was calculated by dividing the volume of sec-butanol added by the volume of sec-butyllithium added, and the calculated molarity was averaged across the three trials to arrive at the actual concentration of 1.15 M.

**Figure S1.** Double Titration of Sec-Butyllithium.
II. Experimental Procedures

3-(2-benzoyloxyphenyl)propionic acid 11: Following the procedure of Barco and Pollini, into a solution of 30% aqueous sodium hydroxide by weight (13 mL) in a round bottom flask with stir bar was dissolved dihydrocoumarin 9 (7.4 g, 50 mmol) by heating for 10 min. The flask was cooled to room temperature; then, benzoyl chloride (7.0 g, 50 mmol, 1 equiv) was added slowly over 30 min with vigorous stirring. The reaction flask was then cooled in an ice bath and acidified with concentrated hydrochloric acid. The precipitate was collected and washed with H₂O. The crude product was dried in vacuo and recrystallized from toluene. The desired product recrystallized as fine white needles. The mother liquor was concentrated and a second recrystallization was completed from toluene (6.6 g, 90%). ¹H NMR (400 MHz, CDCl₃): δ = 8.21 (d, J = 8 Hz, 2 H), δ = 7.65 (t, J = 8 Hz, 1 H), δ = 7.33 – 7.17 (m, 4 H), δ = 2.93 (t, J = 8 Hz, 2 H), δ = 2.67 (t, J = 8 Hz, 2 H).
1-oxo-2,3-dihydro-1H-inden-4-yl benzoate 12: To a flame-dried, two-necked round bottom flask with stir bar was added 11 (3.0 g, 11.1 mmol) and 30 mL of dichloromethane. At room temperature was added thionyl chloride (0.96 mL, 13.3 mmol, 1.2 equiv) and 4 drops of dry N,N-dimethylformamide. The reaction was refluxed at 50 – 60 °C for 3 h.

To a separate flame-dried, Two-necked round bottom flask with stir bar was added aluminum chloride granules (7.93 g, 60 mmol, 5.4 equiv) and 15 mL of dichloromethane, creating a suspension of aluminum chloride when stirred. To this suspension of aluminum chloride was added the contents of the first round bottom flask via cannula. The reaction was then allowed to reflux at 40 °C for 12 h overnight.

The reaction was removed from reflux, cooled to room temperature, and poured into a slurry of ice water. The aqueous and organic layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with saturated sodium bicarbonate and water, dried with magnesium sulfate, and concentrated via rotary evaporation. Upon removal from the vacuum, the oil crystallized as a orange-brown solid. The crude product was taken forward without further purification (2.2 g, 78%). ¹H NMR (400 MHz, CDCl₃):
\[ \delta = 8.23 \ (d, \ J = 8 \ Hz, \ 2 \ H), \ \delta = 7.70 \ (m, \ 2 \ H), \ \delta = 7.55 \ (t, \ J = 8 \ Hz, \ 2 \ H), \ \delta = 7.45 \ (m, \ 2 \ H), \ \delta = 3.08 \ (t, \ J = 6 \ Hz, \ 2 \ H), \ \delta = 2.72 \ (t, \ J = 6 \ Hz, \ 2 \ H). \]

**4-hydroxy-2,3-dihydro-1H-inden-1-one 10:** To a solution of 30\% aqueous sodium hydroxide by weight (10 mL) in a round-bottom flask was added 12 (0.78 g, 3.10 mmol). The suspension was heated with stirring until 12 was completely dissolved. The solution was decolorized with carbon and filtered. The solution was cooled to 0 °C acidified using concentrated hydrochloric acid, and the precipitate was collected by filtration. The wet solid was washed thoroughly with saturated sodium bicarbonate and water (425 mg, 93\%). The product was recrystallized from ethanol to yield off-white to pale orange crystals. \(^1\)H NMR (400 MHz, DMSO-d6): \[ \delta = 9.97 \ (s, \ 1 \ H), \ \delta = 7.28 \ (t, \ J = 8 \ Hz, \ 1 \ H), \ \delta = 7.13 \ (d, \ J = 8 \ Hz, \ 1 \ H), \ \delta = 7.08 \ (d, \ J = 8 \ Hz, \ 1 \ H), \ \delta = 2.97 \ (t, \ J = 6 \ Hz, \ 2 \ H), \ \delta = 2.64 \ (t, \ J = 6 \ Hz, \ 2 \ H). \]

**5-bromo-4-hydroxy-2,3-dihydro-1H-inden-1-one 13:** Into a flame-dried round bottom flask with stir bar was added 10 (100 mg, 0.676 mmol) and 20 mL DCM. Diisopropylamine (50 μL, 0.676 mmol, 1 equiv) was added via syringe, and the
solution was allowed to stir for 30 min. Then, a Soxhlet extractor with a jacketed reflux condenser was added on top of the flask, and recrystallized NBS (107 mg, 0.608 mmol, 0.9 equiv) was placed at the bottom of the extractor. The reaction was then heated to reflux at 50 °C overnight (15 h). The reaction was then removed from reflux, acidified with 3 M hydrochloric acid, extracted with dichloromethane, washed with water and brine, dried with magnesium sulfate, and concentrated. The crude product was purified via column chromatography with a 25% acetone/hexanes mobile phase (102 mg, 66%). ¹H NMR (400 MHz, CDCl₃): δ = 7.49 (d, J = 8 Hz, 1 H), δ = 7.22 (d, J = 8 Hz, 1 H), δ = 5.76 (s, 1 H), δ = 3.11 (t, J = 6 Hz, 2 H), δ = 2.73 (t, J = 6 Hz, 2 H). GC-MS (t_R = 7.41 min, m/z = 226, doublet (1:1)).

1-oxo-2,3-dihydro-1H-inden-4-yl dimethylsulfamate: To a flame-dried round bottom with stir bar was added hydroxyindanone 10 (93 mg, 0.628 mmol) and potassium carbonate (174 mg, 1.26 mmol, 2 equiv). Dry acetone (10 mL) and N,N-dimethylsulfamoyl chloride (0.135 mL, 1.26 mmol, 2 equiv) were added to the flask, and the reaction was refluxed for 4 h. The reaction was then quenched with 3 M hydrochloric acid, transferred to a separatory funnel, extracted three times with ether, washed with water and brine, and concentrated. The crude product was purified via column chromatography with a 35% ethyl acetate/hexanes mobile
phase (149.7 mg, 93%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.68$ (d, $J = 8$ Hz, 1 H), $\delta = 7.53$ (d, $J = 8$ Hz, 1 H), $\delta = 7.42$ (t, $J = 6$ Hz, 1 H), $\delta = 3.24$ (t, $J = 6$ Hz, 2 H), $\delta = 3.07$ (s, 6 H), $\delta = 2.71$ (t, $J = 6$ Hz, 2 H).

1-hydroxy-2,3-dihydro-1H-inden-yl dimethylsulfamate: To a flame dried round 10 mL round bottom flask with stir bottom was added 1-oxo-2,3-dihydro-1H-inden-4-yl dimethylsulfamate (82 mg, 0.322 mmol) dissolved in 5 mL methanol. To the stirred solution was added sodium borohydride (13.7 mg, 0.370 mmol, 1.15 equiv) portionwise. The reaction was left to stir overnight (15 h); then, the reaction was diluted with water, extracted with dichloromethane, washed with water and brine, and dried and concentrated, yielding the desired product without further need for purification (81 mg, quantitative yield). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.32$ (d, $J = 8$ Hz, 1 H), $\delta = 7.26$ (d, $J = 16$ Hz, 1 H), $\delta = 7.20$ (d, $J = 8$ Hz, 1 H), $\delta = 5.24$ (t, $J = 8$ Hz, 1 H), $\delta = 3.15$ (m, 1 H), $\delta = 3.01$ (s, 6 H), $\delta = 2.90$ (m, 1 H), $\delta = 2.50$ (m, 1 H), $\delta = 1.96$ (m, 1 H).
**1H-inden-7-yl dimethylsulfamate 16**: To a flame-dried, two-necked round bottom flask with stir bar was added tosic acid monohydrate (5.7 mg, 0.03 mmol, 0.1 equiv) and 1-hydroxy-2,3-dihydro-1H-inden-yl dimethylsulfamate (45 mg, 0.3 mmol) dissolved in 10 mL toluene. A Dean-Stark trap and reflux condenser were attached, and the reaction was boiled at 130 °C for 3 h. The reaction was then cooled, added to a separatory funnel, washed twice with both 5% aqueous sodium sulfate and brine, and then concentrated to yield the desired product (33.9 mg, 83%) with only minor impurities, which were removed by passing the product through a small silica plug with an ethyl acetate mobile phase. \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ = 7.31 (m, 2 H), δ = 7.13 (dd, J = 12 Hz, 1 H), δ = 6.87 (dt, J = 8 Hz, J = 3 Hz, 1 H), δ = 6.60 (dt, J = 8 Hz, J = 3 Hz, 1 H), δ = 3.56 (t, J = 3 Hz, 2 H), δ = 3.04 (s, 6 H).

**phenyl dimethylsulfamate**: To a suspension of sodium hydride, 60% in mineral oil, in 30 mL N,N-dimethylformamide (DMF) in a flame-dried round bottom under nitrogen was added via cannula a solution of phenol (1.0 g, 10.6 mmol) in 5 mL DMF at 0 °C. The resulting sodium phenoxide solution was stirred for 30 min at room temperature before recooling to 0 °C and treating with N,N-dimethylsulfamoyl
chloride (1.58 mL, 11.2 mmol, 1.05 equiv). The solution was warmed to room temperature, quenched with saturated ammonium chloride, diluted with water, extracted with hexanes, dried with magnesium sulfate, and concentrated yielding the desired product (1.87 g, 88%). GCMS (t_R = 5.91 min, m/z = 201).

![Chemical Structure](image)

**2-bromophenyl dimethylsulfamate:** Following the procedure of Macklin and Snieckus\(^3\), into a flame-dried roundbottom flask with stir bar was added 5 mL tetrahydrofuran, phenyl dimethylsulfamate (201 mg, 1.0 mmol), and tetramethylethlenediamine (0.17 mL, 1.1 mmol, 1.1 equiv). The reaction was cooled to -94 °C using a mixture of hexanes and liquid nitrogen; then, sec-butyllithium (0.96 mL, 1.1 mmol, 1.1 equiv, 1.15 M in cyclohexane) was added slowly via syringe. The reaction was stirred for 45 min between -86 °C and -105 °C, monitored using a thermocouple. Then, a 1 M solution of dibromotetrachloroethane in tetrahydrofuran (391 mg, 1.2 mmol, 1.2 equiv) was added slowly via syringe, and the flask was removed from the cooling bath and warmed to room temperature over 15 min.

The reaction was diluted with water, acidified with 3 M hydrochloric acid, and the organics were extracted with dichloromethane. GCMS analysis showed only ortho-brominated product and no para bromination, with full conversion to the desired product. GC-MS (t_R = 7.52 min, m/z = 281, doublet (1:1)).
dicyclohexylammonium (E)-4-methoxyl-3-methyl-4-oxobut-2-enoate 18: To a flame-dried 500 mL round bottom flask was added 200 mL methanol. The flask was placed into an acetone bath and cooled to -20 °C to -30 °C with dry ice. Into the cooled flask was added citraconic anhydride dropwise (22.4 mL, 1 equiv), followed by dicyclohexylamine dropwise (54.7 mL, 1.1 equiv). The reaction was stirred at -20 °C for 2 h and then warmed to room temperature and concentrated. The crude product was stirred in 150 mL of ethyl acetate for 40 min. The solid was isolated by suction filtration, washed with ethyl acetate, and dried. The filtrate was concentrated to one-half volume via rotary evaporation, and any additional product was collected (51.9 g, 64%).

(E)- 4-((isobutoxycarbonyl)oxy)-2-methyl-4-oxobut-2-enoic acid 19: Into a 250 mL flame-dried round bottom flask was added 18. Into the flask was added 120 mL of dichloromethane; the flask was immersed in an ice bath, and isobutylchloroformate (22.8 mL, 1.1 equiv) was added dropwise. The reaction was stirred at room temperature for 3 h, over which the reaction grew from cloudy to white and opaque, and so viscous that stirring could not occur. The round bottom was then placed in the freezer overnight.
To the round bottom flask in the freezer was added 100 mL of dry
tetrahydrofuran, which was allowed to sit for 1 h. The solution was filtered into a
500 mL filter flask at 0 °C and taken immediately onward to the next reaction.

![Structure of 3-methylfuran-2(5H)-one](image)

**3-methylfuran-2(5H)-one 20:** At 0 °C with stirring, sodium borohydride in H$_2$O
(12.1 g, 2 equiv, 13 M in H$_2$O) was added to the filtrate containing 19, one pipette at
a time. The reaction was allowed to warm to room temperature as it was stirred for
2 h. Then, the co-product was filtered off, and the filtrate was concentrated. The
solid was resuspended in diethyl ether, and the solid was filtered off. The filtrate
was reconcentrated, capped, and stored in the freezer. The crude product was
purified to a clear oil via vacuum distillation. $^1$H NMR (400 MHz, CDCl$_3$): δ = 7.13 (t, J
= 3 Hz, 1 H), δ = 4.75 (quint, J = 2 Hz, 2 H), δ = 1.93 (t, J = 3 Hz, 3 H).

![Structure of trimethyl((3-methylfuran-2-yl)oxy)silane](image)

**trimethyl((3-methylfuran-2-yl)oxy)silane 21:** $^1$H NMR (400 MHz, CDCl$_3$): δ = 6.79
(d, J = 4 Hz, 1 H), δ = 6.13 (d, J = 2 Hz, 1 H), δ = 1.85 (s, 3 H), δ = 0.30 (s, 9 H).
3-(triisopropylsilyl)propionaldehyde 22: Into a flame-dried round bottom flask was dissolved triisopropylsilyl acetylene (5.6 mL, 25 mmol). The flask was cooled to 0 °C and 2.5 M n-butyllithium in hexanes (26.25 mmol, 10.5 mL, 1.05 equiv) was added dropwise, and the reaction was warmed to room temperature and stirred for 1 h. The flask was then cooled back down to 0 °C and N,N-dimethylformamide (3.9 mL, 50 mmol, 2 equiv) was added slowly. Then, the flask was allowed to warm to room temperature and stirred for 1 h. The flask was then again cooled to 0 °C, poured into a 10% aqueous monopotassium phosphate/diethyl ether solution, and the layers were separated. The organic layers were washed with water and brine, dried over anhydrous magnesium sulfate, and stored in the freezer. The crude oil was dissolved in dichloromethane and passed through a 2 in silica plug. The reconcentrated product was dried in vacuo overnight, yielding the desired product as a yellow oil (3.34 g, 64%). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 9.20$ (s, 1 H), $\delta = 2.30$ (s, 3 H), $\delta = 1.11$ (s, 18 H).
(S)-5-((S)-1-hydroxy-3-(triisopropylsilyl)prop-2-yn-1-yl)-3-methylfuran-2(5H)-one 24: A flame dried 25 mL round bottom flask with stir bar was taken into the glove box. In the glove box, the Carriera titanium(IV) catalyst 23 (0.01 equiv) was added to the flask by dissolving it in 13.8 mL diethyl ether and transferring via syringe. The flask was then placed in the glove box freezer for 30 min. Then, to the flask was added the TIPS-propargyl aldehyde 22 (708 μL, 1 equiv) and the siloxyfuran 21 (612 μL, 1.2 equiv). The flask was taken out of the glove box and placed into a Cryobath, where it was stirred at 0 °C for 24 h.

The reaction flask was then removed from the Cryobath and quenched with 5% sodium bicarbonate. The layers were separated, and the aqueous layer was extracted with diethyl ether. The organic layers were combined, washed with water, passed through a 2 in silica plug to remove the catalyst, and reconcentrated to a yellow-orange oil.

To remove the trimethylsilyl protecting group, the crude oil recovered from the silica plug was taken up in methanol (1 M solution) in a round bottom flask, and into this flask was added citric acid granules (1 equiv). The reaction was stirred for 10 min at room temperature; then, the reaction was diluted with water, the organics were extracted with diethyl ether, and the combined organic layers were washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated. The crude oil was purified via column chromatography using a 20% ethyl
acetate/hexanes mobile phase, yielding the desired product as a clear, light yellow oil. $^1$H NMR (400 MHz, CDCl$_3$): Major diastereomer assignment peaks: $\delta = 7.14$ (t, $J = 3$ Hz, 1 H), $\delta = 4.87$ (m, 1 H), $\delta = 4.62$ (m, 1 H). Minor diastereomer assignment peaks: $\delta = 7.08$ (t, $J = 3$ Hz, 1 H), $\delta = 4.94$ (m, 1 H), $\delta = 4.69$ (m, 1 H). GC-MS trace of major diastereomer ($t_R = 10.12$, m/z = 337). GC-MS trace of minor diastereomer ($t_R = 10.08$, m/z = 337).

The Carreira titanium (IV) catalyst was prepared the day before it was needed in the following manner.

![Figure S2](image-url). Preparation of the Carreira Titanium(IV) Catalyst.

Following the procedure of Carreira et al.$^2$, into an oven-dried Schlenk flask with stir bar was added imine 32 (34.6 mg, 2.2 equiv). Into a separate, flame-dried, 1 dram vial was added salicylic acid 33 (15.2 mg, 2.02 equiv). Both the Schlenk flask and 1 dram vial were then taken into the glove box. Into the 1 dram vial was added 1.26 mL of dry, nitrogen-flushed toluene, and into the Schlenk flask was added 3.88 mL of toluene and titanium(IV) isopropoxide (8.8 $\mu$L, 1 equiv). Upon addition of the titanium reagent, the solution in the Schlenk flask immediately turned a bright orange. Both the Schlenk flask and vial were sealed and removed from the glove
box; the Schlenk flask was attached to a Schlenk line and stirred under nitrogen for 1 h, while the 1 dram vial containing 33 was stored separately under positive pressure of nitrogen at room temperature. At 1 h, the salicylic acid solution was added to the Schlenk flask via syringe, and the reaction was allowed to stir for an additional 1 h. Then, the toluene in the Schlenk flask was removed by slowly pulling a vacuum on the Schlenk line, and the red-orange solid in the flask was allowed to dry in vacuo overnight for use the next day.

\[(S)-3\text{-methyl-5-}((2S,3aR,8aR,E)\text{-}3\text{-((triisopropylsilyl)methylene})\text{-}3,3a,8,8a\text{-tetrahydro-2H-indeno[2,1-b]furan-2-yl]furan-2(5H)\text{-}one}\ 27:\] Into a flame-dried 1 dram vial with stir bar was added N-phenyl dimethylacridinium photocatalyst 25 (1.3 mg, 0.05 equiv) and 1,2-dichloroethane (0.25 mL). To this solution was then added indene (9.0 mg, 1.5 equiv), 24 (20 mg, 1.0 equiv), and 2,6-dimethylthiophenol 26 (1.4 mg, 0.20 equiv). After the solution was degassed with nitrogen for 20 min, it was placed under 2 blue LED lamps and was allowed to stir at room temperature for 48 h.

The lamps for the reaction were set up in the following manner. One lamp was placed to the left of the vial, facing the stir plate, and one was placed to the
right. Above the stir plate was placed a fan in order to cool the reaction to keep it at room temperature.

The solution was removed from the lamps, passed through a silica plug using a DCM mobile phase, and concentrated, yielding the crude product as a reddish-brown oil. The crude oil was initially purified using column chromatography using a 25% ethyl acetate/hexanes mobile phase (13.2 mg, 47%). $^1$H NMR (600 MHz, CDCl$_3$): The following peaks were used to characterize the product: $\delta = 4.92$ (m, 1 H), $\delta = 4.86$ (m, 1 H), $\delta = 4.27$ (d, J = 4 Hz, 1 H), $\delta = 3.49$ (t, J = 9 Hz, 1 H), $\delta = 3.22$ (d, J = 2 Hz, 2 H), $\delta = 2.42$ (quint, J = 7 Hz, 1 H), $\delta = 1.67$ (t, J = 1.5 Hz, 1 H). $^1$H-NMR after the column still showed some impurity peaks that could not be assigned.
III. References


IV. NMR Spectra of Compounds

$^1$H NMR spectrum
400 MHz, CDCl$_3$
$^1$H NMR spectrum
400 MHz, DMSO-d$_6$
1:0.17 ratio of desired product to starting material

$^1H$ NMR spectrum
400 MHz, CDCl$_3$
Determination of the regiochemistry of Table 1, entry 1 bromination

HSQC NMR spectrum
600 MHz, CDCl₃
Determination of the regiochemistry of Table 1, entry 1 bromination

HMBC NMR spectrum
600 MHz, CDCl₃
$^{1}$H NMR spectrum
400 MHz, CDCl$_3$
$^{1}$H NMR spectrum
400 MHz, CDCl$_3$
$^1$H NMR spectrum
400 MHz, CDCl$_3$
$^{1}$H NMR spectrum
400 MHz, CDCl$_3$
TIPS

\[
\text{d.r. } 3.84:1
\]

\(^1\text{H NMR spectrum}

400 MHz, CDCl\textsubscript{3}
after 1\textsuperscript{st} column

$^1$H NMR spectrum
400 MHz, CDCl\textsubscript{3}