Development of Ru-Catalyzed Tandem Sequences Involving Ring-Closing Metathesis

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DEVELOPMENT OF Ru-CATALYZED TANDEM SEQUENCES INVOLVING RING-CLOSING METATHESIS

a dissertation

by

YOUn HEe NAM

submitted in partial fulfillment of the requirements

for the degree of

Doctor of Philosophy

March 2013
Abstract

Tandem processes can have several advantages over multiple single step processes. Non-metathesis transformations of ruthenium alkylidenes were studied and applied to tandem processes. Ruthenium catalyzed tandem RCM/hydroacylation that allows access to tricyclic ring systems from readily available substrates was developed. Mechanistic investigations indicated that this reaction may proceed through a mechanism involving [Ru]-H species. A Ru-catalyzed tandem RCM/olefin isomerization/C-H activation sequence that provides significant advantages in terms of rapid elaboration of simple reaction partners to more complex entities was developed.
To God and my family
“I can do all things through him who gives me strength”

--Philippians 4:13
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<th>Definition</th>
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<tr>
<td>Ac</td>
<td>acetyl (CH₃C=O)</td>
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<tr>
<td>BINAP</td>
<td>2,2’-bis(diphenylphosphino)-1,1’-binaphthyl</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>t-butyloxy carbonyl(CO_C₄H₉)</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>Bz</td>
<td>benzoyl</td>
</tr>
<tr>
<td>Cbz</td>
<td>carbobenzyloxy (BnOC=O)</td>
</tr>
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<td>CM</td>
<td>cross metathesis</td>
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<td>carbon monoxide</td>
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<tr>
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<td>4-dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
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<td>dppe</td>
<td>(diphos)1,2-bis(diphenylphosphino)ethane</td>
</tr>
<tr>
<td>EDA</td>
<td>ethyl diazoacetate</td>
</tr>
<tr>
<td>Ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>Eq.</td>
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<td>Grubbs catalyst 2(^{nd}) generation</td>
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<tr>
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</tr>
<tr>
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<td>phenyl</td>
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<tr>
<td>PMP</td>
<td>1-phenyl-3-methyl-5-pyrazolone</td>
</tr>
<tr>
<td>PPh₃</td>
<td>triphenylphosphine</td>
</tr>
<tr>
<td>psi</td>
<td>pounds per square inch</td>
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<tr>
<td>RCM</td>
<td>ring-closing metathesis</td>
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<td>S-Phos</td>
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<td>tetrachloroquinone</td>
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General Experimental Details

Starting materials and reagents were purchased from commercial suppliers and used without further purification except the following: Grubbs’ II catalyst was obtained from Materia was purified by silica gel chromatography with Et₂O to isolate the intensely colored band (cranberry red); triethylamine was distilled over CaH₂. tetrahydrofuran, dichloromethane, toluene, DMF and Et₂O were dried on alumina columns using a solvent dispensing system. All reactions were conducted in oven (135 °C) or flame-dried glassware under an inert atmosphere of dry nitrogen. n-BuLi, t-BuLi and iPr-MgCl was titrated using salicylaldehyde phenylhydrazonementhol in tetrahydrofuran. Bath wax was purchased from fisher. Silica gel column chromatography refers to flash chromatography, and was performed using Baxter brand silica gel 60Å (230-400 Mesh ASTM). Percent (%) Ag refers to silver nitrate treated silica gel, and is measured as wt/wt, AgNO₃ / SiO₂. Infrared (IR) spectra were recorded on a Mattson Galaxy Series FTIR 5000. Proton nuclear magnetic resonance spectra (¹H NMR) were recorded on ether a Varian Unity 300 (300 MHz), a Varian Gemini-400 (400 MHz), a Varian Gemini-500 (500 MHz) or a Varian Unity Inova-500 (500 MHz). Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent reference as the internal standard (CHCl₃: δ 7.26 ppm). Data is reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br = broad, m = multiplet), and coupling constants (Hz). ¹³C NMR spectra were recorded on either a Varian Gemini-400 (100 MHz), a Varian Gemini- 500 (125 MHz) or a Varian Unity Inova-500 (125 MHz) with complete proton decoupling. Chemical shifts (δ) are reported in ppm downfield from

(b) Rabel, F. Chrom. News Vol. 4, No. 1, 1995; EM Separations Technology, Gibbstown, NJ.
tetramethysilane with the solvent as the internal reference (CDCl$_3$: $\delta$ 77.16 ppm). High resolution mass spectral analyses (HRMS) were performed by Mass Spectrometry Facility, Boston College. Melting points were recorded on a Laboratory Devices Mel-Temp and were uncorrected. Bomb reactors were purchased from Parr Instrument Company (model 4714 and 4761).
Chapter 1

Ruthenium Catalyzed Tandem and One-Pot Metathesis/Non-Metathesis Processes
1.1 Introduction

Tandem processes accomplish several chemical transformations in a single reaction vessel to generate useful compounds, both economically and practically, by reducing waste streams and minimizing handling.\(^1\) Ruthenium alkylidene catalysts (Figure 1.1.1.1) are well-known to demonstrate chemoselectivity in olefin metathesis, and are known as precursors to catalysts for other transformations such as olefin isomerizations, olefin hydrogenations, olefin oxidation, cyclization, cycloaddition, rearrangement, cyclopropanation, and others.\(^2\) This review covers tandem catalysis reactions that combined olefin metathesis reactions with non-metathetic transformations, as well as one-pot reactions\(^{2a}\) from 2002 through 2012. However, double metathesis occurring in the same system\(^{2g,h}\) and tandem metathesis/Diels Alder\(^3\) are not taken into consideration in this overview.

**Figure 1.1.1.1** Commercially available Ru-based catalysts for olefin metathesis


1.2 Metathesis/isomerization

1.2.1 RCM/isomerization

Olefin isomerization has been an unpredictable phenomenon in metathesis. Snapper, et al. have demonstrated that this reaction however, can be used as a valuable transformation by designing a controlled tandem RCM/olefin isomerization sequence (Table 1.2.1.1). Isomerization was made possible using metathesis catalyst G2 and modifying the reaction conditions. They used a 95:5 N₂:H₂ gas mixture for a few minutes to favor olefin isomerization over a competitive olefin hydrogenation reaction. This strategy enabled the synthesis of five-, six-, and seven-membered cyclic enol ethers from easily prepared dienes. The authors suggested that the isomerization is sensitive to sterics, because it led only to the less substituted enol ether. They also noted that the isomerization is suppressed significantly by using freshly purified G2. The isomerization activity was then enhanced by treatment with H₂, which suggests the involvement of a Ru-hydride species.

Table 1.2.1.1 Preparation of cyclic enol ethers through a tandem RCM/olefin isomerization sequence using diluted H₂ as a hydride source

Schmidt observed similar results when they treated the metathesis catalyst with other additives that could serve as latent hydride sources. The authors treated G1 with ethyl vinyl ether, which led to a Fischer type carbene [Cl₂PCy₃]₂Ru=CHOEt. Under refluxing toluene, this complex decomposed into a Ru-H complex [Cl₂(CO)(PCy₃)₂Ru-H]. This protocol gave the desired 5-membered enol ethers in moderate yields and regioselectivities (Table 1.2.1.2). The isomerization step, however, proceeded slowly for six- and seven-membered systems and thus, yielded only 10% of the isomerized products. To address this limitation, the authors investigated other additives. They found that the addition of NaBH₄ or NaH to a metathesis mixture accelerates the rate of olefin isomerization. They assumed that a nucleophilic attack by hydride induces the formation of the isomerization active Ru-H species. This protocol allowed for isomerization of six- and seven-membered ring systems, as well as five-membered cyclic enol ethers. The protocol has limited functional group tolerance; for example, substrates containing an alcohol or ester moiety do not lead to the desired olefin isomerized.

products. Furthermore, substrates with unsaturated side chains exhibited incomplete conversion. The authors resolved these limitations by using 2-propanol and NaOH as additives to generate the requisite Ru-H species.\textsuperscript{5b} This improved procedure can be used with substrates possessing alcohol and ester functionalities. An undesired hydrogen transfer was still problematic, however, and partial hydrogen transfer of cyclic enol ethers yielded undesired reduced tetrahydrofurans. The authors also demonstrated that triethylsilane is an effective additive for isomerization. The active catalyst for olefin isomerization was generated by oxidative addition of the silane to the metal complex when the mixture was heated to 110 °C in toluene. The authors applied these protocols to the synthesis of enantiomerically pure dihydrofuran and dihydropyran, which are derived from camphor (scheme 1.2.1.1, eq 1), menthone, (scheme 1.2.1.1, eq 2) or cyclohexylidene-protected glyceraldehydes (scheme 1.2.1.1, eqs 3 and 4).\textsuperscript{6}

---

Table 1.2.1.2 Preparation of cyclic enol ethers through a tandem RCM/olefin isomerization sequence in the presence of additives

<table>
<thead>
<tr>
<th>Additive</th>
<th>Yield (%)</th>
<th>Selectivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EiOCH=CH₂ (77%, 8:1)</td>
<td>72%</td>
<td>(84%, &gt;19:1)</td>
</tr>
<tr>
<td>NaH or NaBH₄ (30 mol %)</td>
<td>74%</td>
<td>(94%, &gt;19:1)</td>
</tr>
<tr>
<td>i-propanol, NaOH</td>
<td>72%</td>
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</tr>
</tbody>
</table>
Scheme 1.2.1.1 Synthesis of enantiomerically pure dihydrofuran and dihydropyran

The preparation of six- to eight-membered oxacycles was reported by Schmidt and Bierant. The author synthesized 3-deoxyglycals via a tandem RCM/olefin isomerization sequence. Isopropanol and NaOH were added to the reaction mixture after completion of the RCM step to generate a Ru-H species (Table 1.2.1.3). The seven-membered ring was obtained with a moderate yield under the same conditions as the six-membered ring (Scheme 1.2.1.2). For an eight-membered ring, however, these conditions only produced a dimer during the metathesis step. The authors were able to obtain a 90% yield of the

desired eight-membered ring product through RCM with G2 in refluxing toluene, followed by olefin isomerization using NaBH₄ as an additive (Scheme 1.2.1.2).

**Table 1.2.1.3** Preparation of 3-deoxyglycals through a tandem RCM/olefin isomerization sequence

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 (5 mol %), toluene; 2-propanol, NaOH, 110 °C</td>
<td>R-O</td>
<td>61%</td>
</tr>
<tr>
<td>G1 (5 mol %), toluene; 2-propanol, NaOH, 110 °C</td>
<td>O-O</td>
<td>54%</td>
</tr>
<tr>
<td>G1 (5 mol %), toluene; 2-propanol, NaOH, 110 °C</td>
<td>O-O</td>
<td>84%</td>
</tr>
</tbody>
</table>

**Scheme 1.2.1.2** Preparation of seven- and eight-membered oxacycles through a tandem RCM/olefin isomerization sequence

This method was then applied to the synthesis of a disaccharide glycal 1.1 containing one septanose and one hexose (Scheme 1.2.1.3). The disaccharide was prepared as a single isomer in a 75% yield starting from ethyl lactate using the tandem RCM/isomerization sequence as a key step.
**Scheme 1.2.1.3** Synthesis of a disaccharide glycal through a tandem RCM/olefin isomerization sequence

The utility of tandem metathesis/olefin isomerization has been demonstrated by Blechert, et al. and Schmidt, et al. in the synthesis of (-)-centrolobine. Blechart’s team reported the synthesis (-)-centrolobine using two effective one-pot reaction sequences in 2005 (Pathway I in Scheme 1.2.1.4). The cyclopentene precursor \( \text{1.2} \) for the tandem sequence was prepared through a reductive epoxide opening and enantioselective allylation. The tandem sequence of diastereoselective ring-rearrangement metathesis of cyclopentene \( \text{1.2} \) and isomerization of terminal to internal double bond resulted in the desired dihydropyran \( \text{1.3} \) with a yield of 55% without isomerization of the endocyclic double bond. To finish the synthesis of (-)-centrolobine, the authors applied another Ru-catalyzed cross-metathesis followed by hydrogenation using a modified Ru catalyst. This

sequence, however, led to benzylic ether cleavage. Finally, the authors completed the synthesis through a Ru-catalyzed cross-metathesis followed by Pd catalyzed hydrogenation as a one-pot operation. Schmidt and colleagues also reported the synthesis of (-)-centrolobine and its stereoisomers in 2009 and 2010 (Pathway 2 in Scheme 1.2.1.4)\(^9\) using tandem RCM/isomerization as one of the key steps. The precursor 1.4 for the tandem sequence was prepared through sequential allylations. The tandem RCM followed by olefin isomerization with Grubbs first generation catalyst and modified Ru catalyst (2-popropanol/NaOH under heating), resulted in desired cyclic enol ether 1.5 in a 93% yield.

Scheme 1.2.1.4 Synthesis of (-)-centrolobin by two tandem olefin metathesis/olefin isomerization sequences

---

Tandem ring-closing metathesis/isomerization was also enabled the regioselective synthesis of polycyclic lactams and sultams (Table 1.2.1.4).\textsuperscript{10} 2-Pyrrolines were obtained from readily available \textit{N},\textit{N}-bisallylamides, via a tandem RCM/isomerization sequence. This was promoted by the Grubbs first generation catalyst and sodium hydride as a hydride source. Under these reaction conditions, bicyclic lactams were obtained in 43-86\% yields. This sequence was also exploited for the synthesis of sultams; sulfonamides produced desired sultams with high yields and regioselectivities.

\textit{Table 1.2.1.4} Preparation of polycyclic lactams and sultams through a tandem RCM/olefin isomerization sequence

\begin{center}
\begin{tabular}{c}
\textbf{Table 1.2.1.4} Preparation of polycyclic lactams and sultams through a tandem RCM/olefin isomerization sequence
\end{tabular}
\end{center}

\begin{center}
\begin{tabular}{c}
\textbf{Table 1.2.1.4} Preparation of polycyclic lactams and sultams through a tandem RCM/olefin isomerization sequence
\end{tabular}
\end{center}

Fustero and colleagues studied the synthesis of fluorinated and nonfluorinated lactam derivatives with various ring sizes using a tandem RCM/isomerization reaction sequence (Table 1.2.1.5).\textsuperscript{11} The authors found that additives were necessary to generate a Ru-hydride species, which is responsible for the isomerization reaction. The difluorinated

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(10) Bressy, C.; Menant, C.; Piva, O. \textit{Synlett} 2005, 577-582.
amides afforded seven-membered lactams with totally regioselective isomerization when the Grubbs second generation catalyst was used in refluxing toluene. The influence of the gem-difluoro moiety was demonstrated by contrasting it with the formation of the corresponding nonfluorinated lactam. When this overall process was applied to nonfluorinated amide, it produced the expected lactam, enamide (67%) as well as another isomeric lactam (29%) that is generated by double bond isomerization toward the opposite side. This implies that the gem-difluoro makes the isomerization step a regioselective process as a result of its inductive effect. This tandem protocol is also efficient for the preparation of different ring size cyclic lactams. The nine-membered ring substrate, however, led to the formation of several lactams with smaller ring-sizes, because the isomerization step is faster than the less favored RCM step.

Table 1.2.1.5 Preparation of unsaturated lactams through a tandem RCM/olefin isomerization

![Diagram](image-url)
In analogy to the synthesis of lactam above, Fustero, et al. prepared fused bicyclic fluorinated uracils.\textsuperscript{12} The regioselectivity of the olefin isomerizations was controlled by the reaction conditions (Table 1.2.1.6). When the reaction was carried out in the presence of Grubbs first generation catalyst at 50 °C in CH\textsubscript{2}Cl\textsubscript{2}, only bicyclic uracil 1.6 was produced, whereas the use of Grubbs second generation catalyst in refluxing toluene gave isomerized bicyclic uracil 1.7 as a single product.

Table 1.2.1.6 Preparation of bicyclic fluorinated uracils through a tandem RCM/olefin isomerization

![Diagram showing the synthesis of bicyclic fluorinated uracils through a tandem RCM/olefin isomerization]

The synthesis of α,β-unsaturated δ-lactones via RCM/isomerization sequence was reported by Schmidt and Kunz in 2012. Hydride sources were examined to catalyze the olefin isomerization reaction by generating the Ru-hydride species. The use of sodium hydroxide with 2-propanol and sodium hydride unfortunately caused complications that lead to a base-induced ring-opening reaction. The use of ethyl vinyl ether, on the other hand, yielded lower conversion of metathesis product. To address the aforementioned issues, 0.2 equivalents of triethylsilane were used as a hydride source, which gave the desired α-pyrones in yields typically higher than 80% (Table 1.2.1.7).

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst (15 mol %)</th>
<th>solvent</th>
<th>temp (°C)</th>
<th>1.6:1.7 ratio</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>G2</td>
<td>CH₂Cl₂</td>
<td>50</td>
<td>72:28</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>G1</td>
<td>CH₂Cl₂</td>
<td>50</td>
<td>100:0</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>G2</td>
<td>toluene</td>
<td>120</td>
<td>0:100</td>
<td>70</td>
</tr>
</tbody>
</table>

The synthesis of α,β-unsaturated δ-lactones via RCM/isomerization sequence was reported by Schmidt and Kunz in 2012. Hydride sources were examined to catalyze the olefin isomerization reaction by generating the Ru-hydride species. The use of sodium hydroxide with 2-propanol and sodium hydride unfortunately caused complications that lead to a base-induced ring-opening reaction. The use of ethyl vinyl ether, on the other hand, yielded lower conversion of metathesis product. To address the aforementioned issues, 0.2 equivalents of triethylsilane were used as a hydride source, which gave the desired α-pyrones in yields typically higher than 80% (Table 1.2.1.7).

As mentioned previously, olefin isomerization is one of the side reactions often observed during the olefin metathesis reaction. It is considered that Ru-H species, responsible for the isomerization reaction, are formed from the decomposition of the ruthenium metathesis catalysts under various conditions; such as high temperature, high dilution, and long reaction times. For example, the diallyl ether gave a ring closing metathesis product 1.8 with a yield of 80% and an RCM/isomerization product 1.9 (20%) with G2 in 40 °C CH₂Cl₂ after 1 hour. Upon extending the reaction time to 24 hours, the tandem RCM/isomerization product 1.9 was increased up to >95% (Table 1.2.1.8). In response, Grubbs and colleagues suggested a means to prevent undesired olefin isomerization. The authors found that acetic acid or quinine-type compounds inhibit the undesired olefin isomerization during the olefin metathesis reaction. The addition of 1,4-benzoquinone to the reaction mixture did not give any isomerization product after 24 hours without reducing catalyst activity. The authors also noted that electron-deficient

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benzoquinones are the most effective additives in suppressing olefin migration, while radical scavengers were not effective in suppressing isomerization.

**Table 1.2.1.8** Tandem RCM/olefin isomerization of diallyl ether

<table>
<thead>
<tr>
<th>Reaction Conditions</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>G2 (5 mol %), CD₂Cl₂, 40 °C, 1 h</td>
<td>1.8 (80%) 1.9 (20%)</td>
</tr>
<tr>
<td>G2 (5 mol %), CD₂Cl₂, 40 °C, 24 h</td>
<td>1.8 (&lt;5%) 1.9 (&gt;95%)</td>
</tr>
<tr>
<td>G2 (5 mol %), 1,4-benzoquinone (10 mol %) CD₂Cl₂, 40 °C, 24 h</td>
<td>1.8 (&gt;95%) 1.9 (none)</td>
</tr>
</tbody>
</table>

Bennasar and colleagues found that a tandem RCM/isomerization took place during the preparation of 2,3-fused ring indole derivatives via ring closing metathesis (Scheme 1.2.1.5).\(^\text{15}\) The RCM step gave a mixture of desired ring closing product 1.10 and tandem RCM/isomerization product 1.11 in a combined yield of 65%.

**Scheme 1.2.1.5** Tandem RCM/isomerization sequence during synthesis of 2,3-fused ring indole derivative

In 2012, Brimble and co-workers demonstrated an elegant example of one-pot RCM/olefin isomerization in the total synthesis of *ent*-macrolide.\(^\text{16}\) Their original plan

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was to use a ring closing metathesis of enamide 1.12 to install the 15-membered ring 1.14. However, they realized that the enamide precursor 1.12 did not undergo macrocyclization. This problem was solved by using a one-pot RCM/isomerization operation (Scheme 1.2.1.6). Diene 1.13 was subjected to the RCM with G2 in refluxing CH₂Cl₂ followed by olefin isomerization with RuH(PPh₃)₃(CO)Cl to afford ent-macrolide successfully in 84% yield.

**Scheme 1.2.1.6** One-pot RCM/olefin isomerization in the synthesis ent-macrolide

---

1.2.2 Isomerization/RCM

The tandem sequence (orthogonal catalysis) of allylic isomerization/ring closing metathesis using Pd-PPh₃ catalyst in conjunction with G2 has been explored by Braddock, et al. (Scheme 1.2.2.1).¹⁷ Under these conditions, the desired ring closing metathesis product was detected by ¹H NMR spectroscopy in a 57% yield. G1 and HG1 catalysts, however, did not generate any in situ tandem reaction product because of its sensitivity to the triphenyl phosphine that is present to activate Pd(0) for the isomerization reaction.

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Nishida, et al. and Arisawa, et al. studied indole synthesis though isomerization followed by olefin metathesis in one-pot.\textsuperscript{18} During the study of cross-metathesis with silyl enol ethers in the presence of G2, the authors found that terminal olefins were isomerized to the internal olefins instead of undergoing a cross-metathesis. The olefin isomerization of the terminal olefin by the Ru-H species that is generated \textit{in situ} by treating G2 with vinyloxytrimethylsilane, produced the more stable enamine. Likewise, both HG1 and HG2 with vinyloxytrimethylsilane catalyzed the olefin isomerization reaction in moderate yields. On the other hand, Grubbs first generation catalyst, however, did not catalyze the olefin isomerization.\textsuperscript{18b} The authors also examined other silyl enol ethers as hydride sources. Ethyl vinyl ether with G2 required longer time (24 hours) to generate isomerization products while acetoxy vinyl ether generated no isomerization product. The authors combined the isomerization reaction with ring closing metathesis and then applied this one-pot operation to the synthesis of indoles. After the isomerization reaction, the resultant enamines obtained by evaporation of the volatile material were subjected to G2 in refluxing benzene to give indoles in up to quantitative yields (Table 1.2.2.1). It was found that a Ts group on the nitrogen, as well as Ac, Bz, Ms,
Boc and CBZ groups generated indoles in high yields (80-94%). The substrates having various substituents on the aromatic ring gave the corresponding indoles with good yields (77-100%). Substrates having a substituent in the 3-position of the aromatic ring, however, generated lower yields of desired RCM products (20-54%), presumably through their steric and chelating effects. This protocol was also found to be useful for the preparation of 2-substituted indoles, as well as 3-substituted indoles.\(^{18d}\)

**Table 1.2.2.1** Preparation of substituted indoles through a one-pot isomerization/RCM sequence

\[
\begin{align*}
\text{G2 (5 mol %), OTMS (1 equiv.), CH}_2\text{Cl}_2, \text{reflux, 1.5 h;} & \quad \text{G2 (5 mol %), benzene, reflux, 1-16 h} \\
R = & \quad \text{Ts 94\%} \quad \text{Ac 82\%} \\
& \quad \text{Ms 75\%} \quad \text{Bz 86\%} \\
& \quad \text{Boc 80\%} \quad \text{CBZ 86\%}
\end{align*}
\]

\[
\begin{align*}
\text{G2 (5 mol %), OTMS (1 equiv.), CH}_2\text{Cl}_2, \text{reflux, 1.5 h;} & \quad \text{G2 (5 mol %), benzene or toluene, reflux, 1-32 h} \\
X = & \quad \text{H 94\%} \quad \text{6-Cl 85\%} \\
& \quad \text{6-OMe 83\%} \quad \text{5-Cl 79\%} \\
& \quad \text{5-OMe 96\%} \quad \text{4-Cl 86\%} \\
& \quad \text{4-OMe 100\%} \quad \text{3-Cl 33\%} \\
& \quad \text{3-OMe 54\%} \quad \text{3-Me 20\%} \\
& \quad \text{4,5,6-triOMe 83\%} \quad \text{6-Me 77\%}
\end{align*}
\]

\[
\begin{align*}
\text{G2 (5 mol %), OTMS (10 mol %), CH}_2\text{Cl}_2, \text{reflux, 1 h;} & \quad \text{G2 (5 mol %), toluene, reflux, 1 h} \\
R = & \quad \text{pTS 59\%} \quad \text{0\%} \\
& \quad \text{Ms 78\%} \quad \text{13\%} \\
& \quad \text{Boc 62\%} \quad \text{23\%} \\
& \quad \text{MeOCO 23\%} \quad \text{64\%} \\
& \quad \text{Ac 11\%} \quad \text{83\%} \\
& \quad \text{CF}_3\text{CO 44\%} \quad \text{21\%}
\end{align*}
\]


The synthesis of benzo-fused heterocycles through one-pot isomerization/RCM has been reported by van Otterlo, et al. The completion of the olefin isomerization reaction with \([\text{RuCl}_2(\text{CO})(\text{PPh}_3)_3]\) was monitored by \(^1\text{H} \text{NMR spectroscopy or TLC}\. Then, \(G2\) was added to the reaction mixture to generate the ring closing metathesis products. This protocol allows for the preparation of a variety of \(N\)- and \(O\)-benzo-fused heterocycles from readily available starting materials (Table 1.2.2.2). In the same way, benzofuran was synthesized through olefin isomerization and RCM sequence in one-pot operation (Scheme 1.2.2.2).

**Table 1.2.2.2** Preparation of benzo-fused heterocycles through a one-pot isomerization/-RCM sequence

\[
\begin{align*}
\text{MeO} & \quad \text{RuCl}_2(\text{CO})(\text{PPh}_3)_3 \\
\text{O}\text{/Pr} & \quad \text{toluene} \\
\rightarrow & \quad \text{MeO} \\
\text{O}\text{/Pr} & \quad \text{G2 (5 mol %)} \\
\rightarrow & \quad \text{MeO} \\
\text{O}\text{/Pr} & \quad \text{G2 (5 mol %)} \\
\rightarrow & \quad \text{MeO} \\
\text{O}\text{/Pr} & \quad \text{G2 (5 mol %)} \\
\rightarrow & \quad \text{X = NTs} \\
\text{O} & \quad \text{76%} \\
\text{O} & \quad \text{83%}
\end{align*}
\]

Condition: \(X = \text{NTs}; \text{RuCl}_2(\text{CO})(\text{PPh}_3)_3 (0.5 \text{ mol %}), \text{toluene, 110 °C}, 2 \text{ h then G2 (5 mol %), 110 °C, 3 h}
\(O : \text{RuCl}_2(\text{CO})(\text{PPh}_3)_3 (1 \text{ mol %}), \text{toluene, 80 °C, then G2 (5 mol %), 60 °C}

\[
\begin{align*}
\text{R}_1 \quad \text{RuCl}_2(\text{CO})(\text{PPh}_3)_3 (1 \text{ mol %}) \\
\text{O} \quad \text{toluene-\text{\(\alpha\)}}_6, 80 °C & \quad \text{G2 (5 mol %)} \\
\rightarrow & \quad \text{yield\*} \\
\text{R}_1 = \text{H, } R_2 = \text{H} & \quad >70\% \\
\text{R}_1 = \text{Me, } R_2 = \text{H} & \quad >70\% \\
\text{R}_1, R_2 = \text{fused benzene ring} & \quad >90\%
\end{align*}
\]

\*by \(^1\text{H} \text{NR spectroscopy}

During the study of the synthesis of certain terpenoids, Wicha, et al. found that sterically congested 1,9-dienes undergo a tandem (orthogonal catalysis) isomerization/ring closing metathesis with G2 catalyst in refluxing benzene to give 7-membered fused ring systems.\textsuperscript{21} The Grubbs metathesis catalysts G1 and G2 are more effective than HG2 and are compatible with double bond isomerization catalyst, [RuClH(CO)(PPh\(_3\))\(_3\)]. In addition, when the metathesis catalyst and [RuClH(CO)(PPh\(_3\))\(_3\)] were used at the same time, the reaction was facilitated (Table 1.2.2.3).

Table 1.2.2.3 Tandem (orthogonal catalysis) isomerization/RCM sequence during the synthesis of medium ring containing bicyclic systems

| Condition | R = H | 49% | 0% |
| Condition | R = CH₃ | 34% | 40% |

Condition A: G2 (5 mol %), benzene, reflux, 72 h
Condition B: G2 (5 mol %), RuCl₃(CO)(PPh₃)₃ (5 mol %), benzene, reflux, 6 h
Condition C: G2 (5 mol %), RuCl₃(CO)(PPh₃)₃ (5 mol %), benzene, reflux, 24 h

Undesired olefin isomerizations of the terminal olefin prior to ring-closing metathesis, giving ring contracted products, can be readily observed during the synthesis of medium and large ring systems. Leino, et al. reported an unexpected ring contraction during the synthesis of fused indenes via ring closing metathesis.\(^\text{(22)}\) Undesired olefin isomerization of the terminal double bond to the more stable internal double bond prior to RCM lead to the desired 15-membered ring \(\textbf{1.16}\), in addition to contracted 14-membered rings \(\textbf{1.14}\) and \(\textbf{1.15}\) (Scheme 1.2.2.3, eq 1). Similarly, Kotha, et al. found the formation of smaller ring systems during the preparation of cyclophane derivatives.\(^\text{(23)}\) The RCM precursor \(\textbf{1.17}\), a bisolefinic compound, gave the 21-membered cyclophane derivative \(\textbf{1.18}\) in a 47% yield (a 1:1.7 mixture of two diastereomers) with Grubbs second generation catalyst in diluted CH₂Cl₂ at room temperature. Under these conditions, the bisolefinic compound \(\textbf{1.17}\) also underwent competitive olefin isomerization prior to ring-

closing metathesis, which generated the ring contracted 20-membered ring 1.19 (Scheme 1.2.2.3, eq 2). When Fustero, et al. prepared chiral fluorinated macrolactones, a similar result was observed.\textsuperscript{24} A reduced 10-membered ring 1.22 was obtained as the major product in a 77% yield, which results from olefin isomerization of diene 1.20 prior to ring-closing metathesis. In contrast, he desired 11-membered lactone 1.21 was obtained in only a 19% yield (Scheme 1.2.2.3, eq 3). Hoppe, et al. also reported a similar problem during the synthesis of (+)-vigulariol.\textsuperscript{25} Ring closing metathesis of dialkenyl tetrahydrofuran with Grubbs second generation catalyst in refluxing benzene gave the desired compound 1.24 in a 45% yield while the ring contracted product 1.25 was also obtained in a 17% yield (Scheme 1.2.2.3, eq 4).

**Scheme 1.2.2.3** Isomeriztion/RCM sequeneces in the synthesis of medium and large ring systems

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1.2.3 CM/isomerization

Snapper, et al. developed a ruthenium catalyzed tandem ring opening cross-metathesis/allylic alcohol isomerization reaction that allows preparation of methyl ketones from strained cyclic olefins in the same reaction vessel (Table 1.2.3.1).\textsuperscript{26} In this protocol, the ruthenium complex was transformed into an effective catalyst for isomerization without a hydride source by heating. The yield of desired methyl ketone was improved by avoiding oligomerization of the strained olefins; the cyclic olefin was added to the reaction slowly and the isomeriation step was performed at higher temperatures (200 °C) with shorter reaction times.

In a similar fashion, the synthesis of methyl ketones via tandem olefin cross-metathesis/isomerization of terminal olefin was demonstrated by the Snapper group (Table 1.2.3.2). Isomerization of allylic alcohols produced in the cross-metathesis occurred at high temperature without an additive. The more hindered terminal olefins required longer reaction time for the metathesis step. Also, phthalimide required a slightly higher catalyst loading for the isomerization step. This tandem protocol is
effective for various terminal olefins. The terminal olefins containing a benzyl ether gave desired ketones with good yield and without hydrogenolysis byproducts. Also, the substrate with ketone functionality did not interfere with the tandem process.

Table 1.2.3.2 Preparation of ketones through tandem CM/isomerization

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Ratio</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me_3SiOH</td>
<td>0.5-2.0 mol%</td>
<td>71%</td>
</tr>
<tr>
<td>Me_3SiOH</td>
<td>0.5-2.0 mol%</td>
<td>69%</td>
</tr>
<tr>
<td>Me_3SiOH</td>
<td>0.5-2.0 mol%</td>
<td>69%</td>
</tr>
<tr>
<td>Me_3SiOH</td>
<td>0.5-2.0 mol%</td>
<td>52%</td>
</tr>
<tr>
<td>Me_3SiOH</td>
<td>0.5-2.0 mol%</td>
<td>63%</td>
</tr>
<tr>
<td>Me_3SiOH</td>
<td>0.5-2.0 mol%</td>
<td>51%</td>
</tr>
</tbody>
</table>

1.2.4 Enyne metathesis/isomerization

During the study of the preparation of hydroxy-functionalized dienes through cross enyne metathesis, Diver, et al. found that heating for an extended period allowed a further reaction: a 1,5-hydride shift of the metathesis product 1.26 to give the shifted diene 1.27. Because the 1,5-hydride shift product 1.27 could not be separated from the diene metathesis product 1.26, an in situ cycloaddition of the (E)-diene 1.26 was used. The favored s-trans conformation 1.27, which is unreactive in the thermal cycloaddition, remained unchanged in the reaction mixture after cycloaddition. Only (E)-diene 1.26

yielded [4+2] cycloaddition product 1.28. The purified E/Z mixture from the ruthenium catalyst showed no 1,5-hydride shift product under the same conditions except the absence of the ruthenium catalyst which only gave unchanged starting material (Scheme 1.2.4.1). Interestingly, addition of NaBH$_4$ to the crude reaction mixture led to 1,5-hydride shift product. These results revealed that the s-trans product 1.27 could be synthesized through a tandem Ru-catalyzed cross enyne metathesis followed by Ru-H catalyzed 1,5-hydride shift.

**Scheme 1.2.4.1** Tandem enyne metathesis/isomerization sequence

1.2.5 Isomerization/enyne metathesis

The synthesis of spirocyclic β-lactams 1.30 via a tandem rearrangement-metathesis was described by Alcaide, et al. The allenyl propargyl rearrangement of enallene 1.29 with G2 followed by ring closing enyne metathesis generated a 30% yield of the

---

(28) This is a typical reagent to generate Ru-H species that are responsible for the isomerization reaction. See reference 5.

spirotcyclic β-lactam 1.30 as a single isomer (Scheme 1.2.5.1). It is noteworthy that this result is the first demonstration of the use of the enallene moiety in RCM.

**Scheme 1.2.5.1** Preparation of spirotcyclic β-lactams through a tandem enallene isomerization/enyne RCM sequence

1.3 Metathesis/hydrogenation

In general, hydrogenation of a resulting C-C-double bond from olefin metathesis can be achieved by using an independent hydrogenation catalyst in a next step or in a single operation if the hydrogenation catalyst is compatible with the metathesis catalyst. Since ruthenium carbene complexes could be modified to catalyze hydrogenation reactions, only one precatalyst is needed for two distinct reactions, metathesis and hydrogenation. This has opened a new phase of a tandem metathesis/hydrogenation sequence.
1.3.1 RCM/hydrogenation

Schmidt and Pohler synthesized cyclopentanols from diallyl carbinols via a tandem ring closing metathesis/hydrogenation. The diallyl carbinols generated corresponding cyclopentenols with quantitative conversion using G2 in toluene monitored by TLC, followed by the addition of NaH and H₂. This tandem sequence produced the desired cyclopentanols in moderated yields (55-92%) (Table 1.3.1.1). With Grubbs first generation catalyst, however, diallyl carbinols suffered numerous drawbacks such as high requirement of catalyst loadings, long reaction times, elevated temperatures and unidentified byproducts in the metathesis step. In substrates containing secondary alcohols, a large excess NaH was required to activate the metathesis catalyst for the hydrogenation reaction, presumably because the deprotonation of the secondary alcohol is faster than the generation of Ru-H species to catalyze hydrogenation.

Table 1.3.1.1 Preparation of cyclopentanols through a tandem RCM/hydrogenation sequence

Cossy and colleagues reported the synthesis of pyrrolidine and tetrahydropyran derivatives via a tandem RCM/hydrogenation sequence (Scheme 1.3.1.1). The trialkylsilane was used as an additive to activate the metathesis catalyst to catalyze

hydrogenation. After completion of the RCM reaction of diallylamine by Grubbs first
generation catalyst in refluxing CH₂Cl₂, trialkylsilane was added to the reaction mixture
to catalyze hydrogenation reaction and generate the desired pyrrolidine derivative in 88%
yield (Scheme 1.3.1.1, eq 1). The authors also investigated the compatibility of the Grubbs
first generation in the presence of trialkylsilanes. The metathetic reactivity of G1 was
preserved in the presence of the trialkylsilane, and the desired pyrrolidine was obtained
with 76% yield (Scheme 1.3.1.1, eq 2). Under the same reaction conditions, the diallyl
ether generated desired tetrahydropyran in 75% yield though the tandem sequence
(Scheme 1.3.1.1, eq 3).

**Scheme 1.3.1.1** Preparation of the pyrrolidine and tetrahydropyran derivatives through a
tandem RCM/hydrogenation sequence

In a similar fashion, Schmidt and colleagues reported the synthesis of a
tetrahydropyran though a tandem sequence. During a study of the preparation of
camphor-derivatives via a tandem RCM/isomerization reaction, the authors found that the substrate underwent three different reactions in a tandem sequence: RCM, followed by isomerization, and lastly hydrogenation reaction (Scheme 1.3.1.2). The ratio of isomerization product to hydrogenation product revealed that the product distribution depends on the reaction time and temperature after the RCM step. The substrate gave incomplete conversion with shorter reaction time. At lower temperature (95 °C), the ratio between isomerization product and hydrogenation product was 2:1.

**Scheme 1.3.1.2** Preparation of tetrahydropyran through a tandem RCM/hydrogenation sequence

![Scheme 1.3.1.2](image)

Schmidt and colleagues also demonstrated the synthesis of chromanes via a tandem RCM/hydrogenation sequence.\(^{(32)}\) During the synthesis of 4H-chromenes using a RCM/isomerization sequence, the authors found that the substrates underwent RCM/hydrogenation instead of RCM/isomerization. Various substituted chromanes were synthesized using this RCM/hydrogenation sequence (Table 1.3.1.2). Under this protocol, 4-methyl-substituted chromanes, as well as the halogenated chromane were obtained in good yields (entries 3, 4 and 6). In contrast, the substrate possessing a nitro group yielded the reduced amine product (entry 5).

Table 1.3.1.2 Preparation of chromanes through a tandem RCM/hydrogenation sequence

![Diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Precursor</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td><img src="image" alt="Image" /></td>
<td>66%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
<td>82%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
<td>65%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
<td>83%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
<td>33%</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
<td>76%</td>
</tr>
</tbody>
</table>

The tandem ring closing metathesis/hydrogenation sequence has been applied to the synthesis of natural products. In 2003, Fürstner and colleagues used the tandem RCM/hydrogenation reaction in the synthesis of (R)-( +)-muscoryidine. The diene RCM precursor 1.31 was prepared via a sequential iron-catalyzed cross-coupling reaction (Scheme 1.3.1.3). The RCM proceeded using ruthenium-indenylidene Ru-6 under high dilution (0.006 M), followed by hydrogenation by subsequent addition of H\textsubscript{2} (50 atm) generated (R)-( +)-muscoryidine in 57 % yield. The authors also applied this tandem process to the synthesis of spermidine alkaloid (-)-isooncinotine using the same ruthenium-indenylidene Ru-6. The (-)-isooncinotine was obtained from compound

1.32 in 75% yield through RCM/hydrogenation using a single ruthenium precatalyst (Scheme 1.3.1.3).

**Scheme 1.3.1.3 Synthesis of (R)-(+)-muscopyridine and the isooncinotine using tandem RCM/hydrogenation sequence**

![Scheme 1.3.1.3 Synthesis of (R)-(+)-muscopyridine and the isooncinotine using tandem RCM/hydrogenation sequence](image)

For the synthesis of bistramide A, Kozmin and colleagues used one-pot, ring closing metathesis/hydrogenation to prepare the pyran fragment.\(^\text{(35)}\) To accomplish these transformations, the author used two distinct catalysts in a one-pot operation. The RCM reaction of diene 1.33 with G2 followed by hydrogenation using H\(_2\) and Pd/C catalyst yielded desired the lactone 1.34 in a yield of 72% (Scheme 1.3.1.4).

---

Another application of this method can be found in the synthesis of gaur acid.\textsuperscript{36} Evans and colleagues reported the synthesis of compound \textbf{1.36} using the tandem RCM/hydrogenation reaction. The precursor \textbf{1.35} for RCM was prepared by stereospecific allylic etherification with secondary alkenyl alcohols. The ring closing metathesis with G2 at 40 °C in dichloroethane followed by hydrogenation with subsequently added H\textsubscript{2} at 70 °C and deprotection of TBS group yielded the desired product \textbf{1.36} in 75% yield (Scheme 1.3.1.5).

The tandem RCM/hydrogenation protocol was also applied effectively to the synthesis of cyclic dinucleotides. The conformationally restricted cyclic dinucleotides were prepared by Nielsen and co-workers via the sequential metathesis/hydrogenation sequence for mimicking nucleic acid secondary structures. When the authors examined the synthesis using two independent reactions for formation of cyclic dinucleotides using Grubbs catalyst followed by hydrogenation with Pd/C, this led to hydrogenation of the double bond, as well as reductive cleavage of the phosphotriester linkage. This problem was solved by performing the hydrogenation with a Ru-hydride species generated in situ from the RCM catalyst. The RCM reaction was performed with G2 in refluxing CH$_2$Cl$_2$. After completion of the RCM reaction as detected by TLC, the reaction mixture was subjected to the hydrogenation under 1000 psi of H$_2$ at 50 °C to yield cyclic dinucleotide in 63% yield (Scheme 1.3.1.6, eq 1). The authors also applied this protocol to the synthesis of a cyclic dinucleotide with a butylene linker between the upper 2'-C position and the 3'-O-phosphate linkage. The cyclic dinucleotide was obtained as a mixture of two phosphorus epimers (48% of R and 17% of S) (Scheme 1.3.1.6, eq 2).

Ramharter and co-workers achieved the total synthesis of (+)-lycoflexine using a tandem enynene RCM/hydrogenation reaction. After enynene metathesis with G2, the ruthenium hydride was generated \textit{in situ} by treating the catalyst with H$_2$. The regioselective hydrogenation of the less substituted double bond of intermediate diene 1.37 in a tandem fashion generated tricyclic carbamate 1.38 in 52% yield (Scheme 1.3.1.7).

**Scheme 1.3.1.7** Synthesis of (+)-lycoflexine via tandem enynene RCM/hydrogenation process

1.3.2 CM/hydrogenation

Cossy and co-workers showed that the rate of cross-metathesis of an α,β-unsaturated ketone, carboxylic acid, or esters with allyl triphenylsilane by HG2 is faster than the rate of olefin hydrogenation by PtO$_2$ in the presence of hydrogen at room temperature.\(^\text{39}\) The saturated γ-silyl carbonyl compounds were obtained through the tandem sequence in 53-80% yields (Table 1.3.2.1). Without PtO$_2$, only metathesis product was obtained; HG2 with hydrogen did not catalyze the hydrogenation reaction under these conditions. However, with HG2 and Pd/C instead of PtO$_2$, the rate of hydrogenation is faster than metathesis producing the saturated compound of allyl triphenylsilane as the major product. The author expanded this protocol to the synthesis of substituted lactones and lactols.\(^\text{40}\) Cross-metathesis of allylic or homoallylic alcohols with acrylic acid using G1, PtO$_2$ and 1 atm of hydrogen followed by hydrogenation led to the hydroxyl acids. These resulting hydroxyl acids underwent cyclization to afford five-
and six-membered lactones in 45-70% yields (Table 1.3.2.2, eq 1). In the same way, lactols were also prepared by using acrolein instead of acrylic acid (Table 1.3.2.2, eq 2). This protocol produced lactones and lactols from both secondary and tertiary unsaturated alcohols. When tertiary alcohols were used as substrates, however, saturated alcohols were also observed. It is also noteworthy that the esterification of the acid is not catalyzed either by G1 or PtO₂ alone, but is catalyzed in the presence of the combination of the two complexes. This result could imply that the active catalyst for esterification is produced under the tandem reaction conditions.

**Table 1.3.2.1** Synthesis of ketone and esters via a tandem (orthogonal catalysis) CM/hydrogenation process

![Chemical reaction formula](image)

**Table 1.3.2.2** Synthesis of lactones and lactols via tandem (orthogonal catalysis) CM/hydrogenation process

![Chemical reaction formula](image)
Chapter 1 – Ruthenium Catalyzed Tandem and One-Pot Metathesis/Non-Metathesis Processes

The synthesis of diols using a tandem cross-metathesis/hydrogenation was reported by Dixneuf and colleagues.\(^{(41)}\) The undecylenic aldehyde that can be obtained from castor oil cracking underwent self-metathesis with HG2 in 50 °C toluene, followed by hydrogenation with 10 bar of H\(_2\) at the same temperature (50 °C) yielding the desired diol in 70% yield (Scheme 1.3.2.1, eq 1). In the same way, 1,12-dodecadiol was obtained with a yield of 72% via cross-metathesis of undecylenic aldehyde with acrolein followed by hydrogenation (Scheme 1.3.2.1, eq 2). The rate of the cross-metathesis of undecylenic aldehyde with acrolein is faster than self-metathesis and the relative rate of two cross-metatheses depends on the ratio of undecylenic aldehyde and acrolein in the reaction mixture. A saturated cyano ester was also synthesized via the tandem sequence (Scheme 1.3.2.1, eq 3).\(^{(42)}\) The cross-metathesis of 10-undecenenitrile with methyl acrylate was not sensitive to the reaction temperature; the cross-metathesis reaction was completed within 1 hour at room temperature and with toluene at 100°C. After the metathesis was completed with HG2 at room temperature, the hydrogenation was performed with subsequently added t-BuOK (30 mol %) and H\(_2\) (20 bar) at 80 °C to generate saturated cyano ester in 97% yield. When the amount of HG2 was increased to 3 mol %, the

saturated amino ester was obtained in 96% yield as a result of nitrile reaction. To achieve full conversion of the nitrile to the amine, tBuOK (more than 20 mol %) and HG2 (more than 3 mol %) was required; 15 mol % of tBuOK gave a mixture of saturated nitrile ester and amino ester and 1 mol % of HG2 gave only saturated nitrile ester.

Scheme 1.3.2.1 Synthesis of diols via a tandem CM/hydrogenation process

1.4. Metathesis/oxidation

1.4.1 RCM/oxidative aromatization

The serendipitous formation of pyrrole and furan as side reactions during the synthesis of pyrroline and dihydrofuran via ring closing metathesis reaction was reported. Stevens, et al. observed the same pyrrole formation in 2004. Particularly, they developed a tandem RCM/dehydrogenation sequence as a new synthetic method for pyrrole synthesis. Although the formation of pyrroline was more favorable, using Grubbs second generation catalyst at elevated temperatures (60 °C), the tandem sequence

generated a mixture of corresponding pyrroline and pyrrole. When RuCl$_3$·H$_2$O was added to the reaction mixture as a co-catalyst in the presence of G2, diallylamines were converted into the corresponding pyrroles in moderate yields (30-74%) at 60 °C in 1,2-dichloroethane (Table 1.4.1.1). To improve the efficiency of the reaction, an ultrasonic bath was utilized to obtain a fine dispersion of the catalyst and increase the catalyst’s active surface. The substrates with electron withdrawing groups on the nitrogen such as Tos, Boc, and Ac did not generate dehydrogenated products, but only the corresponding pyrrolines. Also, a Cl-substituted substrate produced no pyrrole product. The yield for forming pyrrole through the tandem sequence can be significantly improved by adding a hydrogen acceptor.$^{46}$ DDQ was examined initially as one of the hydrogen acceptors, however, the RCM product was not observed due to the loss of the activity of G2 in the presence of DDQ. This result implies that G2 and DDQ are incompatible. This issue was resolved by using tetrachloro-1,4-benzoquinone (chloranil).$^{46}$ The tandem RCM/oxidative aromatization produced a number of pyrroles in high yields under G2 and chloranil without RuCl$_3$·H$_2$O (Table 1.4.1.1).

Table 1.4.1.1 Preparation of pyrroles through a tandem RCM/dehydrogenation sequence with Ru-catalysts

In 2006, Stevens, et al. reported another synthetic method for the pyrrole synthesis.\textsuperscript{47} Aminoalkenyl phosphonates generated predicted pyrroles as a single reaction product under G2 and tetrachloroquinone (TCQ) at room temperature in CH\textsubscript{2}Cl\textsubscript{2}. Various types of pyrroles were synthesized in good yield (70-84\%) (Table 1.4.1.2). Dienes substituted at R\textsubscript{3} did not deliver and RCM product (entry 7). The catalysts G2 and TCQ were compatible with each other, but the RCM step needed reaction times as long as 16 hours in the presence of TCQ. This issue was overcome by adding TCQ to the reaction mixture after 2 hours since the RCM step proceeded to completion faster without TCQ (orthogonal catalysis). This orthogonal catalysis led to an effective reduction in reaction time by 5-7 hours. Although the dehydrogenation reaction could proceed without a ruthenium catalyst, it requires relatively longer reaction times (22 h) compared to when a ruthenium catalyst was present. The authors explained the role of G2 in the

dehydrogenation step; ruthenium coordinates with the hydrogen donor and acceptor, which accelerates the rate of the directed hydrogen transfer from the pyrrole to TCQ. It was also observed that ruthenium catalyzed ring closing metathesis and dehydrogenation in the presence of TCQ accelerate their reactions mutually. When phosphonates with a secondary amine were subjected to the sequential RCM/dehydrogenation reaction, pyrrole was obtained with less than 30% yield in the RCM step. Moreover, pyrrole generated no dehydrogenated product in a step by step sequence while deprotected secondary free amines were converted into the desired pyroles in a tandem sequence in 27-39% yield.

**Table 1.4.1.2** Preparation of 2-phosphopyrroles through a tandem RCM/dehydrogenation sequence

<table>
<thead>
<tr>
<th>entry</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>Bn</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Me</td>
<td>H</td>
<td>Bn</td>
<td>84</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>Bn</td>
<td>H</td>
<td>Bn</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>isooamyl</td>
<td>H</td>
<td>Bn</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>Ph</td>
<td>H</td>
<td>Bn</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>CH₂CH₂Ph</td>
<td>H</td>
<td>Bn</td>
<td>71</td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>H</td>
<td>Me</td>
<td>Bn</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>39</td>
</tr>
<tr>
<td>9</td>
<td>Ph</td>
<td>isoamyl</td>
<td>H</td>
<td>H</td>
<td>27</td>
</tr>
</tbody>
</table>

<sup>a</sup>In case of substrate 3, complete conversion to pyrrole was obtained after 5 h at reflux followed by 12 h at room temperature.
Microwave-assisted synthesis of pyrroles was reported by Xiao, et al.\textsuperscript{48} Microwave irradiation at 150 °C in CH\textsubscript{2}Cl\textsubscript{2} led to tandem ring closing metathesis/oxidative aromatization within 10 minutes in high yields (Table 1.4.1.3). No additive was required for the oxidation step. Oxidative aromatization could be catalyzed by either the metathesis catalyst or its decomposition species at high temperature. Another example of microwave-assisted pyrrole synthesis was demonstrated by Barrow, et al.\textsuperscript{49} They applied this protocol to a flow chemistry system.

Table 1.4.1.3 Preparation of pyrroles through a microwave-assisted RCM/dehydrogenation sequence

<table>
<thead>
<tr>
<th>R</th>
<th>Dehydrogenation product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH\textsubscript{3}</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td>OMe</td>
<td>89%</td>
<td></td>
</tr>
<tr>
<td>Cl</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>NO\textsubscript{2}</td>
<td>98%</td>
<td></td>
</tr>
</tbody>
</table>

Recently, Schmidt, et al. investigated the synthesis of pyrroles and furans using a tandem RCM/oxidative aromatization sequence.\textsuperscript{50} When the Grubbs first generation catalyst was treated with the oxidant \( t\)-BOOH, it was converted into a Ru-(IV)-oxo complex,\textsuperscript{51} which catalyzed the dehydrogenation of the resulting RCM product. They also observed that the oxidative aromatization could be catalyzed by the same Ru-(IV)-oxo complex. When an isolated RCM product was subjected to the dehydrogenation reaction with \( t\)-BOOH in the absence of Grubbs catalyst, the yield of pyrrole dropped to 55% after 15 hours at 20°C while the yield of pyrrole was 82% after 2 hours at 20°C in

\textsuperscript{(49)} Ahmed-Omer, B.; Barrow, D. A.; Wirth, T. \textit{Arkivoc} \textbf{2011}, iv, 26-36.
the presence of G2, t-BOOH and one equivalent of the radical scavenger 3,5-di-t-butyl-4-hydroxytoluene (BHT). This protocol led to an efficient RCM reaction in relatively high reaction concentration (1.0 M of toluene). The RCM of readily available diallyl amines with G1 in 1.0 M of toluene (20 °C), followed by addition of t-BOOH (1.3 equivalents) generated pyrroles in higher than 86% yield (Table 1.4.1.4). The yields revealed that substitution pattern on the N-aryl has a significant effect; in substrates having geminal substitution on R1 and R5 of the N-aryl, a deallylation product was obtained in a 27% yield along with unreacted diallyl starting material (35%) rather than RCM or dehydrogenation products. It is worth note that this protocol produces desired pyrroles with substrates having electron donating groups on the N-aryl as well as electronic withdrawing group which are known to have low reactivity in dehydrogenation.47 The substrates bearing a p-Tos on the N-aryl gave higher yields (62% to 77%) with slightly larger amounts of oxidant (1.3 to 2.0 equivalents) in benzene in lieu of toluene. With more than 2.0 equivalent of oxidant, however, decomposition of the pyrrole reduced the yield of desired product (50%). In the same fashion, furans were synthesized in good yields (Table 1.4.1.5). A similar tandem method particularly employing chloranil or DDQ as the oxidant was also reported.52

Table 1.4.1.4 Preparation of pyrroles through a tandem RCM/dehydrogenation sequence by Ru catalyst and an oxidant

\[
\begin{align*}
\text{Table 1.4.1.4} & \text{ Preparation of pyrroles through a tandem RCM/dehydrogenation sequence by Ru catalyst and an oxidant} \\
& \text{G1 or G2 (5 mol %), toluene or benzene (1.0 M), 20 °C, 0.5 h; t-BuOOH (70% in water, 1.3-2.0 equiv), 0.5 h} \\
\end{align*}
\]

\[
\begin{align*}
| \text{Pyrrole} | \text{Oxadiazole} | \text{AcHN} | \text{H}_2\text{CO} | \text{OCH}_3 | \text{Ac} | \\
| \text{O}_2\text{N} | \text{H}_3\text{C} | \text{H}_3\text{CO} | \text{H}_3\text{C} | \text{Me} | \text{F} | \\
| \text{86%} | \text{89%} | \text{55%} | \text{93%} | \text{87%} | \text{88%} | \\
| \text{77%} | \text{98%} | \text{90%} | \text{...} | \text{87%} | \text{92%} |
\end{align*}
\]

\(^a\) Reaction was performed in ethyl acetate, initial substrate concentration 0.5 M.
\(^b\) Unreacted diallyl starting material (35%) and monoallyl amine (27%) were isolated.
\(^c\) Initial substrate concentration was 0.1 M; RCM conducted at 80 °C, oxidative aromatization at 20 °C.

Table 1.4.1.5 Preparation of furans through a tandem RCM/dehydrogenation sequence

\[
\begin{align*}
\text{Table 1.4.1.5} & \text{ Preparation of furans through a tandem RCM/dehydrogenation sequence} \\
& \text{G1 (5 mol %), benzene (1.0 M), 20 °C, 0.5 h; t-BuOOH (70% in water, 1.3 equiv), 20 °C, 0.5 h} \\
\end{align*}
\]

\[
\begin{align*}
| \text{Furan} | \text{Benzofuran} | \text{Chromone} | \text{Cyclophan} | \\
| \text{R} | \text{O} | \text{O} | \text{O} | \\
| \text{65%} | \text{59%} | \text{52%} | \text{36%} | \text{27%} |
\end{align*}
\]
1.4.2 RCM/allylic oxidation

The synthetic method for the preparation of indenone, a key structural motif common in natural products, was reported by van Otterlo, et al. During the synthesis of indenol via a RCM reaction, they found out that indenol can be dehydrogenated under reaction conditions. Through further investigations, the reaction conditions were optimized for a highly selective process (Scheme 1.4.2.1). Using 5 mol % of G2 at room temperature in CH$_2$Cl$_2$ under inert atmosphere, indenol 1.39 was produced after 2 hours, whereas indenone 1.40 was isolated via a tandem RCM/dehydrogenation sequence at high temperature, 80 °C in toluene. When isolated indenol 1.39 was subjected to anaerobic conditions with G2 at 60 °C, the dehydrogenative oxidation reaction was promoted. This result suggested that the dehydrogenative oxidation takes place via a ruthenium-promoted redox isomerization.

Scheme 1.4.2.1 Selective preparation of indenol and indenone through a tandem RCM/dehydrogenative oxidation

---


In 2011, Schmidt and Krehl reported the synthesis of coumarins, a class of natural product rich in biological activity. Allyl ethers can be converted into the corresponding coumarins in decent yields though a tandem RCM/allylic oxidation reaction (Table 1.4.2.1). When the RCM reaction is completed with G1 in benzene (1.0 M), an oxidant was added to the reaction mixture. Higher concentration and tBuOOH as an oxidant were found to be most effective for the oxidation step. Moreover, the oxidation reaction occurred in the presence of aqueous tBuOOH with only a small decrease in yield (55% to 54% and 58% to 51%). The use of the Umicore M1 catalyst instead of G1 generated coumarins in almost the same yield (58% and 59%). The addition of NEt₃ increased the yields by driving the reaction to completion. This protocol could enable synthesis of various α, β-unsaturated lactones and lactams.

**Table 1.4.2.1 Synthesis of coumarins through a tandem RCM/allylic oxidation sequence**

![Coumarin structures](image)

<table>
<thead>
<tr>
<th>Coumarin</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structure 1" /></td>
<td>59%</td>
</tr>
<tr>
<td><img src="image" alt="Structure 2" /> OMe</td>
<td>55%</td>
</tr>
<tr>
<td><img src="image" alt="Structure 3" /> OEt</td>
<td>51%</td>
</tr>
<tr>
<td><img src="image" alt="Structure 4" /> MeO</td>
<td>40%</td>
</tr>
<tr>
<td><img src="image" alt="Structure 5" /> O₂N</td>
<td>63%</td>
</tr>
<tr>
<td><img src="image" alt="Structure 6" /> Br</td>
<td>61%</td>
</tr>
<tr>
<td><img src="image" alt="Structure 7" /> Br Me</td>
<td>50%</td>
</tr>
<tr>
<td><img src="image" alt="Structure 8" /> Me</td>
<td>39%</td>
</tr>
</tbody>
</table>

*NEt₃ (2.5 equiv.) was added after 3 hours, and the mixture was heated to 80 °C

*concentration = 0.1 M

In a similar fashion, Arisawa, et al. reported the synthesis of 2-quinolones though a RCM/oxidation sequence. During the preparation of 1,2-dihydroquinoline using RCM, they unexpectedly obtained 2-quinolone. They found out that the oxidation reaction is promoted by Ru-catalyst in the presence of an oxidant. The oxidation reaction produced only RCM product when the reaction was performed and purified in a glovebox so that the dihydroquinoline was not readily oxidized under an air or oxygen atmosphere. After further investigation of the formation of 2-quinolone, they found out that \( \text{t-BuOOH} \) is the best suited oxidant for this tandem sequence. The ring closing metathesis of 2-vinyl-N-allylaniline derivatives with 10 mol % of G2 in refluxing benzene for 30 minutes, followed by oxidation using \( \text{t-BuOOH} \) produced 2-quinolones in good yields (Scheme 1.4.2.2). Substitution in the 6-position gave lower yields of desired product because of steric influence. Other protecting groups on the N-atom were examined. The acetyl, mesyl and methoxy carbonyl groups on the N-atom were readily removed in the oxidation step to yield dehydrogenated quinolines without the protecting group. This protocol enables the synthesis of 2-quinolone derivatives which are important structural features found in numerous.

**Scheme 1.4.2.2** Selective preparation of 2-quinolones through a tandem RCM/oxidation

![Scheme 1.4.2.2](image_url)

1.4.3 Metathesis/hydroxylation

In 2006, Blechert, et al. reported a new tandem RCM/dihydroxylation sequence. The ruthenium-carbene complex was converted into ruthenium tetroxide to catalyze dihydroxylation reaction by YbCl$_3$·6H$_2$O and NaIO$_4$. The authors illustrated that the solvent system was critical in obtaining dihydroxylation products in high yields. A 3:3:1 mixture of MeCN/EtOAc/H$_2$O was the most efficient solvent in the oxidation step whereas CH$_2$Cl$_2$ produced lower yields of diol product. After ring closing metathesis reaction of the diene with G1 in refluxing CH$_2$Cl$_2$, the solvent was evaporated for the second step. The resulting residue was then dissolved in a 3:3:1 mixture of MeCN/EtOAc/H$_2$O and YbCl$_3$·6H$_2$O was added followed by NaIO$_4$ to produce cis-1,2-diols with high diastereoselectivities and in good yields (Table 1.4.3.1). In most cases, shorter reaction times led to higher yields in the dihydroxylation step. Also, substrates with electron-deficient double bonds produced higher yield of diol. Other ruthenium-carbenes, Ciba catalyst and Hoveyda-Grubbs first generation catalyst, also produced diol in similar yields to G1. However, the Grubbs second generation catalyst and HG2, both of which have NHC ligands, were ineffective in the dihydroxylation reaction due to slower formation of the ruthenium tetroxide. This protocol was used in a tandem cross-metathesis and dihydroxylation sequence. Instead of the Grubbs I catalyst, the Hoveyda-Grubbs II catalyst was used in this system to obtain higher yields in the CM reaction. However, the overall yields were lower, because the Hoveyda-Grubbs II catalyst was not as efficient as G1 in the hydroxylation step (Scheme 1.4.3.1).

**Table 1.4.3.1** Tandem RCM/dihydroxylation sequence using G1 as a precatalyst

![Scheme 1.4.3.1 Tandem CM/dihydroxylation sequence using HG1 as a precatalyst](image)

At the same time, another synthetic method for diols through a tandem RCM/dihydroxylation sequence was reported by Snapper, et al.\(^{58}\) The Grubbs II catalyst was modified to ruthenium tetroxide by CeCl\(_3\) and NaIO\(_4\) in order to catalyze the dihydroxylation. The use of EtOAc as a solvent in the RCM step made for a more practical protocol by eliminating additional removal of solvent for the dihydroxylation step. After completing RCM with G2 in EtOAc, the reaction mixture was added to a prepared suspension of NaIO\(_4\) and CeCl\(_3\)-7H\(_2\)O in MeCN/H\(_2\)O (6:1). Then, the mixture produced *cis*-dihydroxylated products with diastereoselectivity in good yields within 20 minutes (Table 1.4.3.2). This reaction also exhibited excellent diastereoselectivity when a

---

stereocenter was adjacently placed. On the contrary, when the stereogenic center was located at a distance from the reactive site, lower diastereoselectivity was observed. This sequence was applied to the synthesis of acyclic diols (Table 1.4.3.3). Substrates with trisubstituted olefins also produced desired diols in moderate yields. This protocol allows for the synthesis of five-, six-, and seven-membered cyclic diols as well as acyclic diols with a variety of functional groups.

**Table 1.4.3.2** Tandem RCM/dihydroxylation sequence using G2 as a precatalyst

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield</th>
<th>Diastereoselectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>HO-Ts</td>
<td>63%</td>
<td></td>
</tr>
<tr>
<td>HO-Ts</td>
<td>69%</td>
<td></td>
</tr>
<tr>
<td>HO-Ts</td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td>OAc</td>
<td>60% (22:1)</td>
<td></td>
</tr>
<tr>
<td>OBz</td>
<td>81%</td>
<td></td>
</tr>
<tr>
<td>Ts-NO2</td>
<td>77% (7:1)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1.4.3.3** Tandem CM/dihydroxylation sequence using Grubbs second generation catalyst

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>HO-OMe</td>
<td>77%</td>
</tr>
<tr>
<td>HO-OMe</td>
<td>50%</td>
</tr>
<tr>
<td>AcO</td>
<td>76%</td>
</tr>
<tr>
<td>Ph-OMe</td>
<td>51%</td>
</tr>
<tr>
<td>Ph-Cl</td>
<td>42%</td>
</tr>
</tbody>
</table>

By changing the oxidant, α-hydroxy ketones can be synthesized from the same starting materials in a tandem sequence. After completion of the RCM reaction in
EtOAc, the reaction mixture was diluted with MeCN/H$_2$O and then NaHCO$_3$ and Oxone were added to the reaction mixture in order to activate the ruthenium catalyst for an oxidation reaction. This process generated the desired $\alpha$-hydroxy ketones in 42-61% yield with moderate regioselectivity and excellent diastereoselectivity (Table 1.4.3.4). The diastereoselectivity was excellent; only one diastereomer was observed by $^1$H NMR, however regioselectivity was lower. This process can also be extended to the synthesis of acyclic $\alpha$-hydroxy ketones. Cross-metathesis followed by $\alpha$-ketohydroxylation produced desired products including $\alpha$-ketone-tertiary alcohols in 47-76% yields (Table 1.4.3.5). Similar to the RCM, the regioselectivity of oxidation was low (1:1 to 2:1). Several control experiments revealed that resulting $\beta$-ketoesters experienced isomerization under the basic oxidation conditions. When purified $\beta$-ketoester was subjected to the oxidation reaction conditions equilibration occurred.

Table 1.4.3.4 Tandem RCM/$\alpha$-ketohydroxylation sequence

![Reaction Scheme]

Table 1.4.3.4 Tandem RCM/$\alpha$-ketohydroxylation sequence
The synthesis of enationmerically enriched syn-diols through a tandem cross-
metathesis/dihydroxylation was reported by Plietker, et al. in 2008. After cross-
methathesis with ruthenium-carbene, the ruthenium tetroxide was generated in situ by
CeCl₃·H₂O and NaIO₄ to catalyze the oxidation reaction. For diastereoselective
dihydroxylation, a chiral auxiliary coupled to cinnamic acid was used rather than a chiral
ligand in order to induce chirality, because ruthenium tetroxide is a strong oxidant,
showing low stability at pH >7. Oxazolidinones as chiral auxiliaries allowed for
formation of desired diols in good yield, but with low diastereoselectivities (Scheme
1.4.3.2, eq 2) which is similar to Oppolzer’s camphosultam (Scheme 1.4.3.2, eq 1).
When the carbonyl of the oxazolidinones was substituted for SO₂, the diastereoselectivity
was significantly increased up to 12.0:1.0 (Scheme 1.4.3.2, eq 3). The yield of the
dihydroxylation step can be improved by exchanging the chloride ligand by catalytic
amounts of Bu₄NIO₄ prior to the addition of NaIO₄. Unusually, the electron rich olefin
was used in excess rather than the less electron rich olefin, because the less electron rich
olefin introduced chiral auxiliary is enantiopure. By using dilution, homocoupling

between excess electron rich olefins can be avoided. Several ruthenium catalysts were examined for this process. G1 and HG1 yielded homocoupling products as the major products in the metathesis step while HG2 and NHC-Grela catalysts generated desired metathesis products in high yields (89% and 90%, respectively). Because NHC-Grela catalyst is inefficient in the dihydroxylation step as much as efficiency of HG2, the reaction conditions were optimized with HG2. The cross-metathesis with HG2 in refluxing ethyl acetate followed by asymmetric dihydroxylation produced various diols in good yields and high enantiomeric excess (Table 1.4.3.6). It is remarkable that kinetic resolution of the two stereoisomers was observed during methanolysis, which enables the generation of enantiomerically enriched syn-diols.

Scheme 1.4.3.2 Diastereoselective dihydroxylation using auxiliaries

\[
\begin{align*}
\text{Ph-} & \text{CH}=\text{CH-} & \text{N} & \text{O} & \text{S} & \xrightarrow{\text{RuO}_4 \ 87\%} & \text{Ph-} & \text{CH}=\text{CH-} & \text{N} & \text{O} & \text{S} \\
d.r. & 1.0 & : & 4.6 \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph-} & \text{CH}=\text{CH-} & \text{N} & \text{O} & \text{H}_3\text{C-} & \xrightarrow{\text{RuO}_4 \ 87\%} & \text{Ph-} & \text{CH}=\text{CH-} & \text{N} & \text{O} & \text{H}_3\text{C-} \\
d.r. & 4.1 & : & 1.0 \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph-} & \text{CH}=\text{CH-} & \text{N} & \text{O} & \text{H}_3\text{C-} & \xrightarrow{\text{RuO}_4 \ 87\%} & \text{Ph-} & \text{CH}=\text{CH-} & \text{N} & \text{O} & \text{H}_3\text{C-} \\
d.r. & 12.0 & : & 1.0 \\
\end{align*}
\]
Table 1.4.3.6 Preparation of enantiomerically enriched 1,2-diols via tandem sequence

![Chemical Structure]

1. HG2 (2.5-5 mol %), EIOAc, reflux, 12 h then; Bu₃NI₂O₄ (5 mol %), CeCl₃·7H₂O (20 mol %), NaIO₄ (2 equiv.), MeCN/acetone/H₂O (3:3:1), 0 °C, 30 min;
2. MeMgBr, MeOH, 0 °C, 10 min

Plietker, et al. applied the cross-metathesis/dihydroxylation sequence to the synthesis of anthopleurine, a subunit of a larger polypeptidic structure (Scheme 1.4.3.3). Cross-metathesis of 1,4-dichlorobut-2-ene 1.41 with sulfamidate 1.42 or sultame 1.44 substituted olefins, followed by diastereoselective dihydroxylation and then methanolysis with MeMgBr, generated enantiomerically enriched syn-diols 1.43 and 1.45. The substitution of chloride by trimethylamine and then saponification produced desired products, anthopleurine and ent-anthopleurine, in 87% yield. This protocol allows for the synthesis of anthopleurine in three steps.

Scheme 1.4.3.3 Synthesis of anthopleurine and ent-anthopleurine via a tandem CM/dihydroxylation

Ruthenium catalyzed tandem CM/dihydroxylation was used in the synthesis of the bis-tetrahydropyran core of amphidinol 3.\textsuperscript{62} Ring closing metathesis of diene 1.46 with G1 followed by dihydroxylation with YbCl$_3$·6H$_2$O and NaIO$_4$ and then acetal protection of the resulting diol generated the desired tetrahydropyran 1.47 in 73% yield over 3 steps as a 5:1 mixture of diastereomers (Scheme 1.4.3.4). This sequence enables the preparation of tetrahydropyran intermediates in multigram scale.

**Scheme 1.4.3.4** Synthesis of the tetrahydropyran intermediate of amphidinol 3 using tandem CM/dihydroxylation

1.5 Metathesis/cyclization

Efficient synthesis of complex poly-heterocyclic compounds has been reported through tandem metathesis cyclization sequences. This allows for a rapid access to high levels of molecular complexity.

1.5.1 CM/aza-Michael reaction

In 2007, Fustero, et al. demonstrated the first tandem cross-metathesis/intramolecular aza-Michael reaction. This reaction is particularly useful as a method to generate β-amino carbonyls. In their work, the authors noted the importance of reaction

---

temperature. In refluxing CH$_2$Cl$_2$, no tandem adduct was observed by G1, and only 3% of tandem product was detected with HG2. However, at elevated temperatures, the tandem product was increased to 21% by G2. The yield was significantly increased by adding BF$_3$·OEt$_2$ which is compatible with HG2. The tandem RCM/aza-Michael reaction with 5% of HG2 and BF$_3$·OEt$_2$ in refluxing CH$_2$Cl$_2$ for 4 days generated the desired β-amino carbonyl in 60-99% yields (Table 1.5.1.1). Furthermore, the reaction time was dramatically decreased to 20 minutes by additionally using microwave irradiation. This protocol was applied to the synthesis of enantiomerically enriched substituted amines to produce products in high yields and moderate diastereoselectivities (Table 1.5.1.2). Notably, the stereochemistry of the final product was favored as the trans isomer under thermal reaction conditions, whereas cis isomer was prepared under microwave irradiation.

**Table 1.5.1.1** Preparation of cyclic β-amino carbonyl derivatives through a tandem CM/aza-Michael reaction

\[
\begin{align*}
\text{R1} & \quad \text{R2} & \quad \text{R3} & \quad \text{R4} \\
\text{Me} & \quad 99 (96) & \quad & \\
n-\text{Pr} & \quad 73 (65) & \quad & \\
n-\text{Pn} & \quad 81 (70) & \quad & \\
\text{Me} & \quad 82 (93) & \quad & \\
n-\text{Pr} & \quad 79 (72) & \quad & \\
n-\text{Pn} & \quad 83 (61) & \quad & \\
\end{align*}
\]

*In brackets are the yields obtained when the reaction was performed under microwave irradiation.*
Table 1.5.2 Tandem CM/aza-Michael reaction with enantiomerically enriched substituted amines

\[
\begin{array}{cccc}
\text{Me} & \text{O} & + & \text{CH}_2=\text{CH}-\text{NR}^+\text{C}_2\text{H}_4\text{NH}-\text{Cbz} \\
\rightarrow & \downarrow & \downarrow & \downarrow \\
& & \text{HC} & \text{G}_2 \text{ (5 mol %), BF}_3\cdot\text{OEt}_2 \text{ (1 mol l %)} \\
& & \text{DCM, 45 °C, 4 days or microwave} \\
\end{array}
\]

<table>
<thead>
<tr>
<th>R</th>
<th>% yield (A:B)</th>
<th>% yield (A:B) (μwave)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i-Pr</td>
<td>97 (3:1)</td>
<td>81 (1:4)</td>
</tr>
<tr>
<td>Ph</td>
<td>98 (6:1)</td>
<td>86 (1:2)</td>
</tr>
<tr>
<td>PMP</td>
<td>78 (4:1)</td>
<td>97 (1:2)</td>
</tr>
<tr>
<td>CF₃</td>
<td>76 (5:1)</td>
<td>97 (1:3)</td>
</tr>
</tbody>
</table>

Fustero, et al. further investigated cross-metathesis/aza-Michael reaction to generate chiral β-amino carbonyl compounds. The N-sulfinyl amine was used as a nitrogen source and a stereochemical controller. The cross-metathesis of N-sulfinyl amine with methyl vinyl ketone followed by cyclization with HG2 and Ti(iPrO)₄ in refluxing CH₂Cl₂ afforded pyrrolidine-derived adducts in high yields (R = p-Tol, 95% and R = t-Bu, 92%) and diastereoselectivities (Table 1.5.3). Unlike the pyrrolidine formation, however, cyclization of the six-membered ring occurred in low yields (R=pTol, 30% and R=tBu, 22%). It was observed that the p-tolyl group and t-buthyl group on N-atom generated different stereochemical outcomes. The authors noted that a π-stacking interaction between the p-tolyl group and the α,β-unsaturated ketone resulted in different stereochemical outcome from t-butyl group substituted substrate that takes only steric effects into consideration.

Table 1.5.1.3 Tandem CM–aza-Michael reaction of N-sulfinyl amines and methyl vinyl ketone

\[
\begin{align*}
\text{HN}_R^N + \text{MeO} & \xrightarrow{\text{HG2 (10 mol %), Ti(iPrO)4 (10 mol %)}} \text{MeO} \quad \text{CH}_2\text{Cl}_2, \text{reflux, 48 h} \\
\text{O}_n^+ R & \quad \text{MeO} \\
\text{HN} \quad \text{MeO} \quad \text{CH}_2\text{Cl}_2 & \quad \text{HN} \quad \text{MeO}
\end{align*}
\]

\[
n=1, R = \rho\text{Tol} \\
\text{fBu} & \quad 95\% (89:11) \\
92\% (8:92) \\

n=2, R = \rho\text{Tol} \\
\text{fBu} & \quad 30\% (70:30) \\
22\% (24:76)
\]

The authors also developed a synthetic method for fluorinated γ- and δ-lactams using a tandem CM/intra molecular aza-Michael reaction.\(^6^5\) Cross-metathesis of methyl vinyl ketone with fluorinated amides with HG2 in the presence of titanium(IV) tetraisopropoxide generated the CM products, followed by intra molecular aza-Michael reaction which produced fluorine-containing heterocycles in moderated yields (Table 1.5.1.3, eq 1). Ethyl acrylate as a cross-metathesis partner, however, did not produce the desired lactams with this tandem sequence, but produced only CM products. Asymmetric synthesis of fluorinated lactams was also examined; Enders SAMP hydrazone was used as a chiral auxiliary. The auxiliary attached amide yielded fluorinated lactams though a tandem CM/aza-Michael reaction with decent yields but low stereoseletivity (Table 1.5.1.3, eq 2). This tandem CM/aza-Michael protocol allows for the preparation of N-heterocycles exhibiting intriguing biological properties in a simple manner.

Table 1.5.1.3 Preparation of fluorinated γ- and δ-lactams through a tandem CM/aza-Michael reaction

\[
\begin{align*}
\text{F} & \quad \text{O} & \quad \text{N} & \quad \text{R} & \quad \text{HG2 (5 mol %)} & \quad \text{Ti(Oi-Pr)}_4 (10 \text{ mol %}) & \quad \text{CH}_2\text{Cl}_2, \text{reflux} \\
\text{F} & \quad \text{O} & \quad \text{Me} & \quad \uparrow & \quad \text{Me} & \quad \text{eq 1} & \\
\text{n} & \quad 1, & \quad R = \text{PMP} & \quad 61\% & \quad \text{OMe} \quad 58\% \\
\text{n} & \quad 2, & \quad R = \text{PMP} & \quad 51\% & \quad \text{OMe} \quad 49\%
\end{align*}
\]

\[
\begin{align*}
\text{F} & \quad \text{O} & \quad \text{N} & \quad \text{SAMP} & \quad \text{HG2 (5 mol %)} & \quad \text{Ti(Oi-Pr)}_4 (10 \text{ mol %}) & \quad \text{CH}_2\text{Cl}_2, \text{reflux} \\
\text{F} & \quad \text{O} & \quad \text{Me} & \quad \uparrow & \quad \text{Me} & \quad \text{eq 2} & \\
\text{n} & \quad 1, & \quad 58\% \quad (51:49 \text{ dr}) \\
\text{n} & \quad 2, & \quad 51\% \quad (59:41 \text{ dr})
\end{align*}
\]

Cho, et al. reported that the tandem cross-metathesis/intramolecular aza-Michael reaction was applied to the synthesis of key intermediates 1.50 for pyrrolopiperazinone natural products.\(^6\) Pyrrolopiperazinone is an important skeleton that is present in a class of marine natural products with interesting biological activities.\(^7\) The cross-metathesis of acrolein 1.49 with pyrrole 1.48 containing a chiral auxiliary that controls the asymmetric aza-Michael reaction was performed. Then, the resulting CM adduct was subjected to aza-conjugate addition to give the tandem product in a 56% yield with 3.3:1 diastereoselectivity (Scheme 1.5.1.1). This key intermediate leads to access

pyrrolopiperazinone natural products such as hanishin,\textsuperscript{68a} longamide B,\textsuperscript{69} long amide B methyl ester,\textsuperscript{68a} agesamides\textsuperscript{69} and cyclooroidin\textsuperscript{68b} in a few more steps.

**Scheme 1.5.1.1** Tandem CM/intramolecular aza-Michael addition for asymmetric formal synthesis of pyrrolopiperazinone natural products

Another example using a tandem CM/aza-Michael reaction was reported in the synthesis of the alkaloid *cis*-223B by Stockman, et al.\textsuperscript{70} The cross-metathesis of readily available aminodialkene 1.51 with 1-peneten-3-one 1.52 using GH2 gave the metathesis product 1.54 in a 34% yield as well as the aza-Michael adduct 1.53 in a 62% yield (Scheme 1.5.1.2). The cyclization reaction can be catalyzed by ruthenium species derived

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\textsuperscript{(69)} Trost, b. M.; Dong, G. *Org. Lett.* 2007, 9, 2357-2359.

from decomposition of HG2. This sequence allows for access to the alkaloid cis-223B in an efficient manner.

**Scheme 1.5.1.2** Tandem CM/intramolecular aza-Michael addition for pyrrolizidine alkaloid cis-233B

1.5.2 CM/oxa-Michael reaction

In a similar fashion, tandem cross-metathesis/oxa-Michael addition was investigated by Fuwa, et al. Microwave-assisted tandem cross-metathesis of a hydroxyl alkene and an enone with HG2 at 100°C in CH₂Cl₂, followed by oxa-Michael addition generated diverse substituted tetrahydropyrans in good to excellent yields with high diastereoselectivity (Table 1.5.2.1, eq 1 and 2). This tandem process was catalyzed by only HG2 without other catalysts or additives. At lower temperature (35°C in CH₂Cl₂), no tandem product was observed. By performing several control experiments, it was revealed that the ruthenium hydride species that resulted from decomposition of HG2 under high temperature conditions catalyzed the cyclization step and, thus, the cyclization reaction was retarded in the presence of 2,6-dichloro-1,4-benzoquinone. With a subtle change on reaction conditions, the substrate scope and yield for this tandem sequence

could be significantly enhanced\textsuperscript{72} by using toluene as a solvent instead of CH\(_2\text{Cl}_2\). The yield and diastereoselectivity of the tandem product were improved and various substrates were tolerated (Table 1.5.2.1 eq 3), although the reaction time for completion of conversion was increased. Therefore, a Brønsted acid was used to accelerate the tandem process. The tandem CM/oxa-Michael reaction occurred even at room temperature by HG2 in the presence of CSA to give the desired 2,6-cis-substituted tetrahydropyran derivatives in 48-80% yields with excellent diastereoselectivity (normally > 20:1 dr). To prove that the active catalyst is a ruthenium hydride species as previously suggested\textsuperscript{71,72} in cyclization, mechanistic investigations were carried out. Several commercially available ruthenium hydride complexes were used in the cyclization reaction of δ-hydroxy α,β-unsaturated ketone. The RuH\(_2\)(PPh\(_3\))\(_4\) catalyzed cyclization in refluxing THF gave the desired product in a 78% yield and with 8:1 ratio diastereoselectivity. Also, RuClH(CO)(PPh\(_3\))\(_4\) or RuH\(_2\)(CO)(PPh\(_3\))\(_3\) afforded cyclized adducts in moderate yields (45% and 55%, respectively). Taken together, ruthenium hydride species can be an active catalyst in cyclization reaction.

**Table 1.5.2.1** Preparation of tetrahydropyrans through a tandem CM/oxa-Michael reaction


65
Another microwave-assisted tandem cross-metathesis/cyclization was studied by Cossy, et al.\textsuperscript{73} The cross-metathesis of γ,δ-unsaturated β-ketophosphonate with functionalized olefins produced metathesis adducts and the resulting products underwent a 1,4-addition to generate the desired cyclized products in moderate to excellent yields (Table 1.5.2.2). The formation of tetrahydropyrans occurred in better yields and diastereoselectivity as compared to the formation of tetrahydrofurans. The cyclization reaction was catalyzed either by ruthenium methylidene complex as a Lewis acid or a ruthenium hydride species derived from the thermal decomposition of HG2 without additives. High reaction temperatures of 100°C with microwave irradiation were required to produce cyclized products, whereas at room temperature, only CM product was

generated in a relatively low yield. Importantly, the resulting tandem products, β-ketophosphonates, can be further functionalized by Horner-Wadsworth-Emmons reaction. This protocol can be also applied to the preparation of pyrrolidine substituted β-ketophosphonates via CM/aza-Michael addition.

*Table 1.5.2.2* Preparation of β-ketophosphonates through a tandem CM/oxa-Michael reaction

<table>
<thead>
<tr>
<th>Process</th>
<th>Molecule</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>HG2 (2 X 5 mol %), CH2Cl2, 100 °C (iW), 2 X 15 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 1, 54%</td>
<td>R = Ph, quant.; &gt;3:2 (cis:trans)</td>
<td>77%</td>
</tr>
<tr>
<td>n = 2, 46%</td>
<td>R = Ph, C6H11, 80%; &gt;98:2 (cis:trans)</td>
<td></td>
</tr>
</tbody>
</table>

Fuwa, et al. applied the tandem CM/oxa-Michael addition\(^{(74)}\) to the synthesis of (±)-centrolobine.\(^{(74)}\) The cross-metathesis of a α,β-unsaturated ketone \(^{1.56}\) derived from commercially available p-benzyloxybenzaldehyde and a hydroxyl alkene \(^{1.55}\), followed by cyclization, gave 2,6-*cis*-disubstituted tetrahydropyran \(^{1.57}\) in a 74% yield (Scheme 1.5.2.1). The tandem process allowed for the synthesis of (±)-centrolobine in only four linear steps. The authors also applied the tandem protocol to the synthesis of (-)-exiguolide (Scheme 1.5.2.2).\(^{(75)}\) By using microwave irradiation, HG2 catalyzed cross-metathesis of a hydroxyl alkene \(^{1.58}\) with a ketone \(^{1.59}\) led to silyloxy ketone intermediates \(^{1.60}\). Then, the resulting β-ketone disubstituted tetrahydropyran \(^{1.60}\) was

treated with BF$_3$·OEt$_2$ and Et$_3$SiH without purification in order to generate methylene bis(tetrahydropyran) 1.61 in a 89% yield and with 10:1 diastereoselectivity. This tandem process can lead to complex building blocks from readily available fragments in a concise fashion.

**Scheme 1.5.2.1** Tandem CM/oxa-Michael reaction for the synthesis of (±)-centrolobine

![Scheme 1.5.2.1](image)

**Scheme 1.5.2.2** Tandem CM/oxa-Michael reaction for synthesis of (-)-exiguolide

![Scheme 1.5.2.2](image)

Hong, et al. synthesized SCH 351448 that exhibits efficacy of cholesterol-lowering using a tandem CM/oxa-Michael reaction.$^{76,77}$ The cross-metathesis of compound 1.62

and (E)-crotonaldehyde 1.63 followed by cyclization with HG2 afforded 2,6-cis-tetrahydropyran aldehyde 1.64 in 60-77% yields and with 4-5:1 diastereoselectivity (Scheme 1.5.2.3). This tandem sequence does not require any co-catalyst or additive to activate the nucleophile or α,β-unsaturated aldehyde. After an aldol reaction, one more tandem oxidation/oxa-Michael reaction, and Suzuki coupling, SCH 351448 was obtained.

**Scheme 1.5.2.3** Preparation of 2,6-cis-tetrahydropyran aldehyde via tandem CM/oxa-Michael reaction for synthesis of SCH 351448

1.5.3 CM/conjugate addition

A ruthenium catalyzed tandem cross-metathesis/intramolecular hydroarylation sequence was demonstrated by Xiao, et al. The cross-metathesis of indolyl alkenes and α,β-unsaturated ketones followed by cyclization afforded the desired products in excellent yields with HG2 in DCE at 80°C (Table 1.5.3.1). This protocol was tolerant of various substrates as well as variations in the electronic contribution of the indole ring. Both N-methyl and free N-H substrates were suitable for this tandem process. Both

methyl vinyl ketone and ethyl acrylate as cross-metathesis partners afforded corresponding tandem adducts in 98% and 95% yields, respectively. Moreover, the substrates containing oxygen and nitrogen atoms in the alkenyl chain generated the desired products in 74% and 85% yields under this tandem sequence. 3-alkenyl substituted indoles also generated the tandem product in a 80% yield (Scheme 1.5.3.1, eq 1). It was observed that an actual active catalyst in hydroarylation step can be a ruthenium methylidene complex resulting from the initiation of the CM process. When the purified cross-metathesis product was subjected to hydroarylation reaction with or without HG2, no cyclization product was observed. On the other hand, when the purified cross-metathesis product was subjected to crotonaldehyde and N-methyl indolyl alkene under HG2, cyclized products were isolated\(^{79}\) (Scheme 1.5.3.1, eq 2). This cross-metathesis was catalyzed by HG2 and the cyclization was catalyzed either by ruthenium methylidene complex or ruthenium hydride species generated from the thermal decomposition.

\(^{79}\) The same result was reported in the following reference: Fuwa, H.; Noto, K.; Sasaki, M. *Org. Lett.* 2010, *12*, 1636-1639.
Table 1.5.3.1 Ru-catalyzed tandem CM/intramolecular-hydroarylation sequence

<table>
<thead>
<tr>
<th>R_1</th>
<th>R_2</th>
<th>R_3</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Me</td>
<td></td>
<td>82%</td>
</tr>
<tr>
<td>Me</td>
<td></td>
<td></td>
<td>95%</td>
</tr>
<tr>
<td>Cl</td>
<td>Me</td>
<td></td>
<td>86%</td>
</tr>
<tr>
<td>Me</td>
<td></td>
<td></td>
<td>95%</td>
</tr>
<tr>
<td>Me</td>
<td>OMe</td>
<td></td>
<td>98%</td>
</tr>
<tr>
<td>Me</td>
<td></td>
<td></td>
<td>99%</td>
</tr>
<tr>
<td>Me</td>
<td></td>
<td></td>
<td>95%</td>
</tr>
</tbody>
</table>

* 10 mol % BF₃·Et₂O was added

Scheme 1.5.3.1 Tandem CM/intramolecular hydroarylation sequence

The authors also demonstrated that the tandem cross-metathesis/intramolecular-hydroarylation could be extended to an enantioselective sequence.⁸⁰ The chiral imidazolidinone 1.66 was used as an organocatalyst. After cross-metathesis of ω-indolyl

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alkene with crotonaldehyde, the imidazolidinone 1.66 and trifluoroacetic acid were added. This tandem process generated corresponding hydroarylation products in 65-88% yields and with 84-91% enantioselectivity (Table 1.5.3.2).

**Table 1.5.3.2 Enantioselective CM/intramolecular hydroarylation sequence**

Stereoselective synthesis of α-spirolactones and α–spirolactams via CM/Michael addition was investigated by Rodriguez, et al.\(^81\) After ruthenium catalyzed CM reaction, additives were added to the CM reaction mixture to generate an active catalyst for cyclization. First, they examined phosphines as an additive, based on a previous report.\(^82\) When the tributylphosphine was added to the reaction mixture after completion of the CM reaction of compound 1.67 with acrylonitrile 1.68, the desired tandem product 1.70 was produced in a 60% yield (Scheme 1.5.3.2, eq 1). On the other hand, the purified CM product 1.69 was not effected either by tributylphosphine or tributylphosphine in the presence of G1 (Scheme 1.5.3.2, eq 2). This result illustrates that tributylphosphine acts as a competing ligand to generate an *in situ* active promoter of the spirocyclization. The active catalyst for cyclization could be a ruthenium-phosphine complex or the metal free

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N-heterocyclic carbene (NHC). Significantly, the authors also found that the SIMes (generated from 1.71 and KHMDS) catalyzed CM product 1.69 to generate spirolactone 1.70 in a 85% yield as a single diastereomer (dr > 20:1). Moreover, the NHC Ipr 1.72 afforded the desired spirolactone 1.70 in a 97% yield (Scheme 1.5.3.2, eq 2). This protocol was extended to various substrates. Microwave assisted cross-metathesis of homo-allyl ester and acrylonitrile in the presence of HG2 followed by Michael addition of CM adduct under tributylphosphine or NHC i-Pr 1.72, generated α-spirolactones and α–spirolactams in decent yields (Table 1.5.3.3). To understand the catalytic cycle of a Michael-induced spirocyclization, the involvement of basic properties of NHC to generate the enolate was examined. The reaction of CM product 1.69 with catalytic amount DBU generated a cyclized product as a minor component, whereas stoichiometric amounts of other bases such as K₂CO₃, i-Pr₂EtN, t-BuOK and KHMDS led to a very low conversion (<5%). The authors accounted for the cyclization step involving the nucleophilic properties of NHC. To clearly understand the function of NHC in the cyclization step, however, further experiments data would be necessary. The synthesis of α-spirolactones and α–spirolactams was extended to starting materials from 2-diazo-1,3-diketones 1.73. A Wolff rearrangement of 2-diazo-1,3-diketones 1.73/α-oxo ketene trapping with 1.74 led to a CM precursor, followed by the CM/Michael reaction generating α-spirolactones and α–spirolactams in a single reaction vessel (Table 1.5.3.3).

Scheme 1.5.3.2 Tandem or sequential CM/Michael spirocyclization

Table 1.5.3.3 Synthesis of α-spirolactones and α-spirolactams via tandem CM/Michael addition

Method A: CM/Michael reaction. Starting from 1.75, n-Bu3P was used in cyclization step.
Method B: CM/Michael reaction. Starting from 1.75, NHC i-Pr was used in cyclization step.
Method C: Wolff rearrangement/α-oxo kenele trapping/CM/Michael reaction. Starting from 1.73, NHC iPr was used in cyclization step.
1.5.4 CM/conjugate addition/cyclization

Schmidt, et al. reported the synthesis of γ-butyrolactone though a tandem CM/conjugate addition/lactonization sequence. A cross-metathesis of lactone 1.76 with a methyl acrylate 1.77 under G2 and phenol generated a CM adduct 1.78. The resulting CM product was subsequently subjected to the conjugate addition and lactonization (Scheme 1.5.4.1). The reaction concentration was highly correlated with the yield of metathesis. In most cases, the concentration between 0.05 and 0.5 M generated higher yield, while high reaction concentration (>1.0 M) led to lower yields of desired products along with other byproducts. The addition of phenol increased the yield of CM product as seen in previous reports.

Scheme 1.5.4.1 Tandem CM/conjugate addition/lactonization

1.5.5 RCM/isomerization/cyclization

Nelson and colleagues described a new process combining ring closing metathesis/olefin isomerization/N-acyliminium cyclization sequence. Reactive N-acyliminium intermediates resulting from RCM/isomerization can be cyclized by a

---

tethered nucleophile to generate a polycyclic ring system (Scheme 1.5.5.1). The HG1 was recognized as the most efficient catalyst in this tandem sequence. Utilizing HG1 in refluxing m-xylene, tandem adducts were afforded in 64-100% yields (Table 1.5.5.1). At lower temperature (60°C), however, only a metathesis product was observed. When the purified metathesis product was subjected to HG1, the cyclized product was produced quantitatively within 5 hours. On the other hand, without catalyst, the RCM product only generated 50% of the cyclized product together with 50% of the RCM product. In addition, TFA or BF$_3$·Et$_2$O accelerated the formation of cyclization products. In the presence of 1-2% TFA or BF$_3$·Et$_2$O, diene produced the cyclized product within 1 hour.

From these results, the authors hypothesized that the function of active ruthenium catalyst in nonmetathetic steps can be a Lewis acid rather than involving ruthenium hydride species in these substrates. This protocol was also extended to tethered heteroatom nucleophiles as well as intermolecular addition instead of intramolecular cyclization. This protocol allows for the synthesis of tetrahydro-β-carboline from readily available starting materials.

**Scheme 1.5.5.1 Tandem RCM/isomerization/N-acyliminium cyclization**
An enantioselective version of this RCM/isomerization/cyclization method was reported by You, et al. The use of a chiral phosphoric acid (CPA) enabled the synthesis of enantioenriched indolizinoindoles in good yields and with high enantioselectivities (Table 1.5.5.2). The authors found that the reaction was not sensitive to moisture and higher temperatures allowed for better yields with shorter reaction times. The purified RCM product could be cyclized with 5 mol % of chiral phosphoric acid. This reveals that the N-acyl iminium cyclization is mainly catalyzed by chiral Brønsted acid.

Table 1.5.5.2 Enantioselective synthesis of tetrahydro-β-carboline using tandem RCM/isomerization/cyclization

In a similar manner, the formation of oxazabicyclooctane system from N-alkyliminium ions was reported by Nielsen, et al.\textsuperscript{81, 87} Tandem ring closing metathesis/olefin isomerization products were subsequently trapped by the tethered $O$-nucleophile generated oxazabicyclooctanes in moderate to good yields (Table 1.5.5.3). The purified RCM products were not converted under thermal conditions if a catalyst was absent.

Table 1.5.5.3 Tandem RCM/isomerization/cyclization for preparation of oxazabicyclooctanes

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>82%</td>
</tr>
<tr>
<td></td>
<td>41%</td>
</tr>
<tr>
<td></td>
<td>68%</td>
</tr>
<tr>
<td></td>
<td>85%</td>
</tr>
<tr>
<td></td>
<td>64%</td>
</tr>
</tbody>
</table>

1.6 Metathesis/atom-transfer radical addition

In 1999, Snapper, et al. discovered that Grubbs first generation catalyst can serve as a catalyst for Kharasch addition.\textsuperscript{88} The authors isolated a metal-catalyzed Kharash addition product instead of a metathesis product during the metathesis study. This serendipitous discovery triggered the investigation of ruthenium alkylidene promoted atom transfer radical addition (ATRA). Moreover, it offered a unique opportunity for the development of a new tandem metathesis/ATRA reaction.


1.6.1 RCM/Kharasch reaction

Examples of tandem metathesis/ATRA reactions were described by Snapper, et al in 2005. The ring closing metathesis at room temperature by G1 followed by intramolecular Kharasch addition at elevated temperature generated various bicyclic ring systems (Table 1.6.1.1). This led to two new carbon-carbon bonds and one carbon-halogen bond as well as three highly controlled stereogenic centers that support an atom transfer radical mechanism; another possible pathway is a ruthenium catalyzed oxidative addition/reductive elimination sequence. The Kharasch addition allowed for the installation of a 5-membered lactam as well as a 6-membered lactam while the formation of 7-membered rings was not observed. This protocol was extended to include intermolecular Kharasch additions (Scheme 1.6.1.1, eq 2) and it further enabled tandem RCM, intra- and intermolecular Kharasch additions (Scheme 1.6.1.1, eq 3) that can generate five new bond changes in one operation. This tandem protocol resulted in highly functionalized polycyclic systems that could be further functionalized.

Table 1.6.1.1 Preparation of bicyclic γ-lactam system through a tandem RCM/Kharasch addition

![Diagram of the reaction](attachment:image.png)

The asymmetric tandem process for the generation of bicyclic γ-lactams was described by Sutherland, et al. Through a palladium catalyzed Overman rearrangement/ruthenium catalyzed RCM followed by Kharasch addition, simple allylic alcohol precursors were converted into bicyclic γ-lactams in 39-87% yields (Table 1.6.1.2). The use of 4Å molecular sieves in the Kharasch reaction as an acid scavenger improved the yields. The palladium catalyzed Overman rearrangement was not completed in the substrates possessing ether and amine functionalities. None of the conditions including increasing Pd catalyst loading, longer reaction times or elevated reaction temperatures could improve the conversion. Presumably, this was associated with the coordination of the Pd catalyst with the heteroatom and the adjacent terminal which hampered the rearrangement reaction. This issue was resolved by running the Overman rearrangement under thermal conditions. The asymmetric tandem sequence was

examined with chiral palladium(II) complexes such as (S)-COP-Cl. The tandem rearrangement by chiral palladium(II) comple/RCM/Kharasch reaction generated bicyclic lactams in 51-89% yields and with 89-94% ee (Table 1.6.1.3).

**Table 1.6.1.2 Preparation of bicyclic γ-lactams through an Overman rearrangement/RCM/Kharasch addition**

<table>
<thead>
<tr>
<th>Reaction Conditions</th>
<th>Product Structure</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PdCl₂(MeCN)₂ (10 mol%), toluene, rt, 16 h; G₁ (10-25 mol%), 24-50 °C, 155 °C, 2 h, mol. sieves</td>
<td><img src="image1" alt="Product Structure" /></td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td></td>
<td><img src="image2" alt="Product Structure" /></td>
<td>87%</td>
<td></td>
</tr>
<tr>
<td></td>
<td><img src="image3" alt="Product Structure" /></td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td></td>
<td><img src="image4" alt="Product Structure" /></td>
<td>52%</td>
<td></td>
</tr>
<tr>
<td></td>
<td><img src="image5" alt="Product Structure" /></td>
<td>39%</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1.6.1.3 Asymmetric synthesis of bicyclic γ-lactams ring system through an Overman rearrangement/RCM/Kharasch addition**

<table>
<thead>
<tr>
<th>Reaction Conditions</th>
<th>Product Structure</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S)-COP-Cl (9 mol%), toluene, 38 °C, 5.5 days; G₁ (10 mol%), rt, 1h; 155 °C, 2 h, mol. sieves</td>
<td><img src="image6" alt="Product Structure" /></td>
<td>70%, 89% ee</td>
<td></td>
</tr>
<tr>
<td></td>
<td><img src="image7" alt="Product Structure" /></td>
<td>53%, 89% ee</td>
<td></td>
</tr>
<tr>
<td></td>
<td><img src="image8" alt="Product Structure" /></td>
<td>51%, 94% ee</td>
<td></td>
</tr>
</tbody>
</table>

Another example of bicyclic γ-lactam synthesis was reported by Delaude, et al.\(^9\)\(^1\)

The authors used homobimetallic ruthenium-indenyldene complex Ru-7. The ring closing metathesis of N-benzyl trichloroacetamide 1.79 followed by Kharasch reaction generated

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bicyclic γ-lactams 1.80 in a 89% yield (Scheme 1.6.1.2). This process allows for reaction with only 1 mol % of Ruthenium catalyst, but it has limitations related to substrate scope.

**Scheme 1.6.1.2** Preparation of bicyclic γ-lactams through a tandem RCM/Kharasch addition with bimetallic catalyst Ru-7

![Scheme 1.6.1.2](image)

Schmidt and Pohler reported the synthesis of bicyclic lactones via a tandem RCM/intramolecular Kharasch reaction. After completion of the RCM of substrate 1.81 in the presence of G1 at ambient temperature, the reaction mixture was heated to reflux for the Kharasch addition. Interestingly, unsaturated bicyclic lactone 1.82 was obtained (Scheme 1.6.1.3, eq 1). It was postulated that the bicyclic lactone 1.82 might have gone through the RCM/elimination/intermolecular Kharasch/displacement sequence as reported by Quayle. The influence of the different relationship of substituent (trans 1.83 and cis 1.85) was also examined. Regardless of the different orientation of the benzyloxy group, the desired products 1.84 and 1.86 were obtained in 61 and 62% yields as a single product (Scheme 1.6.1.3, eq 2 and 3). In benzyloxy group substituted substrates, G2 was more efficient.

**Scheme 1.6.1.3** Tandem RCM/intermolecular Kharasch reaction for generating bicyclic lactones

![Scheme 1.6.1.3](image)

Quayle, et al. also observed generation of an unsaturated bicyclic lactone during RCM/Kharasch sequence,\textsuperscript{93} which is similar to a previous report by Schmidt, et al.\textsuperscript{92} The authors investigated the mechanism for producing the unsaturated bicyclic lactone. By performing a \textsuperscript{1}H NMR study, it was observed that the RCM reaction occurred rapidly and that the resulting RCM product 1.88 converted to bicyclic lactone 1.92 via a cyclopentadiene 1.89 (Scheme 1.6.1.4, condition A). To confirm the formation of a cyclopentadiene 1.89, the reaction carried out under the same conditions with additional maleric anhydride. This afforded the Diels-Alder adduct 1.93 in a 92% yield (Scheme 1.6.1.4, condition B). These results suggested the following possible mechanism; after RCM reaction, the thermally unstable RCM adduct 1.88 leads to cyclopentadiene 1.89 and 2,2,2-trichloroacetic acid. Then, the resulting fragments undergo intermolecular Kharasch addition to generate intermediate 1.90 and/or 1.91, followed by S\textsubscript{N}2 or S\textsubscript{N}2’ cyclization to give unsaturated the bicyclic lactone 1.92. The tandem RCM-Kharasch sequence generated different results depending on the ruthenium catalyst used. The G1 generated unsaturated bicyclic lactone 1.94 as the major product while the G2 produced trichlorolactone 1.95 as a major product (Scheme 1.6.1.5).
1.6.2 CM/Kharasch reaction

The tandem cross-metathesis/intermolecular Kharasch reaction was demonstrated by Quayle, et al. (Table 1.6.2.1). The G2 catalyzed cross metathesis of the trichloroacetamide with styrenes followed by intramolecular Kharasch addition at 110°C produced γ-lactams in 23-32% yields. This protocol showed the possibility of tandem CM/Kharasch reactions, however, further optimization is necessary in terms of yield.
1.6.3 Enyne metathesis/Kharasch reaction

An enyne cross-metathesis/Kharasch reaction was described by Severin, et al.\textsuperscript{94} The enyne cross-metathesis of an aromatic alkyne with ethylene followed by intermolecular Kharasch addition generated an 1,5-dichloropent-2-ene derivative (Table 1.6.3.1). The regioisomer, A, was a major product in all cases. The yield of tandem products could be improved by adding magnesium\textsuperscript{95} (R=H, R\textsubscript{1}=CHClCO\textsubscript{2}Et; 42% to 65%), but the E/Z selectivity was still low.

\begin{table}[h]
\centering
\caption{Tandem CM/intermolecular Kharasch addition}
\begin{tabular}{c c c}
\hline
 & & \\
\hline
\multirow{2}{*}{Ph} & O & CCl\textsubscript{3} \\
\multirow{2}{*}{\begin{array}{c}
+ \ \text{G2 (5 mol \%), toluene, 40 \degree C, 12 h:} \\
\end{array}} & \begin{array}{c}
\text{110 \degree C, 3 dyas} \\
\end{array} & \\
\hline
\end{tabular}
\begin{tabular}{c c c c c c}
\hline
 & & & & & \\
\hline
X & & & & & \\
H & & & & & 26\% \\
F & & & & & 32\% \\
Br & & & & & 23\% \\
OMe & & & & & 29\% \\
\hline
\end{tabular}
\end{table}

Chapter 1 – Ruthenium Catalyzed Tandem and One-Pot Metathesis/Non-Metathesis Processes

Table 1.6.3.1 Tandem enyne metathesis/intermolecular Kharasch addition

![Diagram of Tandem enyne metathesis/intermolecular Kharasch addition]

<table>
<thead>
<tr>
<th>R</th>
<th>Yield A (%)</th>
<th>Yield B (%)</th>
<th>Isolated yield A+B (%)</th>
<th>Yield A (%)</th>
<th>Yield B (%)</th>
<th>Isolated yield A+B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>65</td>
<td>5</td>
<td>56</td>
<td>42:58</td>
<td>39</td>
<td>8</td>
</tr>
<tr>
<td>Me</td>
<td>62</td>
<td>4</td>
<td>52</td>
<td>37:63</td>
<td>48</td>
<td>8</td>
</tr>
<tr>
<td>F</td>
<td>49</td>
<td>9</td>
<td>57</td>
<td>33:67</td>
<td>35</td>
<td>12</td>
</tr>
<tr>
<td>CF₃</td>
<td>55</td>
<td>13</td>
<td>47</td>
<td>43:57</td>
<td>41</td>
<td>15</td>
</tr>
</tbody>
</table>

1.7 Metathesis/rearrangement

1.7.1 Claisen rearrangement/RCM

The synthesis of cyclic allylic trichloroacetamides through a one-pot operation was reported by Sutherland, et al. The palladium-catalyzed Overman rearrangement of readily prepared allylic trichloroacetimidates followed by a ruthenium catalyzed RCM reaction generated cyclic allylic trichloroacetamides in 62-93% yields (Table 1.7.1.1). It was essential to add the Grubbs second generation catalyst to the reaction mixture after completion of rearrangement, otherwise, the G2 would be decomposed. This protocol allowed the synthesis of five-, six-, seven-, and eight-membered carbocyclic allylic amides as well as asymmetric synthesis of these compounds using chiral palladium catalysts. The use of chiral palladium catalyst, (S)-COP-Cl or (R)-COP-Cl resulted in

asymmetric rearrangement of allylic trichloroacetimidates,\textsuperscript{97} followed by RCM produced cyclic allylic trichloroacetamides in 90\% and 75\% yields with 88\% ee. (Scheme 1.7.1.1).

\textbf{Table 1.7.1.1} Preparation of cyclic allylic trichloroacetamides through a one-pot, Overman rearrangement/RCM

\begin{center}
\begin{tabular}{c c c}
\hline
Chemistry & Product & Yield \\
\hline
\ce{C_3H_5NCCl_3} & \ce{C_5H_8NCCl_3} & 84\% \\
\ce{C_6H_10NCCl_3} & \ce{C_7H_12NCCl_3} & 89\% \\
\ce{C_7H_12NCCl_3} & \ce{C_8H_14NCCl_3} & 93\% \\
\ce{C_8H_16NCCl_3} & \ce{C_9H_20NCCl_3} & 62\% \\
\hline
\end{tabular}
\end{center}

\textbf{Scheme 1.7.1.1} Asymmetric one-pot Overman rearrangement/RCM

The one-pot rearrangement/RCM protocol was extended to aza-Claisen rearrangement and RCM reaction. Aza-Claisen rearrangement of allylic trichloroacetimide 1.96 by PdCl\(_2\)(MeCN) at room temperature, and then RCM by subsequently adding G1 generated N-(cyclohexenyl)-trichloroacetamides 1.97 and 1.98 in 45% yield over the three steps as 5:1 diastereoisomeric mixtures. By performing the rearrangement step at 0 °C toluene, the yield and diastereoselectivity was improved to 60% and 10:1, respectively (Scheme 1.7.1.2). For five-membered allylic amides, however, palladium catalyzed rearrangement did not occur. The rearrangement proceeded under thermal conditions to afforded low diastereoselectivities of 2:1.

**Scheme 1.7.1.2 Substrate control asymmetric one-pot Overman rearrangement/RCM**

In the course of natural product synthesis, Leighton, et al. developed a tandem cross-metathesis/semipinacol rearrangement reaction. Cross-metathesis of allylic epoxide 1.99 with alkene 1.100 by G1 generated 44% of CM product 1.101 as well as the semipinacol rearrangement product 1.102 in a 27% yield (Scheme 1.7.1.3). The semipinacol rearrangement product was exclusively produced under 5 mol % of HG2 at

refluxing CHCl₃ in a 75% yield as a 5:1 E:Z mixture. To confirm the active catalyst for semipinacol rearrangement, several control experiments were performed. Cross metathesis of 1.103 resulting from rearrangement of 1.99 and 1.100 did not occur (Scheme 1.7.1.4, eq 1). No semipinacol rearrangement was observed when the CM adduct 1.101 was subjected to refluxing CHCl₃ with or without HG2 (Scheme 1.7.1.4, eq 2 and 3). These results reveal that the rearrangement occurs after cross-metathesis and the rearrangement is catalyzed by ruthenium species as a Lewis acid derived from CM. Interestingly, only the epoxide 1.101 undergoes rearrangement while epoxide 1.99 undergoes CM reaction first. The tandem CM/semipinacol rearrangement allows for entantiococontrolled synthesis of bicyclic ketone 1.102 in a concise way.

**Scheme 1.7.1.3 Tandem CM/semipinacol rearrangement**
**Scheme 1.7.1.4** Control experiments for CM/semipinacol rearrangement

![Scheme 1.7.1.4 Control experiments for CM/semipinacol rearrangement](image)

1.8 Metathesis/cyclopropanation

1.8.1 Cyclopropanation/RCM

Diver, et al. reported the formation of cyclopropanation during the enyne metathesis.\(^\text{100}\) The dienyne underwent cyclopropanation followed by RCM reaction (Scheme 1.8.1.1). The formation of cyclopropanation relies on the reaction temperature and substituent. By increasing the reaction temperature, the formation of cyclopropanation was enhanced and bissulfonated substrate generated the cyclopropane product exclusively with G2 in refluxing benzene after 24 hours.

Scheme 1.8.1.1 Cyclopropanation followed by RCM

\[
\begin{align*}
\text{X} & \quad \text{G2 (5 mol%),} \\
\text{Y} & \quad \text{benzene, reflux, 24 h} \\
\text{X = C(CO₂Me)₂} & \quad 45^a \\
\text{X = C(SO₂Ph)₂} & \quad 83^a \\
\text{Y = C(CO₂Me)₂} & \quad 21^a \\
\text{Y = C(SO₂Ph)₂} & \quad 0
\end{align*}
\]

\(^a\) Yield determined by NMR vs mesitylene internal standard

1.8.2 Enyne metathesis/cyclopropanation

Snapper, et al. have investigated a tandem enyne metathesis/cyclopropanation sequence.\(^{101}\) A ruthenium species after metathesis reaction can catalyze cyclopropanation in the presence of diazoester at elevated temperature without modifying the ruthenium species. The cyclopropanation occurred by Grubbs first generation catalyst in less-hindered olefin with moderate E/Z stereoselectivity. This protocol enables the synthesis of five- to seven-membered cycloalkenyl cyclopropanes from readily prepared starting materials (Table 1.8.2.1). Diverse diazo compounds which are considered highly stabilized diazodiesters as well as unstabilized trimethylsilyl diazomethane participated successfully in this sequence. More substituted 1,3-dienes did not complete the cyclopropanation reaction even by increasing the amount of catalyst (20 mol %) or the reaction temperature; 21% of metathesis product was recovered at the end of tandem sequence. It was observed that an active catalyst for cyclopropanation was generated in \textit{situ} by diazo compound. It was observed that once an active catalyst is modified to catalyze cyclopropanation, it cannot activate metathesis reaction again.

Snapper, et al. extended this method to cross-metathesis/cyclopropanation sequence. The cross-metathesis of an aromatic acetylene with octane followed by cyclopropanation generated vinyl cyclopropane. However, the generation of diethyl maleate and fumarate resulting from dimerization of diazoester were problematic. Specifically, these dienophipic side products reacted with cross-metathesis product to generate Diels-Alder product. To improve the yield of desired vinyl cyclopropane, the ethyl diazoacetate was added to the reaction mixture slowly and the concentration of the diazoacetate was maintained to a minimum value. This sequence was used for various reaction partners, although electron poor substrate generated metathesis product as a major product (Table 1.8.3.1). In addition, TBS and benzyl protected alcohols worked well in this sequence. It is worth note that this result was the first demonstration of an NHC ruthenium catalyzed cyclopropanation.

Table 1.8.2.1 Tandem enyne metathesis/cyclopropanation

<table>
<thead>
<tr>
<th>n</th>
<th>Reaction Product</th>
<th>Yield</th>
<th>E/Z Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65% (E/Z = 2.2/1)</td>
<td>65%</td>
<td>2.2/1</td>
</tr>
<tr>
<td>2</td>
<td>68% (E/Z = 2.4/1)</td>
<td>65%</td>
<td>2.2/1</td>
</tr>
<tr>
<td>3</td>
<td>52% (E/Z = 2/1)</td>
<td>65%</td>
<td>2.2/1</td>
</tr>
</tbody>
</table>

1.8.3 CM/cyclopropanation

Snapper, et al. extended this method to cross-metathesis/cyclopropanation sequence. The cross-metathesis of an aromatic acetylene with octane followed by cyclopropanation generated vinyl cyclopropane. However, the generation of diethyl maleate and fumarate resulting from dimerization of diazoester were problematic. Specifically, these dienophipic side products reacted with cross-metathesis product to generate Diels-Alder product. To improve the yield of desired vinyl cyclopropane, the ethyl diazoacetate was added to the reaction mixture slowly and the concentration of the diazoacetate was maintained to a minimum value. This sequence was used for various reaction partners, although electron poor substrate generated metathesis product as a major product (Table 1.8.3.1). In addition, TBS and benzyl protected alcohols worked well in this sequence. It is worth note that this result was the first demonstration of an NHC ruthenium catalyzed cyclopropanation.
Table 1.8.3.1 Tandem cross-metathesis/cyclopropanation

![Tandem cross-metathesis/cyclopropanation diagram]

1.8.4 RCM/isomerization/cyclopropanation

Pérea-Castells, et al. have described the tandem RCM/isomerization/cyclopropanation reaction. The authors prepared compound A, a selective inhibitor of the human inducible isoform of nitric oxide synthase (iNOS) though a tandem RCM/isomerization/cyclopropanation sequence. The ring closing metathesis of the diene in refluxing toluene by G2 followed by isomerization of the resulting double bond and then cyclopropanation by adding a 50% solution of NaOH in water, CHCl₃, and Aliquat 336 generated the desired compound in 55% yield (eq 1). A ruthenium catalyzed cyclopropanation using ethyl diazoacetate (EDA) was also carried out. The EDA was added to the reaction mixture of the diene and G2 in refluxing toluene with a syringe pump over 8 hours to afford the desired cyclopropane in 52% yield as a trans:cis mixture (1.9:1) (eq 2).

---

Scheme 1.8.4.1 Tandem RCM/isomerization/cyclopropanation sequence

1.9 Metathesis/miscellaneous

1.9.1 CM/Wittig olefination

Snapper, et al. have demonstrated cross-metathesis/Wittig olefination sequence in a tandem reaction.\(^{105}\) Ruthenium catalyzed cross-metathesis of terminal olefin with acrolein and methacrolein, followed by ruthenium catalyzed Wittig olefination with diazoacetates generated α,β,γ,δ-unsaturated carbonyl-containing compounds in 59-86% yields with >20:1 $E,E$-selectivity (Table 1.9.1.1). Through the slow addition of the diazoester to the reaction mixture, the dimerization of ethyl diazoacetate was avoided. Also, the yield and $E/Z$ selectivity could be improved. This protocol was extended to Wittig olefination of a ketone by performing tandem sequence at 75 °C toluene, although it yielded a moderate $E/Z$ selectivity of 4:1.

Table 1.9.1.1 Preparation of dienoic esters through tandem CM/Wittig olefination

\[
\begin{align*}
\text{R}_1 \Rightarrow \text{R}_2 & + & \text{R}_3 \Rightarrow \text{R}_4 & \xrightarrow{\text{Ru-5 (5 mol %)}} & \text{CH}_2\text{Cl}_2, 60 ^\circ\text{C}, 10-12 \text{ h} & \xrightarrow{\text{PPPh}_3 (2 \text{ equiv.})} & \text{EDA (3 equiv.)} & \text{R}_1 \Rightarrow \text{R}_2 \\
\text{Me} & + & \text{Me} & & & & & \text{CO}_2\text{Et} \\
\text{R}_1 = \text{n-Hex} & 81\% & \text{n-Hex} & 84\%^a & \text{n-Hex} & 59%^{a,b} & \text{65}\%^b \\
\text{TBSO} & 75\% & \text{CO}_2\text{t-Bu} & & & & & \text{CO}_2\text{Et} \\
\text{BnO} & 72\% & & & & & & \\
\text{AcO} & 86\% & & & & & & \\
\end{align*}
\]

\(^a\) t-Butyl diazoacetate used in place of EDA
\(^b\) HG2 used in place of Ru-X

1.9.2 CM/cycloaddition (Hetero-Pauson-Khand)

Snapper, et al. have demonstrated the preparation of functionalized tricyclic lactones through ruthenium catalyzed RCM/Hetero-Pauson-Khand (HPK) reaction.\(^{106}\) After the RCM step, the reactivity of a ruthenium catalyst was changed by adding reductants and CO to catalyze HPK reaction. NaOMe indeed appeared to be an optimal reductant to activate the catalyst for HPK. The RCM reaction was performed in toluene to 100°C because of substrate possessing Lewis basic functionalities such as a pyridine group that inhibit the metathesis activity by coordinating on the metal and then blocking the necessary coordination site. The RCM with G2 in toluene at 100°C followed via HPK reaction by subsequent addition of NaOMe and CO generated tricyclic lactones compounds as a single diastereomer in 44-76% yield (Table 1.9.2.1). These reactions favor the syn-stereochemical relationship in the five- and six- membered ring, however, increasing the size of the metathesis ring results in the bridge head carbon outside the

lactone inverting. This stereochemical outcome was corresponded to the lower energy diastereomers in MM2 and DFT calculation.

**Table 1.9.2.1** Preparation of tricyclic lactones through tandem RCM/Hetero-Pauson-Khand reaction

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Pyridyl lactone" /></td>
<td>76%</td>
</tr>
<tr>
<td><img src="image2" alt="Phenyl lactone" /></td>
<td>72%</td>
</tr>
<tr>
<td><img src="image3" alt="Heterocyclic lactone" /></td>
<td>71%</td>
</tr>
<tr>
<td><img src="image4" alt="Pyridyl lactone" /></td>
<td>61%</td>
</tr>
<tr>
<td><img src="image5" alt="Phenyl lactone" /></td>
<td>51%</td>
</tr>
<tr>
<td><img src="image6" alt="Heterocyclic lactone" /></td>
<td>41%</td>
</tr>
</tbody>
</table>

It was observed that the pyridyl ketone functionality was required for HPK reaction. When phenyl ketone and pyridyl ketone were subjected to the tandem RCM/HPK reaction, the tricyclic HPK product of the pyridyl ketone was obtained only. No desired HPK product from the phenyl ketone was observed (eq 1). This result reveals that the HPK reaction is sensitive to the Lewis basicity of chelating functionality adjacent to the carbonyl group; the less basic pyrimidine instead of pyridine containing substrate generated only RCM product in the tandem sequence. This protocol enables the preparation of various tricyclic lactones with one ruthenium precatalyst in a single reaction vessel.
1.9.3 Enyne metathesis/metallotropic [1,3]-shift

Lee, et al. have studied enyne metathesis in a subsequent metallotropic [1,3]-shift sequence. The enyne metathesis of 1,3-diynes generated intermediate which subsequently underwent facile metallotropic [1,3]-shift to produce fully conjugated 1,5-diene-3-ynes (Scheme 1.9.3.1). This method allows for synthesis of various ring size silozanes in good yield (Table 1.9.3.1). Unfortunately, the metallotropic [1,3]-shift did not occur in the substrates with sterically hindered substituents and the substrate with an eight-membered siloxane resulted in a sluggish metallotropic [1,3]-shift. The authors applied this protocol to the total synthesis of (3R,9R,10R)-panaxytriol, (+)-asperpentyn, (-)-harveynone, and (-)-tricholomryn A (Scheme 1.9.3.2).

Scheme 1.9.3.1 Tandem enyne metathesis/metallotropic [1,3]-shift

![Scheme 1.9.3.1](image)

Table 1.9.3.1 Enyne metathesis/metallotropic [1,3]-shift

<table>
<thead>
<tr>
<th>enediyne</th>
<th>Product</th>
<th>enediyne</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeSi=CH=CH=CH=O</td>
<td>OMe</td>
<td>Me-Si=CH=CH=CH=O</td>
<td>Me-Si=CH=CH=CH=O</td>
</tr>
<tr>
<td>n = 0</td>
<td>54%</td>
<td>n = 1</td>
<td>66%</td>
</tr>
<tr>
<td>n = 2</td>
<td>68%</td>
<td>n = 3</td>
<td>11%</td>
</tr>
</tbody>
</table>

TBSO

96%

OAc

89%

Scheme 1.9.3.2 Tandem enyne metathesis/metallotropic [1,3]-shift in total synthesis

(3R,9R,10R)-panaxytriol

(+-)-Asperpsntyn

(-)-Harveynone
1.9.4 Enyne metathesis/hydrovinylation

Ruthenium catalyzed tandem enyne metathesis/hydrovinylation has been described by Snapper, et al.\textsuperscript{110} Grubbs first generation catalyst modified by NaOMe in MeOH/toluene catalyzed hydrovinylation in a regioselective fashion. The enyne metathesis with G1 followed by a hydrovinylation of the resulting 1,3-diene with modified G1 generated 1,4-hydrovinylation products in 49-71% yield (Table 1.9.4.1). Substrates possessing a quaternary or sp\textsuperscript{2}-hybridized carbon adjacent to the alkyne produced tandem adducts in higher yield.

**Table 1.9.4.1 Tandem enyne metathesis/1,4-hydrovinylation**

1.9.5 Epimerization/RCM

During the synthesis of BILN 2061, a macrocyclic HCV NS3 protease inhibitor, Zeng, et al. found that ruthenium catalyzed epimerization of vinylcyclopropane occurred.\(^{111}\) The ring closing metathesis of tripeptide diene 1.108 with G1 in 60 °C toluene produced the desired RCM product 1.109 as well as epimerized precursor 1.111 and epimer RCM product 1.110. The epimerization occurred by Grubbs first generation catalyst via ruthenacyclopentene or by the HG1 in the presence of phosphine or nitrogen ligand.

**Table 1.9.5.1 Epimerization/RCM for the synthesis of BILN 2061**

1.9.6 Allylic carboxylation/RCM

Onitsuka, et al. have demonstrated the synthesis of optically active unsaturated γ-lactones by using one-pot sequential asymmetric allylic carboxylation and ring-closing metathesis.\(^{112}\) The asymmetric allylic substitution of mono-substituted allylic chlorides with *trans*-2-butenoic acid by a planar-chiral cyclopentadienyl ruthenium (Cp’ Ru) complex Ru-8 yielded high regioselective allylic esters. Subsequently, the resulting esters were subjected to the G2 catalyzed RCM without any purification to

---


afford α,β-unsaturated γ-lactones with high enantioselectivities (Scheme 1.9.6.1). This method allows for useful chiral building blocks in an atom economy way.

**Scheme 1.9.6.1** One-pot synthesis of γ-lactones via asymmetric allylic substitution/RCM

1.10 Conclusions

Over the past few decades, tandem catalysis has been developed as a powerful and versatile synthetic tool in organic chemistry. Some ruthenium-carbene complexes can activate both olefin metathesis and nonmetathetic reactions in a single operation which allows for two or more mechanistically distinct reactions catalyzed by one precatalyst, achieving high levels of molecular complexity in a concise manner. Although much work to elucidate active catalytic species and mechanistic aspects of the process has yet to be done, the tandem protocols have already extensively contributed to the field of organic chemistry.
Chapter 2

Development of a Tandem Ru-Catalyzed Ring-Closing Metathesis/Hydroacylation Sequence
2.1 Introduction

Tandem processes have several advantages, such as reducing processing steps, purification steps, waste, and cost of reagents, solvent, and products. Ruthenium has a broad range of oxidation and coordination states that provides opportunities to access additional reactivities for developing tandem processes. The Snapper group has explored these advantages and developed several new ruthenium-catalyzed tandem processes (Figure 2.1.1).

**Figure 2.1.1** Examples of Ru-catalyzed tandem reactions developed by the Snapper group

---

As shown in Figure 2.1.1, various tandem reactions involving metathesis have been developed. Hydroacylation can be catalyzed by ruthenium complexes and there is no previous example that combines hydroacylation and metathesis in a tandem fashion. We hypothesized that olefin metathesis could be combined with ruthenium-catalyzed hydroacylation (eq 2.1) to generate polycyclic products in a single step.

![Chemical structure diagram](eq 2.1)

### 2.2 Background of hydroacylation

#### 2.2.1 Intramolecular hydroacylation using rhodium catalysts

Aldehyde hydroacylation of an olefin is a useful C-C bond forming reaction.\(^\text{114}\) Since Sakai and co-workers first reported on hydroacylation in a study on prostanoid synthesis in 1972 (Scheme 2.2.1.1),\(^\text{115}\) many groups have further contributed to the advancement of this area of research in subsequent studies.

**Scheme 2.2.1.1 First reported hydroacylation by Sakai and co-workers**

![Chemical structure diagram](mg114s2f01)

The mechanism of hydroacylation was studied by Milstein who isolated and characterized a key intermediate by X-ray crystallography, a pent-4-enoylhydridorhodium complex.


complex (b) (Scheme 2.2.1.2), using a modified Wilkinson’s catalyst, cis-hydridoalkyl-rhodium(III) trimethylphosphine complex. The slow rate of PMe₃ dissociation makes it relatively stable. The key steps in hydroacylation involve oxidative addition to generate an acyl metal hydride intermediate (b), then addition to the alkene (d), followed by reductive elimination to give the ketone product (e) and to regenerate the catalyst.

**Scheme 2.2.1.2** Mechanism of hydroacylation via hydridoacyl-rhodium(III) complex

The first report of catalytic hydroacylation was demonstrated by Miller and co-workers using 10 mol % Wilkinson’s complex in ethylene saturated chloroform. Also, Larock reported a similar improvement in the efficiency of intramolecular hydroacylation reaction using solvent saturated with ethylene. Ethylene saturates the metal catalyst, thereby reducing the amount of reductive decarbonylation, which is the main side reaction in hydroacylation. Past attempts to extend the process to alternative ring sizes have proven difficult. Synthesis of ring systems larger than cyclopentanones via intramolecular hydroacylation is challenging. Formation of larger rings is generally slower than five-membered ring closures, and undesired decarbonylation becomes

problematic. Following several studies, it is possible to access larger ring systems if a suitable scaffold and additional functionality are incorporated into the substrate. Rigid carbohydrate-derived scaffolds allow access to six-membered ring formation,\textsuperscript{119} dienal substrate generation of a cycloheptanone (Scheme 2.2.1.3),\textsuperscript{120} a cyclopropane ring, which can generate an eight-membered ring\textsuperscript{121} and heteroatom-chelation to produce a medium-ring system (Scheme 2.2.1.4).\textsuperscript{122} These reactions, however, use expensive rhodium catalysts and have limitations in substrate scope.

\textbf{Scheme 2.2.1.3} Hydroacylation for larger ring system using dienal substrate

\textbf{Scheme 2.2.1.4} Hydroacylation for larger ring system using chelation-stabilized intermediate

2.2.2 Hydroacylation using ruthenium catalysts and other catalysts

Rhodium (I) complexes are mainly used in hydroacylation and have been studied extensively. Although there are still only a few methods for intramolecular hydroacylation using other transition metal complexes, some catalysts have been studied and reported on their activity for hydroacylation. In 1982, it was reported that Ru(0) complexes can function as a hydroacylation catalyst; however, achieving only low yields of hydroacylation adducts. A more successful Ru-catalyzed hydroacylation was not described until 1987 when Watanabe and co-workers reported their results.

Watanabe and Kondo showed that dodecacarbonyltriruthenium (Ru₃(CO)₁₂), (η⁶-1,3,5-cyclooctatiene)ruthenium, (Ru(COD)(COT), and bis(η⁵-cyclooctadienyl)ruthenium catalyze intramolecular hydroacylation of olefin with aromatic and heteroaromatic aldehyde. Ru₃(CO)₁₂ showed that it is possible to catalyze hydroacylation in 1 mol % catalyst loading at 200 °C under an initial carbon monoxide pressure of 20 kg cm⁻² (Scheme 2.2.2.1). Several years later, the same group demonstrated ruthenium-catalyzed addition of diene to aldehydes. Although this process used dienes as solvent, it showed that CO was not necessary to suppress the decarbonylated side-product.

Scheme 2.2.2.1 Early example of hydroacylation using Ru(0)
Recently, both the Ryu and Krische groups have explored intermolecular hydroacylation of dienes by ruthenium catalyst (Scheme 2.2.2.2 and 2.2.2.3).\(^{126, 127}\) They found that the ruthenium hydride catalyst promoted the coupling between a variety of 1,3-diene and aryl and alkyl aldehydes, but those worked only for 1,3-diene systems. Their mechanism involves addition of Ru-H to diene generating a π-allyl ruthenium complex, then addition to the aldehyde to generate a alkoxy-ruthenium complex. Afterwards, reductive elimination produces the hydroacylated product and regenerates Ru-H (Scheme 2.2.2.4).

**Scheme 2.2.2.2** Intermolecular hydroacylation by Ryu and co-workers

\[
\text{Scheme 2.2.2.3} \quad \begin{array}{c}
\text{Intermolecular hydroacylation by Krische and co-workers} \\
\end{array}
\]

Eilbracht and co-workers demonstrated that RuCl\(_2\)(PPh\(_3\))\(_3\) catalyzed a sequence of aliphatic Claisen rearrangement and intramolecular hydroacylation at elevated


temperatures. In addition, the Brookhart group reported Co-complexes that can catalyze hydroacylation and work well at low temperatures and low catalyst loadings, but its application has been limited in substrate scope.

2.3 Ru-catalyzed tandem ring-closing metathesis/hydroacylation

2.3.1 Our approach to tandem RCM/hydroacylation using Ru-alkylidenes

We wanted to develop a new method that would be able to overcome limitations of previous hydroacylation studies. Assisted tandem catalysis was considered because of issues arising from the cost of new catalyst and compatibility of new catalyst with ligands from first catalyst. We believed that Ru-benzylidene could serve as a precatalyst for hydroacylation. We set out to design a new tandem ring-closing metathesis/hydroacylation sequence that can be applied to various substrates for the preparation of substituted cyclic ketons. (Scheme 2.3.1.1).

Scheme 2.3.1.1 Approach to Ru-catalyzed tandem process of olefin metathesis/hydroacylation

First, we ran olefin metathesis using a Ru-based catalyst, and then looked to apply it to hydroacylation. The activity required for olefin metathesis, however, is very different than that needed to promote hydroacylation. Hence, reagents or conditions should be introduced to \textit{in situ} modify the active Ru-based catalyst to promote the second step of the tandem transformation. After the ring-closing metathesis reaction with Grubbs’ catalyst, the catalyst can be treated with CO. Carbon monoxide can bind to the ruthenium center, thus weakening the $\pi$-back bonding interaction between ruthenium and the methylidene. The very electrophilic carbon of the methylidene can be trapped by the neighboring aryl group. Carbon insertion into $\pi$-system via a Büchner-type cyclopropanation can proceed resulting in ring expansion of the aromatic ligand and an inactive catalyst form towards olefin metathesis as described by Diver. (Scheme 2.3.1.2).^{130}

\textbf{Scheme 2.3.1.2} Büchner type reaction of Grubbs’ catalyst and CO

\begin{center}
\includegraphics[width=0.7\textwidth]{Scheme2.3.1.2.png}
\end{center}

\textbf{2.3.2 Initial study of Ru-catalyzed tandem metathesis/hydroacylation}

Before developing the tandem sequence, we investigated each step of the sequence individually with Ru-based catalysts. The diene substrate \textbf{2.1} (eq 2.1) provided

---

desired RCM product in a quantitative yield with 5-10 mol % Grubbs’ catalyst with 1 hour. Therefore optimization focused on improving the hydroacylation step. We would first need to verify the activity towards hydroacylation of designed substrate, 1’,2’,3’,4’-tetrahydro-[1,1’-biphenyl]-2-carbaldehyde 2.2, which is the RCM product of substrate 2.1.

First, the activity of the substrate was examined with known hydroacylation-active Ru$_3$(CO)$_{12}$ under reported conditions to afford a 30% yield after 24 h (Table 2.3.2.1, conditions A). Under the same conditions, ruthenium hydride species, RuHCl(CO)(PPh$_3$)$_3$, was also examined (conditions B). However it only gave a small amount of desired product. After confirming the activity towards hydroacylation of the designed substrate, we looked at the reactivity with modified Grubbs’ catalysts that have been altered with CO and NaOMe. Fortunately, intermolecular hydroacylation proceeded with a 63% yield (conditions C).

**Table 2.3.2.1 Activities of ruthenium complexes for hydroacylation**

<table>
<thead>
<tr>
<th>Conditions A</th>
<th>Conditions B</th>
<th>Conditions C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ru$<em>3$(CO)$</em>{12}$ (3 mol %), CO (400 psi), toluene (0.06 M), 200 °C, 24 h</td>
<td>RuHCl(CO)(PPh$_3$)$_3$ (10 mol %), CO (400 psi), toluene (0.06 M), 200 °C, 24 h</td>
<td>G2 (10 mol %), NaOMe (20 mol %), CO (400 psi), toluene (0.06 M), 200 °C, 24 h</td>
</tr>
<tr>
<td>yield: 30% (cis product only)</td>
<td>yield: 11% (cis product only)</td>
<td>yield: 63% (cis product only)</td>
</tr>
</tbody>
</table>

The activity of a modified Grubbs’ catalyst towards hydroacylation had been confirmed. With that result, we investigated reaction conditions for tandem sequence. First, we screened several solvents with substrate 2.1 (Table 2.3.2.2). Toluene afforded a
single diastereomer with cis- fused ring system in 76% yield (>98% conversion). The reaction also produced reduced compound 2.4, which is not a common side product in the hydroacylation reaction. Running the reaction in benzene gave >98% conversion, but produced low amounts of the desired product. THF led to both low conversion and yield of desired product. We hypothesized that the THF oxygen coordinates to the Ru complex and interferes with its catalytic activity.

**Table 2.3.2.2 Screening of solvent in tandem RCM/hydroacylation**

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>conv (%)</th>
<th>2.3</th>
<th>2.4</th>
<th>2.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>toluene</td>
<td>&gt;98</td>
<td>76</td>
<td>17</td>
<td>&lt;1</td>
</tr>
<tr>
<td>2</td>
<td>benzene</td>
<td>&gt;98</td>
<td>21</td>
<td>10</td>
<td>17</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>80</td>
<td>9</td>
<td>6</td>
<td>30</td>
</tr>
</tbody>
</table>

* Conv. Conversions were detected by analysis of $^1$H NMR  
* Yields of purified product  
* Yields were detected by analysis of $^1$H NMR

The temperature of the reaction is an important variable for achieving high conversion. As shown in Table 2.3.2.3, a temperature of 200 °C is necessary for full conversion and high yield of the desired product. This result is similar to that found in a study by Kondo and co-workers. At lower temperatures, the ratio of compound 2.5 over the desired compound 2.3 is increased.

(131) For this reduced byproduct, see: 2.5 Mechanistic studies of the Ru-catalyzed tandem RCM/hydroacylation in this dissertation.
To figure out the effect of base and its potential ability to reduce metal compounds, \(^{132}\) neutralize reaction mixtures, or generate the Ru-H complex, we screened several bases that could serve to carry out these functions (Table 2.3.2.4). Even without base, the reaction gave 67\% of desired product. With base, however, the yield was substantially increased. Sodium methoxide was the most efficient in our reaction, giving a 76\% yield of desired product. When we used fresh sodium methoxide that was made \textit{in-situ} by addition of sodium hydride to distilled methanol, the yield significantly dropped. Methanol may react with the catalyst and generate side products. It is known that Grubbs’ first generation catalyst is decomposed by methanol.\(^{133}\) In a similar fashion, we assume that Grubbs’ second generation might also decompose. Other inorganic bases and secondary and tertiary amine bases were also examined; however, those bases were not as efficient as sodium methoxide. It has been reported that water can be used in the reaction

for reduction of transition metals.\textsuperscript{131, 134} To promote the reduction step, we added water but this additive showed no beneficial effect on the reaction yield (entry 6 and 7).\textsuperscript{118}

**Table 2.3.2.4** Screening of base as reductant in tandem RCM/hydroacylation

\begin{table}[h]
\centering
\begin{tabular}{llllll}
\hline
entry & base & \multicolumn{3}{c}{yields (\%)}
\hline
 & & 2.3\textsuperscript{a} & 2.4\textsuperscript{b} & 2.5\textsuperscript{b}
\hline
1 & none & 67 & 9 & <1
2 & NaOMe & 76 & 17 & <1
3 & NaOMe (0.5 M in MeOH) & 20 & 4 & <5
4 & NaOEt & 58 & 10 & <1
\hline
\end{tabular}
\end{table}

\textsuperscript{a}Yields of purified product
\textsuperscript{b}Yields were detected by analysis of \textsuperscript{1}H NMR

As illustrated in Table 2.3.2.5, when more than 20 mol \% base was added, the yield of desired product dropped and the amount of olefin-isomerized side product increased. It may be possible that adding excessive base may not only act as a reductant, but also act in a basic manner as to generate side products.

**Table 2.3.2.5** Screening of amount of base in tandem RCM/hydroacylation

\begin{table}[h]
\centering
\begin{tabular}{llllll}
\hline
entry & base & \multicolumn{3}{c}{yields (\%)}
\hline
 & & 2.3\textsuperscript{a} & 2.4\textsuperscript{b} & 2.5\textsuperscript{b}
\hline
5 & KO\textsuperscript{Bu} & 47 & 11 & <1
6 & Et\textsubscript{3}N & 58 & 15 & <1
7 & Et\textsubscript{3}N, H\textsubscript{2}O & 55 & 13 & <1
8 & i-Pr\textsubscript{2}NH & 24 & 15 & <5
9 & CsCO\textsubscript{3} & 20 & <5 & <5
\hline
\end{tabular}
\end{table}

To further investigate reaction conditions, we also screened the effect of concentration on the reaction (Table 2.3.2.6). Concentration of 0.06 M was the most efficient for this system. As the reaction concentration decreases, reductive side product 2.4 decreases, but olefin-isomerized side product 2.5 increases. We found that this trend was independent on the amount of catalyst present (entries 1-3 vs. entries 4-7).

Table 2.3.2.6 Screening of concentration of solvent in tandem RCM/hydroacylation

<table>
<thead>
<tr>
<th>entry</th>
<th>mol (%)</th>
<th>2.3</th>
<th>2.4</th>
<th>2.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>67</td>
<td>9</td>
<td>&lt;1</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>60</td>
<td>15</td>
<td>&lt;1</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>76</td>
<td>17</td>
<td>&lt;1</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>22</td>
<td>7</td>
<td>15</td>
</tr>
</tbody>
</table>

>98% conversion for all cases

a Yields of purified product

b Yields were detected by analysis of ^1H NMR

To understand the role of CO, we ran the reactions under CO and N₂ (Scheme 2.3.2.7). When the reaction was carried out with 400 psi of CO, the desired product was
isolated in 70% yield. While in lower pressure of CO (15 psi), the desired product was produced in 32% yield and in the presence of N₂ instead of CO (entry 1) it gave only 10% of the desired product and unidentified byproducts. High pressure of CO was required for better yield of the desired product. CO may bind to Ru metal as a ligand and stabilize the Ru complex. It prevents decomposition of the catalyst and maintained an active catalyst for longer time. It leads to increase the catalyst turn over number.

**Table 2.3.2.7** Screening of function of CO in tandem RCM/hydroacylation

<table>
<thead>
<tr>
<th>entry</th>
<th>X</th>
<th>2.9⁹</th>
<th>2.38¹⁰</th>
<th>2.34¹¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N₂ (15 psi)</td>
<td>10</td>
<td>--⁶</td>
<td>--⁶</td>
</tr>
<tr>
<td>2</td>
<td>CO (15 psi)</td>
<td>32</td>
<td>3</td>
<td>--⁶</td>
</tr>
<tr>
<td>3</td>
<td>CO (400 psi)</td>
<td>70</td>
<td>4</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

⁹ Yields of purified product  
¹⁰ Yields were detected by analysis of ¹H NMR  
⁶ Could not determine by NMR  
¹¹ Added triphenyl phosphite as additive  
>98% conversion for all cases

To determine the most effective pressure of CO, we examined further the effect of CO pressure on the isolated yields (Table 2.3.2.8), and showed that 400 psi was the most efficient pressure in our reaction. To stabilize the catalyst, a precise pressure of CO was necessary. As we increased the pressure of CO, the yield of desired product increased; however, at over 500 psi, the reaction was suppressed. These results are similar to those found in the study by Watanabe and co-workers.¹²⁴ This may be due to the ruthenium
catalyst which needs open coordination sites for addition across the alkene; but high pressures of CO saturate the ruthenium and therefore suppress the reaction.

**Table 2.3.2.8** Screening of pressure of CO in tandem RCM/hydroacylation

<table>
<thead>
<tr>
<th>entry</th>
<th>pressure of CO (psi)</th>
<th>2.3</th>
<th>2.4</th>
<th>2.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>32</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>2</td>
<td>300</td>
<td>60</td>
<td>15</td>
<td>&lt;5</td>
</tr>
<tr>
<td>3</td>
<td>400</td>
<td>76</td>
<td>17</td>
<td>&lt;1</td>
</tr>
<tr>
<td>4</td>
<td>500</td>
<td>52</td>
<td>17</td>
<td>&lt;5</td>
</tr>
<tr>
<td>5</td>
<td>700</td>
<td>42</td>
<td>10</td>
<td>17</td>
</tr>
</tbody>
</table>

*Yields of purified product

Yields were detected by analysis of 1H NMR

>98% conversion for all cases

Could not determine by NMR

To improve reaction efficiency, we changed the Ru-based catalyst (Table 2.3.2.9). Although Grubbs’ second generation catalyst gave high yield of the desired product, it also produced reduced side product 2.4. With Grubbs’ first generation catalyst, the yield of desired product and compound 2.4 decreased. Another problem using G1 was that the side product from olefin isomerization 2.5 was observed. In the case of Hoveyda-Grubbs’ second generation catalyst, the yield of desired product was quite low and unidentified byproducts appeared. These Ru-based catalysts are similar. All have the same 16-electron species, Ru(II) oxidation state, and square pyramidal geometry, but the results were quite different. We thought that the phosphine ligand might have a role in the reaction, so we investigated the role of this ligand.
Table 2.3.2.9 Screening of other Ru-based catalysts in tandem RCM/hydroacylation

<table>
<thead>
<tr>
<th>entry</th>
<th>Ru based catalyst</th>
<th>2.3(^a)</th>
<th>2.4(^b)</th>
<th>2.5(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Grubbs' I</td>
<td>49</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>Grubbs' II</td>
<td>76</td>
<td>17</td>
<td>&lt;1</td>
</tr>
<tr>
<td>3</td>
<td>Hoveyda-Grubbs' II</td>
<td>20</td>
<td>18</td>
<td>15</td>
</tr>
</tbody>
</table>

>98% conversion for all cases  
\(^a\) Yields of purified product  
\(^b\) Yields were detected by analysis of \(^1\)H NMR

To examine the role of phosphine, we added additional phosphines to the reaction (Table 2.3.2.10). First, we added triphenylphosphine and tricyclohexyl phosphine in concentrations matching that of the catalyst (entries 2 and 3). The amount of reduced compound 2.4 decreased, but because of the increased amount of olefin-isomerized compound 2.5, the yield of desired product 2.3 dropped. We did not find a noticeable difference between triphenylphosphine and tricyclohexyl phosphine. To determine the effect of ligand concentration, we examined reaction yields with different amounts of PCy\(_3\) (entries 3, 5-7). We found that by decreasing the amount of ligand, the amount of desired product 2.3 increased; also, the amount of reduced compound 2.4 increased. It is difficult to understand how the phosphate ligand affected the reaction outcome. It may be that the phosphate ligand occupies a Ru coordinate site and alters specific reaction rates. Through previous screenings, we know that the amount of the olefin-isomerized product depends on the amount of base and solvent concentration (Table 2.3.2.5 and
2.3.2.6). Thus, we ran the reaction without base. As expected, olefin-isomerized compound 2.5 decreased, but reduced compound 2.4 increased (entries 3 and 4).\(^{135}\)

**Table 2.3.2.10** Screening of additive in tandem RCM/hydroacylation

<table>
<thead>
<tr>
<th>entry</th>
<th>additive</th>
<th>mol (%)</th>
<th>2.3(^a)</th>
<th>2.4(^b)</th>
<th>2.5(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>--</td>
<td>76</td>
<td>17</td>
<td>&lt;1</td>
</tr>
<tr>
<td>2</td>
<td>PPh(_3)</td>
<td>20</td>
<td>50</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>PCy(_3)</td>
<td>20</td>
<td>51</td>
<td>4</td>
<td>19</td>
</tr>
<tr>
<td>4(^c)</td>
<td>PCy(_3)</td>
<td>20</td>
<td>51</td>
<td>18</td>
<td>&lt;1</td>
</tr>
<tr>
<td>5</td>
<td>PCy(_3)</td>
<td>5</td>
<td>54</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>PCy(_3)</td>
<td>3</td>
<td>56</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>7</td>
<td>PCy(_3)</td>
<td>2.5</td>
<td>76</td>
<td>19</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

>98\% conversion for all cases

\(^a\) Yields of purified product \(^b\) Yields were detected by analysis of \(^1\)H NMR

\(^c\) Without NaOMe

2.3.3 Other reaction conditions

There are examples of rhodium-catalyzed hydroacylation whereby the generation of undesired decarbonylated compounds is suppressed. One example was reported by Bosnich and co-workers who studied cationic rhodium complexes in intermolecular hydroacylations.\(^{136}\) They reported that the cationic rhodium complexes accelerate the oxidative addition and reductive elimination steps. They mentioned that this also serves to suppress decarbonylations. To the best of our knowledge, there are no examples of

(135) The role of base will be discussed more, see: 1.4 Mechanistic Studies of Ru-catalyzed tandem ring-closing in this thesis.

caticonic Ru-catalyzed hydroacylations. To further optimize the reaction conditions, we performed hydroacylation with cationic ruthenium complexes that were made in situ by treating Grubbs’ second generation catalyst with AgClO$_4$ after ring-closing metathesis (Scheme 2.3.3.1). Unfortunately, this modification did not work with our system.

**Scheme 2.3.3.1** Effect of AgClO$_4$ on tandem RCM/hydroacylation

Another example of rhodium-catalyzed hydroacylation that suppresses the generation of undesired decarbonylated compounds was developed by Jun and co-workers who introduced chelation-assisted protocols using 2-amino-3-picoline. This additive facilitates the formation of kinetically favored five-membered metallacycle that can stabilize acyl-metal hydride species, therefore suppressing decarbonylation. To further improve our reaction, we tried this protocol (Scheme 2.3.3.2), but unfortunately, this did not lead to Ru-catalyzed hydroacylation.

2.4 Scope of the tandem process

With the optimized reaction conditions for tandem ring-closing metathesis/hydroacylation of model substrate 2.1 in hand, the substrate scope of the tandem process was investigated (Scheme 2.4.1). To examine electronic effects, we prepared substrates 2.3, 2.8-2.12 with various electronic attributes. An electronic factor plays an important role in the hydroacylation step. Aromatic aldehydes with electron-withdrawing groups gave better yields than those with electron-donating groups. Electron-withdrawing groups accelerate addition of the ruthenium complex to the carbonyl of the aldehyde after addition of Ru-H to olefin.\(^\text{(a)}\) Also, it accelerates the reductive elimination for hydroacylation, producing a better yield of the desired product. It has been reported that substrates with electron-donating groups have a greater propensity for forming byproducts.\(^\text{(b)}\)

Also, to investigate the effects of the site of substitution on the aryl ring on the efficiency of the reaction, the tandem sequence were performed with substrates 2.13-2.18. The ortho-substituent in respect to the diene substrates 2.15 - 2.18 provided more effective transformations. The steric influence of a substituent in the ortho-position

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\(^\text{(a)}\) It will be discussed further in 2.5 mechanistic studies of the Ru-catalyzed tandem RCM/hydroacylation of this dissertation.  
\(^\text{(b)}\) For a representative example, see: Guo, X.; Wang, J.; Li, C. -J. J. Am. Chem Soc. 2009, 131, 15092-15093.
relative to the diene may help populate a more favorable conformer for making the ruthenium alkoxide complex after addition of ruthenium hydride. While a substituent in close proximity to the reacting aldehyde, the effectiveness of the catalyst is reduced (2.13 and 2.14). This steric effect may accelerate the reduction of ketone to produce the reduced side product and suppress production of the desired product (Scheme 2.4.1 and Scheme 2.5.7).

**Scheme 2.4.1 Substrate Scope of 5,6-Fused Ring System**

![Scheme 2.4.1 Substrate Scope of 5,6-Fused Ring System](image)

a Yields are an an average of two runs.
The optimized conditions of the tandem ring-closing metathesis/hydroacylation were also tested with substrates that can produce alternative ring sizes (Scheme 2.4.2). Unfortunately, these conditions were not effective with these substrates. It has been previously observed that generating larger ring systems is a challenge for hydroacylation. Formation of the five membered-ring is kinetically favored and as ring systems increase in size, access of ruthenium complex to the alkene becomes less entropically favored.

In the 5,5-ring fused system 2.19, there is a high amount of olefin-isomerized byproduct. To reduce the olefin-isomerized byproduct, we prepared substrate 2.20 with a methyl, however, it was not effective to improve the yield of desired products. The 5,7-ring system 2.21 gave desired product in moderate yield, but it produced cis and trans diastereomers (cis : trans = 5 : 2). In the case of 7,6-ring system 2.26, it afforded 26% of the desired product. Presumably, the 7,6-ring system is more accessible due to its increased flexibility when compared to the 5,5-ring system. Although diastereoselectivity and low yield are still issues in the 5,7 and 7,6 ring systems, these ring systems do generate hydroacylation product and thus, demonstrate the feasibility of this process. An aliphatic aldehyde, 4b,5,6,7,8,8a-hexahydrophenanthren-9(10H)-one, was also examined in tandem sequence. The formation of the desired product 2.88 was confirmed with mass spectrometry, however the product 2.88 could not isolated due to unidentified byproducts.
2.5 Mechanistic studies of the Ru-catalyzed tandem RCM/hydroacylation

We speculated as to the identity of the possible species of modified catalyst present as either a Ru-H species or further reduced Ru(0) species. Based on this speculation, the hydroacylation in the tandem sequence occurs via one of the following mechanisms: the hydroacyl-metal intermediate mechanism\textsuperscript{117} or the ruthenium alkoxide complex intermediate mechanism.\textsuperscript{126, 127} Several groups have performed mechanistic studies for Rh-catalyzed hydroacylation. Through isolation of the metal hydride intermediate and characterization by X-ray and D-labeling studies, the mechanism of hydroacylation with rhodium has been well-established.\textsuperscript{116, 133b, 139, 140} However, there are few studies that have examined Ru-catalyzed hydroacylation. Thus, there is a need to further examine the mechanism of Ru-catalyzed hydroacylation in order to determine an active catalyst species and mechanism in tandem reaction and understand the results.

First, to understand the results, the product outcomes were more closely studied. After the tandem process, byproducts can be isolated alongside the desired ketone. The major byproducts were identified (Scheme 2.5.1). Olefin isomerization of the initial RCM product 2.7 to the more thermodynamically stable trisubstituted olefin 2.28 was observed. Also, reduced compound 2.4 and 2.27 were generated. However, decarbonylated 2.39 compound known byproduct in hydroacylation could not be found.  

Scheme 2.5.1 Investigation of unexpected side products

2.5.1 Investigation of olefin-isomerized byproduct

The olefin-isomerized byproduct may be due to the base used as a reductant during the reaction or ruthenium species derived from decomposition of G2 at high temperature. The first question we addressed is if it is possible for the olefin-isomerized byproduct 2.28 to produce desired product 2.8 given enough reaction time (eq 2.2). Thus, we conducted the experiment with different reaction times (Table 2.5.1). The extended reaction time, 48 h, gave increased desired product, and olefin-isomerized byproduct was decreased (entry 1 vs 2); but a reaction time greater than 48 h did not lead to more of the desired product (entries 2 and 3). As time progresses, catalytic activity may be reduced.
To confirm that olefin-isomerized aldehyde can produce desired hydroacylated products, the purified naphthaldehyde 2.31 (16 mg) was subjected to the tandem reaction conditions (Scheme 2.5.2). The naphthaldehyde 2.31 was added to the tandem reaction of Cl-substituted aryl aldehyde substrate 2.29 after the metathesis step to ensure that the subjection reaction was performed under identical conditions of the tandem sequence, such that the same modified Ru-catalyst would be present. After completion of reaction, hydroacylated product 2.12 from naphthaldehyde 2.31 was isolated alongside compound 2.31 and 2.17. More than half of the olefin-isomerized aldehyde had reacted with the catalyst to generate desired hydroacylated product. This illustrates that the olefin-isomerized compound can also produce desired products.
Scheme 2.5.2 Producibility of hydroacylation product from olefin-isomerized compound

Next, we had another question regarding whether or not the substrate with electron-withdrawing group 2.32 provides desired product 2.9 via olefin-isomerized compound 2.34 or directly produces desired product 2.9 from olefin metathesis product 2.33 (Scheme 2.5.3).

Scheme 2.5.3 Possible pathway to produce of hydroacylation product

For the purposes of investigating our question, we made enantiomerically-enriched compound 2.35 (68:32 er) (Scheme 2.5.4). After reaction was completed, we found that the enantioselectivity of 2.37 did not change significantly (68:32 er to 65:35 er). However, when hydroacylation step is stopped early, after 1 hour reaction time, a mixtures of 2.9, 2.33 and 2.34 was observed (Scheme 2.5.5). This suggests that olefin isomerization occurs faster than the addition of the Ru-complex to the ketone of the aldehyde or
reductive elimination, and that the olefin-isomerized compound can produce desired product. Further study is needed to understand why the enantioselectivity was not affected even though olefin isomerization was happened.

_Scheme 2.5.4_ Enantiomerically-enriched compound _2.35_ in tandem sequence

Through base screening, we found that the olefin-isomerized product is strongly affected by the amount of base. To figure out the effect of base on the side product, we ran the reactions without base, and then compared the ratio of byproducts (Table 2.5.2). It produced olefin-isomerized-compound _2.28_ as the major byproduct in 20 mol % base. However, without base conditions, reduced compound _2.27_ was the major byproduct. Small amount of PCy₃ as an additive helped to produce desired product (Table 2.3.2.10).
Table 2.5.2 Effect of base and additive on olefin-isomerized compound

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>additive</th>
<th>time (h)</th>
<th>yields (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20 mol %</td>
<td>none</td>
<td>48</td>
<td>47 5</td>
</tr>
<tr>
<td>2</td>
<td>none</td>
<td>none</td>
<td>48</td>
<td>42 30</td>
</tr>
<tr>
<td>3</td>
<td>none</td>
<td>PCy$_3$</td>
<td>48</td>
<td>56 25</td>
</tr>
</tbody>
</table>

$^*$Yields of purified product $^b$Yields were detected by analysis of $^1$H NMR

To examine the effects of the base on other substrates, we also subjected substrates 2.1, 2.6, 2.32 and 2.40 to the tandem reaction conditions with or without base (Scheme 2.5.6). These substrates gave different results depending on their electronic aspects. The yields were improved in the presence of base except in the case of compound 2.40, which produced a large amount of the olefin isomerized compound (41%). Interestingly, compounds 2.6 and 2.40 with electron-rich aromatic rings reduced the amount of byproducts without base. This implies that the rate of elimination of Ru-alkoxide complex is faster than that of reductive elimination to generate desired hydroacylation products.
2.5.6 Effect of base on ratio of compounds

<table>
<thead>
<tr>
<th></th>
<th>A : B : C</th>
<th>A : B : C</th>
<th>A : B : C</th>
<th>A : B : C</th>
</tr>
</thead>
<tbody>
<tr>
<td>with base</td>
<td>76 : 17 : &lt;1</td>
<td>47 : 5 : 17</td>
<td>70 : 4 : &lt;1</td>
<td>37 : 4 : 41</td>
</tr>
</tbody>
</table>

2.5.2 Investigation of reduced byproduct

After confirming that the olefin isomerization compound is able to be generated from hydroacylated product and can be affected from base depending on electronic aspects, we focused on analyzing the reduced byproduct. Through previous experiments, we know that the yield of reduced compound is significantly related to the electronic and steric features of the substrate (Scheme 2.5.7). When substrates have an electron-donating group, yield of the reduced compound was increased (2.4, 2.27, 2.38 vs 2.41). With this result, we generated a Hammett plot for reduced products (Figure 2.5.1). The $\rho$-value for reduced compounds in our hydroacylation reaction was -0.69. This value indicates the formation of positive charge during the rate-determining step. Also, when a substituent is present in close proximity to the aldehyde, the amount of reduced compound was increased (2.38, 2.42 and 2.43).
Scheme 2.5.7 Effect of electronic attributes of the aryl on reduced products

- **Scheme 2.5.7**

  - **Scheme 1**: Effect of electronic attributes of the aryl on reduced products.

  - **Conditions**: Mes$_3$N$_2$N$_2$Mes, Ru$_{Cl}$(PC$_2$)(Ph)$_2$, toluene (0.06 M), rt, 1 h;

  - **Yield**: CO (400 psi), NaOMe (20 mol%), 200 °C, 24 h

  - **Products**:
    - **Yield**: 76% + 2.4% + 17% < 1%

  - **Scheme 2**: Effect of electronic attributes of the aryl on reduced products.

  - **Conditions**: Mes$_3$N$_2$N$_2$Mes, Ru$_{Cl}$(PC$_2$)(Ph)$_2$, toluene (0.06 M), rt, 1 h;

  - **Yield**: CO (400 psi), NaOMe (20 mol%), 200 °C, 24 h

  - **Products**: 58% + 2.27% + 25% < 1% + 2.38% < 1% + 4%

  - **Scheme 3**: Effect of electronic attributes of the aryl on reduced products.

  - **Conditions**: Mes$_3$N$_2$N$_2$Mes, Ru$_{Cl}$(PC$_2$)(Ph)$_2$, toluene (0.06 M), rt, 1 h;

  - **Yield**: CO (400 psi), NaOMe (20 mol%), 200 °C, 24 h

  - **Products**: 30% + 2.41% 45% + 4% 4% < 1% + 2.42% < 1% + 40%

  - **Scheme 4**: Effect of electronic attributes of the aryl on reduced products.

  - **Conditions**: Mes$_3$N$_2$N$_2$Mes, Ru$_{Cl}$(PC$_2$)(Ph)$_2$, toluene (0.06 M), rt, 1 h;

  - **Yield**: CO (400 psi), NaOMe (20 mol%), 200 °C, 24 h

  - **Products**: 77% + 2.43% 5% + 2.43% < 1% + 77%
At the first, we presumed that the reduced compounds could be produced through a side reaction pathway from the hydroacylated compound (eq 2.3). To check this hypothesis, we designed a resubjection experiment. Purified cyclic ketone 2.8 was added to the tandem reaction of CF₃-substituted aryl aldehyde substrate 2.32 after the metathesis step in order to perform the resubjection reaction under identical conditions of the tandem sequence. In contrast to our anticipation, after completion of reaction, there was no reduced product resulting from the F-substituted cyclic ketone 2.8 which was resubjected. The same result was also observed with CF₃-substituted cyclic ketone 2.15 which produced a 40% yield of the reduced side compound 2.42 in the tandem reaction (Scheme 2.5.7) is resubjected to the tandem reaction. Reduced compound was not generated from the ketone and the ketone does not react further once it is form in the reaction condition.

(141) The yield of reduced compound of fluoride substituted compound was 30% in without base condition, see Scheme 2.5.6
2.5.3 Plausible mechanisms

To reveal the origin of the reduced compound, mechanistic studies were undertaken. First, we proposed two plausible mechanisms for the tandem sequence (Scheme 2.5.9 and 2.5.10). We speculated the possible species of modified catalyst may either be a Ru-H species or a Ru(0) species. If the active catalyst is a Ru-H species, the reaction occurs via a ruthenium alkoxide intermediate. Ruthenium hydride is generated \textit{in situ} either by base or thermal decomposition after the RCM step. Resulting ruthenium hydride is added to olefin 2.54, and then it produces ruthenium alkoxide complex 2.55, followed by reductive elimination to produce hydroacylated product 2.3. The substrates with electron-withdrawing groups accelerate the rate from 2.54 to 2.55, thus making the carbonyl group more electrophilic. This also helps accelerate the reductive elimination step to generate 2.3. Otherwise, the electron-donating group would accelerate the loss of
the alkoxy-ruthenium complex to give 2.44. With this proposed mechanism, the steric effect of substituents can be explained well. Sterics in close proximity to the carbonyl are able to accelerate the release of the alkoxy-ruthenium complex since they raise the energy of intermediate 2.55 through electronic and steric factors. The released ruthenium hydroxide complex would produce CO$_2$ and regenerate the Ru-H species.

**Scheme 2.5.9** Proposed possible mechanism via ruthenium alkoxide complex

The other possible mechanism is shown in Scheme 2.5.10. This mechanism involves oxidative addition to the C-H of the aldehyde followed by addition to the alkene, then reductive elimination to give the hydroacylated product. However, the intermediate 2.59 can be involved in another pathway. If intermediate 2.59 undergoes a migratory
insertion into the carbonyl, it could generate intermediate 2.61 and 2.62. Elimination of CO₂ followed by a 1,2-hydride shift (2.63 to 2.64) would result in reduced product 2.64. Then compound 2.44 can olefin isomerize to obtain more thermodynamically stable tetrasubstituted olefin 2.4. The electron-donating group and steric in close proximity to the carbonyl may accelerate the release of carbon dioxide (2.62 to 2.63).

Scheme 2.5.10 Proposed Possible Mechanism via Hydridoacyl-ruthenium(II) complex

In order to figure out the proposed mechanism, we should consider the following factors. First, both mechanisms involve generation of 2.44 followed by isomerization to give reduced compound 2.4. However, 2.44 has not been observed as a reaction
byproduct, so we must confirm that the formation of $2.4$ from $2.44$ is a feasible process (eq 2.4). Secondly, we needed to confirm the identity of the active Ru-species in the hydroacylation step, as a Ru-H complex or Ru(0) speceis.

![Diagram](image)

(eq 2.4)

To support that reduced byproduct $2.4$ could be generated from intermediate $2.44$, compound $2.44$ was synthesized and subjected to the tandem reaction conditions after ring-closing metathesis with substrate $2.29$ to observe if any $2.4$ would be formed (Scheme 2.5.11). As expected, a significant amount of $2.44$ had been converted to $2.4$. In this experiment, we were also able to observe a small amount of the Cl-substituted $2.46$ through NMR analysis in the outcome of the tandem process.

**Scheme 2.5.11** Possibility of formation of the compound $2.4$ from the compound $2.44$

With the aim of figuring out the active catalyst in the hydroacylation step, we designed a crossover experiment. We synthesized deuterated aldehyde having trifluoromethyl $2.47$ and non-deuterated aldehyde having chloride $2.29$. If Ru(0) is the active catalyst, then the mechanism should occur via the hydridoacyl-ruthenium(II) complex intermediate, deuterium should be confined in compound $2.48$ (Scheme 2.5.12).
After RCM reaction, oxidative addition of ruthenium species into the C-D bond of the aldehyde 2.34, resulting ruthenium deuteride 2.80 adds to the alkene followed by reductive elimination giving the hydroacylated product 2.83. If this catalytic cycle is followed deuterium is confined to the same molecule.

Scheme 2.5.12 Crossover experiment involving Ru(0)

However, if a Ru-H complex is the active catalyst, the crossover experiment would lead to deuterium scrambling between the two substrates (Scheme 2.5.13). After RCM step, a Ru-H species is generated *in situ* under the reaction conditions. Once the ruthenium hydride adds to the olefin of deuterium labeled compound 2.34, it reacts with the aldehyde generating a ruthenium alkoxide intermediate 2.86. After β-hydride elimination, a ruthenium deuteride is generated. This resulting ruthenium deuteride can then react with a non-deuterium labeled compound 2.30 generating the crossover deuterium labeled compound 2.49. If the active catalyst is a Ru-H complex, deuterium scrambling should be observed.

**Scheme 2.5.13 Crossover experiment involving Ru-H**

![Scheme 2.5.13 Crossover experiment involving Ru-H](image)
Using high resolution mass spectrometry, compound 2.49 can be detected with a mass of 221 and its natural isotope abundance for deuterium incorporation is observed to be 16% (Figure 2.5.1). In the crossover experiment, the isotope abundance of compound 2.49 was increased from 16% to 46%, indicating that during the reaction, compound 2.17 is generated and deuterium scrambling can account for this observation. This suggests that a Ru-H species is presence in the hydroacylation reaction.
After confirming that a Ru-H species is present in the reaction, a control experiment was performed to identify when deuterium scrambling happens (Scheme 2.5.14). Aldehyde 2.47 and 2.29 are subjected to the tandem process and the hydroacylation step is stopped early, after 30 mins reaction time. A diminished deuterium incorporation of 2.34 was observed. This indicated that H/D scrambling of aldehyde occurs quickly before producing the desired product resulting in deuterium scrambling and loss of deuterium label. This remarkably suggests that Ru-H reversibly reacts with carbonyl faster than producing desired product (2.78 and 2.79 in Scheme 2.5.9). However, we could not definitively rule out the hydroacylation mechanism involving Ru(0).
To further investigate mechanism, we carried out D-labeling studies (Scheme 2.5.15). The substrate with two deuteriums 2.73 yielded only 6% of the reduced compound 2.76. In the case of the substrate with one deuterium, it also showed that the yield of reduced compounds is decreased (2.27 vs 2.68 and 2.72). However, in the High Mass analysis of 2.76, we not only see [M+3], but also [M+2] and [M+1]. This result correlates with the results shown in Scheme 2.5.12. During the reaction, deuterium from the substrate can be scrambled not only within the same substrate, but can also exchange places with hydrogens in the surrounding environment. This result strongly supports our Ru-H mechanism (Scheme 2.5.9). Through $^1$H-NMR, we can confirm that the signal of benzylic proton is decreased (2.68, 2.72 and 2.76). Also, we can observe the triple splitting ($J=19.5$ Hz) of benzylic carbon via $^{13}$C-NMR.
2.6 Conclusion

We have developed a new ruthenium catalyzed tandem ring-closing metathesis/hydroacylation methodology. The modified Grubbs’II catalyst with CO and NaOMe catalyzes the hydroacylation reaction good yield. Toluene is the optimal solvent and 200 °C is necessary for full conversion in hydroacylation step. To prevent catalyst decomposition and increase catalyst turnover, 400 psi of CO is necessary. Ru-H that might be active catalyst in the hydroacylation step is generated either through base or thermal decomposition. We propose possible mechanisms that involve a Ru-H species or a Ru(0) species as an active catalyst. Through analysis of side products, crossover reactions, and deuterated labeling studies, results suggest that the Ru-H mechanism for
hydroacylation in the tandem sequence is the more likely mechanism. This mechanism is also supported by trends observed in studying the scope of the process (Scheme 2.4.1). Electron donating groups in the para-position of aldehyde and substituents in close proximity to the carbonyl accelerate the elimination of the ruthenium alkoxide (2.55 to 2.44 in Scheme 2.5.9) since they raise the energy of intermediate 2.55 through electronic and steric factors. In general, this method is useful in producing tricyclic ring systems, which can also be used in the synthesis of natural products from readily available substrates.

In order to figure out the identity of the active Ru-species in the hydroacylation step, further studies are needed. Improvement of the tandem sequence for aliphatic aldehyde substrates could make this method more powerful.

2. 7 Experimental Details

(A) General procedure for tandem ring-closing metathesis/hydroacylation

\[ \text{(4aS*,9aR*)-2,3,4,4a-tetrahydro-1H-fluoren-9(9aH)-one (2.3).} \]

Grubbs’ II catalyst (37 mg, 0.043 mmol) was weighed into a flame-dried round bottom flask containing a stir bar inside N\(_2\) atmosphere glovebox. The flask was capped with a septum, the edges sealed with electrical tape, and removed from the glovebox. The reaction vessel was put under positive N\(_2\) pressured and toluene (3.0 mL) was added via syringe. A solution of 2-(octa-
1,7-dien-3-yl)benzaldehyde 2.1 (90 mg, 0.43 mmol) in toluene (3.0 mL) was added via syringe. The reaction was then stirred for 1 h at room temperature. At the end of that time period, carbon monoxide was sparged into the reaction mixture for 3 min (purple color is changed to yellow) followed by sodium methoxide (4.6 mg, 0.086 mmol) and a second 3 min sparge of carbon monoxide. The solution of reaction mixture was transferred to bomb reactor (model 4761) with a stir bar using 1.17 mL toluene (concentration is 0.06 M for hydroacylation reaction). The mixture was sealed with a Gage Block Assembly that attached to a carbon monoxide tank. The bomb reactor was placed behind a safety shield and the reactor was pressurized to 400 psi (at room temperature) and released three times. On the fourth pressurization the reactor was heated to 200 °C within 15 min with stirring, and held at this temperature for 24 h in wax bath. The reaction was terminated by cooling to room temperature and gaseous products were discharged. The solution mixture was transferred to round bottom flask with Et₂O then solvent was removed under reduced pressure to provide the crude product which was purified by silica gel chromatography (Et₂O/hexanes, 1/20) to afford product 2.3 (58 mg, 72%) as a clear oil. ¹H NMR (300 MHz, CDCl₃): δ 7.75 (d, J = 7.6 Hz, 1H), 7.56 (td, J = 7.6, 1.2 Hz, 1H), 7.45 (dd, J = 7.5, 1.2 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 3.38 (dt, J = 9.2, 6.8 Hz, 1H), 2.76 (td, J = 6.8, 4.8 Hz, 1H), 2.15-2.06 (m, 2H), 1.71-1.80 (m, 1H), 1.61-1.15 (m, 5H); ¹³C NMR (100 MHz, CDCl₃): δ 207.8, 158.5, 135.8, 134.4, 127.4, 125.0, 124.1, 48.7, 39.0, 31.5, 23.3, 22.8, 22.6; IR (thin film, NaCl): 3060, 3025, 2943, 2904, 2855, 2293, 1713, 1606, 1464, 1295 cm⁻¹; HRMS (ESI+) Calcd for C₁₃H₁₅O₁ [M+H]: 187.1123, found: 187.1131.
(B) General procedure for tandem ring-closing metathesis/hydroacylation

(4aS*,9aR*)-6-fluoro-2,3,4,4a-tetrahydro-1H-fluoren-9(9aH)-one (2.8). Grubbs’ II catalyst (25 mg, 0.029 mmol) was weighed into a bomb reactor (model 4714 from Parr Instrument Company) containing a stir bar inside N_2 atmosphere glovebox. The reactor was capped with a septum, the edges sealed with electrical tape, and removed from the glovebox. The reactor was put under positive N_2 pressured and toluene (1.9 mL) was added via syringe. A solution of 4-fluoro-2-(octa-1,7-dien-3-yl)benzaldehyde (68 mg, 0.29 mmol) in toluene (3.0 mL) was added via syringe. The reaction was then stirred for 1 h at room temperature. At the end of that time period, carbon monoxide was sparged into the reaction mixture for 3 min (purple color is changed to yellow) followed by tricyclohexylphosphine (1.6 mg, 0.0058 mmol) and a second 3 min sparge of carbon monoxide. The septum was replaced with a Gage Block Assembly that attached to a carbon monoxide tank. The bomb reactor was placed behind a safety shield and the reactor was pressurized to 400 psi (at room temperature) and released three times. On the fourth pressurization the reactor was heated to 200 °C within 15 min with stirring, and held at this temperature for 36 h in wax bath. The reaction was terminated by cooling to room temperature and gaseous products were discharged. The solution mixture was transferred to round bottom flask with ether then solvent was removed under reduced pressure to provide the crude product which was purified by silica gel chromatography (Et_2O/hexanes, 1/20) to afford product 2.8 (33 mg, 56%) as a clear oil. ^1H-NMR (500 MHz, CDCl_3): δ 7.68 (dd, J = 8.0, 5.5 Hz, 1H), 7.04 (dd, J = 8.5, 2.0 Hz, 1H), 6.98 (td, J
= 8.8, 2.5 Hz, 1H), 3.30 (q, J = 7.5 Hz, 1H), 2.71 (td, J = 7.0, 5.5 Hz, 1H), 2.07-1.97 (m, 2H), 1.72-1.65 (m, 1H), 1.54-1.41 (m, 2H), 1.37-1.29 (m, 1H), 1.22-1.11 (m, 2H); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)): \(\delta\) 205.9, 167.0 (d, J = 254 Hz), 161.2 (d, J = 9.3 Hz), 132.0 (d, J = 1.9 Hz), 126.2 (d, J = 10.6 Hz), 115.3 (d, J = 23.6 Hz), 111.8 (d, J = 21.8 Hz), 48.7, 38.7 (d, J = 1.9 Hz), 31.0, 23.1, 22.5, 22.2; IR (thin film, NaCl): 3060, 3024, 2926, 2916, 1715, 1614, 1592, 1248, 753, 747, 701 cm\(^{-1}\); HRMS (ESI+) Calcd for C\(_{13}\)H\(_{14}\)F\(_1\)O\(_1\) [M+H]\(^+\): 205.1029, found: 205.1028.

(C) General procedure for tandem ring-closing metathesis/hydroacylation

\[
\begin{align*}
\text{(4aS*,9aR*)-6-(trifluoromethyl)-2,3,4a-tetrahydro-1H-fluoren-9(9aH)-one (2.9).} \\
\text{Grubbs’ II catalyst (26.3 mg, 0.0310 mmol) was weighed into a bomb reactor (model 4714 from Parr Instrument Company) containing a stir bar inside N\(_2\) atmosphere glovebox. The reactor was capped with a septum, the edges sealed with electrical tape, and removed from the glovebox. The reactor was put under positive N\(_2\) pressured and toluene (2.0 mL) was added via syringe. A solution of 2-(octa-1,7-dien-3-yl)-4-(trifluoromethyl)-benzaldehyde (88 mg, 0.31 mmol) in toluene (3.2 mL) was added via syringe. The reaction was then stirred for 1 h at room temperature. At the end of that time period, carbon monoxide was sparged into the reaction mixture for 3 min (purple color is changed to yellow) followed by sodium methoxide (3.3 mg, 0.062 mmol) and a second 3 min sparge of carbon monoxide. The septum was replaced with a Gage Block Assembly that attached to a carbon monoxide tank. The bomb reactor was placed behind a safety shield and the reactor was pressurized to 400 psi (at room temperature) and released three}
\end{align*}
\]
times. On the fourth pressurization the reactor was heated to 200 °C within 15 min with stirring, and held at this temperature for 24 h in wax bath. The reaction was terminated by cooling to room temperature and gaseous products were discharged. The solution mixture was transferred to round bottom flask with ether then solvent was removed under reduced pressure to provide the crude product which was purified by silica gel chromatography (Et$_2$O/hexanes, 1/20) to afford product 2.9 (56 mg, 70%) as a white solid. $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.85 (d, $J = 8.0$ Hz, 1H), 7.72 (s, 1H), 7.62 (d, $J = 8.0$ Hz, 1H), 3.44 (q, $J = 7.4$ Hz, 1H), 2.82 (q, $J = 6.3$ Hz, 1H), 2.20-2.09 (m, 2H), 1.82-1.73 (m, 1H), 1.63-1.51 (m, 2H), 1.46-1.35 (m, 1H), 1.28-1.15 (m, 2H); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 206.5, 158.4, 138.4, 135.6 (q, $J = 32$ Hz), 124.5, 124.5 (q, $J = 3.6$ Hz), 123.7 (q, $J = 272$ Hz), 122.0 (q, $J = 3.6$ Hz), 49.0, 38.9, 31.5, 23.0, 22.6, 22.3; IR (thin film, NaCl): 3070, 3051, 2922, 2915, 2359, 2341, 1724, 1325, 1168, 1130, 1057 cm$^{-1}$; HRMS (ESI+) Calcd for C$_{14}$H$_{14}$F$_3$O$_1$ [M+H]$^+$: 255.0997, found: 255.1003.

(4aS*,9aR*)-6-chloro-2,3,4,4a-tetrahydro-1H-fluoren-9(9aH)-one (2.10). The general procedure for tandem ring-closing metathesis/hydroacylation (C) was followed with 4-chloro-2-(octa-1,7-dien-3-yl)benzaldehyde (44 mg, 0.18 mmol), Grubbs’ II catalyst (15 mg, 0.018 mmol), sodium methoxide (1.9 mg, 0.035 mmol) and toluene (3.0 mL). After metathesis reaction, the reactor was heated at 200 °C for 48 h at 200 °C. The crude reaction mixture was purified by silica gel chromatography (Et$_2$O/hexanes, 1/15) to afford product 2.10 (22 mg, 56%) as a clear oil. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.68 (d, $J$
Chapter 2- Development of a Tandem Ru-Catalyzed Ring-Closing Metathesis /Hydroacylation

= 7.5 Hz, 1H), 7.44 (s, 1H), 7.34 (d, J = 8.0 Hz, 1H), 3.36 (q, J = 7.5 Hz, 1H), 2.76 (q, J = 6.0 Hz, 1H), 2.12-2.06 (m, 2H), 1.77-1.71 (m, 1H), 1.59-1.48 (m, 2H), 1.43-1.36 (m, 1H). 1.26-1.16 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 206.3, 159.8, 140.7, 134.1, 128.0, 125.3, 125.2, 48.6, 38.6, 31.2, 23.1, 22.5, 22.3; IR (thin film, NaCl): 3090, 3071, 3052, 2947, 2892, 2860, 1717, 1597, 1576, 1326, 1065, 826 cm$^{-1}$; HRMS (ESI+) Calcd for C$_{13}$H$_{14}$ClO$_1$ [M+H]$^+$: 221.0733, found: 221.0735.

(4aS*,9aR*)-6-methoxy-2,3,4,4a-tetrahydro-1H-fluoren-9(9aH)-one (2.11). The general procedure for tandem ring-closing metathesis/hydroacylation (C) was followed with 4-methoxy-2-(octa-1,7-dien-3-yl)benzaldehyde (78 mg, 0.32 mmol), Grubbs’ II catalyst (27 mg, 0.032 mmol), sodium methoxide (3.45 mg, 0.0638 mmol) and toluene (5.3 mL). After metathesis reaction, the reactor was heated at 200 °C for 48 h at 200 °C. The crude reaction mixture was purified by silica gel chromatography (Et$_2$O/hexanes, 1/4) to afford product 2.11 (21 mg, 30%) as a white solid. $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 7.72 (d, J = 9.5 Hz, 1H), 6.92-6.89 (m, 2H), 3.91 (s, 3H), 3.35 (dt, J = 9.0, 7.0 Hz, 1H), 2.77 (td, J = 7.0, 5.0 Hz, 1H), 2.14-2.04 (m, 2H), 1.81-1.71 (m, 1H), 1.60-1.50 (m, 2H), 1.46-1.38 (m, 1H), 1.31-1.23 (m, 2H); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 206.2, 165.0, 161.2, 128.9, 125.7, 114.5, 108.8, 55.6, 48.5, 38.7, 30.9, 23.2, 22.4, 22.2; IR (thin film, NaCl): 3068, 3042, 2953, 2926, 2888, 2863, 2840, 1706, 1607, 1596, 1486, 1335, 1279, 1256, 1105, 1092, 757, 540 cm$^{-1}$; HRMS (ESI+) Calcd for C$_{14}$H$_{17}$O$_2$ [M+H]$^+$: 217.1229, found: 217.1230.
(D) General procedure for tandem ring-closing metathesis/hydroacylation

(4aS*,11aR*)-2,3,4,4a-tetrahydro-1H-benzo[b]fluoren-11(11aH)-one (2.12). Grubbs’ II catalyst (28 mg, 0.033 mmol) was weighed into a bomb reactor (model 4714 from Parr Instrument Company) containing a stir bar inside N₂ atmosphere glovebox. The reactor was capped with a septum, the edges sealed with electrical tape, and removed from the glovebox. The reactor was put under positive N₂ pressured and toluene (2.4 mL) was added via syringe. A solution of 3-(octa-1,7-dien-3-yl)-2-naphthaldehyde (86 mg, 0.33 mmol) in toluene (3.0 mL) was added via syringe. The reaction was then stirred for 1 h at room temperature. At the end of that time period, carbon monoxide was sparged into the reaction mixture for 3 min (purple color is changed to yellow) then the septum was replaced with a Gage Block Assembly that attached to a carbon monoxide tank. The bomb reactor was placed behind a safety shield and the reactor was pressurized to 400 psi (at room temperature) with CO and released three times. On the fourth pressurization the reactor was heated to 200 °C within 15 min with stirring, and held at this temperature for 48 h in wax bath. The reaction was terminated by cooling to room temperature and gaseous products were discharged. The solution mixture was transferred to round bottom flask with ether then solvent was removed under reduced pressure to provide the crude product which was purified by silica gel chromatography (Et₂O/hexanes, 1/15) to afford product 2.12 (31.4 mg, 41%) as a white solid. ¹H-NMR (500 MHz, CDCl₃): δ 8.32 (s, 1H), 7.98 (d, J = 8.5 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.85 (s, 1H), 7.58 (ddd, J = 8.5, 7.0, 1.5 Hz, 1H), 7.50 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 3.55 (q, J = 7.5 Hz, 1H), 2.87 (td, J
(4aS*,9aR*)-8-methyl-2,3,4,4a-tetrahydro-1H-fluoren-9(9aH)-one (2.13). The general procedure for tandem ring-closing metathesis/hydroacylation (C) was followed with 2-methyl-6-(octa-1,7-dien-3-yl)benzaldehyde (70 mg, 0.30 mmol), Grubbs’ II catalyst (25 mg, 0.029 mmol), sodium methoxide (3.2 mg, 0.059 mmol) and toluene (5.1 mL). After metathesis reaction, the reactor was heated at 200 °C for 48 h at 200 °C. The crude reaction mixture was purified by silica gel chromatography (Et₂O/hexanes, 1/20) to afford product 2.13 (26 mg, 42%) as a clear oil which crystallized when cooled. \(^1\)H-NMR (500 MHz, CDCl₃): \(\delta\) 7.41 (t, \(J = 7.5\) Hz, 1H), 7.25 (d, \(J = 8.0\) Hz, 1H), 7.09 (d, \(J = 7.0\) Hz, 1H), 3.31 (dt, \(J = 9.0, 6.5\) Hz, 1H), 2.71 (td, \(J = 7.0, 5.0\) Hz, 1H), 2.63 (s, 3H), 2.15-2.06 (m, 2H), 1.75-1.68 (m, 1H), 1.61-1.50 (m, 2H), 1.40-1.33 (m, 1H), 1.26-1.11 (m, 2H); \(^{13}\)C-NMR (125 MHz, CDCl₃): \(\delta\) 208.6, 159.0, 138.8, 133.5, 133.0, 129.1, 122.2, 48.9, 38.5, 31.9, 23.1, 22.9, 22.5, 18.2; IR (thin film, NaCl): 2926, 2855, 1712, 790, 431, 414 cm⁻¹; HRMS (ESI+) Calcd for C₁₇H₁₇O₁ [M+H]⁺: 237.1279, found: 237.1278.
(4aS,9aR)-8-(trifluoromethyl)-2,3,4,4a-tetrahydro-1H-fluoren-9(9aH)-one (2.14). The general procedure for tandem ring-closing metathesis/hydroacylation (C) was followed with 2-(octa-1,7-dien-3-yl)-6-(trifluoromethyl) benzaldehyde (65 mg, 0.23 mmol), Grubbs’ II catalyst (20 mg, 0.023 mmol), sodium methoxide (2.48 mg, 0.0459 mmol) and toluene (3.8 mL). After metathesis reaction, the reactor was heated at 200 °C for 48 h at 200 °C. The crude reaction mixture was purified by silica gel chromatography (Et₂O/hexanes, 1/20) to afford product 2.14 (24 mg, 41%) as a white solid. 

**¹H-NMR** (500 MHz, CDCl₃): δ 7.65-7.64 (m, 3H), 3.38 (dt, J = 10, 6.5 Hz, 1H), 2.81 (td, J = 7.0, 4.0 Hz, 1H), 2.27-2.12 (m, 2H), 1.75-1.68 (m, 1H), 1.62-1.53 (m, 2H), 1.43-1.34 (m, 1H), 1.25-1.18 (m, 1H), 1.14-1.08 (m, 1H); **¹³C-NMR** (125 MHz, CDCl₃): δ 203.3, 160.3, 133.6, 132.7, 128.9, 127.2 (q, J = 34 Hz), 125.0 (q, J = 5.8 Hz), 122.9 (q, J = 273 Hz), 49.3, 38.9, 32.4, 23.1, 23.0, 22.5; **IR** (thin film, NaCl): 3080, 2917, 2908, 1725, 1325, 1302, 1228, 1142, 1114, 1077, 1067, 817 cm⁻¹; **HRMS** (ESI⁺) Calcd for C₁₄H₁₇F₅N₁O₁ [M+NH₄]⁺: 272.1262, found: 272.1262.

(4aS*,9aR*)-5-methyl-2,3,4,4a-tetrahydro-1H-fluoren-9(9aH)-one (2.15). The general procedure for tandem ring-closing metathesis/ hydroacylation (C) was followed with 3-methyl-2-(octa-1,7-dien-3-yl)benzaldehyde (57 mg, 0.25 mmol), Grubbs’ II catalyst (21
mg, 0.025 mmol), sodium methoxide (2.7 mg, 0.050 mmol) and toluene (4.2 mL). After metathesis reaction, the reactor was heated at 200 °C for 48 h at 200 °C. The crude reaction mixture was purified by silica gel chromatography (Et₂O/hexanes, 1/20) to afford product 2.15 (32 mg, 64%) as a pale yellow soled. 

**¹H-NMR** (500 MHz, CDCl₃): δ 7.59 (d, J = 7.5 Hz, 1H), 7.35 (d, J = 7.5 Hz, 1H), 7.25 (t, J = 7.5 Hz, 1H), 3.41 (dt, J = 12, 6.5 Hz, 1H), 2.74 (td, J = 6.5, 1.5 Hz, 1H), 2.46-2.41 (m, 1H), 2.41 (s,3H), 2.29-2.25 (m, 1H), 1.71-1.61 (m, 3H), 1.35-1.25 (m, 1H), 1.16-1.08 (m, 1H), 0.81-0.73 (m, 1H); 

**¹³C-NMR** (125 MHz, CDCl₃): δ 207.5, 157.3, 135.4, 135.2, 134.6, 127.3, 121.4, 49.2, 38.3, 31.7, 23.8, 22.7, 22.7, 17.6; 

**IR** (thin film, NaCl): 3074, 3064, 3048, 3041, 2947, 2934, 2922, 2909, 2855, 1715, 1591, 1491, 1480, 1271, 1260, 1246, 768 cm⁻¹; 

**HRMS** (ESI) Calcd for C₁₄H₁₇O₁ [M+H]⁺: 201.1280, found: 201.1280.

(4aS*,9aR*)-5-(trifluoromethyl)-2,3,4,4a-tetrahydro-1H-fluoren-9(9aH)-one (2.16).

The general procedure for tandem ring-closing metathesis/hydroacylation (C) was followed with 2-(octa-1,7-dien-3-yl)-3-(trifluoromethyl)benzaldehyde (67 mg, 0.23 mmol), Grubbs’ II catalyst (20 mg, 0.023 mmol), sodium methoxide (2.5 mg, 0.047 mmol) and toluene (4.0 mL). The crude reaction mixture was purified by silica gel chromatography (Et₂O/hexanes, 1/20) to afford product 2.16 (45 mg, 77%) as a white solid. 

**¹H-NMR** (400 MHz, CDCl₃): δ 7.94 (dd, J = 7.6, 0.4 Hz, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.49 (t, J = 7.6, Hz, 1H), 3.67 (dt, J = 12, 6.4 Hz, 1H), 2.80 (t, J = 6.2 Hz, 1H), 2.51-
2.47 (m, 1H), 2.37-2.33 (m, 1H), 1.71-1.61 (m, 3H), 1.38-1.25 (m, 1H), 1.14-1.03 (m, 1H), 0.80-0.70 (m, 1H); $^{13}$C-NMR (100 MHz, CDCl$_3$): δ 205.2, 155.7, 137.1, 130.9 (q, $J$ = 4.5 Hz), 127.6, 127.6 (q, $J$ = 4.5 Hz), 127.3 (q, $J$ = 32 Hz), 124.1 (q, $J$ = 272 Hz), 49.8, 39.1, 34.6 (d, $J$ = 1.4 Hz), 24.1, 22.6, 22.5; IR (thin film, NaCl): 2941, 2855, 1725, 1348, 1338, 1319, 1175, 1155, 1113, 1065, 978, 821 cm$^{-1}$; HRMS (ESI+): Calcd for C$_{14}$H$_{14}$F$_3$O$_1$ [M+H]$^{+}$: 255.0997, found: 255.1006.

(4aS*,9aR*)-5-chloro-2,3,4,4a-tetrahydro-1H-fluoren-9(9aH)-one (2.17). The general procedure for tandem ring-closing metathesis/hydroacylation (C) was followed with 3-chloro-2-(octa-1,7-dien-3-yl)benzaldehyde (38 mg, 0.15 mmol), Grubbs’ II catalyst (13 mg, 0.015 mmol), sodium methoxide (1.6 mg, 0.030 mmol) and toluene (2.5 mL). The crude reaction mixture was purified by silica gel chromatography (Et$_2$O/hexanes, 1/30) to afford product 2.17 (28 mg, 85%) as a yellow solid. $^1$H-NMR (400 MHz, CDCl$_3$): δ 7.65 (dd, $J$ = 7.6, 0.4 Hz, 1H), 7.52 (dd, $J$ = 8.0, 1.2 Hz, 1H), 7.30 (t, $J$ = 7.6, Hz, 1H), 3.52 (dt, $J$ = 11.2, 6.4 Hz, 1H), 2.74 (td, $J$ = 7.2, 2.4 Hz, 1H), 2.49-2.41 (m, 2H), 1.73-1.61 (m, 3H), 1.43-1.08 (m, 2H), 0.84-0.74 (m, 1H); $^{13}$C-NMR (125 MHz, CDCl$_3$): δ 206.3, 155.8, 137.7, 134.4, 131.9, 128.8, 122.4, 49.2, 38.6, 31.0, 23.5, 22.7, 22.6; IR (thin film, NaCl): 3076, 3042, 2948, 2858, 1725, 1461, 1254, 1129 cm$^{-1}$; HRMS (ESI+): Calcd for C$_{13}$H$_{14}$Cl$_1$O$_1$ [M+H]$^{+}$: 221.0733, found: 221.0737.
Chapter 2- Development of a Tandem Ru-Catalyzed Ring-Closing Metathesis /Hydroacylation

(4aS*,9aR*)-9-oxo-2,3,4,4a,9,9a-hexahydro-1H-fluorene-5-carbonitrile (2.18). The general procedure for tandem ring-closing metathesis/hydroacylation (D) was followed with 3-formyl-2-(octa-1,7-dien-3-yl)benzonitrile (14 mg, 0.058 mmol), Grubbs’ II catalyst (5.0 mg, 0.0058 mmol), and toluene (1.0 mL). After metathesis reaction, the reactor was heated at 200 °C for 24 h. The crude reaction mixture was purified by silica gel chromatography (Et₂O/hexanes, 1/4) to afford product 2.18 (10 mg, 82%) as a white solid. ¹H-NMR (500 MHz, CDCl₃): δ 7.97 (dd, J = 7.5, 1.0 Hz, 1H), 7.83 (dd, J = 8.0, 1.0 Hz, 1H), 7.49 (t, J = 7.75, Hz, 1H), 3.64 (dt, J = 11, 6.5 Hz, 1H), 2.81 (td, J = 7.0, 2.5 Hz, 1H), 2.05-2.46 (m, 1H), 2.42-2.38 (m, 1H), 1.76-1.63 (m, 3H), 1.44-1.36 (m, 1H), 1.16-1.08 (m, 1H), 0.95-0.87 (m, 1H); ¹³C-NMR (125 MHz, CDCl₃): δ 205.1, 161.5, 137.5, 136.7, 128.5, 128.3, 116.5, 110.1, 48.9, 38.9, 31.9, 23.3, 22.5, 22.4; IR (thin film, NaCl): 3029, 2939, 2934, 2925, 2856, 2230, 1726, 1471, 1331, 1266, 1259 cm⁻¹; HRMS (ESI) Calcd for C₁₄H₁₄N₁O₁ [M+H]⁺: 212.1075, found: 212.1084.

(3aS*,8aR*)-1,3,3a,8a-tetrahydrocyclopenta[a]inden-8(2H)-one (2.19). The general procedure for tandem ring-closing metathesis/hydroacylation (D) was followed with 2-(hepta-1,6-dien-3-yl)benzaldehyde (69 mg, 0.32 mmol), Grubbs’ II catalyst (27 mg, 0.032 mmol), and toluene (5.4 mL). The crude reaction mixture was purified by silica gel
chromatography (Et$_2$O/hexanes, 1/20) to afford product **2.19** (16 mg, 29%) as a clear oil. 

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.65 (d, $J = 7.6$ Hz, 1H), 7.61 (td, $J = 7.4$, 1.2 Hz, 1H), 7.48 (dd, $J = 7.6$, 0.8 Hz, 1H), 7.36 (t, $J = 7.6$ Hz, 1H), 3.78 (t, $J = 7.6$ Hz, 1H), 3.07 (ddd, $J = 9.8$, 6.8, 2.4 Hz, 1H), 2.08-1.83 (m, 4H), 1.63-1.58 (m, 1H), 1.21-1.11 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 209.5, 158.9, 137.6, 135.3, 127.5, 126.1, 123.3, 52.6, 44.1, 33.3, 31.1, 25.0; IR (thin film, NaCl): 2952, 2866, 1710, 1605, 1465, 1335, 1284, 1212, 755 cm$^{-1}$; HRMS (ESI+): Calcd for C$_{12}$H$_{13}$O$_1$ [M+H]: 173.0966, found: 173.0968.

![Chemical structure](image)

(3aS*,8aR*)-3a-methyl-1,3,3a,8a-tetrahydrocyclopenta[a]inden-8(2H)-one  (**2.20**). 

The general procedure for tandem ring-closing metathesis/hydroacylation (C) was followed with 2-(3-methylhepta-1,6-dien-3-yl)benzaldehyde (90 mg, 0.42 mmol), Grubbs’ II catalyst (36 mg, 0.042 mmol), NaOMe (4.5 mg, 0.084 mmol), and toluene (7.0 mL). The crude reaction mixture was purified by silica gel chromatography (Et$_2$O/hexanes, 1/30) to afford product **2.20** (14 mg, 18%) as a clear oil. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.66 (d, $J = 8.0$ Hz, 1H), 7.63 (td, $J = 7.5$, 1.0 Hz, 1H), 7.50 (d, $J = 8.0$ Hz, 1H), 7.35 (td, $J = 7.3$, 1.0 Hz, 1H), 2.64-2.61 (m, 1H), 2.03-1.95 (m, 3H), 1.77-1.71 (m, 1H), 1.67-1.61 (m, 1H), 1.52 (s, 3H), 1.14-1.16 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 210.1, 163.0, 136.7, 135.5, 127.5, 124.3, 123.2, 60.3, 50.6, 41.4, 31.3, 27.4, 26.1; IR (thin film, NaCl): 2953, 2928, 2866, 1710, 1604, 1463, 1450, 1287, 1224, 766 cm$^{-1}$; HRMS (ESI+): Calcd for C$_{13}$H$_{15}$O$_1$ [M+H]: 187.1123, found: 187.1127.
5,6,7,8,9,9a-hexahydrobenzo[a]azulen-10(4bH)-one (2.21). 2-(nona-1,8-dien-3-yl) benz-aldehyde (94 mg, 0.41 mmol) was added to the solution of Grubbs’ II catalyst (34.8 mg, 0.0410 mmol) in toluene (6.9 mL). After being stirred for 1 h at room temperature, the reaction mixture was heated to 40 °C then stirred for 2 h. After cooling mixture solution to room temperature, the solution of reaction mixture was transferred to bomb reactor (model 4761) then sealed with a Gage Block Assembly that attached to a carbon monoxide tank. The bomb reactor was placed behind a safety shield and pressurized to 400 psi (at room temperature) with CO and released three times. On the fourth pressurization the reactor was heated to 200 °C within 15 min with stirring, and held at this temperature for 24 h in wax bath. The reaction was terminated by cooling to room temperature and gaseous products were discharged. The solution mixture was transferred to round bottom flask with Et₂O then solvent was removed under reduced pressure to provide the crude product which was purified by silica gel chromatography (Et₂O/hexanes, 1/20) to afford product 2.21 (52 mg, 63% trans: cis = 1: 3) as a clear oil.

cis-isomer: €H NMR (500 MHz, CDCl₃): δ 7.73 (d, J = 7.5 Hz, 1H), 7.60 (td, J = 7.5, 1.5 Hz, 1H), 7.51-7.49 (m, 1H), 7.36 (td, J = 8.5, 1.0 Hz, 1H), 3.56 (ddd, J = 11, 8.0, 4.0 Hz, 1H), 2.86 (ddd, J = 11, 8.0, 4.5 Hz, 1H), 2.21-2.14 (m, 2H), 1.84-1.29 (m, 8H); 13C NMR (100 MHz, CDCl₃): δ 209.4, 158.7, 136.4, 134.9, 127.5, 125.7, 123.7, 53.1, 44.5, 32.7, 31.4, 28.7, 28.5, 28.2; IR (thin film, NaCl): 2924, 2851, 1710, 1605, 1462, 1289, 1279, 756 cm⁻¹; HRMS (ESI+) Calcd for C₁₄H₁₇O₁ [M+H]: 201.1279, found: 201.1279.

trans-isomer: €H NMR (500 MHz, CDCl₃): δ 7.72 (d, J = 7.5 Hz, 1H), 7.59 (t, J = 7.5 Hz, 1H), 7.51-7.49 (m, 1H), 7.36 (td, J = 8.5, 1.0 Hz, 1H), 3.56 (ddd, J = 11, 8.0, 4.0 Hz, 1H), 2.86 (ddd, J = 11, 8.0, 4.5 Hz, 1H), 2.21-2.14 (m, 2H), 1.84-1.29 (m, 8H); 13C NMR (100 MHz, CDCl₃): δ 209.4, 158.7, 136.4, 134.9, 127.5, 125.7, 123.7, 53.1, 44.5, 32.7, 31.4, 28.7, 28.5, 28.2; IR (thin film, NaCl): 2924, 2851, 1710, 1605, 1462, 1289, 1279, 756 cm⁻¹; HRMS (ESI+) Calcd for C₁₄H₁₇O₁ [M+H]: 201.1279, found: 201.1279.
7.48 (d, \(J = 8.0\) Hz, 1H), 7.36 (td, \(J = 7.5, 1.0\) Hz, 1H), 3.08 (ddd, \(J = 11, 5.5, 5.5\) Hz, 1H), 2.54-2.35 (m, 3H), 1.89-1.46 (m, 8H); \(^{13}\text{C} \text{NMR}\) (100 MHz, CDCl\(_3\)): \(\delta\) 207.9, 156.8, 136.6, 134.6, 127.5, 124.6, 123.5, 55.4, 44.7, 32.2, 29.4, 28.5, 27.2, 25.8

**Synthesis of starting materials of 5, 6 ring systems for tandem ring-closing metathesis/hydroacylation**

![Chemical structure diagram]

**General procedure for methylation (A)**

**Methyl 2-iodobenzoate (S-1).**

2-iodobenzoic acid (7.44 g, 30.0 mmol) in MeOH (12.3 mL) was added 1.8 mL of conc. H\(_2\)SO\(_4\). The mixture was refluxed in air for 2.5 h and then it was cooled, diluted with H\(_2\)O (400 mL) and extracted several times with CH\(_2\)Cl\(_2\). The organic layers were washed with H\(_2\)O, NaHCO\(_3\), brine, and dried over anhydrous MgSO\(_4\). The solvent was removed under reduced pressure give methyl 2-iodobenzoate S-1 (7.47 g, 95%) as a clear oil. Spectral data are in accordance with the literature references.

**General procedure for alkylation using SN2’ reaction**

**Methyl 2-(octa-1,7-dien-3-yI)benzoate (S-3).** To a solution of methyl 2-iodobenzoate S-1 (1.57 g, 5.99 mmol) in dry THF (40 mL) cooled to -78 °C was added dropwise isopropylmagnesium chloride (1.26 M in THF, 7.14 mL, 9.00 mmol). The reaction mixture was stirred at -78 °C for 30 min before adding a daily prepared solution of CuCN

(0.54 mg, 6.0 mmol), LiCl (504 mg, 12.0 mmol) in THF (15 mL) followed, after a further 30 min, by (E)-1-bromohepta-1,6-diene S-2\(^{144}\) (2.26 g, 12.0 mmol) via syringe pump over 1 h. After being stirred for 1 h at -78 °C, the reaction mixture was warmed to room temperature then stirred overnight. The reaction mixture was quenched by addition of NH\(_4\)Cl (20 mL) and extracted with Et\(_2\)O (3 × 30 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous MgSO\(_4\). The solvent was removed under reduced pressure and purified by flash column chromatography (Et\(_2\)O/hexanes, 1/30) to give a clear colorless oil. Then additional purification was run by Ag-impregnated gradient silica gel chromatography (10% Ag, 9:1 Et\(_2\)O: hexanes with a gradient to 50% Et\(_2\)O) to afford methyl 2-(octa-1,7-dien-3-yl)benzoate S-3 (996 mg, 68% yield) as a clear, colorless oil. \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.74 (dd, \(J = 7.6, 1.2 \text{ Hz}, 1\)H), 7.43 (dd, \(J = 7.6, 1.2 \text{ Hz}, 1\)H), 7.32 (dd, \(J = 8.0, 1.2 \text{ Hz}, 1\)H), 7.23-7.19 (m, 1H), 6.00-5.91 (m, 1H), 5.79-5.72 (m, 1H), 5.04-4.89 (m, 4H), 4.24 (q, \(J = 7.2 \text{ Hz}, 1\)H), 3.88 (s, 3H), 2.02 (q, \(J = 7.2 \text{ Hz}, 2\)H), 1.74-1.68 (m, 2H), 1.47-1.23 (m, 2H); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)): \(\delta\) 168.8, 145.7, 142.1, 138.9, 131.8, 130.5, 130.1, 128.0, 125.9, 114.6, 114.6, 52.1, 44.2, 35.2, 33.8, 26.9 cm\(^{-1}\); HRMS (ESI+) Calcd for C\(_{16}\)H\(_{21}\)O\(_2\) [M+H]\(^+\): 245.1542, found: 245.1548.

**General procedure for reduction and oxidation reaction**

\((2-(\text{octa-1,7-dien-3-yl})\text{phenyl})\text{methanol (S-4).}\) To a stirred suspension of LiAlH\(_4\) 95% (684 mg, 18.0 mmol) in THF (50 mL) at 0 °C was slowly added a solution of methyl 2-(octa-1,7-dien-3-yl)benzoate S-3 (1.1 g, 4.5 mmol) in THF (30 mL). The reaction was

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stirred for 2 h at room temperature then the resulting solution was quenched at 0 °C by successive addition of H₂O (0.68 mL), 10% aqueous NaOH solution (1.3 mL) and H₂O (2.0 mL). After white solid was appeared, anhydrous MgSO₄ was added then stirred 1 h more. The reaction mixture was filtered through a plug of Celite and concentrated under reduced pressure to afford (2-(octa-1,7-dien-3-yl)phenyl)methanol S-4 (976 mg, 100%) as a clear, colorless oil. The resulting residue was used without any further purification in the next step.

2-(octa-1,7-dien-3-yl)benzaldehyde (2.1). PCC (1.45 g, 6.74 mmol) and Celite (1.0 g) were added to solution of (2-(octa-1,7-dien-3-yl)phenyl)methanol S-4 (976 mg, 4.51 mmol) in dry CH₂Cl₂ (50 mL) at room temperature for 2.5 h. The reaction mixtures were diluted with Et₂O (50 mL) then filtered through a plug of Celite - Silica with Et₂O and washed with NH₄Cl, NaHCO₃, brine, and dried over anhydrous MgSO₄. The solvent was removed under reduced pressure and purified by flash column chromatography (Et₂O/hexanes, 1/30) to afford 2-(octa-1,7-dien-3-yl)benzaldehyde 2.1 (871 mg, 90%) as a clear oil. 

**¹H-NMR** (300 MHz, CDCl₃): δ 10.34 (s, 1H), 7.83(dd, J = 7.5 1.5 Hz, 1H), 7.55 (td, J = 7.6, 1.5 Hz, 1H), 7.40-7.34 (m, 2H), 6.06-5.95 (m, 1H), 5.83-5.69 (m, 1H), 5.11-4.90 (m, 4H), 4.42 (q, J = 7.3 Hz, 1H), 2.09-2.02(m, 2H), 1.87-1.67 (m, 2H), 1.55-1.26 (m, 2H); 

**¹³C-NMR** (100 MHz, CDCl₃): δ 192.4, 147.2, 141.6, 138.6, 134.0, 133.8, 131.8, 128.2, 126.6, 115.4, 114.8, 42.9, 35.3, 33.9, 27.0; 

**IR** (thin film, NaCl): 3074, 3024, 2997, 2977, 2944, 2896, 2861, 2842, 2735, 2293, 1693, 1639, 1598, 1574, 914 cm⁻¹; 

Methyl 4-fluoro-2-iodobenzoate (S-6). The general procedure for methylation was followed with 4-fluoro-2-iodobenzoic acid S-5 (1.0 g, 3.8 mmol), H$_2$SO$_4$ (0.24 mL, 4.5 mmol), and methanol (3.0 mL). The crude reaction mixture was purified by silica gel chromatography (Et$_2$O/hexanes, 1/20) to afford product S-6 (1.03 g, 98%) as a clear, colorless oil. $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.86 (ddd, $J$ = 8.8, 6.0, 1.6 Hz, 1H), 7.73 (ddd, $J$ = 8.4, 2.8, 1.6 Hz, 1H), 7.14-7.01 (m, 1H), 3.92 (s, 3H); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 165.8, 163.5 (d, $J$ = 257 Hz), 132.7 (d, $J$ = 9.3 Hz), 130.8, 128.7 (d, $J$ = 23.6 Hz), 115.1 (d, $J$ = 21.3 Hz), 94.6 (d, $J$ = 8.4 Hz), 52.5; IR (thin film, NaCl) 3067, 3040, 2895, 1731, 1590, 1579, 1481, 1434, 1293, 1254, 1111, 868 cm$^{-1}$; HRMS (ESI+) Calcd for C$_8$H$_7$F$_1$I$_1$O$_2$[M+H]$^+$: 280.9475, found: 280.9470.

Methyl 4-fluoro-2-(octa-1,7-dien-3-yl)benzoate (S-7). The general procedure for alkylation using SN$_2$’ reaction was followed with methyl 4-fluoro-2-iodobenzoate S-6 (0.97 g, 3.5 mmol), isopropylmagnesium chloride (1.5 M in THF, 3.46 mL, 4.50 mmol), a solution of CuCN (311 mg, 3.46 mmol) and LiCl (290 mg, 6.92 mmol) in THF (10 mL), (E)-1-bromohepta-1,6-diene S-2 (1.3 g, 6.9 mmol), and THF (40 mL). The crude reaction mixture was purified by silica gel chromatography (Et$_2$O/hexanes, 1/20) and Ag-impregnated gradient silica gel chromatography (10% Ag, 9:1 Et$_2$O: hexanes with a gradient to 50% Et$_2$O) to afford product S-7 (575 mg, 63% yield) as a colorless oil. $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 7.83 (dd, $J$ = 9.0, 6.0 Hz, 1H), 7.03 (dd, $J$ = 10.5, 2.5 Hz, 1H), 6.92 (ddd, $J$ = 8.5, 7.5, 2.5 Hz, 1H), 5.96-5.89 (m, 1H), 5.81-5.72 (m, 1H), 5.08-
4.91 (m, 4H), 4.38 (q, J = 7.0 Hz, 1H), 3.88 (s, 3H), 2.05 (q, J = 7.0 Hz, 2H), 1.75-1.63 (m, 2H), 1.48-1.40 (m, 1H), 1.35-1.28 (m, 1H); $^{13}$C-NMR (125 MHz, CDCl$_3$): δ 167.5 164.8 (d, J = 251 Hz), 149.6 (d, J = 7.6 Hz), 141.2, 138.6, 132.8 (d, J = 9.3 Hz), 126.1 (d, J = 3.3 Hz), 115.1, 114.9 (d, J = 22.3 Hz), 114.6, 112.9 (d, J = 21.6 Hz), 52.1, 43.8 (d, J = 1.1 Hz), 35.0, 33.6, 26.7; IR (thin film, NaCl): 3077, 2998, 2979, 2951, 2860, 1725, 1607, 1586, 1435, 1273, 1245, 1116, 915 cm$^{-1}$; HRMS (ESI+) Calcd for C$_{16}$H$_{20}$F$_1$O$_2$ [M+H]$^+$: 263.1447, found: 263.1447.

(4-fluoro-2-(octa-1,7-dien-3-yl)phenyl)methanol (S-8). The general procedure for reduction was followed with LiAlH$_4$ 95% (319 mg, 8.39 mmol), methyl 4-fluoro-2-(octa-1,7-dien-3-yl)benzoate S-7 (553 mg, 2.11 mmol), and THF (40 mL). It afforded crude mixture S-8 (492 mg, 2.10 mmol) as a colorless oil, and the crude mixture was used without any further purification in the next step. $^1$H-NMR (500 MHz, CDCl$_3$): δ 7.24 (dd, J = 8.5, 6.0 Hz, 1H), 6.88 (dd, J = 10.5, 3.0 Hz, 1H), 6.81 (td, J = 8.3, 2.5 Hz, 1H), 5.85-5.78 (m, 1H), 5.73-5.65 (m, 1H), 4.97-4.85 (m, 4H), 4.65-4.57 (m, 2H), 3.56 (q, J = 7.5 Hz, 1H), 1.99 (q, J = 7.2 Hz, 2H), 1.71-1.58 (m, 2H), 1.52-1.21 (m, 3H); $^{13}$C-NMR (125 MHz, CDCl$_3$): δ 163.0 (d, J = 244 Hz), 145.5 (d, J = 6.5 Hz), 141.9, 138.7, 134.2 (d, J = 3.3 Hz), 130.7 (d, J = 8.8 Hz), 114.9, 114.8, 114.1 (d, J = 21.2 Hz), 113.1 (d, J = 21.1 Hz), 62.9, 44.4 (d, J = 1.6 Hz), 34.8, 33.8, 26.9; IR (thin film, NaCl): 3318, 3301, 3076, 2978, 2948, 2885, 2862, 1639, 1611, 1591, 1498, 1416, 1261, 1239, 995, 915 cm$^{-1}$; HRMS (ESI+) Calcd for C$_{15}$H$_{18}$F$_1$ [M-OH]$^+$: 217.1393, found: 217.1400.
4-fluoro-2-(octa-1,7-dien-3-yl)benzaldehyde (2.6). The general procedure for oxidation was followed with (4-fluoro-2-(octa-1,7-dien-3-yl)phenyl)methanol S-8 (492 mg, 2.10 mmol), PCC (720 mg, 3.34 mmol), Celite (700 mg), and dry CH₂Cl₂ (30 mL). The crude reaction mixture was purified by silica gel chromatography (Et₂O/hexanes, 1/30) to afford product 2.6 (460 mg, 94%) as a colorless oil. ¹H-NMR (500 MHz, CDCl₃): δ 10.26 (s, 1H), 7.85 (dd, J = 8.5, 6.0 Hz, 1H), 7.08-7.01 (m, 2H), 5.99-5.92 (m, 1H), 5.79-5.71 (m, 1H), 5.13-4.92 (m, 4H), 4.43 (q, J = 7.3 Hz, 1H), 2.06 (q, J = 7.2 Hz, 2H), 1.81-1.66 (m, 2H), 1.49-1.30 (m, 2H); ¹³C-NMR (125 MHz, CDCl₃): δ 190.5, 166.1 (d, J = 225 Hz), 150.7 (d, J = 8.1 Hz), 140.6, 138.3, 134.6 (d, J = 9.8 Hz), 130.3 (d, J = 2.1 Hz), 115.9, 115.1 (d, J = 22.2 Hz), 114.8, 113.8 (d, J = 21.8 Hz), 42.5 (d, J = 1.6 Hz), 34.9, 33.6, 26.7; IR (thin film, NaCl): 3081, 3061, 3030, 2977, 2949, 2863, 1703, 1693, 1605, 1581, 1230, 915, 818 cm⁻¹; HRMS (ESI+) Calcd for C₁₅H₁₈F₁O₁ [M+H]^+: 233.1342, found: 233.1339.

Methyl 2-amino-4-(trifluoromethyl)benzoate (S-10). The general procedure for methylation was followed with 2-amino-4-(trifluoromethyl)benzoic acid S-9 (2.0 g, 9.8 mmol), H₂SO₄ (0.58 mL, 11 mmol), and methanol (5.9 mL). The crude reaction mixture was purified by silica gel chromatography (Et₂O/hexanes, 1/8) to afford product S-10.
(1.66 g, 78%) as a white solid. \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.97 (d, \(J = 8.0\) Hz, 1H), 6.93 (dd, \(J = 1.0, 0.5\) Hz, 1H), 6.87 (dd, \(J = 8.5, 1.0, 0.5\) Hz, 1H), 5.94 (bs, 2H), 3.92 (s, 3H); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 167.9, 150.3, 135.6 (q, \(J = 32\) Hz), 132.4, 123.7 (q, \(J = 272\) Hz), 113.6 (q, \(J = 3.8\) Hz), 113.2, 112.4 (q, \(J = 3.7\) Hz), 52.0; IR (thin film, NaCl): 3480, 3397, 3367, 1688, 1596, 1441, 1335, 1305, 1245, 1159, 1118, 1093, 782 cm\(^{-1}\); HRMS (ESI+) Calcd for C\(_9\)H\(_9\)F\(_3\)N\(_1\)O\(_2\) [M+H]+: 220.0585, found: 220.0589.

Methyl 2-ido-4-(trifluoromethyl)benzoate (S-11). Methyl 2-amino-4-(trifluoromethyl)benzoate (S-10) (1.53 g, 6.98 mmol) was suspended in 20 mL of aceton, and mixture of conc. H\(_2\)SO\(_4\) (2.0 mL) in H\(_2\)O (20 mL) was added. The mixture was cooled to 0 °C in an ice bath, and a solution of NaN\(_2\) (504 mg, 7.33 mmol) in H\(_2\)O (10 mL) was added dropwise via addition funnel over 10 min, and stirred for 1 h. To this mixture was added dropwise a solution of KI (1.4 g, 8.4 mmol) in H\(_2\)O (10 mL) via addition funnel over 10 min, and the mixture allowed to warm to RT and stirred for 3 h. The reaction was quenched with 20 mL of sat. Na\(_2\)SO\(_4\), the acetone was then evaporated, and the aqueous layer was extracted with Et\(_2\)O (3 \(\times\) 50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous MgSO\(_4\). The solvent was removed under reduced pressure and purified by flash column chromatography on silica gel (Et\(_2\)O/hexanes, 1/20) to afford product S-11 (1.82 g, 79%) as a pale yellow oil which solidified when cooled. \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \(\delta\) 8.22 (d, \(J = 1.0\) Hz, 1H), 7.86 (d, \(J = 8.0\) Hz, 1H), 7.66 (dd, \(J = 8.0, 1.0\) Hz, 1H), 3.96 (s, 3H); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)): \(\delta\) 166.3, 138.8, 138.1 (q, \(J = 3.8\) Hz), 134.1 (q, \(J = 33\) Hz), 131.1, 125.0 (q, \(J = 3.6\) Hz), 122.5 (q, \(J = 272\) Hz), 93.8, 53.0; IR (thin film, NaCl): 3039, 2896, 1736, 1322,

**Methyl 2-(octa-1,7-dien-3-yl)-4-(trifluoromethyl)benzoate (S-12).** The general procedure for alkylation using SN2’ reaction was followed with Methyl 2-iodo-4-(trifluoromethyl)benzoate **S-11** (1.0 g, 3.0 mmol), isopropylmagnesium chloride (1.5 M in THF, 2.7 mL, 4.1 mmol), a solution of CuCN (282 mg, 3.14 mmol), LiCl (263 mg, 6.28 mmol) in THF (15 mL), (E)-1-bromohepta-1,6-diene **S-2** (1.0 g, 5.3 mmol), and THF (35 mL). The crude reaction mixture was purified by silica gel chromatography (Et$_2$O/hexanes, 1/20) and Ag-impregnated gradient silica gel chromatography (10% Ag, 9:1 Et$_2$O: hexanes with a gradient to 50% Et$_2$O) to afford product **S-12** (508 mg, 54% yield) as a yellow oil. **$^1$H-NMR** (400 MHz, CDCl$_3$): $\delta$ 7.83 (d, $J = 8.0$ Hz, 1H), 7.58 (s, 1H), 7.49 (dd, $J = 8.4$, 0.8 Hz, 1H), 5.98-5.90 (m, 1H), 5.81-5.71 (m, 1H), 5.11-4.92 (m, 4H), 4.24 (q, $J = 7.2$ Hz, 1H), 3.94-3.91 (m, 3H), 2.08-2.03 (m, 2H), 1.79-1.67 (m, 2H), 1.50-1.26 (m, 2H); **IR** (thin film, NaCl): 3052, 3041, 2936, 2929, 2921, 2913, 2359, 2340, 1731, 1450, 1331, 1299, 1269, 1241, 1170, 1131, 1092, 917, 767, 760, 751 cm$^{-1}$; **HRMS** (ESI+) Calcd for C$_{17}$H$_{20}$F$_3$O$_2$ [M+H]$^+$: 313.1415, found: 313.1408.

**Methyl (2-(octa-1,7-dien-3-yl)-4-(trifluoromethyl)phenyl)methanol (S-12).** The general procedure for reduction was followed with LiAlH$_4$ 95% (243 mg, 6.39 mmol), Methyl 2-(octa-1,7-dien-3-yl)-4-(trifluoromethyl)benzoate **S-12** (0.5 g, 1.6 mmol), and THF (40 mL). It afforded crude mixture **S-13** (460 mg, 1.62 mmol) and the crude mixture was used without any further purification in the next step. **$^1$H-NMR** (500 MHz, CDCl$_3$): $\delta$ 7.53 (d, $J = 8.0$ Hz, 1H), 7.48 (s, 1H), 7.47 (d, $J = 7.5$ Hz, 1H), 5.94-5.87 (m, 1H), 5.80-
5.73 (m, 1H), 5.07-4.94 (m, 4H), 4.83-4.76 (m, 2H), 3.62 (q, \(J = 7.3\) Hz, 1H), 2.07 (q, \(J = 7.0\) Hz, 2H), 1.82-1.65 (m, 3H), 1.49-1.43 (m, 1H), 1.36-1.28 (m, 1H); IR (thin film, NaCl): 3379, 3361, 3314, 3299, 3089, 3076, 2978, 2948, 1639, 1430, 1331, 1164, 1126, 1078, 916, 751, 697 cm\(^{-1}\); HRMS (ESI+) Calcd for C\(_{16}\)H\(_{23}\)F\(_3\)N\(_1\)O\(_1\)[M+NH\(_4\)]\(^+\): 302.1732, found: 302.1743.

2-(octa-1,7-dien-3-yl)-4-(trifluoromethyl)benzaldehyde (2.32). The general procedure for oxidation was followed with (2-(octa-1,7-dien-3-yl)-4-(trifluoromethyl)phenyl)methanol S-13 (455 mg, 1.60 mmol), PCC (516 mg, 2.40 mmol), Celite (500 mg), and dry CH\(_2\)Cl\(_2\) (30 mL). The crude reaction mixture was purified by silica gel chromatography (Et\(_2\)O/hexanes, 1/20) to afford product 2.32 (420 mg, 93%) as a colorless oil. \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta\) 10.41 (s, 1H), 7.94 (d, \(J = 8.4\) Hz, 1H), 7.61-7.63 (m, 2H), 6.04-5.95 (m, 1H), 5.81-5.71 (m, 1H), 5.17-4.93 (m, 4H), 4.39 (q, \(J = 7.2\) Hz, 1H), 2.07 (q, \(J = 6.8\) Hz, 2H), 1.89-1.70 (m, 2H), 1.53-1.30 (m, 2H); \(^{13}\)C-NMR (100 MHz, CDCl\(_3\)): \(\delta\) 191.3, 148.0, 140.6, 138.4, 136.2, 135.2 (q, \(J = 32\) Hz), 131.7, 125.3 (q, \(J = 3.7\) Hz), 123.7 (q, \(J = 272\) Hz), 123.5 (q, \(J = 3.7\) Hz), 116.4, 115.1, 43.0, 35.1, 33.6, 26.9; IR (thin film, NaCl): 3060, 2980, 2946, 2863, 1698, 1330, 1203, 1171, 1134 cm\(^{-1}\); HRMS (ESI+) Calcd for C\(_{16}\)H\(_{18}\)F\(_3\)O\(_1\)[M+H]\(^+\): 283.1310, found: 283.1299.

Methyl 4-chloro-2-iodobenzoate (S-15). The general procedure for methylation was followed with 4-chloro-2-iodobenzoic acid S-14 (1.0 g, 3.6 mmol), H\(_2\)SO\(_4\) (0.21 mL, 3.9
mmol), and methanol (2.9 mL). The crude reaction mixture was purified by silica gel chromatography (Et$_2$O/hexanes, 1/20) to afford product **S-15** (1.05 g, 100%) as a pale yellow oil which crystallized when cooled. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.87 (d, $J = 2.0$ Hz, 1H), 7.63 (d, $J = 8.5$ Hz, 1H), 7.25 (dd, $J = 8.5, 2.0$ Hz, 1H), 3.79 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 165.9, 141.0, 138.2, 133.1, 131.8, 128.2, 94.7, 52.7; IR (thin film, NaCl): 3060, 3028, 2950, 2919, 1730, 1576, 1549, 1463, 1433, 1285, 1248, 1116, 1032, 830 cm$^{-1}$; HRMS (ESI+) Calcd for C$_8$H$_7$Cl$_1$I$_1$O$_2$ [M+H]$^+$: 296.9179, found: 296.9170.

**Methyl 4-chloro-2-(octa-1,7-dien-3-yl)benzoate (S-16).** The general procedure for alkylation using SN2’ reaction was followed with methyl 4-chloro-2-iodobenzoate **S-15** (0.5 g, 1.7 mmol), isopropylmagnesium chloride (2.0 M in THF, 1.18 mL, 2.4 mmol), a solution of CuCN (152 mg, 1.69 mmol), LiCl (142 mg, 3.38 mmol) in THF (8.0 mL), (E)-1-bromohepta-1,6-diene (608 mg, 3.38 mmol), and THF (25 mL). The crude reaction mixture was purified by silica gel chromatography (Et$_2$O/hexanes, 1/20) and Ag-impregnated gradient silica gel chromatography (10% Ag, 9:1 Et$_2$O: hexanes with a gradient to 50% Et$_2$O) to afford product **S-16** (295 mg, 63% yield) as a colorless oil. $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 7.73 (d, $J = 8.0$ Hz, 1H), 7.24 (d, $J = 2.0$ Hz, 1H), 7.21 (dd, $J = 8.0, 1.5$ Hz, 1H), 5.95-5.88 (m, 1H), 5.81-5.73 (m, 1H), 5.09-4.92 (m, 4H), 4.31 (q, $J = 7.3$ Hz, 1H), 3.89 (s, 3H), 2.08-2.02 (m, 2H), 1.74-1.63 (m, 2H), 1.50-1.39 (m, 1H), 1.35-1.27 (m, 1H); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 167.6, 148.0, 141.0, 138.5, 138.0, 131.6, 128.3, 128.1, 126.0, 115.1, 114.5, 152.1, 43.7, 34.9, 33.5, 26.6; IR (thin film, NaCl): 3039,
(4-chloro-2-(octa-1,7-dien-3-yl)phenyl)methanol (S-17). The general procedure for reduction was followed with LiAlH₄ 95% (76 mg, 2.0 mmol), methyl 4-chloro-2-(octa-1,7-dien-3-yl)benzoate S-16 (0.14 g, 0.50 mmol), and THF (5.0 mL). It afforded crude mixture S-17 (126 mg, 0.504 mmol) and the crude mixture was used without any further purification in the next step. ^1H-NMR (500 MHz, CDCl₃): δ 7.30 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 1.5 Hz, 1H), 7.20 (dd, J = 8.0, 2.0 Hz, 1H), 5.92-5.85 (m, 1H), 5.81-5.73 (m, 1H), 5.05-4.93 (m, 4H), 4.73-4.65 (m, 2H), 3.59 (q, J = 7.5 Hz, 1H), 2.06 (q, J = 7.0 Hz, 2H), 1.75-1.65 (m, 2H), 1.58-1.29 (m, 3H); ^13C-NMR (125 MHz, CDCl₃): δ 144.5, 141.6, 138.4, 136.6, 134.0, 129.9, 127.1, 126.3, 114.8, 114.7, 62.6, 44.1, 34.5, 33.6, 26.7; IR (thin film, NaCl): 3317, 3078, 3060, 3027, 2976, 2936, 2925, 2912, 2907, 2860, 1638, 1500, 1485, 1458, 995 cm⁻¹; HRMS (ESI+) Calcd for C₁₆H₂₀Cl₂O₂ [M+H]^⁺: 279.1152, found: 279.1139.

4-chloro-2-(octa-1,7-dien-3-yl)benzaldehyde (S-18). The general procedure for oxidation was followed with (4-chloro-2-(octa-1,7-dien-3-yl)phenyl)methanol S-17 (94 mg, 0.37 mmol), PCC (121 mg, 0.563 mmol), Celite (100 mg), and dry CH₂Cl₂ (5.0 mL). The crude reaction mixture was purified by silica gel chromatography (Et₂O/hexanes, 1/30) to afford product S-18 (87 mg, 95%) as a colorless oil. ^1H-NMR (500 MHz, CDCl₃): δ 10.28 (s, 1H), 7.77 (d, J = 8.5 Hz, 1H), 7.36-7.33 (m, 2H), 5.99-5.92 (m, 1H), 5.75-5.72 (m, 1H), 5.14-4.93 (m, 4H), 4.37 (q, J = 7.5 Hz, 1H), 2.17-2.04 (m, 2H), 1.83-
1.67 (m, 2H), 1.56-1.41 (m, 1H), 1.39-1.31 (m, 1H); \(^{13}\text{C-NMR}\) (125 MHz, CDCl\(_3\)): \(\delta\) 190.9, 148.9, 140.5, 140.4, 138.3, 132.9, 131.9, 128.3, 126.9, 115.9, 114.8, 42.5, 34.9, 33.5, 26.6; \(\text{IR}\) (thin film, NaCl): 3075, 2977, 2947, 2862, 1693, 1639, 1589, 1560, 1204, 1190, 916, 818 cm\(^{-1}\); \(\text{HRMS}\) (ESI+) Calcd for C\(_{15}\)H\(_{16}\)Cl\(_1\)O\(_1\) [M+H]\(^+\): 249.1046, found: 249.1053.

**Methyl 4-methoxy-2-nitrobenzoate (S-19).** The general procedure for methylation was followed with 4-methoxy-2-nitrobenzoic acid (3.0 g, 15 mmol), H\(_2\)SO\(_4\) (0.89 mL, 17 mmol), and methanol (6.2 mL). The crude reaction mixture was purified by silica gel chromatography (EtOAc/hexanes, 1/10) to afford product S-19 (2.93 g, 91%) as a white solid. \(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)): \(\delta\) 7.77 (d, \(J = 8.4\) Hz, 1H), 7.23 (d, \(J = 2.8\) Hz, 1H), 7.10 (dd, \(J = 8.4, 2.4\) Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H); \(^{13}\text{C-NMR}\) (125 MHz, CDCl\(_3\)): \(\delta\) 165.0, 162.4, 150.9, 132.1, 118.0, 117.5, 109.3, 56.2, 53.0; \(\text{IR}\) (thin film, NaCl): 2935, 2921, 1710, 1515, 1509, 1456, 1440, 1380, 1327, 1291, 1249, 1189, 1136, 1024, 842 cm\(^{-1}\); \(\text{HRMS}\) (ESI+) Calcd for C\(_9\)H\(_{10}\)N\(_1\)O\(_5\) [M+H]\(^+\): 212.0559, found: 212.0567.

**Methyl 2-amino-4-methoxybenzoate (S-20).** To a solution of methyl 4-methoxy-2-nitrobenzoate S-19 (1.0 g, 4.7 mmol) in dry MeOH (30 mL) was 10% Pd/C (100 mg) then hydrogenation was performed under 1 atm of H\(_2\). The reaction was shown
completion by TLC, the solution was filtered through Celite. The solvent was removed under reduced pressure and purified by flash column chromatography on silica gel (Et₂O/hexanes, 1/10) to afford product S-20 (800 mg, 93%) as a white solid. ¹H-NMR (400 MHz, CDCl₃): δ 7.78 (d, J = 8.8 Hz, 1H), 6.23 (dd, J = 8.8, 2.4 Hz, 1H), 6.10 (d, J = 2.4 Hz, 1H), 5.79 (s, 2H), 3.83 (s, 3H), 3.78 (s, 3H); ¹³C-NMR (100 MHz, CDCl₃): δ 168.3, 164.2, 152.5, 133.0, 104.5, 104.4, 99.4, 55.1, 51.2; IR (thin film, NaCl): 3356, 1666, 1617, 1596, 1441, 1315, 1296, 1247, 1222, 1192, 1145, 1111, 1025 cm⁻¹; HRMS (ESI⁺) Calcd for C₉H₁₂N₁O₃ [M+H]⁺: 182.0817, found: 182.0815.

**Methyl 2-iodo-4-methoxybenzoate (S-21).** Methyl 2-amino-4-methoxybenzoate S-20 (818 mg, 4.51 mmol) was suspended in H₂O (10 mL), and a mixture of 1.0 mL of conc. H₂SO₄ in H₂O (10 mL) was added. The mixture was cooled to 0 °C in an ice bath, and a solution of NaNO₂ (326 mg, 4.74 mmol) in H₂O (10 mL) was added dropwise via addition funnel over 10 min, and stirred for 1 h. To this mixture was added dropwise a solution of KI (1.13 g, 6.76 mmol) in H₂O (10 mL) via addition funnel over 10 min, and the mixture allowed to warm to RT and stirred for 3 h. The reaction was quenched with sat. Na₂SO₃ (20 mL) and the aqueous layer was extracted with Et₂O (3 × 50 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous MgSO₄. The solvent was removed under reduced pressure and purified by flash column chromatography on silica gel (Et₂O/hexanes, 1/10) to afford product S-21 (1.19 g, 90%) as a yellow solid. ¹H-NMR (500 MHz, CDCl₃): δ 7.78 (d, J = 9.0 Hz, 1H), 7.55 (d, J = 2.5 Hz, 1H), 6.93 (dd, J = 8.5, 2.5 Hz, 1H), 3.92 (s, 3H), 3.86 (s, 3H); ¹³C-NMR (100 MHz, CDCl₃): δ 166.1, 162.1, 132.7, 127.1, 126.2, 113.8, 95.8, 55.8, 52.3; IR (thin

**Methyl 4-methoxy-2-(octa-1,7-dien-3-yl)benzoate (S-22).** The general procedure for alkylation using SN2’ reaction was followed with methyl 2-iodo-4-methoxybenzoate S-21 (778 g, 2.66 mmol), isopropylmagnesium chloride (1.5 M in THF, 2.3 mL), a solution of CuCN (239 mg, 2.66 mmol), LiCl (223 mg, 5.33 mmol) in THF (10 mL), (E)-1-bromohepta-1,6-diene (850 mg, 4.50 mmol), and THF (30 mL). The crude reaction mixture was purified by silica gel chromatography (Et$_2$O/hexanes, 1/20) and Ag-impregnated gradient silica gel chromatography (10% Ag, 9:1 Et$_2$O: hexanes with a gradient to 50% Et$_2$O) to afford product S-22 (555 mg, 76% yield) as a colorless oil. $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.84 (d, $J = 8.8$ Hz, 1H), 6.84 (d, $J = 2.4$ Hz, 1H), 6.74 (dd, $J = 8.4, 2.4$ Hz, 1H), 6.00-5.92 (m, 1H), 5.82-5.72 (m, 1H), 5.08-4.90 (m, 4H), 4.47 (q, $J = 7.3$ Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 2.04 (q, $J = 6.9$ Hz, 2H), 1.73-1.67 (m, 2H), 1.48-1.26 (m, 2H); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 168.0, 162.5, 149.1, 142.0, 139.0, 132.9, 122.3, 114.7, 114.5, 114.0, 110.7, 55.4, 51.9, 43.9, 35.3, 33.9, 26.9; IR (thin film, NaCl): 2999, 2975, 2949, 1717, 1607, 1571, 1434, 1251, 1237, 1188, 1126, 1085, 1038, 914 cm$^{-1}$; HRMS (ESI+) Calcd for C$_{17}$H$_{23}$O$_3$ [M+H]$^+$: 275.1647, found: 275.1646.

**(4-methoxy-2-(octa-1,7-dien-3-yl)phenyl)methanol (S-23).** The general procedure for reduction was followed with LiAlH$_4$ 95% (298 mg, 7.84 mmol), methyl 4-methoxy-2-(octa-1,7-dien-3-yl)benzoate S-22 (538 mg, 1.96 mmol), and THF (40 mL). It afforded
crude mixture S-23 (488 mg, 1.98 mmol, 100%) and the crude mixture was used without any further purification in the next step. **1H-NMR** (400 MHz, CDCl₃): δ 7.53 (d, J = 8.0 Hz, 1H), 7.09 (d, J = 2.0 Hz, 1H), 7.01 (dd, J = 8.4, 2.0 Hz, 1H), 6.26-6.17 (m, 1H), 6.10-6.00 (m, 1H), 5.31-5.20 (m, 4H), 4.93 (qd, J = 12.0, 4.8 Hz, 2H), 4.08 (s, 3H), 3.93 (q, J = 7.1 Hz, 1H), 2.94 (qd, J = 7.2, 0.8 Hz, 2H), 2.07-1.94 (m, 2H), 1.78-1.54 (m, 3H); **13C-NMR** (100 MHz, CDCl₃): δ 159.8, 144.8, 142.6, 138.8, 130.9, 130.7, 114.7, 114.5, 113.6, 110.8, 63.3, 55.4, 44.5, 35.0, 33.9, 27.0.

4-methoxy-2-(octa-1,7-dien-3-yl)benzaldehyde (S-24). The general procedure for oxidation was followed with (4-methoxy-2-(octa-1,7-dien-3-yl)phenyl)methanol S-23 (478 mg, 1.94 mmol), PCC (667 mg, 3.10 mmol), Celite (600 mg), and dry CH₂Cl₂ (20 mL). The crude reaction mixture was purified by silica gel chromatography (Et₂O/hexanes, 1/20) to afford product S-24 (420 mg, 89%) as a colorless oil. **1H-NMR** (400 MHz, CDCl₃): δ 10.17 (s, 1H), 7.79 (d, J = 9.2 Hz, 1H), 6.86-6.83 (m, 2H), 6.02-5.93 (m, 1H), 5.80-5.71 (m, 1H), 5.10-4.91 (m, 4H), 4.44 (q, J = 7.3 Hz, 1H), 3.87 (s, 3H), 2.05 (q, J = 7.2 Hz, 2H), 1.83-1.66 (m, 2H), 1.51-1.31 (m, 2H); **13C-NMR** (100 MHz, CDCl₃): δ 190.8, 163.9, 149.8, 141.2, 138.5, 134.8, 127.3, 115.3, 114.6, 114.0, 111.2, 55.4, 42.6, 35.0, 33.6, 26.7; **IR** (thin film, NaCl): 3076, 3059, 3023, 3003, 2976, 2947, 2888, 2860, 2941, 1689, 1638, 1605, 1597, 1566, 1287, 1239, 1202, 915 cm⁻¹; **HRMS** (ESI+) Calcd for C₁₆H₂₁O₂ [M+H]⁺: 245.1542, found: 245.1537.
3-iodo-2-naphthoic acid (S-25). The substrate was prepared by the literature procedure. The crude mixture was used without any further purification in the next step.

Methyl 3-iodo-2-naphthoate (S-26). Under Ar atmosphere, the crude mixture 3-iodo-2-naphthoic acid S-25 (1.59 g, 5.34 mmol) was dissolved in 5.3 mL of anhydrous THF and 3.6 mL of anhydrous MeOH. Then trimethylsilyldiazomethane (2.0 M in diethyl ether, 5.30 mL, 10.7 mmol) was slowly added with a small increase of the solution temperature. The brown solution was kept under agitation for 24 h at RT. The solution was evaporated under reduced pressure and purified by flash column chromatography on silica gel (Et$_2$O/hexanes, 1/15) to afford product S-26 (1.05 g, 2 steps 63%) as a yellow solid. $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 8.48 (s, 1H), 8.33 (s, 1H), 7.84 (d, $J$ = 8.0 Hz, 1H), 7.71 (d, $J$ = 8.0 Hz, 1H), 7.58-7.51 (m, 2H), 3.99 (s, 3H); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 167.0, 140.7, 135.7, 131.7, 131.6, 131.2, 128.8, 128.7, 127.3, 126.6, 88.6, 52.6; IR (thin film, NaCl): 3069, 3042, 2919, 1727, 1280, 1270, 1221, 1200, 1135, 1107, 763, 750, 699, 546 cm$^{-1}$; HRMS (ESI+) Calcd for C$_{12}$H$_{10}$I$_1$O$_2$ [M+H]$^+$: 312.9726, found: 312.9718.

Methyl 3-(octa-1,7-dien-3-yl)-2-naphthoate (S-27). The general procedure for alkylation using SN2’ reaction was followed with methyl 3-iodo-2-naphthoate S-26 (0.2 g, 0.64 mmol) in THF (2.5 mL), isopropylmagnesium chloride (1.3 M in THF, 0.74 mL, 0.96 mmol), a solution of CuCN (58 mg, 0.64 mmol), LiCl (27 mg, 0.64 mmol) in THF (2.0 mL), and (E)-1-bromohepta-1,6-diene (0.38 g, 2.0 mmol) in THF (2.0 mL). The crude reaction mixture was purified by silica gel chromatography (Et₂O/hexanes, 1/20) and Ag-impregnated gradient silica gel chromatography (10% Ag, 9:1 Et₂O: hexanes with a gradient to 50% Et₂O) to afford product S-27 (154 mg, 78% yield) as a pale yellow oil. \(^{1}\text{H-NMR}\) (500 MHz, CDCl₃): \(\delta 8.33\) (s, 1H), 7.85 (d, \(J = 8.5\) Hz, 1H), 7.80 (d, \(J = 8.0\) Hz, 1H), 7.75 (s, 1H), 7.56-7.46 (m, 2H), 6.08-6.00 (m, 1H), 5.83-5.75 (m, 1H), 5.08-4.91 (m, 4H), 4.36 (q, \(J = 7.3\) Hz, 1H), 3.96 (s, 3H), 2.17-2.06 (m, 2H), 1.87-1.78 (m, 2H), 1.55-1.36 (m, 2H); \(^{13}\text{C-NMR}\) (125 MHz, CDCl₃): \(\delta 168.7, 142.2, 141.5, 138.9, 134.8, 131.2, 130.9, 129.0, 128.5, 127.9, 127.4, 126.7, 126.1, 114.5, 114.4, 52.2, 44.1, 35.3, 33.8, 26.9; \(\text{IR}\) (thin film, NaCl): 3040, 1722, 1433, 1281, 1267, 1129, 912 cm\(^{-1}\); \(\text{HRMS}\) (ESI+) Calcd for C\(_{20}\)H\(_{23}\)O\(_2\) [M+H]\(^+\): 295.1698, found: 295.1686.

(3-(octa-1,7-dien-3-yl)naphthalen-2-yl)methanol (S-28). The general procedure for reduction was followed with LiAlH₄ 95% (158 mg, 4.60 mmol), methyl 3-(octa-1,7-dien-3-yl)-2-naphthoate S-27 (0.32 g, 1.0 mmol), and THF (15 mL). It afforded crude mixture S-28 (0.28 g, 1.0 mmol, 100%) and the crude mixture was used without any further purification in the next step. \(^{1}\text{H-NMR}\) (500 MHz, CDCl₃): \(\delta 7.84-7.79\) (m, 3H), 7.70 (s, 1H), 7.48-7.42 (m, 2H), 6.06-5.99 (m, 1H), 5.81-5.76 (m, 1H), 5.05-4.87 (m, 6H), 3.75 (q, \(J = 7.3\) Hz, 1H), 2.09 (q, \(J = 7.2\) Hz, 2H), 1.87 (q, \(J = 7.7\) Hz, 2H), 1.68 (bs, 1H), 1.53-
1.37 (m, 2H); $^{13}\text{C-NMR}$ (125 MHz, CDCl$_3$): $\delta$ 142.7, 140.5, 138.7, 137.1, 133.3, 132.0, 127.6, 127.4, 127.3, 126.0, 125.9, 125.6, 114.6, 114.4, 63.8, 44.2, 35.10, 33.7, 27.0; $\text{IR}$ (thin film, NaCl): 3399, 3358, 3341, 3289, 3273, 3222, 3201, 2933, 2928, 2909, 1411, 1385, 993, 912, 886, 775, 531 cm$^{-1}$; $\text{HRMS}$ (ESI+) Calcd for C$_{19}$H$_{26}$N$_{1}$O$_{1}$ [M+NH$_4$]$^+$: 284.2014, found: 284.2018.

$3$-(octa-1,7-dien-3-yl)-2-naphthaldehyde (2.40). The general procedure for oxidation was followed with (3-(octa-1,7-dien-3-yl)naphthalen-2-yl)methanol S-28 (273 mg, 1.04 mmol), PCC (353 mg, 1.64 mmol), Celite (300 mg), and dry CH$_2$Cl$_2$ (7.0 mL). The crude reaction mixture was purified by silica gel chromatography (Et$_2$O/hexanes, 1/20) to afford product 2.40 (245 mg, 90%) as a pale yellow oil. $^1\text{H-NMR}$ (500 MHz, CDCl$_3$): $\delta$ 10.37 (d, $J = 1.5$ Hz, 1H), 8.36 (s, 1H), 7.95 (d, $J = 8.0$ Hz, 1H), 7.84 (d, $J = 8.5$ Hz, 1H), 7.71 (s, 1H), 7.61 (td, $J = 7.5$, 1.5 Hz, 1H), 7.52 (td, $J = 7.5$, 1.5 Hz, 1H), 6.14-6.06 (m, 1H), 5.82-5.74 (m, 1H), 5.13-4.92 (m, 4H), 4.56 (q, $J = 7.0$ Hz, 1H), 2.11-2.06 (m, 2H), 1.85 (q, $J = 7.7$ Hz, 2H), 1.56-1.40 (m, 2H); $^{13}\text{C-NMR}$ (100 MHz, CDCl$_3$): $\delta$ 192.9, 141.8, 141.8, 138.6, 136.3, 135.8, 132.4, 131.1, 129.1, 1291., 127.5, 127.2, 126.5, 115.1, 114.6, 43.0, 35.2, 33.7, 26.9; $\text{IR}$ (thin film, NaCl): 3074, 3060, 3027, 2976, 2932, 2919, 2907, 2861, 1694, 1630, 1173, 913, 894 cm$^{-1}$; $\text{HRMS}$ (ESI+) Calcd for C$_{19}$H$_{21}$O$_{1}$ [M+H]$^+$:265.1592, found: 265.1591.
2-iodo-6-methylbenzoic acid (S-30). Pd(OAc)$_2$ (59 mg, 0.26 mmol) was added to the solution of 2-methylbenzoic acid S-29 (1.0 g, 5.3 mmol) and N-iodosuccinimide (1.3 g, 5.8 mmol) in DMF (20 mL) and the resulting solution was stirred at 100 °C for 20 h. After reaching ambient temperature, water (30 mL) and ether (20 mL) were added and the mixture was extracted with ether (3 x 20 mL). The combined organic layers were washed with water (2 x 10 mL) and brine (2 x 10 mL) dried over MgSO$_4$ and solvent was concentrated under reduced pressure. The crude product S-30 (1.57 g, 94%) was used without further purification. $^1$H NMR (500 MHz, CDCl$_3$): δ 12.50 (bs, 1H), 7.70 (d, $J$ = 8.0 Hz, 1H), 7.22 (dd, $J$ = 8.0, 0.5 Hz, 1H), 7.02 (t, $J$ = 8.0 Hz, 1H), 2.45 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 174.4, 139.0, 136.7, 136.6, 131.0, 129.9, 91.5, 20.3; IR (thin film, NaCl): 1704, 1284, 1241, 772 cm$^{-1}$; HRMS (ESI+) Calcd for C$_8$H$_8$I$_1$O$_2$ [M+H]: 262.9569, found: 262.9565.

Methyl 2-iodo-6-methylbenzoate (S-31). Under N$_2$ atmosphere, the crude mixture 2-iodo-6-methylbenzoic acid S-30 (2.2 g, 8.4 mmol) was dissolved in 20 mL of anhydrous THF and 5.0 mL of anhydrous MeOH. Then trimethylsilyldiazomethane (2.0 M in diethyl ether, 6.3 mL, 13 mmol) was slowly added. The brown solution was kept under (146) Mei, T.-S.; Giri, R.; Maugel, N.; Yu, J.-Q. Angew. Chem., Int. Ed. 2008, 47, 5215-5219.
agitation for 24 h at RT. The crude reaction mixture was purified by silica gel chromatography (Et$_2$O/hexanes, 1/20) to afford product S-31 (2.0 g, 86%) as a colorless oil which solidified when cooled. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.64 (d, $J = 8.0$ Hz, 1H), 7.17 (d, $J = 8.0$ Hz, 1H), 7.00 (t, $J = 8.0$ Hz, 1H), 3.95 (s, 3H), 2.33 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 169.7, 140.3, 136.7, 136.5, 130.8, 129.8, 92.0, 52.7, 20.2; IR (thin film, NaCl): 2951, 1733, 1560, 1439, 1277, 1245, 1190, 1180, 1144, 1099, 1067, 744 cm$^{-1}$; HRMS (ESI+) Calcd for C$_9$H$_{10}$I$_1$O$_2$ [M+H]: 276.9726, found: 276.9722.

**Methyl 2-methyl-6-(octa-1,7-dien-3-yl)benzoate (S-32).** The general procedure for alkylation using SN2’ reaction was followed with methyl 2-iodo-6-methylbenzoate S-31 (828 mg, 3.00 mmol), isopropylmagnesium chloride (1.3 M in THF, 3.5 mL, 4.5 mmol), a solution of CuCN (0.27 g, 3.0 mmol), LiCl (126 mg, 3.00 mmol) in THF (5.0 mL), (E)-1-bromohepta-1,6-diene (1.13 g, 5.98 mmol), and THF (30 mL). The crude reaction mixture was purified by silica gel chromatography (Et$_2$O/hexanes, 1/20) and Ag-impregnated gradient silica gel chromatography (10% Ag, 9:1 Et$_2$O: hexanes with a gradient to 50% Et$_2$O) to afford product S-32 (550 mg, 67% yield) as a colorless oil. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.26 (t, $J = 7.8$ Hz, 1H), 7.09 (d, $J = 8.0$ Hz, 1H), 7.04 (d, $J = 7.5$ Hz, 1H), 5.94-5.86 (m, 1H), 5.80-5.72 (m, 1H), 5.02-4.91 (m, 4H), 3.91 (s, 3H), 3.27 (q, $J = 7.3$ Hz, 1H), 2.29 (s, 3H), 2.03 (q, $J = 7.2$ Hz, 2H), 1.72 (q, $J = 7.8$ Hz, 2H), 1.43-1.36 (m, 1H), 1.31-1.24 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 170.5, 141.6, 141.2, 138.7, 134.6, 134.0, 129.4, 127.8, 124.2, 114.5, 114.3, 51.8, 46.5, 34.8, 33.6, 26.7, 19.7; IR (thin film, NaCl): 3053, 2978, 2951, 1731, 1267, 1234, 1114, 1072, 914, 764, 757, 700 cm$^{-1}$; HRMS (ESI+) Calcd for C$_{17}$H$_{23}$O$_2$ [M+H]$^+$: 259.1698, found: 259.1708.
(2-methyl-6-(octa-1,7-dien-3-yl)phenyl)methanol (S-33). The general procedure for reduction was followed with LiAlH₄ 95% (307 mg, 8.10 mmol), methyl 2-methyl-6-(octa-1,7-dien-3-yl)benzoate S-32 (0.55 g, 2.0 mmol), and THF (20 mL). The crude reaction mixture was purified by silica gel chromatography (Et₂O/hexanes, 1/4) to afford product S-33 (180 mg, 39%) as a colorless oil and 200 mg of recovered Methyl 2-methyl-6-(octa-1,7-dien-3-yl)benzoate S-32 (36%). ¹H-NMR (500 MHz, CDCl₃): δ 7.20 (t, J = 7.5 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 7.06 (d, J = 7.0 Hz, 1H), 6.01-5.94 (m, 1H), 5.81-5.73 (m, 1H), 5.03-4.92 (m, 4H), 4.80-4.72 (m, 2H), 3.75 (q, J = 7.3 Hz, 1H), 2.45 (s, 3H), 2.07 (q, J = 7.0 Hz, 2H), 1.81-1.69 (m, 2H), 1.48-1.26 (m, 3H); ¹³C-NMR (125 MHz, CDCl₃): δ 143.5, 143.4, 138.7, 137.7, 136.3, 128.6, 128.4, 125.0, 114.6, 114.2, 58.6, 44.8, 35.0, 33.7, 27.0, 19.9; IR (thin film, NaCl): 3372, 3363, 3331, 3313, 3230, 3238, 3228, 2929, 1384, 996, 912, 738 cm⁻¹; HRMS (ESI+) Calcd for C₁₆H₂₆N₁O₁ [M+NH₄]⁺: 248.2014, found: 248.2024.

2-methyl-6-(octa-1,7-dien-3-yl)benzaldehyde (S-34). The general procedure for oxidation was followed with (2-methyl-6-(octa-1,7-dien-3-yl)phenyl)methanol S-33 (178 mg, 0.774 mmol), PCC (266 mg, 1.24 mmol), Celite (200 mg), and dry CH₂Cl₂ (5.0 mL). The crude reaction mixture was purified by silica gel chromatography (Et₂O/hexanes, 1/30) to afford product S-34 (154 mg, 88%) as a colorless oil. ¹H-NMR (400 MHz, CDCl₃): δ 10.64 (s, 1H), 7.37 (t, J = 7.8 Hz, 1H), 7.21 (d, J = 7.6 Hz, 1H), 7.09 (d, J = 7.6 Hz, 1H), 6.02-5.93 (m, 1H), 5.81-5.71 (m, 1H), 5.08-4.91 (m, 4H), 4.15 (q, J = 7.2 Hz, 1H), 2.56 (s, 3H), 2.08-2.02 (m, 2H), 1.80-1.71 (m, 2H), 1.47-1.31 (m, 2H); ¹³C-NMR (100 MHz, CDCl₃): δ 194.3, 146.9, 141.8, 140.4, 138.7, 133.1, 132.8, 129.7, 125.9, 115.1,
114.7, 43.6, 35.3, 33.8, 26.9, 20.9; IR (thin film, NaCl): 3074, 2977, 2946, 2888, 2862, 2840, 1692, 1638, 1593, 1578, 1465, 1436, 1414, 1185, 993, 914 cm⁻¹; HRMS (ESI⁺) Calcd for C₁₆H₂₁O₁ [M+H]⁺: 229.1592, found: 229.1591.

2-ido-6-(trifluoromethyl)benzoic acid (S-35). Pd(OAc)₂ (235 mg, 1.05 mmol) was added to the solution of 2-(trifluoromethyl)benzoic acid (2.0 g, 11 mmol) and N-iodosuccinimide (2.6 g, 12 mmol) in DMF(30 mL) and the resulting solution was stirred at 100 °C for 20 h. After reaching ambient temperature, water (30 mL) and ether (20 mL) were added and the mixture was extracted with ether (3 x 20 mL). The combined organic layers were washed with water (2 x 10 mL) and brine (2 x 10 mL) dried over anhydrous MgSO₄ and solvent was concentrated under reduced pressure. The crude product S-35 was used for next step without further purification. ¹H-NMR (500 MHz, CDCl₃): δ 11.25 (bs, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.29 (t, J = 8.0 Hz, 1H); ¹³C-NMR (125 MHz, CDCl₃): δ 172.0, 142.9, 136.9, 131.0, 128.8 (q, J = 32 Hz), 125.9 (q, J = 4.7 Hz), 122.4 (q, J = 272 Hz), 93.1; IR (thin film, NaCl): 3059, 3028, 2922, 2916, 1712, 1400, 1310, 1292, 1175, 1136, 795 cm⁻¹; HRMS (ESI⁺) Calcd for C₈H₄F₃I₂O₂ [M+H]⁺: 315.9208, found: 315.9216.
Methyl 2-iodo-6-(trifluoromethyl)benzoate (S-36). Under N\textsubscript{2} atmosphere, the crude 2-iodo-6-(trifluoromethyl) benzoic acid S-35 was dissolved in 15 mL of anhydrous Et\textsubscript{2}O and 5.0 mL of anhydrous MeOH at 0 °C. The solution trimethylsilyldiazomethane (2.0 M in diethyl ether, 7.9 mL, 16 mmol) was slowly added to the solution until the reaction mixture ceased to generate nitrogen. After stirring at the same temperature for 2 h, reaction solution was concentrated and resulting reside was purified by flash column chromatography on silica gel (Et\textsubscript{2}O/hexanes, 1/30) to afford product S-36 (2.78 g, 2 steps 80%) as a white solid. \textsuperscript{1}H-NMR (500 MHz, CDCl\textsubscript{3}): δ 8.05 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 8.5 Hz, 1H), 7.24 (td, J = 8.0, 0.5 Hz, 1H), 3.99 (s, 3H); \textsuperscript{13}C-NMR (125 MHz, CDCl\textsubscript{3}): δ 167.3, 142.7, 138.0, 130.7, 128.8 (q, J = 32 Hz), 125.8 (q, J = 4.5 Hz), 122.4 (q, J = 273 Hz), 93.6, 53.2; IR (thin film, NaCl): 3042, 2919, 1732, 1429, 1310, 1283, 1209, 1140, 1173, 1140, 1065, 1053, 795 cm\textsuperscript{-1}; HRMS (ESI+) Calcd for C\textsubscript{9}H\textsubscript{7}F\textsubscript{3}I\textsubscript{1}O\textsubscript{2} [M+H]\textsuperscript{+}: 330.9443, found: 330.9450.

Methyl 2-(octa-1,7-dien-3-yl)-6-(trifluoromethyl)benzoate (S-37). The general procedure for alkylation using SN2’ reaction was followed with methyl 2-iodo-6-(trifluoromethyl)-benzoate S-36 (211 mg, 0.640 mmol), isopropyl-magnesium chloride (1.3 M in THF, 0.74 mL, 0.96 mmol), a solution of CuCN (57.6 mg, 0.639 mmol) and LiCl (27 mg, 0.64 mmol) in THF (2.0 mL), (E)-1-bromohepta-1,6-diene S-37 (0.38 g, 2.0 mmol), and THF (3.5 mL). The crude reaction mixture was purified by silica gel chromatography (Et\textsubscript{2}O/hexanes, 1/20) and Ag-impregnated gradient silica gel chromatography (10% Ag, 9:1 Et\textsubscript{2}O: hexanes with a gradient to 50% Et\textsubscript{2}O) to afford
product (55 mg, 28% yield) as a colorless oil. $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 7.32-7.26 (m, 3H), 5.70-5.49 (m, 1H), 5.57-5.49 (m, 1H), 4.86-4.70 (m, 4H), 3.71 (s, 3H), 3.12 (q, $J$ = 7.5 Hz, 1H), 1.84-1.79 (m, 2H), 1.55-1.49 (m, 2H), 1.21-1.16 (m, 1H), 1.08-1.01 (m, 1H); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 168.0, 142.8, 140.5, 138.3, 131.5 (q, $J$ = 1.75 Hz), 130.7, 129.6, 127.4 (q, $J$ = 31 Hz), 124.0 (q, $J$ = 4.5 Hz), 123.5 (q, $J$ = 272 Hz), 115.2, 114.7, 52.5, 45.9, 34.7, 33.4, 26.5; IR (thin film, NaCl): 2953, 1740, 1318, 1281, 1258, 1167, 1135, 1099, 1067, 916 cm$^{-1}$; HRMS (ESI+) Calcd for C$_{17}$H$_{20}$F$_3$O$_2$ [M+H]$^+$: 313.1415, found: 313.1421.

(2-(octa-1,7-dien-3-yl)-6-(trifluoromethyl)phenyl)methanol (S-38). Diisobutylaluminum hydride (0.094 mL, 0.53 mmol) was added dropwise to a magnetically stirred solution of methyl 2-(octa-1,7-dien-3-yl)-6-(trifluoromethyl)benzoate S-37 (55 mg, 0.18 mmol) in CH$_2$Cl$_2$ (5.0 mL) maintained under a nitrogen atmosphere at -78 °C. The resulting mixture was stirred for 2 h at -78 °C then warmed to room temperature. Once the reaction was complete by TLC, the reaction mixture was cooled to -78 °C then quenched with 1 M HCl and diluted with CH$_2$Cl$_2$ (20 mL). The resulting mixture was warmed to room temperature and the organic phase was washed with water (10 mL), brine (10 mL), and dried over anhydrous MgSO$_4$. The solvent was removed under reduced pressure and purified by flash column chromatography (Et$_2$O/hexanes, 1/3) to afford product S-38 (45 mg, 89%) as a colorless oil. $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 7.54 (d, $J$ = 8.0 Hz, 1H), 7.50 (d, $J$ = 7.5 Hz, 1H), 7.40 (t, $J$ = 8.0 Hz, 1H), 5.99-5.92 (m, 1H), 5.80-5.72 (m, 1H), 5.06-4.93 (m, 4H), 4.85-4.82 (m, 2H), 3.92 (q, $J$ = 7.5 Hz, 1H), 2.07 (q, $J$ = 7.5 Hz, 2H), 1.83-1.69 (m, 2H), 1.67 (t, $J$ = 6.5 Hz, 1H), 1.50-1.44 (m, 1H), 1.35-1.28 (m, 1H); $^{13}$C-
NMR (125 MHz, CDCl₃): δ 146.6, 141.9, 138.5, 135.9, 131.2, 129.1 (q, J = 29 Hz), 128.3, 124.6 (q, J = 273 Hz), 123.7 (q, J = 5.9 Hz), 114.8, 114.6, 57.6 (q, J = 2.75 Hz), 43.7, 35.0, 33.6, 26.7 cm⁻¹; HRMS (ESI+) Calcd for C₁₆H₂₀F₃O₁ [M+H]⁺: 285.1466, found: 285.1464.

2-(octa-1,7-dien-3-yl)-6-(trifluoromethyl)benzaldehyde (S-39). The general procedure for oxidation was followed with (2-(octa-1,7-dien-3-yl)-6-(trifluoromethyl)phenyl)methanol S-38 (85 mg, 0.30 mmol), PCC (103 mg, 0.479 mmol), Celite (100 mg), and dry CH₂Cl₂ (6.0 mL). The crude reaction mixture was purified by silica gel chromatography (Et₂O/hexanes, 1/50) to afford product S-39 (75 mg, 89%) as a colorless oil. ¹H-NMR (500 MHz, CDCl₃): δ 10.44 (q, J = 2.7 Hz, 1H), 7.52-7.44 (m, 3H), 5.96-5.89 (m, 1H), 5.78-5.73 (m, 1H), 5.10-4.92 (m, 4H), 4.06 (q, J = 7.5 Hz, 1H), 2.07-2.02 (m, 2H), 1.76-1.69 (m, 2H), 1.46-1.42 (m, 1H), 1.33-1.28 (m, 1H); ¹³C-NMR (125 MHz, CDCl₃): δ 193.2 (d, J = 2.4 Hz), 146.6, 140.9, 138.6, 134.2, 132.1, 131.6, 130.3 (q, J = 32 Hz), 124.4 (q, J = 5.7 Hz), 124.3 (q, J = 273 Hz), 115.8, 114.9, 43.6, 35.2, 33.7, 26.7; IR (thin film, NaCl): 3027, 2933, 2922, 2909, 2861, 1709, 1640, 1312, 1167, 1128, 993, 916, 807 cm⁻¹; HRMS (ESI+) Calcd for C₁₆H₁₈F₃O₁ [M+H]⁺: 283.1310, found: 283.1313.
Methyl 2-amino-3-methylbenzoate (S-40). The compound is prepared according to a procedure of Methyl 2-iodo-6-(trifluoromethyl)benzoate S-36 with 2-amino-3-methylbenzoic acid (1.0 g, 6.6 mmol), solution trimethylsilyl-diazomethane (2.0 M in diethyl ether, 4.0 mL, 8.0 mmol), Et₂O (10 mL), and MeOH (10 mL). The crude reaction mixture was purified by silica gel chromatography (Et₂O/hexanes, 1/10) to afford product S-40 (600 mg, 55%) as a colorless oil and 380 mg of recovered of 2-amino-3-methylbenzoic acid (38%). ¹H-NMR (500 MHz, CDCl₃): δ 7.77 (d, J = 7.5 Hz, 1H), 7.19 (d, J = 7.5 Hz, 1H), 6.60 (t, J = 7.5 Hz, 1H), 5.82 (bs, 2H), 3.87 (s, 3H), 2.17 (s, 3H); ¹³C-NMR (125 MHz, CDCl₃): δ 169.0, 149.0, 134.8, 129.1, 123.0, 115.6, 110.2, 51.5, 17.4; IR (thin film, NaCl): 3491, 3373, 3026, 2928, 2916, 1692, 1613, 1589, 1570, 1465, 1437, 1303, 1281, 1247, 1200, 1087, 751 cm⁻¹; HRMS (ESI+) Calcd for C₉H₁₂N₁O₂ [M+H]⁺: 166.0868, found: 166.0870.

Methyl 2-iodo-3-methylbenzoate (S-41). The compound is prepared according to a procedure of Methyl 2-iodo-4-(trifluoromethyl)benzoate S-11 with methyl 2-amino-3-methylbenzoate S-40 (0.6 g, 3.6 mmol) in 7.0 mL of aceton, and mixture of conc. H₂SO₄ (1.0 mL) in H₂O (15 mL), NaNO₂ (263 mg, 3.82 mmol) in 7.0 mL H₂O, and KI (783 mg, 4.72 mmol) in 7.0 mL H₂O. The crude reaction mixture was purified by silica gel chromatography (Et₂O/hexanes, 1/40) to afford product S-41 (826 mg, 82%) as a colorless oil.¹H-NMR (500 MHz, CDCl₃): δ 7.12 (d, J = 8.0 Hz, 1H), 7.08 (d, J = 7.5 Hz, 1H), 7.02 (t, J = 7.5 Hz, 1H), 3.69 (s, 3H), 2.27 (s, 3H); ¹³C-NMR (125 MHz, CDCl₃): δ 168.7, 143.3, 138.4, 131.7, 127.7, 127.0, 99.9, 52.5, 29.6; IR (thin film, NaCl) 2932,
Methyl 3-methyl-2-(octa-1,7-dien-3-yl)benzoate (S-42). The general procedure for alkylation using SN2’ reaction was followed with methyl 2-iodo-3-methylbenzoate S-41 (646 mg, 2.34 mmol), isopropylmagnesium chloride (1.3 M in THF, 2.3 mL, 3.0 mmol), a solution of CuCN (0.21 g, 2.3 mmol), LiCl (98 mg, 2.3 mmol) in THF (5.0 mL), (E)-1-bromohepta-1,6-diene (884 mg, 4.68 mmol), and THF (15 mL). The crude reaction mixture was purified by silica gel chromatography (Et₂O/hexanes, 1/20) and Ag-impregnated gradient silica gel chromatography (10% Ag, 9:1 Et₂O: hexanes with a gradient to 50% Et₂O) to afford product S-42 (500 mg, 83% yield) as a colorless oil. ¹H-NMR (500 MHz, CDCl₃): δ 7.35 (dd, J = 7.5, 1.0 Hz, 1H), 7.23 (dd, J = 8.0 Hz, 1H), 7.13 (t, J = 7.8 Hz, 1H), 6.15-6.08 (m, 1H), 5.81-5.73 (m, 1H), 5.08-4.91 (m, 4H), 3.92-3.86 (m, 4H), 2.37 (s, 3H), 2.06-2.02 (m, 2H), 1.95-1.87 (m, 1H), 1.80-1.73 (m, 1H), 1.48-1.42 (m, 1H), 1.30-1.24 (m, 1H); ¹³C-NMR (125 MHz, CDCl₃): δ 170.7, 141.0, 140.5, 138.7, 137.6, 133.8, 133.3, 126.9, 125.8, 114.7, 114.5, 52.1, 44.9, 33.8, 32.5, 27.5, 21.2; IR (thin film, NaCl): 3074, 2995, 2976, 2951, 2864, 1727, 1460, 1435, 1281, 1193, 1173, 1135, 993, 913 cm⁻¹; HRMS (ESI+) Calcd for C₁₅H₁₅O₂[M+H]⁺: 276.9726, found: 276.9738.

(3-methyl-2-(octa-1,7-dien-3-yl)phenyl)methanol (S-43). The general procedure for reduction was followed with LiAlH₄ 95% (92 mg, 2.4 mmol), methyl 3-methyl-2-(octa-1,7-dien-3-yl)benzoate S-42 (0.25 g, 0.97 mmol), and THF (10 mL). The crude reaction
mixture was purified by silica gel chromatography (Et$_2$O/hexanes, 1/3) to afford product **S-43** (144 mg, 64%) as a colorless oil. $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 7.26-7.22 (m, 1H), 7.15-7.10 (m, 2H), 6.19-6.12 (m, 1H), 5.81-5.73 (m, 1H), 5.09-4.91 (m, 4H), 4.69 (d, $J$ = 3.0 Hz, 2H), 3.90 (bs, 1H), 2.37 (s, 3H), 2.06 (q, $J$ = 7.0 Hz, 2H), 1.97-1.90 (m, 1H), 1.79 (bs, 1H), 1.65 (bs, 1H), 1.51-1.43 (m, 1H), 1.33-1.24 (m, 1H)

**3-methyl-2-(octa-1,7-dien-3-yl)benzaldehyde (S-44).** The general procedure for oxidation was followed with (3-methyl-2-(octa-1,7-dien-3-yl)phenyl)methanol **S-43** (144 mg, 0.625 mmol), PCC (215 mg, 1.00 mmol), Celite (200 mg), and dry CH$_2$Cl$_2$ (8.0 mL). The crude reaction mixture was purified by silica gel chromatography (Et$_2$O/hexanes, 1/30) to afford product **S-44** (130 mg, 90%) as a colorless oil. $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 10.45 (s, 1H), 7.78 (d, $J$ = 7.5 Hz, 1H), 7.39 (d, $J$ = 8.0 Hz, 1H), 7.26 (t, $J$ = 8.0 Hz, 1H), 6.26-6.20 (m, 1H), 5.78-5.70 (m, 1H), 5.14-4.92 (m, 4H), 4.16 (bs, 1H) 2.42 (s, 3H), 2.08-2.00 (m, 3H), 1.83-1.77 (m, 1H), 1.50-1.44 (m, 1H), 1.31-1.26 (m, 1H); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 193.2, 145.0, 141.8, 138.4, 137.8, 136.4, 135.3, 128.5, 126.7, 115.3, 115.0, 42.7, 35.9, 33.8, 27.6, 21.2; IR (thin film, NaCl): 3080, 3060, 3028, 2975, 2933, 2916, 2907, 2890, 2861, 1689, 1589, 1235, 992, 912, 762, 710 cm$^{-1}$; HRMS (ESI+) Calcd for C$_{16}$H$_{24}$N$_1$O$_1$ [M+NH$_4$]$^+$: 246.1858, found: 246.1869.
**Methyl 2-amino-3-(trifluoromethyl)benzoate (S-45).** The compound is prepared according to a procedure of Methyl 2-iodo-6-(trifluoromethyl)benzoate S-36 with 2-amino-3-(trifluoromethyl)benzoic acid (2.0 g, 9.8 mmol), Et₂O (20 mL), and MeOH (20 mL). The crude reaction mixture was purified by silica gel chromatography (Et₂O/hexanes, 1/30) to afford product S-45 (2.11 g, 99%) as yellow oil which crystallized when cooled. **¹H-NMR** (500 MHz, CDCl₃): δ 7.92 (d, J = 7.5 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 6.52 (t, J = 7.8 Hz, 1H), 6.3 (bs, 2H), 3.75 (s, 3H); **¹³C-NMR** (125 MHz, CDCl₃): δ 168.0, 148.1, 135.5, 131.9 (q, J = 5.4 Hz), 124.6 (q, J = 270 Hz), 114.7, 114.7 (q, J = 30 Hz), 112.2, 51.9; **IR** (thin film, NaCl): 3523, 3364, 3072, 3043, 1670, 1622, 1592, 1581, 1461, 1278, 1254, 1175, 1147, 1107, 1064 cm⁻¹; **HRMS** (ESI⁺) Calcd for C₉H₇F₃N₁O₂ [M+H]⁺: 220.0585, found: 220.0591.

**Methyl 2-iodo-3-(trifluoromethyl)benzoate (S-46).** The compound is prepared according to a procedure of Methyl 2-iodo-4-methoxybenzoate S-21 with methyl 2-amino-3-(trifluoromethyl)benzoate S-45 (2.11 g, 9.63 mmol) in mixture of conc. H₂SO₄ (2.0 mL) in H₂O (30 mL), NaNO₂ (697 mg, 10.1 mmol) in H₂O (15 mL), and KI (2.4 g, 14 mmol) in H₂O (15 mL). The crude reaction mixture was purified by silica gel chromatography (Et₂O/hexanes, 1/20) to afford product S-46 (1.2 g, 38%) as a yellow oil and 1.07 g of
recovered of methyl 2-amino-3-(trifluoromethyl)-benzoate S-45 (51%). \(^1\)H-NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.72 (d, \(J = 8.0\) Hz, 1H), 7.58 (d, \(J = 8.0\) Hz, 1H), 7.50 (t, \(J = 7.5\) Hz, 1H), 3.97 (s, 3H); \(^{13}\)C-NMR (125 MHz, CDCl\(_3\)): \(\delta\) 168.4, 142.2, 135.2 (q, \(J = 30.5\) Hz), 131.7, 129.1 (q, \(J = 5.8\) Hz), 128.1, 122.7 (q, \(J = 273\) Hz, 1C), 89.9, 53.0; IR (thin film, NaCl): 3022, 2928, 2913, 2907, 1737, 1416, 1326, 1286, 1258, 1205, 1176, 1139, 1081 cm\(^{-1}\); HRMS (ESI+) Calcd for C\(_9\)H\(_7\)F\(_3\)I\(_1\)O\(_2\) [M+H]\(^+\): 330.9443, found: 330.9436.

Methyl 2-(octa-1,7-dien-3-yl)-3-(trifluoromethyl)benzoate (S-48). Methyl 2-iodo-3-(trifluoromethyl)benzoate S-46 (198 mg, 0.600 mmol) was dissolved in the THF (5.0 mL) at -78 °C and isopropylmagnesium chloride (1.3 M in THF, 0.7 mL, 0.9 mmol) was added. The resulting solution was stirred 45 min at -60 °C then Et\(_2\)AlCl (1.8 M, 0.53 mL, 1.0 mmol) was added to the mixture solution at -78 °C. 10 min later, the reaction mixture was stirred at 0 °C for 1 h before adding a daily prepared NHC-Cu solution in THF (2.0 mL, 0.0060 mmol). The mixture was allowed to stir at 0 °C for 10 min and cool to -78 °C (dry ice/acetone bath). A solution of (E)-diethyl octa-2,7-dien-1-ylphosphonate S-47 (314 mg, 1.20 mmol) in THF (1.0 mL) was added and the mixture was allowed to warm to 0 °C and stirred at this temperature for 24 h. The reaction mixture was quenched by addition of a saturated aqueous of NH\(_4\)Cl (5.0 mL) and extracted with 5.0 mL of Et\(_2\)O 3 times. The combined organic layer was washed with brine (5.0 mL), dried over anhydrous MgSO\(_4\). The solvent was removed under reduced pressure and purified by flash column chromatography (Et\(_2\)O/hexanes, 1/20) to afford a clear colorless oil. Then additional purification was run by Ag-impregnated gradient silica gel chromatography (10% Ag, 9:1 Et\(_2\)O: hexanes with a gradient to 50% Et\(_2\)O) to afford product S-48 (80 mg,
43%) as a colorless oil. **NHC-Cu**: Imidazolinium salt S-51\(^{147}\) (2.9 mg, 0.0060 mmol, 0.01 equiv) and \(\text{t-BuOK}\) (0.67 mg, 0.0060 mmol) were weighed into a flam-dried round bottom flask containing a stir bar inside \(\text{N}_2\) atmosphere glovebox. The flask was capped with a septum, the edges sealed with electrical tape, and removed from the glovebox. The reaction vessel was put under positive \(\text{N}_2\) pressured and THF (1.0 mL) was added via syringe. At that time, \(\text{CuCl}_2\cdot\text{H}_2\text{O}\) (1.0 mg, 0.0060 mmol) was dissolved in THF (1.0 mL) then added to the solution of NHC. The resulting solution was stirred 30 min at room temperature the used in the reaction. Data for Methyl 2-(octa-1,7-dien-3-yl)-3-(trifluoromethyl)benzoate: \(^1\text{H-NMR}\) (400 MHz, CDCl\(_3\)): \(\delta\) 7.76 (dd, \(J = 8.0, 1.2\) Hz, 1H), 7.59 (d, \(J = 7.6, 1.2\) Hz, 1H), 7.34 (td, \(J = 7.8, 0.8\) Hz, 1H), 6.16-6.08 (m, 1H), 5.83-5.73 (m, 1H), 5.11-4.92 (m, 4H), 3.90-3.84 (m, 4H), 2.11-2.01 (m, 3H), 1.74-1.65 (m, 1H), 1.57-1.44 (m, 1H), 1.36-1.26 (m, 1H); \(^{13}\text{C-NMR}\) (100 MHz, CDCl\(_3\)): \(\delta\) 169.8, 142.5, 139.5, 138.6, 134.8, 132.9, 129.6 (q, \(J = 29\) Hz), 128.3 (q, \(J = 6.2\) Hz), 126.1, 124.2 (q, \(J = 273\) Hz), 116.2, 114.5, 52.5, 44.5 (d, \(J = 2.2\) Hz), 34.0, 33.6, 27.5; \(\text{IR}\) (thin film, NaCl): 2979, 2953, 1738, 1434, 1319, 1279, 1258, 1209, 1125, 1088, 916, 687 cm\(^{-1}\); \(\text{HRMS}\) (ESI+) Calcd for C\(_{17}\)H\(_{20}\)F\(_3\)O\(_2\) [M+H]\(^+\): 313.1415, found: 313.1418.

(2-(octa-1,7-dien-3-yl)-3-(trifluoromethyl)phenyl)methanol (S-49). The general procedure for reduction was followed with \(\text{LiAlH}_4\) 95% (27 mg, 0.72 mmol), methyl 2-(octa-1,7-dien-3-yl)-3-(trifluoromethyl)benzoate S-48 (56 mg, 0.18 mmol), and THF (3.0 mL). The crude reaction mixture was purified by silica gel chromatography (Et\(_2\)O/hexanes, 1/3) to afford product S-49 (48 mg, 94%) as a colorless oil. \(^1\text{H-NMR}\) (500 MHz, CDCl\(_3\)): \(\delta\) 7.74

(d, J = 7.5 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 6.18-6.12 (m, 1H), 5.78-5.72 (m, 1H), 5.14-5.11 (m, 1H), 5.00-4.91 (m, 3H), 4.81 (dd, J = 12.5, 4 Hz, 1H), 4.65(dd, J = 12.5, 6.5 Hz, 1H), 3.96-3.92 (m, 1H), 2.06-1.90 (m, 4H), 1.73-1.67 (m, 1H), 1.56-1.49 (m, 1H), 1.46-1.39 (m, 1H); $^{13}$C-NMR (125 MHz, CDCl$_3$): δ 141.6, 141.0, 140.8, 138.4, 133.7, 129.5 (q, J = 29 Hz), 126.7, 125.5 (m), 124.7 (q, J = 273 Hz), 115.4, 114.7, 62.4, 43.3, 34.0, 33.6, 27.3; IR (thin film, NaCl): 3344, 3080, 3029, 3022, 2978, 2939, 2929, 2920, 2911, 1312, 1154, 1119, 915 cm$^{-1}$; HRMS (ESI+) Calcd for C$_{16}$H$_{20}$F$_3$O$_1$ [M+H]$^+$: 285.1466, found: 285.1476.

2-(octa-1,7-dien-3-yl)-3-(trifluoromethyl)benzaldehyde (S-50). The general procedure for oxidation was followed with (2-(octa-1,7-dien-3-yl)-3-(trifluoromethyl)phenyl)methanol S-49 (48 mg, 0.17 mmol), PCC (58 mg, 0.29 mmol), Celite (50 mg), and dry CH$_2$Cl$_2$ (4.0 mL). The crude reaction mixture was purified by silica gel chromatography (Et$_2$O/hexanes, 1/30) to afford product S-50 (36 mg, 75%) as a colorless oil. $^1$H-NMR (400 MHz, CDCl$_3$): δ 10.44 (s, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 7.6 Hz, 1H), 7.39 (t, J = 7.8 Hz, 1H), 6.24-6.16 (m, 1H), 5.70-5.60 (m, 1H), 5.14-5.11 (m, 1H), 4.91-4.84 (m, 3H), 4.00-3.95 (m, 1H), 2.02-1.93 (m, 3H), 1.74-1.65 (m, 1H), 1.53-1.45 (m, 1H), 1.23-1.17 (m, 1H); $^{13}$C-NMR (100 MHz, CDCl$_3$): δ 191.2, 146.0, 141.0, 138.0, 136.4, 132.8, 130.9 (q, J = 6.0 Hz), 130.2 (q, J = 29 Hz), 126.9, 124.1 (q, J = 273 Hz), 116.6, 115.0, 43.1 (d, J = 2.2 Hz), 37.0, 33.4, 27.2; IR (thin film, NaCl): 3026, 2930, 2919, 2907, 1693, 1313, 1157, 1124, 1103, 916 cm$^{-1}$; HRMS (ESI+) Calcd for C$_{16}$H$_{18}$F$_3$O$_1$ [M+H]$^+$: 283.1310, found: 283.1313.
2-(2,6-dichlorophenyl)hept-6-enenitrile (S-51). Sodium hydride (0.27 g, 11 mmol, 95% dispersion in mineral oil) was weighed into a flamed-dried round bottom flask containing a stir bar inside N₂ atmosphere glovebox. The flask was capped with a septum, the edges sealed with electrical tape, and removed from the glovebox. The reaction vessel was put under positive N₂ pressured and dry THF (15 mL) was added via syringe. The solution of 2-(2,6-dichlorophenyl)acetonitrile (2.0 g, 11 mmol) in dry THF (10 mL) was added dropwise to the mixture of sodium hydride at 0 °C. After the mixture was stirred for 30 min at this temperature, 5-bromopent-1-ene (1.4 mL, 12 mmol) was added dropwise at 0 °C then stirred overnight at room temperature. The reaction was quenched with cold ice water (50 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic layer was washed with saturated aqueous NaHCO₃ solution (20 mL), brine (20 mL), and dried over anhydrous MgSO₄. The solvent was removed under reduced pressure and purified by flash column chromatography (Et₂O/hexanes, 1/40) to afford product S-51 (2.60 g, 95%) as a colorless oil. ¹H-NMR (500 MHz, CDCl₃): δ 7.35 (d, J = 8.0 Hz, 2H), 7.21 (td, J = 8.5, 1.0 Hz, 1H), 5.82-5.73 (m, 1H), 5.06-4.98 (m, 2H), 4.71-4.68 (m, 1H), 2.28-2.20 (m, 1H), 2.13 (q, J = 7.2 Hz, 2H) 1.93-1.85 (m, 1H), 1.77-1.68 (m, 1H), 1.56-1.47 (m, 1H); ¹³C-NMR (125 MHz, CDCl₃): δ 137.4, 135.1, 131.1, 129.8, 129.3, 118.4, 115.5, 32.8, 32.7, 30.3, 26.4; IR (thin film, NaCl): 3076, 3060, 3054, 2996, 2977, 2946, 2902, 2895,
2-(2,6-dichlorophenyl)hept-6-enal \textbf{(S-52)}. To a well-stirred solution of 2-(2,6-dichlorophenyl)hept-6-enenitrile \textbf{S-51} (1.0 g, 3.9 mmol) in CH$_2$Cl$_2$ (20 mL) under nitrogen atmosphere was added dropwise DIBALH (0.77 mL, 4.3 mmol) at -78 °C then stirred for 2 h at this temperature. The reaction was quenched with 2 M HCl (1.0 mL) at -78 °C then diluted with CH$_2$Cl$_2$ (20 mL) and warmed to room temperature. The organic phase was washed with water (10 mL), brine (10 mL), and dried over anhydrous MgSO$_4$. The solvent was removed under reduced pressure and purified by flash column chromatography (Et$_2$O/hexanes, 1/50) to afford product \textbf{S-52} (1.0 g, 99%) as a colorless oil. $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 9.77 (s, 1H), 7.36 (d, $J = 8.0$ Hz, 2H), 7.21 (t, $J = 8.0$ Hz, 1H), 5.80-5.72 (m, 1H), 5.00-4.92 (m, 2H), 4.18 (dd, $J = 5.0$, 9.0 Hz, 1H), 2.41-2.34 (m, 1H), 2.12-2.03 (m, 2H), 1.95-1.88 (m, 1H), 1.56-1.50 (m, 1H), 1.34-1.28 (m, 1H); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 200.2, 138.3, 136.0, 134.9, 129.5, 129.1, 115.0, 55.1, 33.8, 27.5, 26.8; IR (thin film, NaCl): 3076, 3040, 2977, 2950, 2882, 2864, 2820, 1728, 1561, 1435, 1086, 913, 779 cm$^{-1}$; HRMS (ESI+) Calcd for C$_{13}$H$_{15}$Cl$_2$O$_1$ [M+H]$^+$: 257.0500, found: 257.0498.

1,3-dichloro-2-(octa-1,7-dien-3-yl)benzene \textbf{(S-53)}. To a solution of methyltriphenylphosphonium bromide (1.5 g, 4.3 mmol) in THF (15 mL) was added $n$-BuLi (1.6 M, 2.26 mL, 3.61 mmol), while cooling at 0 °C. After being stirred for 10 min, the solution was cooled to -78 °C and 2-(2,6-dichlorophenyl)hept-6-enal \textbf{S-52} (844 mg, 3.28 mmol) in
THF (10 mL) was added dropwise. When addition was complete the solution was stirred for 30 min, warmed to room temperature, and poured onto mixture of ether (30 mL) and water (20 mL). The phase were separated, and the organic phase was washed with 10 mL of water 2 times, brine (10 mL), and dried over anhydrous MgSO₄. The solvent was removed under reduced pressure and purified by flash column chromatography (Et₂O/hexanes, 1/50) to afford product S-53 (711 mg, 85%) as a colorless oil. 

**¹H-NMR** (500 MHz, CDCl₃): δ 7.27 (bs, 2H), 7.06 (t, J = 8.0 Hz, 1H), 6.30-6.23 (m, 1H), 5.82-5.74 (m, 1H), 5.09-4.92 (m, 4H), 4.33 (q, J = 8.5 Hz, 1H), 2.09-2.01 (m, 3H), 1.99-1.92 (m, 1H), 1.47-1.39 (m, 1H), 1.29-1.20 (m, 1H); 

**¹³C-NMR** (100 MHz, CDCl₃): δ 139.3, 138.9, 138.8, 130.1, 128.6, 127.9, 115.7, 114.7, 45.9, 33.8, 31.6, 27.2; 

**IR** (thin film, NaCl): 3077, 3021, 2996, 2977, 2940, 2925, 2915, 2905, 2859, 1640, 1560, 1435, 1416, 1084, 991, 913 cm⁻¹; 

**HRMS** (ESI⁺) Calcd for C₁₄H₁₇Cl₂ [M+H]⁺: 255.0707, found: 255.0708.

**3-chloro-2-(octa-1,7-dien-3-yl)benzaldehyde (2.29).** t-BuLi (1.5 M, 4.9 mL, 7.4 mmol) was added to a flamed-dried round bottom flask containing a stir bar inside N₂ atmosphere with THF (4.0 mL). The reaction mixture was stirred at -78 °C for 10 min before adding a solution of 1,3-dichloro-2-(octa-1,7-dien-3-yl)benzene S-53 (753 mg, 2.95 mmol) in THF (2.0 mL) via syringe pump over 30 min and stirred for 30 min at -78 °C. At this time, dry DMF (1.1 mL, 15 mmol) was added to the reaction mixture then warmed to room temperature naturally. After further stirring for 30 min at room temperature, the mixture was diluted with 30 mL of Et₂O and washed with water (3 × 10 mL), brine (5.0 mL), dried over anhydrous MgSO₄. The solvent was removed under reduced pressure and
purified by flash column chromatography (Et₂O/hexanes, 1/30) to afford product 2.29 (553 mg, 75%) as a colorless oil. ¹H-NMR (500 MHz, CDCl₃): δ 10.29 (s, 1H), 7.70 (dd, J = 8.0, 1.5 Hz, 1H), 7.48 (dd, J = 8.0, 1.5 Hz, 1H), 7.17 (t, J = 8.0 Hz, 1H), 6.16-6.09 (m, 1H), 5.69-5.57 (m, 1H), 5.02 (dd, J = 10.5, 1.5 Hz, 1H), 4.89-4.79 (m, 3H), 4.39 (s, 1H), 1.98-1.91 (m, 3H), 1.75-1.67 (m, 1H), 1.42-1.31 (m, 1H), 1.20-1.11 (m, 1H); ¹³C-NMR (100 MHz, CDCl₃): δ 191.5, 143.9, 141.0, 138.4, 136.7, 135.9, 135.2, 128.8, 127.9, 116.0, 115.0, 43.2, 35.3, 33.7, 27.2; IR (thin film, NaCl): 3077, 2977, 2931, 2860, 1690, 914, 448 cm⁻¹; HRMS (ESI⁺) Calcd for C₁₅H₁₈Cl₁O₁ [M+H]⁺: 249.1046, found: 249.1036.

3-formyl-2-(octa-1,7-dien-3-yl)benzonitrile (S-54). The compound is prepared by the literature procedure with 3-chloro-2-(octa-1,7-dien-3-yl)benzaldehyde 2.29 (0.18 g, 0.72 mmol), Zn(CN)₂ (98 mg, 0.83 mmol), Pd₂dba₂ (33 mg, 0.036 mmol), S-Phos (30 mg, 0.073 mmol), and 2.0 mL of DMF/H₂O (99:1). The crude reaction mixture was purified by silica gel chromatography (Et₂O/hexanes, 1/20) to afford product S-54 (30 mg, 17%) as a colorless oil. ¹H-NMR (500 MHz, CDCl₃): δ 10.45 (s, 1H), 8.12 (dd, J = 8.0, 1.5 Hz, 1H), 7.87 (dd, J = 7.5, 1.5 Hz, 1H), 7.49 (td, J = 7.5, 0.5 Hz, 1H), 6.31-6.25 (m, 1H), 5.77-5.69 (m, 1H), 5.24-4.93 (m, 4H), 4.40 (q, J = 7.0 Hz, 1H), 2.17-2.05 (m, 3H), 1.94-1.86 (m, 1H), 1.60-1.47 (m, 1H), 1.30-1.22 (m, 1H); ¹³C-NMR (125 MHz, CDCl₃): δ 190.4, 150.2, 139.9, 138.7, 138.1, 135.4, 134.4, 127.7, 118.0, 117.4, 115.3, 114.7, 45.4, 35.3, 33.6, 27.2; IR (thin film, NaCl): 3076, 3040, 2977, 2931, 2860, 1690, 914, 448 cm⁻¹; HRMS (ESI⁺) Calcd for C₁₆H₁₈CN₁O₁ [M+H]⁺: 240.1388, found: 240.1391.

Synthesis of starting materials of 5, 5 ring systems for tandem ring-closing metathesis/hydroacylation

**(E)-7-bromohepta-1,5-diene (S-55).** To a stirring solution of (E)-Heptaa-2,6-dien-1-ol (729 mg, 6.50 mmol) in Et₂O (40 mL) was added phosphorus tribromide (0.42 mL, 4.55 mmol) at 0 °C, and the reaction was allowed to warm to room temperature for 2 h. The reaction was quenched with saturated NaHCO₃ (aq) and extracted with 50 mL of Et₂O 3 times. The combined organic layer was washed with brine (20 mL), dried over anhydrous MgSO₄. The solvent was removed under reduced pressure and purified by flash chromatography on a triethylamine-washed silica gel with hexanes to afford product S-55 (600 mg, 75%) as a colorless oil. The silica gel washed with 2% Et₃N used in the chromatography. **¹H-NMR** (500 MHz, CDCl₃): δ 5.82-5.68 (m, 3H), 5.05-4.97 (m, 2H), 3.95 (d, J = 7.5 Hz, 2H), 2.16 (m, 4H); **¹³C-NMR** (125 MHz, CDCl₃): δ 137.7, 135.6, 126.8, 115.1, 33.3, 32.9, 31.4; **IR** (thin film, NaCl): 2996, 2977, 2960, 2948, 2895, 2844, 1660, 1641, 1436, 1204, 992, 967, 914, 748 cm⁻¹; **HRMS** (ESI+) Calc’d for C₇H₁₂Br₁ [M+H]⁺:175.0122, found: 175.0120.

**Methyl 2-(hepta-1,6-dien-3-yl)benzoate (S-56).** The general procedure for alkylation using SN₂’ reaction was followed methyl 2-iodobenzoate S-1 (1.44 g, 5.50 mmol), isopropyl-magnesium chloride (1.5 M in THF, 5.5 mL, 8.25 mmol), a solution of CuCN

(495 mg, 5.50 mmol) and LiCl (462 mg, 11.0 mmol) in THF (15 mL), (E)-7-bromohepta-1,5-diene S-55 (1.62 g, 9.31 mmol), and THF (5.0 mL). The crude reaction mixture was purified by silica gel chromatography (Et₂O/hexanes, 1/30) and Ag-impregnated gradient silica gel chromatography (10% Ag, 9:1 Et₂O: hexanes with a gradient to 50% Et₂O) to afford product S-56 (776 mg, 61%) as a colorless oil. **¹H-NMR** (500 MHz, CDCl₃): δ 7.75 (d, J = 7.5 Hz, 1H), 7.46 (t, J = 7.5 Hz, 1H), 7.35 (d, J = 7.5 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H), 6.00-5.94 (m, 1H), 5.84-5.75 (m, 1H), 5.06-4.92 (m, 4H), 4.27 (q, J = 7.0 Hz, 1H), 3.89 (s, 3H), 2.11-1.92 (m, 2H), 1.84-1.79 (m, 2H); **¹³C-NMR** (125 MHz, CDCl₃): δ 168.6, 145.2, 141.7, 138.5, 131.7, 130.5, 130.0, 127.9, 125.8, 114.7, 114.5, 52.1, 43.6, 34.7, 31.6; **IR** (thin film, NaCl): 2996, 2979, 2950, 1724, 1639, 1434, 1289, 1271, 1254, 1192, 1125, 1076, 914, 716 cm⁻¹; **HRMS** (ESI⁺) Calc’d for C₁₅H₁₉O₂ [M+H]⁺: 231.1385, found: 231.1388.

**(2-(hepta-1,6-dien-3-yl)phenyl)methanol (S-57).** The general procedure for reduction was followed with LiAlH₄ 95% (363 mg, 9.56 mmol), methyl 2-(hepta-1,6-dien-3-yl)benzoate S-56 (550 mg, 2.39 mmol), and THF (50 mL). It afforded crude mixture S-57 (525 mg, 2.39 mmol, 100%) and the crude mixture was used without any further purification in the next step. **¹H-NMR** (500 MHz, CDCl₃): δ 7.36 (d, J = 7.5 Hz, 1H), 7.33-7.26 (m, 2H), 7.22 (t, J = 7.5 Hz, 1H), 5.99-5.91 (m, 1H), 5.85-5.77 (m, 1H), 5.04-4.96 (m, 4H), 4.73 (qd, J = 14.5, 5.5 Hz, 2H), 3.68 (q, J = 7.5 Hz, 1H), 2.13-1.98 (m, 2H), 1.91-1.79 (m, 2H), 1.57-1.51 (m, 1H); **¹³C-NMR** (125 MHz, CDCl₃): δ 142.5, 142.4, 138.6, 138.4, 128.9, 128.5, 127.2, 126.5, 115.0, 114.6, 63.6, 43.7, 34.5, 31.7; **IR** (thin film, NaCl): 3356, 3343, 3336, 3325, 3075, 3020, 2975, 2913, 2901, 1638, 1125, 1093,
1038, 1028, 997, 912, 753, 697, 538 cm$^{-1}$; **HRMS (ESI+)** Calc’d for C$_{14}$H$_{22}$N$_{1}$O$_{1}$ [M+NH$_4$]$^+$: 220.1701, found: 220.1706.

**2-(hepta-1,6-dien-3-yl)benzaldehyde (S-58).** The general procedure for oxidation was followed with (2-(hepta-1,6-dien-3-yl)phenyl)methanol S-57 (525 mg, 2.39 mmol), PCC (770 mg, 3.58 mmol), Celite (700 mg), and dry CH$_2$Cl$_2$ (30 mL). The crude reaction mixture was purified by silica gel chromatography (Et$_2$O/hexanes, 1/30) to afford product S-58 (455 mg, 95%) as a colorless oil. **$^1$H-NMR (500 MHz, CDCl$_3$):** $\delta$ 10.34 (s, 1H), 7.83 (dd, $J$ = 8.0, 1.5 Hz, 1H), 7.55 (td, $J$ = 7.5, 1.5 Hz, 1H), 7.04-7.36 (m, 2H), 6.04-5.97 (m, 1H), 5.84-5.76 (m, 1H), 5.12-4.95 (m, 4H), 4.42 (q, $J$ = 7.5 Hz, 1H), 2.12-1.99 (m, 2H), 1.94-1.80 (m, 2H); **$^{13}$C-NMR (125 MHz, CDCl$_3$):** $\delta$ 192.5, 147.0, 141.5, 138.3, 134.2, 134.0, 131.7, 128.3, 126.8, 115.7, 115.3, 42.3, 34.9, 31.7; **IR (thin film, NaCl):** 2910, 1693, 915 cm$^{-1}$; **HRMS (ESI+)** Calc’d for C$_{14}$H$_{20}$N$_{1}$O$_{1}$ [M+NH$_4$]$^+$: 218.1545, found: 218.1542.

**$(E,Z)$-ethyl 3-methylhepta-2,6-dienoate (S-60).** Triethyl phosphonoacetate S-59 (2.4 mL, 25 mmol) was added to a suspension of NaH (632 mg, 25.0 mmol) in THF (30 mL) under ice cooling and N$_2$. The mixture was stirred at room temperature for 1 h and a solution of hex-5-en-2-one (2.4 mL, 20 mmol) was added under ice cooling bath. The whole mixture was stirred at room temperature until the reaction was complete by TLC and then water (200 mL) was added and extracted with 150 mL of EtOAc 3 times. The combined organic layer was washed with water (20 mL) and brine (20 mL), dried over
anhydrous MgSO₄. The solvent was removed under reduced pressure and purified by flash column chromatography (Et₂O/hexane 1:30) to afford product S-60 (Z isomer 0.73 g, 21%, E isomer 2.4 g, 70%) as a colorless oil. Spectral data are in accordance with the literature reference.¹⁵⁰

**(E)-3-methylhepta-2,6-dien-1-ol (S-61).** The compound is prepared according to a procedure of (2-(octa-1,7-dien-3-yl)-6-(trifluoromethyl)phenyl)methanol S-38 with (E)-ethyl 3-methylhepta-2,6-dienoate S-60 (0.20 g, 1.2 mmol) and Diisobutylaluminium hydride (0.57 mL, 3.2 mmol). The crude reaction mixture was purified by silica gel chromatography (Et₂O/hexanes, 1/2) to afford product S-61 (135 mg, 90%) as a colorless oil. **¹H-NMR (400 MHz, CDCl₃):** δ 5.85-5.75 (m, 1H), 5.44-5.41 (m, 1H), 5.05-4.94 (m, 2H), 4.14 (d, J = 6.8 Hz, 2H), 2.20-2.09 (m, 4H), 1.68 (s, 3H); **¹³C-NMR (100 MHz, CDCl₃):** δ 142.3, 138.4, 123.8, 114.8, 59.5, 40.0, 32.1, 16.4; **IR (thin film, NaCl):** 3346, 3300, 2977, 2948, 2877, 2844, 1641, 1437, 1416, 1383, 996, 911 cm⁻¹.

**(E)-diethyl (3-methylhepta-2,6-dien-1-yl) phosphate (S-62).** Diethylchlorophostate (1.81 mL, 12.5 mmol) and Et₃N (1.74 mL, 12.5 mmol) were added dropwise to a stirred solution of (E)-3-methylhepta-2,6-dien-1-ol S-61 (1.02 g, 8.32 mmol) and DMAP (203 mg, 1.66 mmol) in DCM (50 mL) at 0 °C. Once the addition was complete, the solution was allowed to stir until reaction was complete at room temperature. The reaction was quenched with saturated aqueous NH₄Cl solution (30 mL) and extracted with 20 mL of DCM 3 times. The combined organic layer was washed with brine (20 mL), and dried.

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over anhydrous MgSO$_4$. The solvent was removed under reduced pressure and purified by flash chromatography on a triethylamine-washed silica gel (EtOAc/hexanes, 2/5) to afford product **S-62** (1.5 g, 69%) as a colorless oil. $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 5.83-5.73 (m, 1H), 5.43-5.38 (m, 1H), 5.04-4.93 (m, 2H), 4.56 (t, $J$ = 7.6 Hz, 2H), 4.13-4.06 (m, 4H), 2.21-2.08 (m, 4H), 1.70 (s, 3H), 1.33 (td, $J$ = 7.2, 0.8 Hz, 6H); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 142.2, 138.2, 119.6 (d, $J$ = 5.5 Hz), 115.0, 64.2 (d, $J$ = 4.5 Hz), 63.8 (d, $J$ = 4.5 Hz), 39.0, 32.0, 16.7, 16.4 (d, $J$ = 5.5 Hz); IR (thin film, NaCl): 2982, 2940, 2926, 2902, 1265, 1036 cm$^{-1}$; HRMS (ESI+) Calc’d for C$_{12}$H$_{24}$O$_4$P$_1$ [M+H]$^+$: 263.1412, found: 263.1418.

**Methyl 2-(3-methylhepta-1,6-dien-3-yl)benzoate (S-63).** Methyl 2-iodobenzoate **S-1** (1.5 g, 5.7 mmol) was dissolved in THF (15 mL) at -78 °C and isopropylmagnesium chloride (1.5 M in THF, 5.0 mL, 7.6 mmol) was added. The resulting solution was stirred 30 min at -78 °C then Et$_2$AlCl (1.8 M, 4.43 mL, 7.98 mmol) was added to the mixture solution at -78 °C. The resulting solution was allowed to warm to 0 °C and stirred for 1 h. This mixture solution was added to a stirred suspension of CuCN (684 mg, 7.60 mmol) in THF (18 mL) at -78 °C then a solution of (E)-diethyl (3-methylhepta-2,6-dien-1-yl) phosphate **S-62** (1.0 g, 3.8 mmol) in THF (2.0 mL) was added to the this mixture at -78 °C. The mixture was allowed to warm to room temperature and stirred at this temperature for overnight. The reaction was quenched with Rochelle’s solution extracted with Et$_2$O (3 x 30 mL). The combined organic layer was washed with brine (10 mL), dried
anhydrous MgSO$_4$. The solvent was removed under reduced pressure and purified by flash column chromatography (Et$_2$O/hexanes, 1/30) to afford product S-63 (400 mg, 43%) as a colorless oil. $^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ 7.44-7.36 (m, 2H), 7.30 (ddd, $J$ = 7.6, 1.6, 0.4 Hz, 1H), 7.32 (ddd, $J$ = 7.6, 7.2, 1.6 Hz, 1H), 6.05 (dd, $J$ = 18, 10.8 Hz, 1H), 5.84-5.74 (m, 1H), 5.14-4.90 (m, 4H), 3.77 (s, 3H), 2.05-1.87 (m, 4H), 1.47 (s, 3H); $^{13}$C-NMR (100 MHz, CDCl$_3$): $\delta$ 171.8, 145.8, 144.3, 139.1, 134.0, 129.9, 128.8, 128.0, 126.0, 114.3, 112.8, 52.1, 45.2, 40.0, 29.2, 26.9 cm$^{-1}$; HRMS (ESI+) Calc’d for C$_{16}$H$_{21}$O$_2$ [M+H]$^+$: 245.1539, found: 245.1542.

(2-(3-methylhepta-1,6-dien-3-yl)phenyl)methanol (S-64). The general procedure for reduction was followed with LiAlH$_4$ 95% (246 mg, 6.48 mmol), methyl 2-(3-methylhepta-1,6-dien-3-yl)benzoate S-63 (396 mg, 1.62 mmol), and THF (15 mL). The crude reaction mixture was purified by silica gel chromatography (Et$_2$O/hexanes, 1/3) to afford product S-64 (340 mg, 97%) as a colorless oil. $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 7.51 (dd, $J$ = 7.5, 2.0 Hz, 1H), 7.35 (dd, $J$ = 7.0, 2.0 Hz, 1H), 7.30-7.25 (m, 2H), 6.21 (dd, $J$ = 17.5, 10.5 Hz, 1H), 5.81-5.73 (m, 1H), 5.09 (d, $J$ = 10.5 Hz, 1H), 4.98-4.89 (m, 3H), 4.78 (dd, $J$ = 12.5, 5.5 Hz, 1H), 4.78 (dd, $J$ = 12.5, 7.0 Hz, 1H), 2.02-1.96 (m, 2H), 1.88-1.84 (m, 1H), 1.72-1.62 (m, 2H), 1.46 (s, 3H); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 149.0, 143.9, 140.1, 139.1, 131.0, 127.7, 127.5, 127.1, 114.5, 112.2, 63.5, 45.2, 40.4, 29.2, 27.9 cm$^{-1}$; HRMS (ESI+) Calc’d for C$_{15}$H$_{24}$N$_1$O$_1$ [M+NH$_4$]$^+$: 234.1858, found: 234.1860.

2-(3-methylhepta-1,6-dien-3-yl)benzaldehyde (S-65). The general procedure for oxidation was followed with (2-(3-methylhepta-1,6-dien-3-yl)phenyl)methanol S-64 (335 mg, 1.55
mmol), PCC (500 mg, 2.32 mmol), Celite (500 mg), and dry CH₂Cl₂ (20 mL). The crude reaction mixture was purified by silica gel chromatography (Et₂O/hexanes, 1/30) to afford product **S-65** (280 mg, 84%) as a colorless oil. **¹H-NMR** (400 MHz, CDCl₃): δ 10.66 (s, 1H), 7.94 (dd, J = 7.6, 1.6 Hz, 1H), 7.52 (ddd, J = 8.0, 7.2, 1.6 Hz, 1H), 7.44 (dd, J = 8.4, 1.2 Hz, 1H), 7.36 (tt, J = 7.6, 1.0 Hz, 1H), 6.28 (dd, J = 18, 10.8 Hz 1H), 5.77-5.69 (m, 1H), 5.15 (dd, J = 10.8, 0.8 Hz, 1H), 4.98-4.89 (m, 3H), 2.03-1.97 (m, 3H), 1.78-1.68 (m, 1H), 1.53 (s, 3H); **¹³C-NMR** (100 MHz, CDCl₃): δ 193.2, 148.8, 148.2, 138.4, 135.4, 133.3, 129.6, 127.7, 127.0, 114.8, 113.8, 45.0, 42.1, 28.9, 28.4; **IR** (thin film, NaCl): 3078, 2975, 2940, 2877, 1689, 1640, 1597, 1403, 1198, 996, 915, 765 cm⁻¹; **HRMS** (ESI⁺) Calc’d for C₁₅H₁₉O₁ [M+H]⁺: 215.1436, found: 215.1435.

**Synthesis of starting materials of 5, 7 ring systems for tandem ring-closing metathesis/hydroacylation**

![Chemical structure](image)

(E)-9-bromona-1,7-diene (S-66). The compound is prepared through the same reaction sequence as above described with (E)-nona-2,8-dien-1-ol₁⁵¹ (1.69 g, 12.0 mmol) in DCM (100 mL) and phosphorus tribromide (0.80 mL, 8.6 mmol). The crude reaction mixture was purified by flash chromatography on a triethylamine-washed silica gel with hexanes to afford product **S-66** (1.32 g, 54%) as a colorless oil. **¹H-NMR** (500 MHz,

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CDCl$_3$): $\delta$ 5.84-5.65 (m, 3H), 5.01-4.93 (m, 2H), 3.95 (dd, $J = 7.5, 1.0$ Hz, 2H), 2.08-2.04 (m, 4H), 1.41-1.38 (m, 4H).

**Methyl 2-(nona-1,8-dien-3-yl)benzoate (S-67).** The general procedure for alkylation using SN2’ reaction was followed with methyl 2-iodobenzoate S-1 (1.0 g, 3.8 mmol), isopropylmagnesium chloride (1.5 M in THF, 3.8 mL, 5.7 mmol), a solution of CuCN (346 mg, 3.81 mmol), LiCl (320 mg, 7.62 mmol) in THF (10 mL), (E)-9-bromona-1,7-diene S-66 (1.32 g, 6.49 mmol), and THF (35 mL). The crude reaction mixture was purified by silica gel chromatography (Et$_2$O/hexanes, 1/20) and Ag-impregnated gradient silica gel chromatography (10% Ag, 9:1 Et$_2$O: hexanes with a gradient to 50% Et$_2$O) to afford product S-67 (677 mg, 69% yield) as a colorless oil. $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 7.75(dd, $J = 8.0, 1.5$ Hz, 1H), 7.45 (td, $J = 7.8, 1.5$ Hz, 1H), 7.34 (dd, $J = 8.0, 1.0$ Hz, 1H), 7.23 (td, $J = 7.5, 1.5$ Hz, 1H), 6.00-5.93 (m, 1H), 5.82-5.73 (m, 1H), 5.04-4.89 (m, 4H), 4.23 (q, $J = 7.3$ Hz, 1H), 3.81 (s, 3H), 2.03-1.99 (m, 2H), 1.74-1.67 (m, 2H), 1.40-1.30 (m, 3H), 1.28-1.16 (m, 1H); $^{13}$C-NMR (125 MHz, CDCl$_3$): $\delta$ 168.8, 145.8, 142.1, 139.2, 131.8, 130.6, 130.2, 128.0, 125.9, 114.6, 114.3, 52.2, 44.3, 35.7, 33.8, 29.1, 27.1; IR (thin film, NaCl): 3076, 2996, 2977, 2929, 2857, 1724, 1638, 1446, 1434, 1288, 1266, 1243, 1192, 1125, 1076, 912 cm$^{-1}$; HRMS (ESI) Calc’d for C$_{17}$H$_{23}$O$_2$[M+H]$^+$: 259.1698, found: 259.1692.

*(2-(nona-1,8-dien-3-yl)phenyl)methanol (S-68).* The general procedure for reduction was followed with LiAlH$_4$ 95% (351 mg, 9.24 mmol), methyl 2-(nona-1,8-dien-3-yl)benzoate S-67 (597 mg, 2.31 mmol), and THF (50 mL). The crude reaction mixture
was purified by silica gel chromatography (Et$_2$O/hexanes, 1/3) to afford product **S-68** (529 mg, 99%) as a colorless oil. **$^1$H-NMR** (500 MHz, CDCl$_3$): $\delta$ 7.75 (dd, $J = 8.0$, 1.5 Hz, 1H), 7.45 (td, $J = 7.8$, 1.5 Hz, 1H), 7.34 (dd, $J = 8.0$, 1.0 Hz, 1H), 7.23 (td, $J = 7.5$, 1.5 Hz, 1H), 6.00-5.93 (m, 1H), 5.82-5.73 (m, 1H), 5.04-4.89 (m, 4H), 4.23 (q, $J = 7.3$ Hz, 1H), 3.81 (s, 3H), 2.03-1.99 (m, 2H), 1.74-1.67 (m, 2H), 1.40-1.30 (m, 3H), 1.28-1.16 (m, 1H)

**2-(nona-1,8-dien-3-yl)benzaldehyde (S-69).** The general procedure for oxidation was followed with (2-(nona-1,8-dien-3-yl)phenyl)methanol **S-68** (529 mg, 2.29 mmol), PCC (738 mg, 3.43 mmol), Celite (700 mg), and dry CH$_2$Cl$_2$ (30 mL). The crude reaction mixture was purified by silica gel chromatography (Et$_2$O/hexanes, 1/30) to afford product **S-69** (497 mg, 95%) as a colorless oil. **$^1$H-NMR** (400 MHz, CDCl$_3$): $\delta$ 10.35 (s, 1H), 7.83 (dd, $J = 7.6$, 0.8 Hz, 1H), 7.55 (td, $J = 7.6$, 1.2 Hz, 1H), 7.40-7.35 (m, 2H), 6.05-5.96 (m, 1H), 5.82-5.71 (m, 1H), 5.10-4.90 (m, 4H), 4.38 (q, $J = 7.2$ Hz, 1H), 2.01 (q, $J = 6.9$ Hz, 2H), 1.82-1.49 (m, 2H), 1.43-1.20 (m, 4H); **$^{13}$C-NMR** (125 MHz, CDCl$_3$): $\delta$ 192.5, 147.4, 141.7, 139.0, 134.1, 133.8, 131.7, 128.2, 126.6, 115.4, 114.5, 43.0, 35.7, 33.7, 29.0, 27.2; **IR** (thin film, NaCl): 2929, 2857, 1693, 1638, 1599, 993, 913, 759 cm$^{-1}$; **HRMS** (ESI$^+$) Calc’d for C$_{16}$H$_{21}$O$_1$ [M+H]$^+$: 229.1592, found: 229.1590.

**Substrates for D-labeling studies**

![Diagram](image_url)
Oct-7-en-2-yn-1-ol (S-70). To a solution of propargyl alcohol (1.12 g, 20.0 mmol) in THF (30 mL) and HMPA (8.0 mL) was added n-BuLi (1.15 M, 35 mL, 40 mmol) at -78 °C. After the reaction temperature was warmed to -30 °C, 5-bromo-1-pentene (2.0 mL, 17 mmol) was added to the mixture and stirred at room temperature overnight. The reaction mixture was treated with aqueous saturated NH₄Cl and extracted with Et₂O (3 x 30 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure and purified by flash column chromatography (Et₂O/hexanes, 1/3) to afford product S-70 (1.8 g, 85%) as a colorless oil.

**¹H-NMR** (400 MHz, CDCl₃): δ 5.84-5.72 (m, 1H), 5.07-4.97 (m, 2H), 4.27-4.24 (m, 2H), 2.26-2.21 (m, 2H), 2.15 (q, J = 7.2 Hz, 2H), 1.61 (p, J = 7.2 Hz, 2H), 1.49 (m, 1H); **¹³C-NMR** (100 MHz, CDCl₃): δ 146.9, 137.7, 115.2, 86.2, 51.4, 32.7, 28.0, 18.1; **IR** (thin film, NaCl): 3355, 3346, 3333, 3078, 3023, 2976, 2946, 2915, 2894, 2867, 1641, 1435, 1416, 1137, 1011, 914, 764, 754, 703 cm⁻¹.

Alcohol (SD-1). The substrate was prepared by the literature procedure with LiAlD₄ (1.0 M solution, 12 mL, 12 mmol), NaOMe (1.3 g, 24 mmol), Oct-7-en-2-yn-1-ol S-70 (0.60 g, 4.8 mmol) and THF (30 mL). The reaction mixture was treated with aqueous saturated NH₄Cl and extracted with Et₂O (3 x 30 mL). The crude reaction mixture was purified by silica gel chromatography (Et₂O/hexanes, 1/2) to afford product SD-1 (512 mg, 84%) as a colorless oil containing 4-5% octa-2,7-dien-1-ol based on **¹H-NMR** integrations.

**¹H-NMR** (400 MHz, CDCl₃, * represents a minor peak form octa-2,7-dien-
1-ol): \( \delta \) 5.77-5.67 (m, 1H), 5.60-5.56 (m, 1H), *5.52, 4.96-4.86 (m, 2H), 3.95 (s, 2H), 3.33 (bs, 1H), 2.01-1.95 (m, 4H), 1.40 (p, \( J = 7.6 \) Hz, 2H); \( ^{13} \)C-NMR (100 MHz, CDCl\(_3\)): \( \delta \) 138.5, 132.1, 128.9 (t, \( J = 23.5 \) Hz), 114.5, 63.0, 33.1, 31.5, 28.2; IR (thin film, NaCl): 3373, 3355, 3344, 3330, 3076, 3028, 2996, 2978, 2945, 2860, 2841, 1641, 1438, 1416, 1095, 1063, 996, 910 cm\(^{-1}\).

Allyl bromide (SD-04). To stirring solution of SD-1 (0.50 g, 3.9 mmol) in Et\(_2\)O (20 mL) was dropwised PBr\(_3\) (0.26 mL, 2.8 mmol) at 0 °C. The reaction was warmed to room temperature then stirred additional 1.5 h. The reaction mixture was quenched with saturated aqueous NaHCO\(_3\) (50 mL) in ice bath. The layers were separated, and the organic phase was washed with brine (10 mL) and dried over MgSO\(_4\). The solvent was removed under reduced pressure and purified by flash column chromatography with hexanes to afford product SD-04 (360 mg, 49%) as a colorless oil containing 4-5% 8-bromoocta-1,6-diene S-2 based on \(^1\)H-NMR integrations. \(^1\)H-NMR (400 MHz, CDCl\(_3\), * represents a minor peak form 8-bromoocta-1,6-diene): \( \delta \) 5.84-5.74 (m, 2H), *5.70, 5.04-4.95 (m, 2H), 3.95 (s, 2H), 2.11-2.03 (m, 4H), 1.54-1.43 (m, 2H); \( ^{13} \)C-NMR (100 MHz, CDCl\(_3\), * represents a minor peak form 8-bromoocta-1,6-diene): \( \delta \) 138.4, 136.1, *126.5, 126.3 (t, \( J = 23.5 \) Hz), 114.8, 33.4, 33.1, 31.3, 27.9.
Alcohol (SD-2). The substrate was prepared by the literature procedure\textsuperscript{151} with LiAlH\textsubscript{4} (1.0 M solution, 14.4 mL, 14.4 mmol), NaOMe (1.55 g, 28.8 mmol), Oct-7-en-2-yn-1-ol S-70 (0.6 g, 4.8 mmol) and THF (30 mL). The reaction mixture quenched with D\textsubscript{2}O (4.3 mL, 50 equiv.), and CD\textsubscript{3}OD (2.5 mL). The crude reaction mixture was purified by silica gel chromatography (Et\textsubscript{2}O/hexanes, 1/2) to afford product (505 mg, 83\%) as a colorless oil containing 10\% (E)-octa-2,7-dien-1-ol based on \textsuperscript{1}H-NMR integrations. \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}, * represents a minor peak form(E)-octa-2,7-dien-1-ol): $\delta$ 5.79–5.69 (m, 1H), *5.56, 5.57–5.53 (m, 1H), 4.98–4.88 (m, 2H), 3.98 (d, $J$ = 5.6 Hz, 2H), 3.17 (s, 1H), 2.05–1.97 (m, 4H), 1.45–1.39 (m, 2H); \textsuperscript{13}C-NMR (100 MHz, CDCl\textsubscript{3}, * represents a minor peak form(E)-octa-2,7-dien-1-ol): $\delta$ 138.5, *132.3, 132.0 (t, $J$ = 23 Hz), 129.1, 114.5, 63.1, 33.1, 31.4, 28.2; IR (thin film, NaCl): 3573, 3383, 3375, 3357, 3349, 3339, 3315, 3096, 3076, 2994, 2977, 2949, 2932, 2863, 2840, 1641, 1435, 1416, 1088, 995, 911 cm\textsuperscript{-1}.

Allyl bromide (SD-05). Prepared according to the general procedure described for SD-4 with SD-02 (0.50 g, 3.9 mmol), PBr\textsubscript{3} (0.26 mL, 2.8 mmol) and Et\textsubscript{2}O (20 mL). The crude reaction mixture was purified by silica gel chromatography with hexanes to afford product SD-05 (300 mg, 41\%) as a colorless oil containing (E)-8-bromoocta-1,6-diene based on \textsuperscript{1}H-NMR integrations. \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}): $\delta$ 5.84–5.67 (m, 2H), 5.04–4.94 (m, 2H), 3.95 (d, $J$ = 7.6 Hz, 2H), 2.17–2.03 (m, 4H), 1.54–1.43 (m, 2H); \textsuperscript{13}C-NMR
Alcohol (SD-3). To a stirred solution of Oct-7-en-2-yn-1-ol S-70 (0.60 g, 4.8 mmol) in THF (30 mL) was slowly added LiAlD₄ (1.0 in THF, 12 mL, 12 mmol) then the reaction mixture was heated to reflux. After 2.5 h, the reaction was cooled to 4 °C and carefully quenched with D₂O (4.3 mL, 50 equiv.), followed by CD₃OD (2.5 mL). After stirring for 5 minutes, the suspension was diluted with Et₂O (30 mL) and 10% NaOH solution in D₂O (1.3 mL). After white solid was appeared, the reaction mixture was filtered through a plug of Celite then the organic phases were washed with brine (10 mL), dried over MgSO₄. The solvent was concentrated under reduced pressure to afford The crude reaction mixture was purified by silica gel chromatography (Et₂O/hexanes, 1/2) to afford product SD-3 (540 mg, 88%) as a colorless oil containing 2-3% octa-2,7-dien-1-ol based on ¹H-NMR integrations. ¹H-NMR (400 MHz, CDCl₃): δ 5.80-5.70 (m, 1H), 4.98-4.88 (m, 2H), 4.00 (s, 2H), 2.70 (bs, 1H), 2.04-1.99 (m, 4H), 1.43 (p, J = 7.5 Hz, 2H); ¹³C-NMR (100 MHz, CDCl₃, * represents minor peaks from octa-2,7-dien-1-ol): δ 138.5, *132.5, 132.0 (t, J = 22.6 Hz), *129.1, 128.8 (t, J = 23.4 Hz), 114.5, 63.2, 33.1, 31.4, 28.2; IR (thin film, NaCl): 3405, 3384, 3363, 3076, 3022, 2977, 2944, 2892, 2861, 2840, 1640, 1493, 1449, 994, 911, 718 cm⁻¹.
**Allyl bromide (SD-06).** Prepared according to the general procedure described for SD-04 with SD-03 (0.50 g, 3.9 mmol), PBr₃ (0.26 mL, 2.8 mmol) and Et₂O (20 mL). The crude reaction mixture was purified by silica gel chromatography with hexanes to afford product SD-06 (305 mg, 41%) as a colorless oil containing 2-3% 8-bromoocta-1,6-diene based on ¹H-NMR integrations. ¹H-NMR (400 MHz, CDCl₃): δ 5.81-5.71 (m, 1H), 4.98 (dq, J = 17.6, 2.0 Hz, 1H), 4.95-4.92 (m, 1H), 3.92 (s, 2H), 2.07-2.01 (m, 4H), 1.50-1.43 (m, 2H); ¹³C-NMR (100 MHz, CDCl₃): δ 138.3, 135.6 (t, J = 23 Hz), 126.3 (t, J = 24.2 Hz), 114.8, 33.3, 33.1, 31.2, 27.9; IR (thin film, NaCl): 3067, 3039, 3017, 2927, 2917, 2910, 2897, 2360, 2341, 763, 701, 545, 537 cm⁻¹; HRMS (ESI⁺) Calcd for C₈H₁₂²H₂Br¹ [M+H]⁺: 191.0404, found: 191.0408.

**Ester (SD-7).** The general procedure for alkylation using SN2’ reaction was followed with methyl 4-fluoro-2-iodobenzoate S-6 (288 mg, 1.03 mmol), isopropylmagnesium chloride (1.3 M in THF, 0.85 mL, 1.1 mmol), a solution of CuCN (92.0 mg, 1.03 mmol),
LiCl (43.0 mg, 1.03 mmol) in THF (1.0 mL), SD-4 (0.15 g, 0.79 mmol), and THF (5.0 mL). The crude reaction mixture was purified by silica gel chromatography (Et₂O/hexanes, 1/20) and Ag-impregnated gradient silica gel chromatography (10% Ag, 9:1 Et₂O: hexanes with a gradient to 50% Et₂O) to afford product SD-7 (131 mg, 48% yield) as a colorless oil containing 4-5% methyl 4-fluoro-2-(octa-1,7-dien-3-yl)benzoate S-7 based on ¹H-NMR integrations: ¹H-NMR (500 MHz, CDCl₃, * represents a minor peak form methyl 4-fluoro-2-(octa-1,7-dien-3-yl)benzoate): δ 7.83 (dd, J = 9.0, 6.0 Hz, 1H), 7.02 (dd, J = 10.5, 2.5 Hz, 1H), 6.91 (m, 1H), *5.91 (dd, J = 17.0, 10.5 Hz), 5.80-5.72 (m, 1H), 5.07-4.91 (m, 4H), 4.39 (t, J = 7.5 Hz, 1H), 3.88 (s, 3H), 2.04 (q, J = 7.2 Hz, 2H), 1.74-1.62 (m, 2H), 1.48-1.26 (m, 2H); ¹³C-NMR (125 MHz, CDCl₃, * represents a minor peak form methyl 4-fluoro-2-(octa-1,7-dien-3-yl)benzoate): δ 168.1 165.5 (d, J = 251 Hz), 150.3 (d, J = 7.75 Hz), *114.7, 141.4 (t, J = 23.4 Hz), 139.3, 133.5 (d, J = 8.75 Hz), 126.7 (d, J = 3.25 Hz), 115.6, 115.5 (d, J = 21.6 Hz), 115.2, 113.6 (d, J = 21.6 Hz), 52.7, 44.4 (d, J = 1.0 Hz), 35.6, 34.3, 27.3; IR (thin film, NaCl): 3093, 3072, 3043, 1725, 1608, 1585, 1435, 1295, 1245, 1119, 916, 733 cm⁻¹; HRMS (ESI+) Calcd for C₁₅H₁₉₂H₁F₁O₂ [M+H]^+: 264.1510, found: 264.1515.

Aldehyde (2.65). The general procedure for reduction was followed with LiAlH₄ 95% (47.5 mg, 1.25 mmol), SD-7 (131 mg, 0.500 mmol), and THF (7.0 mL). The crude reaction mixture was purified by silica gel chromatography (Et₂O/hexanes, 1/3) to afford
alcohol (110 mg, 94%) as a colorless oil. The general procedure for oxidation was followed with alcohol (110 mg, 0.47 mmol), PCC (161 mg, 0.749 mmol), Celite (150 mg), and dry CH₂Cl₂ (5.0 mL). The crude reaction mixture was purified by silica gel chromatography (Et₂O/hexanes, 1/30) to afford product 2.65 (95 mg, 87%) as a colorless oil containing 4-5% 4-fluoro-2-(octa-1,7-dien-3-yl)benzaldehyde S-9 based on ¹H-NMR integrations. ¹H-NMR (500 MHz, CDCl₃, * represents a minor peak form 4-fluoro-2-(octa-1,7-dien-3-yl)benzaldehyde): δ 10.25 (s, 1H), 7.84 (dd, J = 9.0, 6.5 Hz, 1H), 7.05 (dd, J = 10.5, 2.5 Hz, 1H), 7.02 (td, J = 8.5, 2.5 Hz, 1H), *5.93 (dd, J = 17.5, 10.5 Hz), 5.78-5.70 (m, 1H), 5.12-4.91 (m, 4H), 4.42 (t, J = 7.5 Hz, 1H), 2.05 (q, J = 7.2 Hz, 2H), 1.81-1.66 (m, 2H), 1.49-1.29 (m, 2H); ¹³C-NMR (125 MHz, CDCl₃, * represents a minor peak form 4-fluoro-2-(octa-1,7-dien-3-yl)benzaldehyde): δ 190.5 (d, J = 2.75 Hz), 166.0 (d, J = 225 Hz), 150.6 (d, J = 8.25 Hz), *140.5, 140.2 (t, J = 23.5 Hz), 138.3, 134.5 (d, J = 10.0 Hz), 130.2 (d, J = 2.75 Hz), 115.7, 115.0 (d, J = 21.87 Hz), 114.7, 113.7 (d, J = 21.87 Hz), 42.3 (d, J = 1.37 Hz), 34.8, 33.5, 26.6; HRMS (ESI+) Calcd for C₁₅H₁₇F₁₂H₁O₁[M+H]⁺: 234.1404, found: 234.1415.

Ester (SD-8). The general procedure for alkylation using SN2’ reaction was followed with methyl 4-fluoro-2-iodobenzoate (288 mg, 1.03 mmol), isopropylmagnesium chloride (1.3 M in THF, 0.85 mL, 1.1 mmol), a solution of CuCN (92.0 mg, 1.03 mmol), LiCl (43.0 mg, 1.03 mmol) in THF (2.0 mL), SD-5 (0.15 g, 0.79 mmol), and THF (5.0
mL). The crude reaction mixture was purified by silica gel chromatography (Et₂O/hexanes, 1/20) and Ag-impregnated gradient silica gel chromatography (10% Ag, 9:1 Et₂O: hexanes with a gradient to 50% Et₂O) to afford product SD-8 (89 mg, 33% yield) as a colorless oil containing 10% methyl 4-fluoro-2-(octa-1,7-dien-3-yl)benzoate S-7 based on ¹H-NMR integrations: ¹H-NMR (500 MHz, CDCl₃, * represents a minor peak form methyl 4-fluoro-2-(octa-1,7-dien-3-yl)benzoate): δ 7.78 (t, J = 7.25 Hz, 1H), 6.97 (d, J = 10.5 Hz, 1H), 6.86 (t, J = 8.0 Hz, 1H), 5.85 (dd, J = 16.6, 10.5 Hz, 1H), 5.72-5.62 (m, 1H), 5.02-4.86 (m, 4H), *4.33, 3.82 (s, 3H), 1.98 (q, J = 7.2 Hz, 2H), 1.68-1.57 (m, 2H), 1.42-1.20 (m, 2H); ¹³C-NMR (125 MHz, CDCl₃, * represents a minor peak form methyl 4-fluoro-2-(octa-1,7-dien-3-yl)benzoate): δ 168.1 164.5 (d, J = 251 Hz), 150.3 (d, J = 7.87 Hz), 141.8, 139.3, 133.5 (d, J = 8.75 Hz), 126.6 (d, J = 2.75 Hz), 115.8, 115.5 (d, J = 21.5 Hz), 115.2, 113.6 (d, J = 21.6 Hz), 52.7, *44.3, 44.1 (d, J = 20.3 Hz), 35.6, 34.3, 27.3; IR (thin film, NaCl): 3041, 2954, 2901, 1724, 1607, 1583, 1435, 1276, 1250, 1116, 106, 760, 699, 540 cm⁻¹; HRMS (ESI⁺) Calcd for C₁₆H₁₉₂H₁F₁O₂[M+H]⁺: 264.1510, found: 264.1518.

Aldehyde (2.69). The general procedure for reduction was followed with LiAlH₄ 95% (32mg, 0.84 mmol), SD-8 (89 mg, 0.34 mmol), and THF (5.0 mL). The crude reaction mixture was purified by silica gel chromatography (Et₂O/hexanes, 1/3) to afford alcohol (77 mg, 96%) as a colorless oil. The general procedure for oxidation was followed with
alcohol (77.0 mg, 0.327 mmol), PCC (112 mg, 0.523 mmol), Celite (100 mg), and dry 
CH₂Cl₂ (5.0 mL). The crude reaction mixture was purified by silica gel chromatography 
(Et₂O/hexanes, 1/30) to afford product 2.69 (91 mg, 87%) as a colorless oil containing 
10% 4-fluoro-2-(octa-1,7-dien-3-yl)benzaldehyde S-9 based on ¹H-NMR integrations. 
¹H-NMR (500 MHz, CDCl₃, * represents a minor peak form 4-fluoro-2-(octa-1,7-dien-3-
yl)benzaldehyde): δ 10.25 (s, 1H), 7.86-7.83 (m, 1H), 7.05 (dd, J = 10.5, 2.5 Hz, 1H), 
7.03 (td, J = 8.0, 2.5 Hz, 1H), 5.94 (dd, J = 17.5, 10.5 Hz, 1H), 5.79-5.71 (m, 1H), 5.12-
4.92 (m, 4H), *4.42, 2.05 (q, J = 7.3 Hz, 2H), 1.80-1.66 (m, 2H), 1.48-1.31 (m, 2H); ¹³C-
NMR (125 MHz, CDCl₃, * represents a minor peak form 4-fluoro-2-(octa-1,7-dien-3-
yl)benzaldehyde): δ 190.5 (d, J = 2.75 Hz), 166.1 (d, J = 225 Hz), 150.7 (d, J = 8.25 Hz), 
140.5, 138.3, 134.6 (d, J = 10.1 Hz), 130.2 (d, J = 4.37 Hz), 115.8, 115.1 (d, J = 22.37 
Hz), 114.8, 113.8 (d, J = 21.5 Hz), *42.4, 42.1 (t, J = 19.9 Hz), 34.8, 33.5, 26.6; HRMS 

Ester (SD-9). The general procedure for alkylation using SN2’ reaction was followed 
with methyl 4-fluoro-2-iodobenzoate (191 mg, 0.682 mmol), isopropylmagnesium 
chloride (1.3 M in THF, 0.57 mL, 0.74 mmol), a solution of CuCN (62 mg, 0.69 mmol), 
LiCl (29 mg, 0.69 mmol) in THF (1.0 mL), SD-6 (100 mg, 0.53 mmol), and THF (5.0 
ml). The crude reaction mixture was purified by silica gel chromatography 
(Et₂O/hexanes, 1/20) and Ag-impregnated gradient silica gel chromatography (10% Ag,
9:1 Et₂O: hexanes with a gradient to 50% Et₂O) to afford product SD-9 (89 mg, 49% yield) as a colorless oil containing 2-3% methyl 4-fluoro-2-(octa-1,7-dien-3-yl)benzoate S-7 based on ¹H-NMR integrations. ¹H-NMR (500 MHz, CDCl₃):  δ 7.84 (dd, J = 8.5, 5.5 Hz, 1H), 7.04 (dd, J = 10.5, 2.5 Hz, 1H), 6.94-6.90 (m, 1H), 5.81-5.73 (m, 1H), 5.08-4.92 (m, 4H), 3.89 (s, 3H), 2.05 (q, J = 7.2 Hz, 2H), 1.75-1.64 (m, 2H), 1.50-1.40 (m, 1H), 1.39-1.29 (m, 1H); ¹³C-NMR (125 MHz, CDCl₃, * represents a minor peak form methyl 4-fluoro-2-(octa-1,7-dien-3-yl)benzoate):  δ 167.5 164.8 (d, J = 251 Hz), 149.6 (d, J = 7.75 Hz), 140.8 (t, J = 23.4 Hz), 138.6, 132.9 (d, J = 8.75 Hz), 126.0 (d, J = 2.75 Hz), 114.9, 114.8 (d, J = 21.3 Hz), 114.5, 112.9 (d, J = 21.3 Hz), 52.0, *43.7, 43.3 (d, J = 20 Hz), 34.9, 33.6, 26.6; IR (thin film, NaCl): 2938, 2931, 2919, 1724, 1607, 1583, 1435, 1277, 1253, 1119, 1093, 918 cm⁻¹; HRMS (ESI⁺) Calcd for C₁₆H₁₈₂H₂F₁O₂ [M+H]⁺: 265.1573, found: 265.1566.

Aldehyde (2.73). The general procedure for reduction was followed with LiAlH₄ 95% (32 mg, 0.84 mmol), SD-09 (89 mg, 0.34 mmol), and THF (5.0 mL). It afforded crude mixture (80 mg, 100%) as colorless oil. It used next step without any further purification. The general procedure for oxidation was followed with crude mixture (80 mg, 0.34 mmol), PCC (116 mg, 0.540 mmol), Celite (100 mg), and dry CH₂Cl₂ (7.0 mL). The crude reaction mixture was purified by silica gel chromatography (Et₂O/hexanes, 1/30) to afford product 2.73 (65 mg, 82%) as a colorless oil containing 10% 4-fluoro-2-(octa-1,7-
dien-3-yl)benzaldehyde S-9 based on $^1$H-NMR integrations. $^1$H-NMR (500 MHz, CDCl$_3$, * represents minor peaks form 4-fluoro-2-(octa-1,7-dien-3-yl)benzaldehyde): $\delta$ 10.24 (s, 1H), 7.84 (dd, $J = 8.5$, 6.0 Hz, 1H), 7.07-7.01 (m, 2H), *5.99, 5.78-5.70 (m, 1H), 5.11-4.91 (m, 4H), *4.42, 2.05 (q, $J = 7.3$ Hz, 2H), 1.80-1.66 (m, 2H), 1.49-1.41 (m, 1H), 1.38-1.31 (m, 1H); $^{13}$C-NMR (125 MHz, CDCl$_3$, * represents a minor peak form 4-fluoro-2-(octa-1,7-dien-3-yl)benzaldehyde): $\delta$ 191.2, 166.7 (d, $J = 255$ Hz), 151.4, 140.8 (t, $J = 23.6$ Hz), 139.0, 135.3 (d, $J = 10$ Hz), 130.9 (d, $J = 2.25$ Hz), 116.4, 115.7 (d, $J = 21.8$ Hz), 115.4, 114.5 (d, $J = 22$ Hz), 42.7 (t, $J = 20$ Hz), 35.5, 34.2, 27.3; IR (thin film, NaCl): 3028, 2937, 2910, 2860, 1701, 1692, 1606, 1579, 1271, 1240, 1187, 917, 822, 758, 746 cm$^{-1}$; HRMS (ESI+) Calcd for C$_{15}$H$_{16}$F$_2$O$_1$ [M+H]$^+$: 235.1467, found: 235.1473.

Substrates for Cross Over Experiments

Alcohol (SD-13). The general procedure for reduction was followed with LiAlD$_4$ (1.0 M solution, 2.52 mL, 2.52 mmol), methyl 2-(octa-1,7-dien-3-yl)-4-(trifluoromethyl)benzoate S-7 (197 mg, 0.631 mmol), and THF (5.0 mL). The crude reaction mixture was purified by silica gel chromatography (Et$_2$O/hexanes, 1/3) to afford product SD-13 (158 mg, 87%) as a colorless oil. $^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ 7.32-7.26 (m, 3H), 5.74-5.67 (m, 1H),
5.52-5.10 (m, 1H), 4.86-4.74 (m, 4H), 3.40 (q, J = 7.3 Hz, 1H), 1.86 (q, J = 7.2 Hz, 2H), 1.76 (bs, 1H), 1.63-1.48 (m, 2H), 1.29-1.21 (m, 1H), 1.16-1.08 (m, 1H); $^{13}$C-NMR (125 MHz, CDCl$_3$): δ 143.3, 142.0, 141.4, 138.5, 130.4 (q, J = 31.8 Hz), 128.5, 124.4 (q, J = 271 Hz), 123.8 (q, J = 3.8 Hz), 123.2 (q, J = 3.8 Hz), 115.2, 114.9, 62.0 (m), 44.2, 34.6, 33.7, 26.9

**Aldehyde (2.47).** The general procedure for oxidation was followed with SD-13 (158 mg, 0.552 mmol), PCC (178 mg, 0.828 mmol), Celite (150 mg), and dry CH$_2$Cl$_2$ (5.0 mL). The crude reaction mixture was purified by silica gel chromatography (Et$_2$O/n-hexane, 1/30) to afford product **2.47** (127 mg, 82%) as a colorless oil. $^1$H-NMR (500 MHz, CDCl$_3$): δ 7.95 (dd, J = 8.5, 1.0 Hz, 1H), 7.63 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 6.03-5.96 (m, 1H), 5.80-5.71 (m, 1H), 5.16-4.93 (m, 4H), 4.38 (q, J = 7.3 Hz, 1H), 2.07 (q, J = 7.2 Hz, 2H), 1.88-1.71 (m, 2H), 1.52-1.30 (m, 2H); $^{13}$C-NMR (125 MHz, CDCl$_3$): δ 191.0 (t, J = 26.8 Hz), 148.0, 140.5, 138.3, 136.1, 135.2 (q, J = 32.2 Hz), 131.7, 125.3 (q, J = 3.7 Hz), 123.7 (q, J = 273 Hz), 123.5 (q, J = 3.7 Hz), 116.4, 115.0, 43.0, 35.1, 33.6, 26.9
2,3,4,9-tetrahydro-1H-fluorene (2.4).\textsuperscript{153} \textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}): \(\delta\) 7.38 (d, \(J = 7.5\) Hz, 1H), 7.27-7.18 (m, 2H), 7.11 (td, \(J = 7.2, 1.5\) Hz, 1H), 3.24 (s, 2H), 2.43 (m, 4H), 1.80 (quint, \(J = 3.0\) Hz, 4H); \textsuperscript{13}C-NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 146.2, 142.7, 141.4, 135.8, 126.0, 123.6, 123.3, 117.4, 40.7, 25.9, 23.2, 22.6, 22.2; HRMS (ESI+) Calcd for C\(_{13}\)H\(_{14}\)[M+H]\(^+\): 171.1174, found: 171.1173.

2',3',4',5'-tetrahydro-[1,1'-biphenyl]-2-carbaldehyde (2.5). \textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 10.15 (s, 1H), 7.89 (dt, \(J = 8.0, 0.8\) Hz, 1H), 7.53 (td, \(J = 7.2, 1.2\) Hz, 1H), 7.36 (t, \(J = 7.2\) Hz, 1H), 7.31 (d, \(J = 7.6\) Hz, 1H), 5.64 (m, 1H), 2.36-2.34 (m, 2H), 2.25-2.21 (m, 2H), 1.86-1.80 (m, 2H), 1.75-1.70 (m, 2H)

1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2-carbaldehyde (2.2). \textsuperscript{1}H-NMR (500 MHz, CDCl\textsubscript{3}): \(\delta\) 10.36 (s, 1H), 7.84 (d, \(J = 7.5\) Hz, 1H), 7.55-7.52 (m, 1H), 7.41 (d, \(J = 7.5\) Hz, 1H), 7.37 (t, \(J = 7.5\) Hz, 1H), 5.99-5.96 (m, 1H), 5.70 (d, \(J = 10\) Hz, 1H), 4.41 (s, 1H), 2.13-2.09 (m, 3H), 1.73-1.69 (m, 2H), 1.55-1.49 (m, 1H)

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Chapter 2- Development of a Tandem Ru-Catalyzed Ring-Closing Metathesis /Hydroacylation

[Chemical structures and NMR spectra]

ppm

ppm

ppm
Chapter 2- Development of a Tandem Ru-Catalyzed Ring-Closing Metathesis / Hydroacylation
Chapter 2- Development of a Tandem Ru-Catalyzed Ring-Closing Metathesis /Hydroacylation
Chapter 2- Development of a Tandem Ru-Catalyzed Ring-Closing Metathesis /Hydroacylation

[Chemical structure images]

[Graphical data]

[Additional chemical structure images]
Chapter 2- Development of a Tandem Ru-Catalyzed Ring-Closing Metathesis /Hydroacylation

[Chemical structures and NMR spectra images]

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Chapter 2 - Development of a Tandem Ru-Catalyzed Ring-Closing Metathesis / Hydroacylation

Sample name:
Sample directory:
Fiducial: Gauss
Pulse Sequence: Gauss [gDOM]
Data collected on: Sep 15 2012

Sample name:
Sample directory:
Fiducial: Gauss
Pulse Sequence: Gauss [gDOM]
Data collected on: Sep 15 2012

Sample name:
Sample directory:
Fiducial: Gauss
Pulse Sequence: Gauss [gDOM]
Data collected on: Sep 15 2012

Sample name:
Sample directory:
Fiducial: Gauss
Pulse Sequence: Gauss [gDOM]
Data collected on: Sep 15 2012
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Chapter 2: Development of a Tandem Ru-Catalyzed Ring-Closing Metathesis /Hydroacylation

[Chemical structures and spectra images]

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[Chemical structures]

[Graphs and spectra]

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[Chemical structures and NMR spectra]

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[Image of chemical structures with NMR spectra]
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[Chemical structures and spectra diagrams]

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Chapter 2- Development of a Tandem Ru-Catalyzed Ring-Closing Metathesis / Hydroacylation
Chapter 2- Development of a Tandem Ru-Catalyzed Ring-Closing Metathesis /Hydroacylation

[Chemical structures and NMR spectra]

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Chapter 2 - Development of a Tandem Ru-Catalyzed Ring-Closing Metathesis / Hydroacylation

[Diagram of chemical structures and NMR spectra]

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Chapter 2- Development of a Tandem Ru-Catalyzed Ring-Closing Metathesis / Hydroacylation

![Diagram of chemical structures]
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Chapter 2- Development of a Tandem Ru-Catalyzed Ring-Closing Metathesis / Hydroacylation

[Diagram of chemical structures and spectra]

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Chapter 2- Development of a Tandem Ru-Catalyzed Ring-Closing Metathesis / Hydroacylation
Chapter 2- Development of a Tandem Ru-Catalyzed Ring-Closing Metathesis / Hydroacylation
Chapter 2- Development of a Tandem Ru-Catalyzed Ring-Closing Metathesis /Hydroacylation

\[
\begin{align*}
\text{Diagram 1} & \\
\text{Diagram 2}
\end{align*}
\]
Chapter 2- Development of a Tandem Ru-Catalyzed Ring-Closing Metathesis /Hydroacylation
Chapter 2: Development of a Tandem Ru-Catalyzed Ring-Closing Metathesis / Hydroacylation

[Diagram of molecular structures and spectra]

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Chapter 3

C-C Bond Formation *via* Ru-catalyzed Tandem Ring-Closing Metathesis/Olefin Isomerization/C-H Activation
3.1 Introduction

The C-H bond is ubiquitous and the most abundant bond in nature. However, it is well known that functionalization of a C-H bond is challenging due to a typically large bond dissociation energy in addition to regioselectivity issues (Table 3.1.1). Since unactivated C-H bonds can be functionalized by use of a transition metal, direct functionalization of C-H bonds has been considered a powerful and ideal method for the formation of carbon-carbon and carbon-heteroatom bonds. More than 500 papers concerning “C-H functionalization” have been published in 2011, which shows the large attention to this topic. Furthermore, methods that also result in the formation of C-C bonds are becoming increasingly important in industrial and academic research setting.

Table 3.1.1 Some specific bond dissociation energies (in Kcal/mol)

<table>
<thead>
<tr>
<th>Bond</th>
<th>Energy (Kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃-H</td>
<td>105.1</td>
</tr>
<tr>
<td>CH₂=CH-H</td>
<td>110</td>
</tr>
<tr>
<td>C₆H₆-H</td>
<td>110.9</td>
</tr>
<tr>
<td>CH₃-Cl</td>
<td>84.6</td>
</tr>
<tr>
<td>CH₃-Br</td>
<td>70.9</td>
</tr>
<tr>
<td>CH₃-I</td>
<td>57.2</td>
</tr>
<tr>
<td>Benzene-H</td>
<td>82.3</td>
</tr>
<tr>
<td>Benzene-H</td>
<td>71.1</td>
</tr>
</tbody>
</table>

3.2 Background of C-C bond formation via ruthenium catalyzed C-H bond activation

In 1963, Kleiman and Dubeck isolated nickel azo-dye complex 3.2 resulting from ortho C-H bond cleavage of azobenzene 3.1.\(^\text{(157)}\) Stoichiometric dicyclopentadienylnickel was reacted with azobenzene 3.1 to form five-membered nickel complex 3.2 (Scheme 3.2.1).

**Scheme 3.2.1** ortho C-H bond cleavage of azobenzene by a nickel complex

\[
\text{Cp}_2\text{Ni} + \text{C}_6\text{H}_4\text{N} = \text{N} + \text{C}=\text{C} \xrightarrow{\text{3.1}} \text{Cp} = \text{N} + \text{C}_6\text{H}_4\text{Ni} = \text{N}
\]

In 1965, Chatt et al. reported oxidative addition of an unactivated C-H bond of naphthalene to a ruthenium complex.\(^\text{(158)}\) A \textit{trans}-[\text{RuCl}_2(\text{Me}_2\text{PCH}_2\text{CH}_2\text{PMe}_2)] was treated with sodium naphthalenide to form \textit{cis}-[\text{RuH}(2\text{-C}_{10}\text{H}_7)(\text{Me}_2\text{PCH}_2\text{CH}_2\text{PMe}_2)] (Scheme 3.2.2).

**Scheme 3.2.2** Oxidative addition of an unactivated C-H bond

Following these pioneering results, a large number of studies that detailed C-C bond formation thorough C-H bond cleavage using stoichiometric, as well as catalytic

---

amounts of transition metal complexes were reported.\textsuperscript{159,160,161} However, all of these studies are met with several limitations including a narrow substrate scope, low yields and regioselectivities. It was not until 1986 that a more successful ruthenium catalyzed C-H activation was described.\textsuperscript{162} Lewis et al. described the first example of regioselective \textit{o}-alkylations of phenol by way of a cyclometalated ruthenium phosphate complex \textit{Ru-3.1} and potassium phenoxide (Scheme 3.2.3). The reactions proceeded with high selectivity for the \textit{ortho}-position, however, low selectivity for mono- over di-substitution was observed. Furthermore, this method was only effective for ethylene.

\textbf{Scheme 3.2.3 Ortho-directed C-H bond activation}

\begin{center}
\includegraphics[width=0.8\textwidth]{Scheme3.2.3.png}
\end{center}

In 1993, Murai et al. made significant progress in achieving C-H activation of ketones with high yield with a wide range of substrates.\textsuperscript{163} The carbonyl group acts as a

\begin{enumerate}
\end{enumerate}
directing group that allows for a more facile, highly regioselective C-H bond cleavage. RuH$_2$(CO)(PPh$_3$)$_3$ was used as a precursor for the Ru(0) catalyst. Oxidative addition of a ruthenium species into the ortho C-H bond of an aromatic ketone, subsequent migratory insertion to an alkene, followed by reductive elimination afforded a newly formed C-C bond (Scheme 3.2.4). Various aromatic ketones were suitable for this reaction and the desired products were generated in 75-100% yield with high regioselectivity (ortho position of ketone). Furthermore, this method was effective using a 1:1 ratio of the ketone and the alkene in many cases. This reaction can be regarded as the first example of chelation-assisted and directed regioselective catalytic C-H activation. Indeed, this result has contributed to the development and emergence of the new field of chelation-assisted regioselective C-H functionalization.

**Scheme 3.2.4 Chelation-assisted regioselective C-H activation by Ru (0)**

After the breakthrough work of Muria and co-workers, a large number of directing groups including phenols, pyridines, pyrimidines, pyrazoles, oxazolines, amides, ketones, oxime ethers, carboxylic acids and hydroxyl groups have been disclosed (Figure
3.2.1 Also, it can be possible site-selective direct C-H functionalization by using different directing groups (Figure 3.2.2).

**Figure 3.2.1** Commonly used directing groups for C-H activations

![Commonly used directing groups for C-H activations](image1)

**Figure 3.2.2** Site-selective directing groups for C-H activations

- (i) α to N
- (ii) β to N
- (iii) γ to N
- (iv) δ to N

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Several mechanisms have been proposed to account for C-H bond metalations.\textsuperscript{165} Depending on the electronic configuration of the metal center, the mechanism of C-H bond cleavage can be classified under various regimes as shown in Scheme 3.2.5. Oxidative additions are typical pathways for electron-rich, low-valent complexes of late transition metals (Re, Fe, Ru, Os, Ir, and Pt) and represent the most common mechanism (Scheme 3.2.5).\textsuperscript{165} In contrast to late transition metals, oxidation additions cannot occur with early transition metals with d\textsuperscript{0} electronic configurations. C-H activation with these species proceed via σ-bond metathesis (Scheme 3.2.5).\textsuperscript{165} Late- or post-transition metals (Pd\textsuperscript{2+}, Pt\textsuperscript{2+}, Pt\textsuperscript{4+}, or Hg\textsuperscript{2+}) prefer electrophilic activation mechanisms typically favored in a strongly polar medium such as water or an anhydrous strong acid. The C-H bond can also be activated through a 1,2 addition to an unsaturated M-X bond (Scheme 3.2.5).\textsuperscript{165} The X in the M=X metal complex of early to middle transition metals assists the reaction by acting as a base. In 1990, Wayland et al. reported methane C-H bond activation through a new pathway involving (tetraxylylporphyrinato)rhodium (II) dimer, [(TXP)Rh]\textsubscript{2} (Scheme 3.2.5).\textsuperscript{166} The generated two metalloradicals, (TMP)Rh·, from [(TXP)Rh]\textsubscript{2}, react with methane via a linear four-centered transition state to generate a new Rh-H bond and Rh-C bond. Recently, base-assisted metalation was proposed as another mechanism for C-H activation (Scheme 3.2.5).\textsuperscript{167} A Lewis-basic heteroatom, such as the oxygen of a

carboxylate, accelerates C-H bond cleavage through a concerted base-assisted deprotonation.

**Scheme 3.2.5** Different mechanisms for C-H bond metalation

3.3 Optimization of tandem RCM/C-H activation

In 2011, Ackermann et al. reported ruthenium catalyzed directed arylations via C-H functionalization. A pyridine group functioned as a directing group and Grubbs’ Ru-based catalysts were found to be efficient catalysts (Scheme 3.3.1). This result inspired us

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to combine metathesis with a C-H activation in a tandem process that could be catalyzed through an *in situ* modified ruthenium alkylidene post-metathesis (Scheme 3.3.2).

**Scheme 3.3.1** Directed arylation by Grubbs’ catalyst

![Scheme 3.3.1 Directed arylation by Grubbs’ catalyst](image)

**Scheme 3.3.2** Initially proposed tandem sequence

![Scheme 3.3.2 Initially proposed tandem sequence](image)

First, in order to examine the above hypothesis, we investigated each individual step of the sequence with Ru-based catalysts. It was found that the Lewis basicity of pyridine caused a problem in the metathesis reaction. Coordination of the pyridine to the catalyst saturates a coordination site on the metal needed for olefin coordination and inhibits reaction. To solve this problem, various conditions for the RCM step were screened (Table 3.3.1). To overcome the reactivity issue, elevated temperatures were examined first. Use of elevated temperatures is one of the commonly used conditions for reactions with nitrogen containing compounds. Initially, NMP was selected as solvent because it is one of the effective solvents for C-H activation. However, reactions performed in NMP resulted in a sluggish RCM reaction (Table 3.3.1, entry 1). We postulate that this is due to the presence of a Lewis basic nitrogen on NMP. Performing

---


the metathesis at elevated temperature (100 °C) in toluene (0.07 M) for 2 hours, however, afforded the desired product 3.4 in 72% yield (Table 3.3.1, entry 2). Typically, optimal reaction conditions for C-H activation include a concentrated reaction solution (1.0 M), therefore RCM was attempted with increased concentrations (3.0 M). However, in 0.3 M concentration of toluene after 2 hours, the conversion significantly diminished (Table 3.1.1, entry 3). Despite prolonged reaction times, the conversion was only marginally improved. Moreover, reaction with G1 yielded poor conversion (Table 3.1.1, entry 4). Next, temperature dependence with G2 was studied. At 160 °C, olefin isomerization occurred prior to ring-closing metathesis producing 3.6 (Table 3.3.1, entry 5). We inferred that the catalyst is decomposing at high concentrations and high temperatures, resulting in the loss of the metathesis activity. Next, we discovered that performing the reaction at a relatively lower temperature (80 °C) for a longer reaction time (overnight reaction) could produce the desired product in 75% yield. The yield of desired product was moderate, but the reaction conditions could be further optimized to reduce reaction time.

(171) It is known that in high (1.0 M) concentration, the RCM step produces side products, so 1.0 M concentration was not tested.
Table 3.3.1 Initial screening of RCM conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>Ru cat.</th>
<th>solvent</th>
<th>concentration</th>
<th>temperature</th>
<th>time</th>
<th>yield of 3.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>G2</td>
<td>NMP</td>
<td>0.05 M</td>
<td>100 °C</td>
<td>2 h</td>
<td>trace (95:5 = 3.3:3.3.4)*</td>
</tr>
<tr>
<td>2</td>
<td>G2</td>
<td>toluene</td>
<td>0.07 M</td>
<td>100 °C</td>
<td>2 h</td>
<td>72%b</td>
</tr>
<tr>
<td>3</td>
<td>G2</td>
<td>toluene</td>
<td>0.3 M</td>
<td>reflux</td>
<td>2 h</td>
<td>45% (50% conversion) overnight; not different</td>
</tr>
<tr>
<td>4</td>
<td>G1</td>
<td>toluene</td>
<td>0.3 M</td>
<td>100 °C</td>
<td>1 h</td>
<td>trace (95:5 = 3.3:3.3.4)*</td>
</tr>
<tr>
<td>5</td>
<td>G2</td>
<td>toluene</td>
<td>0.3 M</td>
<td>160 °C</td>
<td>overnight</td>
<td>(3.4:3.6)</td>
</tr>
<tr>
<td>6</td>
<td>G2</td>
<td>toluene</td>
<td>0.3 M</td>
<td>80 °C</td>
<td>overnight</td>
<td>75%c</td>
</tr>
</tbody>
</table>

*a Yields were calculated by analysis of 1H NMR spectra
b Yields of purified product of 3.4

With the aim of improving the yield and conversion while reducing reaction time, a Brønsted acid was employed to protect the nitrogen lone-pair. Before the RCM reaction was performed, diene 3.3 was treated with camphorsulfonic acid to deactivate the nucleophilicity of nitrogen. The ability of various Grubbs’ catalysts to initiate RCM reactions under these new conditions was investigated (Table 3.3.2). During the screening process, it was found that olefin isomerization is accelerated by acid at high temperature (80 °C to reflux) (entries 1 and 2), as well as at high concentration and longer reaction times (entries 3 and 4). The result in entry 4 led us to decrease the reaction temperature to avoid undesired isomerized side products 3.5 and 3.6. Notably, the RCM reaction was found to be effective at a much lower temperature (40 °C), and thus, reaction conditions that afford a quantitative yield of desired product were discovered (Table 3.3.2, entries 5-9).
Ru-based G2 was the most effective catalyst and in combination with 1.2 equivalents of camphorsulfonic acid at 40 °C afforded full conversion in short reaction times.

Table 3.3.2 Initial screening of RCM conditions with Brønsted acid

<table>
<thead>
<tr>
<th>entry</th>
<th>Ru cat.</th>
<th>concentration</th>
<th>CSA</th>
<th>temperature</th>
<th>time</th>
<th>yield(^b) of 3.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>G2 10 mol %</td>
<td>0.3 M</td>
<td>-</td>
<td>80 °C</td>
<td>overnight</td>
<td>75%(^b)</td>
</tr>
<tr>
<td>2</td>
<td>G2 10 mol %</td>
<td>0.3 M</td>
<td>1.3 equiv.</td>
<td>80 °C</td>
<td>overnight</td>
<td>(3.3 : 3.4 : 3.5 : 3.6) 20 : 70 : 5 : 5</td>
</tr>
<tr>
<td>3</td>
<td>G1 10 mol %</td>
<td>0.08 M</td>
<td>1.0 equiv.</td>
<td>reflux</td>
<td>5 h</td>
<td>56%(^b)</td>
</tr>
<tr>
<td>4</td>
<td>G1 5 mol %</td>
<td>0.1 M</td>
<td>1.0 equiv.</td>
<td>100 °C</td>
<td>overnight</td>
<td>(3.3 : 3.4 : 3.5 : 3.6) 7 : 0 : 85 : 8</td>
</tr>
<tr>
<td>5</td>
<td>G1 10 mol %</td>
<td>0.25 M</td>
<td>1.1 equiv.</td>
<td>40 °C</td>
<td>2 h</td>
<td>60% (not full conversion)</td>
</tr>
<tr>
<td>6</td>
<td>G2 10 mol %</td>
<td>0.25 M</td>
<td>1.1 equiv.</td>
<td>40 °C</td>
<td>2 h</td>
<td>80% (not full conversion)</td>
</tr>
<tr>
<td>7</td>
<td>G1 10 mol %</td>
<td>0.25 M</td>
<td>1.2 equiv.</td>
<td>40 °C</td>
<td>2 h</td>
<td>90% (not full conversion)</td>
</tr>
<tr>
<td>8</td>
<td>G2 10 mol %</td>
<td>0.25 M</td>
<td>1.2 equiv.</td>
<td>40 °C</td>
<td>1 h</td>
<td>quant.</td>
</tr>
<tr>
<td>9</td>
<td>HG2 10 mol %</td>
<td>0.25 M</td>
<td>1.2 equiv.</td>
<td>40 °C</td>
<td>1.5 h</td>
<td>90%</td>
</tr>
<tr>
<td>10</td>
<td>G2 10 mol %</td>
<td>0.25 M</td>
<td>1.2 equiv.</td>
<td>25 °C</td>
<td>1.5 h</td>
<td>70%</td>
</tr>
</tbody>
</table>

\(^a\) Yields were calculated based on analysis of \(^1\)H NMR spectra  
\(^b\) Yields of purified product

With this result in hand, we began to study the C-H activation of ring-closing metathesis product, 2-(cyclohex-2-en-1-yl)pyridine 3.4. First, the same reaction conditions that Ackermann et al. had reported were examined with the exception that toluene was used as solvent since NMP had hampered the metathesis reaction (Table 3.3.1, entry 1). Unfortunately, there was no activity towards 3.4 under aforementioned
conditions with either Grubbs’ first generation catalyst or second generation catalyst (Scheme 3.3.3).

**Scheme 3.3.3** Initial screening of C-H activation

We postulate that the absence of C-H activation activity is a result from either the difference of solvent, substrate, or aryl halide (compare Scheme 3.3.1 and Scheme 3.3.3). To identify the reason, we performed the same reaction with substrate 3.5. As shown in Table 3.3.3, we found the result described by Ackermann was reproducible and toluene was also a suitable solvent for the reaction. This result implies that the lack of activity toward C-H activation with substrate 3.4 is due to the difference in olefin location. It may be crucial for the pyridine-coordinated Ru-complex that the H that undergoes activation be in the same plane (Figure 3.3.1).

**Table 3.3.3** Experiments for identifying the reaction of absence of C-H activation activity of substrate 3.4

<table>
<thead>
<tr>
<th>entry</th>
<th>3.5 (mmol)</th>
<th>3.6 (mmol)</th>
<th>Ru cat. (mol%)</th>
<th>solvent</th>
<th>temperature</th>
<th>time</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>0.5</td>
<td>1.0</td>
<td>G1 5 mol%</td>
<td>NMP (0.5 M)</td>
<td>120 °C</td>
<td>22 h</td>
<td>91%</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>1.0</td>
<td>G1 5 mol%</td>
<td>NMP (0.5 M)</td>
<td>120 °C</td>
<td>20 h</td>
<td>90%&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>1.0</td>
<td>G2 5 mol%</td>
<td>NMP (0.5 M)</td>
<td>120 °C</td>
<td>20 h</td>
<td>70%&lt;sup&gt;b&lt;/sup&gt; (70% conversion)</td>
</tr>
<tr>
<td>4</td>
<td>0.5</td>
<td>1.0</td>
<td>G1 5 mol%</td>
<td>toluene (0.5 M)</td>
<td>120 °C</td>
<td>20 h</td>
<td>90%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reported conditions by Ackermann  <sup>b</sup> Yields were calculated based on analysis of <sup>1</sup>H NMR spectra
Initially, we tried to obtain C-H activation without olefin isomerization, but found that C-H activation would not be effective without prior olefin isomerization. Therefore, the tandem sequence was altered such that olefin isomerization would occur prior to C-H activation (Scheme 3.3.4).

Scheme 3.3.4 Restructured proposed tandem sequence

First, we planned to affect the olefin isomerization by using an in situ generated Ru-H complex. The RCM product 3.4 was treated with G2 and dilute H$_2$ gas (N$_2$:H$_2$ = 95:5).$^{172}$ Unfortunately, dilute H$_2$ gas suppressed the activity of the catalyst for the subsequent C-H activation. It only resulted in the olefin isomerized product. In the optimization of our RCM conditions, we knew that olefin isomerization occurs at temperatures higher than 100 °C and camphorsulfonic acid also accelerates olefin isomerization (Table 3.3.1 and Table 3.3.2). So we assumed that either CSA or elevated

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temperatures the necessary olefin isomerization could be accessed before the C-H activation, so we refocused on identifying conditions for the C-H activation to proceed.

After extensive screening, we found that Ag$^+$ could function as a co-catalyst and that its counter anion can have an effect on the reaction (Table 3.3.4). Ag-complexes for the tandem isomerization/C-H activation with larger carboxylate moieties afforded better yields (Table 3.3.4, entry 5). Ag$^+$ could accelerate ligand exchange between the Cl and the benzoate leading to acceleration of the C-H activation. Similar observations have been reported (Figure 3.3.2).\(^{173}\) The amount of the Ag-salt is also important with equimolar amounts with the Ru catalyst proving most efficient (Table 3.3.4). A control experiment indicates that the co-catalyst is required for C-H activation to occur (Table 3.3.4, entry 6).

**Table 3.3.4** Screen of Ag-based co-catalysts

<table>
<thead>
<tr>
<th>entry</th>
<th>Co-catalyst</th>
<th>yields$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AgOAc (10 mol %)</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>AgNO$_3$ (10 mol %)</td>
<td>28%$^b$</td>
</tr>
<tr>
<td>3</td>
<td>AgNO$_3$ (20 mol %)</td>
<td>10%</td>
</tr>
<tr>
<td>4</td>
<td>Ag$_2$CO$_3$ (5 mol %)</td>
<td>trace</td>
</tr>
<tr>
<td>5</td>
<td>AgOBz (10 mol%)</td>
<td>50%$^b$</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>trace</td>
</tr>
</tbody>
</table>

$^a$ Yields were calculated based on analysis of $^1$H NMR spectra

$^b$ Yields of purified product

With these promising results, we investigated reaction conditions for the tandem sequence (Table 3.3.5). To improve the yield of the desired product, we looked at the effect of base on the transformation. Anhydrous $\text{K}_2\text{CO}_3$ was the most efficient, while $\text{CsCO}_3$ was less efficient and $\text{K}_3\text{PO}_4$, TEMP and 2,6-lutidine were not effective in our system (Table 3.3.5, entries 1-5). Since the reaction needs to be neutralized, more than 2.2 equivalents of base are necessary for optimal yields. Surprisingly, using 2.0-2.5 equivalents of base led to the same result. However, reaction with less than 2.0 equivalents or more than 2.5 equivalents of base diminished the yield (Table 3.3.5, entries 6-11).

**Table 3.3.5** Screening of base and amount of base

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>amount</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$\text{K}_3\text{PO}_4$ 3.0 eq</td>
<td>G2 10 mol %</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>2,6 lutidine 3.0 eq</td>
<td>toluene (0.25 M)</td>
<td>NR</td>
</tr>
<tr>
<td>3</td>
<td>TEMP 2.2 eq</td>
<td>CSA 1.2 eq, 40 °C, 1.5 h</td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>$\text{K}_2\text{CO}_3$ 3.5 eq</td>
<td>AgOBz 0.2 eq, CH$_3$CN 5.0 eq, 200 °C, 22 h</td>
<td>55%</td>
</tr>
<tr>
<td>5</td>
<td>$\text{CsCO}_3$ 2.5 eq</td>
<td>3.0 eq</td>
<td>36%</td>
</tr>
<tr>
<td>6</td>
<td>$\text{K}_2\text{CO}_3$ 1.5 eq</td>
<td></td>
<td>45%</td>
</tr>
<tr>
<td>7</td>
<td>$\text{K}_2\text{CO}_3$ 2.0 eq</td>
<td></td>
<td>71%</td>
</tr>
<tr>
<td>8</td>
<td>$\text{K}_2\text{CO}_3$ 2.3 eq</td>
<td></td>
<td>70%</td>
</tr>
<tr>
<td>9</td>
<td>$\text{K}_2\text{CO}_3$ 2.5 eq</td>
<td></td>
<td>70%</td>
</tr>
<tr>
<td>10</td>
<td>$\text{K}_2\text{CO}_3$ 3.5 eq</td>
<td></td>
<td>55%</td>
</tr>
<tr>
<td>11</td>
<td>$\text{K}_2\text{CO}_3$ 5.0 eq</td>
<td></td>
<td>trace</td>
</tr>
</tbody>
</table>
Additives were examined to improve the yield of the desired product. During the screening of co-solvent, it was found that acetonitrile improved the conversion and yield (Table 3.3.6). When the amount of acetonitrile made up one tenth of solvent mixture, the reaction was most effective. However, if acetonitrile was used as solvent for the entire tandem sequence, the RCM reaction does not occur. The absence of AgOBz produced only trace amount of desired product. We infer that acetonitrile serves as a ligand and its role is to stabilize the Ru-complex by coordinating to Ru. Using NMP (1/10 solvent) also showed improvement in yield of the desired product (Table 3.3.6, entry 5). The dependence on the amount of additive was studied with NMP, despite NMP resulting in lower yield than acetonitrile (Table 3.3.7). Due to an elevated temperature of 200 °C, NMP serves as a more reliable additive; the boiling point of NMP is 202-204 °C while that of acetonitrile is 81-82 °C. It was found that 40 mol % of NMP was most effective for the tandem sequence (Table 3.3.7).

**Table 3.3.6 Screening additive in tandem sequence**

<table>
<thead>
<tr>
<th>entry</th>
<th>Co-catalyst (10 mol %)</th>
<th>additive</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AgOBz (1/100 CH₃CN: toluene)</td>
<td>CH₃CN</td>
<td>52%</td>
</tr>
<tr>
<td>2</td>
<td>AgOBz (1/10 toluene)</td>
<td>CH₃CN (1/10 toluene)</td>
<td>65%</td>
</tr>
<tr>
<td>3</td>
<td>AgOBz (1:1 CH₃CN:toluene)</td>
<td>CH₃CN</td>
<td>&lt; 20%</td>
</tr>
<tr>
<td>4</td>
<td>AgOBz (1/10 toluene)</td>
<td>NMP (1/10 toluene)</td>
<td>59%</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>CH₃CN (1:100 CH₃CN: toluene)</td>
<td>trace</td>
</tr>
</tbody>
</table>
Table 3.3.7 Screening of the amount of NMP as an additive in the tandem sequence

<table>
<thead>
<tr>
<th>entry</th>
<th>NMP</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 eq</td>
<td>39%</td>
</tr>
<tr>
<td>2</td>
<td>1 eq</td>
<td>70%</td>
</tr>
<tr>
<td>3</td>
<td>0.4 eq</td>
<td>71%</td>
</tr>
<tr>
<td>4</td>
<td>0.2 eq</td>
<td>58%</td>
</tr>
</tbody>
</table>

There have been several examples that demonstrated that amino acids and carboxylate moieties can accelerate C-H activation by functioning as a ligand. Amino acids were not effective in our system; Boc-Ile-OH gave 40% yield of desired product while Boc-Val-OH resulted in only trace amount of product. Acetamide and trimethyl acetamide were also examined. In contrast to acetamide, trimethyl acetamide exhibited an improved yield of the desired product (Table 3.3.8, entries 3 and 4). Further investigations were carried out employing trimethyl acetamide. Depending on the electronic attributes of the aryl halide, selected preference for the ligand on Ru could be affected. With electron deficient aryl halides better yields of desired product were obtained with trimethyl acetamide (Table 3.3.8).

Table 3.3.8 Screening of ligand in tandem sequence

<table>
<thead>
<tr>
<th>entry</th>
<th>additive</th>
<th>equival.</th>
<th>temperature</th>
<th>time</th>
<th>yields</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NMP</td>
<td>0.4</td>
<td>220 °C</td>
<td>20 h</td>
<td>58%</td>
</tr>
<tr>
<td>2</td>
<td>NMP</td>
<td>0.4</td>
<td>200 °C</td>
<td>27 h</td>
<td>59%</td>
</tr>
<tr>
<td>3</td>
<td>acetamide</td>
<td>0.4</td>
<td>200 °C</td>
<td>22 h</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>trimethylacetamide</td>
<td>0.3</td>
<td>200 °C</td>
<td>27 h</td>
<td>68%</td>
</tr>
<tr>
<td>5</td>
<td>trimethylacetamide</td>
<td>0.4</td>
<td>200 °C</td>
<td>27 h</td>
<td>67%</td>
</tr>
</tbody>
</table>

Since carboxylates resulted in the improvement of formation of the desired product by accelerating the reactivity of C-H activation, we attempted to use a carboxylic acid in the RCM step as a Brønsted acid, instead of camphorsulfonic acid. However, carboxylic acids proved ineffective in promoting the RCM reaction (Table 3.3.9).

Table 3.3.9 Screening of the effect of carboxylic acid as a Brønsted acid in the RCM

<table>
<thead>
<tr>
<th>entry</th>
<th>acid</th>
<th>yield (%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CSA</td>
<td>quant</td>
</tr>
<tr>
<td>2</td>
<td>camphoric acid</td>
<td>&lt;15% conversion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>entry</th>
<th>acid</th>
<th>yield (%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>pivalic acid</td>
<td>&lt;15% conversion</td>
</tr>
<tr>
<td>4</td>
<td>benzoic acid</td>
<td>&lt;15% conversion</td>
</tr>
</tbody>
</table>

\(^a\) Conversions were calculated based on analysis of \(^1\)H NMR spectra; compare starting material and product in crude NMR.
Next, the scope of coupling partners was examined. Aryl chlorides and aryl bromides yielded arylated compounds 3.9 and 3.13 in good yield with aryl bromides reacting at a faster rate than the chlorides. Noteworthy, selective coupling occurred with 1-bromo-4-chlorobenzene 3.7. After coupling with aryl bromide, further reaction with the aryl chloride of the resulting product 3.13 was not observed (Scheme 3.3.5). However, use of aryl triflate 3.8 produced no coupling product, instead, olefin isomerized product 3.5 was afforded as the major product.

Scheme 3.3.5 Various coupling partners in the tandem sequence

The causative agent for the olefin isomerization was further examined. Control experiments were carried out with the purified RCM product 3.4. When the purified compound 3.4 was subjected to the condition (toluene 0.25 M, at 200 °C, 22 h), less than 5% of isomerized product 3.5 was observed in the crude NMR. This ruled out a simple
thermal isomerization. While in the presence of either G2 (10 mol % of G2, toluene 0.25 M, at 200 °C, 22 h) or acid and base (1.2 equivalents of CSA, 2.2 equivalents of K$_2$CO$_3$, toluene 0.25 M, at 200 °C, 22 h), more than 60% of isomerized product 3.5 was observed in the crude NMR. However, no full conversion was shown. These results lead to the conclusion that the isomerization reaction is catalyzed either by a ruthenium complex derived from decomposition of G2 or by acid or base. Furthermore, the reaction is accelerated by a combination of ruthenium catalyst and acid or base.

During the optimization process, we were able to find the most effective reaction conditions for the RCM/olefin isomerization/C-H activation sequence. Before the RCM reaction was performed, diene 3.3 was treated with 1.2 equivalents of camphorsulfonic acid followed by a ring-closing metathesis reaction initiated with 10 mol % of Grubbs’II in 0.25 M toluene at 40 °C for 2 hours. After the RCM reaction is complete, K$_2$CO$_3$ (2.2 equivalents), AgOBz (10 mol %), NMP (40 mol %), and aryl bromide (2.0-3.0 equivalents) were added to allow for the completion of the sequence after 22 hours at 200 °C.

### 3.4 Scope of the tandem process

Based on the optimized reaction conditions for tandem ring-closing metathesis/C-H activation, we subsequently explored the substrate scope. Various coupling partners were effective in this sequence and the tandem process exhibited high functional group tolerance (Table 3.4.1). Aryl bromides bearing ketone and ester functional groups generated arylated products in 60% and 49% yields, respectively. Also, a cyano group was suitable for this protocol and gave desired product in good yield. Aryl halides with
electron-donating groups generated desired products with better yield than those with 
electron-withdrawing groups and also had faster rates than those with electron-
withdrawing group; para-CF$_3$ substituted aryl bromide 3.15 requires longer reaction time 
to achieve full conversion. Steric factors play an important role in the C-H activation 
step; no desired C-H activation product from ortho- substituted aryl halide was observed 
3.21. Heteroatom containing substrates were also suitable affording thiophen-containing 
3.18, albeit in a lower yield.

**Table 3.4.1** Substrate scope of the tandem process

* NMP was used instead of trimethylacetamide, * (pivaloyloxy)silver was used instead of AgOBz, °chlorobenzen was used
3.5 Conclusion

C-H activation in a tandem sequence utilizing C-H bond functionalization has emerged as a powerful synthetic strategy for synthesizing complex natural products and pharmaceutical targets. Direct C-H functionalization represents an environmentally and economically sound approach because of the minimization of by-product formation and the potential streamline to organic syntheses. As C-H activation is combined with RCM reactions and olefin isomerization as a tandem process, the multi-step strategy provides significant advantages in terms of rapid elaboration of simple reaction partners to more complex entities.

3.6 Future prospects

Pyridine directing groups can afford site-selective directing C-H functionalization. However, these groups can be very challenging to remove after the desired transformation. Thus, the development of easily removable directing groups is necessary. Silicon-tethered PyDipSi-directing groups are a potential solution to this limitation. The PyDipSi-directing group can be easily removed or converted into other valuable functional groups such as boronates, iodides and alcohols. Furthermore, when combining this directing C-H activation with olefin metathesis, this reaction can become more efficient, powerful and environmentally friendly.
3.7 Experimental Details

Synthesis of 2-(octa-1,7-dien-3-yl)pyridine (3.3)

To a flame-dried round bottom flask charged with a magnetic stir bar and N₂ were added sequentially dry THF (2.0 mL) and 2-bromopyridine (0.19 mL, 2.0 mmol). The reaction mixture was cooled down to 0 °C in an ice-water bath and then, (E)-octa-2,7-dien-1-ylmagnesium bromide SM 3.1 (17 mL of 0.15 M solution in THF, 2.5 mmol) was added dropwise to the mixture. The reaction mixture was allowed to stir at 40 °C for overnight under nitrogen, and then cooled to room temperature. The reaction mixture was quenched with NH₄Cl (1 mL) and then, THF was evaporated under reduced pressure. The crude mixture was diluted with Et₂O (10 mL) and saturated aqueous NaHCO₃ solution (15 mL) and then extracted several times with Et₂O until no additional product is extracted. The product was extracted from organic layers with 1 M HCl until the product of organic layer does not show up in the TLC and then, the collected aqueous layers were basified with 10% NaOH solution. When a pH of 8 or higher is reached, the product was extracted with Et₂O. The collected organic layers were washed with brine, and dried over anhydrous MgSO₄ and then the solvent was concentrated under reduced pressure. The product was purified by silica gel chromatography (ethyl acetate/hexanes, 1/10) to afford 2-(octa-1,7-dien-3-yl)pyridine 3.3 (227 mg, 61%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 8.55 (md, J = 4.5 Hz, 1H), 7.60 (mt, J = 7.5 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H),

(175) SM 3.1 can be prepared from (E)-8-bromoocta-1,6-diene via Grignard reaction.
7.12-7.09 (m, 1H), 6.06-5.99 (m, 1H), 5.81-5.73 (m, 1H), 5.11-4.90 (m, 4H), 3.43 (q, \( J = 7.5 \) Hz, 1H), 2.06 (q, \( J = 7.5 \) Hz, 2H), 1.90-1.83 (m, 1H), 1.80-1.72 (m, 1H), 1.48-1.39 (m, 1H), 1.34-1.26 (m, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta \) 164.0, 149.5, 141.1, 138.9, 136.6, 122.4, 121.4, 115.2, 114.6, 52.4, 34.3, 33.8, 26.9; IR (thin film, NaCl): 3076, 3006, 2977, 2932, 2858, 1639, 1589, 1570, 1471, 1434, 1416, 994, 912, 780, 748 cm\(^{-1}\); HRMS (ESI+) Calcd for C\(_{13}\)H\(_{18}\)N\(_1\) [M+H]: 188.1439, found: 188.1443.

**General procedure for tandem ring-closing metathesis/isomerization/C-H activation**

Grubbs’ II catalyst (23 mg, 0.027 mmol) and a magnetic stir bar were placed in a Ace pressure tube then capped with a septum, the edges sealed with electrical tape, and then purged with N\(_2\) 3 times. At the same time, 2-(octa-1,7-dien-3-yl)pyridine 3.3 (50 mg, 0.27 mmol) and camphorsulfonic acid (74 mg, 0.32 mmol, 1.2 eq) were dissolved in toluene (0.75 mL) and then stirred for 10 minutes. The reaction mixture was transferred by using additional 0.25 mL of toluene (The concentration for the reaction is 0.25 M) to the Ace pressure tube containing Grubbs’ II catalyst and then, the reaction mixture was stirred at 40 °C for 2 hours. The reaction mixture was removed from the heat source and the stream of dry N\(_2\) was changed with dry Ar and then stirred additional 5 minutes. Under a constant stream of dry Ar, NMP (10 \( \mu \)L, 0.11 mmol, 0.4 eq), K\(_2\)CO\(_3\) (85 mg, 0.61 mmol, 2.3 eq), AgOBz (6.18 mg, 0.027 mmol, 0.1 eq), and chlorobenzene (55 \( \mu \)L, 0.54 mmol, 2.0 eq) were added and then, the pressure vessel was recapped with Michel-
Miller column plug. **CAUTION**: The solid reagents were added quickly and carefully to the reaction mixture without touching the side of pressure vessel. After 22 hours at 200 °C with stirring, the reaction mixture was cooled, diluted with H₂O (3 mL) and Et₂O (10 mL) and then extracted several times with Et₂O. The organic layers were washed with brine, and dried over anhydrous MgSO₄ and then, solvent was concentrated under reduced pressure. The product was purified by silica gel chromatography (ethyl acetate/hexanes, 1/9) to afford 2-(3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)pyridine **3.9** (44 mg, 70%) as a white solid. **¹H NMR** (500 MHz, CDCl₃): δ 8.51 (dq, J = 5.0, 1.0 Hz, 1H), 7.23 (td, J = 7.5, 2.0 Hz, 1H), 7.13-7.07 (m, 3H), 7.00-6.98 (m, 2H), 6.93 (ddd, J = 7.5, 4.5, 1.0 Hz, 1H ), 6.67 (dt, J = 8.0, 1.0 Hz, 1H), 2.63-2.60 (m, 2H), 2.49-2.47 (m, 2H), 1.87 (quint, J = 3.3 Hz, 4H); **¹³C NMR** (125 MHz, CDCl₃): δ 161.9, 148.9, 143.6, 137.6, 135.7, 135.3, 129.0, 128.0, 126.3, 125.2, 120.8, 32.1, 30.0, 23.3, 23.0; **IR** (thin film, NaCl): 3077, 3054, 3018, 3007, 2997, 2928, 2857, 2833, 1585, 1561, 1464, 1429, 782 cm⁻¹; **HRMS** (ESI+) Calcd for C₁₇H₁₈N₁ [M+H]: 236.1439, found: 236.1433.

2-(4'-methyl-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)pyridine (3.11). The general procedure was followed with Grubbs’ II catalyst (23 mg, 0.027 mmol), 2-(octa-1,7-dien-3-yl)pyridine **3.3** (50 mg, 0.27 mmol), camphorsulfonic acid (74 mg, 0.32 mmol), K₂CO₃ (85 mg, 0.61 mmol), AgOBz (6.18 mg, 0.027 mmol), NMP (10 μL, 0.11 mmol), 1-bromo-4-methylbenzene (137 mg, 0.80 mmol) and toluene (1.0 mL). The crude reaction mixture was purified by silica gel chromatography (ethyl acetate/hexanes, 1/10) to afford
product 3.11 (49 mg, 74%) as a white solid. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.52 (dq, $J = 5.0, 1.0$ Hz, 1H), 7.24 (td, $J = 8.0, 1.5$ Hz, 1H), 6.95-6.91 (m, 3H), 6.88 (md, $J = 8.5$ Hz, 2H), 6.69 (dt, $J = 7.5, 1.0$ Hz, 1H), 2.62-2.59 (m, 2H), 2.47-2.45 (m, 2H), 2.24 (s, 3H), 1.84 (quint, $J = 3.0$ Hz, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 162.1, 148.8, 140.5, 137.4, 135.8, 135.3, 128.8, 128.6, 125.2, 120.7, 32.1, 30.0, 23.4, 23.1, 21.2; IR (thin film, NaCl): 3047, 3020, 3006, 2995, 2928, 2858, 2833, 1585, 1562, 1511, 1464, 1429, 812, 777, 746 cm$^{-1}$; HRMS (ESI+) Calcd for C$_{18}$H$_{20}$N$_{1}$ [M+H]: 250.1596, found: 250.1597.

2-(4'-chloro-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)pyridine (3.13). The general procedure was followed with Grubbs’ II catalyst (23 mg, 0.027 mmol), 2-(octa-1,7-dien-3-yl)pyridine 3.3 (50 mg, 0.27 mmol), camphorsulfonic acid (74 mg, 0.32 mmol), K$_2$CO$_3$ (85 mg, 0.61 mmol), AgOBz (6.18 mg, 0.027 mmol), NMP (10 μL, 0.11 mmol), 1-bromo-4-chlorobenzene (102 mg, 0.53 mmol) and toluene (1.0 mL). The crude reaction mixture was purified by silica gel chromatography (ethyl acetate/hexanes, 1/9) to afford product 3.13 (47 mg, 65%) as a white solid. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.49 (md, $J = 5.0$ Hz, 1H), 7.28 (td, $J = 7.5, 2.0$ Hz, 1H), 7.06 (md, $J = 8.5$ Hz, 2H), 6.96 (ddd, $J = 7.5, 5.0, 1.0$ Hz, 1H ), 6.90 (md, $J = 8.5$ Hz, 2H), 6.67 (dt, $J = 8.0, 1.0$ Hz, 1H), 2.59-2.57 (m, 2H), 2.44-2.41 (m, 2H), 1.83 (quint, $J = 3.3$ Hz, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 161.5, 149.0, 141.9, 136.4, 136.3, 135.6, 132.0, 130.3, 128.1, 125.0, 121.0, 31.9, 30.1, 23.2, 22.9; IR (thin film, NaCl): 3076, 3049, 3006, 2928, 2858, 2833, 1585, 1562, 1490,
6’-(pyridin-2-yl)-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-4-carbonitrile (3.14). The general procedure was followed with Grubbs’ II catalyst (23 mg, 0.027 mmol), 2-(octa-1,7-dien-3-yl)pyridine 3.3 (50 mg, 0.27 mmol), camphorsulfonic acid (74 mg, 0.32 mmol), K$_2$CO$_3$ (85 mg, 0.61 mmol), AgOBz (6.18 mg, 0.027 mmol), NMP (10 μL, 0.11 mmol), 4-bromobenzonitrile (144 mg, 0.80 mmol) and toluene (1.0 mL). The crude reaction mixture was purified by silica gel chromatography (ethyl acetate/hexanes, 1/4) to afford product 3.14 (46 mg, 66%) as a pale yellow solid. $^1$H NMR (500 MHz, CDCl$_3$): δ 8.49 (dq, $J = 5.0$, 1.0 Hz, 1H), 7.37 (md, $J = 8.0$ Hz, 2H), 7.30 (td, $J = 7.5$, 2.0 Hz, 1H), 7.07 (md, $J = 8.0$ Hz, 2H), 6.98 (ddd, $J = 7.5$, 5.0, 1.5 Hz, 1H), 6.66 (dt, $J = 8.0$, 1.0 Hz, 1H), 2.61-2.58 (m, 2H), 2.45-2.42 (m, 2H), 1.85 (quint, $J = 3.0$ Hz, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 160.9, 149.2, 148.6, 138.0, 135.8, 135.7, 131.7, 129.7, 124.7, 121.4, 119.1, 109.9, 31.4, 30.2, 23.0, 22.7; IR (thin film, NaCl): 3050, 3006, 2997, 2931, 2860, 2833, 2226, 1604, 1585, 1562, 1502, 1465, 1430, 841, 782, 748 cm$^{-1}$; HRMS (ESI+) Calcd for C$_{18}$H$_{17}$N$_2$ [M+H]: 261.1392, found: 261.1388.
1-(6′-(pyridin-2-yl)-2',3',4',5'-tetrahydro-[1,1'-biphenyl]-4-yl)ethanone (3.16). The general procedure was followed with Grubbs’ II catalyst (23 mg, 0.027 mmol), 2-(octa-1,7-dien-3-yl)pyridine 3.3 (50 mg, 0.27 mmol), camphorsulfonic acid (74 mg, 0.32 mmol), K$_2$CO$_3$ (85 mg, 0.61 mmol), AgOBz (6.18 mg, 0.027 mmol), trimethylacetamide (10.7 mg, 0.11 mmol), 1-(4-bromophenyl)ethanone (105 mg, 0.53 mmol) and toluene (1.0 mL). The crude reaction mixture was purified by silica gel chromatography (ethyl acetate/hexanes, 1/3) to afford product 3.16 (43.7 mg, 60%) as a white solid. $^1$H NMR (500 MHz, CDCl$_3$): δ 8.49 (dq, $J = 5.0,$ 1.0 Hz, 1H), 7.69 (md, $J = 8.5$ Hz, 2H), 7.25 (td, $J = 7.5,$ 2.0 Hz, 1H), 7.07 (md, $J = 9.0$ Hz, 2H), 6.95 (ddd, $J = 7.5,$ 4.5, 1.0 Hz, 1H ), 6.66 (dt, $J = 8.0,$ 1.0 Hz, 1H), 2.61-2.59 (m, 2H), 2.50 (s, 3H), 2.47-2.45 (m, 2H), 1.85 (quint, $J = 3.3$ Hz, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 197.9, 161.2, 148.9, 148.7, 137.0, 136.7, 135.8, 135.0, 129.1, 128.1, 125.0, 121.2, 31.6, 30.1, 26.6, 23.1, 22.8; IR (thin film, NaCl): 3075, 3048, 3002, 2930, 2859, 2833, 1681, 1602, 1585, 1561, 1465, 1429, 1358, 1267 cm$^{-1}$; HRMS (ESI+) Calcd for C$_{19}$H$_{20}$N$_1$O$_1$ [M+H]: 277.1545, found: 278.1539.

Methyl 6′-(pyridin-2-yl)-2′,3′,4′,5′-tetrahydro-[1,1′-biphenyl]-4-carboxylate (3.17). The general procedure was followed with Grubbs’ II catalyst (23 mg, 0.027 mmol), 2-(octa-1,7-dien-3-yl)pyridine 3.3 (50 mg, 0.27 mmol), camphorsulfonic acid (74 mg, 0.32
mmol), K$_2$CO$_3$ (85 mg, 0.61 mmol), AgOBz (6.18 mg, 0.027 mmol), trimethylacetamide (10.7 mg, 0.11 mmol), methyl 4-bromobenzoate (113 mg, 0.53 mmol) and toluene (1.0 mL). The crude reaction mixture was purified by silica gel chromatography (ethyl acetate/hexanes, 1/4) to afford product 3.17 (38 mg, 49%) as a oil. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.50 (md, $J = 5.0$ Hz, 1H), 7.77 (md, $J = 8.0$ Hz, 2H), 7.25 (td, $J = 8.0$, 2.0 Hz, 1H), 7.05 (md, $J = 8.0$ Hz, 2H), 6.96 (ddd, $J = 7.0$, 4.5, 1.0 Hz, 1H), 6.66 (d, $J = 8.0$ Hz, 1H), 3.85 (s, 3H), 2.61-2.60 (m, 2H), 2.48-2.46 (m, 2H), 1.86 (quint, $J = 3.0$ Hz, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 167.1, 161.3, 149.0, 148.6, 137.1, 136.6, 135.5, 129.2, 129.0, 128.0, 125.0, 121.1, 52.0, 31.6, 30.1, 23.1, 22.8; IR (thin film, NaCl): 3073, 3048, 2996, 2931, 2858, 2834, 1722, 1605, 1585, 1465, 1433, 1278, 1112, 1101, 770 cm$^{-1}$; HRMS (ESI+) Calcd for C$_{19}$H$_{20}$N$_1$O$_2$ [M+H]: 294.1494, found: 294.1480.

2-(2-(naphthalen-2-yl)cyclohex-1-en-1-yl)pyridine (3.10). The general procedure was followed with Grubbs’ II catalyst (23 mg, 0.027 mmol), 2-(octa-1,7-dien-3-yl)pyridine 3.3(50 mg, 0.27 mmol), camphorsulfonic acid (74 mg, 0.32 mmol), K$_2$CO$_3$ (85 mg, 0.61 mmol), AgOBz (6.18 mg, 0.027 mmol), trimethylacetamide (10.7 mg, 0.11 mmol), 2-bromonaphthalene (109 mg, 0.53 mmol) and toluene (1.0 mL). The crude reaction mixture was purified by silica gel chromatography (ethyl acetate/hexanes, 1/9) to afford product 3.10 (48 mg, 64%) as a oil. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.53 (dq, $J = 5.0$, 1.0 Hz, 1H), 7.72-7.70 (m, 1H), 7.66-7.64 (m, 1H), 7.56 (d, $J = 9.0$ Hz, 1H), 7.52 (d, $J = 1.0$ Hz, 1H), 7.40-7.36 (m, 2H), 7.15 (td, $J = 8.0$, 2.0 Hz, 1H), 7.09 (dd, $J = 8.5$, 1.0 Hz, 1H ).
6.90 (ddd, J = 7.5, 5.0, 1.0 Hz, 1H), 6.70 (dt, J = 7.5, 1.0 Hz, 1H), 2.69-2.66 (m, 2H), 2.59-2.57 (m, 2H), 1.91 (quint, J = 3.0 Hz, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 161.8, 148.9, 141.1, 137.4, 136.2, 135.4, 133.4, 132.1, 128.0, 127.9, 127.6, 127.4, 127.3, 125.9, 125.6, 125.3, 120.9, 32.2, 30.1, 23.4, 23.1; IR (thin film, NaCl): 3053, 2929, 2857, 2832, 1584, 1562, 1463, 1429, 818, 785, 776, 746 cm$^{-1}$; HRMS (ESI+) Calcd for C$_{21}$H$_{20}$N$_1$ [M+H]: 286.1596, found: 286.1595.

![Chemical structure](image)

2-(4'- (trifluoromethyl)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)pyridine (3.15). The general procedure was followed with Grubbs’ II catalyst (23 mg, 0.027 mmol), 2-(octa-1,7-dien-3-yl)pyridine 3.3 (50 mg, 0.27 mmol), camphorsulfonic acid (74 mg, 0.32 mmol), K$_2$CO$_3$ (85 mg, 0.61 mmol), AgOBz (6.18 mg, 0.027 mmol), trimethylacetamide (10.7 mg, 0.11 mmol), 1-bromo-4-(trifluoromethyl)benzene (180 mg, 0.80 mmol) and toluene (1.0 mL). The crude reaction mixture was purified by silica gel chromatography (ethyl acetate/hexanes, 1/4) to afford product 3.15 (54 mg, 67%) as a clear oil. $^1$H NMR (500 MHz, CDCl$_3$): δ 8.52 (dq, J = 5.0, 1.0 Hz, 1H), 7.37 (dd, J = 8.0, 0.5 Hz, 2H), 7.31-7.27 (m, 1H), 7.11 (dd, J = 8.0, 0.5 Hz, 2H), 7.00-6.97 (m, 1H), 6.68 (md, J = 7.5 Hz, 1H), 2.62-2.61 (m, 2H), 2.48-2.47 (m, 2H), 1.88-1.87 (m, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 161.2, 149.1, 147.3, 137.3, 136.2, 135.6, 129.2, 128.3 (q, J = 32 Hz), 124.9, 124.8 (q, J = 3.7 Hz), 124.3 (q, J = 271 Hz), 121.2, 31.8, 30.1, 23.1, 22.8; IR (thin film, NaCl): 3075, 3052, 2932, 2861, 2835, 1615, 1586, 1563, 1466, 1430, 1326, 1165, 1124,
2-(4'-methoxy-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)pyridine (3.12). The general procedure was followed with Grubbs’ II catalyst (23 mg, 0.027 mmol), 2-(octa-1,7-dien-3-yl)pyridine 3.3 (50 mg, 0.27 mmol), camphorsulfonic acid (76 mg, 0.33 mmol), K₂CO₃ (75 mg, 0.54 mmol), AgOBz (6.18 mg, 0.027 mmol), NMP (13 μL, 0.13 mmol), 1-bromo-4-methoxybenzene (151 mg, 0.81 mmol) and toluene (1.0 mL). The crude reaction mixture was purified by silica gel chromatography (ethyl acetate/hexanes, 1/4) to afford product 3.12 (50 mg, 71%) as a clear oil. 

**¹H NMR** (500 MHz, CDCl₃): δ 8.51 (md, J = 4.5 Hz, 1H), 7.26-7.23 (m, 1H), 6.94-6.90 (m, 1H), 6.69-6.64 (m, 3H), 3.71 (s, 3H), 2.59-2.58 (m, 2H), 2.45-2.44 (m, 2H), 1.84-1.83 (m, 4H); 

**¹³C NMR** (125 MHz, CDCl₃): δ 162.1, 158.0, 148.8, 136.9, 135.8, 135.2, 135.1, 130.0, 125.3, 120.6, 113.3, 55.1, 32.1, 30.0, 23.3, 23.0; 

**IR** (thin film, NaCl): 3047, 2998, 2930, 2857, 2834, 1606, 1585, 1561, 1510, 1465, 1429, 1290, 1247, 1178, 1037, 834, 784 cm⁻¹; 

**HRMS** (ESI+) Calcd for C₁₈H₂₀N₁O₁ [M+H]: 266.1545, found: 266.1537.

2-(3'-(trifluoromethyl)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)pyridine (3.19). The general procedure was followed with Grubbs’ II catalyst (23 mg, 0.027 mmol), 2-(octa-
1,7-dien-3-yl)pyridine 3.3 (50 mg, 0.27 mmol), camphorsulfonic acid (74 mg, 0.32 mmol), K$_2$CO$_3$ (85 mg, 0.61 mmol), AgOBz (6.18 mg, 0.027 mmol), trimethylacetamide (11 mg, 0.11 mmol), 1-bromo-3-(trifluoromethyl)benzene (182 mg, 0.81 mmol) and toluene (1.0 mL). The crude reaction mixture was purified by silica gel chromatography (ethyl acetate/hexanes, 1/9) to afford product 3.19 (53 mg, 65%) as an oil. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.50 (dq, $J = 5.0$, 1.0 Hz, 1H), 7.33-7.24 (m, 3H), 7.20 (t, $J = 7.5$ Hz, 1H), 7.15 (d, $J = 8.0$ Hz, 1H), 6.97 (ddd, $J = 8.0$, 5.0, 1.0 Hz, 1H), 6.66 (dt, $J = 8.0$, 1.0 Hz, 1H), 2.63-2.60 (m, 2H), 2.50-2.47 (m, 2H), 1.87 (quint, $J = 3.3$ Hz, 4H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 161.3, 149.1, 144.2, 137.3, 136.1, 135.6, 132.2, 130.2 (q, $J = 32$ Hz), 128.3, 125.8 (q, $J = 3.7$ Hz), 124.9, 124.2 (q, $J = 271$ Hz), 123.0 (q, $J = 3.7$ Hz), 121.2, 31.7, 30.2, 23.2, 22.9; IR (thin film, NaCl): 3060, 3006, 2932, 2860, 2835, 1585, 1465, 1430, 1329, 1228, 1165, 1125, 1075 cm$^{-1}$; HRMS (ESI+) Calcd for C$_{18}$H$_7$F$_3$N$_1$ [M+H]: 304.1313, found: 304.1306.

2-(3′-methoxy-3,4,5,6-tetrahydro-[1,1′-biphenyl]-2-yl)pyridine (3.20). The general procedure was followed with Grubbs’ II catalyst (23 mg, 0.027 mmol), 2-(octa-1,7-dien-3-yl)pyridine 3.3 (50 mg, 0.27 mmol), camphorsulfonic acid (74 mg, 0.32 mmol), K$_2$CO$_3$ (85 mg, 0.61 mmol), AgOBz (6.18 mg, 0.027 mmol), NMP (10 μL, 0.11 mmol), 1-bromo-3-methoxybenzene (150 mg, 0.80 mmol) and toluene (1.0 mL). The crude reaction mixture was purified by silica gel chromatography (ethyl acetate/hexanes, 1/4) to afford product 3.20 (46 mg, 65%) as a clear oil. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.51 (dq,
2-(4'-(thiophen-2-yl)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-2-yl)pyridine (3.18). The general procedure was followed with Grubbs’ II catalyst (23 mg, 0.027 mmol), 2-(octa-1,7-dien-3-yl)pyridine 3.3 (50 mg, 0.27 mmol), camphorsulfonic acid (74 mg, 0.32 mmol), K₂CO₃ (85 mg, 0.61 mmol), AgOBz (6.18 mg, 0.027 mmol), trimethylacetamide (11 mg, 0.11 mmol), 2-bromothiophene (131 mg, 0.80 mmol) and toluene (1.0 mL). The crude reaction mixture was purified by silica gel chromatography (ethyl acetate/hexanes, 1/9) to afford product 3.18 (31 mg, 48%) as a clear oil. ¹H NMR (500 MHz, CDCl₃): δ 8.59 (dq, J = 4.5, 1.0 Hz, 1H), 7.45 (td, J = 7.5, 2.0 Hz, 1H), 7.09 (ddd, J = 7.5, 5.0, 1.0 Hz, 1H), 7.03 (dd, J = 5.0, 1.5 Hz, 1H), 6.99 (dt, J = 8.0, 1.0 Hz, 1H), 6.75 (dd, J = 5.0, 3.5 Hz, 1H), 6.54 (dd, J = 3.5, 1.5 Hz, 1H), 2.57-2.53 (m, 4H), 1.88-1.80 (m, 4H); ¹³C NMR (125 MHz, CDCl₃): δ 162.1, 149.4, 145.2, 137.0, 136.1, 129.3, 126.4, 125.6, 124.6, 124.4, 121.6, 32.1, 31.2, 23.2, 22.7; IR (thin film, NaCl): 3070, 2929, 2858, 2830, 1584,
1561, 1465, 1428, 777, 746, 696 cm$^{-1}$; HRMS (ESI+) Calcd for C$_{15}$H$_{16}$N$_1$S$_1$ [M+H]: 242.1003, found: 242.1003.
Chapter 3 – Ru-Catalyzed Ring Closing Metathesis/Olefin Isomerization/C-H Activation

[Chemical structures and spectra]
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[Chemical structures and NMR spectra images]

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