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By
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in partial fulfillment of the requirements for
the degree of Doctor of Philosophy
in the Department of Chemistry
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**Table of Contents:**

Table of Figures: .............................................................................................................................................. 6  
Table of Schemes: ........................................................................................................................................... 12  
Table of Tables: ......................................................................................................................................... 13  
List of Abbreviations: ................................................................................................................................. 14  
Abstract ...................................................................................................................................................... 17  
- CHAPTER 1 - Background and Introduction .............................................................................................. 18  
  1.1 Palladium as a precatalyst .................................................................................................................. 18  
  1.2 γ-Arylation .......................................................................................................................................... 20  
  1.3 Enantioselective synthesis of phenanthridinone analogs with quaternary carbons using the Birch-Heck Sequence .......................................................................................................................... 27  
    1.3.1 Birch reduction – alkylation .......................................................................................................... 29  
    1.3.2 Mizoroki-Heck Reaction ............................................................................................................... 30  
  1.4 Nickel-Catalyzed Mizoroki-Heck Reactions .................................................................................... 36  
  1.5 References ......................................................................................................................................... 40  
- CHAPTER 2 – γ-Arylation of α,β-unsaturated ketones and esters ............................................................... 48  
  2.1 Synthesis of γ-arylated 7-methoxy-4-methylcoumarin: ..................................................................... 48  
    2.1.2 Aryl bromides .............................................................................................................................. 50  
    2.1.3 – Aryl chlorides ........................................................................................................................... 53  
  2.2 Optimization of the γ-arylation of isophorone .................................................................................... 54  
  2.3 Examples of other γ-arylated α,β-unsaturated ketones and esters....................................................... 58  
  2.4 α'-Arylation of 1-acetyl-1-cyclohexane .............................................................................................. 61  
  2.5 γ-Arylation of methyl-1-cyclohexene-1-carboxylate ......................................................................... 62  
  2.6 Consecutive amide formation/ Heck cyclization of methyl-1-cyclohexene-1-carboxylate ............... 66  
  2.7 Conclusions: ....................................................................................................................................... 69  
  2.8 References: ......................................................................................................................................... 70  
- CHAPTER 3 – The Birch-Heck Sequence utilizing Palladium: .................................................................. 73  
Creating Phenanthridinone Analogs .............................................................................................................. 73  
  3.1 The Birch Reduction-Alkylation: ........................................................................................................ 73  
  3.2 Heck precursor synthesis .................................................................................................................... 76  
  3.3 Synthesis of Triflate compounds ....................................................................................................... 79
3.4 The Mizoroki-Heck Reaction ................................................................. 80
3.5 Removal of methyl group from amide nitrogen on Heck product ................... 98
3.6 MOM protection/deprotection protocol to produce (N-H) phenanthridinone analogs .... 99
3.7 Conclusions ......................................................................................... 101
3.8 References .......................................................................................... 103

– CHAPTER 4 – The Birch-Heck Sequence Catalyzed by Nickel .................................. 107
4.1 Nickel as a precatalyst ........................................................................ 108
4.2 Heck reaction using a nickel salt and pyox ligand ........................................ 110
4.3 Exploration of cationic vs. neutral pathway ............................................. 115
4.4 Nickel Mizoroki-Heck reactions of the methyl derivative .............................. 117
4.5 Conclusions .......................................................................................... 125

– CHAPTER 5 – Conclusions ............................................................................. 131
5.1 Conclusions .......................................................................................... 131
5.2 References: ............................................................................................. 135

– CHAPTER 6 – Experimental ........................................................................ 140
6.1 General Experimental Details .................................................................... 140
6.2 γ-arylation General Procedures and Data .................................................. 141
   6.2.1 Synthesis of 7-methoxy-4-methylcoumarin .............................................. 141
       6.2.1.1 Aryl Bromides: ........................................................................ 141
       6.2.1.2 Aryl Chlorides .......................................................................... 169
   6.2.2 γ-arylation of Isophorone General Procedures and Data ....................... 172
   6.2.3 α-arylation of 1-acetyl-1-cyclohexane General Procedures and Data .... 175
   6.2.4 γ-arylation of methyl-1-cyclohexene-1-carboxylate General Procedures and Data... 179
       6.2.4.1 Consecutive amide formation/ Heck cyclization of methyl-1-cyclohexene-1-carboxylate...... 189
6.3 Mizoroki-Heck Reaction .......................................................................... 193
   6.3.1 Birch reduction/alkylation General Procedures and Data ...................... 193
   6.3.2 Benzamide General Procedures and Data ............................................. 211
   6.3.3 Triflation General Procedures and Data .............................................. 231
   6.3.4 Mizoroki-Heck Reaction General procedures and data ......................... 254
   6.3.5 MOM Protection of Secondary Benzamides General Procedures and Data .......... 285
   6.3.6 MOM Protected Mizoroki Heck Reaction General Procedures and Data .......... 290
6.3.7 Deprotection of the MOM Protected Mizoroki Heck product General Procedures and Data

6.4 References:
Table of Figures:

Figure 1: NMR of 3-(3-methoxybenzyl)-5,5-dimethylcyclohex-2-en-1-one ........................................ 60
Figure 2: NMR of 1-(cyclohex-1-en-1-yl)-2-(3-methoxyphenyl)ethan-1-one ........................................ 62
Figure 3: COSY NMR of compound 24................................................................. 65
Figure 4: NMR of compounds B1 and B2............................................................. 68
Figure 5: Rotational features of anilides .................................................................. 78
Figure 6: Acetate Intermediate .............................................................................. 87
Figure 7: $^1$H NMR of the acetate intermediate ....................................................... 87
Figure 8: COSY NMR of the acetate intermediate ..................................................... 88
Figure 9: Acetate Intermediate .............................................................................. 92
Figure 10: Butene Heck products .......................................................................... 95
Figure 11: X-ray crystallography data for cyclized product ....................................... 96
Figure 12: Protection of secondary benzamide ........................................................ 100
Figure 13: MOM deprotection using Fukuyama and Liu’s procedure ....................... 101
Figure 14: Comparison of cationic and neutral nickel-catalyzed Mizoroki-Heck reaction$^{17}$ .... 108
Figure 15: Formation of nickelate intermediate, bridging ligand complex, and reduced nickel 115
Figure 16: $^1$H NMR of compound 1 ................................................................. 142
Figure 17: $^{13}$C NMR of compound 1 ................................................................. 143
Figure 18: $^1$H NMR of compound 2 ................................................................. 144
Figure 19: $^{13}$C NMR of compound 2 ................................................................. 144
Figure 20: $^1$H NMR of compound 3 ................................................................. 145
Figure 21: $^{13}$C NMR of compound 3 ................................................................. 146
Figure 22: $^1$H NMR of compound 4 ................................................................. 147
Figure 23: $^{13}$C NMR of compound 4 ................................................................. 147
Figure 24: $^1$H NMR of compound 5 ................................................................. 148
Figure 25: $^{13}$C NMR of compound 5 ................................................................. 149
Figure 26: $^1$H NMR of compound 6 ................................................................. 150
Figure 27: $^{13}$C NMR of compound 6 ................................................................. 150
Figure 28: $^1$H NMR of compound 7 ................................................................. 151
Figure 29: $^{13}$C NMR of compound 7 ................................................................. 152
Figure 30: $^1$H NMR of compound 8 ................................................................. 153
Figure 31: $^{13}$C NMR of compound 8 ................................................................. 153
Figure 32: $^1$H NMR of compound 9 ................................................................. 154
Figure 33: $^{13}$C NMR of compound 9 ................................................................. 155
Figure 34: $^1$H NMR of compound 10 ............................................................... 156
Figure 35: $^{13}$C NMR of compound 10 ............................................................... 156
Figure 36: $^1$H NMR of compound 11 ............................................................... 157
Figure 37: $^{13}$C NMR of compound 11 ............................................................... 158
Figure 38: $^1$H NMR of compound 12 ............................................................... 159
Figure 39: $^{13}$C NMR of compound 12 ............................................................... 159
Figure 40: $^1$H NMR of compound 13 ............................................................... 160
Figure 41: $^{13}$C NMR of compound 13 ............................................................... 161
Figure 42: $^1$H NMR of compound 14 ................................................................. 162
Figure 43: $^{13}$C NMR of compound 14 ............................................................ 162
Figure 44: $^{19}$F NMR of compound 14 ............................................................ 163
Figure 45: $^1$H NMR of compound 15 ............................................................. 164
Figure 46: $^{13}$C NMR of compound 15 ............................................................ 164
Figure 47: $^1$H NMR of compound 16 ............................................................. 165
Figure 48: $^{13}$C NMR of compound 16 ............................................................ 166
Figure 49: $^1$H NMR of compound 17 ............................................................. 167
Figure 50: $^{13}$C NMR of compound 17 ............................................................ 167
Figure 51: $^1$H NMR of compound 18 ............................................................. 168
Figure 52: $^{13}$C NMR of compound 18 ............................................................ 169
Figure 53: $^1$H NMR of compound 19 ............................................................. 170
Figure 54: $^{13}$C NMR of compound 19 ............................................................ 171
Figure 55: $^1$H NMR of compound 20 ............................................................. 173
Figure 56: $^{13}$C NMR of compound 20 ............................................................ 173
Figure 57: $^1$H NMR of compound 21 ............................................................. 174
Figure 58: $^{13}$C NMR of compound 21 ............................................................ 175
Figure 59: $^1$H NMR of compound 22 ............................................................. 176
Figure 60: $^{13}$C NMR of compound 22 ............................................................ 177
Figure 61: $^1$H NMR of compound 23 ............................................................. 178
Figure 62: $^{13}$C NMR of compound 23 ............................................................ 178
Figure 63: $^1$H NMR of compound 24 ............................................................. 180
Figure 64: $^{13}$C NMR of compound 24 ............................................................ 180
Figure 65: $^1$H NMR of compound 25 ............................................................. 181
Figure 66: $^1$H NMR of compound 26 ............................................................. 182
Figure 67: $^{13}$C NMR of compound 26 ............................................................ 183
Figure 68: $^1$H NMR of compound 27 ............................................................. 184
Figure 69: $^1$H NMR of compound 28 ............................................................. 185
Figure 70: $^{13}$C NMR of compound 28 ............................................................ 185
Figure 71: $^1$H NMR of compound 29 ............................................................. 186
Figure 72: $^{13}$C NMR of compound 29 ............................................................ 187
Figure 73: $^1$H NMR of compound 30 ............................................................. 188
Figure 74: $^{13}$C NMR of compound 30 ............................................................ 188
Figure 75: $^{19}$F NMR of compound 30 ............................................................ 189
Figure 76: $^1$H NMR of compound 31 ............................................................. 190
Figure 77: $^{13}$C NMR of compound 31 ............................................................ 191
Figure 78: Zoom in of $^{13}$C NMR of compound 31 ......................................... 191
Figure 79: HSQC of compound 31 ................................................................. 192
Figure 80: COSY of compound 31 ................................................................. 192
Figure 81: $^1$H NMR of compound 32 ............................................................. 194
Figure 82: $^{13}$C NMR of compound 32 ............................................................ 194
Figure 83: $^1$H NMR of compound 33 ............................................................. 195
Figure 84: $^{13}$C NMR of compound 33 ............................................................ 196
Figure 85: $^1$H NMR of compound 34 ........................................................................................................ 197
Figure 86: $^{13}$C NMR of compound 34 .................................................................................................... 197
Figure 87: $^1$H NMR of compound 35 ........................................................................................................ 198
Figure 88: $^{13}$C NMR of compound 35 .................................................................................................... 199
Figure 89: $^1$H NMR of compound 36 ........................................................................................................ 200
Figure 90: $^{13}$C NMR of compound 36 .................................................................................................... 200
Figure 91: $^1$H NMR of compound 37 ........................................................................................................ 201
Figure 92: $^{13}$C NMR of compound 37 .................................................................................................... 202
Figure 93: $^1$H NMR of compound 38 ........................................................................................................ 203
Figure 94: $^{13}$C NMR of compound 38 .................................................................................................... 203
Figure 95: $^1$H NMR of compound 39 ........................................................................................................ 204
Figure 96: $^{13}$C NMR of compound 39 .................................................................................................... 205
Figure 97: $^1$H NMR of compound 40 ........................................................................................................ 206
Figure 98: $^{13}$C NMR of compound 40 .................................................................................................... 206
Figure 99: $^1$H NMR of compound 41, benzoic acid is still present................................................................. 207
Figure 100: $^1$H NMR of compound 42 ....................................................................................................... 208
Figure 101: $^1$H NMR of compound 43 ....................................................................................................... 209
Figure 102: $^1$H NMR of compound 44 ....................................................................................................... 210
Figure 103: $^{13}$C NMR of compound 44 .................................................................................................... 210
Figure 104: $^1$H NMR of compound 45 ....................................................................................................... 212
Figure 105: $^{13}$C NMR of compound 45 .................................................................................................... 212
Figure 106: $^1$H NMR of compound 46 ....................................................................................................... 213
Figure 107: $^{13}$C NMR of compound 46 .................................................................................................... 214
Figure 108: $^1$H NMR of compound 85 ....................................................................................................... 215
Figure 109: $^{13}$C NMR of compound 47 .................................................................................................... 215
Figure 110: $^1$H NMR of compound 48 ....................................................................................................... 216
Figure 111: $^{13}$C NMR of compound 48 .................................................................................................... 217
Figure 112: $^1$H NMR of compound 49 ....................................................................................................... 218
Figure 113: $^{13}$C NMR of compound 49 .................................................................................................... 218
Figure 114: $^1$H NMR of compound 50 ....................................................................................................... 219
Figure 115: $^{13}$C NMR of compound 50 .................................................................................................... 220
Figure 116: $^1$H NMR of compound 51 ....................................................................................................... 221
Figure 117: $^{13}$C NMR of compound 51 .................................................................................................... 221
Figure 118: $^1$H NMR of compound 52 ....................................................................................................... 222
Figure 119: $^{13}$C NMR of compound 52 .................................................................................................... 223
Figure 120: $^1$H NMR of compound 53 ....................................................................................................... 224
Figure 121: $^{13}$C NMR of compound 53 .................................................................................................... 224
Figure 122: $^1$H NMR of compound 54 ....................................................................................................... 225
Figure 123: $^{13}$C NMR of compound 54 .................................................................................................... 226
Figure 124: $^1$H NMR of compound 55 ....................................................................................................... 227
Figure 125: $^{13}$C NMR of compound 55 .................................................................................................... 227
Figure 126: $^1$H NMR of compound 56 ....................................................................................................... 228
Figure 127: $^{13}$C NMR of compound 56 .................................................................................................... 229
Figure 128: $^1$H NMR of compound 57 ................................................................. 230
Figure 129: $^{13}$C NMR of compound 63 ............................................................. 230
Figure 130: $^1$H NMR of compound 58 ................................................................. 232
Figure 131: $^{13}$C NMR of compound 58 ............................................................. 232
Figure 132: $^{19}$F NMR of compound 58 ................................................................. 233
Figure 133: $^1$H NMR of compound 59 ................................................................. 234
Figure 134: $^{13}$C NMR of compound 59 ............................................................. 234
Figure 135: $^{19}$F NMR of compound 59 ................................................................. 235
Figure 136: $^1$H NMR of compound 60 ................................................................. 236
Figure 137: $^{13}$C NMR of compound 60 ............................................................. 236
Figure 138: $^{19}$F NMR of compound 60 ................................................................. 237
Figure 139: $^1$H NMR of compound 61 ................................................................. 238
Figure 140: $^{13}$C NMR of compound 61 ............................................................. 238
Figure 141: $^{19}$F NMR of compound 61 ................................................................. 239
Figure 142: $^1$H NMR of compound 62 ................................................................. 240
Figure 143: $^{13}$C NMR of compound 62 ............................................................. 240
Figure 144: $^{19}$F NMR of compound 62 ................................................................. 241
Figure 145: $^1$H NMR of compound 63 ................................................................. 242
Figure 146: $^{13}$C NMR of compound 63 ............................................................. 242
Figure 147: $^{19}$F NMR of compound 63 ................................................................. 243
Figure 148: $^1$H NMR of compound 64 ................................................................. 244
Figure 149: $^{13}$C NMR of compound 64 ............................................................. 244
Figure 150: $^{19}$F NMR of compound 64 ................................................................. 245
Figure 151: $^1$H NMR of compound 65 ................................................................. 246
Figure 152: $^{13}$C NMR of compound 65 ............................................................. 246
Figure 153: $^{19}$F NMR of compound 65 ................................................................. 247
Figure 154: $^1$H NMR of compound 66 ................................................................. 248
Figure 155: $^{13}$C NMR of compound 66 ............................................................. 248
Figure 156: $^{19}$F NMR of compound 66 ................................................................. 249
Figure 157: $^1$H NMR of compound 67 ................................................................. 250
Figure 158: $^{13}$C NMR of compound 67 ............................................................. 250
Figure 159: $^{19}$F NMR of compound 67 ................................................................. 251
Figure 160: $^1$H NMR of compound 68 ................................................................. 252
Figure 161: $^1$H NMR of compound 69 ................................................................. 253
Figure 162: $^{13}$C NMR of compound 69 ............................................................. 253
Figure 163: $^{13}$C NMR of compound 69 ............................................................. 254
Figure 164: R-BINAP HPLC data for compound 69........................................... 255
Figure 165: Racemic BINAP HPLC data for compound 69................................. 256
Figure 166: Pd(TFA)$_2$ HPLC data for compound 69......................................... 256
Figure 167: $^1$H NMR of compound 69 ................................................................. 257
Figure 168: $^{13}$C NMR of compound 69 ............................................................. 257
Figure 169: R-BINAP HPLC data for compound 70........................................... 258
Figure 170: Racemic BINAP HPLC data for compound 70................................. 259
Figure 171: $^1$H NMR of compound 70 ................................................................. 259
Figure 172: $^{13}$C NMR of compound 70 .......................................................... 260
Figure 173: R-BINAP HPLC data for compound 71............................................. 261
Figure 174: Racemic BINAP HPLC data for compound 71.................................... 261
Figure 175: $^1$H NMR of compound 71 .............................................................. 262
Figure 176: $^{13}$C NMR of compound 71 ............................................................ 262
Figure 177: R-BINAP HPLC data for compound 72............................................. 263
Figure 178: Racemic BINAP HPLC data for compound 72.................................... 264
Figure 179: $^1$H NMR of compound 72 .............................................................. 264
Figure 180: $^{13}$C NMR of compound 72 ............................................................ 265
Figure 181: R-BINAP HPLC data for compound 73............................................. 266
Figure 182: Racemic BINAP HPLC data for compound 73.................................... 266
Figure 183: $^1$H NMR of compound 73 .............................................................. 267
Figure 184: $^{13}$C NMR of compound 73 ............................................................ 267
Figure 185: R-BINAP HPLC data for compound 74............................................. 268
Figure 186: Racemic BINAP HPLC data for compound 74.................................... 269
Figure 187: $^1$H NMR of compound 74 .............................................................. 269
Figure 188: $^{13}$C NMR of compound 74 ............................................................ 270
Figure 189: R-BINAP HPLC data for compound 75............................................. 271
Figure 190: Racemic BINAP HPLC data for compound 75.................................... 271
Figure 191: $^1$H NMR of compound 75 .............................................................. 272
Figure 192: $^{13}$C NMR of compound 75 ............................................................ 272
Figure 193: R-BINAP HPLC data for compound 76............................................. 273
Figure 194: Racemic BINAP HPLC data for compound 76.................................... 274
Figure 195: $^1$H NMR of compound 76 .............................................................. 274
Figure 196: $^{13}$C NMR of compound 76 ............................................................ 275
Figure 197: R-BINAP HPLC data for compound 77............................................. 276
Figure 198: Racemic BINAP HPLC data for compound 77.................................... 276
Figure 199: $^1$H NMR of compound 77 .............................................................. 277
Figure 200: $^{13}$C NMR of compound 77 ............................................................ 277
Figure 201: COSY NMR of compound 77 ......................................................... 278
Figure 202: COSY NMR of compound 77 ......................................................... 279
Figure 203: Ellipsoid plot of compound 77 ........................................................ 282
Figure 204: Ball-and-stick model of compound 77 ............................................. 282
Figure 205: R-BINAP HPLC data for compound 78............................................. 283
Figure 206: Racemic BINAP HPLC data for compound 78.................................... 284
Figure 207: $^1$H NMR of compound 78 .............................................................. 284
Figure 208: $^{13}$C NMR of compound 78 ............................................................ 285
Figure 209: $^1$H NMR of compound 79 .............................................................. 286
Figure 210: $^{13}$C NMR of compound 79 ............................................................ 287
Figure 211: $^{19}$F NMR of compound 79 ............................................................ 287
Figure 212: $^1$H NMR of compound 80 .............................................................. 288
Figure 213: $^{13}$C NMR of compound 80 ............................................................ 289
Figure 214: $^{19}$F NMR of compound 80 .......................................................... 289
Figure 215: R-BINAP HPLC data for compound 81 ........................................ 291
Figure 216: Racemic BINAP HPLC data for compound 81 .............................. 291
Figure 217: $^1$H NMR of compound 81 .......................................................... 292
Figure 218: $^{13}$C NMR of compound 81 .......................................................... 292
Figure 219: R-BINAP HPLC data for compound 82 ........................................ 293
Figure 220: Racemic BINAP HPLC data for compound 82 .............................. 294
Figure 221: $^1$H NMR of compound 82 .......................................................... 294
Figure 222: $^{13}$C NMR of compound 82 .......................................................... 295
Figure 223: R-BINAP HPLC data for compound 83 ........................................ 296
Figure 224: Racemic BINAP HPLC data for compound 83 .............................. 297
Figure 225: $^1$H NMR of compound 83 .......................................................... 297
Figure 226: $^{13}$C NMR of compound 83 .......................................................... 298
Figure 227: HPLC data for compound 84 .......................................................... 299
Figure 228: $^1$H NMR of compound 84 .......................................................... 299
Figure 229: $^{13}$C NMR of compound 84 .......................................................... 300
Figure 230: $^1$H NMR of compound 85 .......................................................... 301
Figure 231: $^{13}$C NMR of compound 85 .......................................................... 301
Table of Schemes:

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Buchwald Precatalysts</td>
</tr>
<tr>
<td>2</td>
<td>Challenges of (\alpha)-arylation compared to the challenges of (\gamma)-arylation</td>
</tr>
<tr>
<td>3</td>
<td>(\gamma)-arylation examples from 1998 to this work</td>
</tr>
<tr>
<td>4</td>
<td>Mechanism of (\gamma)-arylation</td>
</tr>
<tr>
<td>5</td>
<td>Isophorone derivatives and their potential applications</td>
</tr>
<tr>
<td>6</td>
<td>Examples of (\gamma)-arylation of isophorone and 3-methyl-2-cyclohexen-1-one</td>
</tr>
<tr>
<td>7</td>
<td>Ethyl (E)-4-phenylbut-2-enoate as a precursor</td>
</tr>
<tr>
<td>8</td>
<td>Development of the phenanthridinone Birch-Heck sequence</td>
</tr>
<tr>
<td>9</td>
<td>Generalized Birch reduction-alkylation reaction</td>
</tr>
<tr>
<td>10</td>
<td>Enantioselective Asymmetric Mizoroki-Heck Reactions</td>
</tr>
<tr>
<td>11</td>
<td>Chiral Mizoroki-Heck reactions using palladium and nickel</td>
</tr>
<tr>
<td>12</td>
<td>Cationic Mizoroki-Heck Mechanism</td>
</tr>
<tr>
<td>13</td>
<td>Advances in Nickel-catalyzed Mizoroki-Heck Reaction</td>
</tr>
<tr>
<td>14</td>
<td>Williamson Ether Synthesis of 7-methoxy-4-methylcoumarin</td>
</tr>
<tr>
<td>15</td>
<td>Optimized reaction conditions</td>
</tr>
<tr>
<td>16</td>
<td>Optimized reaction conditions for the Birch reduction-alkylation</td>
</tr>
<tr>
<td>17</td>
<td>enolate (\alpha)-halogenation side reaction</td>
</tr>
<tr>
<td>18</td>
<td>Acid Chloride/Amide formation then Triflation to form Compound C</td>
</tr>
<tr>
<td>19</td>
<td>Cationic Pathway for the Mizoroki-Heck Reaction</td>
</tr>
<tr>
<td>20</td>
<td>Pathways to rearomatized product</td>
</tr>
<tr>
<td>21</td>
<td>Cyclohexane acetate intermediate formation</td>
</tr>
<tr>
<td>22</td>
<td>Acetate intermediate reaction sequence</td>
</tr>
<tr>
<td>23</td>
<td>Butene Derivative Cyclized Product Mechanism</td>
</tr>
<tr>
<td>24</td>
<td>Lv and coworkers oxidative Heck cycle with sacrificial alkene (S.A.)</td>
</tr>
<tr>
<td>25</td>
<td>Williamson-ether synthesis of 7-methoxy-4-methylcoumarin</td>
</tr>
<tr>
<td>26</td>
<td>Reaction conditions for aryl bromides</td>
</tr>
<tr>
<td>27</td>
<td>(\gamma)-arylation of isophorone general procedure</td>
</tr>
<tr>
<td>28</td>
<td>(\alpha)-arylation of 1-acetyl-1-cyclohexane general procedure</td>
</tr>
<tr>
<td>29</td>
<td>Reaction conditions for the consecutive amide formation/ Heck cyclization of methyl-1-cyclohexene-1-carboxylate</td>
</tr>
<tr>
<td>30</td>
<td>Birch/reduction alkylation general reaction sequence</td>
</tr>
<tr>
<td>31</td>
<td>Benzamide general procedure</td>
</tr>
<tr>
<td>32</td>
<td>Triflation general procedure</td>
</tr>
<tr>
<td>33</td>
<td>Palladium catalyzed Mizoroki-Heck general procedure</td>
</tr>
<tr>
<td>34</td>
<td>MOM protection procedure</td>
</tr>
<tr>
<td>35</td>
<td>MOM Heck reaction general procedure</td>
</tr>
<tr>
<td>36</td>
<td>MOM deprotection procedure</td>
</tr>
</tbody>
</table>
Table of Tables:

Table 1: γ-arylated 7-methoxy-4-methylcoumarin using aryl bromides ................................................. 50
Table 2: Various Trials of 3-Bromopyridine .................................................................................................. 52
Table 3: γ-arylated 7-methoxy-4-methylcoumarin using aryl chlorides.................................................. 53
Table 4: Optimization of the γ-arylation of Isophorone ........................................................................... 56
Table 5: Optimization of equivalents of base, temperature, and time for Isophorone ......................... 57
Table 6: γ-arylation of α,β-unsaturated ketones and an ester ................................................................. 58
Table 7: α'-Arylation of 1-acetyl-1-cyclohexane ....................................................................................... 61
Table 8: Initial attempts of γ-arylation of methyl-1-cyclohexene-1-carboxylate .................................. 63
Table 9: Reaction scope of the γ-arylation of methyl-1-cyclohexene-1-carboxylate ............................ 64
Table 10: Consecutive amide formation/Heck cyclization of methyl-1-cyclohexene-1-carboxylate reaction conditions .................................................................................................................. 66
Table 11: Birch Products ......................................................................................................................... 76
Table 12: Secondary and tertiary amide formation using 2-aminophenol or 2-(methylamino)phenol ................................................................................................................................. 79
Table 13: Triflate yields ............................................................................................................................ 80
Table 14: Mizoroki-Heck reaction attempts to synthesize the N-H phenanthridinone benzyl derivative........................................................................................................................................ 82
Table 15: Using a precatalyst to synthesize N-H phenanthridinone benzyl derivative .......................... 85
Table 16: Mizoroki-Heck products for N-Me phenanthridinone derivatives ........................................ 86
Table 17: Reaction Monitoring experiment for acetate intermediate ...................................................... 89
Table 18: Mizoroki-Heck reaction conditions to make N-Me phenanthridinone derivatives with LiOAc additive ........................................................................................................................................ 95
Table 19: Removal of methyl group using aluminum chloride ............................................................... 99
Table 20: Mom protected phenanthridinone derivatives ...................................................................... 100
Table 21: Nickel precatalysts in the Mizoroki-Heck reaction ................................................................. 109
Table 22: Ni(BF₄)₂·6H₂O with a pyox ligand to catalyze the Mizoroki-Heck reaction .......................... 111
Table 23: NiCl₂ in the Mizoroki-Heck reaction. Initial conditions ............................................................. 113
Table 24: Ligand screening: cationic vs. neutral pathway ...................................................................... 116
Table 25: Halide analysis ........................................................................................................................ 118
Table 26: Ligands attempted with the methyl derivative ...................................................................... 119
Table 27: Analysis of Zn/Mn insertion into the Ar-I ............................................................................... 120
Table 28: Investigation of nickel sources ............................................................................................... 122
Table 29: Mizoroki-Heck reaction optimization with sacrificial alkenes (S.A.) ............................... 125
List of Abbreviations:

α – alpha
ACN - acetonitrile
AcO – acetate
APT – attached proton test
Ar – aryl
β - beta
BINAP – 2,2’-Bis(diphenylphosphino)-1,1’-binaphthyl
Bipy – bipyridine
Bn – benzyl
°C – degrees Celsius
COD – 1,5-cyclooctadiene
COSY – homonuclear correlation spectroscopy
cm-1 – wavenumber(s)
CN- nitrile
Cs₂CO₃ – cesium carbonate
CPME – cyclopentyl methyl ether
d – doublet
Δ – reflux
δ – peak
DCM – dichloromethane
DFT – density functional theory
DG-directing group
DMF – N,N-dimethylformamide
DMSO – dimethyl sulfoxide
DPEPhos- bis[(2-diphenylphosphino)phenyl]ether
dppe – 1,2-bis(diphenylphosphino)ethane
dppf – 1,1’-Bis(diphenylphosphino)ferrocene
dq – doublet of quartets
dt – doublet of triplets
e.r. – enantiomeric ratio
ee – enantiomeric excess
equiv. – equivalent
e.r. – enantiomeric ratio
EI – electron impact
Et – ethyl
et al. – and others
ESI – electrospray ionization
FT – Fourier transform
γ-gamma
g – gram(s)
GC – gas chromatography
GCMS – gas chromatography-mass spectrometry
h – hour(s)
hex. - hexane
HPLC – high performance liquid chromatography
HRMS – high resolution mass spectrometry
HSQC – heteronuclear single quantum correlation
Hz – hertz
i – iso
IPA – isopropyl alcohol
IR – infrared spectroscopy
J – coupling constant
KI – potassium iodide
L/Ln/Ln – ligand
LiHMDs – lithium hexamethyldisilazide
m – multiplet or meta
μ – micro
M – metal
mAU – milli arbitrary units
Me – methyl
MHz – megahertz
min. – minute(s)
mAU – milli arbitrary units
mL – milliliter(s)
μL – microliter(s)
μm – micrometer(s)
mm – millimeter(s)
mmol – millimole(s)
mol – mole(s) or molar
m.p. – melting point
MS – mass spectrometry
m/z – mass to charge ratio
M – multiplet
MW – molecular weight
m/z – mass to charge ratio
n- number of units
n.d. – not determined
nm – nanometer
NMR – nuclear magnetic resonance
Nu / Nu- – nucleophile (neutral / anionic)
N-xantphos – 4,6-bis(diphenylphosphino)-10H-phenoxazine
ο – ortho
OMe – methoxy
p – para
Pd G2 – Buchwald’s second generation palladium (II) precatalysts
Pd G3 – Buchwald’s third generation palladium (II) precatalysts
Ph – phenyl
pKa = acid dissociation constant
PPh3 triphenylphosphine
ppm – parts per million
Pr – propyl
psi – pounds per square inch
Pyox – pyridine-oxazoline
q – quartet
Quinox - 2-(4,5-dihydro-2-oxazolyl)quinoline
R – alkyl group
R- rectus
rac - racemic
Rf – retention factor
r.t. – room temperature
rxn - reaction
s – singlet or secondary
S- solvent
t – tert
t – triplet
td – triplet of doublets
OTf – triflate (trifluoromethanesulfonate)
TFA- trifluoroacetic acid
THF – tetrahydrofuran
TLC – thin layer chromatography
TMS – tetramethylsilane
tR – retention time
UV – ultra violet
vacuo – vacuum via rotary evaporation and rotary vane pump
v/v – volume per volume
VWD – variable wavelength detector
X / X – halide or pseudohalide / halide or pseudohalide anion
Xantphos – 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
Y – heteroatom
Abstract

Palladium catalysis is a common synthetic tool utilized by organic chemists to create carbon-carbon bonds. We utilized palladium to catalyze the \( \gamma \)-arylation of \( \alpha, \beta \)-unsaturated ketones, and esters. This work expands on palladium-catalyzed \( \alpha \)-arylation chemistry and extends it to the vinylogous variation at the \( \gamma \)-position. We report the regioselective synthesis of mono-\( \gamma \)-arylated 7-methoxy-4-methylcoumarin. We also report efforts towards applying our reaction conditions to other \( \alpha, \beta \)-unsaturated ketones and esters to expand the scope of our reaction conditions.

In addition, we utilized palladium to catalyze the enantioselective asymmetric intramolecular Mizoroki-Heck reaction to produce potentially bioactive phenanthridinone analogs. We achieve this through the Birch-Heck sequence, a 4-step sequence that includes Birch reduction/alkylation of benzoic acid, acid chloride formation/amide formation, triflation, and then the enantioselective Mizoroki-Heck reaction. In this process, we report N-H and N-Me phenanthridinone analogs' synthesis. A protection/deprotection protocol was found to be the key to accessing phenanthridinone derivatives with N-H.

Besides palladium catalysis, we also explored conducting the enantioselective Mizoroki-Heck reaction with nickel. Nickel catalysis is a relatively new research area that has recently demonstrated success with the enantioselective intramolecular Mizoroki-Heck reaction under mild conditions with high yields and ee values. We proposed that we may access a pathway that could increase our enantioselectivity under relatively mild conditions by using nickel. We report efforts to optimize the nickel catalyzed Heck reaction to minimize side products and to improve the yield of the desired 1,3-diene. In the synthesis of phenanthridinone analogs, we have demonstrated that the Birch-Heck sequence is a simple way of synthesizing chiral phenanthridinone derivatives with quaternary centers.

In total, three areas of transition metal-catalyzed reactions were explored. This involved cross-coupling between enolates and aryl halides and between aryl halides and alkenes. Strategies for enantioselective synthesis were developed, and potentially bioactive phenanthridinone structures were constructed. Finally, the cross-coupling studies looked at both palladium and, the more cost-effective, nickel in the Mizoroki-Heck reaction.
-CHAPTER 1-

Background and Introduction

Around 1700, miners in Brazil had found a metal that was an alloy of gold and palladium, which they named “ouro podre” or worthless gold. It was not until 1803 that palladium was isolated when William Wollaston discovered an impurity during platinum purification. He called his newly found metal “palladium” after the recently discovered asteroid, “Pallas,” named after the Goddess of Wisdom. Wollaston announced palladium’s properties; however, he did not reveal the refining process until right before his death because of its potential commercial value. Palladium was not desirable on the market until the 1930’s when a German company developed and patented uses of alloys of palladium with gold or silver for use in dentistry. Since then, palladium has become an essential tool for chemists to synthesize compounds and has become a staple in forming carbon-carbon bonds.¹

There are two types of carbon-carbon bond formations presented in this dissertation: an enolate/aryl halide coupling using a palladium precatalyst and an aryl halide/alkene coupling using palladium and a chiral ligand. In both cases, a variety of substrates and reaction conditions were explored to develop new, more efficient procedures to construct valuable complex molecular architectures.

1.1 Palladium as a precatalyst

Organic/organometallic chemists commonly use palladium-catalyzed cross-coupling reactions to quickly piece together two different molecules that would otherwise not combine. For these reactions, palladium is in its 0 or +2 oxidation state, its most active forms.³ Palladium precatalysts have been created to make the use of palladium even more convenient and efficient by storing palladium in its more stable state (Pd(II)) with the desired ligand coordinated. These
precatalysts are typically a reductive elimination away from being active as Pd(0) in catalytic cycles. Bruno, Tudge, and Buchwald have created a third generation of phosphine-ligated palladium precatalysts based upon a 2-aminobiphenyl scaffold. Scheme 1 shows the differences in generation two (G2) and generation three (G3) scaffolds. In the G2 precatalyst, monodentate ligands (L in Scheme 1) are used since there are no empty coordination sites for a bidentate ligand to bind due to chlorine being bound to palladium. The G3 scaffold contains a weakly associated mesylate group, which creates a cationic complex leaving two vacant coordination sites available for bidentate ligand binding. The G3 precatalyst can be prepared from a broader range of phosphine ligands due to the two vacant coordination sites. In addition, exchanging chloride for mesylate improves solution stability. These catalysts are easy to synthesize, activate quickly under mild conditions, and can lead to high yields. The palladium precatalysts used in the research presented are xantphos G3 and N-xantphos G3. These catalysts were readily available in the lab and were determined to be the best options for the desired catalysis.

Scheme 1: Buchwald Precatalysts
1.2 γ-Arylation

During my time in the Schmink Lab, we were initially investigating α-arylation chemistry and desired to expand our investigations to arylation of the vinylogous γ-position to illustrate new applications. Over the past two decades, α-arylation chemistry has been extensively studied and analyzed. Recent research has shifted to the investigation of γ-arylation of enolates due to the challenges of obtaining regioselective arylation at the γ-position: avoiding polyarylation products; avoiding α-arylation; preventing β-arylation via Heck reaction; and minimizing condensation side products. α,β-Unsaturated ketones and esters are challenging to selectively mono-γ-arylate due to the dienolate intermediate as shown in Scheme 2, which can lead to multiple unwanted side products from two different nucleophilic carbons formed by deprotonation of the γ-position. Compared to α-arylation, up to five different products may be produced versus only two different products in α-arylation if arylation cannot occur on -R.

Scheme 2: Challenges of α-arylation compared to the challenges of γ-arylation

In contrast, the alkylation of α,β-unsaturated ketone and ester enolates has been thoroughly studied and analyzed. In the past, regioselectivity for the γ-position was controlled by using various metals such as copper and tin. For example, Yamamoto and coworkers cross-
coupled tin dienolates, using palladium, at the γ-position with aryl bromides. A significant drawback to using tin dienolates is their limited availability and the toxicity of tin.⁶,⁷

An important discovery was made by Terao and coworkers in 1998 when they utilized palladium and aryl bromides to selectively γ-arylate α,β-unsaturated ketones, and aldehydes.¹⁴ Their procedure eliminated the use of toxic metals and expanded the scope of the reaction due to widely available aryl bromides and α,β-unsaturated ketones and aldehydes. This lead to a surge of papers from 2005 to 2021 being published on utilizing palladium for γ-arylation, which included our work on the γ-arylation of 7-methoxy-4-methylcoumarin (Scheme 3).¹⁵–¹⁸

A Terao and Coworkers

B Varseev an Maier

C Buchwald and Hyde

D Buchwald and Hyde

E This work

Scheme 3: γ-arylation examples from 1998 to this work
Expanding on the various examples of γ-arylated species as shown in Scheme 3, we began our study to mono-γ-arylate 7-methoxy-4-methylcoumarin. Coumarins are well known for their antibiotic, antifungal, anti-inflammatory, and antiviral activities. More specifically, 4-benzyl-7-methoxycoumarin has been reported by Stefanachi and coworkers to inhibit CYP19, (AR) a key enzyme in the biosynthesis of estrogens that would potentially limit or block pathological activity in ER+ cancer. In addition, it has been found to inhibit CYP17, which is a cytochrome P450-dependent enzyme that is involved in the development of prostatic cancer. Coumarins have also been utilized as additives in food and cosmetics to prepare optical brighteners, dispersed fluorescent, and laser dyes. Chemically the α,β-unsaturated lactone allows for interesting reactivity due to increased acidity of the protons at the α- and γ- positions, which can lead to further functionalization. The vast array of applications for these types of compounds make them valuable structures.

γ-Arylation should be favorable with 7-methoxy-4-methyl coumarin due to the protons in the γ-position being the most acidic and sterically unhindered. Resonance within the α,β-unsaturated ester promotes arylation at either the α- or γ-position, which can make it challenging to achieve mono-arylation at the desired position. Literature precedents have examples of metal-catalyzed approaches to γ-arylate coumarins; however, these approaches utilized Suzuki-Miyaura and Negishi cross-coupling approaches. To the best of our knowledge, the synthesis depicted in our article “Palladium-catalyzed mono-γ-arylation of 7-methoxy-4-methylcoumarin” was the first report of an enolate arylation approach to γ-arylate coumarins.

The catalytic cycle for the γ-arylation of 7-methoxy-4-methylcoumarin, the process developed in our research, is shown in Scheme 4. First, the aryl bromide oxidatively adds to the palladium. Next, 7-methoxy-4-methylcoumarin is deprotonated at the γ-position and exchanges
with bromine on palladium. Finally, reductive elimination occurs to produce the desired product. This generalized procedure follows a similar catalytic cycle for the γ-arylation of α,β-unsaturated esters from silyl ketene acetics proposed by Huang and Hartwig. 

**Scheme 4: Mechanism of γ-arylation**

Application of our reaction conditions to other various α,β-unsaturated ketones and esters was the next logical step to ensure that our reaction conditions were not just specific to 7-methoxy-4-methylcoumarin. Some of the compounds we tried were isophorone, 3-methyl-2-cyclohexen-1-one, ethyl crotonate, 1-acetyl-1-cyclohexane, and methyl-1-cyclohexene-1-carboxylate.

Isophorone was chosen as an example of an α,β-unsaturated ketone due to its importance in industry and medicinal chemistry. Shown in **Scheme 5** are some examples of derivatives of isophorone and their potential uses. A vast array of possible transformations highlights their widespread synthetic utility.
Terao et al. had attempted γ-arylation of isophorone as well as 3-methyl-2-cyclohexen-1-one (Scheme 6-A).\textsuperscript{14} However, they could not avoid polyarylation using their reaction conditions even though it was minimal, 6-8%. We hoped to improve upon their work by preventing polyarylation using our reaction conditions from Chapter 2 for both isophorone and 3-methyl-2-cyclohexen-1-one. Unfortunately, the research presented in this dissertation never achieved total conversion to the desired mono-arylated product; however, a recent article published in 2020 by Yuen and So achieved complete conversion in their study of controlling α- and γ-arylation through ligand control (Scheme 6-B).\textsuperscript{27} Their impressive research used less reactive aryl chlorides to make isophorone derivatives in good to excellent yields (63-90%).

Hyde and Buchwald reported on the palladium-catalyzed γ-arylation of 4-methylcyclohex-2-en-1-one (Scheme 6-C).\textsuperscript{16} In addition to achieving mono-γ-arylation, they were able to synthesize ketoindolines in one pot by using ortho-bromoaniline derivatives. The ability to create cyclohexanone-fused indolines in one step was novel. These types of heterocycles are precursors in the synthesis of some of the Aspidosperma alkaloids, including vindoline\textsuperscript{28-32}, aspidophytine\textsuperscript{33}, and the “Büchi ketone” intermediate.\textsuperscript{34} We report our attempts at a similar process using 2-bromoaniline and methyl-1-cyclohexene-1-carboxylate.
**Scheme 6**: Examples of γ-arylation of isophorone and 3-methyl-2-cyclohexen-1-one.

In 2010, Huang and Hartwig published the palladium-catalyzed γ-arylation of α,β-unsaturated esters from silyl ketene acetics (Scheme 6-D). Their successful reactions prompted us to test ethyl crotonate using our reaction conditions. Ethyl (E)-4-phenylbut-2-enoate has been synthesized by a variety of different reactions \(^{35-42}\); however, enolate arylation of the γ-position has not been achieved to our knowledge. \(^{43}\) Regarding the utility of ethyl (E)-4-phenylbut-2-enoate, it is a precursor to bestatin hydrochloride, an anticancer agent \(^{44}\), it is a precursor to 1,3-diaminoalcohol, an amprenavir intermediate, which is a therapeutic agent for the treatment of
HIV infection\textsuperscript{45}, and it is a precursor to a \textit{syn}-4-hydroxy-5-phenyl-\textgamma-lactam, which is an intermediate of various bioactive molecules.\textsuperscript{46–53}

\textbf{Scheme 7:} Ethyl (E)-4-phenylbut-2-enoate as a precursor\textsuperscript{42}

1-Acetyl-1-cyclohexane and methyl-1-cyclohexene-1-carboxylate do not have any examples of \textgamma-arylation to our knowledge.\textsuperscript{54,55} 1-Acetyl-1-cyclohexane was used to prove that if \textalpha-protons and \textgamma-protons were available for deprotonation, then \textalpha-arylation would be preferred due to the increased acidity of the protons in the \textalpha-position as well as the position being sterically unhindered. We also decided to analyze methyl-1-cyclohexene-1-carboxylate, an \textalpha,\textbeta-unsaturated ester with a similar structure to 1-acetyl-1-cyclohexane. The \textgamma-position should have the most acidic protons in this case, with no \textalpha-protons available.

Our work on the \textgamma-arylation of 7-methoxy-4-methylcoumarin was published in 2019.\textsuperscript{25} The rest of the compounds described were investigated to expand the scope of our reaction conditions to other \textalpha,\textbeta-unsaturated ketones and esters and to improve upon the results of certain compounds that were found in the literature as mentioned previously.
1.3 Enantioselective synthesis of phenanthridinone analogs with quaternary carbons using the Birch-Heck Sequence

Due to challenges with expanding the scope of our reaction conditions to other α,β-unsaturated carbonyl compounds and lack of funding on the γ-arylation project, our focus switched to the synthesis of chiral phenanthridinone analogs using the enantioselective intramolecular Mizoroki-Heck reaction. Creating chiral bioactive compounds, improving enantioselectivity, and synthesizing chiral phenanthridinone analogs from secondary and tertiary benzamides were the main goals of this research.

Phenanthridinone is an example of a flat structure with a rich history of bioactivity. They have been utilized as a critical scaffold in inhibitors of poly ADP ribose polymerase (PARP) and tankyrase\textsuperscript{56–59}, which are targets in the treatment of cancer. In addition, phenanthridinone analogs were the top inhibitor of DNA topoisomerase IB (TOP1) and tyrosyl-DNA phosphodiesterase 1 (TDP1), which are also targets in the treatment of cancer. Inhibition of ADP ribosyltransferase in the anthrax-like toxin \textit{Bacillus cereus} prompts phenanthridinone’s use as an antibacterial.\textsuperscript{60,61} Due to their effectiveness as progesterone receptor antagonists, phenanthridinone analogs can be used as contraceptive agents, abortifacients, and in the treatment of hormone-dependent cancers and endometriosis.\textsuperscript{62} Bioactivity has also been shown for N-substituted tertiary benzamides.\textsuperscript{63–65} This information makes our research all the more valuable since we have provided access to chiral phenanthridinone derivatives from secondary and tertiary benzamides.\textsuperscript{66–73}

Unfortunately, the broad range of phenanthridinone bioactivity undermines therapeutic selectivity and success in clinical settings.\textsuperscript{56–58} Lovering and coworkers in their analysis of drug development candidates since 1980, found that most natural compounds and synthetically made drugs that became successful therapeutics had three-dimensional structures and higher proportions of sp\textsuperscript{3} centers and chiral carbons.\textsuperscript{74,75} Unfortunately, it is fairly challenging to
synthesize these compounds. Indeed, the three most commonly used medicinal chemists’ reactions are amide bond formations, the Suzuki-Miyaura reaction, and nucleophilic aromatic substitution, which all synthesize flat sp² structures. Synthetic chemist’s affinity for these reactions is due primarily to their efficiency and generalizability, but as sp² focused methodologies, they have likely contributed to the creation of structurally limited compound libraries with flat molecular structures. These flat structures have low aqueous solubility, can engage in more promiscuous binding behavior, and often do not completely fill the space in binding pockets, which decreases their binding energy and potency. Non-planar molecules are more soluble and have the potential to improve the interaction between the drug and the target protein, allowing for more potency and selectivity.

A Scifinder search conducted in 2021 failed to show any closely related quaternary carbon analogs of phenanthridinone. Considering Lovering and coworker’s data on sp³ carbon centers and the lack of quaternary phenanthridinone analogs, several projects have been explored to fill those gaps. Most importantly, we report use of the Birch-Heck sequence (Scheme 13), which stems from our past published work on the Birch reduction-alkylation along with the Mizoroki-Heck reaction, to synthesize chiral phenanthridinone analogs. Three different projects will be discussed using the Birch-Heck sequence: (1) synthesizing chiral quaternary phenanthridinone analogs using palladium as the catalyst; (2) providing a pathway to the secondary benzamide phenanthridinone derivates; and (3) optimization of a nickel catalyst, instead of palladium, for the enantioselective intramolecular Heck reaction. All have utilized the same four steps: (1) the Birch reduction-alkylation to install the quaternary carbon center; (2) an amide formation reaction; (3) a triflation procedure for the phenol derivatives; and (4) the
enantioselective intramolecular Mizoroki-Heck reaction to close the ring setting the configuration of the all-carbon quaternary stereocenter.

This process has been proven to rapidly access quaternary phenanthridinone analogs in the research reported. The compounds created could lead to more discriminant binding to produce more potent drugs with fewer side effects due to the greater three-dimensional complexity of the phenanthridinone structures with quaternary stereocenters.

Scheme 8: Development of the phenanthridinone Birch-Heck sequence

1.3.1 Birch reduction – alkylation

One of the critical reactions, as well as the first step, in our sequence is the Birch-reduction-alkylation, which installs the all-important quaternary center quickly and works well to produce alkylated products in high yields with a wide variety of alkyl R-groups. This reaction was discovered in 1944 by Arthur Birch and involves reducing aromatic systems by dissolving metals (Li, Na or K) in liquid ammonia to form 1,4-diene anions. In the final step of the reaction with electron-deficient benzene derivatives, the enolate anion intermediate is quenched with an alkyl halide to generate a quaternary carbon center, Scheme 8.
The second crucial reaction in our sequence is the Mizoroki-Heck reaction. In 1971, Mizoroki and coworkers initially reported this reaction in their discussion of the arylation of olefin with aryl iodide, which is catalyzed by palladium. This reaction was later improved by Heck and Nolley in 1972. Palladium catalyzes a cross-coupling reaction in which an aryl or vinyl halide or pseudohalide is coupled with an olefin, Scheme 9.

Scheme 9: Generalized Birch reduction-alkylation reaction

1.3.2 Mizoroki-Heck Reaction

Since 1971, Mizoroki-Heck reactions have demonstrated success using intermolecular and intramolecular processes. Shibasaki and Overman independently reported the first examples of intramolecular asymmetric Heck reactions in 1989. Shibasaki and coworkers reported the asymmetric synthesis of cis-decalin derivatives by palladium-catalyzed cyclization of prochiral alkenyl iodides, Scheme 10-A. Their work utilized BINAP, one of the most generally reliable and effective ligands for asymmetric Heck reactions, which provided the best enantioselectivity. Shibasaki and coworkers’ research demonstrated for the first time that an intramolecular Heck reaction could be used for enantioselective construction of tertiary carbon stereocenters, although their enantioselectivities were low. Overman and coworkers reported the
asymmetric Heck cyclization for the direct formation of a quaternary carbon stereocenter in 1989. They synthesized spirotricyclic dienones by palladium-catalyzed cyclizations of enol triflate derivatives of 2-dienyl-1,3-cyclohexanediones, Scheme 10-B. Unfortunately, their enantioselectivities were also low. Since 1989, the enantioselective asymmetric Mizoroki-Heck reaction has been improved to yield products with enantioselectivities up to 99%. In 1992, Shibasaki, Sato, and Watanabe improved the ee of previously analyzed cis-decalin derivatives to 91% when they used an alkenyl triflate instead of an alkenyl iodide to promote a cationic Heck mechanism, Scheme 10-A. This swap also allowed for the omission of expensive silver salts and the use of hydrocarbon solvents such as toluene or benzene. Shibasaki and worker’s studies in 1992 claimed that acetate, from Pd(OAc)$_2$, was replacing the dissociated Pd-I inhibiting the cationic pathway, which led to low ee values. Using the alkenyl triflate in 1992, eliminated this deleterious effect from Pd(OAc)$_2$ and promoted a cationic Heck mechanism, which was determined to contribute to the improved enantioselectivity.

Continuing the development of the asymmetric intramolecular Heck reaction, Ozeki and coworkers in 2013 reported on the first asymmetric total synthesis of (+)-taiwaniaquinol D and (−)-taiwaniaquinone D by using an intramolecular Heck reaction in a key step (Scheme 10-C). In 2015, Shen and coworkers reported on the enantioselective arylative dearomatization of indoles using palladium-catalyzed intramolecular reductive Heck reactions (Scheme 10-D). In 2016, Joshi and Pigge reported on the asymmetric construction of 3,3-disubstituted oxindoles and isoindolinones, which demonstrated the use of reactive pyridine anhydrobases in metal-catalyzed transformations as well as providing a new approach to heterocyclic ring systems (Scheme 10-E). All of these examples provided methods to form 5-membered rings, which seems to be common for the intramolecular Mizoroki-Heck reaction.
Scheme 11: Enantioselective Asymmetric Mizoroki-Heck Reactions
In 2019, Cheng and coworkers reported on the enantioselective synthesis of quaternary 3,4-dihydroisoquinolinones via Heck carbonylation reactions in their synthesis of minalrestat analogs (Scheme 10-F).\textsuperscript{90} They demonstrated high ee values for their enantioselective 6-membered ring cyclization. Although the list reported in Scheme 10 is not exhaustive, it represents a variety of reaction conditions for the enantioselective asymmetric palladium-catalyzed Mizoroki Heck reaction that afforded good to excellent yields with good to excellent ee values.\textsuperscript{91–93} Interestingly, although many ring sizes have been formed in intramolecular Heck reactions\textsuperscript{85,91–96}, most literature examples report the synthesis of 5-membered ring products. We, therefore, anticipated that our desired Heck reaction forming a 6-member ring in an enantioselective intramolecular Mizoroki-Heck reaction may be more challenging.

Our research focused on the enantioselective intramolecular Mizoroki-Heck reaction to create chiral phenanthridinone analogs using palladium and nickel as catalysts (Scheme 11). The enantioselective intramolecular Mizoroki-Heck reaction had been used previously in our lab to create tricarbocyclic structures with all-carbon quaternary stereocenters.\textsuperscript{78} We sought to expand this reaction to the synthesis of triheterocyclic structures, like phenanthridinone, using the analogous enantioselective\textsuperscript{92,97} desymmetrizing process.\textsuperscript{95,98–103} In the process, we create a 6-member ring which has relatively few highly enantioselective examples reported in the literature as discussed prior.\textsuperscript{85,94–96} The palladium research became the major focus of my thesis research, while the nickel project made important progress but is still undergoing optimization. The enantioselectivities achieved in this dissertation from the palladium-catalyzed Heck reactions were low for most compounds, so we began investigations into optimization of a nickel catalyzed Heck procedure due to promising results in the literature indicating that high enantioselectivities could be accessed using mild reaction conditions.
Several variations of the Pd-catalyzed Mizoroki-Heck reaction exist; however, our research focused on the cationic mechanism, as shown in Scheme 12. The cationic pathway is identified by the cationic Pd complex in the mechanism. Cabri\textsuperscript{104} and Hayashi\textsuperscript{105} proposed the first examples of the cationic reaction mechanism to describe Heck reactions of aryl triflates in the presence of palladium-diphosphine catalysts. In asymmetric synthesis, the cationic pathway has been the most successful.\textsuperscript{92} This has been the case in our past research\textsuperscript{78} as well, and was true for the asymmetric synthesis of phenanthridinone analogs reported here. Using the aryl triflate substrate promoted the cationic pathway and enhanced stereochemical control.

The mechanism of the Mizoroki-Heck reaction begins with oxidative addition of the aryl halide or pseudohalide (OTf) with palladium (0) forming complex II. Triflate dissociation due to a weak association with palladium creates the cationic palladium complex III. Ligand exchange allows for coordination of the alkene to palladium, complex IV. This step requires
equilibration for the alkene and aryl group to be cis- to one another in order for insertion to occur and may hinder enantioselectivity if a prolonged equilibration time is required. The alkene then undergoes a syn-1,2-insertion to form V, which sets the stereochemistry of the two newly formed stereocenters and is the rate-determining step. β-Hydride elimination with the syn-β-hydrogen (left of palladium in Scheme 12) is possible due to the hydrogen and palladium being syn-coplanar, producing the 1,3-diene product, complex VII. The base can either be used to deprotonate the β-hydrogen, as shown in the mechanism, or it can be used to deprotonate palladium after β-hydride elimination. Palladium (0) can then dissociate and enter into the catalytic cycle. As evidenced through past literature references and witnessed in our work, triflates were found to be the most reactive indicating that a cationic mechanism is favorable.

Scheme 13: Cationic Mizoroki-Heck Mechanism
1.4 Nickel-Catalyzed Mizoroki-Heck Reactions

Due to the high palladium cost, chemists are interested in utilizing cheaper transition metals such as Co\textsuperscript{10–112}, Cu\textsuperscript{113}, and Ni\textsuperscript{114–121}. Nickel is found in group 10 of the periodic table, is more affordable than palladium due to its abundance in nature, is non-toxic, and has some similar properties to palladium, which makes it attractive to study. Research utilizing palladium catalysts for Mizoroki-Heck reactions is extensive; however, research into the enantioselective intramolecular Mizoroki-Heck reaction using nickel catalysts is minimal.\textsuperscript{114–121} Nickel can access a range of oxidation states like palladium; however, in mechanistic cycles, it is known to potentially go through multiple oxidation states anywhere from Ni(0) to Ni(III), which can make it difficult to discern the mechanism and may lead to unwanted side reactions. Palladium, for the most part, involves a two-electron pathway in catalytic cycles (Pd(0)/Pd(II) pathway), although it can access a range of oxidation states.

Nickel’s other properties also cause varying reactivity when compared to palladium. Nickel is less electronegative, has a lower reduction potential, and its atomic radius is smaller than palladium. Oxidative addition occurs quickly compared to palladium due to nickel’s low reduction potential; however, the reduction of nickel is hindered and usually requires an additional reductant such as manganese or zinc. Unfortunately, for the Mizoroki-Heck reaction, the lower electronegativity of nickel results in a weaker agostic interaction with the β-hydrogen relative to palladium. In addition, nickel’s smaller radius results in a more strained geometry in the transition state leading to slower β-hydride eliminations.\textsuperscript{116} Another drawback to utilizing nickel is the harsh conditions that often need to be used, such as high temperatures, very polar solvents, metal additives, and prolonged reaction times to help overcome the barriers to mechanistic steps in the Heck reaction.
Desrosiers and coworkers reported amongst the first examples of an enantioselective intramolecular nickel-catalyzed Mizoroki-Heck cyclization to generate quaternary centers using a chiral nickel precatalyst with ee values up to 96% (Scheme 14-A).\textsuperscript{115} They were also able to demonstrate that a β-hydride elimination could be achieved when nickel was used as the catalyst. Due to nickel’s small atomic radius and low electronegativity, β-hydride eliminations are typically slow; therefore, some type of reductive Heck product may be favorable for nickel reactions.

Qin, Lee, and Zhou reported the first example of a nickel-catalyzed asymmetric reductive Heck reaction in their research synthesizing indolines (Scheme 14-B).\textsuperscript{122} The reductive Heck’s mechanism goes through a reductive elimination as the final step in the mechanistic cycle instead of a β-hydride elimination. Several years later in 2019, Yang, Jin, and Wang reported the nickel-catalyzed asymmetric intramolecular reductive Heck reaction of unactivated alkenes using mild reaction conditions (Scheme 14-C).\textsuperscript{119} Their conditions promoted an increased reaction rate at a lower temperature than reported by Qin et. al. Proton sources, to promote the reductive Heck product, in their reaction came from the nickel salt hydrate, Ni(BF\textsubscript{4})\textsubscript{2}·6H\textsubscript{2}O, and the polar protic solvent, isopropyl alcohol. Protodebromination was not reported in their results, and they had good to excellent yields of the desired compounds with enantioselectivities up to 98%. Other examples of successful reductive Heck reactions are reported in Schemes 14-D and 14-E.\textsuperscript{117,120} Indeed, reductive Heck products are common in the literature for nickel-catalyzed Heck reactions potentially due to the challenges discussed prior with β-hydride eliminations catalyzed by nickel.
**Scheme 14:** Advances in Nickel-catalyzed Mizoroki-Heck Reaction.

We envisioned that we could use the work of Desrosiers et. al. to produce the 1,3-diene compounds that we desired due to their success at overcoming the barrier to β-hydride elimination to access their desired compound. Understanding that β-hydride eliminations are...
typically slow for nickel and that the reductive Heck product may be favorable prompted us to attempt the reaction conditions reported by Yang, Jin, and Wang in the hopes of utilizing mild reaction conditions to achieve the reductive Heck product for our chiral phenanthridinone analogs. Ultimately, the published work in Scheme 14 provided the basis for our initial studies by providing valuable information on the optimization of the nickel catalyzed enantioselective intramolecular Heck reaction.

Prior examples in the literature (Scheme 14) suggested several important considerations as we approached our studies. First, a reductant such as zinc or manganese is almost always required to reduce nickel to a lower oxidation state due to nickel’s low reduction potential. Other additives in the nickel-catalyzed reaction have also been reported to help reduce nickel, such as B$_2$Pin$_2$ (Scheme 14-E). Second, adding exogeneous halide sources, such as LiI, has been found to improve the enantioselectivity of the Heck reaction by helping to favor the neutral pathway. Third, oxazoline-based ligands were abundant in the literature for nickel catalyzed Heck reactions as demonstrated in Scheme 14, which were found to work better than phosphine based ligands. These important concepts helped guide our decisions on the optimization of reaction conditions using nickel to synthesize chiral phenanthridinone analogs.

The impressive work already achieved in nickel catalysis led us to investigate the use of nickel in our enantioselective asymmetric intramolecular Mizoroki-Heck reactions. All but one of the examples presented in Scheme 14 formed five-membered rings. A similar pattern was noted for palladium. Circumstantial evidence suggests that, like the Pd-catalyzed intramolecular Heck reaction, five-member ring formation is more efficient and enantioselective than six-member ring formation. If we can build on the work listed in Scheme 14, we could potentially reduce the time, reduce the temperature, and promote higher yields without loss of
enantioselectivity. Some of the challenges that we faced were 1) avoiding protodehalogenation, 2) limiting or eliminating the reductive Heck product, 3) and enhancing enantioselectivity using chiral ligands.

1.5 References


γ-Arylation of α,β-unsaturated ketones and esters

7-Methoxy-4-methylcoumarin was chosen to investigate the γ-arylation of an α,β-unsaturated ester due to the protons in the γ-position being the most acidic as well as being electronically and sterically unhindered. The challenges we faced were regioselectively arylating the γ-position (versus the alpha-position), avoiding polyarylation, and avoiding condensation side products. Overall, we overcame these challenges to selectively mono-γ-arylate 7-methoxy-4-methylcoumarin in good to excellent yields and this work has been reported in the scientific literature.

Our research’s next logical step was to apply our reaction conditions to other α,β-unsaturated ketones and esters to ensure that our reaction conditions were not just specific to 7-methoxy-4-methylcoumarin. Other α,β-unsaturated ketones and esters that we investigated are isophorone, 3-methyl-2-cyclohexen-1-one, ethyl crotonate, 1-acetyl-1-cyclohexane, and methyl-1-cyclohexene-1-carboxylate.

2.1 Synthesis of γ-arylated 7-methoxy-4-methylcoumarin:

The substrate for our studies was generated from the commercially available 4-methylumbelliferone via protection of the phenol, thereby eliminating an acidic proton that would complicate our efforts at γ-arylation. In that event, deprotonation of the phenol proton may lead to a coupling or aromatic substitution reaction to occur with the Ar-Br. Therefore, the phenol needed to be protected to allow efficient γ-arylated products without unwanted side reactions. A Williamson ether synthesis was utilized to install a methyl group onto the hydroxyl group’s oxygen producing 89% of a white, free-flowing powder.
Dr. Jason R. Schmink achieved the optimization of the γ-arylation of 7-methoxy-4-methylcoumarin. The research presented here is the contribution that I had to explore the scope of these reaction conditions. When xantphos G3 was used in our reaction, it afforded the best reactivity with total consumption of the starting material and suppression of diarylated products. N-Xantphos G3 had similar reactivity but is more expensive, so xantphos was chosen as the ligand in the G3 scaffold. DPEPhos, DPPF, and MorDalPhos ligands in a G3 complex, and PA-PPh ligand in a G2 complex were also attempted. However, none were as efficient as xantphos at producing mono-arylated product. Next, various bases were attempted to deprotonate the γ-position. LiHMDS, a strong base that is soluble in THF, was found to be the optimal base. It’s strength stems from the fact that nitrogen is less electronegative than oxygen, which means that it does not stabilize a negative charge as well as oxygen making it more reactive as a base. The bulky groups on the nitrogen minimize nucleophilic side reactions that would impede the compound’s ability to function as a base. Although carbonate bases were found to be the best base in γ-arylation procedures in the literature, they did not work for our reaction conditions. Carbonate bases (pKa~10) do not solubilize completely in THF and they are weaker bases than LiHMDS (pKa ~26). Out of all of the polar aprotic solvents screened, THF heated at 70°C worked the best. Pressure buildup in the vial due to evaporated THF, b.p. = 66°C, may have increased the reaction rate due to more collisions of the molecules in solution. While toluene, a
non-polar solvent, provided an incomplete reaction with small amounts of diarylated product formed.

\[
\text{Scheme 16: Optimized reaction conditions}
\]

2.1.2 Aryl bromides

The synthesis of 7-methoxy-4-methylcoumarin followed the optimized reaction conditions as shown in Table 1. First, attempts were made with aryl bromides due to their widespread availability and good reactivity in the literature.

Table 1: \(\gamma\)-arylated 7-methoxy-4-methylcoumarin using aryl bromides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
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<td>1</td>
<td>bromobenzene</td>
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<td>2</td>
<td>2</td>
<td>2-bromoanisole</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>3-bromoanisole</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>4-bromoanisole</td>
<td>88</td>
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<tr>
<td>5</td>
<td>5</td>
<td>4-bromoveratrole</td>
<td>90</td>
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<tr>
<td>6</td>
<td>6</td>
<td>4-bromo-N,N-dimethylaniline</td>
<td>66</td>
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<td>7</td>
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<td>70</td>
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<tr>
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<td>10</td>
<td>4-bromotoluene</td>
<td>65</td>
</tr>
<tr>
<td>11</td>
<td>11</td>
<td>2-bromo-4-tert-butyltoluene</td>
<td>68</td>
</tr>
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<td>12</td>
<td>12</td>
<td>4-bromo-4-tert-butylbenzene</td>
<td>75</td>
</tr>
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<td>13</td>
<td>4-chlorobromobenzene</td>
<td>70</td>
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<td>4-bromobenzotrifluoride</td>
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<tr>
<td>15</td>
<td>15</td>
<td>4-bromobenzonitrile</td>
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<tr>
<td>16</td>
<td>16</td>
<td>5-bromobenzofuran</td>
<td>92</td>
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<tr>
<td>17</td>
<td>17</td>
<td>2-bromopyridine(^b)</td>
<td>57</td>
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<tr>
<td>18</td>
<td>18</td>
<td>3-bromopyridine(^b)</td>
<td>32</td>
</tr>
</tbody>
</table>

\(^{a}\)Isolated yield after column chromatography. \(^{b}\)Incomplete Reaction.
Electron-rich aryl bromides and sterically diverse aryl bromides worked well in entries 1-11. When we attempted 4-chlorobromobenzene, oxidative addition into the Ar-Br bond occurred, yielding 4-Cl-Ar on the product. This confirms that Br derivatives react faster in the oxidative addition step than Cl derivatives under the reported reaction conditions. Electronegative CF$_3$ in entry 13 had only 30% of the product isolated. Electronegative aryl groups can help to weaken the Ar-Br bond, which makes oxidative addition easier; however, they may hinder reductive elimination. 4-Bromobenzonitrile is a lot less electron-withdrawing than 4-bromobenzotrifluoride, which in turn provided better reactivity in entry 14. Heterocycle 5-bromobenzofuran, entry 16, yielded 92% of the desired product. Derivatives made from 2- and 3-bromopyridine had incomplete reactions with low isolated yields, entries 17-18. Pyridine rings have been known to coordinate via their nitrogen atom to palladium$^{12-14}$, which may be why the reaction is being impeded.$^2$ Attempts were made in Table 2 to increase the yield of 3-bromopyridine; however, none successfully improved the GC yield.

An extended reaction time of 48 hours was thought to allow for equilibration in the reaction yielding more product; however, less product was produced, entry 2. Lowering the amount of aryl halide to 1.00 equivalent was thought to potentially reduce the amount of pyridine that could associate with the palladium at the nitrogen, increasing the ability of the palladium to oxidatively add into the Ar-Br bond; unfortunately, the yield was even worse, entry 3. Having 1.05 eq. of 7-methoxy-4-methylcoumarin only yielded 20% of the product in the GC, with the major species being the starting material, entry 4. Lower temperatures were thought to slow the reaction, leading to less product, which was consistent with the data obtained. Raising the temperature to 80°C could have accelerated the reaction leading to pyridine’s association and
dissociation from palladium promoting the desired product; unfortunately, the product formation was lower than the standard conditions listed in entry 1 on Table 2.

**Table 2: Various Trials of 3-Bromopyridine**

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aryl Halide Amounts (mmol)</th>
<th>Coumarin amounts (mmol)</th>
<th>Reaction conditions</th>
<th>Time (h)</th>
<th>Results Product/S.M.*</th>
</tr>
</thead>
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<td>1a</td>
<td>1.05</td>
<td>1.00</td>
<td>standard</td>
<td>24</td>
<td>65/35</td>
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<tr>
<td>2</td>
<td>1.05</td>
<td>1.00</td>
<td>standard</td>
<td>48</td>
<td>50/50</td>
</tr>
<tr>
<td>3</td>
<td>1.00</td>
<td>1.00</td>
<td>standard</td>
<td>24</td>
<td>40/60</td>
</tr>
<tr>
<td>4</td>
<td>1.00</td>
<td>1.05</td>
<td>standard</td>
<td>24</td>
<td>20/80</td>
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<td>1.05</td>
<td>1.00</td>
<td>Standard, 60°C</td>
<td>24</td>
<td>10/90</td>
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<tr>
<td>6</td>
<td>1.00</td>
<td>1.00</td>
<td>Standard, 60°C</td>
<td>48</td>
<td>30/70</td>
</tr>
<tr>
<td>7</td>
<td>1.05</td>
<td>1.00</td>
<td>Standard, 80°C</td>
<td>24</td>
<td>50/50</td>
</tr>
</tbody>
</table>

* Values reported are GC yields. * Standard conditions

Not all aryl bromides worked well with our chemistry, Figure 3. Vinyl bromide 1 had only one peak in the GC attributed to 7-methoxy-4-methylcoumarin; however, there may have been a peak hidden in the 7-methoxy-4-methylcoumarin peak due to compound 1 in Figure 3 dimerizing via cross-coupling. Aryl bromide 2 contained a messy GC potentially due to the sulfur coordinating to the palladium.

![Chemical structures]

**Figure 3: Aryl bromides that did not work**
2.1.3 – Aryl chlorides

Next, we wanted to see if our reaction conditions would work with the less reactive aryl chlorides to expand our scope even further. When the standard conditions were attempted with 4-chloroanisole, no product peak was found in the GC, Table 3, entry 1. In entry 2, the precatalyst was switched to the more electron-rich N-xantphos, the heat was increased to 90°C, and 48 hours later, by GCMS, 84% of the desired product was formed. Xantphos G3 at 90°C was attempted with chlorobenzene for 24 hours; however, the reaction was incomplete, with 55% of the product being produced. Using the conditions listed in the reaction scheme in Table 3, we were finally able to isolate 70% of pure product, entry 4.

**Table 3**: γ-arylated 7-methoxy-4-methylcoumarin using aryl chlorides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Ar-X</th>
<th>GC Yield (%)</th>
<th>Isolated Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>-</td>
<td>4-chloroanisole</td>
<td>-</td>
<td>n/a</td>
</tr>
<tr>
<td>2&lt;sup&gt;a,d&lt;/sup&gt;</td>
<td>-</td>
<td>4-chloroanisole</td>
<td>84</td>
<td>n/a</td>
</tr>
<tr>
<td>3&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>-</td>
<td>chlorobenzene</td>
<td>55</td>
<td>n/a</td>
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<tr>
<td>4&lt;sup&gt;e&lt;/sup&gt;</td>
<td>19</td>
<td>chlorobenzene</td>
<td>100</td>
<td>70</td>
</tr>
</tbody>
</table>

<sup>a</sup> Incomplete reaction.  <sup>b</sup> 70 °C, Xantphos G3 90 °C. Xantphos G3 48 h.  <sup>c</sup> Isolated yield after column chromatography.
It is well known that aryl chlorides using bidentate phosphine ligands require a high-energy Pd-L₂ pathway, which is why higher temperatures are typically required.\textsuperscript{15} Aryl chlorides are electron-rich, which hinders oxidative addition. Mao, Walsh, and coworkers reported\textsuperscript{15} N-xantphos to have an acidic phenoxazine N-H (pKₐ \sim 21 in DMSO).\textsuperscript{16} In basic reaction conditions, the phenoxazine N-H deprotonates and associates with a main group metal, in our case lithium, and the ligand pi-system.\textsuperscript{17} Mao and coworkers argue that the main group metal, lithium, cooperates with the palladium center to lower the barrier for the oxidative addition of aryl chlorides, making N-xantphos superior to xantphos. Their explanation for cooperativity between palladium and the main group metal stemmed from Zhang and coworkers’ research. Zhang et al. analyzed protonated and deprotonated N-xantphos via \textsuperscript{31}P{\textsuperscript{1}H} NMR, where there was a slight shift of the PPh₂ moiety after deprotonation. They also completed DFT calculations to compare the natural charges of protonated N-xantphos to deprotonated N-xantphos. Only slight changes in those charges, qₚ = 0.926 to 0.923\textsuperscript{1} and qₒ = -0.501 to -0.517\textsuperscript{2} suggest that the electronic structure at the phosphorous and oxygen atoms is mostly unchanged upon deprotonation of N-xantphos.\textsuperscript{17} Our results were consistent with their results when we used N-xantphos and LiHMDS in our reaction sequence; however, the mechanism of this process is unknown.\textsuperscript{18}

With the promising results of γ-arylation using 7-methoxy-4-methylcoumarin, we moved onto the exploration of using our optimized reaction conditions on other α,β-unsaturated ketones and esters in attempts to flex the utility of these conditions.

### 2.2 Optimization of the γ-arylation of isophorone

Next, we investigated the synthesis of γ-arylated isophorone based upon the promising work from Terao and coworkers\textsuperscript{6} and Hyde and Buchwald.\textsuperscript{8} Our goals were to expand the scope

\textsuperscript{1} qₚ = atomic partial charge of Phosphorous
\textsuperscript{2} qₒ = atomic partial charge of Oxygen
of our reaction conditions to other α,β-unsaturated ketones and esters and improve upon Terao and coworkers’ research by eliminating polyarylation. First, we attempted to optimize γ-arylation of isophorone using the previously optimized reaction conditions from 7-methoxy-4-methylcoumarin (Table 4, entry 1). Unfortunately, only starting material remained after 24 hours under those conditions, so we undertook a reevaluation of the reaction conditions.

Our study took a systematic look at the reaction conditions, in particular, the nature of the base, the choice of catalyst, the reaction temperature, and solubilizing the base with water. Switching the base to cesium carbonate, which is commonly used in both α- and γ-arylation chemistry6–9 produced 3% of compound C (Table 4, entry 2). Lowering the temperature to 50°C lowered the amount of energy that was available to overcome the activation barrier to diarylation, which should lead to a higher yield of mono-arylated product. The reaction was incomplete; however, 53% of compound C was made (entry 3). Switching the precatalyst from xantphos G3 to N-xantphos G3 decreased compound C, but it eliminated side products D-G (entry 4). A longer reaction time of 48 hours increased the amount of compound C without introduction of any side products (entry 5). Raising the temperature to 70°C with N-xantphos G3 consumed all of compound A and increased compound C; however, side products E and F were still present albeit in low yields (entry 6). Ultimately, N-xantphos significantly suppressed diarylation compared to xantphos using the same reaction conditions. Deprotonation of the nitrogen in N-xantphos may consume some of the base, leaving less base available for the second deprotonation.
Cesium carbonate was slightly soluble in THF, so a small percentage of water in entries 7-8 was added to help solubilize the base; unfortunately, compound C was found in small amounts. Switching the precatalyst to dppf G3 did not improve the reaction, entry 9. As a ligand, dppf has been previously shown to be reactive in arylation reactions\(^2,19–21\) and has a smaller bite angle (99°) than xantphos, (108°) and N-xantphos (114°). A slightly smaller bite angle in combination with the phenyl rings attached to the phosphines was thought to potentially cause steric hindrance around the palladium, making it more difficult for diarylation to occur; however, the reaction failed both at 50°C and 70 °C. Potassium carbonate instead of cesium carbonate did not improve the reaction even while using 18-crown-6 to sequester potassium to make the base
more reactive (entries 11-13). Potassium tert-butoxide, another common base in α-arylation chemistry\(^{22-25}\), was attempted in entries 14-15 but only afforded a trace of C at 70 °C.

Next, the equivalents of base, temperature, and time were explored in Table 5. Lower than three equivalents of cesium carbonate and lower temperatures lead to less C produced, entries 1-8. Lower temperatures and more equivalents of cesium carbonate in entries 9,10, and 11 had promising results; however, the yields of C were low. To achieve mono-γ-arylation at low temperatures, long reaction times greater than 48 hours would be required. Higher temperatures, higher equivalents of base, and longer reaction times were the most favorable conditions since only small amounts of the polyarylated species were produced in entry 13 vs. higher amounts in entries 12.

**Table 5: Optimization of equivalents of base, temperature, and time for Isophorone**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Eq. of Base</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>A (%) (^a)</th>
<th>B (%) (^a)</th>
<th>C (%) (^a)</th>
<th>D (%) (^a)</th>
<th>E (%) (^a)</th>
<th>F (%) (^a)</th>
<th>G (%) (^a)</th>
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<td>12</td>
<td>3</td>
<td>70</td>
<td>24</td>
<td>-</td>
<td>1</td>
<td>70</td>
<td>-</td>
<td>16</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>4</td>
<td>70</td>
<td>48</td>
<td>24</td>
<td>13</td>
<td>63</td>
<td>-</td>
<td>trace</td>
<td>trace</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^a\)Values reported are GC yields.
2.3 Examples of other γ-arylated α,β-unsaturated ketones and esters

Shown in Table 6 are the results of coupling various aryl bromides with isophorone (A), 3-methyl-2-cyclohexen-1-one (A1), and ethyl crotonate (A2). These substrates had similar results with incomplete reactions and minimal amounts of polyarylated products. The positions that we attempted to γ-arylate are circled in the image in Table 6.

**Table 6: γ-arylation of α,β-unsaturated ketones and an ester**

<table>
<thead>
<tr>
<th>Entry</th>
<th>S.M.</th>
<th>Ar-X</th>
<th>L</th>
<th>Time (h)</th>
<th>Temp (˚C)</th>
<th>S.M. (%)</th>
<th>B (%)</th>
<th>C (%)</th>
<th>D (%)</th>
<th>E (%)</th>
<th>F (%)</th>
<th>Isolated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>3-bromoanisole</td>
<td>L2</td>
<td>72</td>
<td>50</td>
<td>24</td>
<td>19</td>
<td>58</td>
<td>-</td>
<td>n/a</td>
<td>n/a</td>
<td>35 (20)</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>3-bromoanisole</td>
<td>L2</td>
<td>72</td>
<td>55</td>
<td>10</td>
<td>4</td>
<td>86</td>
<td>trace</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>3</td>
<td>A1</td>
<td>4-bromoanisole</td>
<td>L2</td>
<td>24</td>
<td>50</td>
<td>12</td>
<td>78</td>
<td>10</td>
<td>-</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>4</td>
<td>A1</td>
<td>4-bromoanisole</td>
<td>L2</td>
<td>48</td>
<td>50</td>
<td>9</td>
<td>72</td>
<td>14</td>
<td>5</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>5</td>
<td>A</td>
<td>4-bromo-N,N-dimethylaniline</td>
<td>L2</td>
<td>72</td>
<td>50</td>
<td>29</td>
<td>68</td>
<td>3</td>
<td>-</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>6</td>
<td>A</td>
<td>4-bromo-N,N-dimethylaniline</td>
<td>L2</td>
<td>72</td>
<td>55</td>
<td>27</td>
<td>66</td>
<td>6</td>
<td>-</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>7</td>
<td>A</td>
<td>bromobenzene</td>
<td>L2</td>
<td>72</td>
<td>50</td>
<td>17</td>
<td>trace</td>
<td>83</td>
<td>-</td>
<td>n/a</td>
<td>n/a</td>
<td>34 (21)</td>
</tr>
<tr>
<td>8</td>
<td>A</td>
<td>4-bromobenzotrifluoride</td>
<td>L2</td>
<td>72</td>
<td>50</td>
<td>trace</td>
<td>-</td>
<td>19</td>
<td>81</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>9</td>
<td>A</td>
<td>1,2-dibromobenzene</td>
<td>L2</td>
<td>24</td>
<td>70</td>
<td>24</td>
<td>47</td>
<td>29</td>
<td>-</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>10</td>
<td>A1</td>
<td>1,2-dibromobenzene</td>
<td>L2</td>
<td>24</td>
<td>70</td>
<td>3</td>
<td>90</td>
<td>8</td>
<td>-</td>
<td>n/a</td>
<td>trace</td>
<td>n/a</td>
</tr>
<tr>
<td>11</td>
<td>A1</td>
<td>1,2-dibromobenzene</td>
<td>L1</td>
<td>24</td>
<td>70</td>
<td>trace</td>
<td>90</td>
<td>trace</td>
<td>-</td>
<td>n/a</td>
<td>10</td>
<td>n/a</td>
</tr>
<tr>
<td>12</td>
<td>A2</td>
<td>4-bromoanisole</td>
<td>L1</td>
<td>24</td>
<td>70</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>8</td>
<td>84</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>13</td>
<td>A2</td>
<td>4-bromoanisole</td>
<td>L1</td>
<td>24</td>
<td>23</td>
<td>trace</td>
<td>-</td>
<td>-</td>
<td>67</td>
<td>27</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

*Values reported are GC yields. †Incomplete reaction. ‡Isolated yield after column chromatography. Compound numbers shown in parentheses. ‡‡2 mol% Xantphos Pd G3, 3 eq LiHMDS.

While the results of using various aryl bromides were promising, the reactivity greatly varied. These results were disappointing since one of the project's goals would be to apply the optimized reaction conditions to various aryl halides that could produce the desired mono γ-arylated products in good to excellent yields. When bromoanisole derivatives were examined,
isophorone in entry 2 had a higher yield than entry 1 with using an elevated temperature of 55°C. In addition, 3-methyl-2-cyclohexen-1-one (A1), which is similar in structure to isophorone, with 4-bromoanisole had half of (A1) remaining and half of mono-arylated product produced, entry 3. Through resonance, the methoxy group is electron-donating to the ortho- and para- positions, strengthening the Ar-Br bond hindering oxidative addition. Polyarylated species were not apparent in the GC; however, when the reaction was run for 48 hours, diarylated product was present. Without the methyl groups at the β-position in A1 vs. A, the α-protons are sterically unhindered. α-Arylation might have been the preferred mono-arylated species; however, this was never confirmed via NMR analysis. When another electron-rich aryl halide, 4-bromo-N,N-dimethylaniline, was used with isophorone in entries 5 and 6, small amounts of γ-arylated product were present. Bromobenzene had the best reaction results with the most amount of γ-arylated species in the GC at 50°C for 72 hours, entry 7. These results were comparable to entry 2, which required a slightly higher temperature. More electron density in the aryl ring might hinder oxidative addition, so we attempted 4-bromobenzotrifluoride, which contained the very electron-withdrawing trifluoromethyl group. 4-Bromobenzotrifluoride coupled with isophorone yielded the diarylated product as the major product, entry 8. The CF₃ group is electron-withdrawing, which weakens the Ar-Br bond, making oxidative addition faster. The acidity of the proton in the γ-position, once mono-arylation is achieved, is even more acidic, which promotes diarylation. 1,2-Dibromobenzene did not work well for isophorone or 3-methyl-2-cyclohexen-1-one, entries 9-11. At 70°C, a peak in the GC corresponding to cyclized product F formed, entry 11. This may occur through a sequential γ-arylation and then a Mizoroki Heck reaction to form the cyclized product.
During optimization of isophorone, compounds 20, entry 1, and 21, entry 7 in Table 6 were isolated under initial reaction conditions before complete optimization to confirm the final product’s configuration. The low isolated yields compared to the GC yields may be attributed to loss of product from using the high vacuum system to dry the compounds, which were oils. As an example, the NMR of 3-(3-methoxybenzyl)-5,5-dimethylcyclohex-2-en-1-one is shown in Figure 1. The protons are labeled as proof of the γ-arylated product, C, which were compared to values in the literature.\textsuperscript{26}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{nmr.png}
\caption{NMR of 3-(3-methoxybenzyl)-5,5-dimethylcyclohex-2-en-1-one}
\end{figure}

Previous work by Dr. Jason R. Schmink proved that ethyl crotonate might be a viable compound for our proposed γ-arylation reaction conditions due to diarylated and triarylated compounds being present in the GC.\textsuperscript{27} The reaction conditions initially explored by Dr. Jason Schmink are reported in Table 6, entry 12. When the reaction was attempted at room temperature for 24 hours, the diarylated product was the primary product with significantly less triarylated product, a trace amount of starting material, and other various side products present in
the GC, entry 13. The reaction quickly forms the diarylated species even at room temperature, making it challenging to produce mono-arylated product. Unfortunately, incomplete reactions that produced polyarylated species for compounds A, A1, and A2 prompted us to stop the investigation and move onto other more promising compounds.

2.4 α'-Arylation of 1-acetyl-1-cyclohexane

Applying our reaction conditions from 7-methoxy-4-methylcoumarin to the arylation of 1-acetyl-1-cyclohexane proved successful. Only one peak in the GC was present for entries 1 and 2 in Table 7. Unfortunately, when we isolated the product and analyzed it via NMR spectroscopy, we found that we produced the α'-arylated product F. α'-Arylated product was expected due to the increased acidity of the protons at the α'-position compared to the γ-position. In addition, that position is sterically unhindered compared to the methylene protons at the γ-position.

Table 7: α'-Arylation of 1-acetyl-1-cyclohexane

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>Ar-Br</th>
<th>Isolated yield C (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Isolated Yield F (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>bromobenzene</td>
<td>-</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>23</td>
<td>3-bromoanisole</td>
<td>-</td>
<td>90</td>
</tr>
</tbody>
</table>

<sup>a</sup>Values reported are GC yields
As proof of $\alpha'$-arylated product, shown in Figure 2 is the $^1$H NMR spectrum for 1-(cyclohex-1-en-1-yl)-2-(3-methoxyphenyl)ethan-1-one. The spectrum was compared to the literature spectrum for the phenyl derivative to confirm the assignments.\textsuperscript{28}

\textbf{Figure 2:} NMR of 1-(cyclohex-1-en-1-yl)-2-(3-methoxyphenyl)ethan-1-one

Due to the $\alpha'$-arylated product being produced in excellent yields at 50°C, it was apparent that the $\gamma$-arylated product was not favored and that the $\alpha'$ protons are the most acidic. Our interest in $\gamma$-arylated products led us to investigate other substrates. The site of arylation has a preference for the least hindered carbanion position, which is supported by both data obtained from 1-(cyclohex-1-en-1-yl)-2-(3-methoxyphenyl)ethan-1-one and isophorone.

\textbf{2.5 $\gamma$-Arylation of methyl-1-cyclohexene-1-carboxylate}

$\alpha,\beta$-unsaturated ketones are prone to $\alpha$-arylation, so our focus shifted to another $\alpha,\beta$-unsaturated ester, methyl-1-cyclohexene-1-carboxylate. We wanted to investigate if $\gamma$-arylation
happens primarily at methyl carbons or if this process could be applied to methylene carbons. Cesium carbonate was screened as a potential base due to the promising results from isophorone. Only peaks correlating to starting materials A, B, and other impurities were found in the GC.

Table 8.

Table 8: Initial attempts of γ-arylation of methyl-1-cyclohexene-1-carboxylate

![Chemical Reaction Diagram]

Due to the disappointing results from cesium carbonate, we switched the base to lithium hexamethyldisilazide due to its reactivity in our 7-methoxy-4-methylcoumarin research. Switching the base led to 31% of the mono-arylated product being produced and other side products being present in the GC in Table 9, entry 1. Lowering the temperature from 70°C to 50°C proved beneficial to eliminate side products and produced only mono-arylated product in the GC (entries 1-4). Using 5% or 3% of the precatalyst in entries 3 and 4, respectively, did not significantly affect the reaction. With those conditions in mind, various aryl bromides were explored in entries 5-15; however, meager yields of the product were obtained due to problems in the purification process. These results confirm that we can arylate methylene carbons in good
crude yields with aryl bromides with electron-withdrawing groups, neutral, and electron-donating groups; however, we still had to confirm what mono-arylated species we made.

Determining what mono-arylated product we produced proved challenging. COSY NMR analysis of the benzene derivative indicated that the γ-arylated product was the most likely structure; however, we think that we made a γ-arylated β,γ-unsaturated ester. Since we are starting with an α,β-unsaturated ester, the γ-arylated product may form and then isomerize via palladium to the β,γ-unsaturated ketone to be in conjugation with the aryl ring. We compared our proton NMR (Chapter 6.2.4, Figure 63) to examples in the literature. We were able to rule out the α' product and γ' product based upon a comparison of our proton NMR to the literature.
The β-product was not a good fit either due to the coupling between H₅ and H₆. Since both protons are coupled to the same methylene protons, we propose that H₆ and H₅ are being coupled to H₁. H₆ is strongly coupled to other methylene protons, which are attributed to the H₂ protons.

Figure 3: COSY NMR of compound 24

The most important information we received from this experiment was that we were able to γ-arylate a methylene carbon using our reaction conditions at low temperatures. We propose that we synthesized the γ-arylated β,γ-unsaturated ester-based upon our NMR studies.
2.6 Consecutive amide formation/ Heck cyclization of methyl-1-cyclohexene-1-carboxylate

Application of the standard reaction conditions to 2-bromoaniline yielded no product (A) in the GC; however, two side products were detected corresponding to B and C in Table 10. We found these to be very interesting products of presumably a tandem reaction sequence, acylation and Heck cross-coupling or vice versa; consequently, we decided to explore this event further.

Table 10: Consecutive amide formation/ Heck cyclization of methyl-1-cyclohexene-1-carboxylate reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base</th>
<th>Time (h)</th>
<th>Temp (˚C)</th>
<th>A (%)</th>
<th>B (%)</th>
<th>C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>LiHMDS</td>
<td>24</td>
<td>50</td>
<td>Trace</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>LiHMDS</td>
<td>24</td>
<td>70</td>
<td>18</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>LiHMDS</td>
<td>24</td>
<td>100</td>
<td>-</td>
<td>63</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>Toluene</td>
<td>LiHMDS</td>
<td>24</td>
<td>110</td>
<td>-</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>LiHMDS</td>
<td>24</td>
<td>100</td>
<td>-</td>
<td>32</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>THF</td>
<td>LiHMDS</td>
<td>48</td>
<td>100</td>
<td>-</td>
<td>69</td>
<td>31</td>
</tr>
<tr>
<td>7</td>
<td>THF</td>
<td>Cs2CO3</td>
<td>24</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>THF</td>
<td>LiHMDS</td>
<td>48</td>
<td>100</td>
<td>-</td>
<td>62</td>
<td>36</td>
</tr>
<tr>
<td>9</td>
<td>CPME</td>
<td>KOtBu</td>
<td>24</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>83</td>
</tr>
<tr>
<td>10</td>
<td>THF</td>
<td>LiHMDS</td>
<td>48</td>
<td>100</td>
<td>-</td>
<td>38</td>
<td>62</td>
</tr>
<tr>
<td>11</td>
<td>THF</td>
<td>LiHMDS</td>
<td>48</td>
<td>100</td>
<td>-</td>
<td>44</td>
<td>56</td>
</tr>
<tr>
<td>12</td>
<td>THF</td>
<td>LiHMDS</td>
<td>48</td>
<td>100</td>
<td>-</td>
<td>74</td>
<td>26</td>
</tr>
<tr>
<td>13</td>
<td>THF</td>
<td>LiHMDS</td>
<td>24</td>
<td>100</td>
<td>-</td>
<td>88</td>
<td>12</td>
</tr>
<tr>
<td>14</td>
<td>THF</td>
<td>LiHMDS</td>
<td>24</td>
<td>100</td>
<td>-</td>
<td>100</td>
<td>-</td>
</tr>
</tbody>
</table>

- **Incomplete Reaction**
- **Values reported are GC yields**
- **4% N-Xantphos Pd G3**
- **4eq LiHMDS**
- **5% Xantphos Pd G3**
- **3% Xantphos Pd G3**

Conditions the same as Entry 3, but after 24 hours, 1% Xantphos Pd G3 was added and the reaction was left for an additional 24 h at 100˚C.

Compound C was selectively produced when the reaction was run at 50˚C, Table 10, entry 1. Raising the temperature promoted a Mizoroki-Heck product to be made in increasing yields in entries 1-3. Switching the solvent to toluene to attempt the reaction at a higher temperature slowed the cyclization process (entry 4). When the precatalyst was switched to N-
xantphos G3, entry 5, the cyclization process was hindered. Leaving the reaction for 48 hours with the conditions listed in entry 2 had minimal effect on B’s production. Switching the base to cesium carbonate shut down the reaction entirely (entry 7). Increasing the amount of LiHMDS and increasing the reaction time to 48 hours did not increase B. Switching the solvent to CPME and switching the base to potassium tert-butoxide generated product C selectively. Increasing the amount of xantphos G3 decreased the amount of B produced, entry 10. Lowering the amount of precatalyst also reduced the amount of B, entry 11.

Due to changes in the reaction conditions not increasing the amount of B produced, we began to wonder if the reaction was stalling. To probe if the reaction was stalling, 1% of precatalyst was added after 24 hours. The reaction was placed back on the pie reactor for an additional 24 hours. This increased the amount of B produced significantly in entry 12, which confirmed our suspicions that the reaction was stalling. With these extremely promising results in mind, we repeated the reaction conditions; however, we amended our procedure. We added in 5% xantphos G3 after 6 hours, in addition to the 4% catalyst that was initially added, and left the reaction for an additional 18 hours at 100°C, entry 13. This amendment increased the amount of product but did not fully convert C to B. Finally, we added 10% xantphos G3 after 6 hours and left the reaction for an additional 18 hours at 100°C (entry 14). This selectively produced cyclized product B. We isolated 88% of cyclized product B; however, we could not separate the alkene constitutional isomers formed as shown in compound B, Figure 4.
Figure 4: NMR of compounds B1 and B2

While exploring various reaction conditions, we isolated both the cyclized product B and the amide product C to confirm our hypothesis of what was being produced. When analyzing the cyclized product’s NMR, it was discovered that two different alkene constitutional isomers had formed, Table 10, compound B. There should have only been one peak due to one proton at around 8.50 ppm to 9.00 ppm where an amide N-H proton would appear; however, there were two peaks. Also, there should have only been 2 protons in the vinylic region when there were 4 protons. The proton NMR was compared to England’s, Merey’s, and Padwa’s work, where they isolated compound B1.31 The peaks for B1 were assigned accordingly. Other peak assignments as shown in Figure 4 and other NMR data from C13APT, HSQC, and COSY experiments were
used to confirm our suspicions (Chapter 6.2.4.1, compound 31). Only one peak due to the cyclized product was present in the GC, which did not confirm nor deny our suspicions.

2.7 Conclusions:

We were able to successfully regioselectively mono-γ-arylale 7-methoxy-4-methylcoumarin utilizing the optimized reaction conditions. Also, we were able to use less reactive aryl chlorides with slight modifications to our reaction. The less expensive xantphos G3 precatalyst could be utilized for most of the substrates except for aryl chlorides, which required more electron-rich N-xantphos G3.

Expanding our reaction conditions to isophorone, 3-methyl-2-cyclohexen-1-one, ethyl crotonate, and methyl-1-cyclohexene-1-carboxylate proved challenging. We were unable to achieve mono-γ-arylated products in good to excellent yields. 1-acetyl-1-cyclohexane yielded only mono-α'-arylated product due to the most acidic protons on the α'-carbon, which was confirmed by comparing the \(^1\)H NMR spectrum to literature values. Methyl-1-cyclohexene-1-carboxylate had the best results that eliminated polyarylation, consumed the starting material, produced γ-arylated product, and demonstrated that γ-arylation could successfully occur on a more hindered methylene carbon using our reaction conditions. Unfortunately, the yields were low due to issues in the purification process and removing carbazole, which is reductively eliminated from the precatalyst before palladium enters the catalytic cycle, from the products. In addition, the sequential amide formation/Mizoroki-Heck reaction of methyl-1-cyclohexene-1-carboxylate had some promising results; however, the reaction produced constitutional isomers, which could not be separated. The utility of this reaction sequence was not enough to continue with this research. Due to the lack of funding and publishable results, we decided to end our studies on the γ-arylation project.
2.8 References:


27. Schmink, J. R. *Dr. Jason Schmink’s research.*


Moving on from the $\gamma$-arylation project, we decided to shift our focus to the synthesis of chiral phenanthridinone analogs, which had initial success in the Malachowski Lab. We desired to combine the significant bioactivity of phenanthridinone, as noted in the introduction, with the demonstrated success of drugs with $sp^3$ carbons and quaternary stereocenters through use of the Birch-Heck sequence. The initial goal of this project was to synthesize phenanthridinone analogs with a secondary benzamide; however, we did find literature examples proving the bioactivity of phenanthridinone analogs with tertiary benzamides.$^{1-5}$ In the research presented, the Mizoroki-Heck reaction of triflates with secondary benzamides failed to give the desired products. Several methods were attempted to 1) use triflate compounds with secondary benzamides in the Heck reaction, 2) remove the methyl group from the tertiary benzamide in the Heck product, and 3) use a protection/deprotection protocol to achieve the Heck product with a secondary benzamide. The tools developed in the process have enabled a range of analogs to be synthesized and have laid a foundation for the efficient and enantioselective synthesis of a variety of phenanthridinone structures in the future.

3.1 The Birch Reduction-Alkylation:

Previous work in our lab, accomplished by Dr. Andrew Krasley$^6$, optimized the Birch reduction-alkylation procedure utilized in this research as shown in Scheme 17.
One of the best solvents for nucleophilic substitution is ammonia. Besides providing a medium for the alkali metal electrons to reduce the aromatic ring, the ammonia solvent improves the efficiency of the alkylation reactions, particularly with secondary alkyl halides. Initial studies of benzoic acid in the Birch reaction, by past members of the Malachoski Lab, found that certain alkyl bromides and iodides were not producing the desired products and only benzoic acid remained after working up the reaction. Dr. Andrew Krasley completed a thorough analysis of the Birch reduction-alkylation conditions to rule out potential issues due to technique, chemical quality, and other variables in this complex reaction. The reduction of benzoic acid was observed due to the dark blue color of the reaction when lithium metal was added to the round bottom flask containing benzoic acid dissolved in ammonia. Alkylation of the benzoic acid dianion was not occurring. The most likely explanation that we came to was the formation of a stable carbanion from alkylating agents that underwent nucleophilic attack by the benzoic acid dianion to form a cyclic tertiary halide via α-halogenation. The cyclic tertiary halide can then be deprotonated at the γ-position to rearomatize the ring to regenerate benzoic acid. We found that alkyl chlorides significantly enhanced the yield for alkyl halides, which were capable of forming stable carbanions from reductive loss of halide in benzoic acid substrates. More specifically, it was proposed that the use of chloride reduces a competing ring oxidation process with less electronegative bromides that lead to recovered benzoic acid after elimination of H-Br.

**Scheme 17:** Optimized reaction conditions for the Birch reduction-alkylation

One of the best solvents for nucleophilic substitution is ammonia. Besides providing a medium for the alkali metal electrons to reduce the aromatic ring, the ammonia solvent improves the efficiency of the alkylation reactions, particularly with secondary alkyl halides. Initial studies of benzoic acid in the Birch reaction, by past members of the Malachoski Lab, found that certain alkyl bromides and iodides were not producing the desired products and only benzoic acid remained after working up the reaction. Dr. Andrew Krasley completed a thorough analysis of the Birch reduction-alkylation conditions to rule out potential issues due to technique, chemical quality, and other variables in this complex reaction. The reduction of benzoic acid was observed due to the dark blue color of the reaction when lithium metal was added to the round bottom flask containing benzoic acid dissolved in ammonia. Alkylation of the benzoic acid dianion was not occurring. The most likely explanation that we came to was the formation of a stable carbanion from alkylating agents that underwent nucleophilic attack by the benzoic acid dianion to form a cyclic tertiary halide via α-halogenation. The cyclic tertiary halide can then be deprotonated at the γ-position to rearomatize the ring to regenerate benzoic acid. We found that alkyl chlorides significantly enhanced the yield for alkyl halides, which were capable of forming stable carbanions from reductive loss of halide in benzoic acid substrates. More specifically, it was proposed that the use of chloride reduces a competing ring oxidation process with less electronegative bromides that lead to recovered benzoic acid after elimination of H-Br.

**Scheme 17:** Optimized reaction conditions for the Birch reduction-alkylation

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Scheme 18: enolate α-halogenation side reaction

The Birch reduction-alkylation is one of the critical reactions in our sequence because it installs a quaternary center and creates a symmetrical 1,4-cyclohexadiene structure. Therefore, it sets the stage for the key enantioselective Heck desymmetrization and cyclization reaction.

Table 11 shows all of the Birch products that were synthesized. Most Birch reactions worked well with little to no benzoic acid remaining in the $^1$H NMR, entries 1-9, and 15; however, not all arylc halides produced the Birch products in high yields. 2-Chloroacetamide formed the Birch product, an impurity, and had remaining benzoic acid, entry 10. 1,1,1-Trifluoro-2-iodoethane yielded only a trace of the product, with the primary species being benzoic acid, entry 11. The trifluoroalkyl moiety forms a stable carbanion due to reductive loss of the iodine, promoting α-iodination of the 1,4-cyclohexadiene enolate. The CF$_3$ group is very electron-withdrawing due to electronegative fluorine, which stabilizes the carbanion via the polar effect. 1-(Chloromethyl)-1-H-benzotriazole did yield some Birch product; however, mainly benzoic acid and 1-(chloromethyl)-1-H-benzotriazole remained in the GC, entry 12. Part of the problem was that the alkylating reagent was not solubilizing in ammonia. 1-(Chloromethyl)-1-H-benzotriazole did not dissolve well in THF either, so the solid alkylating agent was added slowly.
to solubilize the alkylating agent in small amounts. This increased the amount of Birch product produced; however, there was still too much benzoic acid in the NMR for us to continue with this crude product.

2-Bromoacetophenone, entry 13, and 2-(chloromethyl)anthraquinone, entry 14, had messy GCs with no product peak and very impure NMRs. 2-Bromoacetophenone may form a stable carbanion due to reductive loss of the bromine, promoting α-bromination of the 1,4-cyclohexadiene enolate. 2-(Chloromethyl)anthraquinone may also promote the enolate α-halogenation side reaction. Since we had other very successful alkyl halides that worked exceptionally well, we did not attempt further optimization for these alkyl halides.

**Table 11: Birch Products**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R-X</th>
<th>Yield (%)</th>
<th>Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>benzyl chloride</td>
<td>94</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>chloroacetonitrile</td>
<td>80</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>iodoctahexane</td>
<td>96</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>1-iodo-2-methylpropane</td>
<td>94</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>methyl chloromethyl ether</td>
<td>90</td>
<td>36</td>
</tr>
<tr>
<td>6</td>
<td>1-(chloromethyl)naphthalene</td>
<td>90</td>
<td>37</td>
</tr>
<tr>
<td>7</td>
<td>4-bromo-1-butene</td>
<td>89</td>
<td>38</td>
</tr>
<tr>
<td>8</td>
<td>4-bromo-1-butyne</td>
<td>97</td>
<td>39</td>
</tr>
<tr>
<td>9</td>
<td>2-bromobutane</td>
<td>93</td>
<td>40</td>
</tr>
<tr>
<td>10</td>
<td>2-chlorooctamide</td>
<td>55</td>
<td>41</td>
</tr>
<tr>
<td>11</td>
<td>1,1,1-trifluoro-2-iodoethane</td>
<td>Trace</td>
<td>42</td>
</tr>
<tr>
<td>12</td>
<td>1-(chloromethyl)-1-H-benzotriazole</td>
<td>&gt;100</td>
<td>43</td>
</tr>
<tr>
<td>13</td>
<td>2-bromoacetophenone</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>2-(chloromethyl)anthraquinone</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>iodonemethane</td>
<td>92</td>
<td>44</td>
</tr>
</tbody>
</table>

*a* Trace amount of benzoic acid in NMR. *b* Significant amount of benzoic acid in NMR. *c* NMR very impure. *d* No workup done. *e* GC is a mess

**3.2 Heck precursor synthesis**

Both the cationic and neutral catalytic cycles of the Heck reaction were explored. The cationic cycle was promoted with both secondary and tertiary benzamides using an aryl triflate
electrophile. The neutral catalytic cycle was studied with an aryl bromide electrophile. Our synthetic pathway allowed either aryl triflate or aryl bromide groups to be connected to the symmetrical Birch products through an amide linker, which was formed in a nucleophilic acyl substitution reaction.

The reaction sequence to synthesize the triflate Heck substrate on the path to phenanthridinone analogs, which past members of the Malachowski Lab optimized, is listed in Scheme 19. In the sequence, the Birch product is converted to an acid chloride (A) and is immediately coupled with 2-(methylamino)phenol or 2-bromoaniline to form benzamide (B). This process is efficient and produces high yields. Triflation of the benzamide formed from 2-(methylamino)phenol gives compound (C), which can then be utilized in the Mizoroki-Heck reaction.

Scheme 19: Acid Chloride/Amide formation then Triflation to form Compound C.

Atropisomers were found to form when we analyzed both the tertiary benzamide compounds and their triflated products using NMR spectroscopy. The signals were broad in the proton NMR at room temperature and coalesced when heated to produce peaks that could be properly analyzed. Atropisomerism occurs when there is hindered rotation about a single bond.
due to steric or electronic constraints, causing two or more conformers to experience slow interconversion.\textsuperscript{10} Atropisomerism can lead to kinetic resolution in the Heck reaction\textsuperscript{11}, potential for temperature control of the isomer interconversion equilibrium, and might have an impact on the enantioselectivity.\textsuperscript{12} The tertiary benzamide has restricted rotation around the N-Ar or N-(C=O) bond. Slow interconversion of the atropisomers at room temperature causes signal broadening in the NMR. Heating the NMR sample in DMSO-\textsubscript{d\textsubscript{6}} at 100°C caused the peaks to coalesce due to increasing the rate at which the atropisomers interconvert by overcoming the barrier to rotation between the conformers.\textsuperscript{11–14}

\textbf{Figure 5:} Rotational features of anilides

In the Heck reaction, heating to 80°C likely equilibrates the atropisomers leading to easy interconversion. Nevertheless, one atropisomer may react faster in the Heck reaction than another, either during oxidative addition or the critical enantiodifferentiating 1,2-migratory insertion. The chiral ligand controls the enantioselectivity, but there might be a rate difference between atropisomers that helps to improve the enantioselectivity.

Results for the amide formations are listed in \textbf{Table 12}. Since the acyl chlorides were immediately reacted in the amide formation, their yields and characterization are not reported. The yields in entries 1-10 were high for all of the different compounds. When taken in deuterated chloroform, analysis of the tertiary benzamide compounds via NMR proved difficult due to atropisomer formation and the restricted rotation around the N-Ar or N-(C=O) bond most likely due to steric interactions with the methyl group. Secondary benzamides have free rotation around
the N-Ar or N-(C=O) bond due to hydrogen being small. Therefore, the secondary benzamides do not have the same issues with steric interactions allowing for NMRs to be taken at room temperature in deuterated chloroform.

**Table 12:** Secondary and tertiary amide formation using 2-aminophenol or 2-(methylamino)phenol

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>-R</th>
<th>Yield (%)</th>
<th>Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-H</td>
<td>-CH₂Ph</td>
<td>90</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>-H</td>
<td>-CH₂CN</td>
<td>84</td>
<td>46</td>
</tr>
<tr>
<td>3ᵇ</td>
<td>-H</td>
<td>-CH₂Ph</td>
<td>94</td>
<td>47</td>
</tr>
<tr>
<td>4</td>
<td>-CH₃</td>
<td>-CH₂Ph</td>
<td>&gt;100</td>
<td>48</td>
</tr>
<tr>
<td>5</td>
<td>-CH₃</td>
<td>-CH₂CN</td>
<td>96</td>
<td>49</td>
</tr>
<tr>
<td>6</td>
<td>-CH₃</td>
<td>-cyclohexane</td>
<td>97</td>
<td>50</td>
</tr>
<tr>
<td>7</td>
<td>-CH₃</td>
<td>-isobutyl</td>
<td>99</td>
<td>51</td>
</tr>
<tr>
<td>8</td>
<td>-CH₃</td>
<td>-CH₂OCH₃</td>
<td>90</td>
<td>52</td>
</tr>
<tr>
<td>9</td>
<td>-CH₃</td>
<td>-1-methylnaphthalene</td>
<td>94</td>
<td>53</td>
</tr>
<tr>
<td>10</td>
<td>-CH₃</td>
<td>-CH₂CH₂CH=CH₂</td>
<td>99</td>
<td>54</td>
</tr>
<tr>
<td>11</td>
<td>-CH₃</td>
<td>-CH₂CH=CH=CH₂</td>
<td>&gt;100</td>
<td>55</td>
</tr>
<tr>
<td>12</td>
<td>-CH₃</td>
<td>-sec-butyl</td>
<td>99</td>
<td>56</td>
</tr>
<tr>
<td>13</td>
<td>-CH₃</td>
<td>-CH₃</td>
<td>94</td>
<td>57</td>
</tr>
</tbody>
</table>

ᵇValues from GC. ᵇᵇ2-bromoaniline was used.

### 3.3 Synthesis of Triflate compounds

Triflation of the benzamide is necessary for the compounds made from 2-(methylamino)phenol to be reactive in the Heck reaction. Past research determined that triflates had the best reactivity and enantioselectivity in the Heck reaction when compared to I > Br > Cl.⁴ The triflation reaction has the lowest yields in our reaction sequence. Impurities in the amide compounds and potential degradation of the compounds on the silica gel column could contribute to the low yields.
Table 13: Triflate yields

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>-R</th>
<th>Yield (%)</th>
<th>Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-H</td>
<td>-CH3Ph</td>
<td>70</td>
<td>58</td>
</tr>
<tr>
<td>2</td>
<td>-H</td>
<td>-CH3CN</td>
<td>57</td>
<td>59</td>
</tr>
<tr>
<td>3</td>
<td>-CH3</td>
<td>-CH3Ph</td>
<td>84</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>-CH3</td>
<td>-CH3CN</td>
<td>64</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>-CH3</td>
<td>cyclohexane</td>
<td>56</td>
<td>62</td>
</tr>
<tr>
<td>6</td>
<td>-CH3</td>
<td>-isobutyl</td>
<td>60</td>
<td>63</td>
</tr>
<tr>
<td>7</td>
<td>-CH3</td>
<td>-CH3OCH3</td>
<td>52</td>
<td>64</td>
</tr>
<tr>
<td>8</td>
<td>-CH3</td>
<td>-1-methylnapthalene</td>
<td>62</td>
<td>65</td>
</tr>
<tr>
<td>9</td>
<td>-CH3</td>
<td>-CH3CH=CH=CH3</td>
<td>80</td>
<td>66</td>
</tr>
<tr>
<td>10b</td>
<td>-CH3</td>
<td>-sec-butyl</td>
<td>38</td>
<td>67</td>
</tr>
<tr>
<td>11</td>
<td>-CH3</td>
<td>-CH3CH=CH=CH3</td>
<td>12</td>
<td>68</td>
</tr>
<tr>
<td>12</td>
<td>-CH3</td>
<td>-CH3</td>
<td>88</td>
<td>69</td>
</tr>
</tbody>
</table>

*a Isolated Yield  b Column Chromatography of amide before Triflation*

3.4 The Mizoroki-Heck Reaction

As indicated in Chapter 1, the cationic pathway for the Mizoroki-Heck reaction has had massive success in palladium-catalyzed research\textsuperscript{15–20}. The enantiomeric selectivity is attributed to the alkene-coordination step or the alkene-insertion step. Cationic complex (III, Scheme 20) is generated by dissociation of the triflate anion. The alkene substrate can then complex with palladium at the vacant coordination site (IV). Alkene-insertion into the palladium-Ar bond then affords intermediate (V) where a new chiral carbon center is generated, Scheme 20. A cationic complex makes palladium more electron-deficient and is proposed to promote faster insertion into the alkene. β-Hydride elimination affords compound VI, which dissociates from palladium to yield the Heck product (VII).

The stereochemistry is ultimately controlled by chiral bidentate ligand (BINAP), coordinated to palladium to maintain the rigid chiral surroundings. Aryl bidentate phosphorous ligands were previously found to be successful in the Mizoroki-Heck reaction\textsuperscript{19,20} Previous Malachowski lab members discovered that BINAP was the best ligand for our reaction conditions to produce the highest enantiomeric ratios.\textsuperscript{6,21}
Our original focus was to create phenanthridinone analogs from secondary benzanides due to examples in the literature presenting bioactivity.\textsuperscript{22–28} We repeated the work of Dr. Andrew Krasley\textsuperscript{6} in Table 14, entry 1, and received the same inconclusive results. The original reaction conditions yielded protodehalogenated product, C, as the major species. A small percentage of the desired Heck product was present in the GC; however, only 25\% of B was produced after 48 hours. Optimization of this reaction occurred by changing the temperature, solvent, and palladium source in attempts to suppress protodehalogenation as well as promote the formation of Heck product B.
Table 14: Mizoroki-Heck reaction attempts to synthesize the N-H phenanthridinone benzyl derivative

![Chemical structure diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Palladium source</th>
<th>Solvent</th>
<th>Temp. (˚C)</th>
<th>Time</th>
<th>A (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>B (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>C (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>D (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Other impurities (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>DMF</td>
<td>80</td>
<td>48 h</td>
<td>-</td>
<td>25</td>
<td>62</td>
<td>trace</td>
<td>14</td>
</tr>
<tr>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>DMF</td>
<td>80</td>
<td>71 h</td>
<td>37</td>
<td>13</td>
<td>30</td>
<td>trace</td>
<td>25</td>
</tr>
<tr>
<td>3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>DMF</td>
<td>100</td>
<td>22h 32 min</td>
<td>-</td>
<td>-</td>
<td>30</td>
<td>-</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Toluene</td>
<td>80</td>
<td>22 h 15 min</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Pd(TFA)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>DMF</td>
<td>80</td>
<td>24 h</td>
<td>98</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> Crude yield in GC. <sup>b</sup> GC a complex mixture.

We repeated the reaction conditions from entry 1 but allowed the reaction to go for 72 hours. This yielded a messy GC with multiple side products, entry 2. Next, the temperature was raised to 100˚C in attempts to force the Heck reaction to occur; however, this had the opposite effect, and no Heck product was present in the GC (entry 3). All of the starting material was consumed to create undesired side products. When the solvent was changed to toluene, the reaction was completely shut down, and only starting material remained, entry 4. Finally, the palladium source was changed to palladium (II) trifluoroacetate in attempts to promote the cationic Heck mechanism. Sabrina Tran had success using this palladium source in the N-Me phenanthridinone Heck reaction conditions around the same time that this optimization work was occurring<sup>21</sup>. Unfortunately, this change did not consume much of the starting material, and the
only product present in the GC was compound C. Due to the lack of Heck product B being produced and the production of multiple unwanted side products, our focus shifted to different reaction conditions to synthesize the desired phenanthridinone analogs.

Our past work on the γ-arylation of methyl-1-cyclohexene-1-carboxylate, where a tandem amide formation / Heck cyclization occurred, proved that a secondary benzamide could be utilized in the Heck reaction. Inspired by that work, we analyzed different bases and their equivalents in Table 15 due to rearomatized product D being the major product in entry 1 when our past reaction conditions were attempted. Application of our reaction conditions to compound A in Table 15 did not produce Heck product B. Changes to the amount of base added, entries 1-3, did not limit the amount of D produced. Switching the base to potassium tert-butoxide (conjugate acid pK_a ≈ 17)²⁹, a weaker base than LiHMDS (conjugate acid pK_a ~26)³⁰, in entry 4 did not make the desired product and lead to an incomplete reaction with undesired side products. Cesium carbonate, in entry 5, was attempted due to its marginal solubility in THF, which would limit reactivity; however, none of compound B was produced. Raising the precatalyst amount consumed all of the starting material and led to exclusively the rearomatized product, entry 6. Based upon these results, rearomatization is likely facilitated by palladium. This may occur at high temperatures via oxidative addition into the PhCH_2-C(quaternary) bond (Scheme 21, Pathway A) or a C-H insertion into the bis-allylic position (Scheme 21, Pathway B). In pathway A, the base may be deprotonating the amide nitrogen forming an amide anion, which can assist in directing palladium to insert into the PhCH_2-C(quaternary) bond. Both pathways produce toluene in addition to the rearomatized product.
Scheme 21: Pathways to rearomatized product
The synthesis of phenanthridinone analogs from secondary benzamides was not possible in our hands; therefore, our focus changed to working with N-Me tertiary benzamide derivatives in the construction of phenanthridinone analogs.

Past members of the Malachowski lab had already optimized reaction conditions for triflated tertiary benzamides in the Heck reaction.\textsuperscript{6,21} We were able to synthesize phenanthridinone analogs in good to excellent yields using their conditions; however, the reaction times sometimes took longer than 24 hours to react and the e.r. values were low for some substrates, Table 16.\textsuperscript{6,21} Using lower temperatures is a standard method to improve enantioselectivities; however, when past members of the Malachowski Lab had attempted temperatures lower than 80°C, enantioselectivities were not improved.\textsuperscript{21} We attributed this to the kinetic resolution of the atropisomers of the triflate starting material. We think that one of the
atropisomers is more favorable to proceed through the Heck reaction, which is why elevated temperatures are necessary for equilibration of those isomers.

**Table 16: Mizoroki-Heck products for N-Me phenanthridinone derivatives**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Time</th>
<th>Isolated Yield (%)</th>
<th>e.r.</th>
<th>ee (%)</th>
<th>Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-CH₂Ph</td>
<td>42 h 42 min</td>
<td>84</td>
<td>9:1</td>
<td>80</td>
<td>69</td>
</tr>
<tr>
<td>2a</td>
<td>-CH₂CN</td>
<td>24 h</td>
<td>97</td>
<td>8:1</td>
<td>81</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>-C₆H₁₁Cyclohexane</td>
<td>103 h 5 min</td>
<td>24</td>
<td>3:1</td>
<td>55</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>-CH₂H₂H₂Napthalene</td>
<td>48 h</td>
<td>31</td>
<td>7:1</td>
<td>74</td>
<td>75</td>
</tr>
<tr>
<td>5b</td>
<td>-CH₂CH₂CH₂CH₃</td>
<td>21 h 27 min</td>
<td>7</td>
<td>8:1</td>
<td>79</td>
<td>76</td>
</tr>
<tr>
<td>6</td>
<td>Cyclized butene product</td>
<td>21 h 27 min</td>
<td>54</td>
<td>42:1⁴</td>
<td>95</td>
<td>77</td>
</tr>
<tr>
<td>7c</td>
<td>-sec-butyl</td>
<td>72 h</td>
<td>26</td>
<td>3:1</td>
<td>51</td>
<td>78</td>
</tr>
</tbody>
</table>

*No LiOAc was used. 10 mol % Pd(OAc)₂, 14 mol % R-BINAP. HPLC has three peaks. The peaks in the HPLC were not entirely resolved which is why this number may be elevated.*

In addition to the products, we detected a compound in the GC of the Heck reaction with a mass that corresponded to an acetate group, from the reduction of Pd(OAc)₂, attached to the cyclized product at either C9 or C10, **Figure 6**. The acetate compound was thought to be a key intermediate in our reaction based on its growth and disappearance during the reaction process. During the purification of the cyclohexane derivative using column chromatography, we were able to isolate the acetate intermediate and we characterized it using proton and COSY NMR, **Figures 7 and 8**. From the proton NMR (**Figure 7**), it is not clear where the acetate group was added. A COSY NMR (**Figure 8**) was taken to confirm the configuration of the acetate compound. The two most important couplings are shown in **Figure 8**. These couplings should occur if the acetate group is attached at C9 (**C**, **Figure 6**). H₁₁ is only coupled to the H₁₀ and H₁₀ is coupled to both H₁ and H₀, so compound C (**Figure 6**) is the actual structure of the acetate intermediate forming in the Heck reaction.
Figure 6: Acetate Intermediate

Figure 7: $^1$H NMR of the acetate intermediate
Figure 8: COSY NMR of the acetate intermediate

Next, we wanted to confirm if compound C was an intermediate in the synthesis of the 1,3-diene. The cyclohexane derivative was chosen to monitor disappearance of the acetate intermediate with time due to an analyzable amount of compound C (Table 17) in the GC under standard conditions. A lower palladium and ligand loading than the standard conditions were utilized to slow the reaction further to be able to monitor the reaction. The acetate compound forms quickly within half an hour into the reaction, entry 1. This means that the 1,3-diene forms and is immediately reacted with acetate to create the acetate compound, which we can monitor through entries 1-3. In Table 17, we also witnessed compound C’s disappearance with extended reaction times and growth of compound B without major impurity peaks in the GC in entries 4-9.
Table 17: Reaction Monitoring experiment for acetate intermediate

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time</th>
<th>B (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>C (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>30 min</td>
<td>3</td>
<td>31</td>
</tr>
<tr>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>60 min</td>
<td>4</td>
<td>44</td>
</tr>
<tr>
<td>3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>90 min</td>
<td>5</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>19 h 52 min</td>
<td>38</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>24 h</td>
<td>45</td>
<td>55</td>
</tr>
<tr>
<td>6</td>
<td>43 h 43 min</td>
<td>62</td>
<td>36</td>
</tr>
<tr>
<td>7</td>
<td>59 h 39 min</td>
<td>76</td>
<td>21</td>
</tr>
<tr>
<td>8</td>
<td>83 h 48 min</td>
<td>93</td>
<td>7</td>
</tr>
<tr>
<td>9</td>
<td>102 h 19 min</td>
<td>97</td>
<td>3</td>
</tr>
</tbody>
</table>

<sup>a</sup> Values are GC yields  
<sup>b</sup> Incomplete reaction

With the acetate intermediate (C) being the major product after 30 minutes, we believe that the 1,3-diene, complex III (Scheme 22), is being formed, then the palladium reinserts via Pd-H 1,2-insertion to create the allylic complex, IV (Scheme 22). A potential explanation is the hydrogen attached to the palladium after β-hydride elimination is not being removed from complex III (Scheme 22), and therefore promotes a 1,2 insertion into the double bond to create complex IV (Scheme 22). We speculate that the palladium-allylic complex is a resting state, which may be an energy minimum. Extra electron density from the allylic complex may stabilize cationic palladium better than association with the alkene. The allylic complex that forms is electrophilic, which is prone to nucleophilic addition. Acetate, as the nucleophile, may help to push or extract palladium out of the energy low and to move the cycle forward. Acetate is a soft nucleophile, so it will attack the allylic complex instead of palladium, proceeding via the mechanism shown in Scheme 23. Literature examples were in agreement with our hypothesis due to numerous reports discussing the interception of a palladium allylic complex by
nucleophiles.31–34 Palladium dissociation from the double bond and deprotonation by the base to yield the 1,3-diene is slowed by this process. The cationic Heck mechanism may promote reinsertion into the double bond to yield allylic complex IV (Scheme 22) due to the weakly associated triflate making palladium electron deficient. The allylic complex allows for more electron density to be shared with palladium stabilizing the cationic complex. Also, the weakly associated triflate allows palladium to have an empty coordination site (III), which allows for the double bond to associate closely with the palladium promoting reinsertion into the double bond.

Scheme 22: Cyclohexane acetate intermediate formation
Adding another acetate source was hypothesized to increase compound VI (Scheme 22)\(^{31}\); however, we\(^{35}\) found that the addition of lithium acetate to the reaction accelerated the reaction to produce the 1,3-diene (III, Scheme 23) as the major product.\(^{31,35}\) We proposed that palladium was reinserting into the freshly formed double bond in compound III, formed by the Heck cycle, to make the allylic complex IV. Acetate, from lithium acetate, can attack the allylic complex forming the acetate intermediate (VI). We hypothesized that, after the acetate intermediate forms (VI, Scheme 23), the re-insertion of palladium into the allylic C-OAc bond was happening quickly, promoting β-hydride elimination (Scheme 23, VI--\(\rightarrow\)VIII). After β-hydride elimination, the acetate group remains as a ligand on palladium (X, Scheme 23) and the palladium complex is no longer cationic. As a neutral Pd complex, it has less affinity for the newly created double bond, which in turn prevents a Pd-H 1,2-insertion from occurring to reform the stable allylic complex IV. Electron-poor metal centers bearing electron donating groups, such as compound X, react rapidly in the reductive elimination reaction (X\(\rightarrow\)XI, Scheme 23), since the ligands lose electron density as the reaction proceeds.\(^{36,37}\) Ultimately this should produce acetic acid (XI) in our reaction.

Another proposed mechanism from complex VI to produce the 1,3-diene product is that palladium may associate with the double bond on the top face of complex VI, acetate leaves, and the allylic complex can reform. Palladium may then complete a β-hydride elimination to make complex III and then dissociate from the product. We are currently unsure which mechanism dominates to reform the 1,3-diene from the acetate intermediate based upon our prior mechanistic study in Table 17 where it appears that the acetate intermediate forms quickly and then eventually is consumed to produce the 1,3-diene with extended reaction times.
**Figure 9: Acetate Intermediate**

**Scheme 23:** Acetate intermediate reaction sequence.
Using similar conditions to Table 16, with the addition of lithium acetate, good to excellent yields were obtained for compounds 69 to 77. Enantiomeric ratios improved with the addition of lithium acetate from Table 16. This contradicts our past research\textsuperscript{6,9} and the literature\textsuperscript{38}, which hinted that the cationic cycle could lead to the best e.r. values for our compounds. While we do not have a definitive reason as to why enantiomeric ratios were improved, a theory is that additional acetate in solution may promote an anionic Heck mechanism. Amatore and Jutand were the first to report an anionic Heck mechanism promoted by acetate in 2000.\textsuperscript{39} They proposed that an anionic palladium complex required less equilibration before the 1,2-insertion step than the cationic palladium complex to make the aryl group and the alkene cis- to one another for insertion to occur. This increased the rate of insertion and improved enantioselectivities, which prompted us to consider an anionic mechanism for our new set of reaction conditions.

When the benzyl derivative was run with Pd(TFA)\textsubscript{2} to eliminate acetate from the reaction and to ensure a cationic palladium complex in the reaction, 65\% of the product was isolated which had an e.r. value of 10:1, entry 1. The difference between using Pd(TFA)\textsubscript{2} and Pd(OAc)\textsubscript{2} was minimal for the benzyl derivative (entry 2), which had an e.r. value of 9:1 without lithium acetate added. This indicates that the cationic complex may not have as much of an effect on the enantioselectivity as we originally proposed. When lithium acetate was added to the reaction, the enantioselectivity of the benzyl derivative was increased to 11:1 in entry 2, which also indicates that the cationic complex may not be the key to higher enantioselectivities.

Continuing our analysis, benzyl derivatives 69 and 70 had the same e.r. values; however, the yield of compound 70 was low in Table 18 compared to compound 69. Potentially cyanide could coordinate to palladium, which could hinder the reaction leading to a lower yield. This is
not the case with the acetonitrile derivative in entry 4; however, the enantiomeric ratio is lower. Cyanide coordination to the palladium directly participating in the Heck reaction could affect the enantioselectivity versus compound 70. The isobutyl derivative unsurprisingly had a lower e.r. due to the group’s bulkiness interfering with PdL$_2$ from accessing the appropriate configuration, entry 5. Similar results for the cyclohexane derivative (entry 6) and the naphthalene derivative (Entry 8) occurred. Ultimately, the size of the R-group could have an impact on the enantioselectivity. For example, the methyl derivate had an e.r. of 12:1$^{21}$ and the ethyl derivative had an e.r. of 10:1 (not shown)$^{35}$, which are much higher than entries 4, 5, and 7. Using MOM as an R group proved beneficial for the Heck reaction due to a high e.r. of 20:1, which is one of the highest e.r. values achieved using our reaction conditions. The results in the table indicate that both size of the compound and functionalized groups may have an impact on the enantioselectivity of the Heck reaction. R groups that were sterically hindered lead to lower e.r. values while relatively unhindered R-groups lead to higher e.r. values. R-groups that could competitively bind to palladium also hindered the e.r. values. Interesting reactivity was found when we analyzed the butene derivatives Heck products. When 3-butene as an R-group was subjected to Heck reaction conditions, two different products were found in the GC. The first peak, at 13.8 min, was due to the 1,3-diene product (compound 76) and the second peak, at 14.8 min, was due to an unusual cyclized product (77). When the Heck reaction was run without lithium acetate, the cyclized product was the major product (54% isolated product). When lithium acetate was used, the 1,3-diene product was the major product (55% isolated product). When these products were analyzed using chiral HPLC, the 1,3-diene, in entry 8, had a significantly lower e.r. value than the cyclized product, entry 9. The additional cyclization traps the ring in a specific formation, which likely increases the enantioselectivity.
Table 18: Mizoroki-Heck reaction conditions to make N-Me phenanthridinone derivatives with LiOAc additive.

![Reagents and conditions](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Isolated Yield (%)</th>
<th>e.r.</th>
<th>ee (%)</th>
<th>e.r. without LiOAc</th>
<th>Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a,e</td>
<td>CH$_2$Ph</td>
<td>65</td>
<td>n/a</td>
<td>n/a</td>
<td>10:1</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>CH$_2$Ph</td>
<td>92</td>
<td>11:1</td>
<td>83</td>
<td>9:1</td>
<td>69</td>
</tr>
<tr>
<td>3</td>
<td>CH$_2$Ph(3-CN)</td>
<td>57</td>
<td>11:1</td>
<td>83</td>
<td>n/a</td>
<td>70</td>
</tr>
<tr>
<td>4a</td>
<td>CH$_2$CN</td>
<td>97</td>
<td>8:1</td>
<td>81</td>
<td>8:1</td>
<td>71</td>
</tr>
<tr>
<td>5</td>
<td>Isobutyl</td>
<td>83</td>
<td>7:1</td>
<td>76</td>
<td>n/a</td>
<td>72</td>
</tr>
<tr>
<td>6</td>
<td>C$<em>6$H$</em>{11}$Cyclohexane</td>
<td>59</td>
<td>6:1</td>
<td>70</td>
<td>3:1</td>
<td>73</td>
</tr>
<tr>
<td>7b</td>
<td>CH$_2$OCH$_3$</td>
<td>88</td>
<td>20:1</td>
<td>91</td>
<td>n/a</td>
<td>74</td>
</tr>
<tr>
<td>8</td>
<td>CH$_2$H$_2$N$_2$Naphthalene</td>
<td>65</td>
<td>8:1</td>
<td>79</td>
<td>7:1</td>
<td>75</td>
</tr>
<tr>
<td>9b</td>
<td>CH$_2$CH$_2$CH=CH$_2$</td>
<td>55</td>
<td>12:1</td>
<td>62</td>
<td>8:1</td>
<td>76</td>
</tr>
<tr>
<td>10</td>
<td>Cyclized butene product</td>
<td>14</td>
<td>14:1</td>
<td>87</td>
<td>42:1$^d$</td>
<td>77</td>
</tr>
</tbody>
</table>

* No LiOAc was used. $^a$ 10 mol % Pd(OAc)$_2$, 14 mol % R-BINAP. $^b$ HPLC has three peaks. $^c$ The peaks in the HPLC were not entirely resolved which is why this number may be elevated. $^d$ Pd(TFA)$_2$ was used instead of Pd(OAc)$_2$.

Figure 10: Butene Heck products

NMR data such as proton, C13APT, COSY, and HSQC were run in attempts to determine the structure of the isolated cyclized product; however, we were unable to elucidate the structure. Fortunately, we were able to grow crystals of the cyclized product and an x-ray crystal structure was obtained, which confirmed the product’s configuration and stereochemistry at the chiral centers, Figure 11.
The proposed mechanism for the cyclization process is shown in Scheme 25. There are various potential reaction pathways for this transformation; however, we believe an allylic complex might be the key to the cyclized product based upon our lithium acetate studies. Nonetheless, the mechanism of this reaction is complex due to the proton on C13 (Figure 11) coming forward. This indicates that palladium would have to be on the backside of the complex in order for this to happen. When palladium forms the allylic complex, it should remain on the top face of our compound. This is demonstrated by the addition of acetate to the opposite face of our compounds, which was confirmed by Dr. Malachowski using NOESY NMR, which did not have a coupling between the proton attached to the same carbon as the acetate and the benzylic hydrogen (VI, Scheme 23). This is in agreement with Larock and Han’s work where they indicated that acetate, as a soft nucleophile, should add to the opposite face of the molecule to where palladium is attached.
After helpful conversations with Dr. Patrick Walsh at the University of Pennsylvania, we propose that the cyclized product is forming via the complex mechanism reported in Scheme 25. When lithium acetate is present in solution, acetate attacks the allylic complex to form the acetate intermediate (XI, Scheme 25) via the pathway marked in dark blue. Then, palladium can insert into the C-O bond and proceed via the mechanism reported in Scheme 23 to generate the 1,3-diene. There is not a vacant site on palladium, when acetate is attached, to coordinate with the alkene leading to more 1,3-diene (77) being produced. In addition, this process makes palladium uninterested in the less electron-donating alkene from butene. Without lithium acetate, the 5-membered ring forms as the major product (VIII, Scheme 25). This occurs using many ligand exchanges for palladium to be guided to the back-side of the complex by the butenyl group’s alkene. Then, another series of ligand exchanges allows for palladium to be in position to reinsert into the olefin in complex IV (Scheme 25) to create the allylic complex. Carbocyyclization\textsuperscript{33} of the allylic complex with the alkene bond forms a 5-membered ring, complex VI. Finally, β-hydride elimination, then dissociation of the compound from palladium produces compound VIII. These results support the hypothesis that the allylic complex is a resting state in the reaction due to the cyclized product forming selectively when lithium acetate was not present. This provided a second example of a reaction that intercepts the allylic complex.
3.5 Removal of methyl group from amide nitrogen on Heck product

Since we could not directly use a secondary amide in the Heck reaction, we decided to take our tertiary amide Heck products and remove the methyl group to provide the desired NH phenanthridinone analogs. Aluminum chloride has been used as a mild reagent to remove methyl groups from ethers and aryl methyl ethers.\textsuperscript{40-42} However, our attempts to remove the methyl group using aluminum chloride failed to produce the desired phenanthridinone (N-H) analogs.
### Table 19: Removal of methyl group using aluminum chloride

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temp (˚C)</th>
<th>Time</th>
<th>A (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>B (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Other (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Toluene</td>
<td>23</td>
<td>20 h 30 min</td>
<td>-</td>
<td>-</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>85</td>
<td>18 h 22 min</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>CPME</td>
<td>23</td>
<td>20 h 30 min</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>CPME</td>
<td>85</td>
<td>22 h 30 min</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Toluene</td>
<td>85</td>
<td>24 h 11 min</td>
<td>-</td>
<td>-</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>N,N-dimethylaniline</td>
<td>85</td>
<td>76 h 24 min</td>
<td>-</td>
<td>-</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>Anisole</td>
<td>85</td>
<td>48 h 43 min</td>
<td>-</td>
<td>-</td>
<td>100</td>
</tr>
</tbody>
</table>

<sup>a</sup> Values reported are GC yields  
<sup>b</sup> Inconclusive Results

In all of the reaction conditions, either no reaction occurred, or undesired side products were formed. Due to minimal examples of demethylation of tertiary amides in the literature<sup>43-45</sup>, failed alternative methods by other group members<sup>6,35</sup>, and these disappointing results, we decided to attempt a protection/deprotection protocol of the amide to produce the desired phenanthridinone analogs.

### 3.6 MOM protection/deprotection protocol to produce (N-H) phenanthridinone analogs

Qin et al. had published a paper on structurally simple phenanthridine analogs in which they synthesized both N-MOM (methoxymethyl) and N-PMB (p-methoxybenzyl) protected phenanthridinone derivatives as intermediates in their reaction sequence.<sup>46</sup> They provided examples of the deprotection of a PMB group and a lithium aluminum hydride (LAH) reduction of the N-MOM benzamides of phenanthridinones on the path to phenanthridine derivatives. This publication proved that benzamides could undergo a protection/deprotection protocol successfully. This prompted us to investigate our secondary benzamides’ MOM protection/deprotection protocol to produce the desired N-H phenanthridinone analogs using the procedure outlined by Qin et al. as shown in Figure 12.
Figure 12: Protection of secondary benzamide

In the reaction, sodium hydride was used to deprotonate the secondary benzamide and then the resulting amide anion was treated with methyl chloromethyl ether (MOM-Cl). Good yields of compounds 79 and 80 were isolated by column chromatography. When these compounds were subjected to the standard Mizoroki-Heck reaction conditions, the yields and enantiomeric ratios were similar to the N(Me) derivatives, Table 20. Lithium acetate was utilized for the benzyl derivative 81 because it decreased reaction time to 24 hours rather than 48 hours. The acetonitrile derivative 82 did not use lithium acetate because it was found to hinder the Mizoroki-Heck reaction and led to the production of the rearomatized side product with the triflate group reductively cleaved in addition to the desired product.

Table 20: Mom protected phenanthridinone derivatives

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield</th>
<th>e.r.</th>
<th>ee (%)</th>
<th>Compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>-CH₂Ph</td>
<td>81%</td>
<td>12:1</td>
<td>84%</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>-CH₂CN</td>
<td>73%</td>
<td>10:1</td>
<td>81%</td>
<td>82</td>
</tr>
</tbody>
</table>

*2.0 eq LiOAc

With the desired MOM protected products in hand, we then attempted various reaction conditions to try to remove the MOM group. First, we attempted to use various concentrations of
hydrochloric acid in methanol, which is a common method for deprotecting MOM groups.\textsuperscript{47,48} Concentrated hydrochloric acid was attempted by stirring at room temperature overnight, and only starting material remained. Heating the solutions to 62°C for 4 hours did not change the reactivity. Another method was attempted by slowly adding trifluoroacetic acid (TFA) to the Heck product and heating the reaction to 70°C overnight.\textsuperscript{46} This also failed to promote MOM group deprotection.

Since the other deprotection strategies did not work, we attempted conditions reported by Fukuyama and Liu in their work on the stereocontrolled total synthesis of (±)-gelsemine.\textsuperscript{49} Their deprotection protocol worked well for the benzyl derivative producing the secondary benzamide product with a matching enantiomeric ratio to the N-Me phenanthridinone analog. The deprotection of the acetonitrile derivative was not attempted due to time constraints on finishing this research. Finally, we were able to access secondary benzamides, which were previously unable to be synthesized.

![chemical structure](image)

**Figure 13:** MOM deprotection using Fukuyama and Liu’s procedure

### 3.7 Conclusions

In conclusion, we were able to synthesize chiral phenanthridinone analogs using the Birch-Heck sequence. The Birch reduction/alkylation is a facile way of producing quaternary centers in high yields. Tertiary amide triflates (60-69) formed atropisomers which were characterized using high-temperature NMR to equilibrate the isomers and coalesce the NMR
proton, carbon and fluorine signals. As stated previously, atropisomers introduce the potential for kinetic resolution in the Heck reaction\textsuperscript{11}, but we overcame that complication by heating the reactions at elevated temperatures to allow for atropisomer equilibration during the reaction.\textsuperscript{12} The Mizoroki-Heck reaction was accomplished with good to excellent yields and good to excellent enantiomeric ratios when lithium acetate was used. We discovered that an allylic complex forms when the palladium reinserts into the olefin after β-hydride elimination in our reaction. This allylic complex is proposed to be a resting state, which can then undergo nucleophilic addition or a 1,2-insertion. Nucleophilic addition of an acetate group leads to the 1,3-diene being produced at a faster rate and with higher e.r. values. Acetate, as the nucleophile, may help to push or extract palladium out of the energy low and to move the cycle forward. Acetate may also contribute to an anionic Heck cycle, which was found in the literature to increase the rate at the 1,2-insertion step and increase enantioselectivities when compared to the cationic cycle.\textsuperscript{39}

Further analysis of the various compounds synthesized indicated that R groups that were sterically hindered led to lower e.r. values while relatively unhindered R-groups led to higher e.r. values. R-groups that could competitively bind to palladium also hindered the e.r. values. An important discovery of a tandem Mizoroki-Heck reaction/cyclization via a 1,2-insertion led to an increase in the e.r. value for the butene derivative. This proves that additional functionalization of the 1,3-diene is possible and may lead to future endeavors.

Several important conclusions about the (N-H) phenanthridinone derivative were discovered in this research. First, secondary benzamides will not produce the desired phenanthridinone products under similar reaction conditions used for the tertiary benzamides. Second, using xantphos G3 as a precatalyst like the research presented in Chapter 2, section 6
did not produce the Heck product. Third, removing the methyl group from the nitrogen on the Heck product proved challenging, and aluminum chloride yielded none of the desired product. Finally, the MOM protection/deprotection protocol successfully produced the N-H phenanthridinone analog for the benzyl derivative with a matching enantiomeric ratio to the N-Me analog. Deprotection procedures using standard conditions in the literature such as using concentrated HCl in methanol or TFA did not deprotect the MOM group, which is why we had to use a more involved procedure reported by Fukuyama and Liu.49

Future research using this work should explore other derivatives using the MOM protection/deprotection on a larger scale. The acetonitrile derivative should also be deprotected. This opens doors in our research in both the palladium Heck project and the nickel Heck project to produce potentially bioactive compounds. The bioactivity of both the N-H and N-Me phenanthridinone analogs will be explored with our biological collaborators at Lankenau Institute of Medical Research.

3.8 References
6. Krasley, A. T. Exploration of Synthetic Pathways to Quaternary Carbon Stereocenters and


CHAPTER 4

The Birch-Heck Sequence Catalyzed by Nickel

Desrosiers and coworkers presented the first enantioselective intramolecular nickel-catalyzed Mizoroki-Heck coupling to generate quaternary stereocenters using a nickel precatalyst.\(^1\) They were able to successfully synthesize 3,3’-disubstituted oxindoles with quaternary stereocenters in good to excellent yields. However, Yang, Jin, and Wang’s work on synthesizing a variety of benzene-fused cyclic compounds bearing a quaternary stereogenic center in a highly enantioselective manner inspired us to investigate nickel as a catalyst.\(^2\) Both of these examples utilize an enantioselective Heck reaction with internal alkenes to form bicyclic structures with high enantioselectivities using relatively mild conditions. Switching to nickel from palladium could have several benefits such as making our research more cost-effective, increasing the rate of the reaction, and allowing for more mild reaction conditions to be utilized. In addition, we had hoped that our enantioselectivities would improve based upon the promising research on the enantioselective intramolecular Mizoroki-Heck reactions presented in the literature and in Chapter 3.\(^1-11\)

Srydstrup et al.\(^12\), Watson et al.\(^13\), and Jamison et al.\(^14\) reported on the use of Ni(0) catalyst precursors combined with aryl triflates or pivalates in the Mizoroki-Heck reaction using a cationic mechanism. Their conditions were limited due to Ni(0) complex’s high sensitivity to air and moisture and the need for electron-rich alkenes. As reported, the most successful reaction conditions required a combination of a Ni(II) catalyst precursor with an external reductant such as zinc or manganese.\(^13,15,16\) This procedure allowed for milder reaction conditions and facilitated the cross-coupling of both electron-rich and poor alkenes, which we desired for our compounds.
Due to the success with our palladium research using a cationic Heck mechanism, we began to wonder if the same was true for nickel. Desrosiers and coworkers investigated both the cationic and neutral pathways for the nickel-catalyzed Mizoroki Heck reaction, Figure 14.\textsuperscript{1,17} When they attempted reaction conditions that promoted a cationic pathway, only a 17\% yield of the desired oxindole was produced with poor enantioselectivity. Neutral pathway conditions significantly improved the yield and enantioselectivity. Having an exogeneous halide source, 50 mol \% of LiI, was found to maintain the high level of conversion while also improving the enantioselectivity at 60\°C. Overman and coworkers also observed improved selectivity in the neutral pathway when halide salts were added.\textsuperscript{18} For these reasons, the focus of our research utilized Ar-Br rather than Ar-OTf to promote a neutral pathway. In addition, we explored the use of halide salts to improve the reactivity of our reported conditions.

**Figure 14:** Comparison of cationic and neutral nickel-catalyzed Mizoroki-Heck reaction\textsuperscript{17}

### 4.1 Nickel as a precatalyst

Using Desrosiers and coworker’s studies\textsuperscript{1} as a starting point, we set out to investigate nickel precatalysts in the Mizoroki-Heck reaction to form the desired phenanthridinone analogs. We began by using the reaction conditions from Desrosiers and coworkers; however, we ran the reaction at 55\°C (Table 21, entry 1). To our delight, there was a peak with the corresponding mass of the 1,3-diene. Unfortunately, many side products constituted the majority of material in the crude product’s GC. With the promising results of forming the 1,3-diene, we decided to
optimize the nickel-catalyzed Heck reaction. If successful, then it would represent, to our knowledge, the first example of an intramolecular enantioselective Heck reaction to generate tricyclic structures using nickel catalysis.1–11

Table 21: Nickel precatalysts in the Mizoroki-Heck reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ni Precatalyst</th>
<th>LiI eq</th>
<th>Time</th>
<th>A (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>B (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>C (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>D (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>E (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>F (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NiCl₂(R,R-QuinoxP*)</td>
<td>0.5</td>
<td>44 h 26 min</td>
<td>8</td>
<td>12</td>
<td>37</td>
<td>38</td>
<td>13</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>NiCl₂(R,R-QuinoxP*)</td>
<td>0.5</td>
<td>15 h 26 min</td>
<td>52</td>
<td>11</td>
<td>8</td>
<td>13</td>
<td>17</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>(DPEPhos)Ni(o-toly)Cl</td>
<td>0.5</td>
<td>16 h 39 min</td>
<td>89</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>(XantPhos)Ni(o-toly)Cl</td>
<td>0.5</td>
<td>23 h 44 min</td>
<td>65</td>
<td>14</td>
<td>11</td>
<td>-</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>(dppe)Ni(o-toly)Cl</td>
<td>0.5</td>
<td>16 h 8 min</td>
<td>93</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>(dppe)Ni(o-toly)Cl</td>
<td>0.5</td>
<td>21 h 16 min</td>
<td>-</td>
<td>36</td>
<td>25</td>
<td>trace</td>
<td>-</td>
<td>40</td>
</tr>
<tr>
<td>7</td>
<td>(dppe)Ni(o-toly)Cl</td>
<td>0.5</td>
<td>21 h 45 min</td>
<td>-</td>
<td>32</td>
<td>25</td>
<td>23</td>
<td>21</td>
<td>trace</td>
</tr>
<tr>
<td>8&lt;sup&gt;c&lt;/sup&gt;</td>
<td>(dppe)Ni(o-toly)Cl</td>
<td>1</td>
<td>21 h 45 min</td>
<td>-</td>
<td>37</td>
<td>26</td>
<td>trace</td>
<td>37</td>
<td>-</td>
</tr>
<tr>
<td>9&lt;sup&gt;d&lt;/sup&gt;</td>
<td>(dppe)Ni(o-toly)Cl</td>
<td>1</td>
<td>21 h 45 min</td>
<td>-</td>
<td>37</td>
<td>26</td>
<td>trace</td>
<td>37</td>
<td>-</td>
</tr>
<tr>
<td>10&lt;sup&gt;d&lt;/sup&gt;</td>
<td>(dppe)Ni(o-toly)Cl</td>
<td>1</td>
<td>96 h 25 min</td>
<td>83</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>7</td>
<td>-</td>
</tr>
<tr>
<td>11&lt;sup&gt;e&lt;/sup&gt;</td>
<td>(dppe)Ni(o-toly)Cl</td>
<td>1</td>
<td>24 hr 35 min</td>
<td>95</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup>Values from GC. <sup>b</sup>Reaction run at 55°C. <sup>c</sup>No base used. <sup>d</sup>Zn used instead of Mn as reducing agent. <sup>e</sup>NH instead of N(Me).

Repeating the reaction conditions from entry 1 at 80°C for less time yielded about the same amount of B as entry 1 with less side products C-F; however, there was an abundance of starting material left. The R, R-QuinoxP* ligand was expensive (100 mg = $141 from Sigma-Aldrich, 4/8/2021); therefore, we only had a small amount of synthesized precatalyst to use. We decided to explore non-chiral nickel precatalysts that were available in our lab in entries 3-11. At
the time, we wanted to ensure the production of 1,3-diene Heck product while also gaining insight into the types of ligands that should be investigated using nickel precatalysts without using up the expensive chiral precatalyst. Out of the various precatalysts explored in entries 3-6, (dpff)Ni(o-tolyl)Cl had the best results producing minimal side products and 36% of the 1,3-diene, entry 7. Analysis of the precatalysts showed that flexible ligands were unsuccessful, which is why DPEPhos and dppe failed. R,R-QuinoxP* has bulky tert-butyl groups attached to the phosphines, which may block the substrate from getting close to nickel versus sterically unhindered dpff. Most importantly, from these reactions, we discovered that ridged ligands, such as R,R-QuinoxP*, xantphos, and dpff, showed a small formation of compound C. Ultimately with the high cost of the chiral ligand and no conditions that ultimately improved the synthesis of the 1,3 diene, we chose to explore other reaction conditions.

4.2 Heck reaction using a nickel salt and pyox ligand

Yang, Jin, and Wang reported on the nickel-catalyzed asymmetric intramolecular reductive Heck reaction of unactivated alkenes. As discussed prior, reductive Heck reactions may be favorable for nickel due to nickel’s affinity for slow β-hydride eliminations. From their research, we learned the importance of using pyox ligands with nickel. The nitrogen atom of the pyridine ring is electron-poor, increasing the rate of the reduction of nickel. The nitrogen of the oxazoline ring is electron-rich, which can help promote oxidative addition. This balance is optimal for the Heck reaction where some steps require the metal to be electron-rich, and others need the metal to be electron-poor. In addition, 100 mg of (S)-tert-Butyl-2-(2-pyridyl)oxazoline is eight times less expensive than R,R-QuinoxP*. We attempted to utilize Yin, Jin, and Wang’s reaction conditions with our substrates; however, we had disappointing results. The poor results were attributed to either the polar protic solvent or water in the nickel salt acting in polar aprotic
solvants as proton sources, which promoted protodehalogenation of the starting material.\textsuperscript{20} Wang et. al. had proposed that the isopropanol in their reaction protonates the Ni-alkyl complex after 1,2-insertion; however, in our reaction, aryl-nickel protonation was faster than the 1,2-insertion. Both polar protic and polar aprotic solvents were investigated using the nickel salt in Table 22. Out of all of the reaction conditions screened in Table 22, none of them produced cyclized product. Either the reaction returned unreacted starting material or produced compounds E and F.

Table 22: Ni(BF\textsubscript{4})\textsubscript{2}·6H\textsubscript{2}O with a pyox ligand to catalyze the Mizoroki-Heck reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nickel Eq.</th>
<th>Ligand eq.</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Temp (˚C)</th>
<th>A (%)\textsuperscript{a}</th>
<th>B (%)\textsuperscript{a}</th>
<th>C (%)\textsuperscript{a}</th>
<th>D (%)\textsuperscript{a}</th>
<th>E (%)\textsuperscript{a}</th>
<th>F (%)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.15</td>
<td>0.15</td>
<td>iPrOH</td>
<td>22</td>
<td>55</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>0.05</td>
<td>0.05</td>
<td>iPrOH</td>
<td>17</td>
<td>55</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>0.15</td>
<td>0.15</td>
<td>DMF</td>
<td>17</td>
<td>55</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>0.15</td>
<td>0.15</td>
<td>DMF</td>
<td>27</td>
<td>80</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>92</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>0.15</td>
<td>0.15</td>
<td>DMSO</td>
<td>17</td>
<td>55</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>99</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>0.15</td>
<td>0.15</td>
<td>iPrOH</td>
<td>27</td>
<td>80</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>95</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>0.15</td>
<td>0.15</td>
<td>CPME</td>
<td>49</td>
<td>55</td>
<td>83</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Values from GC

Eliminating proton sources was our logical next step. We switched to using NiCl\textsubscript{2}, which was readily available, is cheap, and has shown reactivity in catalyzing reactions.\textsuperscript{21–23} Shown in
Table 23 are the reaction conditions screened for the benzyl derivative using NiCl$_2$ and the pyox ligand. Lower temperatures were initially attempted due to Desrosiers and coworker's studies which showed great reactivity at 60°C.\(^1\) When the reaction was run at 55 °C, the reaction went to completion; however, primarily protodebrominated product E was present with small amounts of B and C in the GC. The low amounts of compound B indicate that the amount of energy in the reaction is not enough to overcome the barrier for 1,2-insertion to close the ring and to overcome the barrier to β-hydride elimination. Compared to palladium, nickel is known to be faster at oxidative additions\(^2^4\) and 1,2-insertions\(^2^4\), but is significantly slower at β-hydride eliminations.\(^2^4\) Nickel has a low reduction potential and electronegativity; consequently, oxidative addition occurs readily and reduction of the metal is hindered.\(^2^5\) Also, β-hydride eliminations are slower due to nickel being smaller than palladium, which leads to poor orbital overlap with the σ* of the C-H bond.\(^2^4\) Higher temperatures should help overcome the activation energy necessary for these reactions to occur; however, this does not help to explain the high amount of protodebrominated product at low temperatures.\(^2^6^-^2^8\)

Without an outside proton source in the reaction, we proposed that Ni-H, formed from β-hydride elimination, could be used to produce compounds C and E. Nickel should complete the catalytic cycle; however, it may not be reduced to Ni(0) by zinc. Instead, it can oxidatively add into another Ar-Br bond and then reductively eliminate to produce compound E. Due to the high amount of protodebrominated product, Ni-H could not be the only path to produce E. Another possibility is that nickel is inserting into the Ar-Br bond, and then compound E is being generated in the standard workup conditions. Higher temperatures should help overcome the activation energy necessary for the 1,2-insertion and the β-hydride elimination to occur, which should decrease the amounts of E and F produced.\(^2^6^-^2^8\) By increasing the temperature in entries
2-5, we were able to limit the amount of protodebrominated product formed, improve the yield of compound B, and decrease the reaction time to 10 minutes. This the fastest reaction time that we have to date of running Heck reactions.\textsuperscript{29,30} When the temperature was raised to 150°C, the reaction stalled potentially due to the temperature being too close to the boiling point of DMF. The best reaction conditions are listed in entry 4, where the reaction was run at 120 °C for 10 minutes.

**Table 23:** NiCl\(_2\) in the Mizoroki-Heck reaction. Initial conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>LiI Eq.</th>
<th>Time</th>
<th>Temp (°C)</th>
<th>A (%)(^a)</th>
<th>B (%)(^a)</th>
<th>C (%)(^a)</th>
<th>D (%)(^a)</th>
<th>E (%)(^a)</th>
<th>F (%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^d)</td>
<td>LiI</td>
<td>1</td>
<td>23h 47 min</td>
<td>55</td>
<td>-</td>
<td>11</td>
<td>16</td>
<td>-</td>
<td>61</td>
<td>12</td>
</tr>
<tr>
<td>2(^d)</td>
<td>LiI</td>
<td>1</td>
<td>15 h</td>
<td>80</td>
<td>-</td>
<td>41</td>
<td>48</td>
<td>-</td>
<td>11</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>LiI</td>
<td>1</td>
<td>10 min</td>
<td>100</td>
<td>-</td>
<td>47</td>
<td>49</td>
<td>-</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>LiI</td>
<td>1</td>
<td>10 min</td>
<td>120</td>
<td>-</td>
<td>48</td>
<td>49</td>
<td>-</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>LiI</td>
<td>1</td>
<td>21 h 9 min</td>
<td>150</td>
<td>77</td>
<td>3</td>
<td>1</td>
<td>14</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>6(^b,d)</td>
<td>LiI</td>
<td>0.5</td>
<td>23 h 45 min</td>
<td>55</td>
<td>59</td>
<td>4</td>
<td>5</td>
<td>-</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>7(^c)</td>
<td>LiI</td>
<td>1</td>
<td>18 h 26 min</td>
<td>120</td>
<td>50</td>
<td>20</td>
<td>24</td>
<td>-</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>LiI</td>
<td>-</td>
<td>10 min</td>
<td>120</td>
<td>-</td>
<td>40</td>
<td>49</td>
<td>-</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>LiI</td>
<td>1</td>
<td>10 min</td>
<td>120</td>
<td>-</td>
<td>48</td>
<td>49</td>
<td>-</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>LiBr</td>
<td>1</td>
<td>18 h 45 min</td>
<td>120</td>
<td>91</td>
<td>3</td>
<td>3</td>
<td>-</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>KI</td>
<td>1</td>
<td>10 min</td>
<td>120</td>
<td>-</td>
<td>43</td>
<td>56</td>
<td>-</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>12(^e)</td>
<td>KI</td>
<td>1</td>
<td>10 min</td>
<td>120</td>
<td>-</td>
<td>29</td>
<td>50</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^a\) Values from GC. \(^b\) Manganese is the reducing agent. \(^c\) 3.0 eq Na\(_2\)CO\(_3\). \(^d\) 1 hour ligand association occurred before placing the vial in the pie reactor. \(^e\) 1.0 eq. 18-crown-6

Next, we moved onto the investigation of additives to improve reactivity. When we were still exploring lower temperatures, manganese was used instead of zinc to reduce nickel, entry 6. Starting material was the major species in the GC, which indicated that manganese was inferior
to zinc, entry 1, as a reductant for our reaction. Sodium carbonate, a weak base, was added in entry 7 to sequester protons in solution, limiting protodehalogenation, and to participate in the $\beta$-hydride elimination if nickel could not access the $\beta$-hydrogen. However, the reaction stalled, and equal amounts of compounds B and C were produced.

Desrosiers et. al. and Overman et. al. both reported on the addition of exogenous halides to improve yields and enantioselectivity of their products through the promotion of a neutral Heck mechanism.$^{1,18}$ The necessity of adding LiI was probed in entries 8 and 9. When LiI was not present in the reaction, entry 8, there was about four times more of the protodebrominated product present than in the reaction with LiI added, entry 9. Our results made us question the purpose of the halide salt in our reaction because prior literature explanations of keeping a neutral cycle did not explain why protodehalogenation was hindered. Another function of exogeneous halide sources was discussed by Wang and coworkers when they also experienced increased reactivity when iodide sources were added into their nickel catalyzed reactions.$^9$ They cited Colon and Kelsey’s investigation into the kinetic effect of the added halide salts on nickel-catalyzed coupling of aryl chlorides with excess reducing metal.$^{31}$ Colon and Kelsey’s studies showed that halide salts accelerated the reduction of NiCl$_2$ to active catalyst in the sequence I$>$Br$>$Cl$>$ no salt$^{31}$ They proposed that the added halide associates to nickel to make a pentacoordinate nickelate complex, which can form a bridged Zn complex to facilitate electron transfer. In addition, halogen exchange was not supported by their data because neither bromobenzene nor iodobenzene were detected in the presence of added halide salts. Added halogens that act as bridging ligands in the reduction of nickel by zinc could explain the role of lithium iodide in our reaction, since halogen exchanged starting material was not present in our GC data.
Based on the success of lithium iodide in minimizing the protodehalogenation side reaction, we decided to explore different metal halide additives. Lithium bromide, entry 2, hindered the reaction, with starting material being the major species in the GC. Excess bromide in solution might force equilibration of the reaction towards the starting material. Potassium iodide, the most ionic halide salt, was the best additive to limit the amount of protodehalogenated product (E), entry 3. To make the iodide more reactive, we used 1.0 eq of 18-crown-6 in entry 4 to sequester the potassium. This change to the conditions eliminated the protodehalogenated product; however, it led to more over-reduced product C. While it is not clear how the halide improves our reaction, we can confirm that the iodide interferes with the production of the protodehalogenated product. With the optimized temperature and halide additive in hand, we decided to explore different ligands in attempts to produce the 1,3-diene selectively.

4.3 Exploration of cationic vs. neutral pathway

To confirm our suspicions from Desrosiers et.al.’s work, we also ran experiments with Ar-Br and Ar-OTf to probe a neutral vs. cationic pathway. Switching the ligand from pyox to 2,2’-bipyridine yielded similar results to the pyox ligand with using a neutral pathway, entry 1. Although these results were not an improvement on the conditions reported in Table 23, the bipyridine ligand had comparable results to the pyox ligand and was more cost-efficient, so it was used in subsequent reaction screening. Next, we attempted to use racemic BINAP and the triflate precursor due to their success in our palladium research; however, the reaction failed and only had starting material and compound F. BINAP may be too bulky with nickel for oxidative
addition and the 1,2 insertion to occur. Nickel is smaller than palladium, so more cumbersome ligands may shield the substrate from the catalyst. We also attempted to use aryl triflate starting material instead of aryl bromide with the pyox ligand; however, the reaction failed to produce cyclized product.

**Table 24: Ligand screening: cationic vs. neutral pathway**

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Nickel Eq.</th>
<th>Ligand</th>
<th>Ligand eq.</th>
<th>Time</th>
<th>Temp.</th>
<th>A (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>B (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>C (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>D (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>E (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>F (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>0.1</td>
<td>2,2'-bipyridine</td>
<td>0.1</td>
<td>10 min</td>
<td>120</td>
<td>-</td>
<td>41</td>
<td>44</td>
<td>-</td>
<td>-</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>OTf</td>
<td>0.15</td>
<td>rac-BINAP</td>
<td>0.15</td>
<td>19 h 21 min</td>
<td>55</td>
<td>57</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>43</td>
</tr>
<tr>
<td>3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>OTf</td>
<td>0.1</td>
<td>pyox</td>
<td>0.1</td>
<td>10 min</td>
<td>120</td>
<td>93</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>7</td>
</tr>
</tbody>
</table>

<sup>a</sup> Values from GC  
<sup>b</sup> 1 h ligand association  
<sup>c</sup> No KI

These results confirmed that a neutral pathway is required for our precursors to progress through the Mizoroki-Heck reaction to produce cyclized products. Research in optimization of the ligand is still occurring in our lab. One of the critical parts of our research is to make chiral compounds, which requires the use of chiral ligands. Other pyox-type ligands will be explored in our lab due to the promising initial results. A major issue with optimization using the benzyl derivative specifically was that compounds B and C could not be separated using column...
chromatography to be able to produce accurate HPLC data, which explains the absence of yields and e.r.’s.

4.4 Nickel Mizoroki-Heck reactions of the methyl derivative

Attempts to isolate the 1,3-diene without the over-reduced side product forming for the benzyl derivative proved difficult. We decided to analyze the methyl derivative next due to it being sterically unhindered and having great success in the palladium-catalyzed Heck reactions. First, attempts were made in entries 1 and 2 (Table 25) to utilize the benzyl derivative reaction conditions; however, the reaction was incomplete after 10 minutes. We were able to isolate compounds B (compound 84, Chapter 6, 4%) and C (compound 85, Chapter 6, 21%) from entry 1 via column chromatography and characterize them using $^1$H NMR (see experimental data in Chapter 6.3.7). Unfortunately, when we took HPLC data, the 1,3-diene had a 1:1 ratio. In the interest of further optimizing the reaction conditions for yield and efficiency, we turned to analyze the effect of halides in the reaction.

We switched the halide to iodide to eliminate one type of halide in our reaction sequence due to having Br, Cl, and I present and potentially accelerate oxidative addition. The Ar-I bond is longer than Ar-Br due to iodide having a larger atom size, which decreases the strength of the bond. When we ran the same reaction conditions with the iodide substrate, the results were similar to entry 1 with bromine, so we switched to analyzing our reaction conditions using the iodide substrate, entry 3. Increasing the amount of potassium iodide limited the amount of protodehalogenated product E but lead to an increased yield of compound D, entry 4. The reaction is possibly proceeding faster than 10 minutes due to the assisted reduction of nickel through the nickelate complex. The extra reaction time could lead to palladium-catalyzed isomerization of the alkene to the 1,4-diene, which has been witnessed in palladium-catalyzed
Heck reactions that we have conducted. Not using any potassium iodide decreased cyclized product B’s yield and increased the amount of protodehalogenated product E (entry 5), which was consistent with our data from the benzyl derivative. Switching the additive from KI to LiI increased protodehalogenated product E, entry 6, which is consistent with our data from the benzyl derivative. When we added triethylamine as a proton scavenger, entry 7, there was no effect on the reaction versus entry 4.

Table 25: Halide analysis

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>KI</th>
<th>A (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>B (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>C (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>D (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>E (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>F (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>1.0</td>
<td>-</td>
<td>51</td>
<td>32</td>
<td>17</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Br</td>
<td>1.0</td>
<td>-</td>
<td>39</td>
<td>22</td>
<td>8</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>I</td>
<td>1.0</td>
<td>-</td>
<td>52</td>
<td>32</td>
<td>13</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>I</td>
<td>3.0</td>
<td>-</td>
<td>50</td>
<td>34</td>
<td>16</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>I</td>
<td>-</td>
<td>-</td>
<td>43</td>
<td>27</td>
<td>16</td>
<td>14</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>I</td>
<td>LiI</td>
<td>2 eq</td>
<td>47</td>
<td>31</td>
<td>13</td>
<td>9</td>
<td>-</td>
</tr>
<tr>
<td>7&lt;sup&gt;d&lt;/sup&gt;</td>
<td>I</td>
<td>3.0</td>
<td>-</td>
<td>54</td>
<td>30</td>
<td>13</td>
<td>2</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> Values from GC. <sup>b</sup> 1 eq Zn. <sup>c</sup> Ni(COD). <sup>d</sup> 1.0 eq Et,N

Next, we explored various ligands that were readily available to screen using a neutral Heck cycle. Since Ni(COD)₂ and NiCl₂ had similar reactivity, this is demonstrated later on in Table 28, we used them interchangeably while attempting different reaction conditions, Table 26, entry 1. When we tried to use racemic BINAP, the reaction yielded mainly starting material, entry 2. When we utilized a quinox ligand, entry 3, less Heck product B was produced, and more of the protodehalogenated product was present. These reactions confirmed the need for
oxazoline-based ligands in our reaction. Other chiral ligands are being explored in our lab to improve the enantioselectivity as well as the yield of the 1,3-diene products.

**Table 26: Ligands attempted with the methyl derivative**

![Reaction Scheme]

With every reaction that yielded protodehalogenated product, we began to question whether the zinc was inserting into the Ar-X bond rather than nickel promoting protodehalogenation. We wanted to study the reaction without the Ni catalyst added to the solution and use deuterium as a marker to be able to produce compound B. In entry 1 (Table 27), although the reaction was incomplete, the most prominent peak at 10.4 min in the GC had a mass of 228 g/mol, which corresponds to deuterated product B. Potassium iodide does not restrict this
process as it does with the nickel catalyst present. From this experiment, we conclude that zinc functions as a reductant to nickel under our normal reaction conditions, but it can also compete with nickel to insert into the Ar-I bond and potentially lead to protodehalogenation side reactions. Also, a peak at 11.9 min had a mass of 227 g/mol, which may be due to compound D or an isomer of D. When manganese was used instead of zinc, only starting material remained, entry 3. Manganese does not insert into the aryl-halide bond, which may potentially eliminate the protodehalogenated product in our reaction. More investigation into this process needs to be done to potentially limit the zinc-enabled protodehalogenation process and investigate its impact on the reaction with nickel.

Table 27: Analysis of Zn/Mn insertion into the Ar-I

<table>
<thead>
<tr>
<th>Entry</th>
<th>D2O</th>
<th>Reductant</th>
<th>Time</th>
<th>A (%) a</th>
<th>B (%) a</th>
<th>C (%) a</th>
<th>D (%) a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5 eq</td>
<td>Zn</td>
<td>20 min</td>
<td>36</td>
<td>47</td>
<td>-</td>
<td>17</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>Zn</td>
<td>16 h 19 min</td>
<td>-</td>
<td>-</td>
<td>47</td>
<td>53</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>Mn</td>
<td>18 h 12 min</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

a Values from GC

A series of optimization conditions are shown in Table 28. The best reaction conditions are shown in entry 1, which had the most product and the least amount of side products D and E. The reaction was rerun, but no zinc was added in entry 2 to confirm that zinc was necessary in the reaction sequence. No reaction occurred, which confirmed that zinc is needed to reduce nickel chloride to be active in the reaction. When we attempted to use manganese instead of zinc, entry 3, all of the starting material was consumed, there was a minimal amount of 1,3-diene, and
the protodehalogenated product was the major product. This contradicts the results in our metal insertion study in Table 27, where manganese did not insert into the Ar-I bond to contribute to protodehalogenation. This suggests that the major path to protodehalogenation does not involve manganese or zinc and can happen with just the Ni/L catalyst. Zinc was the best reductant for our reaction sequence.

Next, we attempted to investigate NiI\textsubscript{2}, NiBr\textsubscript{2}, and Ni(COD)\textsubscript{2} in comparison to NiCl\textsubscript{2}, Table 28, entries 4-6, which would also further probe the role of halides in the reaction. Nickel chloride had the best results in entry 1; however, these reaction conditions were not run with the bromine derivative. Nickel bromide, entry 4, and nickel iodide, entry 5 had similar results to nickel chloride, so these results are inconclusive. The reaction using Ni(COD)\textsubscript{2} had 0.5 eq of nickel and 0.5 eq of ligand because Ni(COD)\textsubscript{2} is Ni(0) and does not need to be reduced, which makes it prone to degradation. Ni(COD)\textsubscript{2} had similar reactivity to NiCl\textsubscript{2} when bipyridine was used as the ligand, entry 6. More reactions need to be done to explore the effect of these nickel sources.

We decided to vary the amounts of reactants when using Ni(COD)\textsubscript{2} and bipyridine to optimize reactants’ quantities since entry 6 had similar reactivity to NiCl\textsubscript{2} and the pyox ligand in entry 1. We raised the amounts of Ni(COD)\textsubscript{2} and ligand in entries 7 and 8 and found that the conditions that were the most similar to entry 1 was when one equivalent of nickel and base was used. Next, we added zinc to the Ni(COD)\textsubscript{2} reactions to see if it was needed to reduce nickel after β-hydride elimination, to hinder protodehalogenation, and increase the reactivity of nickel. However, it increased the amount of protodehalogenated product E, entries 9-10, which is consistent with our data on zinc inserting into the aryl-halide bond. That process promotes protodehalogenation. More investigation into this process needs to be completed in the future.
Table 28: Investigation of nickel sources

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Zn Eq.</th>
<th>KI</th>
<th>Ni Source</th>
<th>Nickel Eq</th>
<th>L Eq</th>
<th>Temp (°C)</th>
<th>Time</th>
<th>A (%)</th>
<th>B (%)</th>
<th>C (%)</th>
<th>D (%)</th>
<th>E (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I</td>
<td>3</td>
<td>1</td>
<td>NiCl₂</td>
<td>0.20</td>
<td>L₁</td>
<td>120</td>
<td>10 min</td>
<td>-</td>
<td>50</td>
<td>32</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>I</td>
<td>1</td>
<td>1</td>
<td>NiCl₂</td>
<td>0.1</td>
<td>L₁</td>
<td>120</td>
<td>16 h 48 min</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>1.5</td>
<td>1</td>
<td>NiCl₂</td>
<td>0.1</td>
<td>L₁</td>
<td>120</td>
<td>26 h 22 min</td>
<td>-</td>
<td>11</td>
<td>-</td>
<td>2</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>Br</td>
<td>1.5</td>
<td>1</td>
<td>NiBr₂</td>
<td>0.20</td>
<td>L₂</td>
<td>100</td>
<td>10 min</td>
<td>-</td>
<td>52</td>
<td>18</td>
<td>9</td>
<td>21</td>
</tr>
<tr>
<td>5</td>
<td>Br</td>
<td>1.5</td>
<td>1</td>
<td>NiI₂</td>
<td>0.20</td>
<td>L₂</td>
<td>100</td>
<td>10 min</td>
<td>-</td>
<td>53</td>
<td>18</td>
<td>8</td>
<td>21</td>
</tr>
<tr>
<td>6</td>
<td>Br</td>
<td>-</td>
<td>1</td>
<td>Ni(COD)₂</td>
<td>0.5</td>
<td>L₂</td>
<td>120</td>
<td>10 min</td>
<td>-</td>
<td>49</td>
<td>10</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>7</td>
<td>Br</td>
<td>-</td>
<td>1</td>
<td>Ni(COD)₂</td>
<td>1</td>
<td>L₂</td>
<td>120</td>
<td>10 min</td>
<td>-</td>
<td>57</td>
<td>7</td>
<td>6</td>
<td>29</td>
</tr>
<tr>
<td>8</td>
<td>Br</td>
<td>-</td>
<td>1</td>
<td>Ni(COD)₂</td>
<td>1.5</td>
<td>L₂</td>
<td>120</td>
<td>10 min</td>
<td>-</td>
<td>44</td>
<td>7</td>
<td>18</td>
<td>30</td>
</tr>
<tr>
<td>9</td>
<td>Br</td>
<td>0.5</td>
<td>1</td>
<td>Ni(COD)₂</td>
<td>1</td>
<td>L₂</td>
<td>120</td>
<td>10 min</td>
<td>48</td>
<td>9</td>
<td>13</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Br</td>
<td>1.5</td>
<td>1</td>
<td>Ni(COD)₂</td>
<td>1</td>
<td>L₂</td>
<td>120</td>
<td>10 min</td>
<td>41</td>
<td>8</td>
<td>12</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Br</td>
<td>-</td>
<td>1</td>
<td>Ni(COD)₂</td>
<td>1</td>
<td>L₂</td>
<td>120</td>
<td>10 min</td>
<td>55</td>
<td>9</td>
<td>9</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Br</td>
<td>-</td>
<td>1</td>
<td>Ni(COD)₂</td>
<td>1</td>
<td>L₂</td>
<td>120</td>
<td>10 min</td>
<td>-</td>
<td>52</td>
<td>9</td>
<td>-</td>
<td>39</td>
</tr>
<tr>
<td>13</td>
<td>Br</td>
<td>1.5</td>
<td>1</td>
<td>NiCl₂</td>
<td>0.10</td>
<td>L₂</td>
<td>120</td>
<td>10 min</td>
<td>15</td>
<td>16</td>
<td>25</td>
<td>21</td>
<td>13</td>
</tr>
</tbody>
</table>

* Values from GC with 3 eq of zinc added after 10 minutes of stirring; † 1 eq K₂CO₃; ‡ 1 eq Cy₂NMe; § 2 eq NaH

In entries 11-12, we added 1 eq K₂CO₃ and 1 eq Cy₂NMe, respectively, to eliminate any protons in the reaction that could potentially lead to protodehalogenation. Unfortunately, the addition of base did not affect the outcome of the reaction significantly. Sodium hydride as a stronger base or potential proton source in entry 13 gave a messy GC with lots of side products present. Excess protons in our reaction can cause unwanted side products to form. Since we were unable to limit the amount of protodehalogenated product through variations on the components in our reaction, we investigated other sources to help limit protodehalogenation.

As discussed prior, we hypothesized that Ni-H was not getting reduced after the β-hydride elimination in the Heck sequence and was then involved in creating unwanted side products, the
over-reduced product (Table 28, C), the alkene product (Table 28, D) and the
protodehalogenated material (Table 28, E). A search in the literature about this particular
problem led us to Lv and coworkers work where they utilized a sacrificial alkene in their Heck
reaction to sequester H2 from nickel in the last step of their synthesis of arylated γ,δ- and δ,ε-
unsaturated carboxamides to regenerate Ni(0), Scheme 26.33 We hoped that by adding a
sacrificial alkene into our reactions, we could limit, or eliminate, the over-reduced product and
the protodebrominated product by trapping protons in the reaction by hydrogenation of the
alkene.

Scheme 25: Lv and coworkers oxidative Heck cycle with sacrificial alkene (S.A.)

We attempted to utilize cyclohex-2-en-1-one (S.A.1) as a sacrificial alkene to eliminate
side products C and E. At 80°C after 10 minutes with Ni(COD)2 (1 eq.) and bipyridine, all of the
starting material was consumed and 53% of the 1,3-diene was present in the GC, entry 1.
Cyclohex-2-en-1-one is sterically unhindered where the alkene is located and is polarized
towards the carbonyl group, which may contribute to it acting as a good sacrificial alkene. In
addition, we also analyzed 1,1-diphenyl ethylene (S.A.2) and trans-cinnamaldehyde (S.A.3) as
sacrificial alkenes in entries 2-3. 1,1-diphenyl ethylene, entry 2, yielded mostly protodehalogenated product (E), possibly due to the steric hindrance around the alkene. Trans-cinnamaldehyde had similar results to entry 1, which may indicate that polarized alkenes are better sacrificial alkenes for our reaction.

We then probed the reactivity of S.A.1 versus S.A.3 with nickel chloride and zinc; however, after 10 minutes, mainly starting material was present in the GC, so the temperature was increased to 100 °C, and the reaction was resumed for another 10 minutes. The reaction using S.A.1 ran to completion; however, S.A.3 did not. To analyze the sacrificial alkenes properly, we decided to run both of the reactions at 150 °C in entries 6-7. S.A.1 was the superior sacrificial alkene that limited protodehalogenation and had a high amount of compound B.

Next, we wanted to explore the best temperature for our reaction to run with (S.A.1) and KI to minimize protodehalogenation, entries 8-10. Entry 9 contained the best results achieved during this research which had the most compound B and limited side products. After optimizing the sacrificial alkene additive’s reaction conditions, we returned to explore the effect of the halide additive. Adding potassium iodide, entry 10, hindered the reaction and there was significantly less of the 1,3-diene product (B) at 150°C. Changing the additive to LiI, entry 11, or NaI, entry 12, also hindered the reaction with less of the 1,3-diene product (B) being produced than in entry 9. Raising the temperature to 150°C, near the boiling point of DMF, was not favorable for our reactions. The optimal temperature determined was 120°C that limited side products and maximized the amount of 1,3-diene formed.
Table 29: Mizoroki-Heck reaction optimization with sacrificial alkenes (S.A.)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Zn Eq.</th>
<th>KI</th>
<th>Ni Source</th>
<th>Nickel eq.</th>
<th>L eq</th>
<th>S.A.</th>
<th>Temp. (˚C)</th>
<th>Time (min)</th>
<th>A (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>B (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>C (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>D (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>E (%)&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>Ni(COD)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>80</td>
<td>10</td>
<td>-</td>
<td>53</td>
<td>22</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>LiI(1)</td>
<td>NiCl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0.2</td>
<td>0.20</td>
<td>2</td>
<td>80</td>
<td>10</td>
<td>-</td>
<td>48</td>
<td>8</td>
<td>1</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>-</td>
<td>Ni(COD)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>80</td>
<td>10</td>
<td>-</td>
<td>52</td>
<td>22</td>
<td>23</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>-</td>
<td>NiCl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0.2</td>
<td>0.20</td>
<td>1</td>
<td>80 (10min)-&lt;br&gt;100(10min)</td>
<td>20</td>
<td>-</td>
<td>45</td>
<td>20</td>
<td>13</td>
<td>21</td>
</tr>
<tr>
<td>5</td>
<td>1.5</td>
<td>-</td>
<td>NiCl&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0.2</td>
<td>0.20</td>
<td>3</td>
<td>80 (10min)-&lt;br&gt;100(10min)</td>
<td>20</td>
<td>46</td>
<td>16</td>
<td>-</td>
<td>2</td>
<td>35</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>-</td>
<td>Ni(COD)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>150</td>
<td>10</td>
<td>-</td>
<td>54</td>
<td>28</td>
<td>18</td>
<td>0.20</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>-</td>
<td>Ni(COD)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>150</td>
<td>10</td>
<td>-</td>
<td>42</td>
<td>22</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>1</td>
<td>Ni(COD)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>100</td>
<td>10</td>
<td>-</td>
<td>53</td>
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<td>19</td>
<td>7</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>1</td>
<td>Ni(COD)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>120</td>
<td>10</td>
<td>-</td>
<td>63</td>
<td>18</td>
<td>13</td>
<td>6</td>
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<tr>
<td>10</td>
<td>-</td>
<td>1</td>
<td>Ni(COD)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>150</td>
<td>10</td>
<td>-</td>
<td>36</td>
<td>15</td>
<td>16</td>
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<sup>a</sup>Values from GC.

Unfortunately, even with the best reaction conditions, there was still a complex mixture of products and protodehalogenation. Other members of the Malachowski lab are still investigating this project to attempt to understand the mechanism of this reaction.

4.5 Conclusions

In conclusion, the nickel-catalyzed Mizoroki-Heck reaction has had promising results.
during optimization. We learned several important lessons from the research presented. First, we learned that nickel precatalysts do not work well with our substrate. Second, when we attempted to use Ni(BF₄)₂·6H₂O, proton sources from the solvent as well as from the salt hydrate contributed to making the protodebrominated side product. Even with polar aprotic solvents, the major product produced was the protodehalogenated product. Third, pyox ligands were found to be the best ligands to use with nickel due to their push-pull nature being favorable for Heck reaction conditions. BINAP, a phosphorous based ligand, did not work with nickel; however, it was found to be the best ligand for our palladium research. Fourth, various metal halide additives were screened to help reduce the amount of protodehalogenated product. Potassium iodide, the most ionic halide salt, was found to be the best additive that is predicted to help reduce nickel via a nickelate complex. Fifth, bromide and iodide substrates can be used without much change in the Heck reaction results. More research needs to be done to investigate reactivity between halide substrates. Sixth, zinc can insert into the aryl-halide bond and may contribute to the closing of the ring to make the over-reduced product. Ongoing studies of the effect of zinc are being investigated by another graduate student in our lab, Diana Rachii.³⁴ Seventh, nickel chloride was found to have the best results of all of the nickel sources, although there was not much of a difference between using NiCl₂, NiI₂, or NiBr₂ as confirmed by Diana Rachii.³⁴ Finally, one of the most important discoveries in our research was the benefit of using a sacrificial alkene. Cyclohex-2-en-1-one was found to be the best sacrificial alkene to sequester H₂ from nickel, which may be attributed to its alkene being sterically unhindered as well as being polarized towards the carbonyl.

The promising results of this project have inspired our lab to continue research in using nickel to catalyze the Mizoroki-Heck reaction to make phenanthridinone analogs. The process is
particularly useful because of the speed of the reactions and the significantly lower cost of the nickel transition metal catalyst. The research presented in this dissertation attempted to limit the amount and yield of side products in the reaction. Next steps in the optimization sequence are to explore other ligands and eventually find a chiral ligand to enhance the enantiomeric ratio to a level worthy of publication.

4.6 References


32. Tran Tien, S. Sabrina Tran’s Thesis. (2019).


5.1- Conclusions

A variety of transition metal catalyzed cross-coupling reactions were explored with both palladium and nickel including enolate cross-coupling and the enantioselective Mizoroki-Heck reaction. Buchwald G3 palladium precatalysts have been successful in catalyzing the γ-arylation of α,β-unsaturated ketones and esters. The γ-arylation of 7-methoxy-4-methylcoumarin worked exceptionally well with electron-rich, electron-poor, and sterically diverse aryl bromides. Aryl chlorides were also tolerated when higher temperatures and N-xantphos G3 was used.35

Attempts at expanding our reaction conditions to other α,β-unsaturated ketones and esters exhibited the limited scope of our conditions due to a lack of selectivity. Polyarylation products could not be avoided in the synthesis of isophorone, 3-methyl-2-cyclohexen-1-one, and ethyl crotonate. We were able to confirm that when α'-protons were available, for example, with 1-acetyl-1-cyclohexane, mono-α'-arylated product was produced. We had more promising results when we utilized methyl-1-cyclohexene-1-carboxylate to eliminate α-protons, which should allow for γ-arylation to occur.

The γ-arylation of methyl-1-cyclohexene-1-carboxylate worked well for electron-rich aryl halides; however, there were issues with isolating the products, which lead to low yields. The γ-arylated product we isolated did not have the double bond in the α, β-position; instead, we confirmed that the double bond had shifted to the β, γ-position. This reaction ultimately proved that we could arylate methylene carbons selectively. When 2-bromoaniline was attempted in the γ-arylation of methyl-1-cyclohexene-1-carboxylate, a sequential amide formation/ Mizoroki Heck reaction occurred which formed a 5 membered ring. Unfortunately, this reaction produced
constitutional isomers that were inseparable. Due to the lack of funding and the numerous problems presented, we made the decision to stop research on this project and continue to the Birch-Heck sequence, which is the main research area in the Malachowski Lab.

The Birch-Heck sequence is a method developed by the Malachowski lab, which has been used to synthesize potentially bioactive drug precursors.\textsuperscript{29,30} Our focus was to create phenanthridinone analogs which have shown bioactivity in the literature.\textsuperscript{36-53} The Birch reduction-alkylation creates quaternary carbon centers in high yields from inexpensive, commercially available materials.\textsuperscript{54,55} A sequential acid chloride/amide formation produces the benzamide in high yields. We propose that atropisomers are forming in the tertiary benzamides due to the need for high-temperature NMR to resolve the peaks.\textsuperscript{56-59} The tertiary benzamide has restricted rotation around the N-Ar or N-(C=O) bond, which leads to the formation of 2 different atropisomers.\textsuperscript{57} Triflation of the amide phenol products was found to have the lowest yields in the reaction sequence. Either the benzamides had impurities or the triflates were degrading in the column, which could explain the low yields obtained. Atropisomers were also present in the triflate compounds. Finally, the enantioselective Mizoroki-Heck reaction had several important discoveries. Atropisomers introduced the potential for kinetic resolution in the Heck reaction.\textsuperscript{56} We overcame that complication by heating the reactions at elevated temperatures to allow for equilibration of the rotational isomers in the Heck reaction.\textsuperscript{57} Initial studies using past Malachowski Lab members conditions\textsuperscript{29,32} for the Heck reaction had low yields and low e.r. values. We were able to improve the yields and e.r. values by adding lithium acetate into our reaction, which was determined to cause progression of the Heck reaction past a palladium allylic complex and was proposed to potentially cause the reaction to proceed through an anionic mechanism instead of a cationic mechanism.
In our studies, we also discovered that an acetate intermediate was present in our reaction. Our lab discovered an acetate intermediate formed quickly after the 1,3-diene was produced when excess acetate was added to our reactions. To make the acetate compound we isolated, palladium would have to reinsert into the olefin after the 1,3-diene is produced. Our current hypothesis as to why palladium would reinsert is that a palladium allylic complex is formed, which is a resting state. This was confirmed by two different examples of nucleophilic attack of the allylic complex. When excess acetate is added, it can attack the allylic complex, which is why we see the acetate intermediate in our reaction. Another example of interception of the palladium allylic complex was when we used the butene derivative in the Heck reaction. The butene derivative not only yielded the 1,3-diene, but it also formed a product with a 5-membered ring. The cyclized product was also made by interception of a palladium allylic complex. The structure of the cyclized product was confirmed using X-ray crystallography. Ultimately, we determined that additional functionalization of the allylic complex may help palladium out of the energy low, which moves the cycle forward.

Another important discovery in our research was applying a protection/deprotection protocol to access N-H phenanthridone analogs. Secondary benzamides did not produce the desired Heck products using our standard reaction conditions. Attempts at removing the methyl group from the tertiary phenanthridinone Heck products proved futile as well. Using a protection strategy, we were able to synthesize the MOM-protected Heck products in high yields. Removal of the MOM group did not occur when standard acid cleavage protocols were attempted, but ether cleavage with TMS-I and hydrolysis of the hydroxymethyl group provided the secondary benzamide phenanthridinone product without compromising the enantioselectivity of the Heck reaction. Ultimately, this process provides access to N-H phenanthridinone products that could
not be accessed using the Heck reaction. This opens doors in both the palladium project and nickel project to synthesize potentially bioactive compounds.

We also had some success with our attempts at nickel catalyzed Heck reactions. We learned several important lessons from the research presented. Both nickel precatalysts and Ni(BF₄)₂·6H₂O did not work with our substrate. Proton sources from both the solvent and the nickel salt were proposed to promote protodebromination. Pyox ligands were found to have the best reactivity with nickel; whereas, BINAP was found to be the best ligand for our palladium research. Pyox ligands benefit from the electron-poor nitrogen atom of the pyridine ring and the electron-rich nitrogen of the oxazoline ring. Oxidative-addition is promoted by the electron-rich oxazoline ring, and the reduction of nickel is promoted by the pyridine ring. This balance is optimal for the Heck reaction vs. electron-rich BINAP.¹⁹ Metal halide additives were found to minimize the amount of protodehalogenated product via a proposed nickelate complex, which helps to reduce nickel. Studies to investigate the purpose of the halide salts are ongoing in our lab. Zinc, as an additive, was found insert into the aryl-halide bond and could contribute to the closing of the ring to make the over-reduced product. Finally, one of the most important discoveries in our research was the benefit of using a sacrificial alkene, which was found to limit protodebromination. Unfortunately, when we obtained HPLC data using the methyl derivative, the e.r. was 1:1 when we used (S)-4-(tert-butyl)-2-(pyridin-2-yl)-4,5-dihydrooxazole as the ligand. A screening of chiral ligands will need to be accomplished in future studies on this project.

We demonstrated the benefit of using palladium to synthesize C-C bonds via γ-aylation and in the Mizoroki-Heck reaction. We made significant discoveries in our enantioselective Mizoroki-Heck reaction using nickel and palladium, respectively. We improved upon the work
of past members of the Malachowski lab and provided a strategy to access N-H phenanthridinone analogs. While important discoveries in the optimization of the nickel project were achieved, studies are ongoing in our lab.

5.2-References:
136


32. Tran Tien, S. Sabrina Tran’s Thesis. (2019).


6.1 General Experimental Details

**General:** Unless otherwise noted, all reagents were purchased from commercial sources and used as received without further purification. Solvent was purchased from Sigma-Aldrich (anhydrous, sure-seal) or similar vendor and used as received. Anhydrous tetrahydrofuran (THF) was obtained by distillation from benzophenone-sodium under argon. Ligands were purchased from Strem Chemical, Inc. and the Buchwald G3 precatalysts were prepared in accordance with literature procedures\(^1\). When performing air sensitive reactions, reagents and solvents were transferred using either stainless steel cannulae or plastic syringes equipped with stainless steel needles. Air-sensitive reactions were performed under a positive pressure of either nitrogen (N\(_2\)) or argon (Ar) in reaction vessels sealed with rubber septa.

Thin layer chromatography was carried out on silica gel plates and eluted plates were visualized with UV light (254/365 nm) or basic potassium permanganate (KMnO\(_4\)). Flash chromatography was carried out on silica gel (60 Å, 230-400 mesh) or with Biotage® Sfär Silica - 60 μm 20 g or 10 g columns. All yields refer to isolated yields of analytically pure product unless otherwise noted. Melting points were measured on a digital melting point apparatus and are uncorrected. \(^1\)H and \(^{13}\)C \({}^{1}\)H NMR spectra were recorded at 400 MHz and 100 MHz, respectively, on a Bruker 400 MHz instrument. Spectra were recorded in ppm and referenced to residual solvent CHCl\(_3\) (7.28 ppm) or DMSO (2.50 ppm). \(^1\)H NMR data are presented as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=doublet of doublets, etc.), integration, and coupling constant(s) in Hertz (Hz). \(^{13}\)C NMR data are reported in ppm relative to the solvent signal, CDCl\(_3\) (77.0 ppm) or DMSO (39.5 ppm). \(^{13}\)C NMR experiments were conducted with either the broad band decoupled (CPD) or the attached proton test (APT) pulse sequence. GC analyses were performed with a EI-MS detector fitted with a 30 m x 0.25 mm column filled with crosslinked 5% PH ME siloxane (0.25 um film thickness); gas pressure 7.63 psi He. Analysis of samples involved heating from 70 to 250\(^\circ\)C (10\(^\circ\)C / min), then hold at 250\(^\circ\)C for 5 minutes. Low resolution, electron impact (EI mass spectral data is presented as follows: mass ion peak (relative intensity). High-resolution mass spectroscopy data were collected on the Thermo Q-Exactive Orbitrap, a high resolution mass spectrometer. The ionization method was heated electrospray (HESI). Samples were introduced via UHPLC with no chromatography. Mobile phase was 80:20 Water (0.1% formic acid): Acetonitrile (0.1% formic acid), flow rate of 0.2mL/min. IR data was obtained with an FT-IR spectrometer and all were recorded as thin films. HPLC analysis was conducted using an Agilent 1100 fitted with a VWD at 210 nm using a CHIRACEL OD-H 4.6 mm x 250 mm, 5 μm column, run with the specified conditions.
6.2 γ-arylation General Procedures and Data

6.2.1 Synthesis of 7-methoxy-4-methylcoumarin

Scheme 26: Williamson-ether synthesis of 7-methoxy-4-methylcoumarin

A similar procedure to Bing Gong et al was used. A three-necked 1000 mL roundbottom flask with a mechanical stir bar was charged with 4-umbelliferone (22.6 g, 128 mmol), potassium carbonate (35.5 g, 257 mmol), methyl iodide (16 mL, 257 mmol), and acetone (500 mL). The reaction was left to reflux for 6 hours and then was left to cool overnight. The next day, a standard extraction was done using ethyl acetate. Magnesium sulfate was used to dry the solution and gravity filtration was performed. A white free flowing powder was isolated yielding 15.6 g (89%) of pure product. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.43 (d, 1H, $J=8.8$), 6.78 (m, 2H), 6.08 (d, 1H, $J=1.1$), 3.81 (s, 3H), 2.33 (d, $J=1.2$) ppm. Spectral data were in accordance with the literature.

6.2.1.1 Aryl Bromides:

Scheme 27: Reaction conditions for aryl bromides

All reactions were prepared at the 1.0 mmol scale in a glovebox using 8-mL screw cap vials with a Teflon-coated stir bar. The vial was charged with 4% Xantphos Pd G3 (0.038 g, 0.04 mmol), 7-methoxy-4-methylcoumarin (0.190 g, 1 mmol), and an aryl bromide (1.05 mmol). Next, 3 mL of a 1.0 M LiHMDS solution was added. Finally, 2 mL of THF was added to the reaction vial. The reaction was capped, removed from the glovebox, and allowed to stir on an aluminum block preheated to 70 °C for 24 hours. Upon completion, the reaction was allowed to cool. A standard workup was completed using about 2.5 mL of a 2.0 M HCl solution and dichloromethane to extract. Magnesium sulfate was utilized to dry the sample before gravity filtering and removing the solvent under reduced pressure. Completion was checked using TLC and GC-MS. The crude reaction mixture was loaded onto a silica gel column using a wet load technique. The yields reported in this thesis are from one trial only.
4-benzyl-7-methoxycoumarin: Using the general procedure outlined above with bromobenzene (126 μL, 1.2 mmol), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 60% petroleum ether / 30% DCM/ 10% ethyl acetate (R_f = 0.36) and 0.261 g (98%) of an orange powder was isolated. m.p. 137-139 °C. IR (neat): 3065, 2921, 2852, 1704, 1606, 1512, 1277 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.55 (d, 1H, \(J=8.4\) Hz), 7.38-7.23 (m, 6H), 6.84-6.81 (m, 2H), 6.01 (s, 1H), 4.09 (s, 2H), 3.88 (s, 1H) ppm. \(^13\)C (100 MHz, CDCl\(_3\)): δ 162.6, 161.4, 155.6, 154.7, 136.2, 129.0, 127.2, 125.7, 112.8, 112.6, 112.4, 101.0, 55.7, 38.2, 29.7 ppm. EI MS, \(m/z\): 266 (100), 249 (3), 237 (45), 233 (19), 207 (15), 194 (4), 178 (8), 165 (19), 152 (12), 139 (3), 128 (2), 115 (7), 105 (2), 91 (8), 76 (6), 65 (6), 51 (4). Spectral data were in accordance with the literature\(^4\). HRMS (ESI): M+1 calculated for C\(_{17}\)H\(_{15}\)O\(_3\), 267.1021; found, 267.1022.

Figure 16: \(^1\)H NMR of compound 1
Figure 17: $^{13}$C NMR of compound 1

7-methoxy-4-(2-methoxybenzyl)coumarin: Using the general procedure outlined above with 2-bromoanisole (131 μL), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 60% petroleum ether / 30% DCM / 10% ethyl acetate (Rf = 0.31) and 0.277 g (93%) of an light yellow powder was isolated. m.p. 131-132 °C. IR (neat): 3079, 2893, 2836, 1710, 1607, 1237, 1205, 810, 575 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.51 (d, 1H, $J$ = 7.9), 7.17 (t, 1H, $J$ = 7.8), 6.98 (d, 1H, $J$ = 7.8), 6.82-6.79 (m, 2H), 6.75-6.72 (m, 2H), 5.77 (s, 1H), 3.94 (s, 2H), 3.76 (s, 3H), 3.71 (s, 1H) ppm. $^{13}$C (100 MHz, CDCl$_3$): $\delta$ 162.5, 161.7, 157.2, 155.4, 155.1, 130.6, 128.7, 125.6, 124.4, 120.8, 113.2, 112.3, 111.7, 110.6, 100.9, 55.7, 55.4, 32.0 ppm. EI MS, m/z: 296 (100), 281 (11), 265 (12), 253 (19), 237 (15), 221 (8), 207 (16), 190 (52), 177 (5), 162 (37), 151 (12), 131 (6), 115 (7), 91 (10), 77 (8), 65 (6), 51 (4). HRMS (ESI): M+1 calculated for C$_{18}$H$_{17}$O$_4$, 297.1127; found, 297.1127.
Figure 18: $^1$H NMR of compound 2

Figure 19: $^{13}$C NMR of compound 2
7-methoxy-4-(3-methoxybenzyl)coumarin: Using the general procedure outlined above with 3-bromoanisole (133 μL), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 60% petroleum ether / 30% DCM / 10% ethyl acetate (R\textsubscript{f} = 0.27) and 0.297 g (88%) of an light yellow powder was isolated. m.p. 157-158 °C. IR (neat): 2995, 2944, 2837, 1708, 1611, 1290, 1148, 1043, 841, 758, 698 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 7.55 (d, 1H, J = 8.7), 7.27 (m, 1H), 6.84 (m, 3H), 6.82 (d, 1H, J= 1.7), 6.77 (m, 1H), 6.03 (s, 1H), 4.06 (s, 2H), 3.88 (s, 3H), 3.80 (s, 3H) ppm. \textsuperscript{13}C (100 MHz, CDCl\textsubscript{3}): δ 162.6, 161.4, 160.0, 155.6, 154.5, 137.7, 130.0, 125.7, 121.3, 115.0, 112.8, 112.6, 112.4, 112.3, 101.0, 55.7, 55.2, 38.2 ppm. EI MS, m/z: 296 (100), 281 (12), 267 (14), 253 (28), 237 (22), 225 (5), 207 (11), 194 (5), 165 (11), 153 (8), 126 (5), 89 (6), 76 (5). HRMS (ESI): M+1 calculated for C\textsubscript{18}H\textsubscript{17}O\textsubscript{4}, 297.1127; found, 297.1126.

**Figure 20:** \textsuperscript{1}H NMR of compound 3
Figure 21: $^{13}$C NMR of compound 3

7-methoxy-4-(4-methoxybenzyl)coumarin: Using the general procedure outlined above with 4-bromoanisole (131 μL), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 60% petroleum ether / 30% DCM/ 10% ethyl acetate ($R_f = 0.25$) and 0.268 g (90%) of an light yellow powder was isolated. m.p. 161-162 °C. IR (neat): 3079, 2830, 2836, 1710, 1607, 1237, 1205, 8010, 575 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl₃): δ 7.56 (d, 1H, $J = 8.8$), 7.16 (d, 2H, $J = 8.6$), 6.89 (dd, 2H, $J_1 = 6.7$, $J_2 = 2$), 6.83 (m, 2H), 6.00 (s, 1H), 4.03 (s, 2H), 3.88 (s, 3H), 3.82 (s, 3H) ppm. $^{13}$C (100 MHz, CDCl₃): δ 162.5, 161.5, 158.7, 155.6, 155.1, 130.0, 128.0, 125.6, 114.4, 112.8, 112.4, 112.3, 101.0, 55.7, 55.3, 37.3 ppm. EI MS, m/z: 296 (100), 281 (25), 267 (12), 253 (19), 237 (6), 207 (13), 165 (8), 151 (7), 135 (5), 121 (5), 91 (5), 78 (6). HRMS (ESI): M+1 calculated for C$_{18}$H$_{17}$O$_4$, 297.1127; found, 297.1127.
Figure 22: $^1$H NMR of compound 4

Figure 23: $^{13}$C NMR of compound 4
4-(3,4-dimethoxybenzyl)-7-methoxycoumarin: Using the general procedure outlined above with 4-bromoveratrole (151μL, 1.05 mmol), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 50% petroleum ether / 30% DCM/ 20% ethyl acetate (Rf = 0.30) and 0.2925g (90%) of a yellow flake-like powder was isolated. m.p. 179-181°C. IR (neat): 3074, 2995, 2838, 1703, 1608, 1509, 1388, 1275, 1132, 1026, 810 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.57 (d, 1H, J=8.6), 6.90-6.74 (m, 5H), 6.02 (s, 1H), 2.14 (s, 2H), 3.89-3.87 (m, 9H). ¹³C (100 MHz, CDCl₃): δ 162.3, 161.5, 155.5, 155.1, 149.3, 148.3, 128.5, 125.6, 121.3, 112.8, 112.4, 112.3, 112.1, 111.6, 101.0, 56.0, 55.9, 55.7, 37.8 ppm. EI MS, m/z: 326 (100), 311 (12), 283 (10), 267 (8), 207 (9), 152 (11), 120 (8). HRMS (ESI): M+1 calculated for C₁₉H₁₉O₅, 327.1233; found, 327.1232. (HRMS not entirely clean)

Figure 24: ¹H NMR of compound 5
Figure 25: $^{13}$C NMR of compound 5

4-(4-(dimethylamino)benzyl)-7-methoxycoumarin Using the general procedure outlined above with 4-bromo-$N,N$-dimethylaniline (0.221 g), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 60% petroleum ether / 30% DCM/ 10% ethyl acetate ($R_f = 0.32$) and 0.204 g (66%) of a yellow solid was isolated. Melting point: 206 – 208 °C. IR (neat): 3069, 2975, 2897, 2842, 2790, 1712, 1606, 1519, 1342, 1279, 1263, 1132, 985, 873, 847, 813, 752, 709, 575, 479 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.58 (dd, 1H, $J =$ 9.5, 2.7 Hz), 7.10 (d, 2H, $J =$ 8.7, 2.8 Hz), 6.81–6.84 (m, 2H), 6.70–6.73(dd, 2H, $J =$ 8.7, 2.0 Hz), 6.03 (s, 1H), 3.99 (s, 2H), 3.87 (s, 3H), 2.95 (s, 6H) ppm. $^{13}$C (100 MHz, CDCl$_3$): δ 162.5, 161.6, 155.7, 155.6, 149.7, 129.7, 125.7, 123.6, 113.0, 112.99, 112.3, 112.2, 101.0, 55.7, 40.6, 37.3 ppm. EI MS, m/z: 309 (100), 134 (20), 294 (16), 280 (7), 266 (7), 118 (7). HRMS (ESI): M+1 calculated for C$_{19}$H$_{20}$O$_3$N, 310.1443; found, 310.1446.
**Figure 26:** $^1$H NMR of compound 6

**Figure 27:** $^{13}$C NMR of compound 6
7-methoxy-4-(2,4,6-trimethylbenzyl)coumarin: Using the general procedure outlined above with 2-bromomesitylene (161 μL), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 60% petroleum ether / 30% DCM/ 10% ethyl acetate (Rf = 0.49) and 0.249 g (81%) of an light yellow powder was isolated. m.p:190-196 °C. IR (neat): 3073, 2923, 2846, 1711, 1605, 1386, 1277, 988, 844 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.76 (d, 1H, J=8.8 Hz), 6.97 (d, 1H, J= 2.5 Hz), 6.95-6.94 (m, 2H), 6.89 (d, 1H, J=2.5 Hz), 5.55 (t, 1H, J=1.4 Hz), 4.04 (d, 2H, J=1.2 Hz), 3.92 (s, 3H), 2.32 (s, 3H), 2.18 (s, 6H) ppm. ¹³C (100 MHz, CDCl₃): δ 162.6, 161.6, 155.3, 154.1, 137.0, 136.9, 129.2, 129.1, 124.8, 113.2, 112.4, 112.4, 110.1, 101.0, 55.8, 31.0, 20.9, 19.8 ppm. EI MS, m/z: 308 (100), 293 (10), 280 (8), 265 (39), 251 (7), 235 (3), 222 (4), 207 (4), 191 (4), 179 (5), 157 (6), 137 (9), 117 (6), 103 (3), 91 (5), 77(3), 63 (2), 51 (1). HRMS (ESI): M+1 calculated for C₂₀H₂₁O₃, 309.1491; found, 309.1489.

Figure 28: ¹H NMR of compound 7
Figure 29: $^{13}$C NMR of compound 7

7-methoxy-4-(naphthalene-2-ylmethyl)coumarin: Using the general procedure outlined above with 2-bromonaphthalene (0.218 g, 1.05 mmol), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 60% petroleum ether/30% DCM/10% ethyl acetate ($R_f = 0.32$) and 0.234 g (74%) of a dark yellow/orange free-flowing powder was isolated. m.p. 137-139 °C. IR (neat): 3014, 2970, 1698, 1606, 1390, 1278, 1124, 1020, 842, 747, 476 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.83-7.76 (m, 3H), 7.67 (s, 1H), 7.56 (d, 1H, $J = 8.8$ Hz), 7.50-7.45 (m, 2H), 7.34 (dd, 1H, $J = 8.4$, 1.6 Hz), 6.84 (d, 1H, $J = 2.5$ Hz), 6.79 (dd, 1H, $J_1 = 8.8$, 2.5 Hz), 4.11 (s, 2H), 3.73 (s, 3H) ppm. $^{13}$C (100 MHz, CDCl$_3$): δ 162.6, 161.4, 155.6, 154.5, 133.7, 133.6, 132.5, 128.7, 127.7, 127.6, 126.9, 126.4, 126.0, 125.7, 112.8, 112.7, 112.3, 101, 53.7, 38.4 ppm. EI MS, m/z: 316 (100), 288 (28), 207 (45). HRMS (ESI): M+1 calculated for C$_{21}$H$_{17}$O$_3$, 317.1178; found, 317.1177.
Figure 30: $^1$H NMR of compound 8

Figure 31: $^{13}$C NMR of compound 8
**7-methoxy-4-(3-methylbenzyl)coumarin:** Using the general procedure outlined above with 3-bromotoluene (127 μL), the crude reaction mixture was purified using column flash chromatography (silica gel, 60 Å) with 60% petroleum ether / 30% DCM / 10% ethyl acetate (Rf = 0.38) and 0.1972 g (70%) of a light yellow free flowing powder was isolated. m.p. 113-115 °C. IR (neat): 3003, 2888, 1781, 1713, 1607, 1390, 1277, 1131, 986, 846, 832, 703, 588 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.56 (d, 1H, J=9.0 Hz), 7.28-7.22 (m, 1H), 7.24 (t, 1H, J=8.0 Hz), 7.10 (d, 1H, J=8.0 Hz), 7.04 (d, 2H, J= 8.0 Hz), 6.85-6.82 (m, 2H), 6.02 (s, 1H), 4.04 (s, 2H), 3.88 (s, 3H), 2.35 (s, 3H) ppm. ¹³C (100 MHz, CDCl₃): δ 162.6, 161.4, 155.6, 154.8, 138.7, 136.1, 129.7, 128.8, 127.9, 126.0, 125.7, 112.9, 112.6, 112.3, 101.0, 55.7, 38.1, 21.4 ppm. EI MS, m/z: 280 (100), 265 (6), 251 (24), 237 (28), 207 (9), 194 (5), 178 (6), 165 (15), 151 (5), 139 (6), 89 (4), 76 (4). HRMS (ESI): M+1 calculated for C₁₈H₁₇O₃, 281.1178; found, 281.1178.

![Figure 32: ¹H NMR of compound 9](image)
Using the general procedure outlined above with 4-bromotoluene (129 μL), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 60% petroleum ether / 30% DCM/ 10% ethyl acetate ($R_f = 0.58$) and 0.1823g (65%) of a light yellow/brown free-flowing powder was isolated. m.p. 155-157 °C. IR (neat): 3090, 3000, 2895, 1702, 1606, 1394, 1274, 1143, 983, 852, 831, 819, 577, 461 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.56 (d, 1H, $J=8.6$ Hz), 7.17-7.12 (m, 4H), 6.85-6.82 (m, 2H), 6.02 (s, 1H), 4.05 (s, 2H), 3.88 (s, 3H), 2.36 (s, 3H) ppm. $^{13}$C (100 MHz, CDCl$_3$): δ 162.6, 161.4, 155.6, 154.9, 136.8, 133.1, 129.6, 128.9, 125.7, 112.9, 112.5, 112.3, 101.0, 55.7, 37.8, 21.0 ppm. EI MS, m/z: 280 (100), 265 (7), 251 (28), 237 (26), 221 (5), 178 (7), 165 (15), 151 (6), 139 (10), 89 (5), 77 (6). HRMS (ESI): M+1 calculated for C$_{18}$H$_{17}$O$_3$, 281.1178; found, 281.1177.

**Figure 33:** $^{13}$C NMR of compound 9
Figure 34: $^1$H NMR of compound 10

Figure 35: $^{13}$C NMR of compound 10
7-methoxy-4-(5-(tert-buty1)-2-methylbenzyl)-coumarin: Using the general procedure outlined above with 2-bromo-4-tert-buty1toluene (199 μL), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 65% petroleum ether / 30% DCM/ 5% ethyl acetate (Rf = 0.30) and 0.228 g (68%) of a light yellow free flowing powder was isolated. m.p. 101-104 °C. IR (neat): 2961, 2867, 1722, 1609, 1505, 1462, 1426, 1387, 1345, 1267, 1206, 1152, 1132, 1043, 1023, 983, 876, 849, 836, 825, 814, 746, 721, 702, 634, 608, 555, 487 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.65 (d, 1H, J=8.7 Hz), 7.28 (dd, 1H, J= 8.0,2.1 Hz), 7.18 (d, 1H, J=8.0 Hz), 7.13 (d, 1H, J=2.0 Hz), 6.90 (td, 2H, J=8.0, 2.5 Hz), 5.70 (s, 1H), 4.06 (d, 2H, J=0.8 Hz), 3.91 (s, 3H), 2.21 (s, 3H), 1.30 (s, 9H) ppm. \(^{13}\)C (100 MHz, CDCl\(_3\)): δ 162.6, 161.6, 155.3, 154.8, 149.5, 133.7, 133.4, 127.2, 125.1, 124.6, 113.1, 112.4, 111.5, 101.0, 55.8, 35.8., 34.3, 31.4, 18.8 ppm. EI MS, m/z: 336 (50), 321 (100), 308 (1), 293 (2), 279 (4), 265 (1), 251 (2), 235 (1), 219 (5), 205 (2), 191 (2), 178 (2), 161 (4), 145 (2), 132 (3), 115 (3), 91 (2), 77 (1), 57 (2). HRMS (ESI): M+1 calculated for C\(_{22}\)H\(_{25}\)O\(_3\), 337.1804; found, 337.1803.

Figure 36: \(^1\)H NMR of compound 11
Figure 37: $^{13}$C NMR of compound 11

4-(4-(tert-butyl)benzyl)-7-methoxy-coumarin: Using the general procedure outlined above with 1-bromo-4-tert-butylbenzene (182 μL), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 60% petroleum ether / 30% DCM/ 10% ethyl acetate ($R_f = 0.43$) and 0.241 g (75%) of a light yellow free flowing powder was isolated. m.p. 158-160 °C. IR (neat): 2965, 1714, 1606, 1460, 1411, 1385, 1275, 1261, 1152, 1132, 1039, 1020, 984, 891, 847, 811, 790, 708, 599, 579, 485, 476, 452 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.56 (dd, 1H, $J= 5.8,3.7$ Hz), 7.35 (dd, 2H, $J= 6.6, 2.0$ Hz), 7.15 (d, 2H, $J=8.3$ Hz), 6.82 (m, 2H), 5.98 (s, 1H), 4.03 (s, 2H), 3.86 (s, 3H), 1.31 (s, 9H) ppm. $^{13}$C (100 MHz, CDCl$_3$): δ 162.6, 161.5, 155.5, 155.0, 150.2, 133.0, 128.7, 125.9, 125.6, 112.9, 112.4, 112.3, 101.0, 55.7, 37.6, 34.5, 31.3 ppm. EI MS, m/z: 322 (51), 307 (100), 294 (1), 279 (3), 266 (11), 249 (1), 237 (3), 233 (1), 207 (1), 191 (2), 178 (2), 166 (4), 154 (4), 140 (3), 126 (6), 104 (1), 91 (3), 77 (2), 57 (2). HRMS (ESI): M+1 calculated for C$_{21}$H$_{23}$O$_3$, 323.1647; found, 323.1648.
Figure 38: $^1$H NMR of compound 12

Figure 39: $^{13}$C NMR of compound 12
4-(4-chlorobenzyl)-7-methoxycoumarin: Using the general procedure outlined above with 1-bromo-4-chlorobenzene (0.202 g, 1.05 mmol), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 60% petroleum ether / 30% DCM/ 10% ethyl acetate (Rf = 0.32) and 0.210 g (70%) of a light yellow free-flowing powder was isolated. m.p. 148-150 °C. IR (neat): 3087, 3006, 2935, 1703, 1600, 1395, 1294, 1019, 831, 463 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.49 (dd, 1H, J = 5.4, 4.0 Hz), 7.31 (d, 2H, J = 8.4 Hz), 7.17 (d, 2H, J = 2 Hz), 6.83-6.81 (m, 2H), 5.97 (s, 1H), 4.05 (s, 2H), 3.87 (s, 3H) ppm. ¹³C (100 MHz, CDCl₃): δ 162.7, 161.2, 155.6, 154.1, 134.7, 133.1, 130.3, 129.1, 125.5, 112.6, 112.5, 112.4, 101.1, 55.8, 37.5 ppm. EI MS, m/z: 300 (100), 272 (31), 257 (1), 237 (17), 165 (24), 151 (11), 89 (9). HRMS (ESI): M+1 calculated for C₁₇H₁₄O₃Cl, 301.0631; found, 301.0633.

Figure 40: ¹H NMR of compound 13
Figure 41: $^{13}$C NMR of compound 13

7-methoxy-4-(4-(trifluoromethyl)benzyl)-2H-chromen-2-one: The reaction was prepared according to the general procedure outlined above using 4-bromobenzotrifluoride (147 µL). The crude mixture was purified using column chromatography (silica gel, 60 Å) with 60% petroleum ether / 33% dichloromethane / 7% ethyl acetate (R$_f$ = 0.35) and 0.102 g (30%) of a yellow solid was isolated. m.p. = 126-127 °C. IR (neat): 3082, 2922, 1705, 1605, 1326, 1121 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.63 (d, 2H, $J = 8.1$Hz), 7.49 (d, 1H, $J = 8.7$Hz), 7.38 (d, 2H, $J = 8.0$Hz), 7.28 (s, 2H), 6.87-6.83 (m, 2H), 6.00 (s, 1H), 4.15 (s, 2H), 3.89 (s, 3H) ppm. $^{13}$C NMR (100 MHz, CDCl$_3$): δ 162.8, 161.1, 155.7, 153.5, 140.4, 129.7 (q, $J=32$ Hz), 129.3, 125.9 (q, $J=3.8$ Hz), 125.5, 124.0 (d, $J=271$ Hz), 112.9, 112.5, 112.4, 101.2, 55.8, 37.9 ppm. $^{19}$F (376 MHz, CDCl$_3$): -62.6(s) ppm. El MS, $m/z$: 334 (100), 306 (45), 291 (30). HRMS (ESI): M+1 calculated for C$_{18}$H$_{14}$O$_3$F$_3$, 335.0895; found, 335.0894.
Figure 42: $^1$H NMR of compound 14

Figure 43: $^{13}$C NMR of compound 14
Figure 44: $^{19}$F NMR of compound 14

4-((7-methoxy-2-oxo-2H-chromen-4-yl)methyl)benzonitrile: Using the general procedure outlined above with 4-bromobenzonitrile (0.191g, 1.05 mmol), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 50% petroleum ether / 30% DCM/ 20% ethyl acetate (R$_f$ = 0.35) and 0.2772g (95%) of an orange powder was isolated. m.p. 135-137 °C. IR (neat): 2925, 2227, 1702, 1606, 1134, 836, 578 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.66 (d, 2H, $J=$ 8.2 Hz), 7.44 (d, 1H, $J=$8.8 Hz), 7.38 (d, 3H, $J=$ 8.1 Hz), 7.28 (s, 1H), 6.85 (m, 2H), 6.00 (s, 1H), 4.15 (s, 2H), 3.89 (s, 3H). $^{13}$C (100 MHz, CDCl$_3$): δ 162.9, 161.0, 155.7, 153.0, 141.8, 132.8, 129.7, 125.4, 118.4, 113.0, 112.7, 112.3, 111.4, 101.2, 55.8, 38.1 ppm. El MS, m/z: 291 (100), 263 (57), 248 (19), 232 (3), 220 (5), 203 (6), 190 (16), 177 (7), 165 (9), 151 (15), 140 (5), 116 (6), 101 (4), 89 (7), 69 (7), 51 (3). HRMS (ESI): M+1 calculated for C$_{18}$H$_{14}$O$_3$N, 292.0974; found, 292.0974.
Figure 45: $^1$H NMR of compound 15

Figure 46: $^{13}$C NMR of compound 15
4-(benzofuran-5-ylmethyl)-7-methoxycoumarin: Using the general procedure outlined above with 5-bromobenzofuran (132 μL), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 60% petroleum ether / 30% DCM/ 10% ethyl acetate (R_f = 0.25) and 0.2816 g (92%) of a light grey/green free flowing powder was isolated. m.p. 123-126 °C. IR (neat): 3114, 3078, 2896, 1694, 1604, 1394, 1269, 1202, 1142, 829, 744, 617 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.65 (d, 1H, \(J=2.2\) Hz), 7.58 (d, 1H, 8.7 Hz), 7.48 (m, 2H), 7.17 (dd, 1H, \(J=8.4,1.7\) Hz), 6.83 (m, 2H), 6.74 (dd,1H, \(J=2.1, 0.8\) Hz), 6.02 (s, 1H), 4.18 (s, 2H), 3.88 (s, 3H). \(^{13}\)C (100 MHz, CDCl\(_3\)): δ 162.6, 161.4, 155.6, 155.1, 154.1, 145.7, 130.6, 128.1, 125.7, 125.2, 121.4, 112.8, 112.6, 112.4, 111.8, 106.4, 101.0, 55.7, 38.0 ppm. EI MS, m/z: 306 (100), 289 (3), 263 (16), 249 (4), 235 (4), 207 (13), 189 (8), 178 (9), 161 (5), 131 (7), 117 (4), 89 (8), 77 (4), 63 (4). HRMS (ESI): M+1 calculated for C\(_{19}\)H\(_{15}\)O\(_4\), 307.0970; found, 307.0970.

Figure 47: \(^1\)H NMR of compound 16
Figure 48: $^{13}$C NMR of compound 16

7-methoxy-4-(pyridin-2-ylmethyl)coumarin: Using the general procedure outlined above with 2-bromopyridine (100 μL), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 20% petroleum ether / 30% DCM / 50% ethyl acetate ($R_f = 0.36$) and 0.152 g (57%) of a yellow/brown powder was isolated. m.p. 101-104 °C. IR (neat): 3094, 2922, 2851, 1713, 1614, 1286, 1144, 839, 581 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): δ 8.58 (d, 1H, $J$=4.2 Hz), 7.66-7.59 (m, 2H), 7.22-7.17 (m, 2H), 6.81-6.78 (m, 2H), 6.07 (s, 1H), 4.25 (s, 2H), 3.84 (s, 3H) ppm. $^{13}$C (100 MHz, CDCl$_3$): δ 162.7, 161.3, 156.9, 155.6, 153.4, 149.8, 137.0, 126.2, 123.3, 122.2, 112.8, 112.4, 101.0, 55.7, 41.1 ppm. EI MS, m/z: 267 (54), 239 (100), 224 (59), 210 (5), 196 (22), 178 (4), 167 (26), 154 (6), 141 (5), 117 (16), 84 (7), 63 (5), 51 (5). HRMS (ESI): M+1 calculated for C$_{16}$H$_{14}$O$_3$N, 268.0974; found, 268.0973.
Figure 49: $^1$H NMR of compound 17

Figure 50: $^{13}$C NMR of compound 17
Using the general procedure outlined above with 3-bromopyridine (101 μL), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 10% DCM/90% ethyl acetate (Rf = 0.23) and 0.0859 g (32%) of a yellow free flowing powder was isolated. m.p. 138-140 °C. IR (neat): 3003, 2908, 1704, 1608, 1281, 1137, 835, 717 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 8.88-8.56 (m, 2H), 7.57-7.55 (m, 1H), 7.51 (d, 1H, J= 8.7 Hz), 7.32-7.28 (m, 1H), 6.87-6.84 (m, 2H), 6.00 (s, 1H), 4.10 (s, 2H), 3.89 (s, 3H) ppm. ¹³C (100 MHz, CDCl₃): δ 162.9, 161.0, 155.7, 153.3, 150.1, 148.7, 136.4, 132.0, 125.4, 123.8, 112.8, 112.6, 112.3, 101.2, 55.8, 35.3 ppm. EI MS, m/z: 267 (100), 238 (35), 224 (41), 207 (42). HRMS (ESI): M+1 calculated for C₁₆H₁₄O₃N, 268.0974; found, 268.0974.

Figure 51: ¹H NMR of compound 18
All reactions were prepared at the 1.0 mmol scale in a glovebox using 8-mL screw cap vials with a Teflon-coated stir bar. The vial was charged with 4% Nixantphos Pd G3 (0.04 mmol), 7-methoxy-4-methylcoumarin (1mmol), LiHMDS (3 eq) and an aryl chloride (1.05 mmol). Finally, 5 mL of THF was added to the reaction vial. The reaction was capped, removed from the glovebox, and allowed to stir on an aluminum block preheated to 90 °C for 24-48 hours. Upon completion, the reaction was allowed to cool. A standard workup was completed using about 2.5 mL of a 2.0 M HCl solution and dichloromethane to extract. Magnesium sulfate was utilized to dry the sample before gravity filtering and removing the solvent under reduced pressure. Completion was checked using TLC and GC-MS. The crude reaction mixture was loaded onto a silica gel column using a wet load technique. The yields reported in this thesis are from one trial only.
4-benzyl-7-methoxycoumarin: Using the general procedure outlined above with chlorobenzene (107 μL) for 24 hours, the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 60% petroleum ether / 30% DCM/ 10% ethyl acetate ($R_f$ = 0.35) and 0.185 g (70%) of a light yellow free-flowing powder was isolated. m.p. 139-142 °C. IR (neat): 3064, 3001, 2905, 1705, 1608, 1389, 1277, 1135, 988, 836, 700 576 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.55 (d, 1H, $J$=8.6 Hz), 7.38-7.24 (m, 5H), 6.85-6.82 (m, 2H), 6.01 (s, 1H), 4.09 (s, 2H), 3.88 (s, 3H) ppm. $^{13}$C (100 MHz, CDCl$_3$): δ 162.6, 161.4, 155.6, 154.7, 136.2, 129.0, 128.9, 127.2, 125.6, 112.8, 112.6, 112.4, 101.0, 55.7, 38.1 ppm. EI MS, m/z: 266 (100), 237 (49), 207 (18), 165 (19). Spectral data were in accordance with the literature$^4$. HRMS (ESI): M+1 calculated for C$_{17}$H$_{15}$O$_3$, 267.1021; found, 267.1021.

Figure 53: $^1$H NMR of compound 19
Figure 54: $^{13}$C NMR of compound 19
6.2.2 γ-arylation of Isophorone General Procedures and Data

![Chemical structure]

**Scheme 28: γ-arylation of isophorone general procedure**

All reactions were prepared at the 1.0 mmol scale in a glovebox using 8-mL screw cap vials with a Teflon-coated stir bar. The vial was charged with 4% Nixantphos Pd G3 (0.038 g, 0.04 mmol), cesium carbonate (0.978 g, 3 mmol), isophorone (150μL), and an aryl bromide (1.05 mmol). Finally, 5 mL of THF was added to the reaction vial. The reaction was capped, removed from the glovebox, and allowed to stir on an aluminum block preheated to 50 °C for 72 hours. Although incomplete, the reaction was allowed to cool. A standard workup was completed using about 2.5 mL of a 2.0 M HCl solution and dichloromethane to extract. Magnesium sulfate was utilized to dry the sample before gravity filtering and removing the solvent under reduced pressure. Completion was checked using TLC and GC-MS. The crude reaction mixture was loaded onto a silica gel column using a wet load technique. The yields reported in this thesis are from one trial only.

![Chemical structure]

**3-(3-methoxybenzyl)-5,5-dimethylcyclohex-2-en-1-one:** Using the general procedure outlined above with 3-bromoanisole (133 μL), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 60% petroleum ether / 30% DCM/ 10% ethyl acetate (Rf = 0.32) and 0.0864 g (35%) of a yellow oil was isolated. IR (neat): 2955, 2835, 1663, 1598, 1276, 1047, 781, 698 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.25 (t, 1H, J=8.0 Hz), 6.81 (dd, 1H, J=8.2, 2.3 Hz), 6.77 (d, 1H, J= 7.5 Hz), 6.71-6.70 (m, 1H), 5.93 (s, 1H), 3.81 (s, 3H), 3.48 (s, 2H), 2.23 (s, 2H), 2.14 (s, 2H), 0.99 (s, 6H) ppm. ¹³C (100 MHz, CDCl₃): δ 200.1, 161.9, 159.8, 138.4, 129.7, 125.9, 121.5, 114.9, 112.2, 55.2, 51.1, 44.5, 43.3, 33.6, 28.2 ppm. EI MS, m/z: 244 (100), 229 (23), 211 (6), 201 (5), 188 (72), 173 (8), 159 (56), 145 (36), 131 (4), 121 (34), 103 (4), 91 (18), 77 (13), 67 (8), 55 (4). Spectral data were in accordance with the literature⁵.
**Figure 55:** $^1$H NMR of compound 20

**Figure 56:** $^{13}$C NMR of compound 20
3-benzyl-5,5-dimethylcyclohex-2-en-1-one: Using the general procedure outlined above with bromobenzene (111 μL), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 63% petroleum ether / 30% DCM/ 7% ethyl acetate (Rf = 0.38) and 0.0733 g (34%) of a yellow/brown oil was isolated. IR (neat): 3028, 2956, 2868, 1664, 1453, 1367, 1275, 751, 700, 519 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.34-7.23 (m, 3H), 7.18-7.16 (m, 2H), 5.91 (s, 1H), 3.49 (s, 2H), 2.21 (s, 2H), 2.13 (s, 2H), 0.98 (s, 6H) ppm. \(^{13}\)C (100 MHz, CDCl\(_3\)): \(\delta 200.1, 162.1, 136.9, 129.1, 128.7, 126.9, 125.8, 51.1, 44.5, 43.3, 33.6, 28.2\) ppm. EIMS, m/z: 214 (45), 199 (8), 181 (3), 171 (4), 158 (100), 141 (4) 129 (41), 115 (23), 102 (2), 91 (26), 77 (6), 67 (12), 51 (3). Spectral data were in accordance with the literature\(^5\).

Figure 57: \(^1\)H NMR of compound 21
6.2.3 α-arylation of 1-acetyl-1-cyclohexane General Procedures and Data

All reactions were prepared at the 1.0 mmol scale in a glovebox using 8-mL screw cap vials with a Teflon-coated stir bar. The vial was charged with 4% Nixantphos Pd G3 (0.04 mmol), LiHMDS (3 eq.), 1-acetyl-1-cyclohexane (1 mmol), and an aryl bromide (1.05 mmol). Finally, 5 mL of THF was added to the reaction vial. The reaction was capped, removed from the glovebox, and allowed to stir on an aluminum block preheated to 50 °C for 72 hours. A standard workup was completed using about 2.5 mL of a 2.0 M HCl solution and dichloromethane to extract. Magnesium sulfate was utilized to dry the sample before gravity filtering and removing the solvent under reduced pressure. Completion was checked using TLC and GC-MS. The crude reaction mixture was loaded onto a silica gel column using a wet load technique. The yields reported in this thesis are from one trial only.
1-(cyclohex-1-en-1-yl)-2-phenylethan-1-one: Using the general procedure outlined above with bromobenzene (111 μL), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 95% petroleum ether / 5% ethyl acetate (Rf = 0.41) and 0.172 g (85%) of a yellow free flowing oil was isolated. IR (neat): 3028, 2930, 2858, 1656, 1635, 1495, 1453, 1434, 1377, 1274, 1247, 1189, 1135, 1074, 992, 921, 792, 738, 702, 626, 612, 542, 478 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.23-7.20 (m, 2H), 7.16-7.11 (m, 3H), 6.95-6.93 (m, 1H), 3.86 (s, 2H), 2.19-2.15 (m, 4H), 1.57-1.48 (m, 4H) ppm. ¹³C (100 MHz, CDCl₃): δ 198.6, 141.1, 139.1, 135.5, 129.3, 128.5, 126.6, 44.0, 26.2, 23.3, 21.9, 21.5 ppm. Spectral data were in accordance with the literature⁶. EI MS, m/z: 200 (3), 128 (1), 115 (1), 109 (100), 91 (13), 81 (55), 65 (8), 53 (8).

Figure 59: ¹H NMR of compound 22
1-(cyclohex-1-en-1-yl)-2-(3-methoxyphenyl)ethan-1-one: Using the general procedure outlined above with 3-bromoanisole (133 μL), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 94% petroleum ether / 6% ethyl acetate with one drop of triethylamine (Rf = 0.48) and 0.210 g (90%) of a yellow free flowing oil was isolated. IR (neat): 2931, 2835, 2859, 1656, 1635, 1597, 1583, 1489, 1452, 1434, 1378, 1257, 1188, 1148, 1045, 993, 921, 872, 764, 703, 689, 618, 581, 546, 478 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.08 (t, 1H, \(J = 7.6\) Hz), 6.89 (t, 1H, \(J = 3.6\) Hz), 6.67-6.63 (m, 3H), 3.79 (s, 2H), 3.65 (s, 3H), 2.11 (t, 4H, \(J = 3.2\) Hz), 1.51-1.46 (m, 4H) ppm. \(^{13}\)C (100 MHz, CDCl\(_3\)): \(\delta\) 198.5, 159.7, 141.2, 139.0, 137.0, 129.5, 121.6, 114.9, 112.1, 5.2, 44.1, 26.2, 23.3, 21.9, 21.5 ppm. EI MS, m/z: 230 (13), 202 (13), 121 (8), 109 (100), 91 (8), 81 (46), 65 (5), 53 (9).

Figure 60: \(^{13}\)C NMR of compound 22
Figure 61: $^1$H NMR of compound 23

Figure 62: $^{13}$C NMR of compound 23
6.2.4 γ-arylation of methyl-1-cyclohexene-1-carboxylate General Procedures and Data

All reactions were prepared at the 1.0 mmol scale in a glovebox using 8-mL screw cap vials with a Teflon-coated stir bar. The vial was charged with 4\% Xantphos Pd G3 (0.04 mmol), LiHMDS (3 eq.), methyl-1-cyclohexene-1-carboxylate (1 mmol), and an aryl bromide (1.05 mmol). Finally, 5 mL of THF was added to the reaction vial. The reaction was capped, removed from the glovebox, and allowed to stir on an aluminum block preheated to 50 °C for 24 hours. A standard workup was completed using about 2.5 mL of a 2.0 M HCl solution and dichloromethane to extract. Magnesium sulfate was utilized to dry the sample before gravity filtering and removing the solvent under reduced pressure. Completion was checked using TLC and GC-MS. The crude reaction mixture was loaded onto a silica gel column using a wet load technique. The yields reported in this thesis are from one trial only.

methyl 3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-carboxylate: Using the general procedure outlined above with bromobenzene (111 \( \mu \)L), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 94\% petroleum ether / 6\% ethyl acetate with one drop of triethylamine (Rf = 0.31) and 0.135 g (63\%) of a yellow free flowing oil was isolated. IR (neat): 3023, 2946, 2863, 173, 1598, 1494, 1444, 1433, 1256, 1208, 1155, 1035, 1024, 934, 905, 848, 830, 759, 744, 694 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.27-7.25 (m, 2H), 7.20-7.16 (m, 2H), 7.13-7.09 (m, 1H), 6.02 (dt, 1H, \( J = 3.3, 1.6 \) Hz), 3.58 (s, 3H), 3.19-3.13 (m, 1H), 2.37-2.23 (m, 2H), 1.86-1.73 (m, 3H), 1.65-1.59 (m, 1H) ppm. \(^{13}\)C (100 MHz, CDCl\(_3\)): \( \delta \) 174.8, 141.9, 139.1, 128.3, 127.2, 125.3, 121.4, 51.9, 41.9, 27.2, 24.9, 21.4 ppm. EI MS, m/z: 216 (36), 201 (1), 184 (10), 157 (100), 141 (13), 129 (28), 115 (21), 102 (3), 91 (57), 77 (10), 65 (2), 51 (3).

-When 5\% Xantphos Pd G3 was used, 60\% of compound 35 was isolated.
Figure 63: $^1$H NMR of compound 24

Figure 64: $^{13}$C NMR of compound 24
methyl 4’-methoxy-3,4,5,6-tetrahydro-[1,1’-biphenyl]-3-carboxylate: Using the general procedure outlined above with 4-bromoanisole (131 μL), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 85% petroleum ether / 15% diethyl ether (Rf = 0.31) and 0.0979 g (40%) of a light yellow solid was isolated. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.28-7.24 (m, 2H), 6.79-6.76 (m, 2H), 5.99 (dt, 1H, $J$ = 3.4, 1.6 Hz), 3.72 (s, 3H), 3.63 (s, 3H), 3.21-3.18 (m, 1H), 2.36-2.27 (m, 2H), 1.92-1.75 (m, 3H), 1.71-1.60 (m, 1H) ppm. ESI MS, m/z: 246 (34), 231 (1), 187 (100), 172 (5), 159 (5), 145 (6), 131 (1), 121 (29), 103 (2), 91 (1), 79 (60), 63 (1), 51 (1).

Figure 65: $^1$H NMR of compound 25
**methyl 3'-methoxy-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-carboxylate:** Using the general procedure outlined above with 3-bromoanisole (μL), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 85% petroleum ether / 10% dichloromethane / 5% EtOAc (Rf = 0.26) and 0.133 g (45%) of a light yellow solid was isolated. 

\(^1\)H NMR (400 Hz, CDCl\(_3\)): δ 7.10 (t, 1H, J = 8.0 Hz), 6.86 (d, 1H, J = 7.8 Hz), 6.80 (t, 1H, J = 2.0 Hz), 6.67 (dd, 1H, J = 8.2, 2.0 Hz), 6.02 (dt, 1H, J = 3.4, 1.7 Hz), 3.68 (s, 3H), 3.58 (s, 3H), 3.17-3.13 (m, 1H), 2.36-2.23 (m, 2H), 1.86-1.73 (m, 3H), 1.66-1.56 (m, 1H) ppm. \(^13\)C (100 MHz, CDCl\(_3\)): δ 174.8, 159.6, 143.5, 139.0, 129.2, 121.7, 117.9, 112.5, 111.3, 55.2, 51.9, 41.9, 27.2, 24.8, 21.4 ppm. EI MS, m/z: 246 (60), 231 (1), 214 (1), 187 (100), 172 (8), 159 (13), 145 (10), 131 (3), 121 (47), 103 (3), 91 (7), 79 (19), 59 (2), 50 (1).

- Isolated yield when reaction was run at 60°C = 30%

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**Figure 66:** \(^1\)H NMR of compound 26
methyl 3-(benzofuran-5-yl)cyclohex-1-ene-1-carboxylate: Using the general procedure outlined above with 5-bromobenzofuran (132 μL), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 85% petroleum ether / 10% dichloromethane / 5% ethyl acetate (Rf = 0.28) and 0.120 g (47%) of a solid was isolated. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.45 (s, 2H), 7.29 (d, 1H, $J$ = 8.6 Hz), 7.21 (dd, 1H, $J$ = 8.6, 1.4 Hz), 6.59 (d, 1H, $J$ = 1.2 Hz), 5.99 (t, 1H, $J$= 1.6 Hz), 3.58 (s, 3H), 3.18-3.16 (m, 1H), 2.38-2.28 (m, 2H), 1.90- 1.73 (m, 3H), 1.65-1.56 (m, 1H) ppm. EI MS, m/z: 256 (44), 241 (1), 197 (100), 181 (5), 169 (10), 155 (10), 141 (8), 131 (44), 115 (7), 102 (1), 89 (2), 79 (12), 63 (2), 51 (1).
**Figure 68:** $^1$H NMR of compound 27

**methyl 4'-(dimethylamino)-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-carboxylate:** Using the general procedure outlined above with 4-bromo-n,n-dimethylaniline (0.211 g), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 80% petroleum ether / 20% ethyl acetate / one drop of triethylamine (RF = 0.69) and 0.0949g (37%) of an yellow solid was isolated. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.24 (d, 2H, $J = 8.9$ Hz), 6.62 (d, 2H, $J = 8.8$ Hz), 5.96 (dt, 1H, $J = 3.3, 1.7$ Hz), 3.64 (s, 2H), 3.23-3.17 (m, 1H), 2.87 (s, 6H), 2.38-2.28 (m, 2H), 1.89-1.77 (m, 3H), 1.69-1.60 (m, 1H) ppm. $^{13}$C (100 MHz, CDCl$_3$): $\delta$ 175.2, 149.9, 138.5, 130.0, 125.9, 118.1, 112.3, 51.8, 41.9, 40.6, 27.0, 25.0, 21.5 ppm. EI MS, m/z: 259 (100), 244 (3), 228 (5), 200 (71), 184 (10), 172 (28), 158 (10), 144 (5), 134 (11), 115 (6), 100 (4), 89 (1), 77 (3), 59 (2).
Figure 69: $^1$H NMR of compound 28

Figure 70: $^{13}$C NMR of compound 28
**methyl 3-(pyridin-3-yl)cyclohex-1-ene-1-carboxylate:** Using the general procedure outlined above with 3-bromopyridine (101 μL), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 80% ethyl acetate / 10% petroleum ether / one drop of triethylamine (Rf = 0.36) and 0.128g (59%) of a yellow viscous oil was isolated. IR (neat): 3030, 2946, 2863, 1729, 1567, 1433, 1413, 1209, 1190, 1157, 1059, 1022, 929, 906, 858, 832, 801, 753, 709, 621, 540, 515, 458 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 8.66 (d, J = 1.8 Hz), 8.49 (dd, 1H, J = 4.7, 1.3 Hz), 7.68 (dt, 1H, J = 8.0, 2.0 Hz), 7.24 (ddd, 1H, J = 7.9, 4.8, 0.4 Hz), 6.21 (dt, 2H, J = 3.5, 1.8 Hz), 3.74 (s, 3H), 3.34-3.29 (m, 1H), 2.51-2.36 (m, 2H), 2.05-1.86 (m, 3H), 1.83-1.73 (m, 1H) ppm. ¹³C (100 MHz, CDCl₃): 174.4, 148.3, 146.9, 137.1, 136.4, 132.5, 123.2, 123.1, 52.0, 41.8, 26.9, 24.7, 21.2 ppm. El MS, m/z: 217 (22), 202 (2), 185 (17), 158 (100), 143 (16), 130 (15), 117 (9), 103 (2), 92 (35), 77 (6), 65 (4), 51 (4).

**Figure 71:** ¹H NMR of compound 29
Figure 72: $^{13}$C NMR of compound 29

methyl 4'-fluoro-3,4,5,6-tetrahydro-[1,1'-biphenyl]-3-carboxylate: Using the general procedure outlined above with 1-bromo-4-fluorobenzene (115 μL), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 94% petroleum ether / 6% ethyl acetate / one drop of triethylamine (Rf = 0.29) and 0.0964 g (41%) of an oil was isolated. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.25-7.20 (m, 2H), 6.89-6.83 (m, 2H), 5.96 (dt, 1H, $J = 3.4$, 1.7 Hz), 3.59 (s, 3H), 3.17-3.12 (m, 1H), 2.33-2.20 (m, 2H), 1.87-1.70 (m, 3H), 1.67-1.55 (m, 1H) ppm. $^{13}$C (100 MHz, CDCl$_3$): 174.7, 162.1 (d, $J = 244$ Hz), 138.1, 137.9 (d, $J = 3.4$ Hz), 126.9, 126.8, 121.3, 115.1, 114.9, 51.9, 41.8, 27.3, 24.8, 21.4 ppm. $^{19}$F NMR (376 MHz, DMSO) δ -115.69 (s) ppm. EI MS, m/z: 234 (28), 219 (1), 202 (5), 175 (100), 159 (10), 147 (22), 133 (17), 120 (4), 109 (67), 96 (2), 77 (5), 59 (2).
Figure 73: $^1$H NMR of compound 30

Figure 74: $^{13}$C NMR of compound 30
Figure 75: $^{19}$F NMR of compound 30

6.2.4.1 Consecutive amide formation/ Heck cyclization of methyl-1-cyclohexene-1-carboxylate

Scheme 30: Reaction conditions for the consecutive amide formation/ Heck cyclization of methyl-1-cyclohexene-1-carboxylate

The reaction was prepared at the 1.0 mmol scale in a glovebox using 8-mL screw cap vials with a Teflon-coated stir bar. The vial was charged with 4% Xantphos Pd G3 (0.04 mmol), LiHMDS (3 eq.), methyl-1-cyclohexene-1-carboxylate (1 mmol), and 2-bromoaniline (1.05 mmol). Finally, 5 mL of THF was added to the reaction vial. The reaction was capped, removed from the glovebox, and allowed to stir on an aluminum block preheated to 100 °C for 6 hours. After 6 hours, the vial was removed from the aluminum block, was cooled to room temperature,
and 10% Xantphos Pd G3 was added. The vial was placed back on the aluminum block set to 100 °C for 18 hours. A standard workup was completed using a 2.0 M HCl solution and dichloromethane to extract. Magnesium sulfate was utilized to dry the sample before gravity filtering and removing the solvent under reduced pressure. Completion was checked using TLC and GC-MS. The crude reaction mixture was loaded onto a silica gel column using a wet load technique. The yields reported in this thesis are from one trial only.

\[ \text{31} \]

**spiro[cyclohexane-1,3'-indolin]-3-en-2'-one + spiro[cyclohexane-1,3'-indolin]-2-en-2'-one:**

Using the general procedure outlined above with 2-bromoaniline (119 µL), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 80% petroleum ether / 20% ethyl acetate (RF = 0.23) and 0.175 g (88%) of a light yellow solid was isolated. EI MS, m/z: 199 (100), 182 (28), 170 (54), 159 (1), 152 (7), 145 (81), 130 (12), 117 (38), 103 (4), 90 (12), 77 (10), 63 (6), 51 (5). NMR assignments shown in Figures 76 -80.

**Figure 76:** $^1$H NMR of compound 31
**Figure 77:** \(^{13}\text{C}\) NMR of compound 31

**Figure 78:** Zoom in of \(^{13}\text{C}\) NMR of compound 31
Figure 79: HSQC of compound 31

Figure 80: COSY of compound 31
6.3 Mizoroki-Heck Reaction

6.3.1 Birch reduction/alkylation General Procedures and Data

Scheme 31: Birch/reduction alkylation general reaction sequence

Procedure:
A flame dried 3-necked roundbottom flask with a stir bar, connected to a Dewar condenser, under argon, was charged with benzoic acid (1.0 eq) which was dissolved in THF (0.43 mL / mmol) and cooled to -78°C. Ammonia (7 mL / mmol) was distilled into the flask and lithium (4.0 eq) was added in small pieces until a dark blue color was maintained for 30 minutes. Isoprene was added dropwise to quench the lithium and produce a bright yellow opaque solution. Alkylating agent (2.0 eq) in THF (0.43 mL / mmol) was added slowly dropwise. When the addition was complete the reaction was maintained at -78°C while the color faded to white/off-white over 1h. The reaction was then warmed to room temperature and the ammonia was allowed to evaporate under a stream of argon. Once evaporated the reaction was quenched with water, and washed with diethyl ether. The aqueous layer was acidified with 6N HCl (until pH ~1), and then extracted with diethyl ether. The combined organic layers were washed with saturated sodium thiosulfate, brine, dried with MgSO4, and concentrated in vacuo.

1-benzylcyclohexa-2,5-diene-1-carboxylic acid: Using the general procedure and workup outlined above with benzyl chloride (3.8 mL), 3.3502 g (94%) of a white crystalline solid was isolated. m.p. = 71.9-75.0°C. FTIR-ATR: 3827, 3027, 2861, 2815, 1692, 1494, 1443, 1412, 1308, 1287, 1270, 939, 776, 759, 697, 632, 596 527, 500, 469 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.28 – 7.14 (m, 3H), 7.17 – 7.09 (m, 2H), 5.91 – 5.77 (m, 4H), 3.03 (s, 2H), 2.56 (dhept, J = 23.1, 1.2 Hz, 2H), 2.36 (dhept, J = 23.1, 1.6 Hz, 1H) ppm. ¹³C NMR (101 MHz, CDCl₃) δ 179.87, 136.25, 130.55, 127.80, 126.55, 126.42, 48.94, 46.06, 26.01 ppm. Spectral data were in accordance with the literature.⁷ EI MS, m/z: 214 (1), 196 (1), 165 (7), 152 (5), 139 (2), 123 (14), 115 (3), 105 (6), 92 (100), 79 (30), 65 (17), 51 (7).
**Figure 81**: $^1$H NMR of compound 32

**Figure 82**: $^{13}$C NMR of compound 32
1-(cyanomethyl)cyclohexa-2,5-diene-1-carboxylic acid: Using the general procedure and workup outlined above with chloroacetonitrile (2.204 g, 18.0 mmol). 2.335 g (80%) of a tan solid was isolated. m.p. = 98.3-102.3°C. FTIR-ATR: 3150, 2937, 2810, 2582, 2269, 1719, 1682, 1452, 1416, 1405, 1383, 1323, 1288, 1223, 1213, 1085, 1034, 937, 889, 836, 727, 667, 630, 567, 472 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): 6.15 (dt, 2H, J = 10.3, 3.4 Hz), 5.76 (dt, 2H, J = 10.4, 2.0 Hz), 2.81-2.78 (m, 2H), 2.76 (s, 2H) ppm. \(^{13}\)C (100 MHz, CDCl\(_3\)) 176.6, 129.4, 123.4, 45.8, 28.2, 26.1 ppm. Spectral data were in accordance with the literature.\(^8\) EI MS, m/z: 160 (4), 131 (1), 124.0 (100), 117 (6), 105 (8), 91 (8), 79 (18), 65 (2), 55 (20).

Figure 83: \(^1\)H NMR of compound 33
[1,1'-bi(cyclohexane)]-2,5-diene-1-carboxylic acid: Using the general procedure and workup outlined above with benzoic acid (3.09 g, 25.34 mmol). 5.00 g (96%) of an off-white solid was isolated. m.p.= 120.5-125.5°C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.93 (dtd, $J = 10.6, 3.3, 1.6$ Hz, 2H), 5.74 (ddt, 2H, $J = 19.6, 10.6, 2.0$ Hz), 2.62 (tdd, 2H, $J = 5.4, 3.4, 2.1$ Hz), 1.77 – 1.70 (m, 3H), 1.63 (d, 3H, $J = 12.6$ Hz), 1.22 (qt, 2H, $J = 12.9, 3.3$ Hz), 1.12 – 0.95 (m, 3H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 180.6, 126.7, 125.7, 51.8, 45.9, 27.6, 26.6, 26.5, 26.3 ppm. EI MS, m/z: 206 (1), 160 (4), 131 (1), 124 (100), 117 (6), 105 (8), 91 (8), 79 (18), 65 (2), 5 (20).
Figure 85: $^1$H NMR of compound 34

Figure 86: $^{13}$C NMR of compound 34
1-isobutylcyclohexa-2,5-diene-1-carboxylic acid: Using the general procedure and workup outlined above with benzoic acid (2.06 g, 16.89 mmol) and 1-iodo-2-methylpropane (3.60 mL, mmol). 2.87 g (94%) of an orange oil was isolated. $^1$H NMR (400 MHz, CDCl$_3$) δ 5.89 (dtd, 2H, $J = 10.5, 3.3, 1.7$ Hz), 5.78 (dp, 2H, $J = 10.5, 1.9$ Hz), 2.66 (ttd, 2H, $J = 3.1, 2.0, 0.8$ Hz, 2H), 1.76 – 1.65 (m, 3H), 0.89 (d, 6H, $J = 6.4$ Hz) ppm. $^{13}$C (101 MHz, CDCl$_3$) 181.3, 127.4, 125.6, 48.2, 47.7, 26.1, 24.8, 24.2 ppm. Spectral data were in accordance with the literature.$^9$ EI MS, m/z: 180 (1), 135 (61), 123 (49), 115 (2), 105 (15), 91 (49), 79 (63), 65 (10), 57 (100), 51 (8).

**Figure 87:** $^1$H NMR of compound 35
Figure 88: $^{13}$C NMR of compound 35

1-(methoxymethyl)cyclohexa-2,5-diene-1-carboxylic acid: Using the general procedure and workup outlined above with benzoic acid (3.02 g, 24.76 mmol). 3.74 g (90%) of a white solid was isolated. m.p. = 66.9-70.5$^\circ$C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.01 – 5.93 (m, 2H), 5.84 (dt, 2H, $J = 10.5, 2.0$ Hz), 3.52 (s, 2H), 3.37 (s, 3H), 2.71 (m, 2H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 178.2, 127.2, 124.4, 78.7, 59.5, 49.2, 26.3 ppm. Spectral data were in accordance with the literature. EI MS, m/z: 136 (5), 122 (15), 106 (100), 91 (47), 77 (42), 65 (9), 51 (10).
Figure 89: $^1$H NMR of compound 36

Figure 90: $^{13}$C NMR of compound 36
1-(naphthalen-1-ylmethyl)cyclohexa-2,5-diene-1-carboxylic acid: Using the general procedure and workup outlined above with 1-(chloromethyl)napthalene (2.28 g, 18.7 mmol). 4.43 g (90%) of a light-yellow solid was isolated. m.p. = 130.5-133.8. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.09 (ddd, 1H, $J = 7.2, 2.8, 1.6$ Hz), 7.82 (dd, 1H, $J = 7.8, 1.8$ Hz), 7.76 – 7.70 (m, 1H), 7.46 (tdt, 2H, $J = 10.6, 6.8, 3.5$ Hz), 7.39 – 7.34 (m, 2H), 5.87 (dt, 2H, $J = 10.5, 1.9$ Hz), 5.79 (dt, 2H, $J = 10.3, 3.2$ Hz), 3.56 (s, 2H), 2.54 (dheptd, 1H, $J = 13.0, 1.8$ Hz), 2.36 (dhept, 1H, $J = 13.1, 1.8$ Hz) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 179.8, 133.7, 132.7, 128.6, 128.6, 127.5, 126.8, 126.2, 125.5, 125.3, 125.1, 124.8, 49.3, 41.7, 26.0 ppm. EI MS, m/z: 218 (100), 202 (35), 189 (8), 163 (2), 152 (2), 141 (13), 115 (8), 108 (8), 91 (4), 65 (3).

GCMS shows the mass for: MW: 218.30. Birch degrades in GCMS.

Figure 91: $^1$H NMR of compound 37
Figure 92: $^{13}$C NMR of compound 37

1-(but-3-en-1-yl)cyclohexa-2,5-diene-1-carboxylic acid: Using the general procedure and workup outlined above with benzoic acid (3.19 g, 26.08 mmol). 4.12 g (89%) of a dark yellow free flowing oil was isolated. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.93 (dtd, 2H, $J$ = 10.6, 3.4, 1.8 Hz), 5.86 – 5.71 (m, 3H), 5.00 (dq, 1H, $J$ = 17.1, 1.7 Hz), 4.94 (dq, 1H, $J$ = 10.2, 1.5 Hz), 2.66 (dtt, 2H, $J$ = 4.3, 3.3, 2.1 Hz), 2.00 (ddddd, 2H, $J$ = 12.7, 6.4, 3.2, 1.6 Hz), 1.84 – 1.75 (m, 2H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 181.0, 138.1, 133.8, 130.2, 128.5, 126.5, 126.4, 114.7, 47.6, 38.4, 28.6, 26.2 ppm. EI MS, m/z: 177 (1), 160 (3), 133 (11), 123 (5), 115 (1), 105 (6), 91 (100), 79 (20), 65 (6), 55 (11).
Figure 93: $^1$H NMR of compound 38

Figure 94: $^{13}$C NMR of compound 38
1-(but-3-yn-1-yl)cyclohexa-2,5-diene-1-carboxylic acid: Using the general procedure and workup outlined above with benzoic acid (2.05 g, 16.8 mmol). 2.88 g (89%) of a tan solid was isolated. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.02 – 5.92 (m, 2H), 5.70 (dp, 3H, $J = 10.6, 2.0$ Hz), 2.76 – 2.56 (m, 2H), 2.16 – 1.91 (m, 7H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 156.5, 127.3, 125.5, 83.9, 68.6, 47.4, 37.6, 26.1, 13.8 ppm. EI MS, m/z: 176 (1), 131 (68), 123 (5), 116 (10), 105 (7), 91 (100), 77 (24), 65 (9), 51 (8).

Figure 95: $^1$H NMR of compound 39
Figure 96: $^{13}$C NMR of compound 39

1-(sec-butyl)cyclohexa-2,5-diene-1-carboxylic acid: Using the general procedure and workup outlined above with benzoic acid (2.06 g, 16.9 mmol). 2.82 g (93%) of an orange oil was isolated. $^1$H NMR (400 MHz, CDCl$_3$) δ 5.97-5.91 (m, 2H), 5.74-5.70 (m, 2H), (2.76-2.56 (m, 2H), 1.86-1.78 (m, 1H), 1.53-1.43 (m, 2H), 0.88 (dd, 8H, $J = 16.3, 7.2$ Hz) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) δ 181.4, 127.0, 126.6, 125.7, 125.6, 52.5, 42.6, 26.5, 24.4, 13.6, 12.4 ppm. EI MS, m/z: 180 (1%$^+$), 135 (2), 123 (100), 115 (1), 105 (17), 91 (11), 79 (41), 65 (2), 57 (13), 51 (6).
Figure 97: $^1$H NMR of compound 40.

Figure 98: $^{13}$C NMR of compound 40.
1-(2-amino-2-oxoethyl)cyclohexa-2,5-diene-1-carboxylic acid: Using the general procedure and workup outlined above with benzoic acid (2.10 g, 17.2 mmol) and 2-chloroacetamide (3.21 g, 34.3 mmol). 1.71 g (55%) of a light-yellow oil was isolated. $^1$H NMR (400 MHz, CDCl$_3$) δ 5.93 (ddq, 2H, $J = 10.4, 3.3, 1.9$ Hz), 5.84 (ddt, 1H, $J = 10.4, 3.7, 2.0$ Hz), 2.71 (dqt, 1H, $J = 9.2, 3.5, 2.0$ Hz), 2.41 (m, 1H), 2.22-2.16 (m, 1H) ppm.

GCMS had benzoic acid peak only. Proton NMR has product peaks, however, there is still a lot of benzoic acid and another impurity, which is shown in Figure _.

Figure 99: $^1$H NMR of compound 41, benzoic acid is still present.
1-(2,2,2-trifluoroethyl)cyclohexa-2,5-diene-1-carboxylic acid: Using the general procedure and workup outlined above with benzoic acid (3.02 g, 24.7 mmol) and 1,1,1-trifluoro-2-iodoethane (4.87 mL, 49.4 mmol). 3.05 g of a crude solid was isolated. The NMR contained mainly benzoic acid with a trace amount of product.

Figure 100: $^1$H NMR of compound 42

Ammonium 1-((1H-benzo[d][1,2,3]triazol-1-yl)methyl)cyclohexa-2,5-diene-1-carboxylate: Using the general procedure and workup outlined above with benzoic acid (2.08 g, 17.0 mmol) and 1-(chloromethyl)-1H-benzotriazole. 6.42 g (>100%) of a white solid was isolated. No workup was done besides transferring the solid to another roundbottom flask using methanol and
concentrating the solution in vacuo to produce a white solid. $^1$H NMR (400 MHz, CD$_3$OD) δ 7.88 (d, 1H, $J = 7.9$ Hz), 7.83 (d, 1H, $J = 8.4$ Hz), 7.48 (ddd, 1H, $J = 8.2$, 6.9, 1.0 Hz), 7.36 (ddd, 1H, $J = 8.1$, 6.8, 1.0 Hz), 5.96 (dt, 2H, $J = 10.5$, 2.0 Hz), 5.60 (dt, 1H, $J = 10.5$, 3.4 Hz), 4.96 (s, 2H), 2.40 (dhept, 1H, $J = 23.0$, 1.8 Hz), 1.94 (dp, 1H, $J = 23.0$, 2.8 Hz) ppm.

![Figure 101: $^1$H NMR of compound 43](image.png)

1-methylcyclohexa-2,5-diene-1-carboxylic acid: Using the general procedure and workup outlined above with benzoic acid (3.02 g, 24.7 mmol) and iodomethane (3.08 mL, 49.5 mmol). 3.15 g (92%) of a white solid was isolated. $^1$H NMR (400 MHz, CDCl$_3$) δ 5.87-5.83 (m, 2H), 5.78 (dt, 2H, $J = 10.4$, 1.9 Hz), 2.74-2.59 (m, 2H), 1.37 (s, 3H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) δ 181.6, 128.1, 125.0, 43.7, 27.2, 25.9 ppm. Spectral data were in accordance with the literature.$^{10}$ EI MS, m/z: 138 (2), 105 (1), 93 (100), 77 (53), 65 (9), 51 (8).
**Figure 102:** $^1$H NMR of compound 44

**Figure 103:** $^{13}$C NMR of compound 44
6.3.2 Benzamide General Procedures and Data

Scheme 32: Benzamide general procedure

**General Acid Chloride synthesis procedure:**
In a round bottom flask with a stir bar, oxalyl chloride (2.2 eq) was dissolved in DCM. Then a catalytic amount of DMF (1.38 μL/mmol) was added. The Birch product (1.0 mmol) was dissolved in DCM and added dropwise to the flask. The reaction was refluxed under Argon for an hour until it turned deep yellow. Once completed, the reaction was concentrated under vacuum to remove excess oxalyl chloride and taken immediately to the next step without further characterization of these intermediates.

**Benzamide synthesis procedure:**
In a round bottom flask with a stir bar, purified 2-(methylamino) phenol or 2-aminophenol or 2-bromoaniline (1.3-1.6 eq) was dissolved in DCM and cooled to 0°C. Triethylamine (2.5 eq) was added dropwise and after a few minutes, the acid chloride in DCM was added. The mixture was allowed to warm to room temperature and react overnight. The reaction mixture was diluted with DCM and washed with NaHCO₃, 1N HCl, water, brine and dried with MgSO₄. The product was then concentrated under vacuum. NMRs were taken in (CD₃)₂SO and were heated to 100°C. Heat was needed to coalesce the peaks due to atropisomers that formed in the reaction.

1-benzyl-N-(2-hydroxyphenyl)cyclohexa-2,5-diene-1-carboxamide: Using the general procedure and workup outlined above, (0.216 g, 0.93 mmol) of the acid chloride was used. This reaction yielded 0.248 (87%) of an orange solid. ¹H NMR (400 MHz, CDCl₃): δ 8.84 (s, 1H), 7.71 (s, 1H), 7.26-7.17 (m, 5H), 7.11 (ddd, 1H, J = 8.8, 6.3, 2.6 Hz), 7.01 (d, 1H, J = 7.6 Hz), 6.85-6.79 (m, 2H), 6.00 (dt, 2H, J = 10.4, 3.4 Hz), 5.83 (dt, 2H, J = 10.4, 2.0 Hz), 3.19 (s, 2H), 2.70 (dp, 1H, J = 23.5, 3.0 Hz), 2.57 (dh, 1H, J = 23.5, 1.7 Hz) ppm. ¹³C (100 MHz, CDCl₃): δ 174.3, 148.9, 136.7, 130.6, 128.0, 127.4, 127.3, 126.5, 122.2, 120.2, 120.0, 50.2, 44.0, 26.2 ppm. EI MS, m/z:
305 (9), 214 (11), 196 (14), 170 (47), 152 (4), 136 (18), 105 (58), 91 (100), 77 (18), 65 (14), 51 (4).

Figure 104: $^1$H NMR of compound 45

Figure 105: $^{13}$C NMR of compound 45
N-(2-hydroxyphenyl)-1-isobutylecyclohexa-2,5-diene-1-carboxamide: Using the general procedure and workup outlined above, (0.229 g, 1.20 mmol) of the acid chloride was used. This reaction yielded 0.315 g (99%) of a dark orange solid. ¹H NMR (400 MHz, CDCl₃): δ 7.82 (s, 1H), 7.17-7.15 (m, 1H), 7.11 (td, 1H, J = 7.7, 1.6 Hz), 6.98 (dd, 1H, J = 8.2, 1.5 Hz), 6.87 (td, 1H, J = 7.6, 1.4 Hz), 6.31-6.26 (m, 2H), 5.84 (dt, 2H, J = 10.4, 2.1 Hz), 3.01-2.83 (m, 4H) ppm. ¹³C (100 MHz, CDCl₃): δ 171.3, 147.9, 130.5, 127.2, 125.1, 124.7, 121.9, 120.8, 119.2, 117.1, 47.4, 27.1, 26.1 ppm. EI MS, m/z: 209 (15), 196 (62), 136 (67), 117 (32), 105 (23), 92 (100), 77 (25), 65 (18), 51 (12).

Figure 106: ¹H NMR of compound 46
1-benzyl-N-(2-bromophenyl)cyclohexa-2,5-diene-1-carboxamide: Using the general procedure and workup outlined above, (0.550 g, 2.36 mmol) of the acid chloride was used. 0.819g (94%) of a red/tan solid was isolated. $^1$H NMR (400 MHz, CDCl$_3$): δ 8.43 (dd, 1H, $J = 8.2, 1.6$ Hz), 8.31 (s, 1H), 7.48 (dd, 1H, $J = 8.0, 1.4$ Hz), 7.33-7.29 (m, 1H), 7.25-7.16 (m, 5H), 6.95 (td, 1H, $J = 7.7, 1.6$ Hz), 5.99 (dt, 2H, $J = 10.2, 3.4$ Hz), 5.82 (dt, 2H, $J = 10.4, 2.0$ Hz), 3.21 (s, 2H), 2.73 (dp, 1H, $J = 23.4, 3.0$ Hz), 2.56 (dh, 1H, $J = 23.4, 1.8$ Hz) ppm. $^{13}$C (100 MHz, CDCl$_3$): δ ppm. EI MS, m/z: 367 (9), 276 (18), 262 (3), 196 (30), 170 (14), 152 (4), 120 (4), 105 (30), 91 (100), 77 (11), 63 (3).

**Figure 107:** $^{13}$C NMR of compound 46
Figure 108: $^1$H NMR of compound 85

Figure 109: $^{13}$C NMR of compound 47
1-benzyl-N-(2-hydroxyphenyl)-N-methylcyclohexa-2,5-diene-1-carboxamide: Using the general procedure and workup outlined above, (5.36g, 23.0 mmol) of the acid chloride was used. This reaction yielded >100% of a light brown solid. IR (neat): 3164, 3027, 1616, 1582, 1494, 1450, 1414, 1289, 1135, 1063, 1031, 798, 756, 695, 674, 630, 586, 508, 476 cm\(^{-1}\).\(^{1}\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta \) 9.08 (s, 1H), 7.08 (m, 6H), 6.85 (dd, 1H, \(J=7.7, 1.5\) Hz), 6.75 (d, 1H, \(J=8.0\) Hz), 6.60 (t, 1H, \(J=7.6\) Hz), 5.46 (d, 2H, \(J=9.5\) Hz), 5.22 (d, 2H, \(J=6.0\) Hz), 3.04 (s, 3H), 2.99 (s, 2H), 1.91 (q, 2H, \(J=23\) Hz) ppm. \(^{13}\)C (100 MHz, DMSO-\(d_6\)): \(\delta \) 138.1, 131.4, 129.2, 127.5, 126.1, 119.1, 116.2, 50.5, 46.4, 39.0, 26.0 ppm. EI MS, \(m/z\): 319 (9), 227 (23), 210 (7), 196 (13), 167 (51), 150 (59), 135 (5), 123 (80), 105 (100), 91.0 (98), 77 (28), 65 (17), 51 (9).

**Figure 110:** \(^{1}\)H NMR of compound 48
Figure 111: $^{13}$C NMR of compound 48

1-(cyanomethyl)-N-(2-hydroxyphenyl)-N-methylcyclohexa-2,5-diene-1-carboxamide: Using the general procedure outlined above with 1-(cyanomethyl)cyclohexa-2,5-diene-1-carbonyl chloride (1.1228, 6.18 mmol), 1.5938 g (96%) of a dark yellow/brown oil was isolated. $^1$H NMR (400 MHz, DMSO-d$_6$, 100 degrees): 9.24 (s, 1H), 7.08 (td, 1H, $J$ = 8.0, 1.6 Hz), 7.00 (dd, 1H, $J$ = 8.0, 1.6 Hz), 6.80 (dd, 1H, $J$ = 8.2, 1.1 Hz), 6.66 (td, 1H, $J$ = 7.6, 1.1 Hz), 5.56 (s, 4H), 3.05 (s, 3H), 2.73 (s, 2H), 2.38 (d, 1H, $J$ = 24.0 Hz), 2.02 (d, 1H, $J$ = 24 Hz) ppm. $^{13}$C (100 MHz, DMSO-d$_6$): 170.1, 154.1, 153.1, 137.1, 130.8, 129.9, 129.6, 129.0, 127.9, 127.3, 127.0, 125.5, 124.1, 119.8, 119.2, 119.0, 116.8, 116.4, 47.4, 46.2, 38.9, 30.2, 26.3 ppm. EI MS, m/z: 268 (14), 150 (100), 135 (5), 123 (62), 108 (14), 91 (28), 77 (13), 65 (9), 51 (5).
Figure 112: $^1$H NMR of compound 49

Figure 113: $^{13}$C NMR of compound 49
N-(2-hydroxyphenyl)-N-methyl-[1,1'-bi(cyclohexane)]-2,5-diene-1-carboxamide: Using the general procedure outlined above with [1,1'-bi(cyclohexane)]-2,5-diene-1-carbonyl chloride (1.61 g, 7.16 mmol), 2.16 g (97%) of a light brown solid was isolated. $^1$H NMR (400 MHz, DMSO-d$_6$ 100 degrees): 9.10 (s, 1H), 7.07 (td, 1H, $J = 7.9$, 1.6 Hz), 13.8 (dd, 1H, $J = 7.8$, 1.5 Hz), 6.79 (dd, 1H, $J = 8.2$, 1.5 Hz), 6.64 (td, 1H, $J = 7.4$, 1.2 Hz), 5.34 (s, 4H), 3.00 (s, 3H), 2.23 (q, 2H, $J = 23.0$ Hz), 1.93 (tt, $J = 12.0$, 3.2 Hz, 1H), 1.61 (dd, 6H, $J = 37.6$, 11.6 Hz), 1.15 (qt, 3H, $J = 12.8$, 3.3 Hz), 0.98 (qt, 1H, $J = 12.7$, 3.4 Hz), 0.83 (qd, 2H, $J = 12.5$, 3.0 Hz) ppm. $^{13}$C (100 MHz, DMSO-d$_6$): 176.5, 152.0, 129.4, 128.6, 126.9, 125.8, 125.3, 120.7, 111.2, 54.0, 46.2, 39.6, 27.8, 26.7, 26.6, 26.5 ppm. EI MS, m/z: 311 (5), 228 (15), 210 (1), 196 (2), 151 (21), 135 (1), 123 (100), 105 (21), 83 (32), 67 (3), 55 (18).

Figure 114: $^1$H NMR of compound 50
Figure 115: $^{13}$C NMR of compound 50

N-(2-hydroxyphenyl)-1-isobutyl-N-methylcyclohexa-2,5-diene-1-carboxamide: Using the general procedure outlined above with 1-isobutylcyclohexa-2,5-diene-1-carbonyl chloride (1.18 g, 5.93 mmol), 1.68 g (99%) of a tan solid was isolated. $^1$H NMR (400 MHz, DMSO-d$_6$, 100 degrees): 9.11 (s, 1H), 7.07 (td, 1H, $J = 7.7$, 1.6 Hz), 6.95 (dd, 1H, $J = 7.8$, 1.6 Hz), 6.79 (d, 1H, $J = 8.1$), 6.65 (td, 1H, $J = 7.5$, 1.2 Hz), 5.44 (d, 2H, $J = 9.4$ Hz), 5.31 (d, 2H, $J = 7.5$ Hz), 3.00 (s, 3H), 2.33 (d, 1H, $J = 22.8$ Hz), 2.12 (d, 1H, $J = 22.8$ Hz), 1.62-1.52 (m, 3H), 0.81 (d, 6H, $J = 6.5$ Hz) ppm. $^{13}$C (100 MHz, DMSO-d$_6$): 174.0, 154.1, 130.2, 129.7, 128.9, 123.1, 119.4, 116.7, 50.0, 39.0, 26.3, 24.9, 24.3 ppm. Mass of the product not found in the GC.
Figure 116: $^1$H NMR of compound 51

Figure 117: $^{13}$C NMR of compound 51
N-(2-hydroxyphenyl)-1-(methoxymethyl)-N-methylcyclohexa-2,5-diene-1-carboxamide:

Using the general procedure outlined above with 1-(methoxymethyl)cyclohexa-2,5-diene-1-carbonyl chloride (2.30 g, 12.31 mmol), 3.04 g (90%) of a light brown solid was isolated. $^1$H NMR (400 MHz, DMSO-d$_6$ 100 degrees): 9.11 (s, 1H), 7.07 (td, 1H, $J = 7.8$, 1.6 Hz), 6.96 (dd, 1H, $J = 7.8$, 1.6 Hz), 6.79 (d, 1H, $J = 8.1$ Hz), 6.65 (dd, 1H, $J = 7.4$, 1.3 Hz), 5.49 (d, 2H, $J = 9.4$ Hz), 5.37 (s, 2H), 3.42 (s, 2H), 3.18 (s, 3H), 3.01 (s, 3H), 2.33 (d, 1H, $J = 22.8$ Hz), 2.12 (d, 1H, $J = 22.9$ Hz) ppm. $^{13}$C (100 MHz, DMSO-d$_6$): 154.0, 130.3, 129.2, 127.9, 127.3, 126.1, 125.9, 119.2, 116.3, 80.0, 59.0, 50.3, 38.6, 26.4 ppm. EI MS, m/z: 273 (5), 242 (3), 228 (4), 210 (3), 195 (3), 167 (4), 150 (100), 135 (9), 123 (47), 105 (51), 91 (50), 77 (26), 65 (13), 51 (7).

**Figure 118:** $^1$H NMR of compound 52
Figure 119: $^{13}$C NMR of compound 52

N-(2-hydroxyphenyl)-N-methyl-1-(naphthalen-1-ylmethyl)cyclohexa-2,5-diene-1-carboxamide: Using the general procedure and workup outlined above with 1-(chloromethyl)napthalene (2.17 g, 7.69 mmol). 2.68 g (94%) of a light-yellow solid was isolated. $^1$H NMR (400 MHz, CDCl$_3$): 8.10-8.07 (m, 1H), 7.83-7.80 (m, 1H), 7.73 (t, 1H, $J$ = 4.0), 7.49-7.41 (m, 2H), 7.38-7.36 (m, 2H), 5.87 (dt, 2H, $J$ = 10.5, 1.6 Hz), 5.79 (dt, 2H, $J$ = 10.5, 3.2 Hz), 3.56 (s, 2H), 2.54 (dsept, 1H, $J$ = 23.2, 1.6 Hz), 2.36 (dquint, 1H, $J$ = 23.1, 2.0 Hz) ppm. $^{13}$C (100 MHz, CDCl$_3$) 179.8, 133.7, 133.1, 132.7, 128.6, 128.5, 127.5, 126.8, 126.2, 125.5, 125.3, 125.1, 124.8, 49.3, 41.7, 30.0 ppm. EI MS, m/z: 218 (100), 202 (35), 189 (8), 163 (2), 152 (2), 141 (13), 115 (8), 108 (8), 91 (4), 65 (3).
Figure 120: $^1$H NMR of compound 53

Figure 121: $^{13}$C NMR of compound 53
1-(but-3-en-1-yl)-N-(2-hydroxyphenyl)-N-methylcyclohexa-2,5-diene-1-carboxamide: Using the general procedure and workup outlined above with 1-(but-3-en-1-yl)cyclohexa-2,5-diene-1-carbonyl chloride (1.28 g, 6.51 mmol). 1.82 g (99%) of a dark red/brown oil was isolated. $^1$H NMR (400 MHz, DMSO-d$_6$ 100 degrees): 9.10 (s, 1H), 7.07 (td, 1H, $J = 8.0$, 1.7 Hz), 6.96 (dd, 1H, $J = 7.8$, 1.6 Hz), 6.79 (dd, 1H, $J = 8.1$, 1.2 Hz), 6.65 (td, 1H, $J = 7.6$, 1.3 Hz), 5.76 (ddt, 4H, $J = 16.9$, 10.3, 6.4 Hz), 5.44-5.36 (m, 4H), 4.94-4.89 (m, 1H), 4.87-4.84 (m, 1H), 3.01 (s, 3H), 2.31 (d, 1H, $J = 22.9$ Hz), 2.10 (d, 1H, $J = 21.7$ Hz), 1.88-1.83 (m, 2H), 1.74-1.69 (m, 2H) ppm. $^{13}$C (100 MHz, DMSO-d$_6$): 173.6, 154.1, 139.7, 130.3, 128.9, 123.9, 119.4, 116.7, 114.3, 49.4, 38.9, 28.6, 26.3 ppm. EI MS, m/z: 283 (1), 228 (1), 192 (3), 150 (25), 134 (3), 123 (5), 105 (11), 91 (100), 77 (13), 65 (11), 51 (6).

Figure 122: $^1$H NMR of compound 54
Figure 123: $^{13}$C NMR of compound 54

1-(but-3-yn-1-yl)-N-(2-hydroxyphenyl)-N-methylcyclohexa-2,5-diene-1-carboxamide: Using the general procedure and workup outlined above with 1-(but-3-yn-1-yl)cyclohexa-2,5-diene-1-carbonyl chloride (2.88 g, 14.8 mmol). 5.15 g (>100%) of an oil was isolated. $^1$H NMR (400 MHz, CDCl$_3$): 7.18 (dt, 1H, $J = 7.8$, 1.6 Hz), 7.05 (dd, 1H, $J = 7.8$, 1.4 Hz), 6.90 (d, 1H, $J = 7.8$ Hz), 6.81 (t, 1H, $J = 7.6$ Hz), 5.58 (s, 2H), 5.49 (d, 2H, $J = 20.6$ Hz), 3.19 (s, 3H), 2.36 (d, 1H), 2.05 (d, 5H, $J = 7.2$), 1.91 (t, 1H, $J = 2.4$ Hz) ppm. $^{13}$C (100 MHz, CDCl$_3$): 126.3, 120.8, 84.8, 68.2, 53.4, 49.3, 39.6, 38.2, 26.2, 13.7 ppm. EI MS, m/z: 281 (9), 264 (15), 251 (1), 228 (1), 176 (2), 160 (1), 150 (49), 135 (4), 123 (100), 108 (15), 91 (69), 77 (14), 65 (12), 51 (6).
Figure 124: $^1$H NMR of compound 55

Figure 125: $^{13}$C NMR of compound 55
1-(sec-butyl)-N-(2-hydroxyphenyl)-N-methylcyclohexa-2,5-diene-1-carboxamide: Using the general procedure and workup outlined above with 1-(sec-butyl)cyclohexa-2,5-diene-1-carbonyl chloride (1.66 g, 8.35 mmol). 2.31 g (99%) of a light brown solid. $^1$H NMR (400 MHz, CDCl$_3$): 7.18 (td, 1H, $J = 7.8, 1.6$ Hz), 7.02 (dd, 1H, $J = 7.8, 1.5$ Hz), 6.88 (dd, 1H, $J = 8.2, 0.9$ Hz), 6.78 (td, 1H, $J = 7.6, 1.1$ Hz), 5.48-5.35 (m, 4H),3.16 (s, 3H), 2.39 (d, 1H, $J = 23.4$ Hz), 2.26-2.13 (m, 2H), 1.42-1.37 (m,1H), 0.97-0.69 (m, 9H) ppm. $^{13}$C (100 MHz, CDCl$_3$): 129.4, 125.6, 125.3, 120.7, 54.7, 42.8, 39.6, 26.6, 13.8, 12.7 ppm. El MS, m/z: 285 (7), 256 (1), 228 (28), 151 (44), 135 (8), 123 (100), 105 (48), 94 (12), 77 (24), 57 (38).

**Figure 126:** $^1$H NMR of compound 56
Figure 127: $^{13}$C NMR of compound 56

N-(2-hydroxyphenyl)-N,1-dimethylcyclohexa-2,5-diene-1-carboxamide: Using the general procedure and workup outlined above with 1-methylcyclohexa-2,5-diene-1-carbonyl chloride (2.34 g, 14.96 mmol). 3.41 g (94%) of a tan solid. $^1$H NMR (400 MHz, CDCl$_3$): 7.17 (td, 1H, $J = 7.7$, 1.6 Hz), 7.08 (dd, 1H, $J = 7.8$, 1.5 Hz), 6.91 (d, 1H, $J = 7.7$ Hz), 6.83 (t, 1H, $J = 7.6$ Hz), 5.60 (s, 2H), 5.50 (s, 2H), 3.22 (s, 3H), 2.43 (s, 1H), 2.10 (s, 1H), 1.35 (s, 3H) ppm. $^{13}$C (100 MHz, CDCl$_3$): 154.0, 130.6, 130.4, 129.4, 128.9, 127.8, 127.7, 122.4, 119.4, 116.8, 45.6, 38.8, 29.6, 25.9 ppm. EI MS, m/z: 150 (98), 123 (100), 108 (30), 93 (75), 77 (50), 65 (21), 51 (12).
Figure 128: $^1$H NMR of compound 57

Figure 129: $^{13}$C NMR of compound 63
6.3.3 Triflation General Procedures and Data

![Chemical structure diagram](image)

**Scheme 33:** Triflation general procedure

The procedure was adapted from Darses and co-workers. A flame-dried flask with a stir bar, under argon, was charged with benzamide (1.0 eq) which was dissolved in DCM (2.5 mL/mmol). Pyridine (2.0 eq) was added and the solution was stirred at -20°C (70:30, H₂O:MeOH dry ice bath) for 10 minutes. Tf₂O (3.0 eq) was added slowly in a dropwise manner and stirred for a few minutes before the bath was removed and the reaction was allowed to warm to room temperature with the total reaction time being 1 hour. The reaction was worked up by adding saturated sodium bicarbonate and was extracted with DCM. The organic layers were washed with 1 N HCl. The organic layers were washed with brine, dried over magnesium carbonate and concentrated in vacuo.

**1-benzyl-N-(2-hydroxyphenyl)cyclohexa-2,5-diene-1-carboxamide:** Using the general procedure outlined above with 1-benzyl-N-(2-hydroxyphenyl)cyclohexa-2,5-diene-1-carboxamide (0.315 g, 0.66 mmol), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 90% hexanes/ 10% ethyl acetate (Rf = 0.26) and 0.202 g (70%) of a yellow viscous oil was isolated. ¹H NMR (400 MHz, CDCl₃) δ 8.37 (dd, 1H, J = 8.3, 1.7 Hz), 7.97 (s, 1H), 7.37 (ddd, 1H, J = 8.5, 7.5, 1.5 Hz), 7.29 – 7.10 (m, 8H), 5.99 (dt, 2H, J = 10.3, 3.4 Hz), 5.78 (dt, 2H, J = 10.4, 2.0 Hz), 3.19 (s, 2H), 2.70 (dp, 1H, J = 12.7, 3.0 Hz), 2.51 (dhept, 1H, J = 12.9, 1.9 Hz) ppm. ¹³C NMR (101 MHz, CDCl₃) δ 172.4, 139.0, 137.2, 130.8, 130.7, 129.0, 128.2, 127.8, 127.1, 126.3, 124.9, 123.2, 121.3, 118.4 (CF₃, q, J = 320.3 Hz) 51.2, 43.5, 26.0 ppm. ¹⁹F NMR (376 MHz, DMSO) δ -73.30 (s) ppm. EI MS, m/z: 437 (9), 346 (28), 270 (2), 213 (7), 196 (19), 168 (17), 135 (15), 108 (7), 91 (100), 65 (7).
Figure 130: $^1$H NMR of compound 58

Figure 131: $^{13}$C NMR of compound 58
Using the general procedure outlined above with 1-(cyanomethyl)-N-(2-hydroxyphenyl)cyclohexa-2,5-diene-1-carboxamide (2.23 g, 8.77 mmol), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 70% hexanes/30% ethyl acetate (Rf = 0.37) and 1.94 g (57%) of a light yellow oil was isolated. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.27 (dd, 1H, J = 8.3, 1.6 Hz), 7.94 (s, 1H), 7.39 (ddd, 1H, J = 8.8, 7.4, 1.5 Hz), 7.28 (dd, 1H, J = 8.3, 1.5 Hz), 7.19 (ddd, 1H, J = 8.4, 7.4, 1.6 Hz), 6.32 – 6.25 (m, 2H), 5.79 (dt, 3H, J = 10.4, 2.1 Hz), 2.95 – 2.90 (m, 2H), 2.89 (s, 2H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) δ 169.9, 139.0, 130.8, 130.3, 129.2, 125.6, 124.2, 123.3, 121.5, 118.5 (d, J=322 Hz), 117.3, 48.0, 26.9, 26.0 ppm. $^{19}$F NMR (376 MHz, DMSO) δ -73.17 (s) ppm. EI MS, m/z: 386 (0.1), 269 (2), 241 (3), 196 (2), 135 (15), 119 (31), 92 (100), 78 (14), 52 (7).

**Figure 132:** $^{19}$F NMR of compound 58
Figure 133: $^1$H NMR of compound 59

Figure 134: $^{13}$C NMR of compound 59
Figure 135: $^{19}$F NMR of compound 59

2-(1-benzyl-N-methylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate: using the general procedure outlined above with 1-benzyl-N-(2-hydroxyphenyl)-N-methylcyclohexa-2,5-diene-1-carboxamide (2.3075 g, 7.22 mmol), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 1% triethylamine/79% hexanes/20% ethyl acetate ($R_f=0.38$) and 2.7401 g (84%) of a yellow oil was isolated. FTIR-ATR: 3029, 2925, 1647, 1494, 1418, 1348, 1247, 1207, 1136, 1078, 979, 946, 896, 766, 704, 672, 628, 592, 571, 495, 473 cm$^{-1}$. $^1$H NMR (400 MHz, DMSO) $\delta$ 7.47 – 7.32 (m, 4H), 7.17 – 7.10 (m, 3H), 7.05 (dd, 2H, $J_1=7.6$, 1.8 Hz), 5.55-5.46 (m, 4H), 3.20 (s, 3H), 3.01 (s, 2H), 2.14 (d, 1H, $J=23.2$ Hz), 1.97 (d, 1H, $J=23.2$ Hz) ppm. $^{13}$C NMR (101 MHz, DMSO) $\delta$ 173.1, 145.6, 137.7, 131.4, 130.0, 129.6, 127.9, 127.5, 126.2, 125.4, 121.7, 118.6 (d, $J=322$ Hz), 50.9, 46.5, 39.9, 25.9 ppm. $^{19}$F NMR (376 MHz, DMSO) $\delta$ -73.61 (s) ppm. EI MS, m/z: 451 (1), 360 (30), 284 (14), 227 (6), 210 (45), 168 (14), 149 (38), 122 (10), 105 (100), 77 (21), 51 (4).
Figure 136: $^1$H NMR of compound 60

Figure 137: $^{13}$C NMR of compound 60
Figure 138: $^{19}$F NMR of compound 60

2-(1-(cyanomethyl)-N-methylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate: Using the general procedure outlined above using 1-(cyanomethyl)-N-(2-hydroxyphenyl)-N-methylcyclohexa-2,5-diene-1-carboxamide (0.9828 g, 3.66 mmol), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 30% ethyl acetate/70% hexanes ($R_f=0.34$) and 0.9434 g (64%) of an yellow viscous oil was isolated. FTIR-ATR: 3028, 1648, 1494, 1416, 1358, 1247, 1207, 1135, 1077, 890, 830, 799, 755, 737, 672, 627, 591, 571, 518, 465 cm$^{-1}$. 1H (400 MHz, DMSO, 100°C): 7.52-7.44 (m, 3H), 7.40-7.38 (m, 1H), 5.85 (s, 2H), 5.66 (d, 2H, $J=9.4$), 3.23 (s, 3H), 2.77 (s, 2H), 2.62 (d, 1H, 22.9), 2.35 (d, 1H, $J=22.2$ Hz) ppm. $^{13}$C (100 MHz, CDCl$_3$): 170.6, 170.3, 145.1, 138.2, 133.4, 131.3, 130.7, 130.3, 130.1, 129.8, 129.6, 128.8, 127.5, 127.3, 126.1, 124.6, 124.3, 123.2, 122.1, 120.0, 118.6, 116.9, 47.0, 39.1, 30.1, 29.8, 26.4, 25.9 ppm. $^{19}$F NMR (376 MHz, DMSO) $\delta$ -73.49 (s) ppm. EI MS, m/z: 400 (1), 360 (1), 331 (1), 282 (11), 255 (2), 239 (1), 218 (19), 203 (1), 186 (1), 170 (1), 149 (100), 134 (40), 118 (6), 91 (30), 65 (5).
Figure 139: $^1$H NMR of compound 61

Figure 140: $^{13}$C NMR of compound 61
2-(N-methyl-[1,1'-bi(cyclohexane)])-2,5-diene-1-carboxamido)phenyl trifluromethanesulfonate: Using the general procedure outlined above using N-(2-hydroxyphenyl)-N-methyl-[1,1' bi(cyclohexane)]-2,5-diene-1-carboxamide (1.38 g, 4.42 mmol), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 20% ethyl acetate/80% hexanes (Rf = 0.0.41) and 1.10 g (56%) of a white solidified oil was isolated. m.p. = 45.2-48.3°C. $^1$H NMR (400 MHz, DMSO) δ 7.50-7.35 (m, 4H), 5.55 (d, 2H, $J = 8.5$ Hz), 5.38 (d, 2H, $J = 9.8$ Hz), 3.15 (s, 3H), 2.41 (d, 1H, $J = 23.6$ Hz), 2.26 (d, 1H, $J = 22.7$ Hz), 1.98 (t, 1H, $J = 12.0$ Hz), 1.62 (dd, 5H, $J = 32.7$, 11.1 Hz), 1.18 (q, 2H, $J = 25.5$, 12.8 Hz), 1.00 (q, 1H, $J = 25.2$, 12.4 Hz), 0.86 (q, 2H, $J = 24.4$, 12.0 Hz) ppm. $^{13}$C NMR (101 MHz, DMSO) δ 173.6, 145.7, 137.9, 131.5, 130.0, 129.6, 127.2, 125.5, 121.7, 118.6 (d, $J = 322$ Hz), 53.8, 46.9, 39.9, 34.4, 27.7, 26.9, 26.7, 26.5 ppm. $^{19}$F NMR (376 MHz, DMSO) δ -73.65 (s) ppm. EI MS, m/z: 443 (3) 360 (77), 284 (89), 227 (5), 210 (5), 160 (38), 122 (27), 105 (71), 83 (100), 55 (37).
Figure 142: $^1$H NMR of compound 62

Figure 143: $^{13}$C NMR of compound 62
Figure 144: $^{19}$F NMR of compound 62

2-(1-isobutyl-N-methylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate: Using the general procedure outlined above using N-(2-hydroxyphenyl)-1-isobutyl-N-methylcyclohexa-2,5-diene-1-carboxamide (1.11 g, 3.88 mmol), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 20% ethyl acetate/80% hexanes ($R_f = 0.40$) and 0.9720 g (60%) of a light yellow oil was isolated. $^1$H (400 MHz, DMSO, 100°C): 7.50-7.36 (m, 4H), 5.45 (dd, 4H, $J = 30.4$, 10.0 Hz), 3.18 (s, 3H), 2.51 (d, 1H, $J = 24.0$ Hz), 2.30 (d, 1H, $J = 24.0$ Hz), 1.59 (m, 3H), 0.83 (d, 6H, $J = 6.4$ Hz) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) δ 173.4, 145.6, 138.0, 131.5, 129.9, 129.7, 128.8, 124.8, 121.7, 118.6 (d, $J = 322$ Hz), 49.9, 49.7, 39.8, 26.2, 24.9, 24.2 ppm. $^{19}$F NMR (376 MHz, DMSO) δ -73.62 (s) ppm. El MS, m/z: 417 (1), 360 (4), 284 (58), 253 (1), 218 (4), 150 (6), 134 (70), 107 (2), 91 (41), 57 (100).
Figure 145: $^1$H NMR of compound 63

Figure 146: $^{13}$C NMR of compound 63
Figure 147: $^{19}$F NMR of compound 63

2-(1-(methoxymethyl)-N-methylcyclclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate: Using the general procedure outlined above using N-(2-hydroxyphenyl)-1-(methoxymethyl)-N-methylcyclclohexa-2,5-diene-1-carboxamide (2.14 g, 7.85 mmol), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 30% ethyl acetate/70% hexanes ($R_f = 0.28$) and 1.66 g (52%) of a white solid was isolated. m.p. = 55.7-58.0°C. $^1$H NMR (400 MHz, DMSO) δ 7.52 – 7.39 (m, 3H), 7.37 (d, 1H, $J = 7.9$ Hz), 5.61 (d, 2H, $J = 10.6$ Hz), 5.58 – 5.50 (m, 2H), 3.46 (s, 1H), 3.19 (d, 6H, $J = 8.8$ Hz), 2.49 (d, 1H, $J = 23.6$ Hz), 2.30 (d, 1H, $J = 23.6$ Hz) ppm. $^{13}$C (100 MHz, CDCl$_3$) 171.9, 145.7, 137.4, 131.6, 130.0, 129.6, 126.3, 126.0, 121.7, 118.6 (d, $J = 326$ Hz), 79.7, 59.3, 51.0, 39.6, 26.2 ppm. $^{19}$F NMR (376 MHz, DMSO) δ -73.58 (s) ppm. EI MS, m/z: 405 (10), 375 (8), 360 (39), 314 (3), 284 (11), 268 (6), 242 (1), 227 (5), 210 (22), 182 (1), 166 (1), 149 (89), 122 (25), 105 (100), 77 (24), 51 (4).
Figure 148: $^1$H NMR of compound 64

Figure 149: $^{13}$C NMR of compound 64
Figure 150: $^{19}$F NMR of compound 64

2-(N-methyl-1-(naphthal-1-ylmethyl)cyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate: 5-methyl-6a-(naphthalen-1-ylmethyl)-6a,10a-dihydrophenanthridin-6(5H)-one: Using the general procedure outlined above using N-(2-hydroxyphenyl)-N-methyl-1-(naphthalen-1-ylmethyl)cyclohexa-2,5-diene-1-carboxamide (0.96 g, 2.61 mmol), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 20% ethyl acetate/80% hexanes ($R_f = 0.31$) and 0.81 g (62%) of a yellow viscous oil was isolated. $^1$H NMR (400 MHz, DMSO) $\delta$ 8.05 – 7.96 (m, 1H), 7.80 (dd, 1H, $J = 6.7$, 4.0 Hz), 7.70 (d, 1H, $J = 7.4$ Hz), 7.46 – 7.28 (m, 8H), 5.59 (d, 2H, $J = 10.0$ Hz), 5.33 (d, 4H, $J = 9.9$ Hz), 3.57 (s, 2H), 3.22 (s, 3H), 2.06 (d, 1H, $J = 23.2$ Hz), 1.80 (dp, 1H, $J = 23.3$, 2.4 Hz) ppm. $^{13}$C NMR (101 MHz, DMSO) $\delta$ 173.4, 145.7, 137.8, 134.1, 133.8, 133.7, 131.4, 130.0, 129.6, 129.4, 128.7, 128.0, 127.1, 125.5, 125.4, 125.3, 125.2, 125.1, 121.7, 118.7 (CF$_3$, q, $J = 322.1$ Hz), 51.5, 41.5, 40.0, 25.8. ppm. $^{19}$F NMR (376 MHz, DMSO) $\delta$ -73.58 ppm. El MS, m/z: 210 (45), 141 (33), 115 (11), 105 (100), 77 (32).
Figure 151: $^1$H NMR of compound 65

Figure 152: $^{13}$C NMR of compound 65
2-(1-(3-cyanobenzyl)-N-methylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate: Using the general procedure outlined above using 1-(but-3-en-1-yl)-N-(2-hydroxyphenyl)-N-methylcyclohexa-2,5-diene-1-carboxamide (0.93 g, 3.27 mmol), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 20% ethyl acetate/80% hexanes (Rf = 0.35) yielding 1.09 g (80%) of an orange solid. m.p. = 51.7-52.9°C. 1H NMR (400 MHz, DMSO) δ 7.52 – 7.45 (m, 3H), 7.40 (d, 1H, J = 7.2 Hz), 5.80 (ddt, 1H, J = 17.0, 10.4, 6.4 Hz), 5.68 (d, 2H, J = 9.8 Hz), 5.54 (d, 2H, J = 10.3 Hz), 4.96 (dd, 1H, J = 17.2, 1.6 Hz), 4.90 (dd, 1H, J = 10.2, 1.2 Hz), 3.24 (s, 3H), 2.55 (d, 1H, J = 23.3 Hz), 2.36 (d, 1H, J = 23.3 Hz), 1.96 – 1.84 (m, 2H), 1.80 – 1.76 (m, 2H) ppm. 13C NMR (101 MHz, DMSO) δ 170.1, 145.6, 139.4, 137.9, 131.4, 129.9, 129.7, 127.8, 125.5, 121.7, 118.6 (q, J = 322 Hz), 114.5 ppm. 19F NMR (376 MHz, DMSO) δ -73.60 (s) ppm. EI MS, m/z: 414 (1), 360 (3), 324 (3), 284 (25) 266 (1), 218 (3), 149 (22), 122 (16), 91 (100), 55 (9).

Figure 153: 19F NMR of compound 65
Figure 154: $^1$H NMR of compound 66

Figure 155: $^{13}$C NMR of compound 66
2-(1-(sec-butyl)-N-methylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate: Using the general procedure outlined above using 1-(sec-butyl)-N-(2-hydroxyphenyl)-N-methylcyclohexa-2,5-diene-1-carboxamide (0.71 g, 2.50 mmol), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 20% ethyl acetate/80% hexanes (Rf = 0.41) yielding 0.40 g (38%) of a yellow oil. $^1H$ NMR (400 MHz, DMSO) $\delta$ 7.50-7.36 (m, 4H), 5.53 (s, 2H), 5.38 (s, 2H), 3.16 (s, 3H), 2.43 (d, 1H, $J$ = 22.4 Hz), 2.25 (d, 1H, $J$ = 22.8 Hz), 2.09-2.02 (m, 1H), 1.45-1.38 (m, 1H), 0.86-0.82 (m, 4H), 0.73 (d, 3H, $J$ = 6.7 Hz) ppm. $^{13}C$ NMR (101 MHz, DMSO) $\delta$ 173.8, 145.7, 137.9, 131.5, 130.0, 129.7, 126.9, 125.8, 125.4, 121.7, 118.6 (d, $J$ = 311 Hz) 54.6, 43.3, 40.0, 26.5, 24.8, 14.1, 12.9 ppm. $^{19}F$ NMR (376 MHz, DMSO) $\delta$ -73.63 (s) ppm. EI MS, m/z: 417 (4), 360 (74), 284 (61), 227 (4), 210 (4), 150 (7), 134 (48), 105 (100), 77 (29), 57 (76).
Figure 157: $^1$H NMR of compound 67

Figure 158: $^{13}$C NMR of compound 67
Figure 159: $^{19}$F NMR of compound 67

2-(1-(but-3-yn-1-yl)-N-methylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate: Using the general procedure and workup outlined above with 1-(but-3-yn-1-yl)-N-(2-hydroxyphenyl)-N-methylcyclohexa-2,5-diene-1-carboxamide (0.13 g, 0.32 mmol), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 20% ethyl acetate/80% hexanes ($R_f = 0.39$) and 0.74 g (12%) of a yellow solid was isolated. $^1$H NMR (400 MHz, DMSO) $\delta$ 7.36-7.28 (m, 4H), 6.06-5.26 (m, 4H), 3.29 (s, 3H), 2.84-2.27 (m, 2H), 2.07 (s, 4H) ppm. EI MS, m/z: 412 (3), 360 (3), 308 (5), 284 (35), 264 (8), 218 (7), 176 (1), 149 (53), 131 (30), 115 (8), 91 (100), 65 (9).

-$^{13}$CPD was too dilute. This data was taken prior to the discovery that DMSO and elevated temperatures were needed for the NMR.
Figure 160: $^1$H NMR of compound 68

2-(N,1-dimethylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate: Using the general procedure and workup outlined above with N-(2-hydroxyphenyl)-N,1-dimethylcyclohexa-2,5-diene-1-carboxamide (3.07 g, 12.61 mmol), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 20% ethyl acetate/80% hexanes ($R_f = 0.24$) and 4.16 g (88%) of an orange solid was isolated. m.p. = 60.2-65.4°C. $^1$H NMR (400 MHz, DMSO) $\delta$ 7.54-7.49 (m, 3H), 7.42 (d, 1H, $J = 7.8$ Hz), 5.88 (s, 2H), 5.69 (d, 2H, $J = 8.5$ Hz), 3.25 (s, 3H), 2.80 (s, 3H), 2.65 (d, 1H, $J = 22.2$ Hz), 2.37 (d, 1H, $J = 21.6$ Hz) ppm. $^{13}$C NMR (101 MHz, DMSO) $\delta$ 173.3, 145.6, 131.3, 129.8, 129.7, 129.6, 124.0, 121.7, 117.1, 45.7, 39.6, 29.2, 25.9 ppm. $^{19}$F NMR (376 MHz, DMSO) $\delta$ -73.61 (s) ppm. EI MS, m/z: 375 (2), 284 (42), 253 (1), 218 (5), 149 (38), 134 (61), 120 (11), 93 (100), 77 (36), 51 (5).
Figure 161: $^1$H NMR of compound 69

Figure 162: $^{13}$C NMR of compound 69
Figure 163: $^{13}$C NMR of compound 69

6.3.4 Mizoroki-Heck Reaction General procedures and data

![Chemical structure](image)

**Scheme 34:** Palladium catalyzed Mizoroki-Heck general procedure

A flame dried vial under argon was charged with aryl triflate diene (1.0 eq) which was dissolved in DMF. In a separate flame dried vial with a stir bar, under argon, Pd(OAc)$_2$ (0.2 eq) and (R or racemic) BINAP (0.24 eq) was dissolved in DMF and stirred for 1 hour. To the palladium mixture, Cy$_2$NMe (2.0 eq) was added and the solution was stirred for an additional 10 minutes. The aryl triflate diene was then added to the Pd/Cy$_2$NMe vial via syringe. Finally, lithium acetate (2.0 eq) was added to the vial. The vial was capped with a pressure relief cap and stirred at 80°C. Upon completion the reaction mixture was filtered using a pipet pack with cotton, followed by silica gel, and topped with celite. Excess EtOAc was used to rinse any
compound off the celite and silica gel. The organic layer was concentrated in vacuo and columned on silica gel.

6a-benzyl-5-methyl-6a,10a-dihydrophenanthridin-6(5H)-one: Using the general procedure outlined above with 2-(1-benzyl-N-methylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (0.0741 g, 0.16 mmol), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) using a gradient solvent from 0% to 20% ethyl acetate in hexanes (Rf = 0.30) and 0.0402 g (92%) of a yellow cloudy oil was isolated. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.30 (dtd, $J$ = 9.45, 6.7, 1.7 Hz, 1H), 7.28 – 7.14 (m, 4H), 7.10 (td, 1H, $J$ = 7.4, 1.1 Hz), 7.00 (ddd, 3H, $J$ = 10.7, 8.2, 1.4 Hz), 6.11 – 5.99 (m, 2H), 5.95 (dddd, 1H, $J$ = 9.2, 4.5, 2.8, 1.4 Hz), 5.55 (ddt, 1H, $J$ = 9.3, 3.1, 1.0 Hz), 3.60 (t, 1H, $J$ = 3.0 Hz), 3.38 (s, 3H), 2.95 (d, 1H, $J$ = 13.3 Hz), 2.83 (d, 1H, $J$ = 13.4 Hz) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) δ 172.6, 139.2, 136.6, 130.6, 130.5, 128.6, 128.3, 128.2, 127.8, 126.7, 126.2, 125.0, 124.7, 123.5, 114.3, 46.7, 41.3, 40.1, 30.0 ppm. EI MS, m/z: 301 (1), 210 (100), 195 (27), 180 (9), 167 (11), 152 (10), 139 (2), 127 (2), 115 (3), 91 (11), 77 (2), 65 (4), 51 (1). HPLC: CHIRALCEL OD-H 4.6mm x 250 mm, 5μm column, 20 μL injection, 97.5: 2.5 Hex:IPA, 1mL/min, 30 min, 210 nm VWD UV. $t_{R1}$ = 12.55 min., Area (mAU) = 702.79; $t_{R2}$ = 21.02 min., Area (mAU) = 7484.02; er = 1:11

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**Figure 164: R-BINAP HPLC data for compound 69**

Racemic BINAP: 97% yield yellow cloudy oil

HPLC: CHIRALCEL OD-H 4.6mm x 250 mm, 5μm column, 20 μL injection, 97.5: 2.5 Hex:IPA, 1mL/min, 30 min, 210 nm VWD UV. $t_{R1}$ = 12.55 min., Area (mAU) = 5476.50; $t_{R2}$ = 21.09 min., Area (mAU) = 5434.51; er = 1:1.
**Figure 165:** Racemic BINAP HPLC data for compound 69

R-BINAP data using Pd(TFA)$_2$:

HPLC: CHIRALCEL OD-H 4.6 mm x 250 mm, 5μm column, 20 μL injection, 97.5: 2.5 Hex:IPA, 1 mL/min, 30 min, 210 nm VWD UV. $t_R_1 = 11.68$ min., Area (mAU) = 5639.12; $t_R_2 = 19.507$ min., Area (mAU) = 56940.2; $er = 1:10$

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**Figure 166:** Pd(TFA)$_2$ HPLC data for compound 69

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Figure 167: $^1$H NMR of compound 69

Figure 168: $^{13}$C NMR of compound 69
3-((5-methyl-6-oxo-5,10a-dihydrophenanthridin-6a(6H)-yl)methyl)benzonitrile: Using the general procedure and workup outlined above with 2-(1-(3-cyanobenzyl)-N-methylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (0.084 g, 0.18 mmol), the crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) using a gradient solvent from 0% to 30% ethyl acetate in hexanes (Rf = 0.30) and 0.034 g (58%) of a cloudy white solidified oil was isolated. m.p. = 60.2-63.9°C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.47\) (dt, 1H, \(J = 7.5, 1.5\) Hz), \(7.36 - 7.26\) (m, 4H), \(7.18\) (dd, 1H, \(J = 7.5, 1.7\) Hz), \(7.11\) (td, 1H, \(J = 7.4, 1.1\) Hz), \(6.94\) (dd, 1H, \(J = 8.2, 1.1\) Hz), \(6.11\) (dd, 1H, \(J = 9.4, 5.1\) Hz), \(6.03\) (dddd, 1H, \(J = 8.9, 5.2, 2.6, 1.0\) Hz), \(5.92\) (dd, 1H, \(J = 9.4, 0.9\) Hz), \(5.66\) (dd, 1H, \(J = 9.4, 3.5\) Hz), \(3.50\) (t, 1H, \(J = 3.0\) Hz), \(3.36\) (s, 3H), \(2.97\) (q, 2H, \(J = 13.4\) Hz) ppm. \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 171.6, 139.0, 138.2, 134.9, 133.9, 130.5, 129.7, 128.9, 128.2, 128.1, 127.9, 125.6, 125.5, 125.0, 123.7, 118.8, 114.3, 112.2, 46.7, 41.0, 39.9, 30.1 ppm. EI MS, m/z: 326 (4), 210 (100), 195 (25), 180 (11), 167 (11), 152 (13), 139 (3), 116 (6), 89 (4), 77 (2), 63 (2), 51 (1). HPLC: CHIRALCEL OD-H 4.6mm x 250 mm, 5μm column, 20 μL injection, 97.5: 2.5 Hex:IPA, 1mL/min, 30 min, 210 nm VWD UV. \(t_R1 = 10.677\) min., Area (mAU) = 9330; \(t_R2 = 11.735\) min., Area (mAU) = 883; er = 11:1

![Figure 169: R-BINAP HPLC data for compound 70](image)

Racemic BINAP: 57% of a white solid was isolated. m.p. = 145.2-148.8°C.

HPLC: CHIRALCEL OD-H 4.6mm x 250 mm, 5μm column, 20 μL injection, 97.5: 2.5 Hex:IPA, 1mL/min, 20 min, 210 nm VWD UV. \(t_R1 = 11.063\) min., Area (mAU) = 4172; \(t_R2 = 12.151\) min., Area (mAU) = 4305; er = 1:1
**Figure 170:** Racemic BINAP HPLC data for compound 70

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**Figure 171:** $^1$H NMR of compound 70
2-(5-methyl-6-oxo-5,10a-dihydrophenantridin-6a(6H)-yl)acetonitrile: Using the general procedure outlined above using 2-(1-(cyanomethyl)-N-methylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (0.282 g, 0.70 mmol) and no lithium acetate, the crude reaction mixture was purified using an automated column flash chromatography system (Biotage column) with 30% ethyl acetate/70% hexanes (Rf= 0.23) and 0.170 g (97%) of a yellow opaque oil was isolated. FTIR-ATR: 3042, 3012, 2928, 2853, 2247, 1659, 1598, 1498, 1472, 1498, 1457, 1308, 1268, 1044, 750, 710, 681, 608, 543, 474, 457. $^1$H NMR (400 MHz, CDCl$_3$): 7.34–7.26 (m, 2H), 7.09 (td, 1H, $J$=7.5, 0.8 Hz), 6.99 (d, 1H, $J$= 8.1 Hz), 6.19–6.12 (m, 2H), 6.07 (dd, 1H, $J$= 9.1, 4.8 Hz), 5.70 (d, 1H, $J$=9.0 Hz), 3.93 (d, 1H, $J$=4.8 Hz), 3.41 (s, 3H), 2.91 (d, 1H, $J$=16.3 Hz), 2.67 (d, 1H, $J$=16.3 Hz) ppm. $^{13}$C (100 MHz, CDCl$_3$) 169.3, 139.0, 128.4, 127.8, 127.0, 126.9, 126.5, 125.2, 124.4, 123.8, 117.1, 114.4, 44.6, 38.4, 30.5, 23.1 ppm. EI MS, m/z: 250 (23), 233 (2), 222 (4), 210 (100), 195 (27), 180 (13), 167 (18), 152 (11), 141 (100), 127 (45), 113 (21), 105 (51).
152 (12), 139, (4), 127 (2), 115 (3), 104 (3), 89 (2), 77 (4), 51 (2). HPLC: CHIRALCEL OD-H 4.6mm x 250 mm, 5μm column, 20 μL injection, 97.5: 2.5 Hex:IPA, 1mL/min, 60 min, 210 nm VWD UV. $t_{R1} = 44.77$ min., Area (mAU) = 7213; $t_{R2} = 53.53$ min., Area (mAU) = 68196; $er = 1:9$

![Figure 173: R-BINAP HPLC data for compound 71](image)

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Racemic BINAP: 83% of a light yellow oily solid was isolated. m.p. = 118.3-121.8°C.

HPLC: CHIRALCEL OD-H 4.6mm x 250 mm, 5μm column, 20 μL injection, 97.5: 2.5 Hex:IPA, 1mL/min, 60 min, 210 nm VWD UV. $t_{R1} = 45.94$ min., Area (mAU) = 23396; $t_{R2} = 55.52$ min., Area (mAU) = 23487; $er = 1:1$

![Figure 174: Racemic BINAP HPLC data for compound 71](image)

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Figure 175: $^1$H NMR of compound 71

Figure 176: $^{13}$C NMR of compound 71
6a-isobutyl-5-methyl-6a,10a-dihydrophenanthridin-6(5H)-one: Using the general procedure outlined above using 2-(1-isobutyl-N-methylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (0.111 g, 0.27 mmol), the crude reaction mixture was purified using an automated column flash chromatography system with 20% ethyl acetate/80% hexanes (Rf = 0.33) and 0.0591 g (83%) of a light yellow opaque oil was isolated. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.30\) (d, 1H, \(J = 7.9\) Hz), 7.20 (dd, 1H, \(J = 7.4, 1.6\) Hz), 7.08 (td, 1H, \(J = 7.4, 1.1\) Hz), 6.97 (d, 1H, \(J = 7.0\) Hz), 6.12 (dd, 1H, \(J = 9.3, 5.3\) Hz), 6.02 – 5.96 (m, 2H), 5.53 (ddt, 1H, \(J = 9.3, 2.3, 1.1\) Hz), 3.68 (t, 1H, \(J = 2.8\) Hz), 3.34 (s, 3H), 1.83 (ddt, 1H, \(J = 13.4, 11.4, 6.7\) Hz), 1.42 (qd, 2H, \(J = 14.1, 5.9\) Hz), 0.84 (dd, 6H, \(J = 14.4, 6.7\) Hz) ppm. \(^{13}\)C (100 MHz, CDCl\(_3\)) 173.1, 139.1, 131.7, 128.6, 128.5, 127.8, 126.7, 125.1, 124.0, 123.3, 114.2, 44.7, 43.8, 41.9, 29.8, 24.7, 24.4, 23.8 ppm. EI MS, m/z: 266 (25), 250 (1), 224 (10), 210 (100), 195 (17), 180 (12), 167 (10), 152 (8), 141 (1), 131 (2), 115 (2), 104 (1), 91 (1), 77 (2), 63 (1). HPLC: CHIRALCEL OD-H 4.6mm x 250 mm, 5μm column, 20 μL injection, 97.5: 2.5 Hex:IPA, 1mL/min, 30 min, 210 nm VWD UV. \(t_\text{R1} = 7.30\) min., Area (mAU) = 9110; \(t_\text{R2} = 8.00\) min., Area (mAU) = 1266; er = 7:1

**Figure 177:** R-BINAP HPLC data for compound 72

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Racemic BINAP: 68% of a light-yellow solidified oil was isolated.

HPLC: CHIRALCEL OD-H 4.6mm x 250 mm, 5μm column, 20 μL injection, 97.5: 2.5 Hex:IPA, 1mL/min, 20 min, 210 nm VWD UV. \(t_\text{R1} = 7.25\) min., Area (mAU) = 6500; \(t_\text{R2} = 7.92\) min., Area (mAU) = 6505; er = 1:1.
Figure 178: Racemic BINAP HPLC data for compound 72

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Figure 179: $^1$H NMR of compound 72
Using the general procedure and workup outlined above with 2-(N-methyl-[1,1'-bi(cyclohexane)]-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (0.064 g, 0.15 mmol), the crude reaction mixture was purified using an automated column flash chromatography system with 20% ethyl acetate/80% hexanes (Rf= 0.35) and 0.064 g (59%) of a cloudy oil was isolated. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.30 (td, 1H, $J = 7.9, 1.7$ Hz), 7.19 (dd, 1H, $J = 7.4, 1.6$ Hz), 7.07 (td, 1H, $J = 7.4, 1.1$ Hz), 6.97 (dd, 1H, $J = 8.1, 1.1$ Hz), 6.15 (dd, 1H, $J = 9.6, 5.1$ Hz), 6.02 – 5.93 (m, 2H), 5.48 (dd, 1H, $J = 9.5, 2.2$ Hz), 3.85 (s, 1H), 3.35 (s, 3H), 1.76 – 1.63 (m, 2H), 1.55 (s, 6H), 1.49 – 1.24 (m, 4H), 1.12 – 0.79 (m, 4H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) δ 172.4, 139.3, 129.2, 128.6, 128.4, 127.7, 127.0, 124.9, 124.6, 123.3, 114.2, 48.7, 40.5, 40.2, 39.8, 28.7, 28.3, 26.8, 26.4, 26.2 ppm. EI MS, m/z: 293 (7), 210 (100), 195 (11), 180 (4), 167 (6), 152 (4), 139 (1), 115 (1), 91 (1), 77 (1), 55 (3). HPLC: CHIRALCEL OD-H 4.6mm x 250 mm, 5μm column, 20 μL injection, 97.5:
2.5 Hex:IPA, 1mL/min, 20 min, 210 nm VWD UV. $t_{R1} = 8.445$ min., Area (mAU) = 13749; $t_{R2} = 9.660$ min., Area (mAU) = 2461; $er = 6:1$.

![Graph](image1.png)

**Figure 181:** R-BINAP HPLC data for compound 73

Racemic BINAP: 57% of a cloudy oil was isolated.

HPLC: CHIRALCEL OD-H 4.6mm x 250 mm, 5μm column, 20 μL injection, 97.5: 2.5 Hex:IPA, 1mL/min, 20 min, 210 nm VWD UV. $t_{R1} = 8.434$ min., Area (mAU) = 8127; $t_{R2} = 9.623$ min., Area (mAU) = 8152; $er = 1:1$

![Graph](image2.png)

**Figure 182:** Racemic BINAP HPLC data for compound 73
Figure 183: $^1$H NMR of compound 73

Figure 184: $^{13}$C NMR of compound 73
6a-(methoxymethyl)-5-methyl-6a,10a-dihydrophenanthridin-6(5H)-one: Using the general procedure and workup outlined above with 2-(1-(methoxymethyl)-N-methylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (0.084 g, 0.21 mmol), the crude reaction mixture was purified using an automated column flash chromatography system with 30% ethyl acetate/70% hexanes (Rf= 0.35) and 0.047 g (88%) of a yellow cloudy oil was isolated. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.33 – 7.22 (m, 2H), 7.07 (td, 1H, $J = 7.5, 1.1$ Hz), 6.96 (d, 1H, $J = 8.1$ Hz), 6.14 – 6.08 (m, 1H), 6.05 (ddddd, 1H, $J = 8.8, 5.1, 2.3, 1.1$ Hz), 5.84 – 5.75 (m, 2H), 3.97 (t, 1H, $J = 3.2$ Hz), 3.52 (d, 1H, $J = 8.8$ Hz), 3.42 (d, 1H, $J = 8.8$ Hz), 3.37 (s, 3H), 3.31 (s, 3H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 170.7, 139.1, 128.1, 127.7, 127.6, 127.4, 126.1, 125.7, 124.6, 123.3, 114.1, 73.3, 59.4, 47.3, 36.7, 30.1 ppm. HPLC: CHIRALCEL OD-H 4.6mm x 250 mm, 5μm column, 20 μL injection, 97.5: 2.5 Hex:IPA, 1mL/min, 30 min, 210 nm VWD UV. $t_R1$ =17.919 min., Area (mAU) =15457; $t_R2$ = 19.525 min., Area (mAU) = 768 ; er = 20:1.

**Figure 185:** R-BINAP HPLC data for compound 74

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Racemic BINAP: 77% of a yellow cloudy oil was isolated.

HPLC: CHIRALCEL OD-H 4.6mm x 250 mm, 5μm column, 20 μL injection, 97.5: 2.5 Hex:IPA, 1mL/min, 30 min, 210 nm VWD UV. $t_R1$ = 18.661 min., Area (mAU) =7062; $t_R2$ = 21.155 min., Area (mAU) = 6663; er = 1:1.
Figure 186: Racemic BINAP HPLC data for compound 74

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Figure 187: $^1$H NMR of compound 74
Figure 188: $^{13}$C NMR of compound 74

5-methyl-6a-(naphthalen-1-ylmethyl)-6a,10a-dihydropenantridin-6(5H)-one: Using the general procedure and workup outlined above with 2-(N-methyl-1-(naphthalen-1-ylmethyl)cyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (0.066 g, 0.13 mmol), the crude reaction mixture was purified using an automated column flash chromatography system with 20% ethyl acetate/80% hexanes (Rf = 0.21) and 0.030 g (65%) of a cloudy oil was isolated. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.74 (dd, 2H, $J = 29.1, 8.0$ Hz), 7.65 (d, 1H, $J = 9.3$ Hz), 7.41 (d, 2H, $J = 5.5$ Hz), 7.32 (t, 1H, $J = 7.0$ Hz), 7.27 – 7.18 (m, 4H), 7.06 (d, 1H, $J = 7.0$ Hz), 6.99 (t, 1H, $J = 7.4$ Hz), 6.86 (d, 1H, $J = 9.2$ Hz), 6.13 (d, 1H, $J = 10.4$ Hz), 6.02 (d, 1H, $J = 9.0$ Hz), 5.95 (d, 1H, $J = 8.3$ Hz), 5.48 (d, 1H, $J = 9.2$ Hz), 3.75 (s, 1H), 3.46 (d, 1H, $J = 13.6$ Hz), 3.34 (d, 1H, $J = 13.6$ Hz), 3.29 (s, 3H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 172.3,
138.9, 133.8, 132.9, 132.7, 130.2, 129.0, 128.7, 128.7, 128.7, 127.7, 127.7, 126.4, 125.5, 125.3, 125.0, 124.5, 124.2, 124.1, 123.3, 114.0, 46.7, 41.7, 38.1, 30.0 ppm. EI MS, m/z: 209 (100), 178 (23), 166 (4), 152 (16), 141 (51), 127 (2), 115 (16), 104 (4), 90 (4), 76 (5), 63 (5), 51 (3). HPLC: CHIRALCEL OD-H 4.6mm x 250 mm, 5μm column, 20 μL injection, 97.5: 2.5 Hex:IPA, 1mL/min, 30 min, 210 nm VWD UV.  

- GCMS will not show the correct mass for the product due to degradation of the naphthalene part in the GC

Figure 189: R-BINAP HPLC data for compound 75

Racemic BINAP: 0.030 g (57%) of a cloudy white oil was isolated.

HPLC: CHIRALCEL OD-H 4.6mm x 250 mm, 5μm column, 20 μL injection, 97.5: 2.5 Hex:IPA, 1mL/min, 30 min, 210 nm VWD UV.  

- GCMS will not show the correct mass for the product due to degradation of the naphthalene part in the GC

Figure 190: Racemic BINAP HPLC data for compound 75
**Figure 191:** $^1$H NMR of compound 75

**Figure 192:** $^{13}$C NMR of compound 75
6a-(but-3-en-1-yl)-5-methyl-6a,10a-dihydrophenanthridin-6(5H)-one: Using the general procedure and workup outlined above with 2-(1-(3-cyanobenzyl)-N-methylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (0.060 g, 0.14 mmol), the crude reaction mixture was purified using an automated column flash chromatography system with 20% ethyl acetate/80% hexanes (Rf= 0.36) and 0.021 g (55%) of a clear colorless oil was isolated. \( ^1 \)H NMR (400 MHz, CDCl\(_3 \)) \( \delta \) 7.26 (dt, 1H, \( J = 7.8, 1.6 \) Hz), 7.22 (dd, 1H, \( J = 7.4, 1.4 \) Hz), 7.08 (td, 1H, \( J = 7.4, 1.0 \) Hz), 6.98 (d, 1H, \( J = 8.2 \) Hz), 6.15 (dd, 1H, \( J = 9.5, 5.2 \) Hz), 6.01 (dddd, 1H, \( J = 9.3, 5.2, 3.1, 1.0 \) Hz), 5.95 (dd, 1H, \( J = 9.5, 0.8 \) Hz), 5.67 (ddt, 1H, \( J = 17.0, 10.3, 6.4 \) Hz), 5.54 (dd, 1H, \( J = 9.2, 2.6 \) Hz), 4.96-4.87 (m, 2H), 3.67 (s, 1H), 3.35 (s, 3H), 2.16 - 1.97 (m, 2H), 1.70 - 1.62 (m, 1H), 1.59 - 1.48 (m, 5H) ppm. \( ^{13} \)C NMR (101 MHz, CDCl\(_3 \)) \( \delta \) 160.1, 139.0, 137.8, 130.2, 128.7, 128.6, 127.9, 126.3, 125.1, 124.9, 123.4, 114.9, 114.3, 44.7, 41.5, 34.2, 29.9, 29.0 ppm. EI MS, m/z: 265 (19), 248 (5), 236 (15), 224 (14), 210 (100), 195 (25), 180 (23), 167 (16), 152 (14), 139 (3), 128 (3), 115 (4), 104 (1), 91 (2), 77 (4), 63 (1), 51 (1). HPLC: CHIRALCEL OD-H 4.6mm x 250 mm, 5\( \mu \)m column, 20 \( \mu \)L injection, 97.5: 2.5 Hex:IPA, 1mL/min, 30 min, 210 nm VWD UV. \( t_{R1} \) = 9.032 min., Area (mAU) = 1755.4; \( t_{R2} \) = 9.697 min., Area (mAU) = 144.3; er = 12:1.

![Figure 193: R-BINAP HPLC data for compound 76](image)

Racemic BINAP: 67% of a yellow cloudy oil was isolated.

HPLC: CHIRALCEL OD-H 4.6mm x 250 mm, 5\( \mu \)m column, 20 \( \mu \)L injection, 97.5: 2.5 Hex:IPA, 1mL/min, 15 min, 210 nm VWD UV. \( t_{R1} \) = 8.93 min., Area (mAU) = 4715; \( t_{R2} \) = 9.49 min., Area (mAU) = 4491; er = 1:1
Figure 194: Racemic BINAP HPLC data for compound 76

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Figure 195: $^1$H NMR of compound 76
Figure 196: $^{13}$C NMR of compound 76

8-methyl-4-methylene-3a,4,5,6,8,12b-hexahydrocyclopenta[h]phenanthridin-7(1H)-one: 0.0056 g (14%) of a white solidified oil was isolated. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.28 (td, 1H, $J$ = 7.8, 4.0 Hz), 7.16 (dd, 1H, $J$ = 7.3, 1.5 Hz), 7.03 (dt, 1H, $J$ = 7.4, 1.0 Hz), 6.99 (d, 1H, $J$ = 8.1 Hz), 6.06-6.02 (m, 1H), 5.70 (qt, 1H, $J$ = 5.2, 2.0 Hz), 4.98-4.96 (m, 1H), 4.88 (q, 1H, $J$ = 2.4 Hz), 3.93 (s, 1H), 3.39 (s, 3H), 2.76 (dd, 1H, $J$ = 11.5, 5.7 Hz), 2.54-2.39 (m, 2H), 2.18 (dt, 1H, $J$ = 17.9, 5.2 Hz), 2.01 (qq, 1H, $J$ = 11.5, 2.4 Hz), 1.70-1.58 (m, 2H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 154.0, 139.0, 129.2, 128.3, 127.6, 127.3, 124.4, 123.0, 114.8, 106.9, 50.1, 44.6, 36.9, 31.2, 30.1, 30.0, 29.9 ppm. EI MS, m/z: 265 (100), 250 (58), 236 (29), 222 (9), 210 (5), 194 (6), 184 (9), 172 (13), 159 (6), 144 (15), 130 (6), 115 (9), 103 (4), 91 (9), 77 (10), 65 (3), 51 (3). HPLC: CHIRALCEL OD-H 4.6mm x 250 mm, 5µm column, 20 µL injection, 97.5: 2.5 Hex:IPA, 1mL/min, 15 min, 210 nm VWD UV. $t_{R1}$ = 5.165 min., Area (mAU) = 539; $t_{R2}$ = 5.344 min., Area (mAU) = 7656; er = 1:14.
Figure 197: R-BINAP HPLC data for compound 77

Racemic BINAP: 14% of a white solidified oil was isolated.
HPLC: CHIRALCEL OD-H 4.6mm x 250 mm, 5μm column, 20 μL injection, 97.5: 2.5
Hex:IPA, 1mL/min, 15 min, 210 nm VWD UV. $t_{R1} = 7.78$ min., Area (mAU) = 2430; $t_{R2} = 8.03$ min., Area (mAU) = 2195; $er = 1:1$

Figure 198: Racemic BINAP HPLC data for compound 77
**Figure 199:** $^1$H NMR of compound 77

**Figure 200:** $^{13}$C NMR of compound 77
Figure 201: COSY NMR of compound 77

-Peaks assigned are the characteristic peaks of compound 77
X-ray crystallography of compound 77:

Crystals were grown by crystallizing the sample by dissolving 4.6 mg of compound 82 in 110 μL acetonitrile in a small vial. This vial was placed in a larger vial filled with hexanes (110 μL) and was left until crystals were formed. The crystals were long thin and colorless and were stacked in sheets. The crystals were analyzed by the University of Delaware.

Figure 202: COSY NMR of compound 77
Datablock: bilm001

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test-name_ALERT_alert-type_alert-level.

Click on the hyperlinks for more details of the test.

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**Author Response:** On close inspection of the connectivity and application of CIP rules, C2=S, C3=R, C13=R.

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0 ALERT level A = Most likely a serious problem - resolve or explain
0 ALERT level B = A potentially serious problem, consider carefully
2 ALERT level C = Check. Ensure it is not caused by an omission or oversight
7 ALERT level G = General information/check it is not something unexpected
0 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
2 ALERT type 2 Indicator that the structure model may be wrong or deficient
3 ALERT type 3 Indicator that the structure quality may be low
4 ALERT type 4 Improvement, methodology, query or suggestion
0 ALERT type 5 Informative message, check

Figure 203: Ellipsoid plot of compound 77

Figure 204: Ball-and-stick model of compound 77
6a-(sec-butyl)-5-methyl-6a,10a-dihydrophenanthridin-6(5H)-one: Using the general procedure and workup outlined above with 2-(1-(sec-butyl)-N-methylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (0.15 g, 0.36 mmol). The crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 80% hexanes/20% ethyl acetate (Rf = 0.31) and 0.0253 g (26%) of a cloudy yellow oil was isolated. £H NMR (400 MHz, CDCl$_3$) δ 7.30 (tt, 1H, $J$ = 7.5, 1.8 Hz), 7.19 (ddd, 1H, $J$ = 7.3, 3.2, 1.6 Hz), 7.07 (tdd, 1H, $J$ = 7.3, 2.9, 1.1 Hz), 6.97 (dt, 1H, $J$ = 8.2, 1.6 Hz), 6.17 (td, 1H, $J$ = 9.2, 4.9 Hz), 5.99 (ddddd, 1H, $J$ = 10.8, 6.0, 2.3, 1.0 Hz), 5.94 (dt, 1H, $J$ = 9.7, 1.2 Hz), 5.49 (ddtd, 1H, $J$ = 9.4, 2.6, 1.0 Hz), 3.88 (s, 1H), 3.36 (d, $J$ = 1.0 Hz, 4H), 1.56 – 1.33 (m, 1H), 0.99 – 0.81 (m, 3H), 0.86 – 0.72 (m, 4H) ppm. £C NMR (101 MHz, CDCl$_3$) δ 129.2, 128.4, 128.3, 128.2, 128.0, 127.8, 127.7, 127.0, 125.3, 125.1, 125.0, 124.8, 123.3, 114.2, 114.2, 41.1, 40.7, 37.4, 36.9, 29.9, 29.8, 25.0, 24.5, 14.8, 14.2, 12.6, 12.5. EI MS, m/z: 267 (1), 238 (2), 210 (100), 195 (18), 180 (8), 167 (9), 152 (7), 139 (2), 127 (1), 115 (2), 77 (2). HPLC: CHIRALCEL OD-H 4.6mm x 250 mm, 5µm column, 20 µL injection, 97.5: 2.5 Hex:IPA, 1mL/min, 20 min, 210 nm VWD UV. $t_{R1}$ = 7.778 min., Area (mAU) = 2840; $t_{R2}$ = 12.125 min., Area (mAU) = 926; er = 3:1.

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Figure 205: R-BINAP HPLC data for compound 78

Racemic BINAP: 0.0403 g (47%) of a cloudy white oil was isolated.

HPLC: CHIRALCEL OD-H 4.6mm x 250 mm, 5µm column, 20 µL injection, 97.5: 2.5 Hex:IPA, 1mL/min, 20 min, 210 nm VWD UV. $t_{R1}$ = 7.734 min., Area (mAU) = 3391; $t_{R2}$ = 12.056 min., Area (mAU) = 3450; er = 1:1
Figure 206: Racemic BINAP HPLC data for compound 78

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Figure 207: $^1$H NMR of compound 78
Figure 208: $^{13}$C NMR of compound 78

6.3.5 MOM Protection of Secondary Benzamides General Procedures and Data

Scheme 35: MOM protection procedure

Unwashed NaH (60% dispersion in mineral oil) (1.10 eq) was added to a flame dried roundbottom flask in the glovebox and a septum was added to seal the flask. The roundbottom flask was removed from the glovebox and was placed in an ice bath. Anhydrous THF from the still was then added to the roundbottom flask and the solution was stirred for 1 h. Then, methylchloromethyl ether (2.0 eq) was added slowly at 0°C. After a few minutes of stirring, the flask was removed from the bath and the mixture was stirred overnight at room temperature.
2-(1-benzyl-N-(methoxymethyl)cyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate: Using the general procedure and workup outlined above with 2-(1-benzylcyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (1.55 g, 3.53 mmol), the crude reaction mixture was purified using an automated column flash chromatography system with 20% ethyl acetate/80% hexanes (Rf= 0.36) and 0.96 g (56%) of a white solidified oil was isolated. $^1$H NMR (400 MHz, DMSO) $\delta$ 7.52 – 7.46 (m, 1H), 7.41 – 7.29 (m, 3H), 7.13 (td, 3H, $J$ = 5.8, 2.8 Hz), 7.06 – 7.04 (m, 2H), 5.55 (d, 2H, $J$ = 10.0 Hz), 5.46 (d, 2H, $J$ = 10.0 Hz), 4.90 (s, 1H), 3.23 (s, 3H), 3.02 (s, 2H), 2.11 (d, 1H, $J$ = 23.5 Hz), 1.95 (d, 1H, $J$ = 23.0 Hz) ppm. $^{13}$C NMR (101 MHz, DMSO) $\delta$ 174.0, 146.0, 137.5, 132.9, 131.5, 130.4, 129.1, 128.0, 127.6, 126.3, 125.4, 121.3, 81.2, 56.5, 46.5, 25.8 ppm. $^{19}$F NMR (376 MHz, DMSO) $\delta$ -73.63 (s). ESI MS, m/z: 481 (0.1), 449 (3), 389 (2), 358 (7), 314 (2), 282 (5), 253 (15), 196 (3), 168 (23), 134 (1), 105 (100), 77 (1), 51 (1).

**Figure 209:** $^1$H NMR of compound 79
Figure 210: $^{13}$C NMR of compound 79

Figure 211: $^{19}$F NMR of compound 79
2-(1-(cyanomethyl)-N-(methoxymethyl)cyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate: Using the general procedure and workup outlined above with 2-(1-(cyanomethyl)cyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (1.52 g, 3.94 mmol). 1.02 g (60%) of a cloudy yellow oil was isolated. $^1$H NMR (400 MHz, DMSO) δ 7.55 – 7.39 (m, 4H), 5.81 (s, 2H), 5.67 (d, 2H, $J = 9.8$ Hz), 4.88 (s, 2H), 3.24 (s, 3H), 2.79 (s, 2H), 2.60 (d, 1H, $J = 23.4$ Hz), 2.30 (d, 1H, $J = 23.5$ Hz) ppm. $^{13}$C NMR (101 MHz, DMSO) δ 171.8, 145.9, 133.9, 133.1, 130.8, 129.2, 127.9, 125.3, 121.4, 118.6 (d, $J = 322$), 117.9, 81.2, 56.5, 48.2, 30.1, 26.2 ppm. $^{19}$F NMR (376 MHz, DMSO) δ -73.55 (s) ppm. EI MS, m/z: 399.1 (1), 270 (1), 253 (38), 196 (1), 164 (13), 149 (1), 134 (15), 117 (73), 91 (100), 65 (11).

**Figure 212:** $^1$H NMR of compound 80
Figure 213: $^{13}$C NMR of compound 80

Figure 214: $^{19}$F NMR of compound 80
6.3.6 MOM Protected Mizoroki Heck Reaction General Procedures and Data

Scheme 36: MOM Heck reaction general procedure

A flame dried vial under argon was charged with aryl triflate diene (1.0 eq) which was dissolved in DMF. In a separate flame dried vial with a stir bar, under argon, Pd(OAc)$_2$ (0.2 eq) and (R or racemic) BINAP (0.24 eq) was dissolved in DMF and stirred for 1 hour. To the palladium mixture, Cy$_2$NMe (2.0 eq) was added and the solution was stirred for an additional 10 minutes. The aryl triflate diene was then added to the Pd/Cy$_2$NMe vial via syringe. Finally, lithium acetate (2.0 eq) was added to the vial for the benzyl derivative only. The vial was capped with a pressure relief cap and stirred at 80°C. Upon completion the reaction mixture was filtered using a pipet pack with cotton, followed by silica gel, and topped with celite. Excess EtOAc was used to rinse any compound off the celite and silica gel. The organic layer was concentrated in vacuo and columned on silica gel.

6a-benzyl-5-(methoxymethyl)-6a,10a-dihydrophenanthridin-6(5H)-one: Using the general procedure and workup outlined above with 2-(1-benzyl-N-(methoxymethyl)cyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (0.12 g, 0.24 mmol). The crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 80% hexanes/20% ethyl acetate (Rf = 0.38) and 0.065 g (81%) of a cloudy white oil was isolated. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.35 – 7.13 (m, 7H), 7.03 – 7.01 (m, 2H), 6.11 – 6.04 (m, 2H), 5.94 (dddd, 1H, J = 9.2, 4.6, 3.0, 1.4 Hz), 5.59 (d, 1H, J = 10.6 Hz), 5.55 (dd, 1H, J = 9.4, 2.9 Hz), 5.18 (d, 1H, J = 10.6 Hz), 3.59 (t, 1H, J = 3.0 Hz), 3.39 (s, 3H), 3.01 (d, 1H, J = 13.3 Hz), 2.86 (d, 1H, J = 13.4 Hz) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 174.1, 137.9, 136.3, 130.7, 130.2, 128.7, 128.4, 128.3, 128.1, 126.8, 125.9, 125.3, 124.7, 124.2, 115.6, 74.0, 56.4, 46.8, 40.9, 40.2 ppm. EI MS, m/z: 331 (0.1), 300 (2), 284 (1), 270 (1), 254 (1), 239 (10), 224 (19), 208 (10), 196 (16), 178 (29), 165 (6), 152 (8), 139 (3), 127 (1), 115 (2), 91 (49), 77 (3), 65 (5), 51 (1). HPLC: CHIRALCEL OD-H 4.6mm x 250 mm, 5μm column, 20 μL injection, 97.5: 2.5 Hex:IPA, 1mL/min, 20 min, 210 nm VWD UV. $t_{R1}$ = 8.753 min., Area (mAU) = 8981; $t_{R2}$ = 11.478 min., Area (mAU) = 765; er = 12:1
Figure 215: R-BINAP HPLC data for compound 81

Racemic BINAP: 0.0778 g (79%) of a cloudy white oil was isolated.

HPLC: CHIRALCEL OD-H 4.6mm x 250 mm, 5μm column, 20 μL injection, 97.5: 2.5 Hex:IPA, 1mL/min, 40 min, 210 nm VWD UV. $t_{R1} = 8.651$ min., Area (mAU) = 2578; $t_{R2} = 11.319$ min., Area (mAU) =2471; $er = 1:1$

Figure 216: Racemic BINAP HPLC data for compound 81
Figure 217: $^1$H NMR of compound 81

Figure 218: $^{13}$C NMR of compound 81
2-(5-(methoxymethyl)-6-oxo-5,10a-dihydrophenanthridin-6a(6H)-yl)acetonitrile: Using the general procedure and workup outlined above with 2-(1-(cyanomethyl)-N-(methoxymethyl)cyclohexa-2,5-diene-1-carboxamido)phenyl trifluoromethanesulfonate (0.062 g, 0.14 mmol). The crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 70% hexanes/30% ethyl acetate (Rf = 0.31) and 0.030 g (73%) of a cloudy yellow oil was isolated. 1H NMR (400 MHz, DMSO) δ 7.33-7.26 (m, 3H), 7.12 (td, 1H, J = 6.4, 1.6 Hz), 6.20-6.16 (m, 2H), 3.92 (d, 1H, J = 4.7 Hz), 3.40 (s, 3H), 2.90 (d, 1H, J = 16.4 Hz), 2.69 (d, 1H, J = 16.4 Hz) ppm. 13C NMR (101 MHz, DMSO) δ 170.6, 137.7, 128.6, 127.9, 127.3, 126.2, 126.2, 125.2, 124.4, 124.0, 116.9, 115.7, 74.4, 56.5, 44.7, 38.7, 22.9 ppm. EI MS, m/z: 280 (35), 248 (32), 234 (35), 219 (7), 208 (79), 192 (100), 180 (73), 165 (41), 152 (24), 139 (9), 127 (4), 115 (5), 102 (2), 90 (15), 77 (10), 63 (7), 51 (5). HPLC: CHIRALCEL OD-H 4.6mm x 250 mm, 5μm column, 20 μL injection, 97.5: 2.5 Hex:IPA, 1mL/min, 60 min, 210 nm VWD UV. tR1 = 36.55 min., Area (mAU) = 796.80; tR2 = 43.02 min., Area (mAU) = 7792.30; er = 1:10

**Figure 219:** R-BINAP HPLC data for compound 82

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Racemic BINAP: 68% of a yellow cloudy oil was isolated.

HPLC: CHIRALCEL OD-H 4.6mm x 250 mm, 5μm column, 20 μL injection, 97.5: 2.5 Hex:IPA, 1mL/min, 60 min, 210 nm VWD UV. tR1 = 36.99 min., Area (mAU) = 3391.8; tR2 = 43.92 min., Area (mAU) = 3422.8; er = 1:1

293
Figure 220: Racemic BINAP HPLC data for compound 82

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Figure 221: $^1$H NMR of compound 82
Figure 222: $^{13}$C NMR of compound 82

6.3.7 Deprotection of the MOM Protected Mizoroki Heck product General Procedures and Data

Scheme 37: MOM deprotection procedure

Procedure adapted from Fukuyama and Liu.$^{12}$ To a solution of (Heck Product) in acetonitrile at 0°C was added TMS-I (4.6 eq). Then, the mixture was stirred at 0°C for 1 hr. The reaction was quenched with saturated aqueous NaHCO$_3$ and extracted with EtOAc. The organic layers were combined, washed with brine, dried over magnesium sulfate and concentrated. The resulting crude product was used in the next step. To a solution of crude product in MeOH at room temperature was added Et$_3$N (2.98 eq). The reaction was stirred for 1 h at 55 °C in a pie

295
After cooling to room temperature, the reaction was quenched in saturated aq. Ammonium chloride and hexane/EtOAc (1:1 mixture) was added. The organic layer was separated and the aqueous layer was extracted with hexane. The organic layers were combined, washed with brine, dried over magnesium sulfate, and concentrated.

6a-benzyl-6a,10a-dihydrophanthridin-6(5H)-one: Using the general procedure and workup outlined above with 6a-benzyl-5-(methoxymethyl)-6a,10a-dihydrophanthridin-6(5H)-one (0.031 g, 0.94 mmol), the crude reaction mixture was purified using an automated column flash chromatography system with 20% ethyl acetate/80% hexanes (Rf= 0.43) and 0.0156 g (58%) of a white solid was isolated. m.p. = 76.4-81.5°C. ¹H NMR (400 MHz, CDCl₃) δ 8.45 (s, 1H), 7.27-7.17 (m, 5H), 7.11-7.04 (m, 3H), 6.76 (d, 1H, J = 7.8 Hz), 6.10 (dd, 1H, J = 9.5, 4.0 Hz), 6.01-5.97 (m, 2H), 5.63 (dd, J = 9.5, 2.9 Hz, 1H), 3.65 (t, 1H, J = 2.8 Hz), 3.00 (s, 2H) ppm. ¹³C NMR (101 MHz, CDCl₃) δ 173.8, 136.5, 136.0, 130.6, 129.3, 128.3, 128.2, 128.1, 127.8, 126.8, 125.4, 124.6, 124.5, 123.8, 115.1, 46.9, 40.9, 39.9 ppm. EI MS, m/z: 289 (15), 208 (2), 196 (100), 178 (44), 167 (21), 152 (12), 139 (6), 128 (5), 115 (6), 91 (39), 77 (4), 65 (5), 51 (2). HPLC: CHIRALCEL OD-H 4.6mm x 250 mm, 5μm column, 20 μL injection, 97.5: 2.5 Hex:IPA, 1mL/min, 40 min, 210 nm VWD UV. tᵣ₁ = 19.631 min., Area (mAU) = 792; tᵣ₂ = 31.14 min., Area (mAU) =8828; er = 11:1

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**Figure 223:** R-BINAP HPLC data for compound 83
Racemic BINAP: 0.014 g (52%) of a clear oil was isolated.

HPLC: CHIRALCEL OD-H 4.6mm x 250 mm, 5μm column, 20 μL injection, 97.5: 2.5 Hex:IPA, 1mL/min, 40 min, 210 nm VWD UV. \( t_{R1} = 19.590 \) min., Area (mAU) = 1955; \( t_{R2} = 31.299 \) min., Area (mAU) = 1886; \( \varepsilon = 1:1 \)

![HPLC data for racemic BINAP](image)

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**Figure 224:** Racemic BINAP HPLC data for compound 83

![1H NMR of compound 83](image)

**Figure 225:** \(^1\)H NMR of compound 83
Figure 226: $^{13}$C NMR of compound 83

5,6a-dimethyl-6a,10a-dihydrophenanthridin-6(5H)-one: Using the general procedure and workup outlined above with N-(2-bromophenyl)-N,1-dimethylcyclohexa-2,5-diene-1-carboxamide (0.103 g, 0.33 mmol). The crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 80% hexanes/20% ethyl acetate (Rf = 0.27) and 0.003 g (4%) of a cloudy oil was isolated. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.30 (td, 1H, $J = 7.8, 1.6$ Hz), 7.23 (dd, 1H, $J = 7.4, 1.4$ Hz), 7.08 (td, 1H, $J = 7.4, 1.1$ Hz), 6.99 (d, 1H, $J = 8.1$ Hz), 6.09 (dd, 1H, $J = 9.2, 5.0$ Hz), 6.02 (dddd, 1H, $J = 9.2, 5.1, 2.9, 1.0$ Hz), 5.89 (dd, 1H, $J = 9.3, 0.9$ Hz), 5.58 (dd, 1H, $J = 9.3, 2.8$ Hz), 3.48 (t, 1H, $J = 2.8$ Hz), 3.35 (s, 3H), 1.23 (s, 3H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) δ 173.4, 139.0, 131.8, 128.6, 127.8, 126.6, 125.2, 124.2, 123.3, 114.3, 44.3, 40.8, 29.9, 23.4 ppm. EI MS, m/z: 224 (80), 210 (100), 195 (22), 182 (25), 167 (27), 152 (12), 139 (5), 128 (4), 115 (7), 104 (3), 91 (5), 77 (6), 63 (5), 51 (4). Spectral data were in accordance with the literature$^{10,13}$. HPLC: CHIRALCEL OD-H 4.6mm x 250 mm, 5μm column,
20 μL injection, 97.5: 2.5 Hex:IPA, 1mL/min, 40 min, 210 nm VWD UV. $t_{R1} = 9.626$ min., Area (mAU) = 12604; $t_{R2} = 10.669$ min., Area (mAU) = 10738; er = 1:1

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**Figure 227:** HPLC data for compound 84

**Figure 228:** $^1$H NMR of compound 84
Figure 229: $^{13}$C NMR of compound 84

5,6a-dimethyl-6a,9,10,10a-tetrahydrophenanthridin-6(5H)-one: Using the general procedure and workup outlined above with N-(2-bromophenyl)-N,1-dimethylcyclohexa-2,5-diene-1-carboxamide (0.103 g, 0.33 mmol). The crude reaction mixture was purified using column flash chromatography (silica gel, 60Å) with 80% hexanes/20% ethyl acetate (Rf = 0.40) and 0.0163 g (21%) of an oil was isolated. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.26 (td, 1H, $J = 8.0$, 1.6 Hz), 7.17 (dd, 1H, $J = 7.4$, 1.5 Hz), 7.03 (td, 1H, $J = 7.4$, 1.1 Hz), 6.98 (d, 1H, $J = 8.1$ Hz), 5.74-5.69 (m, 1H), 5.65-5.60 (m, 1H), 3.37 (s, 3H), 2.96 (dddt, 1H, $J = 18.0$, 5.0, 2.6, 1.3 Hz), 2.80 (dd, 1H, $J = 10.3$, 6.2 Hz), 2.30-2.22 (m, 1H), 2.08-1.98 (m, 1H), 1.91-1.83 (m, 1H), 1.05 (s, 3H) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$) δ 173.9, 139.0, 129.9, 128.9, 127.4, 127.3, 126.1, 126.1, 124.4, 123.0, 114.5, 41.6, 40.0, 32.7, 30.0, 29.9, 24.3 ppm. El MS, m/z: 227 (100), 212 (47), 198 (11), 182 (7), 173 (100), 158 (12), 144 (46), 130 (22), 115 (20), 103 (9), 91 (12), 77 (20), 63 (8), 51 (10).
Figure 230: $^1$H NMR of compound 85

Figure 231: $^{13}$C NMR of compound 85
6.4 References:


