Azulene Chemistry

What follows is a summary of the synthesis reactions related to Azulene, its generation and its derivatives based on the references I was able to review. I hope that this summary will be of help to those who might be interested in this subject.


TABLE 3. Synthesis of Substituted Azulenes

<table>
<thead>
<tr>
<th>entry</th>
<th>diazo ketone&lt;sup&gt;5&lt;/sup&gt; (Ar)</th>
<th>azulene (yield)&lt;sup&gt;6&lt;/sup&gt;</th>
<th>entry</th>
<th>diazo ketone&lt;sup&gt;5&lt;/sup&gt; (Ar)</th>
<th>azulene (yield)&lt;sup&gt;6&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19 (C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;)</td>
<td>20&lt;sup&gt;o&lt;/sup&gt; (64-72%)</td>
<td>7</td>
<td>53 (4-Me-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;)</td>
<td>73 (47%)&lt;sup&gt;o&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>48 (2-Cl-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;)</td>
<td>68 (58-61%)</td>
<td>8</td>
<td>54 (4-Cl-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;)</td>
<td>74 (61%)&lt;sup&gt;o&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>49 (2-I-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;)</td>
<td>69 (73%)</td>
<td>9</td>
<td>55 (3,4-di-Cl-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;)</td>
<td>75 (19%)&lt;sup&gt;o&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>50 (3-Br-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;)</td>
<td>70 (54%)</td>
<td>10</td>
<td>65 (4-NO&lt;sub&gt;2&lt;/sub&gt;-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;)</td>
<td>76 (21%)&lt;sup&gt;o&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>51 (3-Br-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;)</td>
<td>71 (38%)</td>
<td>11</td>
<td>56 (4-CN-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;)</td>
<td>77 (39%)&lt;sup&gt;o&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>52 (3-CF&lt;sub&gt;3&lt;/sub&gt;-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;)</td>
<td>72 (40%)</td>
<td>12</td>
<td>67 (C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;, R&lt;sup&gt;2&lt;/sup&gt; = CH&lt;sub&gt;3&lt;/sub&gt;)</td>
<td>78 (58%)&lt;sup&gt;o&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> 0.005–0.01 equiv of Rh<sub>2</sub>(OCO(t-Bu))<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt, 45–90 min; then add 3 equiv of DMAP, 5 equiv of Ac<sub>2</sub>O, rt, 5 min. <sup>b</sup> R<sup>2</sup> = H unless otherwise indicated. <sup>c</sup> Isolated yield of products purified by chromatography on silica gel. <sup>d</sup> Aiso, T.; Ita, S.; Morita, N. Tetrahedron Lett. 1998, 39, 6695. <sup>e</sup> Estimated yield; 22% overall yield from 4-methylidibromomethane (27). <sup>f</sup> EtO used as solvent.

Scheme 1

Scheme 2  Reagents and conditions:  

a) $\text{PdCl}_2(\text{PPh}_3)_2$, CICONR$_2$, CsF, THF, reflux;  
b) KOH (excess), 5a, EtOH-H$_2$O, reflux;  
c) DIBAL-H, 5b, -78 °C.

Scheme 2  Stille cross-coupling reactions of azulenylltin compound 3b with 4-bromo- or 4-iodotoluene

Scheme 3  Stille cross-coupling reactions of azulenylltin compounds 3a and 3b with aryl bromides

Scheme 4  Stille cross-coupling reactions of azulenylltin compound 3b with acyl chlorides

Scheme 5  Palladium-catalyzed direct azulenyllboronate formation

Scheme 6  Borylation using azulen-2-yllithium as a reagent

Scheme 9  Iodine-metal exchange reactions of 6-iodoazulene (23) and the reactions of the resulting azulényl-substituted metallic reagents with electrophiles


The following thesis has an excellent synthesis review section.


Table 2 Optimization of Catalytic System

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalytic system</th>
<th>Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(dba)$_2$ (5 mol%), PPh$_3$ (20 mol%)</td>
<td>24 h, 50 °C</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>Pd(dba)$_2$ (5 mol%), SPhos (10 mol%)</td>
<td>45 min, r.t.</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>Pd(dba)$_2$ (5 mol%), SPhos (10 mol%), i-PrI</td>
<td>30 min, r.t.</td>
<td>76</td>
</tr>
</tbody>
</table>
**Table 3** Negishi Cross-Coupling of Monobromoazulenes with Organozinc Reagents

\[
\text{R}^1 = \text{Cl, H, CO}_2\text{Et} \quad \text{R}^2 = \text{aryl, hetaryl, alkyl, benzyl}
\]

**Table 4** Negishi Cross-Coupling of 1,3-Dibromoazulene (3d) with Organozinc Reagents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0.5 h</td>
<td><img src="image" alt="Diagram" /></td>
</tr>
</tbody>
</table>

a) Azulene halogenation and cross-coupling

\[ \text{Azulene} + \text{Halogen} \rightarrow \text{AzuleneHalogen} + \text{Product} \]

b) Azulene triflate formation and cross-coupling (Ref. [21])

\[ \text{Azulene} + \text{R}^3 \rightarrow \text{AzuleneTriflate} + \text{Product} \]

c) Azulenesulfonium salt formation and cross-coupling (this study)

\[ \text{Azulene} + \text{Sulfonium Salt} \rightarrow \text{Azulenesulfonium Salt} + \text{Product} \]

Scheme 1. Strategies for azulene cross-coupling. DMAP = 4-dimethylaminopyridine, TF = trifluoromethanesulfonyl.

Scheme 2. Synthesis of the parent sulfonium salt 11a and its X-ray crystal structure.

Scheme 3. Optimization of cross-coupling parameters.

Scheme 4. Variation of the organoboron coupling partner.


See the following review:


Scheme 2 Synthesis of 2-chloroazulenes 1 and 2 by Nozoe's procedure.

Scheme 2. Pd-catalyzed arylations C2- or C3- positions of guaiazulene with aryl bromides
Scheme 4. Pd-catalyzed arylation at C1-position of azulene with aryl bromides

Scheme 7. Au-catalyzed alkylations at C1-position of azulene with methyl vinyl ketone

Scheme 11. Ni-catalyzed alkylation of azulene with a 2-bromopropionate

Scheme 1. Reported metal-catalyzed methods for azulene C-H bond functionalization and C-C bond formation (a-f) and stoichiometric C-N bond generation (g)
Scheme 2. Azulene C–H bond functionalization and C–C and C–N bond formation by carbene or nitrene insertion

Previous work

This work

Table 1. Catalytic functionalization of azulene by carbene transfer from ethyl diazoacetate catalyzed by Tp(CF₃)₂BrCu(NCCH₃).a

<table>
<thead>
<tr>
<th>entry</th>
<th>cat:EDA:azuleneb</th>
<th>mmol EDA</th>
<th>1%</th>
<th>2%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1:50:100</td>
<td>1.98</td>
<td>37</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1:75:50</td>
<td>0.62</td>
<td>28</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>1:100:50</td>
<td>2.4</td>
<td>11</td>
<td>39</td>
</tr>
</tbody>
</table>

aConditions: azulene was dissolved in CH₂Cl₂ along with Tp(CF₃)₂BrCu(NCCH₃) and a solution of EDA in the same solvent was added for 14 h with a syringe pump under inert atmosphere. See the Table S1 in the SI for experimental details. bMmoll ratio.

Table 2. Catalytic functionalization of azulene with ethyl 2-phenyl diazoacetate.a

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>cat:PhEDA:azuleneb</th>
<th>3%</th>
<th>4%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tp(CF₃)₂BrCu(L)</td>
<td>1:50:100</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Rh₂(OOCCF₃)₄</td>
<td>1:50:100</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Tp(CF₃)₂BrCu(L)</td>
<td>1:100:50</td>
<td>32</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>Rh₂(OOCCF₃)₄</td>
<td>1:100:50</td>
<td>0</td>
<td>46</td>
</tr>
</tbody>
</table>

aConditions employed as described Table 1. L = CH₂CN. See Table S2 in the SI for full experimental details. bMmoll ratio.


The following thesis have a good reviews worth a look:


**Scheme 2. Molecular Transformation of 2-Bromo-6-Pyrrolidinylazulene 4**

**Scheme 4. Synthesis of 6-Arylazoazulenes 13a–13d via the S$_3$Ar Reaction of 1 with Arylhydrazines and Conversion to 6-Phenylazoazulene (14)**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>R$^1$</th>
<th>R$^2$</th>
<th>Product, Yields [a]</th>
<th>Product, Yield [%][b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>CO$_2$Me</td>
<td>H</td>
<td>2a, 92</td>
<td>3a, 95</td>
</tr>
<tr>
<td>2</td>
<td>1b</td>
<td>CO$_2$Me</td>
<td>6-Pr</td>
<td>2b, 85</td>
<td>3b, 96</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>CO$_2$Me</td>
<td>7-Pr</td>
<td>2c, 84</td>
<td>3c, 89</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>CO$_2$Me</td>
<td>6-Me</td>
<td>2d, 75</td>
<td>3d, 75</td>
</tr>
<tr>
<td>5</td>
<td>1e</td>
<td>Ph</td>
<td>H</td>
<td>2e, 70</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>1f</td>
<td>H</td>
<td>H</td>
<td>3a, 66</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>1g</td>
<td>H</td>
<td>6-Pr</td>
<td>3b, 63</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>1h</td>
<td>H</td>
<td>5-Pr</td>
<td>3c, 71</td>
<td>–</td>
</tr>
</tbody>
</table>

[a] 3 equiv. of silyl enol ether was employed. [b] Isolated yield.

**Table 2. Reaction of 2H-cyclohepta[b]furan-2-ones with aryl-substituted silyl enol ethers.**