Flow Synthesis of Triptycene via Triple Cycloaddition of Ynolate to Benzyne

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Abstract Flow synthesis of triptycene was achieved using triple cycloaddition of ynlolate to benzyne. Employing the borate-type benzyne precursor, side reactions triggered by the addition of alkyl lithium to benzyne were efficiently suppressed under microflow conditions, thus producing triptycene with a higher yield than that obtained under the corresponding batch conditions. Furthermore, ynlolate prepared from \( \text{Br_2} \), \( \text{O} \), and \( \text{Br} \) under microflow conditions was continuously added to the flow reaction with benzyne, which successfully synthesized triptycene in only one minute.

Keywords triptycene, ynlolate, benzyne, flow synthesis, cycloaddition borate

Triptycenes are symmetric compounds with three benzene rings fixed by a bicyclo[2.2.2]octatriene bridgehead system. Based on their unique and rigid skeleton, the compounds have been utilized in fields such as host–guest chemistry, supramolecular chemistry, and material chemistry. Studies have reported several synthetic methods for triptycene synthesis, e.g., the Diels–Alder reaction of anthracenes and benzynes or quinones, the intramolecular Friedel–Crafts reaction, and the [2+2+2] cycloaddition of alkynes. Furthermore, we have recently developed a new synthetic method for triptycene based on a triple cycloaddition of one ynlolate to three benzyne molecules. Therefore, it is important to generate benzyne incrementally. Moreover, the generation of benzyne using a strong base, such as alkyl- or aryllithium, competes with the side reactions triggered by the addition of the base to benzyne. Thus, suppression of these side reactions is key to improving the yield but is not easily achieved in a batch system because inefficient mixing causes an uneven distribution of concentration and temperature in the reaction vessel.

These issues in the batch system could be solved using microflow systems, which have the potential to provide constant reaction parameters, such as reaction temperature, time, and concentration, due to high mixing efficiency and rapid heat transfer. Furthermore, the rapid diffusion of the reaction mixture helps suppress undesired contact of intermediates or the product with the starting materials and reagents. Therefore, it has been illustrated that the microflow conditions are beneficial in many exothermic reactions via unstable intermediates such as alkylthiolium-initi-
lated reactions. For example, Yoshida and co-workers reported that the efficient formation and reaction of benzynes were achieved using microflow systems.\textsuperscript{10} We have reported the flow synthesis of ynolate from \( \text{a,b-dibromoester using alkyllithium} \)\textsuperscript{pd} or lithium naphthalenide and achieving other reactions of ynolates under microflow conditions.\textsuperscript{11} Based on these results, we envisioned that microflow systems could improve the efficiency of the synthesis of triptycene through the precise control of reaction conditions. Thus, this report details the flow synthesis of triptycene via triple cycloaddition of ynolate and benzynes using flow microreactors.

The investigation began with the reaction using \( o\)-bromoiodobenzene and \( \text{PhLi} \) for the preparation of benzynes (Table 1).\textsuperscript{10a} The reaction was carried out using a Comet X-01 mixer (Techno Applications Co., Ltd, Tokyo, Japan) as a microreactor. A solution of lithium ynolate 1 was prepared in advance by our method in a batch system.\textsuperscript{pd} In entry 1, a solution of \( \text{PhLi} \) (0.97 M) and a mixture of ynolate 1 (0.12 M) and benzene precursor 2 (0.70 M) were pumped into the reactor at a 1.0 mL/min in a ratio of \( 1/2/\text{PhLi} = 1:6:8 \). The solutions were mixed at \( –20 \) °C, and the resulting mixture flowed through a tube with 0.8 mL volume, where the residence time was approximately 24 s, into the aqueous \( \text{HCl} \) solution to quench the reaction. The yield of triptycene was estimated by NMR to be approximately 21%. In each entry, the ratio of \( o\)-bromoiodobenzene to \( \text{PhLi} \) was changed to 1:8:11 and 1:3:4, the rate was increased to 3\( \) °C, and the reaction was performed at 23 °C to provide triptycene with yields of 33% and 31%, respectively (entries 6 and 7).

For comparison, the reaction was also performed in the batch system under the conditions corresponding to entry 6 in Table 1, and triptycene 3 was obtained with a 31% NMR yield (25% isolated yield), which was slightly less than that obtained in the microflow conditions (Scheme 2). This may indicate that the microflow system improved the efficiency of the triple cycloaddition of ynolate to benzynes. However, we realized that it is not easy to suppress the side reactions under these microflow conditions, because the formation of many byproducts was observed on the GC–MS analysis of the crude products (see Figure S1 in the Supporting Information). The major byproducts were biphenyls and \( o\)-terphenyls, which would be formed by the addition of aryllithium intermediates to benzynes. Although this result indicates that benzene was generated efficiently, most of the benzene was wasted in the side reactions.

**Table 1** Flow Synthesis of Triptycene Using \( o\)-Bromoiodobenzene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conc of 1 (M)</th>
<th>( 1/2/\text{PhLi} )</th>
<th>( \text{T} ) (°C)</th>
<th>( s ) mL/min</th>
<th>( t ) (s)</th>
<th>Yield (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.12</td>
<td>1:6:8</td>
<td>–20</td>
<td>1.0</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>0.12</td>
<td>1:6:8</td>
<td>0</td>
<td>1.0</td>
<td>24</td>
<td>31</td>
</tr>
<tr>
<td>3</td>
<td>0.12</td>
<td>1:6:8</td>
<td>22</td>
<td>1.0</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>0.075</td>
<td>1:8:11</td>
<td>5</td>
<td>1.0</td>
<td>24</td>
<td>27</td>
</tr>
<tr>
<td>5</td>
<td>0.20</td>
<td>1:3:4</td>
<td>0</td>
<td>1.0</td>
<td>24</td>
<td>17</td>
</tr>
<tr>
<td>6</td>
<td>0.12</td>
<td>1:6:8</td>
<td>0</td>
<td>1.5</td>
<td>16</td>
<td>33</td>
</tr>
<tr>
<td>7</td>
<td>0.12</td>
<td>1:6:8</td>
<td>0</td>
<td>2.0</td>
<td>12</td>
<td>31</td>
</tr>
</tbody>
</table>

\( ^{a} \) Molar ratio of concentrations.  
\( ^{b} \) NMR yields.

Thus, we changed the precursor of benzene to \( o\)-(trifluoromethanesulfonyloxy)phenylboronic acid pinacol ester 4 developed by Hosoya and co-workers (Table 2).\textsuperscript{12,13} It has been reported that the treatment of alkyllithium with \( 4 \) generates borosilicate complex 5, which is stable at 0 °C and then converts into benzene when warmed to room temperature. Based on this, we envisioned that the undesired addition reactions to benzene could be suppressed using precursor 4 because, by the formation of the borate complex in advance, the coexistence of nucleophilic butyllithium and benzene can be avoided. Slow generation of benzene could also be achieved by temperature control of the borate complex solutions in the second step. The microreactor system consisted of two mixers, A and B. The solutions of precursor 4 and \( s\)-BuLi were introduced into the microreactor and combined in mixer A at \( –78 \) °C. The resulting solution of borate complex 5 was mixed with a solution of ynolate 1 in mixer B and then passed through the tube maintained at the indicated temperature. In entry 1, the ratio of \( 1/4/s\)-BuLi was 1:6:6, and the reaction was performed at 23 °C to provide triptycene 3 with a 19% yield. When the reaction temperature was elevated to 40 °C and 60 °C, the yield of 3 increased to 33% and 29%, respectively (entries 2 and 3). However, the use of 5 or 8 equivalents of 4 and \( s\)-BuLi diminished the
yield (entries 4 and 5). In entry 6, the reaction employed a higher concentration of the solutions in comparison with entry 2, which resulted in no influence on the NMR yield and a 31% isolated yield of 3. It should be emphasized that GC-MS analysis of the crude products indicated considerable suppression of side reactions (see Figure S2 in the Supporting Information). The main byproducts were o-bromophenylboronic acid pinacol ester and biphenylene formed via dimerization of benzyne. These results suggest that the almost complete consumption of s-BuLi was achieved in the first step, and thus, the competitive addition reactions to benzyenes were largely suppressed. Therefore, although the yield was as much as one of the first approach as shown in Table 1, purification of triptycene 3 was much easier to perform in this approach. Furthermore, the batch reaction, which was performed under the conditions corresponding to entry 6 in Table 2, synthesized triptycene 3 with a 21% yield (24% NMR yield, Scheme 3). Thus, the reaction efficiency of the triple cycloaddition reaction was also improved under the microflow conditions probably due to the high mixing efficiency.

Finally, ynolate 1, prepared under the microflow conditions, was directly employed for the flow synthesis of triptycene (Scheme 4). The solutions of o,a-dibromoester (1.20 M) and lithium naphthalenide (0.25 M) were mixed in mixer A at 22 °C to produce ynolate 1. At the same time, the solutions of benzyne precursor 4 (0.38 M) and s-BuLi (0.38 M) were pumped into mixer B. These two resulting solutions were then introduced into mixer C, and the reaction mixture passed through a tube maintained at 40 °C for 16 s. Triptycene 3 was successfully obtained with a 16% yield judged by the NMR spectra. Although the yield was less than that of the prior flow systems, the current flow system provided advantages, including that the whole reaction was completed in only one minute.

In conclusion, we have developed flow synthesis of triptycene using triple cycloadditions of ynolate-benzyne under microflow conditions. Using Hosoya’s benzyne precursor, dramatic suppression of side reactions, and improvement in yield compared with the corresponding batch system was achieved. This can be attributed to the microflow conditions, such as efficient mixing and rapid heat...

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conc of 1 (M)</th>
<th>1/4 s-BuLi</th>
<th>T (°C)</th>
<th>t (s)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1^c</td>
<td>0.05</td>
<td>1:6:6</td>
<td>23</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>2^c</td>
<td>0.05</td>
<td>1:6:6</td>
<td>40</td>
<td>16</td>
<td>33</td>
</tr>
<tr>
<td>3^c</td>
<td>0.05</td>
<td>1:5:5</td>
<td>60</td>
<td>32</td>
<td>29</td>
</tr>
<tr>
<td>4^c</td>
<td>0.05</td>
<td>1:8:8</td>
<td>40</td>
<td>32</td>
<td>22</td>
</tr>
<tr>
<td>5^e</td>
<td>0.05</td>
<td>1:8:8</td>
<td>40</td>
<td>32</td>
<td>20</td>
</tr>
<tr>
<td>6^e</td>
<td>0.075</td>
<td>1:6:6</td>
<td>40</td>
<td>16</td>
<td>33 (31)^e</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Scheme 3</th>
<th>Batch synthesis of triptycene 3 using borate-type benzyne precursor 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scheme 4</td>
<td>Flow synthesis of triptycene, including the preparation of ynolate 1</td>
</tr>
</tbody>
</table>

Table 2 Flow Synthesis of Triptycene Using O-(Trifluoromethanesulfonyloxy)phenylboronic Acid Pinacol Ester

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^a Molar ratio of concentrations.
^b NMR yields.
^c Residence time between mixer A and B: 24 s.
^d Residence time between mixer A and B: 48 s.
^e Isolated yield.
transfer. The flow reaction was also performed using yno- late, which was prepared under microflow conditions, syn-
thesizing the triptycene in only one minute. This is the first report for flow synthesis of triptycene, as far as we know.

Further improvement of the reaction efficiency is now un-
der investigation in our group.

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References and Notes

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