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Flow synthesis of triptycene via triple cycloaddition of ynolate to benzyne

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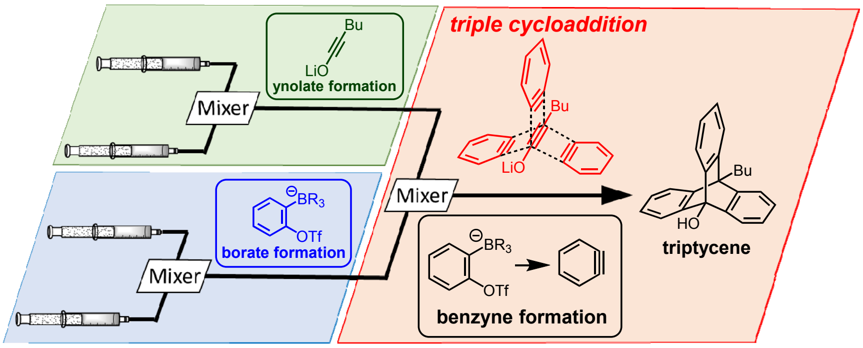

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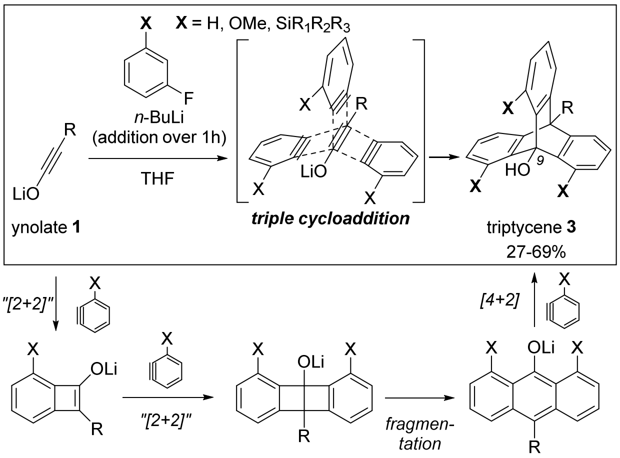
Abstract Flow synthesis of triptycene was achieved using triple cycloaddition of ynolate to benzyne. Employing the borate-type benzyne precursor, side reactions triggered by the addition of alkyllithium to benzyne were efficiently suppressed under microflow conditions, thus producing triptycene with a higher yield than that obtained under the corresponding batch conditions. Furthermore, ynolate prepared from α,α-dibromoester under microflow conditions was continuously added to the flow reaction with benzyne, which successfully synthesized triptycene in only one minute.

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

Triptycenes are symmetric compounds with three benzene rings fixed by a bicyclo[2,2,2]octatriene bridgehead system.[1] Based on their unique and rigid skeleton, the compounds have been utilized in fields such as host–guest chemistry, supramolecular chemistry, and material chemistry.[2] Studies have reported several synthetic methods for triptycene synthesis, *e.g.,* the Diels–Alder reaction of anthracenes and benzynes[3] or quinones,[4] the intramolecular Friedel–Crafts reaction,[5] and the [2+2+2] cycloaddition of alkynes.[6] Furthermore, we have recently developed a new synthetic method for triptycene based on a triple cycloaddition of one ynolate **1**[7] to three benzynes **2** (Scheme 1).[8] This method can be easily performed, where alkyllithium is added to a mixture of ynolate and a benzyne precursor. The yield of triptycene **3** varies from 27% to 69% when employing fluorobenzene or 3-fluoroanisole as the benzyne precursor. In the cases that resulted in low yields, abundant benzyne byproducts were produced. Generally, short-lived benzynes should be trapped by an excess of arynophiles. However, the triple cycloaddition reaction does not use the excess ynolate because the reaction needs at least three equivalents of benzyne to ynolate. Therefore, it is important to generate benzynes 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.

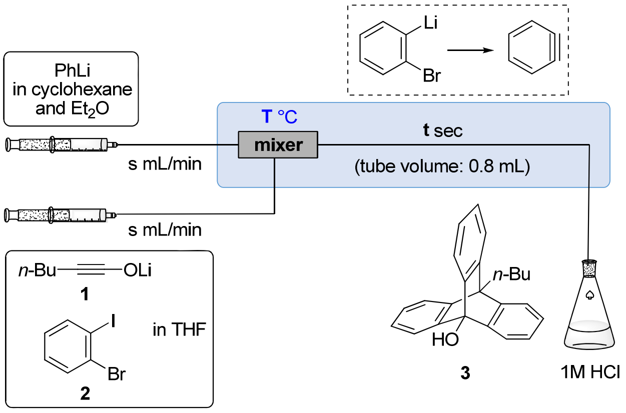


Scheme 1. Synthesis of triptycene via triple cycloaddition of ynolate to benzyne.

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.[9] 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 alkyllithium-initiated reactions. For example, Yoshida and coworkers reported that the efficient formation and reaction of benzyne were achieved using microflow systems.[10] We have reported the flow synthesis of ynolate from α,α-dibromoester using alkyllithium[7d] or lithium naphthalenide and achieving other reactions of ynolates under microflow conditions.[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 benzyne using flow microreactors.

The investigation began with the reaction using *o*-bromoiodobenzene and PhLi for the preparation of benzyne (Table 1).[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.[7d] In entry 1, a solution of PhLi (0.97 M) and a mixture of ynolate **1** (0.12 M) and benzyne precursor **2** (0.70 M) were pumped into the reactor at a 1.0 mL/min in a ratio of **1**:**2**: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 sec, into the aqueous HCl solution to quench the reaction. The yield of triptycene **3** was estimated by NMR to be approximately 21%. In entries 2 and 3, the reaction temperature was increased to 0 °C and 22 °C, which resulted in higher yields of **3**. When the ratio of **1**:**2**:PhLi was changed to 1:8:11 and 1:3:4, the yields were diminished (entries 4 and 5). The faster flow rates (1.5 and 2.0 mL/min), with residence times of 16 and 12 sec, were effective, thus synthesizing the product with yields of 33 and 31%, respectively (entries 6 and 7).

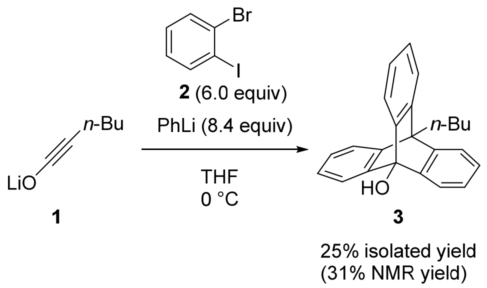
Table 1. Flow synthesis of triptycene using *o*-bromoiodobenzene.



Entry	Concentration of **1** (M)	**1**: **2**: PhLi[a]	T (°C)	s (mL/min)	t (sec)	Yield (%)[b]
1	0.12	1:6:8	−20	1.0	24	21
2	0.12	1:6:8	0	1.0	24	31
3	0.12	1:6:8	22	1.0	24	25
4	0.075	1:8:11	5	1.0	24	27
5	0.20	1:3:4	0	1.0	24	17
6	0.12	1:6:8	0	1.5	16	33
7	0.12	1:6:8	0	2.0	12	31

[a] molar ratio of concentrations, [b]NMR yields.

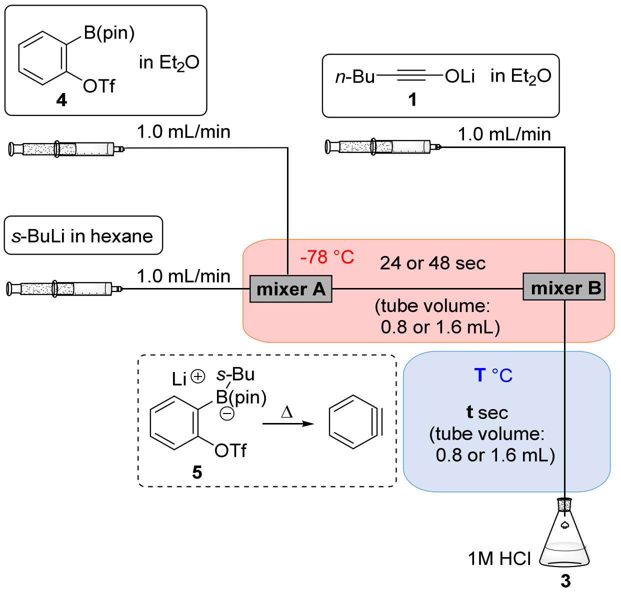
For comparison, the reaction was also performed in the batch system under the conditions corresponding to entry 6 in Table 1, and triptycene **3** was obtained with a 31% NMR yield (25% isolated yield), which was slightly less than that obtained in the microflow conditions (Scheme 2). This may indicate 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 still observed on the GC-MS analysis of the crude products (See Figure S1 in supporting information). The major byproducts were biphenyls and *o*-terphenyls, which would be formed by the addition of aryllithium intermediates to benzyne. Although this result indicates that benzyne was generated efficiently, most of the benzyne was wasted in the side reactions.



Scheme 2 Batch synthesis of triptycene **3** using *o*-bromoiodobenzene.

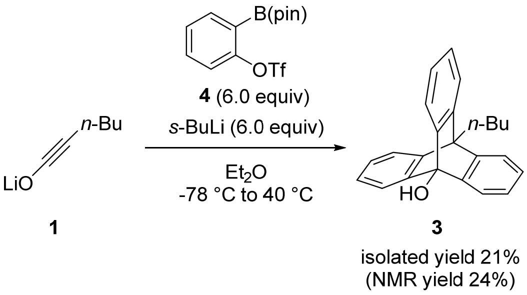
Thus, we changed the precursor of benzyne to *o*-(trifluoromethanesulfonyloxy)phenylboronic acid pinacol ester **4** developed by Hosoya and coworkers (Table 2).[12],[13] It has been reported that the treatment of alkyllithium with **4** generates borate complex **5,** which is stable at 0 °C and then converts to benzyne when warmed to room temperature. Based on this, we envisioned that the undesired addition reactions to benzyne could be suppressed using precursor **4** because, by the formation of the borate complex in advance, the coexistence of nucleophilic butyllithium and benzyne can be avoided. Slow generation of benzyne 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 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 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 benzynes 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.

Table 2 Flow synthesis of triptycene using *O*-(trifluoromethanesulfonyloxy)phenylboronic acid pinacol ester.



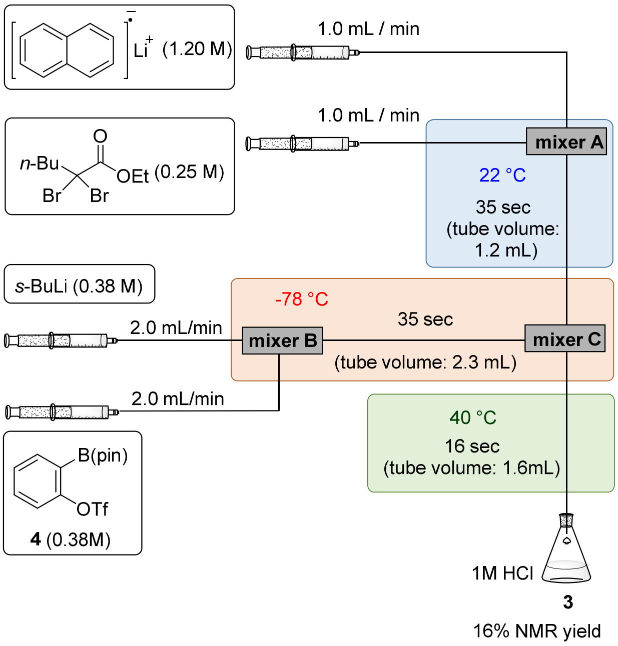
Entry	Concentration of **1** (M)	**1**:**4**: *s*-BuLi[a]	T (°C)	t (sec)	Yield (%)[b]
1[c]	0.05	1:6:6	23	16	19
2[c]	0.05	1:6:6	40	16	33
3[c]	0.05	1:6:6	60	32	29
4[c]	0.05	1:5:5	40	32	22
5[c]	0.05	1:8:8	40	32	20
6[d]	0.075	1:6:6	40	16	33 (31)[b]

[a]molar ratio of concentrations, [b]NMR yields. [c,d]Residence time between mixer A and B is 24 and 48sec, respectively. [b]isolated yield.



Scheme 3. Batch synthesis of triptycene **3** using borate-type benzyne precursor **4**.

Finally, ynolate **1**, prepared under the microflow conditions, was directly employed for the flow synthesis of triptycene (Scheme 4). The solutions of α,α-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 sec. 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.



Scheme 4. Flow synthesis of triptycene, including the preparation of ynolate.

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 transfer. The flow reaction was also performed using ynolate, which was prepared under microflow conditions, synthesizing 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 under investigation in our group.

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Click here to insert acknowledgment text. Funding sources and grant numbers should be given above in the Funding Information section.

Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

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(13) **Representative procedure for synthesis of 9-hydroxyltriptycene 3 using benzyne precursor 4**
Solution A: *o*-(Trifluoromethanesulfonyloxy)arylboronic acid pinacol ester (**4**, 1.58 g, 4.50 mmol) was dissolved in Et$_2$O (10.0 mL), and resulting solution was put in a syringe. **Solution B**: *s*-BuLi (0.97 M in cyclohexane and hexane) was diluted with hexane to be 0.45 M solutions, 10.0 mL of which was put in a syringe. **Solution C**: To a solution of ethyl 2,2-dibromohexanoate (227 mg, 0.750 mmol) in Et$_2$O (3.0 mL), cooled to -78 °C under argon atmosphere, was added dropwise a solution of *t*-BuLi (1.50 M in pentane, 2,0 mL, 3.0 mmol). The resulting yellow solution was stirred for 30 min at -78 ˚C and then for another 30 min at 0 °C. The resulting colorless solution of ynolate was diluted with Et$_2$O to make total volume of 10.0 mL and put in a syringe. **Reaction**: A flow microreactor system consisting of two micromixers (**M1** and **M2**, comet X each) and two microtube reactors (**R1**: ϕ = 1000 μm, L = 100 cm, V = 0.8 mL and **R2**: ϕ = 1000 μm, L = 100 cm, V = 0.8 mL) was used. **M1, M2** and **R1** were dipped in a cooling bath at -78 °C and **R2** was dipped in a warming bath at 40 °C. Solutions A and B were introduced to **M1** using syringe pumps in a flow rate of 1.0 mL/min each. The resulting solution was passed through **R1** and was mixed with solution C (flow rate: 1.0 mL/min) in **M2**. The resulting solution was then poured into 1M HCl. After a steady state was reached, the product solution was collected for 120 s (corresponding to 0.15 mmol of ynolate solution). The collected mixture was extracted with CHCl$_3$. The combined organic phase was washed with brine, dried over MgSO$_4$, filtered and concentrated. The crude product (24% NMR yield) was purified by silica gel column chromatography (hexane:EtOAc = 25:1) to afford compound **3** (15.2 mg, 31%) as a white solid.
Triptycene 3: ^{1}H NMR (600 MHz, CDCl$_3$) δ: 7.54 (d, J = 6.9 Hz, 3H), 7.39 (d, J = 6.9 Hz, 3H), 7.03-7.08 (m, 6H), 3.25 (s, 1H), 2.93 (t, J = 7.6 Hz, 2H), 2.12-2.17 (m, 2H), 1.79-1.85 (m, 2H), 1.16 (t, J = 7.2 Hz, 3H). The NMR spectrum was matched with that of our previous report.
