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Anthranoxides as Highly Reactive Arynophiles for Synthesis of Triptycenes

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Dedicated to Professor Koichi Fukase on the occasion of his 60th birthday

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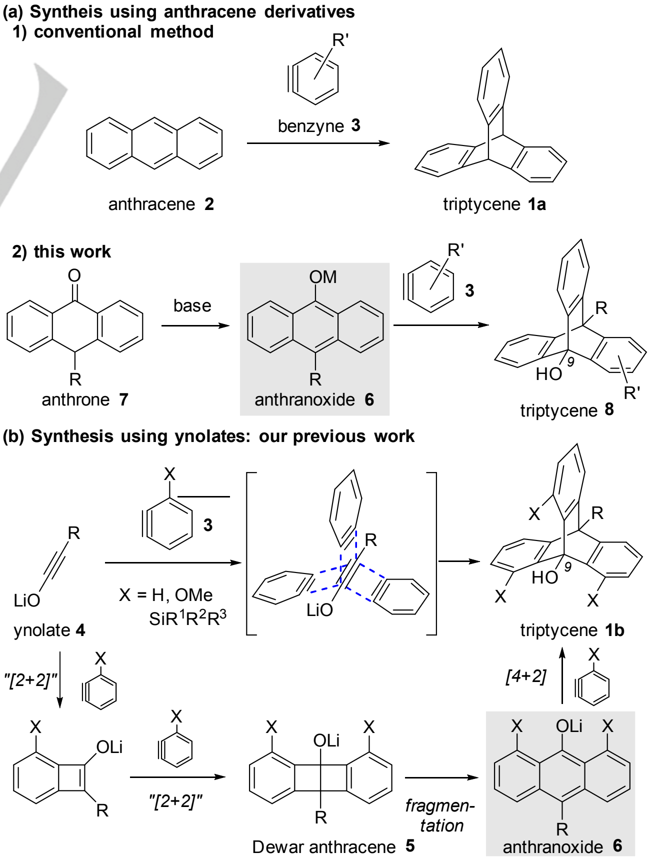
Abstract: We report herein an efficient method to synthesize triptycenes by the reaction of benzynes and anthranoxides, which are electron-rich and readily prepared from the corresponding anthrones. Using this method, 1,9-*syn*-substituted triptycenes were regioselectively obtained employing 3-methoxybenzynes. This method was also applied to synthesize pentiptycenes. A DFT study revealed that the cycloaddition of lithium anthranoxide and benzyne proceeds stepwise.

Triptycenes **1**,[1] which consist of an arene-fused bicyclo[2,2,2]octatriene bridgehead system, are aromatic compounds having a three-dimensional rigid molecular structure. Based on this unique structure, triptycenes are widely used in the field of molecular recognition,[2] molecular machine,[3] supramolecular chemistry,[4] materials science[5] and as metal ligands.[6] To synthesize triptycene **1a**, cycloaddition reactions between anthracenes **2** and benzynes **3**[7] are commonly utilized (Scheme 1a(1)). The conventional method focuses mainly on the preparation of arynes,[8] and the easily available benzyne precursors do not always provide triptycenes efficiently.[8a - f] Therefore, the use of more reactive arynophiles is one way to resolve this drawback, but this was not sufficiently investigated so far. In literature, a few electron-rich anthracenes[9] such as 9-acetoxyanthracenes,[9c,e] 9-methoxyanthracenes,[9a,d,f] and 1,4-dioxysulfonylanthracenes[9i] were applied in triptycene syntheses. These anthracenes, however, usually require a multistep preparation, are less reactive[9e,h] or are easily oxidized and not isolated in pure form.[9g,i] Thus, it is desirable to develop anthracenes which are sufficiently reactive and easily handled.

Recently, we developed a novel one-pot synthesis of triptycenes **1b** using a triple cycloaddition of benzynes to ynolates[10] **4** (Scheme 1b).[11] The key of this reaction is the *in situ* generation of anthranoxides **6** via a double [2+2] cycloaddition of ynolates **4** with two equivalents of benzynes followed by fragmentation of the resulting Dewar anthracenes **5**. The anthranoxides **6** subsequently reacted with the third equivalent of benzyne in a [4+2] cycloaddition. In addition, using 3-methoxy-[11a] or 3-silylbenzynes, sterically congested 1,8,13-tri-functionalized triptycenes **1b** were selectively obtained where three methoxy or silyl groups were located at the same side of the C9-hydroxyl group. During these studies, we noticed that anthranoxide **6** is a highly reactive arynophile for the [4+2] cycloaddition due to the strong electron-donating effect of the oxide moiety. In addition,



Scheme 1. Synthetic methods of triptycene.

the regioselectivity was effectively controlled using unsymmetrically substituted benzynes. Furthermore, anthranoxide **6**, which is sensitive to oxygen and water, can be readily prepared from the corresponding anthrones **7**, which are stable in air (Scheme 1a(2)). This synthesis method is not well established as there was only one report that mentioned the utilization of anthrone to directly synthesize triptycene.[6c] Hence, we herein describe a novel triptycenes synthesis using anthrones as an arynophile precursor.

First, anthranoxides **6a,b** prepared from anthrone (**7a**) reacted with benzyne derived from 1,2-dibromobenzene (**9a**) in a ratio of 3:1 (Table 1, entries 1 and 2), because the short-lived aryne can be rapidly trapped by excess arynophiles. We found that two types of base, *tert*-butyllithium and sodium hydride, effectively generated anthranoxides **6a,b**. When *tert*-butyllithium was used to deprotonate anthrone (**7a**), 9-hydroxytriptycene (**8a**) was obtained in 62% yield along with a small amount of byproduct resulting from the addition of *tert*-butyllithium to anthrone (entry 1).[12] On the other hand, the use of sodium hydride provided higher triptycene **8a** yields (73%, entry 2). These yields are much higher than that when 9-acetoxyanthracene is used to access triptycene **8a** (22% overall yield).[13] When the ratio of **7a** to **9a** was changed to 2:1, 1:1 and 1:2 (entries 3-5), the reactions using sodium hydride afforded triptycene **8a** in lower yields (50-62%). However, when a ratio of **7a**:**9a** was 1:3 (entry 6), **8a** was obtained in a yield comparable to that of entry 2. This suggests that an excess of benzynes over arynophiles is alternatively effective for this method, unless generation of many byproducts from benzynes is problematic for purification.

Table 1. Reaction of anthranoxides with benzyne in various ratios

entry	base	**7a**:**9a**	Yield (%)
1	*t*-BuLi[a]	3:1	62
2	NaH[b]	3:1	73
3	NaH[b]	2:1	58
4	NaH[b]	1:1	50
5	NaH[b]	1:2	62
6	NaH[b]	1:3	73

[a] Ratio of *t*-BuLi to **7a** was 1:1. [b] Ratio of NaH to **7a** was 1.5 :1. [c] Ratio of *n*-BuLi to **9a** was 1.2:1.

Applying the 3:1 ratio of anthrone **7** and benzyne precursor **9** as the standard condition for both bases, the cycloaddition reaction was performed using various benzyne precursors (Table 2). The two standard conditions successfully worked for 4,5-dimethoxybenzyne (from **9b**, entry 1), 4,5-difluorobenzyne (from **9c**, entry 2) and naphthalyne (from **9d**, entry 3), which provided the corresponding triptycenes **4b-d** in acceptable yields.

To examine the regioselectivity, unsymmetrical benzynes were employed next. Using *o*-fluorotoluene (**9e**) as a precursor, 3-methylbenzyne (**3e**) was reacted with anthranoxide **6b** to afford triptycenes **8ea** and **8eb** in 16 and 31% yield, respectively (entry 4). The structure of these products was determined by nuclear Overhauser effect (NOE) experiments and X-ray crystallographic analysis. These results corresponded well with the fact that C2-position of **3e** are more electrophilic and more sterically hindered than C1-position, and a mixture of regioisomers is generally formed.[14] In contrast, 3-methoxybenzyne generated from 3-fluoroanisole (**9f**) showed perfect regioselectivity to produce 1,9-*syn*-substituted triptycene **8f** in satisfactory yields (entry 5). This high regioselectivity agrees with our previous work concerning the triple cycloaddition of ynolates and benzynes, and therefore negative hyperconjugation might be critical in this case as well.[11a] Additionally, in the case of iodophenyl triflate **9g** as a 3-methoxybenzyne precursor, sodium hydride was less effective than *tert*-butyllithium, the yields were 38% and 64%, respectively (entry 6). 3-Methoxybenzynes with additional methoxy or fluoro groups also worked well in this reaction to selectively provide 1,9-*syn*-substituted triptycenes **8h-j** (entries 7–9). It should be noted that 3-fluoro-6-methoxybenzyne (**3k**) derived from **9k** provided triptycene **8ka** and **8kb** in a 2.7:1 ratio (entry 10). According to previous reports,[15] the C1-position of **3k** is more electrophilic than the C2-position, but our result indicated the opposite. This might be related to the significant interaction between lithium and the methoxy group.

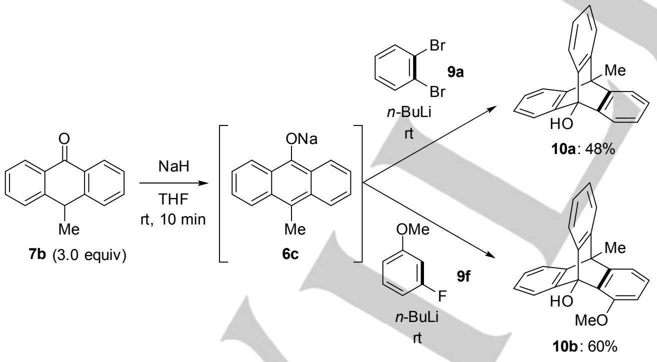
Table 2. Reaction of anthranoxides with various benzynes.

entry	precursor	product	entry	precursor	product
1			6		
2			7		
3			8		

4			9		
5			10		

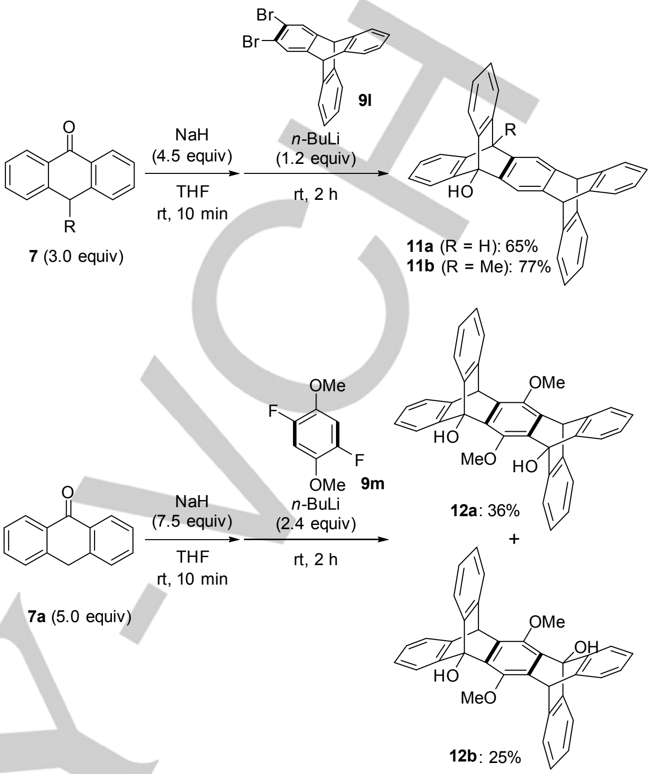
[a] *n*-BuLi was added over 5‑10 min.

Employing 10-methylanthranoxide **6c** as an arynophile in this reaction, which was generated from 10-methylanthrone (**7b**), unsubstituted and 3-methoxybenzynes produced the corresponding 10-methyl-9-hydroxytriptycenes **10a** and **10b** in 48 and 60% yield, respectively (Scheme 2). The X-ray crystallographic analysis of **10b** revealed the stereochemistry, and a high regioselectivity was observed in this case as well.



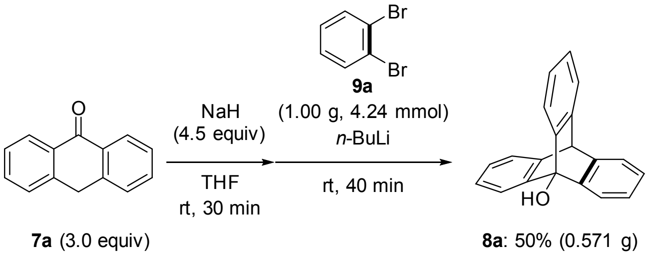
Scheme 2. Synthesis of 9-hydroxytriptycene.

This method was further applied to synthesize pentiptycenes (Scheme 3). The reaction of triptycyne, derived from 3,4-dibromotriptycene (**9l**),[16] with anthranoxides at standard conditions was successful, providing pentiptycenes **11a** and **11b** in satisfactory yield. Furthermore, 1,4-difluoro-2,5-dimethoxybenzene (**9m**) reacted as a 1,4-benzdiyne equivalent[17] in this method. The double [4+2] cycloaddition after treating **9m** with 2.4 equivalents of *n*-butyllithium produced pentiptycenes **12a** and **12b** in 36% and 25% yield, respectively.



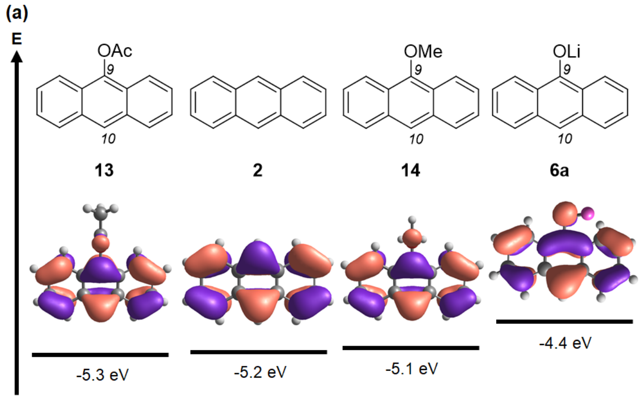
Scheme 3. Synthesis of pentiptycenes.

This method was also applied to gram-scale synthesis (Scheme 4). Starting with 1.00 g of 1,2-dibromobenzene (**9a**), 0.571 g of 9-hydroxytriptycene (**8a**) was successfully obtained in 50% yield at standard conditions.



Scheme 4. Gram-scale synthesis of 9-hydroxytriptycene.

Theoretical calculations at the B3LYP/6-31G** level were used to shed light on the reactivity and structural feature of lithium anthranoxide **6a**. As shown in Figure 1a, the HOMO energy level of 9-acetoxyanthracene[9c,e] (**13**, -5.3 eV) and 9-methoxyanthracene[9a,d,f] (**14,** -5.1 eV), generally used as arynophiles to synthesize triptycenes, is almost similar to that of anthracene (**2**, -5.2 eV). By contrast, lithium anthranoxide **6a** has a much higher HOMO energy level of -4.4 eV, which clearly indicated that **6a** would react more easily with benzyne (LUMO energy level of -1.9 eV) than with anthracenes **2**, **13**, and **14**. In addition, based on calculations of atomic charges (Figure 1b), the C9 and C10 positions of **6a** are the most electron-positive and negative carbons, respectively. The differences in the natural bond orbital (NBO) charge values (Δq) are significantly larger than the corresponding values of **13** and **14**, suggesting that anthranoxide **6a** has a more polarized structure compared to **13** and **14**.



(b)

	q(C9)	q(C10)	Δq
13	0.348	-0.188	0.536
14	0.356	-0.197	0.553
6a	0.385	-0.259	0.644

Figure 1. (a) HOMO energy levels, (b) NBO charges, q (e), Δq = q(C9)-q(C10). Values are obtained at the B3LYP/6-31G** level. NBO charges were calculated using the NBO 3.1 program.[18]

Next, the overall process of the cycloaddition reaction between lithium anthranoxide **6a** and benzyne was computed. Calculated energy profiles are illustrated in Figure 2. The cycloaddition reaction takes place in two steps.[19] In the first step, bond formation between the C10 position of **6a** and benzyne occurs, displaying an activation energy of 8.2 kcal/mol during the reaction course from reactant complex **15** to the intermediate **16** via **TS1**. In the second step, the bridged structure is generated by cyclization to afford triptycene **17** (-56.5 kcal/mol) via **TS2**. The reactants in the isolated system have the highest energy in the profile, and the highest energy barrier is observed for the first step (**15** to **TS1**) with only 8.2 kcal/mol. Thus, this cycloaddition reaction proceeds smoothly and is highly exothermic (-56.5 kcal/mol). In addition, this energy barrier is lower than that of the cycloaddition reaction between anthracene (**2**) and benzyne (for detail, see supporting information).

In conclusion, an efficient and regioselective method to synthesize triptycenes using anthranoxides and benzynes was developed. Anthranoxides, which were easily prepared from the corresponding stable anthrones using *tert*-butyllithium or sodium hydride, exhibited high reactivity toward various benzynes and satisfactory regioselectivity applying 3-methoxybenzynes. This method was also suitable for synthesizing pentiptycenes. DFT calculations revealed that lithium anthranoxide has a high HOMO energy level, and its cycloaddition with benzyne proceeds stepwise, displaying low energy barriers. This method provides a useful strategy to access functionalized triptycenes and iptycenes which potentially lead to functional materials. The syntheses of iptycenes are now further investigated in our group.

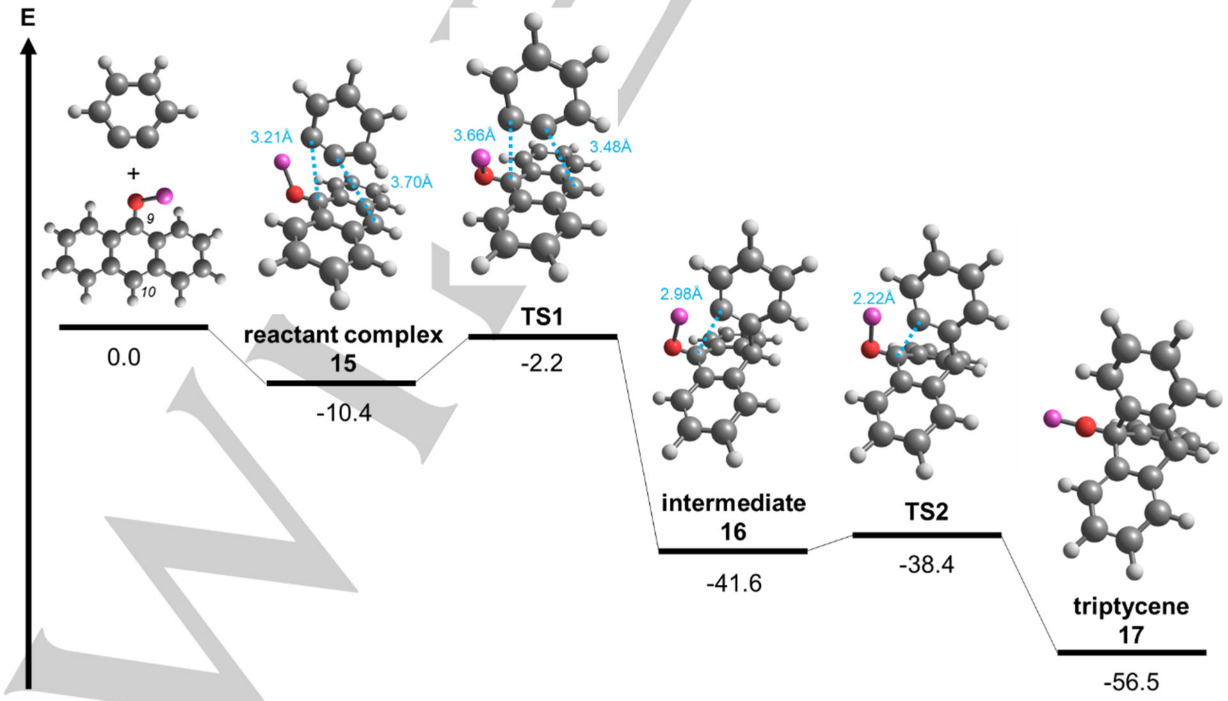


Figure 2. Calculated energy profiles for the cycloaddition reaction between lithium anthranoxide **6a** and benzyne. Units are in Å and kcal/mol.

Acknowledgements

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Keywords: triptycene • anthracene • benzyne • cycloaddition

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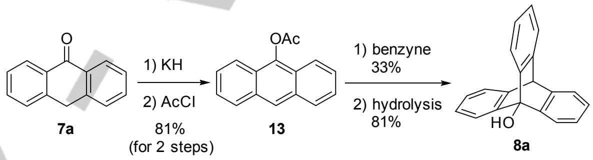

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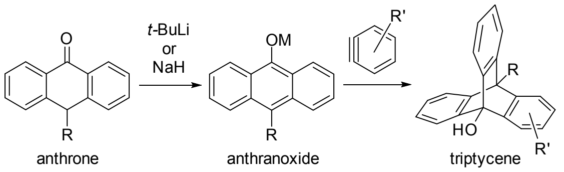

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