# Dioxygen-Triggered Transannular Dearomatization of Benzo[5]helicene Diols: Highly Efficient Synthesis of Chiral π-Extended Diones**

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***Abstract:*** *Oxidative dearomatization is a powerful strategy in organic synthesis. However, reports on using dioxygen as the oxidant, as it is environmentally friendly, readily available (air), and easy to handle, are rather limited. Helicene diols can undergo transannular dearomatization triggered by dioxygen to give diones in quantitative yields within several minutes. By virtue of this, the chirality is successfully transferred from helicity to central chirality to form distorted π-extended diones having two all-carbon quaternary stereocenters. The optical resolution was achieved by column chromatography, and the structures and the absolute configurations of the chiral diones were determined by X-ray analysis.*

**T**he physical and chemical properties of aromatic materials have been hot topics not only in academia but also in industry. Dearomatization—the use of aromaticity as a functional group—is considered as a powerful transformation.[1] Practical applications have been realized not only in the construction of carbon–carbon and carbon–heteroatom bonds,[1c,d] but also in materials science for memory and switches.[2] For oxidative dearomatization, phenols are the most frequently used substrates in the preparation of complex compounds.[3] Recently, Koyama, Hiroto, and Shinokubo[4] provided an exceptionally facile method to construct π-extended [2,2]-metacyclophanes utilizing intermolecular oxidative dearomatization. However, most of the oxidants used in oxidative dearomatization are hypervalent iodine reagents and transition-metal reagents, which are usually expensive, highly reactive, and require harsh reaction conditions.[1c,d] The reports on utilizing dioxygen, as a benign and clean oxidant, in oxidative dearomatization, especially for the large π-conjugated systems, are rather limited.

Helicenes, as a member of polycyclic aromatic hydrocarbons formed by *ortho*-annulated aromatic or heteroaromatic rings, have attracted increasing interest because of their conjugated skeletons and intriguing helical chirality.[5] Recently, optically pure helicenes having diverse functional groups are employed in several different fields, such as high-optical-rotation complexes,[6] organoelectronics,[7] asymmetric gold catalysis,[8] redox-triggered chiroptical switches,[9] and proteinlike tetrameric ααββ-heteroaggregates.[10] Although the stereoselective synthesis of helicenes has been realized by virtue of organometallic catalysis[11] and Diels–Alder additions[12] during the last decade, most of the helicenes employed in optically active forms, as in asymmetric synthesis[13] and self-assembly,[14] were resolved by semi-preparative or preparative high performance liquid chromatography (HPLC), which is an expensive and impractical strategy. It has been a significant challenge to find a convenient and efficient strategy to obtain optically pure helicenes.

Herein, we report a practical method for the synthesis of helicenes and their optical resolution. Moreover, the helicene diols could undergo highly efficient transannular dearomatization reactions triggered by dioxygen (Figure 1). To the best of our knowledge, this work represents the first example of the transannular dearomatization reactions using dioxygen as the oxidant.
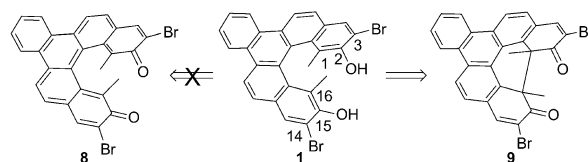


***Figure 1.*** Dioxygen-triggered transannular dearomatization reactions.

Our work focuses on exploring efficient synthetic strategies for functionalized helicenes and their applications in asymmetric synthesis. Previously, our group reported an efficient method to construct multifunctionalized benzo[5]-helicenes.[15] Unfortunately, they were all optically unstable at room temperature and could not be resolved. Thus, we rationally designed an optically stable diol (**1**) as shown in Figure 1: 1) the two methyl groups at C1 and C16 could effectively hinder racemization; 2) the two hydroxy groups at C2 and C15 could be used for optical resolution and as binding sites; 3) the two Br atoms at C3 and C14 could be modified after helicene formation to form chiral spaces.

Given the above-mentioned features, we first tried to synthesize the 1,16-disubstituted helicene diols (Scheme 1). Through the reductive coupling of **2a** and **2b**,[16] the dienes **3a** and **3b**, respectively, were obtained.[17] The subsequent Diels–Alder reactions proceeded smoothly, thus giving the adducts

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201400486.
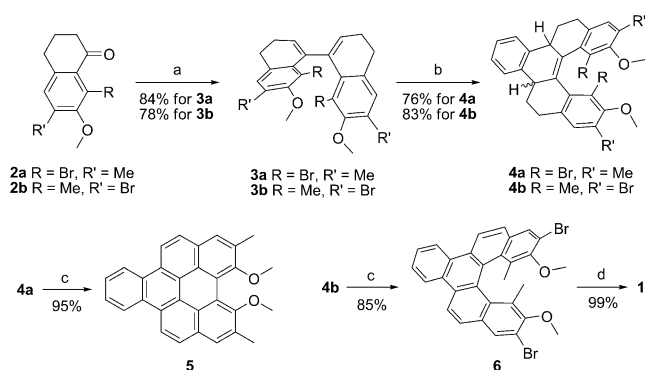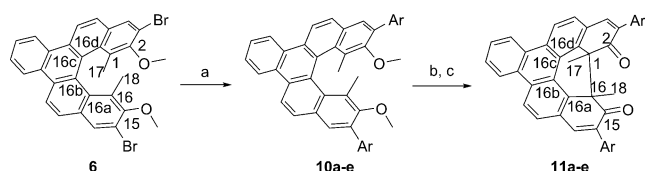
**Scheme 1.** Preparation of the dehydrobenzo[5]helicene **5** and benzo[5]-helicene diol **1**: a) Zn (2.0 equiv), TMSCl (4.0 equiv), conc. HCl, THF, −78 °C to RT, 3 h; b) 2-carboxybenzene diazonium chloride (2.0 equiv), DCE, 2-methyloxirane, reflux, 2 h; c) DDQ (10.0 equiv), xylene, reflux, 12 h; d) BBr₃, CH₂Cl₂, 0–5 °C, 30 min. DCE = 1,2-dichloroethane, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, THF = tetrahydrofuran, TMS = trimethylsilyl.

**Table 1:** The Suzuki–Miyaura cross-coupling reactions of **6** and the dearomatization reactions of diaryl-functionalized helicenes **10a–e**.

| Entry | Ar | Product | Yield [%][a] | Product | Yield [%][b] |
|---|---|---|---|---|---|
| 1 | phenyl | **10a** | 96 | **11a** | 99 |
| 2 | 3-thienyl | **10b** | 90 | **11b** | 99 |
| 3 | 4-fluorophenyl | **10c** | 93 | **11c** | 99 |
| 4 | 4-chlorophenyl | **10d** | 85 | **11d** | 99 |
| 5 | 4-nitrophenyl | **10e** | 75 | **11e** | 99 |

[a] Yield of product isolated after step a. [b] Yield of product isolated after steps b and c.

**4a** and **4b** in excellent yields. After the oxidation of the adducts by DDQ, **5** and **6** were obtained in satisfactory yields (for the crystal structures of **5** and **6**, see the Supporting Information). Finally, the desired helicene diol **1** was prepared quantitatively by demethylation.

With **1** in hand, we tried to achieve optical resolution and determine the racemization barrier. Therefore, (1*S*)-(+)-10-camphorsulfonyl chloride (**7**) was used to obtain the diastereomers. Interestingly, the reaction was completed within several minutes, and only a minute amount of the sulfonate was obtained. According to the characterization results, the quinone-like helical dione **8** (Figure 1) was supposed to be produced. By screening the influence of various factors, we found that this process was greatly accelerated under an oxygen atmosphere rather than under inert conditions, and light had negligible effects on the reaction (for details, see the Supporting Information). Thus, we suggested that such a transformation was achieved through a dioxygen-triggered radical process.[3]

To investigate whether this transformation was universal, five different aryl groups were introduced to the scaffold (Scheme 2). After demethylation of **10a–e** and subsequent stirring in a CH₂Cl₂ solution open to the air, similar transformations took place (Table 1). Fortunately, we obtained a single crystal of **11a** (for details, see the Supporting Information) by slow evaporation of the acetone solution.



**Scheme 2.** The Suzuki–Miyaura cross-coupling reactions of **6** and the dearomatization reactions of **10a–e**: a) arylboronic acid (3.0 equiv), [Pd(PPh₃)₄] (10 mol%), K₂CO₃ (10.0 equiv), toluene/EtOH/H₂O (v/v/v, 2:2:1), reflux, 12 h; b) BBr₃ (10.0 equiv), CH₂Cl₂, 0–5 °C, 20 min; c) CH₂Cl₂, stirring under air, RT, 15 min.

According to the crystal structure, our proposed structure **8** was not correct. And the transannular dearomatization reaction took place to give the dione **9** (Figure 1) with two all-carbon quaternary stereocenters.

By comparison of the crystal structures of **5**, **6**, and **11a**, the helical framework was found to be more stable, from a thermodynamic point of view, after the dearomatization reactions. For **6**, the torsional angles for C1-C16d-C16c-C16b, C16d-C16c-C16b-C16a, and C16c-C16b-C16a-C16 were 28.75°, 28.19°, and 25.32°, respectively (sum of 82.26°). For **11a**, they were 10.65°, 8.78°, and 2.97°, respectively (sum of 22.4°). By comparison, **5**, which had a total torsion angle of 22.4° (1.23°, 14.32°, and 6.85° for each torsion) caused by the repulsion of the two methoxy groups, it was fair to draw the conclusion that the transannular dearomatization process greatly released the torsional strain of the helical structure. Moreover, for **11a**, along the single bond between C1 and C16, the two methyl groups are in an *anti* conformation (173.12°), while the C1−C2 and C16−C15 bonds are in a gauche conformation (65.89°). With the distance between C1 and C16 decreasing from 3.077 Å in **6** to 1.550 Å in **11a**, the distance between the two oxygen atoms was shortened from 4.685 Å to 2.694 Å, thus making the molecule a potential bidentate ligand.

To obtain optically active diones the helicenes needed to be first resolved. Since all the helicene diols were susceptible to oxygen in the solution, we incorporated the chiral auxiliary before the oxidation (Scheme 3). Given the solubility, we chose the diphenyl-substituted Diels–Alder adduct as a precursor, which was readily synthesized from **4b** in 95% yield. By demethylation and reaction with **7**, a mixture of diastereomers of sulfonates was obtained. After the oxidation of the sulfonates and the subsequent optical resolution by column chromatography, (−)-(*S,S,M*)-**13** and (+)-(*S,S,P*)-**14** could be easily obtained, and their optical rotations ([α]$_D^{25}$) were found to be −1460° and +1660° (*c* = 1.0 mg mL$^{-1}$, CH₂Cl₂), respectively.

[5]Helicenes usually undergo racemization even at room temperature. Therefore, we examined the racemization barrier of the 1,16-dimethylbenzo[5]helicene (DMB[5]H). Because the sulfonates were transformed into diones after hydrolysis, it was difficult for us to determine this barrier of the optically pure helicene diols directly. Because (−)-(*S,S,M*)-**13** and (+)-(*S,S,P*)-**14** had two O atoms, which are smaller than a methyl group, at C2 and C15, it was reasonable that the two chiral auxiliaries had a very small effect on the racemization barrier.[18]
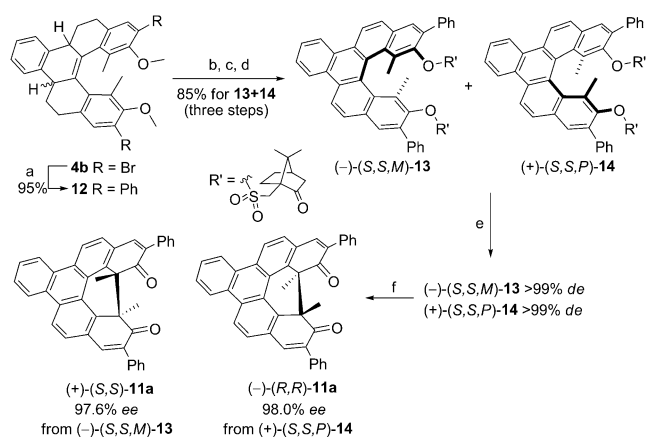
**Scheme 3.** Synthesis and optical resolution of the diones: a) phenyl-boronic acid (3.0 equiv), [Pd(PPh$_3$)$_4$] (10 mol%), K$_2$CO$_3$ (10.0 equiv), toluene/EtOH/H$_2$O (v/v/v, 2:2:1), reflux, 12 h; b) BBr$_3$ (10.0 equiv), CH$_2$Cl$_2$, 0–5°C, 20 min; c) **7** (3.0 equiv), Et$_3$N, DMAP (5 mol%), CH$_2$Cl$_2$, RT, 5 h; d) DDQ (10.0 equiv), xylene, reflux, 12 h; e) optical resolution by column chromatography (for details, see the Supporting Information); f) KOH (10.0 equiv), CH$_2$Cl$_2$/MeOH (v/v, 1:1), 60°C in open air, 12 h. The *de* values were determined by $^1$H NMR spectroscopy. The *ee* values were determined by HPLC using a chiral stationary phase. DMAP = 4-(*N*,*N*-dimethylamino)pyridine.



**Figure 2.** ECD spectra (*c*, 0.1 mm, CH$_2$Cl$_2$, 25°C) of (−)-(*S*,*S*,*M*)-**13**, (+)-(*S*,*S*,*P*)-**14**, (+)-(*S*,*S*)-**11a**, and (−)-(*R*,*R*)-**11a**.

To investigate the racemization barrier of the DMB[5]H core, we first performed variable-temperature $^1$H NMR experiments (for details, see the Supporting Information). According to the results, (−)-(*S*,*S*,*M*)-**13** did not undergo racemization, even at 383 K. Afterwards, we examined the sample at higher temperatures, but, unfortunately, the sulfonates decomposed (>150°C). However, when keeping the sample under 120°C for 12 hours, no racemization was observed. So it is fair to conclude that 1,16-dimethylbenzo[5]-helicenes do not undergo racemization at temperatures below 120°C. This temperature is sufficiently high that the majority of common reactions could be performed without loss of optical purity. Recently, Suemune, Usui, and co-workers[19] found that the racemization barrier of 1-methyl[5]helicene ($\Delta G^{\neq}$ 38.6 kcal mol$^{-1}$, 473 K) was even higher than that of [6]helicene ($\Delta G^{\neq}$ 36.9 kcal mol$^{-1}$, 469 K). Our helicenes had two methyl groups at the most sterically hindered positions, so it was reasonable to say that 1,16-dimethylbenzo[5]helicenes had better thermal stability than [6]helicene.

To assign the absolute configuration of the helicenes, we compared the electronic circular dichroism (ECD) spectra with those of other [5]helicenes.[20] Because the two chiral auxiliaries had no absorption from $\lambda = 330$ to 500 nm, the ECD spectra (Figure 2) in this region displayed the signals of helicity. For the reported [5]helicenes, the negative Cotton effect (or positive Cotton effect) was always observed at the maximum absorption peak for *P* helicenes (or *M* helicenes). Moreover, as a general principle, laevorotatory (or dextro-rotatory) carbohelicenes had *M* helicity (or *P* helicity). By virtue of these points above, the absolute configurations of the diastereomers were unambiguously assigned: (−)-**13** possessed *M* helicity, while (+)-**14** possessed *P* helicity.[5e]

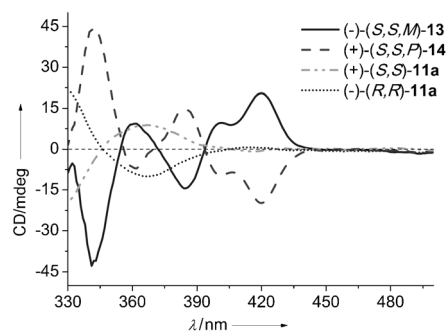After the reactions of hydrolysis and dearomatization (Scheme 3), the optically active diones (+)-(*S*,*S*)-**11a**

($[\alpha]_D^{25} = +280°$ *c* = 1.0 mg mL$^{-1}$, CH$_2$Cl$_2$) and (−)-(*R*,*R*)-**11a** ($[\alpha]_D^{25} = -270°$ *c* = 1.0 mg mL$^{-1}$, CH$_2$Cl$_2$) were obtained quantitatively. For the diones, a small negative Cotton effect (or positive Cotton effect) at the maximum absorption peak was found for (+)-(*S*,*S*)-**11a** [or (−)-(*R*,*R*)-**11a**] (Figure 2). To make sure of the absolute configuration of the diones, we prepared (+)-(*S*,*S*)-**9** using a similar procedure and optical resolution based on **4b**. Fortunately, the single crystal of (+)-(*S*,*S*)-**9**[21] was obtained, in which the Br atoms helped ascertain the absolute configuration of the diones (see the Supporting Information).

In conclusion, we have discovered a highly efficient dioxygen-triggered transannular dearomatization reaction of 1,16-dimethylbenzo[5]helicene diols, and it resulted in chiral π-extended diones, having two quaternary carbon centers, in quantitative yields. Given the satisfactory thermal stability of the scaffold, helicene sulfonates could be easily resolved by column chromatography. Absolute configurations were undoubtedly assigned as (+)-(*P*)-helicene diols [or (−)-(*M*)-helicene diols] and gave (−)-(*R*,*R*)-diones [or (+)-(*S*,*S*)-diones], as determined with the help of X-ray analysis. The results presented herein will provide new opportunities for the construction of chiral π-extended systems and chiral bidentate ligands. The application of these π-extended diones in asymmetric synthesis are under way in our laboratory.

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[21] CCDC 979354 (*rac*-**5**), 979355 (*rac*-**6**), 979356 (*rac*-**11a**), and 979350 ((+)-(*S,S*)-**9**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.